Intramolecular addition of acyldiazenecarboxylates onto double bonds in the synthesis of heterocycles

José V. Prata,[a] Dina-Telma S. Clemente,[b] Sundaresan Prabhakar,*[b] Ana M. Lobo,[b] Isabel Mourato (in part)[b] and Paula S. Branco (in part)[b]

[a] *Secção de Química Orgânica, Departamento de Engenharia Química, Instituto Superior de Engenharia de Lisboa, Instituto Politécnico de Lisboa, R. Conselheiro Emídio Navarro, 1, 1949-014, Lisboa, Portugal. E-mail: jvprata@deq.isel.pt*

[b] *Secção de Química Orgânica Aplicada, Departamento de Química, Centro de Química Fina e Biotecnologia and SINTOR-UNINOVA, campus Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, Quinta da Torre, 2829-516, Monte de Caparica, Portugal. E-mail: sp@dq.fct.unl.pt*

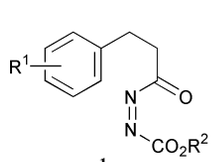
Received (in Cambridge, UK) 14th November 2001, Accepted 7th December 2001
First published as an Advance Article on the web 23rd January 2002

Appropriate aryl-substituted unsymmetrical azodicarbonyl compounds, generated from bishydrazides by oxidation, undergo intramolecular cyclisations to furnish a variety of useful heterocycles such as *N*-substituted oxindoles, carbostyrils, benzazepinones, benzazocinones, benzimidazolones, benzoxazinones and pyrazolones in varying degrees of efficiency. Methods are described to remove the *N*-acyl groups from the heteroaromatic compounds. Under mildly acidic conditions where equal opportunities are available for an *ipso* or a normal cyclisation it is the former process that occurs preferentially. Evidence is presented in favour of a C-to-C migration in the *ipso* product for the formation of a methoxy-substituted carbostyril derivative. One of the spiro substances is shown to participate in dienone–phenol rearrangement to provide the corresponding quinolone–phenol in high yield.

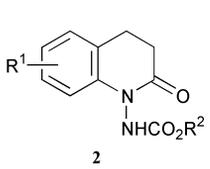
Introduction

Intermolecular electrophilic amination of activated aromatics and other electron-rich olefins with diethyl azodicarboxylate either acid-catalysed or otherwise has been known for well over fifty years.[1] Recently variants of this basic reaction have been developed to achieve high yields of the aryl amino compounds with the use of more electrophilic azodicarboxylates in conjunction with $LiClO_4$[2] or $ZrCl_4$[3] as the Lewis acid catalyst. However, the intramolecular version of such a reaction was not reported until 1994, when it was shown that a variety of appropriately substituted 2-(3-arylpropanoyl)diazenecarboxylates [N^1-β-arylpropionyl-N^2-(methoxycarbonyl)azines] **1** led to *N*-substituted amino dihydrocarbostyrils **2** and spiro-γ-lactams **3** in synthetically useful yields.[4]

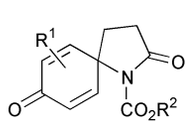
We describe herein details pertaining to the above work and also report results of our study on structurally related substances that show that the reaction is of general applicability. Thus other important heterocyclic systems such as oxindoles, benzazepinones, benzazocinones, benzimidazolones, benzoxazinones and pyrazolones can all be successfully prepared by this method with varying degrees of efficiency.[5]



1



2

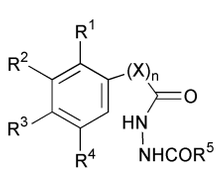


3

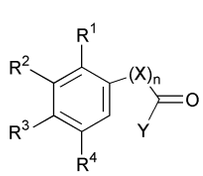
Results

Preparation of starting materials

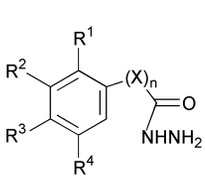
The bishydrazides of general structure **4A–E**, required as starting materials, are readily obtained in excellent yields by hydrazinolysis of methyl esters **5a** of arylalkanoic acids or those (**5b**) of aryloxyalkanoic acids to the hydrazides **5A–C** and **5e** followed by acylation of the latter with appropriate acid chlorides. The utilisation of readily available monohydrazides **6a** and **6b** in conjunction with acid chlorides **5c** provided an alternative route to some of these substances **4**.



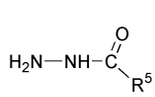
4A-D X= CH_2 (n = 1-4)
4E X= OCH_2 (n=1)



5a X= CH_2 (n = 1-3) , Y = OMe
b X= OCH_2 (n=1), Y= OMe
c X=CH_2 (n = 1,3,4), Y =Cl



5A-C X= CH_2 (n = 1-3)
5E X= OCH_2 (n=1)



6a R^5 = OMe
b R^5 = OPh

Cyclisations

Oxidation of diacylhydrazines **4** to the reactive azodicarbonyl compounds of type **1** was achieved with several reagents.

Table 1 Oxidative cyclisations of N^2-(arylacetyl)carbazates **4A**,**7** to oxindoles **9**, **8**

Starting materials **4A** X = CH_2; n = 1		Products **9**		Yield (%)[a]
a.	$R^1 = R^2 = R^3 = R^4 = H$, R^5 = OMe			
b.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5$ = OMe	**b**.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5$ = OMe	51
c.	$R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OPh	**c**.	$R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OPh	60
d.	$R^1 = H$, $R^2 = R^3 = R^4 = R^5$ = OMe	**d**.	$R^1 = H$, $R^2 = R^3 = R^4 = R^5$ = OMe	40
e.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5$ = OMe	**e**.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5$ = OMe	41
f.	$R^2 = R^3 = H$, $R^1 = R^4 = R^5$ = OMe	**e**.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5$ = OMe	5
		f.	$R^1 = R^4 = H$, R^2 = OH, $R^3 = R^5$ = OMe	5
g.	$R^1 = R^3 = R^4 = H$, R^2 = Me, R^5 = OMe	**g**.	$R^1 = R^3 = R^4 = H$, R^2 = Me; R^5 = OMe	28
7		**8**		85

[a] All the compounds were obtained through **method 3b** (see text).

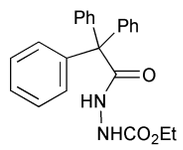
Depending on the electronic nature of the substituent(s) present on the aromatic ring, very little, partial or complete cyclisation to heterocycles was observed during oxidation; in the former two instances a protic or Lewis acid, in necessary quantities, was added to the mixture to bring the reactions to rapid conclusion. The following reagents/methods were used in the oxidative cyclisation step:

1) Method 1: NBS–pyridine[6] followed by acid (BF_3·Et_2O)
2) Method 2a: Iodobenzene diacetate (IBDA)[7]
Method 2b: IBDA followed by acid (BF_3·Et_2O)
3) Method 3a: Iodobenzene bistrifluoroacetate (IBBTA)[7]
Method 3b: IBBTA followed by acid (BF_3·Et_2O)
4) Method 4: Silver oxide on Celite support[8] followed by acid (BF_3·Et_2O or TFA).

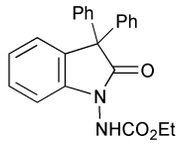
Oxindoles. The first member of the series to be examined, the unsubstituted methyl N^2-(phenylacetyl)carbazate **4Aa** (Table 1) on oxidation (IBBTA) in CH_2Cl_2 developed an orange colour presumably due to the formation of the corresponding azodicarbonyl compound, which on treatment with BF_3·Et_2O resulted in evolution of gas. The ^{1}H NMR spectrum and GC–MS of the crude product showed it to be a mixture of methyl phenylacetate and iodobenzene. On the other hand, compound **7**, derived from triphenylacetic acid, underwent oxidative cyclisation in excellent yield to furnish the known oxindole derivative **8**.[9] Siting a methoxy group *meta* to the side chain as in **4Ab** also largely suppressed the fragmentation process and a 51% yield of the product **9b** was obtained. Similarly the phenyl urethane **4Ac** furnished the corresponding oxindole **9c** in 60% yield. Whilst the dimethoxy compound **4Ae** underwent ring closure to **9e** without incident, the regioisomeric carbamate **4Af** containing *p*-methoxys groups behaved anomalously. The two minor products of the reaction, each isolated in 5% yield, were **9e** and a phenol, presumably **9f**. The spectral data of the former (^{1}H NMR, IR) as well as its mobility in the TLC plates were identical with those of the oxindole **9e** obtained directly from the bishydrazide **4Ae** (*vide infra* Discussion). Compound **9f** was characterised as the *O*,*N*-dimethyl derivative **10** by alkylation (MeI–K_2CO_3–Me_2CO). The activation provided by a methyl group (**4Ag**) was also found to be sufficient for cyclisation to occur (to afford **9g**).

Carbostyril derivatives. The reactivity and chemistry of azodicarbonyl compounds derived from N^2-(3-arylpropionyl)-carbazates (**4B series**) were largely similar to those described above. However, a few important differences were noticed. Thus unlike **4Aa** the first member of this series, **4Ba**, underwent ring closure to the carbostyril **12a** (Table 2) in modest yield (44%). Another notable difference observed in this series was that, in appropriate cases, spiro-γ-lactams could be isolated and characterised.

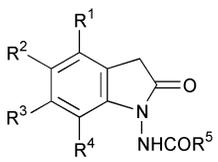
Thus, whilst **4Bb**, on oxidation with IBBTA furnished the quinolone **12b** (71%) its regioisomer **4Bc** afforded with the same oxidant only the γ-lactam **11c** in modest yield (25%). Ag_2CO_3, however, gave a mixture of **11c** (17%) and, of mechanistic relevance, the quinolone **12b** (50%) (*vide infra* Discussion).



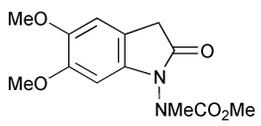
7



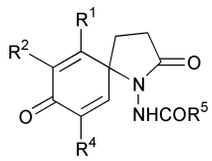
8



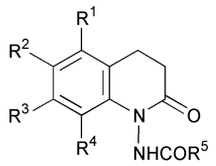
9b-g



10



11



12

The trimethoxy **4Bf** and bromotrimethoxy **4Bg** compounds furnished principally the corresponding γ-lactams (**11f** and **11g**), the respective quinolones (**12f**, **12g**) constituting the minor products of the reactions. On the other hand, the *m*-dimethoxy isomer **4Bh** yielded solely the quinoline **12h** (64%). The veratrole derivative **4Be** provided an opportunity to test the existence, if any, of preference for 1,5-addition (γ-lactam) over the 1,6-process (δ-lactam). Accordingly, reaction of **4Be** with IBDA (1 equiv.), which only liberates a weak acid, *i.e.*, HOAc, during the oxidation, was carried out in the absence of BF_3·Et_2O. No trace of the quinolone **12e** could be detected in the reaction mixture. Only **11e**, presumably the kinetically controlled product, was isolated, albeit in poor yield (4%). The same compound could, however, be obtained in 50% yield when IBBTA was employed. An acid-catalysed rearrangement (H_2SO_4–HOAc) of the latter provided a phenol, presumably **12k** (91%), that was methylated (CH_2N_2) to **12e** (87%). The phenyl carbamate **12h** derived from **4Bh** on mild alkaline hydrolysis liberated the synthetically useful amino compound **13b**, which could be reacylated with PhOCOCl to the starting material, showing that no structural alteration of **12h** had occurred during its hydrolysis. Deamination of **13b** to the known 6,8-dimethoxy-3,4-dihydrocarbostyril[10] **13c** could be accomplished in good yield either with $NaNO_2$–HOAc at room temperature or under neutral conditions with *N*-nitroso-diphenylamine in benzene under reflux.[11] The known *N*-amino compound **13a**[12] could also be obtained from the methyl carbamate **12a** by heating it with conc. HCl.

Table 2 Oxidative cyclisations of N^2-(3-arylpropionyl)carbazates **4B** to spirodienone-γ-lactams **11** and dihydroquinolones **12**

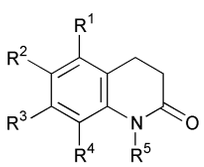
Starting materials **4B** X = CH_2; n = 2		Products **11**		Yield (%); Method	Products **12**		Yield (%); Method
a.	$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OMe$				**a**.	$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OMe$	44; 3b 62; 4
b.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$				**b**.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$	71; 3a
c.	$R^1 = R^2 = R^4 = H$, $R^3 = R^5 = OMe$	**c**.	$R^1 = R^2 = R^4 = H$, $R^5 = OMe$	25; 3a 17; 4	**b**.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$	50; 4
d.	$R^1 = R^3 = H$, $R^2 = R^4 = R^5 = OMe$				**d**.	$R^1 = R^3 = H$, $R^2 = R^4 = R^5 = OMe$	40; 3a 74; 4
e.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$	**e**.	$R^1 = R^4 = H$, $R^2 = R^5 = OMe$	4; 2a 41; 2b 50; 3a 13; 4	**e**.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$	25; 2b 12; 3a 54; 4
f.	$R^1 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$	**f**.	$R^1 = H$, $R^2 = R^4 = R^5 = OMe$	47; 4 [a] 49; 4 [b]	**f**.	$R^1 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$	13; 3a 29; 4 [a] 22; 4 [b]
g.	$R^1 = Br$, $R^2 = R^3 = R^4 = R^5 = OMe$	**g**.	$R^1 = Br$, $R^2 = R^4 = R^5 = OMe$	70; 4	**g**.	$R^1 = Br$, $R^2 = R^3 = R^4 = R^5 = OMe$	6; 4
h.	$R^1 = R^3 = H$, $R^2 = R^4 = OMe$, $R^5 = OPh$				**h**.	$R^1 = R^3 = H$, $R^2 = R^4 = OMe$, $R^5 = OPh$	64; 3a
i.	$R^1 = R^4 = OMe$, $R^2 = R^3 = H$, $R^5 = OPh$				**i**. **j**.	$R^1 = R^4 = H$, $R^2 = OH$, $R^3 = OMe$, $R^5 = OPh$ $R^1 = R^4 = H$, $R^2 = R^3 = OMe$, $R^5 = OPh$	33; 3b 3; 3b
11e.	$R^1 = R^4 = H$, $R^2 = R^5 = OMe$				**k**.	$R^1 = R^4 = H$, $R^2 = OH$, $R^3 = R^5 = OMe$	91 [c]

[a] With $BF_3 \cdot Et_2O$. [b] With TFA. [c] From the dienone–phenol rearrangement of **11e**.

Table 3 Oxidative cyclisations of N^2-(4-arylbutanoyl)carbazates **4C** to benzazepinones **15** and spirodienone-δ-lactam **14**

Starting materials **4C** X = CH_2; n = 3		Products		Yield (%) [a]
a.	$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OMe$	**15a**.	$R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OMe$	4
b.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$	**15b**.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5 = OMe$	82
c.	$R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = OPh$	**15c**	$R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = OPh$	55
d.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$	**15d**	$R^1 = R^4 = H$, $R^2 = R^3 = R^5 = OMe$	60
e.	$R^1 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$	**14e** **15e**	$R^1 = H$, $R^2 = R^4 = R^5 = OMe$ $R^1 = H$, $R^2 = R^3 = R^4 = R^5 = OMe$	45 5

[a] All the compounds were obtained through **method 3b**; **14e** was also obtained from **method 3a** in 45% (see text).

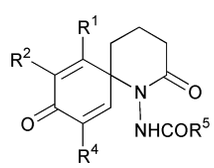


13

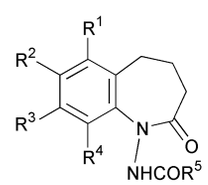
a: $R^1=R^2=R^3=R^4=H;R^5=NH_2$
b: $R^1=R^3=H;R^2=R^4=OMe;R^5=NH_2$
c: $R^1=R^3=R^5=H;R^2=R^4=OMe$
d: $R^1=R^4=H;R^2=R^3=OMe;R^5=N(Me)CO_2Ph$

The *p*-dimethoxy compound **4Bi** on oxidation gave a complex mixture of products from which a phenol was isolated in 33% yield. The formation of a phenol is very reminiscent of the chemical behaviour of **4Af**, which also bears such *para*-substituents. On the basis of its spectral characteristics and elemental composition, $C_{17}H_{16}N_2O_5$, the structure **12i** is proposed for the product. It was characterised as the *O*,*N*-dimethyl compound **13d**.

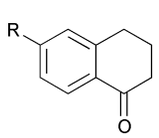
Benzazepinones. Methyl N^2-(4-phenylbutanoyl)carbazate **4Ca**, on oxidation with IBBTA followed by treatment with $BF_3 \cdot Et_2O$, furnished the first member of the benzazepinone series **15a** in poor 4% yield (Table 3). The major product was identified as 1-tetralone **16a** by comparison with an authentic sample (IR and its 2,4-dinitrophenylhydrazone derivative). The presence of a MeO group *meta* to the alkyl side chain as in **4Cb** strongly favoured the formation of 7-membered lactam **15b** (82%). 6-Methoxytetralone **16b** was isolated as a minor product (6%). Similarly the phenyl carbazate **4Cc** furnished **15c** from which the known ε-lactam **17b** [13] could be derived by hydrolysis and subsequent deamination of **17a**.



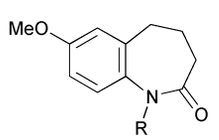
14



15



16a: R=H
16b: R=OMe



17a: R=NH_2
17b: R=H

Whilst the veratrole derivative **4Cd** furnished **15d** (60%), the trimethoxy compound **4Ce** afforded exclusively the spirolactam **14e** (45%) with IBBTA. Even in the presence of $BF_3 \cdot Et_2O$ the above reaction still afforded **14e** as the predominant product (45%) along with only a 5% yield of **15e**. This probably indicates that the cyclohexadienone structure **14e** is preferred

Table 4 Oxidative cyclisations of N^2-(5-arylpentanoyl)carbazates **4D** to benzazocinones **18**

Starting materials **4D** X = CH_2; n = 4		Products **18**		Yield (%)[a]
a.	$R^1 = R^2 = R^3 = R^4 = H$, R^5 = OPh			
b.	$R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OPh	**b**.	$R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OPh	24
c.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5$ = OMe	**c**.	$R^1 = R^3 = R^4 = H$, $R^2 = R^5$ = OMe	44
d.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5$ = OMe	**d**.	$R^1 = R^4 = H$, $R^2 = R^3 = R^5$ = OMe	61

[a] All the compounds were obtained through **method 3b** (see text).

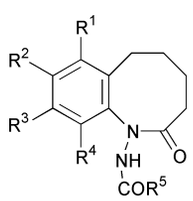
Table 5 Oxidative cyclisations of N^2-(2-aryloxyacetyl)carbazates **4E** to benzoxazinones **23**

Starting materials **4E**		Products		Yield (%)[a]
a.	$R^1 = R^2 = R^3 = R^4 = H$, R^5 = OPh			
b.	$R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OPh	**23b**	$R^1 = R^3 = R^4 = H$, R^2 = OMe, R^5 = OPh	39
c.	$R^1 = R^3 = H$, $R^2 = R^4$ = OMe, R^5 = OPh	**23c**	$R_1 = R_3 = H$, $R^2 = R^4$ = OMe, R^5 = OPh	18
d.	$R^1 = R^4 = H$, $R^2 = R^3$ = OMe, R^5 = OPh	**24**		12

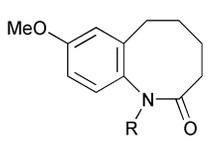
[a] All the compounds were obtained through **method 3b**; **23c** was also obtained from **method 3a** in 40% (see text).

when the carbonyl group is flanked on either side by substituents (OMe) compared with the corresponding sterically crowded trimethoxybenzazepinone **15e**.

Benzazocinones. The formation of an 8-membered ring also occurred with three (**4Db**, **4Dc** and **4Dd**) of the four substances examined, to give **18b**, **18c** and **18d** in 24, 44 and 61% yield, respectively (Table 4). The bishydrazide **4Da** failed to cyclise to the corresponding heteroaromatic compound (**18**).



18

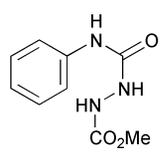


19a: R=NH_2
19b: R=H

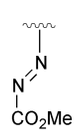
As with **15c**, the hydrolysis of **18b** and deamination of the resulting product **19a** provided the known 8-methoxy-3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one[14] **19b**.

Benzimidazolones and benzoxazinones. Having thus developed a new method for the synthesis of oxindoles and their homologues, it was considered worthwhile to examine the viability of the process to form systems incorporating two heteroatoms in a ring. With this end in view the semicarbazide **20** and the phenoxy compounds **4E**, prepared in the usual manner, were subjected to oxidation. Compound **20** afforded on reaction with NBS–pyridine the corresponding azodicarbonyl compound **21** as a red oil (92%) possessing a strong infrared absorption, *inter alia* at 1780 cm^{-1} indicative of the presence of the azodicarbonyl system.[15] The latter compound in $CHCl_3$ on exposure to $BF_3{\cdot}Et_2O$ furnished the *N*-aminobenzimidazolone **22** in 57% yield. Although its role is not clearly understood the use of KHF_2 in conjunction with $BF_3{\cdot}Et_2O$ improved the yield to 76%.

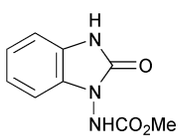
Whereas the phenoxyacetic acid derivative **4Ea** on oxidation (IBBTA) followed by addition of $BF_3{\cdot}Et_2O$ led to a complex mixture from which no useful compound could be isolated, the ether **4Eb** yielded the benzoxazine derivative **23b** in 39% yield (Table 5). On the other hand **4Ec**, wherein the aromatic ring is doubly activated by OMe groups, on exposure to IBBTA at −15 °C to rt directly furnished **23c**, without requiring $BF_3{\cdot}Et_2O$, in 40% yield. The veratrole derivative **4Ed**, despite the presence of an activating methoxy group at an appropriate position to favour cyclisation, underwent, on oxidation, a reaction which generated a wealth of products from which only the known *o*-methoxy-*p*-benzoquinone **24** could be isolated albeit in poor yield.



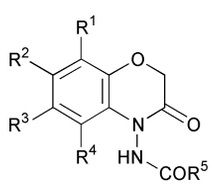
20



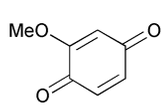
21



22



23

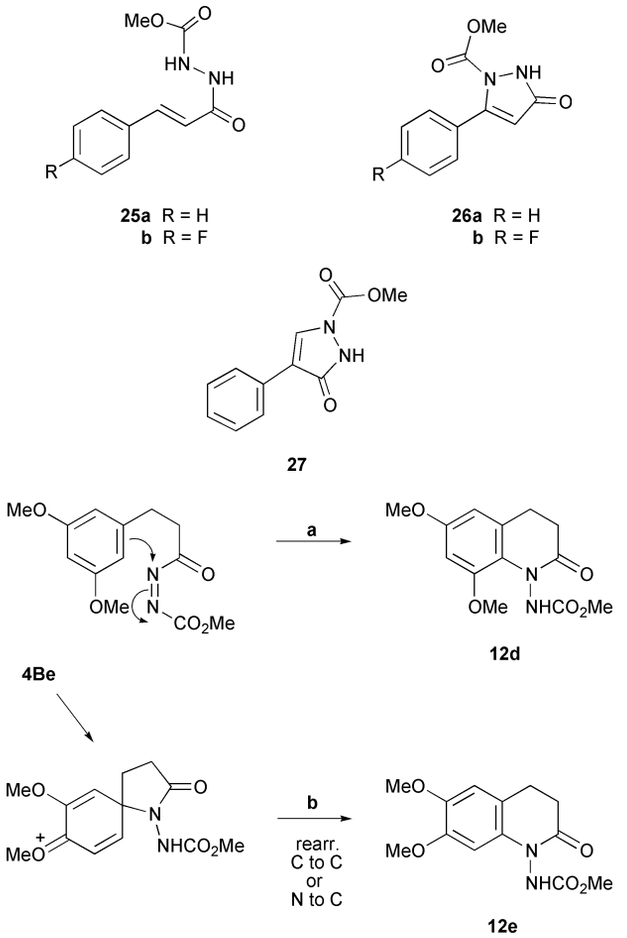


24

Pyrazolones. Finally it was thought worthwhile to examine the chemistry of azodicarbonyl compounds incorporating an *E* double bond. With this end in view cinnamic acid was converted into the corresponding diacylhydrazine derivative **25a**. On oxidation followed by work up in the usual manner (**method 3b**) it yielded a mixture from which two isomeric compounds were obtained. The major product (45%) analysed for $C_{11}H_{10}N_2O_3$. It possessed IR absorptions at 3300–2200, 1748, 1616 and 1595 cm^{-1}. This information coupled with its ^1H NMR signals: δ 3.75 (3H, s), 6.00 (1H, s), 7.40 (5H, m), 11.03 (1H s, exchangeable with D_2O) uniquely defined its structure to be 1-methoxycarbonyl-5-phenyl-1,2-dihydropyrazol-3-one **26a**. The minor compound (9%) exhibited very similar spectroscopic features except that the 1H singlet now appeared at considerably lower field, δ 8.54. Therefore this product is assigned the structure 1-methoxycarbonyl-4-phenyl-1,2-dihydropyrazol-3-one **27**. The *p*-fluoro compound **25b** also underwent cyclisation to **26b** in rather poor yield (23%). Its 4-aryl isomer was not formed in the reaction (*vide infra* Discussion).

Discussion

The intramolecular electrophilic amination that leads to the heterocyclic compounds described above can, in principle, occur *via* two distinct mechanisms as shown for the **4B** series (Scheme 1): **a**, which involves the direct formation of the heterocycle or **b**, an *ipso* substitution and subsequent rearrangement of the cationic spirodienone formed as an intermediate.



Scheme 1

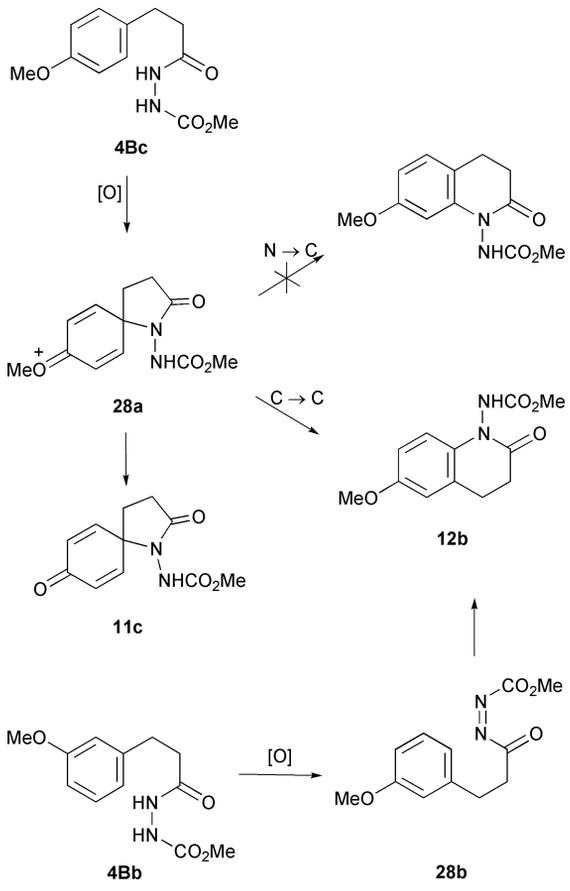
Although it is reasonable to assume that process **a** is the one that is involved in the formation of **12d** it becomes difficult to choose *a priori* between the two alternatives for the formation of **12e** from the dimethoxy compound **4Be** since both C-to-C and N-to-C migration would give one and the same compound (**12e**).

However, evidence in favour of a C-to-C migration in the cationic intermediate **28a** was forthcoming from the results of the oxidation of **4Bc**. The carbostyril obtained (**12b**) was indistinguishable from that generated from its regioisomer **4Bb** (Scheme 2).

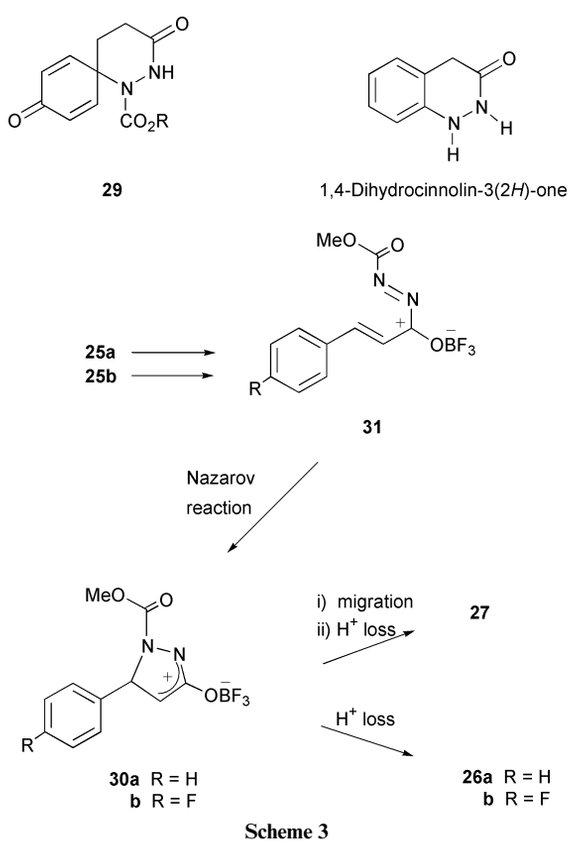
Worthy of mention is the intriguing fact that *all cyclisations* involving azadicarbonyl compounds take place in such a manner as to place one of the nitrogen atoms always *exo* to the newly formed ring even for cases where both processes *i.e.*, *exo* and *endo*, are equally possible. The reaction of **4Bc** with IBDA at room temperature is illustrative. Spiro-lactam **11c** was the only isolable compound obtained from the reaction mixture, in 4% yield. Its IR spectrum in $CHCl_3$ contained absorptions at 1756 (NCO_2Me), 1720 (γ-lactam) and 1668 (dienone) cm^{-1} and is consistent with the pyrrolidone structure.[4b] A probable reason would be that structures of the type **29** are intrinsically less stable than the corresponding *exo* products. This could be due to greater destabilisation engendered by nitrogen lone pair–lone pair interactions in the geometrically constrained 6-membered-ring system.

Of relevance in this context is the easy conversion of 1,4-dihydro-cinnolin-3(2*H*)-one to the isomeric *N*-aminooxindole under strongly acidic conditions.[16]

The formation of pyrazolones from the cinnamic acid derivatives probably involves a Nazarov reaction[17] (a diaza analogue) leading to the cyclic cation **30** (**a** and **b**), generated *via* **31** (Scheme 3). Proton loss from the former accounts for **26a**. A similar H^+ loss subsequent to the phenyl migration in **30a** produces **27**. This is consistent with the results obtained for the fluoro compound **25b**. Both the formation of **30b** and an aryl migration therein would be expected to be disfavoured *vis-à-vis* **25a** due to the electronegativity of the fluorine atom in the aromatic ring.



Scheme 2

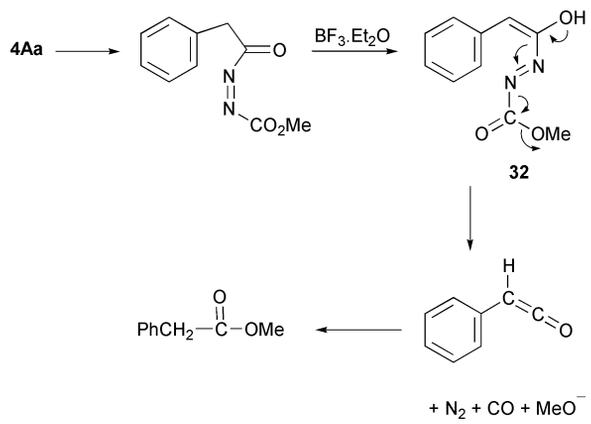


Scheme 3

Limitations and side reactions

Although, in general, aromatic rings substituted with activating electron-donating methoxy groups furnish useful products, *i.e.* heterocycles and/or enone-lactams in reasonable yields, there are, not surprisingly, instances where other competing processes occur either partially or exclusively from an intermediate containing a multiplicity of functional groups.

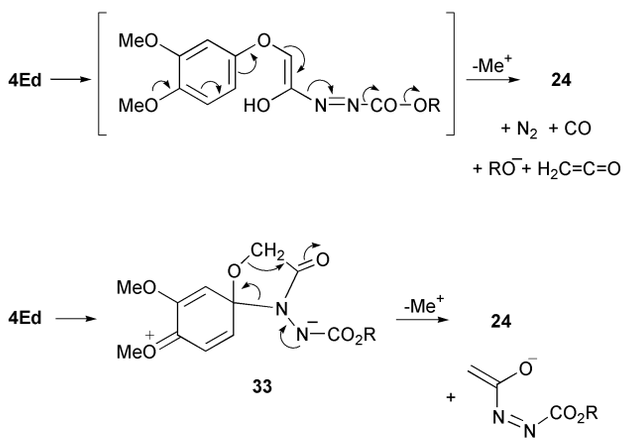
Thus the formation of methyl phenylacetate from **4Aa** with the oxidant and $BF_3{\cdot}Et_2O$ is an example (Scheme 4). It could be



Scheme 4

rationalised by postulating involvement of the enol **32**, easily formed under the action of a Lewis acid, suffering a fragmentation to N_2, CO, phenylketene and MeO^-. Recombination of the latter two species would give rise to the observed product. Consistent with the mechanism is that the triphenyl analogue **7**, lacking the requisite acidic hydrogens, undergoes cyclisation to oxindole derivative **8** in high yield (85%).

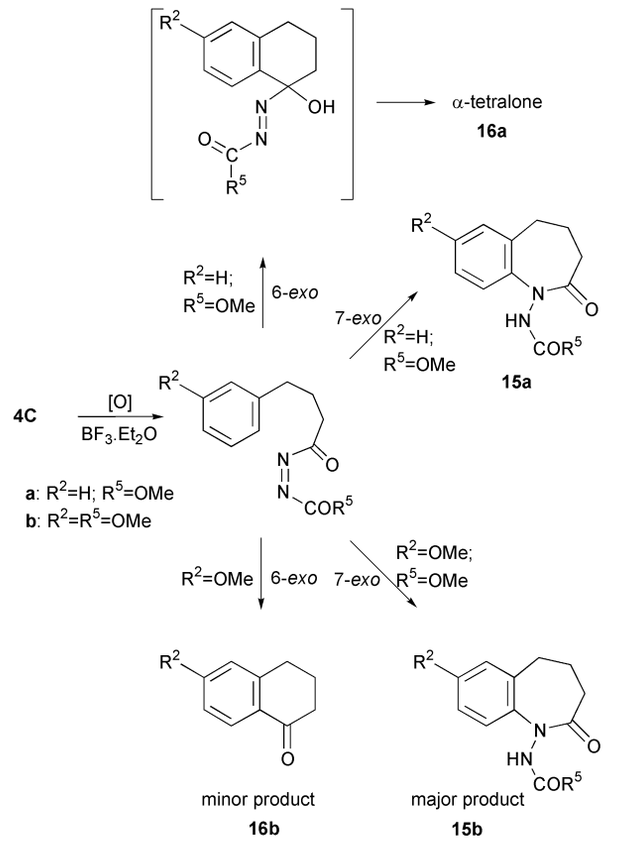
A similar mechanism may well operate in the formation of **24** from **4Ed**, although the involvement of the spiro compound **33** in such a fragmentation could not be ruled out (Scheme 5).



Scheme 5

A different chemical behaviour is exhibited by the azodicarbonyl derived from **4Ca**. The expected product, the benzazepinone **15a**, and 1-tetralone **16a** were obtained, albeit in low yields, indicating that in the absence of sufficient electronic activation in the aromatic ring a 1,6-*exo* cyclisation to the carbonyl group of the azodicarbonyl group also occurs with equal facility (Scheme 6). However, placement of a MeO group *para* to the site of cyclisation largely overcomes this problem and, as a consequence, a 1,7-*exo*-addition product, the benzazepinone **15b**, is isolated as the major product.

An aryl methoxy substituent occasionally interferes in an interesting manner with the normal course of the cyclisation reaction. For example, the substrate **4Af** containing *p*-methoxy groups did not yield, as anticipated, the substance **9h**



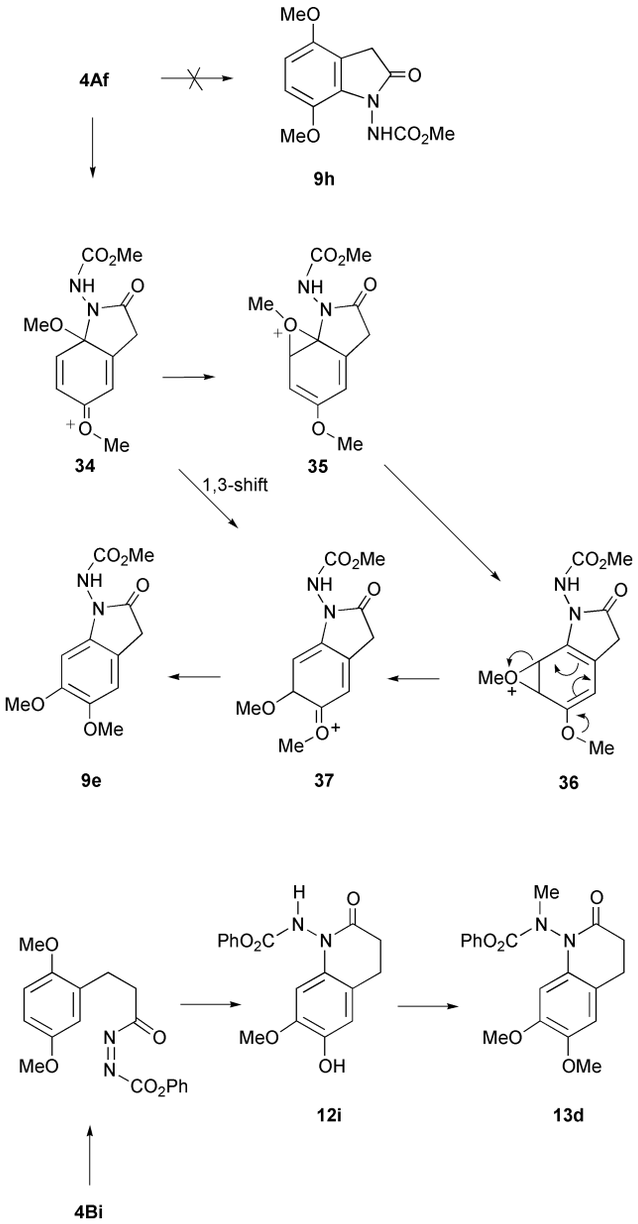
Scheme 6

(Scheme 7). Instead a product, isolated in low yield, possessed in its ^{1}H NMR spectrum, besides two MeO signals, two aromatic hydrogens appearing as 1H singlets suggesting that the *para* positions in the aromatic ring are unsubstituted. In fact the spectrum was found to be identical with that of **9e** obtained from **4Ae**. The respective TLC mobilities and IR spectra of the samples were also practically identical. A possible mechanism for the transformation **4Af** to **9e** would involve an *ipso* substitution at the *ortho* carbon bearing the methoxy group to give the cation **34**. The latter undergoes successive migrations (**35** ⟶ **36** ⟶ **37**) to **37**, which loses a proton to generate **9e**. The structure **12i** is assigned to the phenol similarly obtained from **4Bi** because it possessed in its ^{1}H NMR spectrum *inter alia* two aromatic protons well separated from those due to the phenyl group, at δ 6.73 (1H, s) and 6.88 (1H, s). These δ-values are very similar to those observed for the phenol **12k** (δ 6.63, 6.81) derived from the dienone **11e** by acid catalysis.

Experimental

Melting points were recorded on a Reichert-Thermovar hot-stage apparatus and are reported uncorrected. Infrared spectra were measured on a Buck Scientific M500 spectrometer as KBr pellets, unless stated otherwise. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Brüker CXP 300 (300 MHz) and Brüker ARX 400 (400 MHz) spectrometers using $CDCl_3$ as solvent and tetramethylsilane as internal standard, unless stated otherwise; *J*-Values are given in Hz. Mass spectra were obtained on a Shimadzu QP1000 EX (electron impact; 70 eV) spectrometer. High-resolution mass spectra (electron impact) were determined at the Mass Spectrometry Laboratory of Imperial College of Science, Technology and Medicine, University of London. Elemental analyses were performed at the Microanalyses Service of Imperial College of Science, Technology and Medicine, University of London.

All reagents and solvents were reagent grade and were purified and dried by standard methods. Those methyl or ethyl esters used as starting materials that were not commercially



Scheme 7

available were prepared from the corresponding acids by standard procedures. Organic extracts were dried over anhydrous sodium sulfate or magnesium sulfate. Analytical thin-layer chromatography was performed on E. Merck Kieselgel 60, F-254 silica gel 0.2 mm thick plates. Preparative TLC (PTLC) used E. Merck Kieselgel 60, F-254 silica gel 0.5, 1 and 2 mm thick plates (20 × 20 cm). Column chromatography was done on E. Merck Kieselgel 60 (240–400 μm) silica gel.

General procedure for the preparation of monohydrazides (5A, 5B, 5C and 5E) [18]

The methyl esters of 2-arylacetic, 3-arylpropionic, 4-arylbutanoic and 2-aryloxyacetic acids (1 equiv.) were heated with stirring at 110–120 °C with hydrazine hydrate (98%) (1.1–4 equiv.). On completion of the reaction (0.5–3 h, TLC control; CH_2Cl_2–MeOH; 9 : 1) the mixture was cooled, benzene was added, and the solid that separated was filtered off. The crystalline solids obtained were taken up in AcOEt, filtered, and dried or purified by recrystallisation.

2-Phenylacetylhydrazine 5Aa. Obtained from methyl phenylacetate (2.78 g, 18.51 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.99 cm^3, 20.41 mmol) in 89% yield (2.47 g) as a colourless solid, after trituration with Et_2O; mp 115–117 °C [lit.,[18] 116 °C (from water)]; ν_{max}/cm^{-1} 3290, 1640.

2-(3-Methoxyphenyl)acetylhydrazine 5Ab. Obtained from methyl 2-(3-methoxyphenyl)acetate (4.20 g, 23.31 mmol) and $NH_2NH_2{\cdot}H_2O$ (1.24 cm^3, 25.56 mmol) in 88% yield (3.72 g) as a colourless solid; mp 92–93 °C (from MeOH); ν_{max}/cm^{-1} 3430–3340, 1640; δ_H 3.29 (2H, br s), 3.54 (2H, s), 3.80 (3H, s), 6.82 (3H, m), 6.87 (1H, br s), 7.23 (1H, t, *J* 7.8) (Calc. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.86; H, 6.99; N, 15.35%).

2-(3,4,5-Trimethoxyphenyl)acetylhydrazine 5Ad. Prepared from methyl 2-(3,4,5-trimethoxyphenyl)acetate (1.85 g, 7.70 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.41 cm^3, 8.47 mmol) in quantitative yield as a colourless solid; mp 105–107 °C (lit.,[19] 104–106.5 °C); ν_{max}/cm^{-1} 3285, 1640.

2-(3,4-Dimethoxyphenyl)acetylhydrazine 5Ae. Obtained from methyl 2-(3,4-dimethoxyphenyl)acetate (2.50 g, 11.89 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.63 cm^3, 12.99 mmol) in quantitative yield as a colourless solid; mp 105–106 °C (lit.,[20] 106–107 °C).

2-(2,5-Dimethoxyphenyl)acetylhydrazine 5Af. Prepared from methyl 2-(2,5-dimethoxyphenyl)acetate (1.70 g, 8.09 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.43 cm^3, 8.86 mmol) in 99% yield (1.69 g) as a colourless solid; mp 128–129 °C; ν_{max}/cm^{-1} 3300, 1642; δ_H 3.38–2.15 (2H, br s, exchangeable with D_2O), 3.53 (2H, s), 3.76 (3H, s), 3.82 (3H, s), 6.84–6.79 (3H, m), 7.05 (1H, br s, exchangeable with D_2O) (Calc. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.20; H, 6.59; N, 12.64%).

2-(3-Methylphenyl)acetylhydrazine 5Ag. Obtained from methyl 2-(3-methylphenyl)acetate (1.30 g, 7.92 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.42 cm^3, 8.65 mmol) as a colourless solid in 99% yield (1.29 g); mp 102–103 °C; ν_{max}/cm^{-1} 3290, 1642; δ_H 2.34 (3H, s), 3.20–1.80 (2H, br s, exchangeable with D_2O), 3.53 (2H, s), 6.65 (1H, br s, exchangeable with D_2O), 7.04 (1H, d, *J* 7.6), 7.06 (1H, s), 7.10 (1H, d, *J* 7.6), 7.23 (1H, t, *J* 7.6) (Calc. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.86; H, 7.30; N, 16.81%).

3-Phenylpropanoylhydrazine 5Ba. Prepared from methyl dihydrocinnamate (32.80 g, 0.20 mol) and hydrazine hydrate (35 cm^3, 0.72 mol) in 92% yield (30.18 g) as a colourless solid; mp 102–104 °C (from MeOH) [lit.,[21] 101–102 °C]; ν_{max}/cm^{-1} 3300, 1636; δ_H 2.63 (2H, t, *J* 7.9), 2.95 (2H, t, *J* 7.9), 3.54 (2H, br s), 7.10 (1H, br s), 7.25 (5H, m).

3-(3-Methoxyphenyl)propanoylhydrazine 5Bb. Obtained from methyl 3-(3-methoxyphenyl)propionate (8.90 g, 45.82 mmol) and hydrazine hydrate (8 cm^3, 0.165 mol) in 87% yield (7.76 g) as a colourless solid; mp 90–92 °C (from $CHCl_3$–hexane); ν_{max}/cm^{-1} 3300, 3290, 3180, 1632; δ_H 2.45 (2H, t, *J* 7.7), 2.95 (2H, t, *J* 7.7), 3.79 (3H, s), 3.87 (2H, br s), 6.70 (1H, m), 6.77 (3H, m), 7.03 (1H, t, *J* 7.7) (Calc. for $C_{10}H_{14}N_2O_2$: *M*, 194.1055. Found: M^+, 194.1048).

3-(4-Methoxyphenyl)propanoylhydrazine 5Bc. Prepared from methyl 3-(4-methoxyphenyl)propionate (8.90 g, 45.82 mmol) and hydrazine hydrate (8 cm^3, 0.165 mol) in 93% yield (8.30 g) as a colourless solid; mp 130–131 °C (from MeOH); ν_{max}/cm^{-1} 3300, 3280, 1632; δ_H 2.42 (2H, t, *J* 7.6), 2.90 (2H, t, *J* 7.6), 3.78 (3H, s), 3.34 (2H, br s), 6.82 (3H, d, *J* 8.4; 2H, ArH + 1H, NH), 7.10 (2H, d, *J* 8.4). The substance was characterised as the bishydrazide **4Bc**.

3-(3,5-Dimethoxyphenyl)propanoylhydrazine 5Bd. Prepared from methyl 3-(3,5-dimethoxyphenyl)propionate (2.12 g, 9.45 mmol) and hydrazine hydrate (1.6 cm^3, 32.98 mmol) in 88%

yield (1.86 g) as a colourless solid; mp 134–135 °C (from EtOH); ν_{max}/cm^{-1} 3320, 1640; δ_H 2.44 (2H, t, *J* 7.6), 2.90 (2H, t, *J* 7.6), 3.07 (2H, s), 3.77 (6H, s), 6.32 (1H, d, *J* 2.0), 6.40 (2H, m), 6.75 (1H, br s) (Calc. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 59.16; H, 7.30; N, 12.40%).

3-(3,4-Dimethoxyphenyl)propanoylhydrazine 5Be. Methyl 3-(3,4-dimethoxyphenyl)propionate (4.24 g, 18.91 mol) and hydrazine hydrate (3.2 cm^3, 65.97 mmol) gave as above the hydrazide **5Be** (3.70 g) in 87% yield as a colourless solid; mp 134–135 °C (from EtOH) (lit.,[22] 136.5–137 °C); ν_{max}/cm^{-1} 3330, 1640; δ_H 2.43 (2H, t, *J* 7.6), 2.90 (2H, t, *J* 7.6), 3.67 (2H, br s), 3.84 (6H, s), 6.71 (2H, m), 6.78 (1H, s), 7.16 (1H, br s).

3-(3,4,5-Trimethoxyphenyl)propanoylhydrazine 5Bf. Methyl 3-(3,4,5-trimethoxyphenyl)propionate (2.54 g, 9.99 mmol) and hydrazine hydrate (1.6 cm^3, 32.98 mmol) gave as above the hydrazide **5Bf** (2.15 g) in 85% yield as a colourless solid; mp 127–128 °C (from EtOH); ν_{max}/cm^{-1} 3330, 3280, 1644; δ_H 2.44 (2H, t, *J* 7.7), 2.91 (2H, t, *J* 7.7), 3.82 (3H, s), 3.84 (8H, s, 2 × OMe, NH_2), 6.41 (2H, s), 6.86 (1H, br s). It was characterised as the bishydrazide **4Bf**.

3-(2,5-Dimethoxyphenyl)propanoylhydrazine 5Bi. Methyl 3-(2,5-dimethoxyphenyl)propionate (2.24 g, 9.99 mmol) and hydrazine hydrate (1.6 cm^3, 32.98 mmol) gave as above **5Bi** (2.17 g) in 97% yield as a colourless solid; mp 94–95 °C (from EtOH); ν_{max}/cm^{-1} 3470, 3320, 1660; δ_H 2.45 (2H, t, *J* 7.8), 2.92 (2H, t, *J* 7.8), 3.75 (3H, s), 3.79 (3H, s), 3.87 (2H, br s), 6.74 (3H, m), 6.84 (1H, br s) (Calc. for $C_{11}H_{16}N_2O_3$: C, 57.12; H, 6.72; N, 12.30. Found: C, 57.20; H, 6.59; N, 12.64%).

4-Phenylbutanoylhydrazine 5Ca. Obtained from methyl 4-phenylbutanoate (3.00 g, 16.83 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.9 cm^3, 18.55 mmol) as a colourless solid in quantitative yield; mp 104–144 °C (from AcOEt; the large melting range is attributed to polymorphism) [lit.,[23] 78–79 °C (from $CHCl_3$)]; ν_{max}/cm^{-1} 3330, 3210, 1640; δ_H 1.99 (2H, quintet, *J* 7.4), 2.24–2.15 (2H, m), 2.66 (2H, t, *J* 7.4), 3.90 (2H, br s, exchangeable with D_2O), 6.79 (1H, br s, exchangeable with D_2O), 7.30–7.16 (5H, m).

4-(3,4-Dimethoxyphenyl)butanoylhydrazine 5Cd. Obtained from methyl 4-(3,4-dimethoxyphenyl)butanoate (1.80 g, 7.55 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.4 cm^3, 8.25 mmol) as a thick oil that crystallised on storage, in quantitative yield; mp 84–85 °C (from EtOH); ν_{max}/cm^{-1} 3310, 3200, 1646; δ_H 1.97 (2H, quintet, *J* 7.4), 2.33–2.15 (2H, m), 2.60 (2H, t, *J* 7.4), 3.94–3.77 (2H, br s, exchangeable with D_2O), 3.86 (3H, s), 3.87 (3H, s), 6.67 (1H, br s, exchangeable with D_2O), 6.73–6.69 (2H, m), 6.79 (1H, d, *J* 8.6) (Calc. for $C_{12}H_{18}N_2O_3$: *M*, 238.1317. Found: M$^+$, 238.1318).

4-(3,4,5-Trimethoxyphenyl)butanoylhydrazine 5Ce. Obtained from methyl 4-(3,4,5-trimethoxyphenyl)butanoate (2.07 g, 7.71 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.52 cm^3, 10.72 mmol) as a yellowish oil in quantitative yield. An analytical sample was prepared (PTLC; CH_2Cl_2–MeOH; 9 : 1) as a colourless oil that crystallised on storage; mp 68–69 °C; ν_{max} (film)/cm^{-1} 3310, 1660; δ_H 1.98 (2H, quintet, *J* 7.4), 2.60 (2H, t, *J* 7.4), 2.17 (2H, m), 3.82 (3H, s), 3.85 (6H, s), 3.89 (2H, br s, exchangeable with D_2O), 6.39 (2H, s), 6.63 (1H, br s, exchangeable with D_2O). Characterised as the bishydrazide **4Ce**.

2-Phenoxyacetylhydrazine 5Ea. Obtained from methyl 2-phenoxyacetate (1.34 g, 8.06 mmol) and $NH_2NH_2{\cdot}H_2O$ (1.56 cm^3, 32.16 mmol) in 87% yield (1.16 g) as a colourless solid; mp 108–110 °C (lit.,[24] 110–111 °C); ν_{max}/cm^{-1} 3300, 3200, 1668, 1644, 1618, 1598sh; δ_H 3.86 (2H, br s, exchangeable with D_2O), 4.58 (2H, s), 6.91 (2H, d, *J* 8.4), 7.03 (1H, t, *J* 7.4), 7.32 (2H, t, *J* 7.9), 7.78 (1H, br s, exchangeable with D_2O).

2-(3-Methoxyphenoxy)acetylhydrazine 5Eb. Prepared from methyl 2-(3-methoxyphenoxy)acetate (1.52 g, 7.75 mmol) and $NH_2NH_2{\cdot}H_2O$ (1.5 cm^3, 30.92 mmol) in 90% yield (1.37 g) as a colourless solid; mp 108–109 °C (lit.,[25] 106 °C); ν_{max}/cm^{-1} 3305, 3200, 1668, 1642, 1620, 1600sh; δ_H 3.92 (2H, br s, exchangeable with D_2O), 3.80 (3H, s), 4.56 (2H, s), 6.52–6.45 (2H, m), 6.59 (1H, dd, *J* 8.2, *J* 2.0), 7.21 (1H, t, *J* 8.2), 7.71 (1H, br s, exchangeable with D_2O).

2-(3,5-Dimethoxyphenoxy)acetylhydrazine 5Ec. Obtained from methyl 2-(3,5-dimethoxyphenoxy)acetate (1.02 g, 4.51 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.88 cm^3, 18.14 mmol) as a colourless solid in 85% yield (863 mg); mp 140–142 °C (from AcOEt); ν_{max}/cm^{-1} 3310, 3225, 1654, 1620, 1600sh; δ_H 3.77 (6H, s), 4.00–3.25 (2H, br s, exchangeable with D_2O), 4.54 (2H, s), 6.07 (2H, d, *J* 2.0), 6.15 (1H, t, *J* 2.0), 7.27 (1H, br s, exchangeable with D_2O) (Calc. for $C_{10}H_{14}N_2O_4$: C, 53.09, H, 6.24; N, 12.38. Found: C, 53.35; H, 6.04; N, 12.22%).

2-(3,4-Dimethoxyphenoxy)acetylhydrazine 5Ed. Prepared from methyl 2-(3,4-dimethoxyphenoxy)acetate (600 mg, 2.65 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.52 cm^3, 10.72 mmol) in 88% yield (530 mg) as a colourless solid; mp 129–130 °C (from AcOEt); ν_{max}/cm^{-1} 3310, 3275, 1648, 1624sh; δ_H 3.84 (3H, s), 3.87 (3H, s), 4.10–3.25 (2H, br s, exchangeable with D_2O), 4.54 (2H, s), 6.39 (1H, dd, *J* 8.7, *J* 2.7), 6.53 (1H, d, *J* 2.7), 6.79 (1H, d, *J* 8.7), 7.71 (1H, br s, exchangeable with D_2O) (Calc. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.30; H, 6.13; N, 12.43%).

General procedures for the preparation of bishydrazides 4.

(A) From the corresponding monohydrazides 5.

The appropriate hydrazide and sodium bicarbonate (2 equiv./mmol hydrazide) in CH_2Cl_2 (10 cm^3/mmol hydrazide) was treated dropwise, under inert atmosphere at rt and with stirring, with methyl or phenyl chloroformate (1.1 equiv./mmol hydrazide) dissolved in the same solvent (1 cm^3/mmol chloroformate). On completion of the reaction (2–20 h, TLC control; $CHCl_3$–EtOH; 9 : 1 or CH_2Cl_2–MeOH; 9 : 1/9.5 : 0.5) the mixture was poured into water and the products extracted with CH_2Cl_2, and the organic phase was washed with water and dried. The residue obtained on evaporation of the solution was purified by crystallisation or by column chromatography.

Methyl 2-(2-phenylacetyl)hydrazinecarboxylate 4Aa. Obtained from **5Aa** (2.40 g, 15.98 mmol) as a colourless solid in 84% yield (2.80 g) after crystallisation from Et_2O; mp 91–93 °C; ν_{max}/cm^{-1} 3260, 1758, 1718, 1668sh, 1652; δ_H 3.61 (2H, s), 3.73 (3H, s), 6.87 (1H, br s, exchangeable with D_2O), 7.37–7.29 (5H, m), 7.55 (1H, br s, exchangeable with D_2O); *m*/*z* 208 (M$^+$, 3%), 176 (9), 118 (52), 91 (100) (Calc. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.61; H, 5.76; N, 13.39%).

Methyl 2-[2-(3-methoxyphenyl)acetyl]hydrazinecarboxylate 4Ab. Obtained from **5Ab** (1.00 g, 5.55 mmol) in 94% yield (1.25 g), mp 87–88 °C, used as such without crystallisation; ν_{max}/cm^{-1} 3340, 3200, 1728, 1680, 1660; δ_H 3.59 (2H, s), 3.73 (3H, s), 3.80 (3H, s), 6.85 (4H, m, ArH + NH), 7.26 (1H, t, *J* 7.8), 7.55 (1H, br s) (Calc. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.17; H, 5.71; N, 11.61%).

Methyl 2-[2-(3,4,5-trimethoxyphenyl)acetyl]hydrazinecarboxylate 4Ad. Obtained from **5Ad** (1.70 g, 7.08 mmol) in 40% yield (850 mg) as a colourless solid after crystallisation from CH_2Cl_2–AcOEt; mp 135–136 °C; ν_{max}/cm^{-1} 3345, 3195, 1726, 1664; δ_H 3.58 (2H, s), 3.75 (3H, s), 3.84 (3H, s), 3.86 (6H, s), 6.53 (2H, s), 6.63 (1H, br s, exchangeable with D_2O), 7.26 (1H, br s, exchangeable with D_2O); *m*/*z* 298 (M$^+$, 20%), 266 (41), 208 (37), 181 (100) (Calc. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.39; H, 6.03; N, 9.27%).

Methyl 2-[2-(3,4-dimethoxyphenyl)acetyl]hydrazinecarboxylate 4Ae. Obtained from **5Ae** (2.50 g, 11.89 mmol) in 70% yield (2.22 g) as a colourless solid after crystallisation from CH_2Cl_2–Et_2O; mp 135–137 °C; ν_{max}/cm^{-1} 3310, 1748, 1724, 1696; δ_H 3.59 (2H, s), 3.75 (3H, s), 3.88 (3H, s), 3.89 (3H, s), 6.58 (1H, br s, exchangeable with D_2O), 6.84 (3H, m), 7.21 (1H, br s, exchangeable with D_2O); *m*/*z* 268 (M^+, 10%), 236 (29), 178 (38), 151 (100) (Calc. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.69; H, 5.88; N, 10.31%).

Methyl 2-[2-(2,5-dimethoxyphenyl)acetyl]hydrazinecarboxylate 4Af. Prepared from **5Af** (1.50 g, 7.135 mmol) as a colourless solid in 29% yield (560 mg) after crystallisation from CH_2Cl_2; mp 149–150 °C; ν_{max}/cm^{-1} 3290, 1768, 1660; δ_H 3.60 (2H, s), 3.72 (3H, s), 3.76 (3H, s), 3.85 (3H, s), 6.53 (1H, br s, exchangeable with D_2O), 6.80 (1H, dd, *J* 8.8, *J* 2.8), 6.849 (1H, d, *J* 8.8), 6.853 (1H, d, *J* 2.8), 7.65 (1H, br s, exchangeable with D_2O); *m*/*z* 268 (M^+, 32%), 236 (51), 178 (34), 151 (100) (Calc. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.60; H, 5.85; N, 10.25%).

Methyl 2-[2-(3-methylphenyl)acetyl]hydrazinecarboxylate 4Ag. Prepared from **5Ag** (1.20 g, 7.31 mmol) as a colourless oil, which was purified by column chromatography (CH_2Cl_2–MeOH; 9 : 1) to yield a colourless solid in 76% yield (1.24 g); mp 100–101 °C; ν_{max}/cm^{-1} 3260, 3200, 1724, 1670; δ_H 2.34 (3H, s), 3.58 (2H, s), 3.73 (3H, s), 6.80 (1H, br s, exchangeable with D_2O), 7.09 (2H, d, *J* 8.0), 7.11 (1H, s), 7.23 (1H, t, *J* 8.0), 7.46 (1H, br s, exchangeable with D_2O); *m*/*z* 222 (M^+, 5%), 190 (8), 132 (58), 105 (100) (Calc. for $C_{11}H_{14}N_2O_3$: C, 59.43; H, 6.35; N, 12.61. Found: C, 59.38; H, 6.23; N, 12.56%).

Methyl 2-(3-phenylpropanoyl)hydrazinecarboxylate 4Ba. Obtained from **5Ba** (820 mg, 4.99 mmol) in 96% yield (1.07 g) after crystallisation (from CH_2Cl_2–MeOH); mp 119–120 °C; ν_{max}/cm^{-1} 3300, 3250, 1735, 1668; δ_H 2.53 (2H, t, *J* 7.8), 2.98 (2H, t, *J* 7.8), 3.73 (3H, s), 6.99 (1H, br s), 7.24 (5H, m), 7.71 (1H, br s) (Calc. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.64; H, 6.39; N, 12.73%).

Methyl 2-[3-(3-methoxyphenyl)propanoyl]hydrazinecarboxylate 4Bb. Obtained from **5Bb** (970 mg, 4.99 mmol) in 86% yield (1.08 g); mp 100–103 °C; ν_{max}/cm^{-1} 3280, 3200, 1715, 1666; δ_H 2.53 (2H, t, *J* 7.8), 2.95 (2H, t, *J* 7.8), 3.73 (3H, s), 3.78 (3H, s), 6.77 (3H, m), 6.96 (1H, br s), 7.20 (1H, t, *J* 8.2), 7.65 (1H, br s) (Calc. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 56.92; H, 6.31; N, 11.03%).

Methyl 2-[3-(4-methoxyphenyl)propanoyl]hydrazinecarboxylate 4Bc. Obtained from **5Bc** (970 mg, 4.99 mmol) in 97% yield (1.22 g); mp 102–103 °C; ν_{max}/cm^{-1} 3220, 3020, 1728, 1664; δ_H 2.50 (2H, t, *J* 7.8), 2.90 (2H, t, *J* 7.8), 3.74 (3H, s), 3.78 (3H, s), 6.71 (1H, br s), 6.84 (2H, d, *J* 8.6), 7.11 (2H, d, *J* 8.6), 7.50 (1H, br s) (Calc. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 56.92; H, 6.31; N, 11.03%).

Methyl 2-[3-(3,5-dimethoxyphenyl)propanoyl]hydrazinecarboxylate 4Bd. Obtained from **5Bd** (1.12 g, 4.99 mmol) in 94% yield (1.33 g); mp 125–127 °C; ν_{max}/cm^{-1} 3240, 1732, 1666; δ_H 2.53 (2H, t, *J* 7.8), 2.92 (2H, t, *J* 7.8), 3.74 (3H, s), 3.77 (6H, s), 6.33 (3H, m), 6.86 (1H, br s), 7.49 (1H, br s) (Calc. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.44; H, 6.51; N, 9.74%).

Methyl 2-[3-(3,4-dimethoxyphenyl)propanoyl]hydrazinecarboxylate 4Be. Obtained from **5Be** (1.12 g, 4.99 mmol) in 94% yield (1.33 g); mp 76–78 °C; ν_{max}/cm^{-1} 3485, 3300, 3200, 1734, 1668; δ_H 2.52 (2H, t, *J* 7.6), 2.93 (2H, t, *J* 7.6), 3.75 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.77 (4H, m), 7.46 (1H, br s) (Calc. for $C_{13}H_{18}N_2O_5$: *M*, 282.1216. Found: M^+, 282.1199).

Methyl 2-[3-(3,4,5-trimethoxyphenyl)propanoyl]hydrazinecarboxylate 4Bf. Obtained from **5Bf** (1.21 g, 4.76 mmol) in 92% yield (1.37 g); mp 117–119 °C; ν_{max}/cm^{-1} 3470, 3240, 3020, 1752, 1676; δ_H 2.53 (2H, t, *J* 7.6), 2.93 (2H, t, *J* 7.6), 3.75 (3H, s), 3.82 (3H, s), 3.84 (6H, s), 6.43 (2H, s), 6.8 (1H, br s), 7.48 (1H, br s) (Calc. for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.62; H, 6.59; N, 8.78%).

Methyl 2-[3-(2-bromo-3,4,5-trimethoxyphenyl)propanoyl]-hydrazinecarboxylate 4Bg. Compound **4Bf** (200 mg, 0.64 mmol) in CH_2Cl_2 (20 cm^3) was treated with NBS (128 mg, 0.72 mmol) in the same solvent (5 cm^3) and the mixture stirred at rt (15 min) after which time TFA (50 mm^3, 0.65 mmol) was added. On completion of the reaction (TLC control; CH_2Cl_2–5% MeOH) the organic phase was washed with water and dried. Evaporation of the solution followed by crystallisation of the residue gave the title compound in 98% yield (245 mg); mp 99–101 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3300, 3270, 1752, 1664; δ_H 2.55 (2H, t, *J* 7.6), 3.05 (2H, t, *J* 7.6), 3.75 (3H, s), 3.84 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 6.66 (1H, s), 6.67 (1H, br s), 7.47 (1H, br s) (Calc. for $C_{14}H_{19}BrN_2O_6$: C, 42.98; H, 4.90; N, 7.16. Found: C, 43.10; H, 4.60; N, 7.10%).

Phenyl 2-[3-(3,5-dimethoxyphenyl)propanoyl]hydrazinecarboxylate 4Bh. Obtained from **5Bd** (1.12 g, 4.99 mmol) in 97% yield (1.66 g); mp 113–114 °C; ν_{max}/cm^{-1} 3210, 3020, 1728, 1624; δ_H 2.55 (2H, t, *J* 7.8), 2.94 (2H, t, *J* 7.8), 3.74 (6H, s), 6.53 (3H, m), 7.12 (2H, d, *J* 7.8), 7.21 (2H, t, *J* 7.8), 7.35 (2H, t, *J* 7.8), 7.68 (1H, br s) (Calc. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.84; H, 5.90; N, 7.91%).

Phenyl 2-[3-(2,5-dimethoxyphenyl)propanoyl]hydrazinecarboxylate 4Bi. Obtained from **5Bi** (1.12 g, 4.99 mmol) in 89% yield (1.53 g); mp 103–104 °C; ν_{max}/cm^{-1} 3310, 3230, 1760, 1684; δ_H (CD_2Cl_2) 2.52 (2H, t, *J* 7.7), 2.90 (2H, t, *J* 7.7), 3.69 (3H, s), 3.76 (3H, s), 6.74 (3H, m), 7.17 (2H, d, *J* 7.2), 7.21 (2H, t, *J* 7.2), 7.34 (2H, t, *J* 7.8), 7.53 (1H, br s) (Calc. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.13. Found: C, 62.89; H, 5.84; N, 8.14%).

Methyl 2-(4-phenylbutanoyl)hydrazinecarboxylate 4Ca. Obtained from **5Ca** (2.89 g, 16.215 mmol) in 90% yield (3.43 g) as a colourless oil, which crystallised on storage; an analytical sample was obtained by PTLC (CH_2Cl_2–MeOH; 9 : 1); mp 66.5–68 °C; ν_{max}/cm^{-1} 3250, 1748, 1680; δ_H 2.00 (2H, quintet, *J* 7.4), 2.22 (2H, t, *J* 7.4), 2.67 (2H, t, *J* 7.4), 3.75 (3H, s), 6.88 (1H, br s, exchangeable with D_2O), 7.33–7.15 (5H, m), 7.48 (1H, br s, exchangeable with D_2O); *m*/*z* 236 (M^+, 6%), 204 (6), 147 (53), 91 (100) (Calc. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.26; H, 6.69; N, 11.83%).

Methyl 2-[4-(3,4-dimethoxyphenyl)butanoyl]hydrazinecarboxylate 4Cd. Prepared from **5Cd** (1.69 g, 7.09 mmol) as a colourless solid in 67% yield (1.40 g) after crystallisation from CH_2Cl_2–Et_2O; mp 117.5–119 °C; ν_{max}/cm^{-1} 3350, 3225, 1756, 1696; δ_H 1.98 (2H, quintet, *J* 7.4), 2.22 (2H, t, *J* 7.4), 2.62 (2H, t, *J* 7.4), 3.75 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.73–6.72 (2H, m), 6.79 (1H, d, *J* 8.6), 6.93 (1H, br s, exchangeable with D_2O), 7.56 (1H, br s, exchangeable with D_2O); *m*/*z* 296 (M^+, 32%), 207 (69), 164 (100) (Calc. for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.65; H, 6.92; N, 9.32%).

Methyl 2-[4-(3,4,5-trimethoxyphenyl)butanoyl]hydrazinecarboxylate 4Ce. Obtained from **5Ce** (1.96 g, 7.30 mmol) as a colourless oil after column chromatography (hexane–AcOEt; 1 : 1 to 2 : 8 gradient) in 50% yield (1.20 g); ν_{max}(film)/cm^{-1} 3300, 1746, 1672; δ_H 2.00 (2H, quintet, *J* 7.4), 2.24 (2H, t, *J* 7.4), 2.62 (2H, t, *J* 7.4), 3.76 (3H, s), 3.82 (3H, s), 3.85 (6H, s), 6.42 (2H, s), 6.85 (1H, br s, exchangeable with D_2O), 7.50 (1H, br s, exchangeable with D_2O); *m*/*z* 326 (M^+, 67%), 294 (13), 237 (97), 194 (100) (Calc. for $C_{15}H_{22}N_2O_6$: *M*, 326.1478. Found: M^+, 326.1459).

Phenyl 2-(2-phenoxyacetyl)hydrazinecarboxylate 4Ea. Obtained from **5Ea** (823 mg, 4.95 mmol) and phenyl chloroformate (0.68 cm^3, 5.40 mmol), following the general procedure; work-up involved solvent evaporation, dissolution of the residue in MeOH, filtration off of insolubles, and concentration of the solution to half of its initial volume. The resulting solution was poured into water and the precipitate thus formed was washed successively with water and Et_2O and dried. The title compound was obtained in 92% yield (1.30 g) as a colourless solid; mp 85–87 °C; ν_{max}/cm^{-1} 3485, 3365, 3275, 3230, 1758sh, 1742, 1688; δ_H 4.68 (2H, s), 6.95 (2H, d, *J* 8.1), 7.05 (1H, t, *J* 7.3), 7.42–7.14 (8H, m), 8.33 (1H, br s, exchangeable with D_2O); *m*/*z* 286 (M^+, 0.1%), 192 (9), 107 (4), 94 (100) (Calc. for $C_{15}H_{14}N_2O_4 \cdot H_2O$: C, 59.21; H, 5.30; N, 9.21. Found: C, 58.85; H, 5.03; N, 9.07%).

Phenyl 2-[2-(3-methoxyphenoxy)acetyl]hydrazinecarboxylate 4Eb. Obtained from **5Eb** (1.30 g, 6.63 mmol) in 86% yield (1.8 g) as a colourless solid; mp 68–70 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3500, 3385, 3290, 3260, 1764sh, 1748, 1694; δ_H 3.78 (3H, s), 4.63 (2H, s), 6.55–6.46 (2H, m), 6.59 (1H, dd, *J* 8.0, *J* 2.0), 7.25–7.10 (4H, m), 7.36 (2H, t, *J* 8.0), 8.59–7.00 (2H, very br s, exchangeable with D_2O); *m*/*z* 316 (M^+, 0.7%), 222 (36), 124 (100), 94 (75) (Calc. for $C_{16}H_{16}N_2O_5 \cdot H_2O$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.10; H, 5.25; N, 8.46%).

Phenyl 2-[2-(3,5-dimethoxyphenoxy)acetyl]hydrazinecarboxylate 4Ec. Obtained from **5Ec** (666 mg, 2.94 mmol) in 75% yield (762 mg) as a colourless solid; mp 132–134 °C; ν_{max}/cm^{-1} 3325, 3200, 1744, 1692; δ_H 3.76 (6H, s), 4.62 (2H, s), 6.11 (2H, d, *J* 1.8), 6.15 (1H, d, *J* 1.8), 7.04 (1H, br s, exchangeable with D_2O), 7.16 (2H, m), 7.23 (1H, m), 7.37 (2H, m), 8.35 (1H, br s, exchangeable with D_2O); *m*/*z* 346 (M^+, 4.8%), 252 (68), 153 (88), 94 (100) (Calc. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.95; H, 5.08; N, 8.06%).

Phenyl 2-[2-(3,4-dimethoxyphenoxy)acetyl]hydrazinecarboxylate 4Ed. Obtained from **5Ed** (476 mg, 2.10 mmol) as a colourless solid in 97% yield (708 mg); mp 76–77 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3510, 3410, 3310, 3250, 1766sh, 1748, 1692; δ_H 3.84 (3H, s), 3.86 (3H, s), 4.62 (2H, s), 6.43 (1H, dd, *J* 8.6, *J* 2.8), 6.57 (1H, d, *J* 2.8), 6.78 (1H, d, *J* 8.6), 7.05 (1H, br s, exchangeable with D_2O), 7.17 (2H, m), 7.24 (1H, m), 7.37 (2H, m), 8.37 (1H, br s, exchangeable with D_2O); *m*/*z* 346 (M^+, 2.4%), 252 (24), 153 (100), 94 (52) (Calc. for $C_{17}H_{18}N_2O_6 \cdot H_2O$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.33; H, 5.45; N, 7.70%).

(B) From the corresponding acids

Oxalyl dichloride (2.5 equiv./mmol acid) was slowly added, at rt and under nitrogen, to a solution of the appropriated arylalkanoic acid in benzene (3 cm^3/mmol acid) containing DMF (0.04 cm^3/mmol acid). After a 30 min stirring period, the solvent and the excess of the oxalyl dichloride were removed by evaporation. The crude acyl chloride thus obtained was dissolved in CH_2Cl_2 (2 cm^3/mmol acid), $NaHCO_3$ (2 equiv./mmol acid) was added, and the resulting suspension was treated with methyl[26a] or phenyl carbazate[26b] (1.05 equiv./mmol acid) in CH_2Cl_2 (2 cm^3/mmol carbazate) during 15 min. On completion of the reaction (TLC control, *ca*. 2.5 h; CH_2Cl_2–MeOH; 9.5 : 0.5), water and CH_2Cl_2 were added to the mixture and the organic phase was washed with brine, dried, and evaporated. The resulting oils were purified by column chromatography.

Phenyl 2-[2-(3-methoxyphenyl)acetyl]hydrazinecarboxylate 4Ac. Obtained from 2-(3-methoxyphenyl)acetic acid (1.10 g, 6.62 mmol) after column chromatography (CH_2Cl_2–MeOH; 100 : 0/95 : 5 gradient), as a colourless oil in 69% yield (1.37 g), which crystallised on storage; mp 97–98 °C (from CH_2Cl_2–Et_2O); ν_{max}/cm^{-1} 3270, 1750, 1684; δ_H 3.65 (2H, s), 3.80 (3H, s), 6.90–6.80 (3H, m), 7.00 (1H, br s, exchangeable with D_2O), 7.37–7.12 (6H, m), 7.37–7.33 (1H, br s, exchangeable with D_2O); *m*/*z* 300 (M^+, absent), 206 ($M^+ - 94$, 79%), 121 (87), 94 (100) (Calc. for $C_{16}H_{16}N_2O_4$: *M*, 300.1110. Found: M^+, 300.1095.

Methyl 2-[4-(3-methoxyphenyl)butanoyl]hydrazinecarboxylate 4Cb. Obtained from 4-(3-methoxyphenyl)butanoic acid (855 mg, 4.40 mmol) after column chromatography (AcOEt–hexane; 8 : 2), as a colourless oil in 79% yield (930 mg); ν_{max}(film)/cm^{-1} 3285, 1742, 1680; δ_H 2.00 (2H, quintet, *J* 7.4), 2.22 (2H, t, *J* 7.4), 2.65 (2H, t, *J* 7.4), 3.75 (3H, s), 3.79 (3H, s), 6.81–6.69 (3H, m), 6.87 (1H, br s, exchangeable with D_2O), 7.19 (1H, t, *J* 8.2), 7.48 (1H, br s, exchangeable with D_2O); *m*/*z* 266 (M^+, 8.6%), 234 (3), 177 (100), 121 (61) (Calc. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.41; H, 6.79; N, 10.52%).

Phenyl 2-[4-(3-methoxyphenyl)butanoyl]hydrazinecarboxylate 4Cc. Obtained from 4-(3-methoxyphenyl)butanoic acid (743 mg, 3.82 mmol) after column chromatography (AcOEt–hexane; 7 : 3), as a colourless oil in 80% yield (1.01 g), which crystallised on storage; mp 93.5–95 °C (from Et_2O); ν_{max}/cm^{-1} 3310, 1782, 1682; δ_H 2.02 (2H, quintet, *J* 7.4), 2.24 (2H, t, *J* 7.4), 2.65 (2H, t, *J* 7.4), 3.78 (3H, s), 6.80–6.68 (3H, m), 6.95 (1H, br s, exchangeable with D_2O), 7.25–7.10 (4H, m), 7.36 (2H, t, *J* 7.8), 7.50 (1H, br s, exchangeable with D_2O); *m*/*z* 328 (M^+, 0.5%), 234 (47), 122 (100), 94 (99) (Calc. for $C_{18}H_{20}N_2O_4$: *M*, 328.1423. Found: M^+, 328.1445).

Phenyl 2-(5-phenylpentanoyl)hydrazinecarboxylate 4Da. Obtained from 5-phenylbutanoic acid (940 mg, 5.27 mol) after column chromatography (AcOEt–hexane; 6 : 4), as a colourless oil in 85% yield (1.40 g), which crystallised on storage; mp 105–106 °C; ν_{max}/cm^{-1} 3300, 3200, 1764sh, 1748, 1666; δ_H 1.67 (4H, m), 2.24 (2H, m), 2.60 (2H, t, *J* 7.4), 7.25–7.10 (8H, m, 1H exchangeable with D_2O), 7.37–7.30 (3H, m), 7.73 (1H, br s, exchangeable with D_2O); *m*/*z* 312 (M^+, 0.1%), 218 (30), 91 (100) (Calc. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.68; H, 6.71; N, 9.06%).

Phenyl 2-[5-(3-methoxyphenyl)pentanoyl]hydrazinecarboxylate 4Db. Obtained from 5-(3-methoxyphenyl)pentanoic acid[27a] (935 mg, 4.49 mmol) after column chromatography (AcOEt–hexane; 6 : 4), as a colourless oil in 66% yield (1.02 g), which crystallised on storage; mp 45–47 °C; ν_{max}(film)/cm^{-1} 3260, 1752sh, 1738, 1670; δ_H 1.70 (4H, m), 2.26 (2H, m), 2.60 (2H, t, *J* 7.3), 3.77 (3H, s), 6.78–6.68 (3H, m), 7.18–7.10 (3H, m), 7.22 (1H, t, *J* 7.5), 7.35 (2H, t, *J* 7.8), 7.37 (1H, br s, exchangeable with D_2O), 7.44 (1H, br s, exchangeable with D_2O); *m*/*z* 342 (M^+, 0.4%), 248 (70), 121 (83), 94 (100) (Calc. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.51; H, 6.63; N, 8.01%).

Methyl 2-[5-(3-methoxyphenyl)pentanoyl]hydrazinecarboxylate 4Dc. Obtained from 5-(3-methoxyphenyl)pentanoic acid[27a] (723 mg, 3.47 mmol) after column chromatography (AcOEt–hexane; 7 : 3), as a colourless oil in 95% yield (920 mg); ν_{max}(film)/cm^{-1} 3280, 1744, 1680; δ_H 1.70 (4H, m), 2.24 (2H, m), 2.61 (2H, t, *J* 7.3), 3.75 (3H, s), 3.79 (3H, s), 6.66 (1H, br s, exchangeable with D_2O), 6.73–6.72 (2H, m), 6.76 (1H, d, *J* 7.5), 7.19 (1H, t, *J* 7.5), 7.25 (1H, exchangeable with D_2O); *m*/*z* 280 (M^+, 3%), 191 (67), 121 (100) (Calc. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.02; H, 7.03; N, 9.98%).

Methyl 2-[5-(3,4-dimethoxyphenyl)pentanoyl]hydrazinecarboxylate 4Dd. Obtained from 5-(3,4-dimethoxyphenyl)pentanoic acid[27b] (931 mg, 3.91 mmol) after column chromatography (AcOEt–hexane; 7 : 3), as a colourless oil in 70% yield (848 mg), which crystallised upon trituration with Et_2O; mp 105.5–106.5 °C; ν_{max}/cm^{-1} 3345, 3300, 1778, 1670; δ_H 1.70 (4H, m), 2.25 (2H,

m), 2.58 (2H, t, *J* 7.4), 3.74 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.70 (2H, m), 6.73 (1H, br s, exchangeable with D_2O), 6.78 (1H, d, *J* 8.6), 7.35 (1H, br s, exchangeable with D_2O); *m*/*z* 310 (M^+, 27%), 177 (47), 151 (100) (Calc. for $C_{15}H_{22}N_2O_5$: *M*, 310.1529. Found: M^+, 310.1528.

Methyl 2-(3-phenylpropenoyl)hydrazinecarboxylate 25a. Cinnamic acid (3.0 g, 20.25 mmol) in CH_2Cl_2 (200 cm^3), cooled in an ice-bath, was treated with Et_3N (2.85 cm^3, 20.45 mmol) followed by dropwise addition of ethyl chloroformate (1.94 cm^3, 20.29 mmol). After being stirred for 10–15 min the mixture was treated with methyl carbazate (1.84 g, 20.43 mmol) in CH_2Cl_2 (5 cm^3). On completion of the reaction (TLC control; CH_2Cl_2–MeOH; 95 : 5) dil. aq. HCl (5%) was added and the organic phase was separated, then washed with water and dried. Evaporation of the solution and recrystallisation of the residue obtained gave the title compound (3.79 g) in 85% yield, mp 164–166 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3320, 3190, 1728, 1668; δ_H 3.75 (3H, s), 6.49 (1H, d, *J* 15.7), 7.32 (3H, m), 7.43 (2H, m), 7.53 (1H, br s), 7.67 (1H, d, *J* 15.7), 8.73 (1H, br s) (Calc. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.75; H, 5.55; N, 12.51%).

Methyl 2-[3-(4-fluorophenyl)propenoyl]hydrazinecarboxylate 25b. Similarly prepared from *p*-fluorocinnamic acid (2.00 g, 12.04 mmol) in 99% yield (2.84 g), compound **25b** had mp 180–183 °C (from CH_2Cl_2); ν_{max}/cm^{-1} 3260, 1728, 1664; δ_H 3.78 (3H, s), 6.34 (1H, d, *J* 15.7), 7.04 (2H, m), 7.15 (1H, br s), 7.43 (2H, m), 7.64 (1H, d, *J* 15.6), 8.22 (1H, br s) (Calc. for $C_{11}H_{11}FN_2O_3$: C, 55.46; H, 4.65; N, 11.76. Found: C, 55.58; H, 4.56; N, 11.76%).

(C) From the corresponding acyl chlorides

Ethyl 2-(2,2,2-triphenylacetyl)hydrazinecarboxylate 7. Triphenylacetyl chloride (92.4 mg, 0.30 mmol) was added to a solution of ethyl carbazate (33 mg, 0.32 mmol) and pyridine (0.5 cm^3) in CH_2Cl_2 (5 cm^3). On completion of the reaction the organic phase was washed successively with ice-cold aq. HCl (0.5 M) and water, and dried. Evaporation of the solution followed by crystallisation of the resulting solid gave the title compound (100 mg, 89%); mp 174–175 °C (from CH_2Cl_2); ν_{max}/cm^{-1} 3400, 3260, 1740, 1688; δ_H (DMSO-d_6) 1.18 (3H, t, *J* 7), 4.05 (2H, q, *J* 7), 7.24 (15H, m), 9.14 (1H, br s), 9.60 (1H, br s) [Calc. for $C_{23}H_{22}N_2O_3$: *M*, 374.1630 (*M* + H, 375.170 85). Found: M^+, 375.1707].

Procedures of oxidative cyclisations. Method 1[6] (NBS–Pyridine and $BF_3{\cdot}Et_2O$ or $BF_3{\cdot}Et_2O$–KHF_2)

Methyl 2-(phenylcarbamoyl)diazenecarboxylate 21. A vigorously stirred suspension of methyl 2-(phenylcarbamoyl)-hydrazinecarboxylate[28] **20** (150 mg, 0.72 mmol) in CH_2Cl_2 (5 cm^3) containing pyridine (64 mm^3, 0.79 mmol), under nitrogen atmosphere, was cooled to −10 °C, treated with NBS (140 mg) (0.79 mmol) portionwise, stirred for 10 min at −10 °C, and then allowed to rise to rt. On completion of the reaction (15 min, TLC control; CH_2Cl_2–MeOH; 95 : 5) the solvent was evaporated off and the residue was triturated with Et_2O. The organic phase was washed with water, dried, and evaporated, yielding a reddish oil in 92% (137 mg), which was briefly characterised and used directly in the next step; ν_{max}(film)/cm^{-1} 3290, 1780, 1740; δ_H (CD_3CN) 4.07 (3H, s), 7.24 (1H, m), 7.43 (2H, m), 7.69 (2H, m), 9.35 (1H, br s, exchangeable with D_2O).

Methyl *N*-(2-oxo-2,3-dihydro-1*H*-benzoimidazol-1-yl)carbamate 22. Method 1a ($BF_3{\cdot}Et_2O$). To a solution of the above azo compound **21** (78.7 mg, 0.38 mmol) in $CHCl_3$ (5 cm^3) at rt under nitrogen was added $BF_3{\cdot}Et_2O$ (93.5 mm^3, 0.76 mmol) and the mixture was stirred for 30 h, after which TLC (CH_2Cl_2–MeOH; 9 : 1) showed the completion of the reaction. The mixture was treated with saturated aq. $NaHCO_3$ and extracted with Et_2O. The extract was washed with brine, dried, and evaporated, yielding the title compound (45 mg, 57%) as a colourless solid; mp 192–194 °C (from CH_2Cl_2); ν_{max}/cm^{-1} 3285, 1752, 1716; δ_H (CD_3CN) 3.76 (3H, s), 7.07–7.01 (4H, m), 8.08 (1H, br s, exchangeable with D_2O), 8.77 (1H, br s, exchangeable with D_2O); *m*/*z* 207 (M^+, 61%), 175 (100), 148 (56) (Calc. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.38; H, 4.31; N, 19.99%).

Method 1b ($BF_3{\cdot}Et_2O$ and KHF_2). To a suspension of potassium hydrogen difluoride (100 mg, 1.28 mmol) in $CHCl_3$ (3 cm^3) contained in a polyethylene flask, at rt and under nitrogen, was added $BF_3{\cdot}Et_2O$ (93.5 mm^3, 0.76 mmol) and the mixture was stirred for 5 min. A solution of the previously prepared diazene **21** (78.7 mg, 0.38 mmol) in $CHCl_3$ (5 cm^3) was then added and the TLC control (CH_2Cl_2–MeOH; 9 : 1) after 19 h showed the completion of the reaction. Work-up as above yielded the title compound (60 mg, 76%), identical (TLC, IR, ^1H NMR) to the compound prepared by **method 1a**.

Method 2a[7] (IBDA)

Methyl (7-methoxy-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-1-yl)carbamate 11e. To a solution of **4Be** (200 mg, 0.71 mmol) in CH_2Cl_2 (7 cm^3) protected from light was added, with stirring, IBDA (228 mg, 0.71 mmol) in portions. When the reaction was adjudged to be complete (TLC, $CHCl_3$–EtOH; 9 : 1), the products formed were isolated and purified as above to give the title compound **11e** in 4% yield (8 mg), as a colourless solid; mp 185–189 °C (from EtOAc–pentane); ν_{max}/cm^{-1} 3220, 1710, 1690, 1640; δ_H 2.33 (2H, td, *J* 7.7, *J* 1.6), 2.66 (2H, td, *J* 7.7, *J* 1.6), 3.70 (3H, s), 3.73 (3H, s), 5.77 (1H, m), 6.33 (1H, d, *J* 9.9), 6.39 (1H, br s), 6.85 (1H, ddd, *J* 9.9, *J* 2.1, *J* 0.6) (Calc. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.22; H, 5.36; N, 10.44%)

Method 2b (IBDA and $BF_3{\cdot}Et_2O$)

Compound 11e and methyl (6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12e. The above reaction was conducted with **4Be** (500 mg, 1.77 mmol) and IBDA (568 mg, 1.77 mmol) in CH_2Cl_2 (25 cm^3). When all the starting material had reacted, $BF_3{\cdot}Et_2O$ (0.22 cm^3, 1.78 mmol) was added and the mixture was stirred until the completion of the reaction. The mixture was treated with saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated. Purification by column chromatography (EtOAc–MeOH; 95 : 5) followed by PTLC (Et_2O) furnished product **11e** (193 mg, 41%), and title compound **12e** (125.5 mg, 25%) as a colourless solid; mp 165–166 °C (from EtOAc–hexane); ν_{max}/cm^{-1} 3220, 1755, 1660; δ_H 2.77 (2H, m), 2.91 (2H, m), 3.82 (3H, s), 3.86 (3H, s), 3.87 (3H, s), 6.69 (1H, s), 6.77 (1H, s), 6.88 (1H, br s) (Calc. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.94; H, 5.82; N, 10.00%).

Method 3a[7] (IBBTA). General procedure

The appropriate bishydrazide in CH_2Cl_2 (10 cm^3/mmol bishydrazide), protected from light and under inert atmosphere was treated at rt with freshly crystallised IBBTA (1.0 equiv./mmol bishydrazide **4A**, **4B** or **25** or 1.1 equiv./mmol bishydrazide **4C**–**E**) in portions (1 h) or dissolved in CH_2Cl_2 (10 cm^3/mmol oxidant) during 10–15 min. The mixture was found to acquire a yellow or orange-yellow colour and the course of the reaction was monitored by TLC (CH_2Cl_2–MeOH; 90 : 10 or 95 : 5). For suitably activated aromatics, the consumption of the starting material resulting in the formation of the spiro compound and/or the quinolone occurred smoothly at room temperature (**method 3a**). In cases where the conversion was found to be slow, addition of $BF_3{\cdot}Et_2O$ was found to be

advantageous (**method 3b**). On completion of the reaction the products were isolated and purified as detailed above.

Methyl (2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-1-yl)carbamate 11c. Compound **4Bc** (200 mg, 0.79 mmol) gave, after column chromatography (EtOAc–hexane; 70 : 30), product **11c** (25%, 47 mg) as a viscous oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3390, 1756, 1720, 1668, 1632; δ_H 2.28 (2H, t, *J* 7.8), 2.65 (2H, t, *J* 7.8), 3.74 (3H, s), 6.32 (2H, d, *J* 10.2), 6.60 (1H, s), 6.88 (2H, d, *J* 10.2) (Calc. for $C_{11}H_{12}N_2O_4$: *M*, 236.0797. Found: M^+, 236.0809).

Methyl (6-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)-carbamate 12b. Obtained in 71% yield (211 mg) as a colourless solid from **4Bb** (300 mg, 1.19 mmol); mp 165–166 °C (from EtOAc); ν_{max}/cm^{-1} 3200, 1736, 1665; δ_H 2.75 (2H, m), 2.95 (2H, m), 3.78 (3H, s), 3.79 (3H, s), 6.73 (1H, d, *J* 2.7), 6.76 (1H, dd, *J* 8.7, *J* 2.7), 6.94 (1H, br s), 7.10 (1H, d, *J* 8.7) (Calc. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.97; H, 5.70; N, 10.95%).

Methyl(6,8-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)-carbamate 12d. Obtained from **4Bd** (1.02 g, 3.61 mmol) after column chromatography (CH_2Cl_2–MeOH; 95 : 5) in 40% yield (400 mg) as a colourless solid; mp 178–180 °C (from EtOAc); ν_{max}/cm^{-1} 3230, 1740, 1676; δ_H 2.66 (3H, m), 3.27 (1H, m), 3.72 (3H, s), 3.79 (3H, s), 3.84 (3H, s), 6.34 (1H, d, *J* 2.2), 6.39 (1H, d, *J* 2.2), 7.38 (1H, br s) (Calc. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.43; H, 5.54; N, 9.84%).

Compounds 11e and 12e from 4Be. Isolated in 50% (235 mg) and 12% yeild (59.5 mg), respectively, from **4Be** (500 mg, 1.77 mmol) after column chromatography (AcOEt–MeOH; 95 : 5) and PTLC (Et_2O, 5×); identical (TLC, IR, ^1H NMR) to the compounds previously prepared by **methods 2a** and **2b**.

Methyl (6,7,8-trimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12f. Isolated in 13% yield (132 mg) as a colourless solid from **4Bf** (1.02 g, 3.26 mmol); mp 143–144 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3230, 1748, 1680; δ_H 2.68 (3H, m), 3.20 (1H, m), 3.75 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.91 (3H, s), 6.50 (1H, s), 7.36 (1H, s) (Calc. for $C_{14}H_{18}N_2O_6$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.95; H, 5.68; N, 8.78%).

Phenyl (6,8-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12h. Similarly, **4Bh** (1.21 g, 3.51 mmol) gave **12h** (774 mg, 64%) as a colourless solid; mp 164–166 °C (from EtOAc); ν_{max}/cm^{-1} 3260, 1760, 1692; δ_H 2.67 (3H, m), 3.25 (1H, m), 3.79 (3H, s), 3.84 (3H, s), 6.34 (1H, s), 6.43 (1H, s), 7.17 (3H, m), 7.33 (2H, t, *J* 7.6), 7.65 (1H, br s) (Calc. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.02; H, 5.27; N, 8.11%).

Methyl (8,10-dimethoxy-2,9-dioxo-1-azaspiro[5.5]undeca-7,10-dien-1-yl)carbamate 14e. Obtained from **4Ce** (430 mg, 1.32 mmol) in 45% yield (185 mg) after PTLC (CH_2Cl_2–MeOH; 95 : 5; 3×), as a slight yellowish solid; mp 224–225 °C (from benzene); ν_{max}/cm^{-1} 3225, 1746, 1684, 1656, 1624; δ_H 2.04 (3H, br s), 2.24 (1H, br s), 2.66 (2H, br s), 3.70 (9H, s), 5.67 (1H, br s), 6.11 (1H, br s), 6.36 (1H, br s, exchangeable with D_2O); *m*/*z* 310 (M^+, 3%), 280 (4), 236 (35), 179 (21), 149 (100) (Calc. for $C_{14}H_{18}N_2O_6$: *M*, 310.1165. Found: M^+, 310.1151).

Phenyl (5,7-dimethoxy-3-oxo-3,4-dihydro-2*H*-benzo[1,4]-oxazin-4-yl)carbamate 23c. Oxidation of **4Ec** (150 mg, 0.43 mmol) with IBBTA (204 mg, 0.47 mmol) at −15 °C to rt, followed by 1 h of stirring at rt, yielded the title compound in 40% yield (60 mg) after PTLC (CH_2Cl_2–MeOH; 95 : 5; 2×), as a colourless solid; mp 109–110 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3290, 1760, 1712; δ_H 3.77 (3H, s), 3.90 (3H, s), 4.54 (1H, d, *J* 14.4), 4.74 (1H, d, *J* 14.4), 6.26 (2H, s), 7.25–7.15 (3H, m), 7.34 (2H, t, *J* 7.7), 7.41 (1H, br s, exchangeable with D_2O); *m*/*z* 342 (M^+, 18%), 250 (31), 208 (56), 94 (100) (Calc. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.67; H, 4.63; N, 8.05%).

Method 3b (IBBTA and $BF_3{\cdot}Et_2O$). General procedure

The **method 3a** was followed up until the addition of the oxidant was complete and, after a stirring period of 0.5–1 h, $BF_3{\cdot}Et_2O$ (1.0–1.05 equiv./mmol bishydrazide) was added to the mixture. After an additional stirring period of 0.5–1.5 h aq. $NaHCO_3$ (5–10%) was added, the mixture was extracted with CH_2Cl_2, and the extract was washed with brine and dried. Evaporation of the solution furnished, in general, oils, which were purified by column chromatography and/or PTLC.

Oxidation of methyl 2-(2-phenylacetyl)hydrazinecarboxylate 4Aa

Compound **4Aa** (208 mg, 1.0 mmol) in CH_2Cl_2 (5 cm^3) was treated with IBBTA (430 mg, 1.00 mmol) and $BF_3{\cdot}Et_2O$ (123 mm^3, 1.00 mmol). On addition of the $BF_3{\cdot}Et_2O$ a vigorous evolution of gas occurred, accompanied by a change in the colour of the solution to light yellow. TLC control (hexane–AcOEt; 6 : 4) showed a complex mixture that was worked up, and then purified by column chromatography (CH_2Cl_2) to yield an oil consisting in iodobenzene and methyl phenylacetate (19%) (4 : 1; ^1H NMR); *m*/*z* (PhI) 204 (90%), 77 (100), 51 (50) (*m*/*z* identical to authentic sample); *m*/*z* ($PhCH_2CO_2Me$) 150 (30%), 91 (100), 65 (20) (*m*/*z* identical to authentic sample).

Methyl (5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl)carbamate 9b. Obtained from **4Ab** (119 mg, 0.50 mmol) in 51% yield (60 mg) after PTLC (CH_2Cl_2–MeOH; 9 : 1); mp 118–120 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3260, 3190, 1752, 1714; δ_H 3.56 (2H, s), 3.79 (6H, s), 6.86–6.79 (3H, m), 7.40 (1H, br s, exchangeable with D_2O); *m*/*z* 236 (M^+, 100%), 204 (17), 177 (34), 149 (71), 162 (29) (Calc. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.06; H, 5.03; N, 11.71%).

Phenyl (5-methoxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl)carbamate 9c. Obtained from **4Ac** (322 mg, 1.07 mmol) in 60% yield (191 mg) after PTLC (CH_2Cl_2–MeOH; 95 : 5; 2×); mp 171–173 °C (from AcOEt); ν_{max}/cm^{-1} 3340, 1776, 1720; δ_H 3.61 (2H, s), 3.80 (3H, s), 6.84 (1H, d, *J* 8.0), 6.89 (1H, s), 6.92 (1H, d, *J* 8.0), 7.43–7.15 (6H, m, 1H exchangeable with D_2O); *m*/*z* 298 (M^+, 30%), 204 (91), 177 (9), 162 (63), 149 (8), 94 (100) (Calc. for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.07; H, 4.80; N, 9.28%).

Methyl (5,6,7-trimethoxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl)-carbamate 9d. Obtained from **4Ad** (75 mg, 0.25 mmol), under reflux, in 40% yield (30 mg) after PTLC (CH_2Cl_2–MeOH; 9 : 1); mp 155–156 °C (from AcOEt–Et_2O); ν_{max}/cm^{-1} 3235, 1756, 1712; δ_H 3.51 (1H, br s), 3.55 (1H, br s), 3.83 (6H, s), 3.86 (3H, s), 3.87 (3H, s), 6.65 (1H, s), 7.11 (1H, br s, exchangeable with D_2O); *m*/*z* 296 (M^+, 100%), 264 (6), 237 (8), 222 (29), 209 (20), (Calc. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.75; H, 5.17; N, 9.38%).

Methyl (5,6-dimethoxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl)carbamate 9e. Obtained from **4Ae** (134 mg, 0.50 mmol) in 41% yield (54 mg) after PTLC (CH_2Cl_2–MeOH; 9 : 1); mp 171–174 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3315, 1758, 1728; δ_H 3.53 (2H, s), 3.82 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 6.56 (1H, s), 6.86 (1H, s), 7.15 (1H, br s, exchangeable with D_2O); *m*/*z* 266 (M^+, 100%), 234 (10), 207 (11), 192 (22), 179 (41) (Calc. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.86; H, 5.23; N, 10.48%).

Oxidation of methyl 2-[2-(2,5-dimethoxyphenyl)acetyl]-hydrazinecarboxylate 4Af

Following the general procedure, the TLC control (hexane–AcOEt; 30 : 70) of the reaction with **4Af** (295 mg, 1.10 mmol) showed a complex mixture which was worked up to yield a dark brown oil, which was purified by PTLC (CH_2Cl_2–MeOH; 95 : 5, 3×, followed by hexane–AcOEt; 30 : 70, 2×), to yield an oil in 5% (13.8 mg) identical with compound **9e** obtained from **4Ae**; ν_{max}(film)/cm^{-1} 3282, 1747, 1728; δ_H 3.53 (2H, s), 3.82 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 6.56 (1H, s), 6.86 (1H, s), 7.03 (1H, br s, exchangeable with D_2O).

In another experiment with **4Af** (300 mg, 1.12 mmol), the isolated crude brown oil (340 mg) was dissolved in acetone (10 cm^3), MeI (318 mm^3, 5 mmol) and K_2CO_3 (138 mg, 1 mmol) were added, and the mixture was refluxed for 14 h. On work-up in the usual manner an oil (16 mg, 5%), isolated by PTLC (hexane–AcOEt; 30 : 70; 2×), was identified as methyl (5,6-dimethoxy-2-oxo-2,3-dihydro-1*H*-indol-1-yl)(methyl)carbamate **10**; ν_{max}(CH_2Cl_2)/cm^{-1} 1740, 1726 cm^{-1}; δ_H 3.33 (3H, s), 3.51 (2H, s), 3.71 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.42 (1H, s), 6.89 (1H, s); *m*/*z* 280 (M$^+$, 70%), 266 (19), 265 (26), 207 (100), 192 (25) (Calc. for $C_{13}H_{16}N_2O_5$: *M*, 280.1059. Found: M$^+$, 280.1060).

Methyl (5-methyl-2-oxo-2,3-dihydro-1*H*-indol-1-yl)carbamate 9g. In the case of **4Ag** (222 mg, 1.00 mmol) a strong evolution of gas was observed on addition of the Lewis acid. Compound **9g** was isolated by PTLC (CH_2Cl_2–MeOH; 9 : 1) in 28% yield (61 mg); mp 152–154 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3180, 1774, 1762sh, 1710; δ_H 2.34 (3H, s), 3.56 (2H, s), 3.80 (3H, s), 6.81 (1H, d, *J* 8.0), 7.01 (1H, br s, exchangeable with D_2O), 7.08–7.07 (2H, m); *m*/*z* 220 (M$^+$, 89%), 188 (38), 161 (40), 146 (36), 133 (100) (Calc. for $C_{11}H_{12}N_2O_3$: *M*, 220.0848. Found: M$^+$, 220.0847).

Ethyl (2-oxo-3,3-diphenyl-2,3-dihydro-1*H*-indol-1-yl)carbamate 8. Obtained from **7** (100 mg, 0.27 mmol) in 85% yield (85 mg) as a colourless solid; mp 164–166 °C (from dil. AcOH) (lit.,[9] 166–167 °C); ν_{max}/cm^{-1} 3230, 1740, 1704; δ_H (DMSO-d_6) 1.26 (3H, t, *J* 6.9), 4.17 (2H, q, *J* 6.9), 6.99 (1H, d, *J* 7.4), 7.13 (1H, t, *J* 7.4), 7.20 (4H, m), 7.33 (9H, m).

Methyl (2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12a. Isolated as a colourless solid (131 mg, 44%) from **4Ba** (300 mg, 1.35 mmol); mp 192–194 °C (from EtOAc); ν_{max}/cm^{-1} 3180, 1745, 1665; δ_H 2.78 (2H, m), 2.99 (2H, m), 3.80 (3H, s), 6.94 (1H, br s), 7.20 (3H, m), 7.04 (1H, m) (Calc. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.68; H, 5.48; N, 12.51%).

Phenyl (6-hydroxy-7-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12i. Compound **4Bi** (300 mg, 0.87 mmol) and BF_3·Et_2O (54 mm^3, 0.44 mmol), following the general procedure, gave after PTLC (CH_2Cl_2–MeOH; 95 : 5; 2×) a phenol, presumably **12i**, in 33% yield (94 mg) as a colourless solid; mp 165–175 °C (decomp.) (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3430, 3200, 1768, 1672; δ_H (CD_2Cl_2) 2.75 (2H, m), 2.92 (2H, m), 3.87 (3H, s), 5.71 (1H, br s), 6.73 (1H, s), 6.88 (1H, s), 7.25 (4H, m), 7.34 (2H, t, *J* 7.7) (Calc. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.52. Found: C, 61.91; H, 4.90; N, 8.49%).

Phenyl (6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12j. This by-product, from the above reaction, and formed in 3% yield (8.9 mg), had mp 185–189 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3220, 3190, 1772, 1676; δ_H 2.80 (2H, m), 2.92 (2H, m), 3.87 (3H, s), 3.90 (3H, s), 6.70 (1H, s), 6.86 (1H, s), 7.22–7.40 (6H, m) (Calc. for $C_{18}H_{18}N_2O_5$: *M*, 342.1216. Found: M$^+$, 342.1195).

Methylation of **12i** with diazomethane in MeOH–Et_2O gave a mixture, which was separated by PTLC (CH_2Cl_2–MeOH; 95 : 5) into a compound (62%) identical with the above by-product **12j** (mp, IR, TLC and ^{1}H NMR) and presumably *O*,*N*-dimethylated product, phenyl (6,7-dimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)(methyl)carbamate **13d** in 31% yield as a colourless solid, mp 109–110 °C; ν_{max}/cm^{-1} 1748, 1700; (Calc. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.99; H, 5.64; N, 7.85%).

Oxidation of methyl 2-(4-phenylbutanoyl)hydrazinecarboxylate 4Ca

On addition of BF_3·Et_2O to the reaction mixture of **4Ca** (369 mg, 1.56 mmol), following the general oxidation procedure, a vigorous evolution of gas occurred with concomitant change in the orange colour of the solution to yellow. Work-up of the mixture and purification by PTLC (hexane–AcOEt; 7 : 3) furnished the compounds **15a** and **16a** described below.

Methyl (2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)-carbamate 15a. Isolated as a colourless oil that crystallised on storage in 4% yield (15 mg); mp 175.5–176 °C (from AcOEt–hexane); ν_{max}(film)/cm^{-1} 3260, 1747, 1679; δ_H 2.22 (2H, quintet, *J* 7.2), 2.39 (2H, t, *J* 7.2), 2.95 (2H, m), 3.77 (3H, s), 7.23–7.18 (3H, m; 1H exchangeable with D_2O), 7.31–7.28 (2H, m); *m*/*z* 234 (M$^+$, 60%), 202 (19), 160 (14), 147 (85), 132 (100), 119 (46), 91 (42) (Calc. for $C_{12}H_{14}N_2O_3$: *M*, 234.1004. Found: M$^+$, 234.0996).

3,4-Dihydronaphthalen-1(2*H*)-one 16a. Obtained as a colourless oil in 20% yield (45 mg); ν_{max}(film)/cm^{-1} 1680. It was further characterised as the 2,4-dinitrophenylhydrazone derivative, obtained as red crystals in 67% yield; mp 263–265 °C; mixed mp 264–265 °C (with an authentic sample prepared from commercial 1-tetralone).

Oxidation of methyl 2-[4-(3-methoxyphenyl)butanoyl]hydrazine-carboxylate 4Cb

From **4Cb** (429 mg, 1.61 mmol), work-up of the mixture yield a red oil which was purified by column chromatography (AcOEt–hexane; 7 : 3) to furnish the compounds **15b** and **16b** described below.

Methyl (7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepin-1-yl)carbamate 15b. Isolated as a colourless solid (350 mg) in 82% yield; mp 141–142 °C (AcOEt); ν_{max}/cm^{-1} 3215, 1744, 1668; δ 2.20 (2H, quintet, *J* 7.2), 2.38 (2H, t, *J* 7.2), 2.92 (2H, m), 3.76 (3H, s), 3.81 (3H, s), 6.73 (1H, d, *J* 2.8), 6.81 (1H, dd, *J* 8.8, *J* 2.8), 7.22 (1H, d, *J* 8.8), 7.26–7.20 (1H, br s, exchangeable with D_2O); *m*/*z* 264 (M$^+$, 100%), 232 (16), 189 (35), 177 (83), 162 (91), 149 (26), 121 (40), 91 (42) (Calc. for $C_{13}H_{16}N_2O_4$: C, 59.07; H, 6.11; N, 10.60. Found: C, 58.83; H, 6.15; N, 10.39%).

6-Methoxy-3,4-dihydronaphthalen-1(2*H*)-one 16b. Obtained as a thick colourless oil (18 mg) in 6% yield that crystallised out from AcOEt–hexane; mp 75–77 °C (lit.,[29] 82 °C); ν_{max}/cm^{-1} 1674 cm^{-1}.

Oxidation of phenyl 2-[4-(3-methoxyphenyl)butanoyl]hydrazine-carboxylate 4Cc

From **4Cc** (602 mg, 1.83 mmol), work-up of the mixture yield a red oil, which was purified by column chromatography (AcOEt–hexane; 6 : 4) to furnish the compounds **15c** and **16b** described below.

Phenyl (7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepin-1-yl)carbamate 15c. Isolated as a colourless amorphous solid (330 mg) in 55% yield; mp 154–155 °C (from Et_2O); ν_{max}/cm^{-1} 3220, 1772, 1670; δ_H 2.21 (2H, quintet, *J* 7.2), 2.41 (2H, t,

J 7.2), 2.93 (2H, m), 3.82 (3H, s), 6.74 (1H, d, *J* 2.8), 6.85 (1H, dd, *J* 8.8, *J* 2.8), 7.18–7.11 (2H, m), 7.20 (1H, t, *J* 7.8), 7.29 (1H, d, *J* 8.8), 7.34 (2H, t, *J* 7.8), 7.59 (1H, br s, exchangeable with D_2O); *m*/*z* 326 (M^+, 10%), 232 (80), 190 (20), 162 (100), 94 (89) (Calc. for $C_{18}H_{18}N_2O_4$: C, 66.23; H, 5.56; N, 8.59. Found: C, 65.92; H, 5.78; N, 8.37%).

Compound 16b. Obtained as a thick colourless oil (15 mg) in 4.7% yield, identical (IR, ^{1}H NMR, TLC) to the compound obtained from **4Cb**.

Methyl (7,8-dimethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)carbamate 15d. Isolated as a colourless solid (240 mg) in 60% yield after PTLC (CH_2Cl_2–MeOH; 95 : 5) from **4Cd** (400 mg, 1.35 mmol); mp 170–172 °C (from AcOEt); ν_{max}/cm^{-1} 3303, 1753, 1679; δ_H 2.20 (2H, quintet, *J* 7.2), 2.38 (2H, t, *J* 7.2), 2.88 (2H, m), 3.78 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 6.68 (1H, s), 6.83 (1H, s), 7.22 (1H, br s, exchangeable with D_2O); *m*/*z* 294 (M^+, 100%), 262 (17), 220 (25), 207 (81), 192 (63), 179 (27), 151 (37) (Calc. for $C_{14}H_{18}N_2O_5$: C, 57.12; H, 6.17; N, 9.52. Found: C, 57.42; H, 6.36; N, 9.58%).

Oxidation of methyl 2-[4-(3,4,5-trimethoxyphenyl)butanoyl]-hydrazinecarboxylate 4Ce

From **4Ce** (176 mg, 0.54 mmol), work-up of the mixture yielded an oil, which was purified by PTLC (CH_2Cl_2–MeOH; 9 : 1) to furnish the compounds **14e** and **15e** described below.

Methyl (8,10-dimethoxy-2,9-dioxo-1-azaspiro[5.5]undeca-7,10-dien-1-yl)carbamate 14e. Obtained in 45% yield (75 mg), identical (IR, TLC) to the compound isolated using **method 3a**.

Methyl (7,8,9-trimethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)carbamate 15e. Isolated in 5% yield (9 mg) as a colourless solid; mp 56–59 °C; ν_{max}/cm^{-1} 3280, 1744, 1690; δ_H 1.96 (2H, m), 2.25 (1H, m), 2.38 (2H, m), 2.57 (1H, m), 3.72 (3H, s), 3.866 (3H, s), 3.874 (3H, s), 3.93 (3H, s), 6.50 (1H, s), 7.80 (1H, br s, exchangeable with D_2O); *m*/*z* 324 (M^+, 100%), 292 (4), 250 (39), 237 (47), 222 (99), 209 (15), 181 (6) (Calc. for $C_{15}H_{20}N_2O_6$: *M*, 324.1321. Found: M^+, 324.1303).

Oxidation of phenyl 2-(5-phenylpentanoyl)hydrazinecarboxylate 4Da

From **4Da** (690 mg, 2.2 mmol), on addition of $BF_3{\cdot}Et_2O$, a vigorous evolution of gas occurred. TLC control (CH_2Cl_2–MeOH; 95 : 5) after 1 h of stirring showed a complex mixture of products, which was worked up and tentatively purified (column and PTLC), always giving impure materials.

Phenyl (8-methoxy-2-oxo-1,2,3,4,5,6-hexahydrobenzo[*b*]azocin-1-yl)carbamate 18b. Obtained from **4Db** (600 mg, 1.75 mmol) in 24% yield (140 mg) after column chromatography (AcOEt–hexane; 6 : 4) as a colourless solid; mp 158–160 °C (from Et_2O); ν_{max}/cm^{-1} 3230, 1768, 1656; δ_H 1.42 (1H, m), 1.83 (1H, m), 1.96 (1H, m), 2.13 (2H, m), 2.45 (1H, m), 2.76 (1H, m), 2.90 (1H, m), 3.83 (3H, s), 6.76 (1H, d, *J* 2.8), 6.82 (1H, dd, *J* 8.8, *J* 2.8), 7.19–7.12 (2H, m), 7.21 (1H, m), 7.34 (3H, m), 7.63 (1H, br s, exchangeable with D_2O); *m*/*z* 340 (M^+, 1.4%), 246 (70), 204 (24), 162 (59), 94 (100) (Calc. for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.00; H, 6.08; N, 8.19%).

Methyl (8-methoxy-2-oxo-1,2,3,4,5,6-hexahydrobenzo[*b*]azocin-1-yl)carbamate 18c. Obtained from **4Dc** (550 mg, 1.96 mmol) in 44% yield (240 mg) after column chromatography (AcOEt–hexane; 7 : 3) as a colourless solid; mp 172–173 °C (from AcOEt–Et_2O); ν_{max}/cm^{-1} 3230, 1752, 1670; δ_H[conformer A (A) and conformer B (B); ratio 8 : 2] 1.24 (1H, m; B), 1.50–1.33 (1H, m; A), 1.60 (1H, m; B), 1.90–1.73 (3H, m; 1H, A and 2H, B), 2.02–1.90 (1H, m; A), 2.20–2.02 (2H, m; A), 2.27 (1H, m; B), 2.48–2.36 (1H, m; A), 2.60 (1H, m; B), 2.68 (1H, m; B), 2.93–2.74 (2H, m; A), 2.97 (1H, m; B), 3.75 (3H, s; A), 3.78 (3H, s; B), 3.81 (3H, s; B), 3.82 (3H, s; A), 6.73 (1H, d, *J* 2.8; B), 6.75 (1H, d, *J* 2.8; A), 6.79 (2H, m; A and B), 7.09 (1H, d, *J* 8.7; B), 7.30 (1H, d, *J* 8.7; A), 7.34 (1H, br s, exchangeable with D_2O; A), 7.63 (1H, br s, exchangeable with D_2O; B); *m*/*z* (A) 278 (M^+, 100%), 205 (30), 161 (95); *m*/*z* (B) 278 (M^+, 100%), 246 (33), 162 (60) (Calc. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.50; H, 6.40; N, 9.99%).

Methyl (8,9-dimethoxy-2-oxo-1,2,3,4,5,6-hexahydrobenzo[*b*]-azocin-1-yl)carbamate 18d. Obtained from **4Dd** (420 mg, 1.35 mmol) in 61% yield (255 mg) after column chromatography (AcOEt–hexane; 6 : 4) as a colourless solid; mp 184–186 °C (from Et_2O); ν_{max}/cm^{-1} 3222, 1752, 1662; δ_H 1.39 (1H, m), 1.79 (1H, m), 1.97 (1H, m), 2.12 (2H, m), 2.43 (1H, m), 2.76 (2H, m), 3.78 (3H, s), 3.86 (3H, s), 3.90 (3H, s), 6.68 (1H, s), 6.89 (1H, s), 7.20 (1H, br s, exchangeable with D_2O); *m*/*z* 308 (M^+, 100%), 276 (17), 234 (56), 192 (51) (Calc. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.52; H, 6.72; N, 9.00%).

Oxidation of phenyl 2-(2-phenoxyacetyl)hydrazinecarboxylate 4Ea

Compound **4Ea** (408 mg, 1.42 mmol) treated in the usual manner gave a complex mixture (TLC control, CH_2Cl_2–MeOH; 95 : 5), from which no useful compound could be isolated.

Phenyl (7-methoxy-3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-4-yl)carbamate 23b. Obtained from **4Eb** (460 mg, 1.45 mmol) in 39% yield (176 mg) after column chromatography (AcOEt–hexane; 6 : 4) as an oil which crystallised on storage; mp 122–124 °C (from Et_2O–hexane); ν_{max}/cm^{-1} 3320, 3260, 1738, 1702; δ_H 3.78 (3H, s), 4.75 (2H, s), 6.63–6.58 (2H, m), 7.26–7.00 (5H, m; 1H exchangeable with D_2O), 7.37 (2H, m); *m*/*z* 314 (M^+, 24%), 220 (83), 150 (77), 94 (100) (Calc. for $C_{16}H_{14}N_2O_5$: *M*, 314.0903. Found: M^+, 314.0902).

Phenyl (5,7-dimethoxy-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)carbamate 23c. Obtained from **4Ec** (462 mg, 1.33 mmol) in 18% yield (84 mg) after column chromatography (CH_2Cl_2–MeOH; 98 : 2), identical (IR, ^{1}H NMR, TLC) to the compound isolated using **method 3a**.

Oxidation of phenyl 2-[2-(3,4-dimethoxyphenoxy)acetyl]-hydrazinecarboxylate 4Ed

From **4Ed** (548 mg, 1.58 mmol), TLC control (CH_2Cl_2–MeOH; 98 : 2) showed a complex mixture from which 2-methoxy [1,4]benzoquinone **24** could be isolated in 12% yield (27 mg) after column chromatography (CH_2Cl_2), as a yellow solid; mp 140–141 °C (lit.,[30] 140 °C); ν_{max}/cm^{-1} 1676, 1648, 1592; δ_H 3.84 (3H, s), 5.95 (1H, s), 6.72 (2H, s); *m*/*z* 138 (M^+, 100%), 123 (12), 108 (90), 82 (38) (Calc. for $C_7H_6O_3$: *M*, 138.0317. Found: M^+, 138.0324).

Methyl 3-oxo-5-phenyl-2,3-dihydro-1*H*-pyrazole-1-carboxylate 26a. From **25a** (500 mg, 2.27 mmol), the title compound was obtained in 45% yield (220 mg) after PTLC (CH_2Cl_2) followed by crystallisation (from CH_2Cl_2–MeOH); mp 155–159 °C; ν_{max}/cm^{-1} 3300, 2200, 1748, 1616, 1595; δ_H (DMSO-d_6) 3.75 (3H, s), 6.00 (1H, s), 7.40 (5H, m), 11.03 (1H, br s) (Calc. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.28; H, 4.68; N, 12.76%).

Methyl 3-oxo-4-phenyl-2,3-dihydro-1*H*-pyrazole-1-carboxylate 27. The mother-liquor from the above crystallisation was evaporated to dryness and the residue was purified by PTLC (same developer as above). The title compound **27** was obtained as a colourless solid in 9% yield (44 mg); mp 191–193 °C (from CH_2Cl_2–MeOH); ν_{max}/cm^{-1} 3300, 2200, 1749, 1617; δ_H (DMSO-

d_6) 3.92 (3H, s), 7.40 (5H, m), 8.54 (1H, s), 11.02 (1H, br s) (Calc. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.38; H, 4.58; N, 12.85%).

Methyl 5-(4-fluorophenyl)-3-oxo-2,3-dihydro-1*H*-pyrazole-1-carboxylate 26b. Following the above procedure, **25b** (500 mg, 2.10 mmol) yielded the title compound in 23% yield (113 mg) after column chromatography (CH_2Cl_2) followed by crystallisation (from CH_2Cl_2–MeOH); mp 175–177 °C; ν_{max}/cm^{-1} 3300, 2200, 1744, 1608; δ_H (DMSO-d_6) 3.71 (3H, s), 6.00 (1H, s), 7.21 (1H, d, *J* 8.6), 7.23 (1H, d, *J* 8.6), 7.49 (1H, d, *J* 8.6), 7.50 (1H, d, *J* 8.6), 10.99 (1H, br s) (Calc. for $C_{11}H_9FN_2O_3$: C, 55.93; H, 3.84; N, 11.86. Found: C, 55.69; H, 4.11; N, 11.73%).

Method 4[8] (Ag_2CO_3 and BF_3·Et_2O or TFA). General procedure

A suspension of Ag_2CO_3 on Celite (5 equiv./mmol bishydrazide), previously azeotropically dried by distillation with benzene, and the substrate in dry benzene (40 cm^3 mmol^{-1}) was heated under reflux (*ca.* 5–8 h) until all the starting material had been consumed (TLC control; CH_2Cl_2–acetone; 85 : 15). The initial yellow colour was replaced by a black precipitate of silver as the reaction proceeded. The mixture was filtered hot over a pad of Celite and the filtrate was treated with either BF_3·Et_2O or TFA (1.0 equiv./mmol bishydrazide). The products were isolated by evaporation of the solution under reduced pressure and the residue thus obtained was purified either by PTLC (CH_2Cl_2–acetone; 85 : 15) or column chromatography.

Compound 12a. A suspension of **4Ba** (100 mg, 0.45 mmol) and Ag_2CO_3 on Celite (1.35 g, 2.25 mmol) in benzene (4.5 cm^3) was heated for 8 h. Work-up subsequent to the addition of BF_3·Et_2O (55 mm^3, 0.45 mmol), as indicated above, gave a residue, which was purified by PTLC to give the title compound in 62% yield (62 mg).

Compounds 11c, 12b. Similarly, compounds **11c** (19.7 mg, 17%) and **12b** (62 mg, 50%) were obtained from **4Bc** (126 mg, 0.50 mmol).

Compound 12d. Obtained in 74% yield (104 mg) from **4Bd** (141 mg, 0.50 mmol).

Compounds 11e, 12e. From **4Be** (142 mg, 0.50 mmol) were obtained products **11e** (17.0 mg, 13%) and **12e** (75 mg, 54%).

Methyl (7,9-dimethoxy-2,8-dioxo-1-azaspiro[4.5]deca-6,9-dien-1-yl)carbamate 11f and compound 12f. Compounds **11f** and **12f** were isolated from **4Bf** (156 mg, 0.50 mmol), in the presence of BF_3·Et_2O, in 47% (69 mg) and 29% yield (45 mg), respectively. Compound **11f** was obtained as a colourless solid; mp 226–228 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3280, 1760, 1720, 1668; δ_H 2.37 (2H, t, *J* 7.8), 2.68 (2H, t, *J* 7.8), 3.70 (6H, s), 3.71 (3H, s), 5.78 (2H, s), 6.61 (1H, br s) (Calc. for $C_{13}H_{16}N_2O_6$: *M*, 296.1008. Found: M$^+$, 296.1016).

Compounds 11f, 12f. Similarly, compounds **11f** (48 mg, 49%) and **12f** (23 mg, 22%) were isolated by PTLC from reaction of **4Bf** (104 mg, 0.33 mmol) with TFA.

Methyl (6-bromo-7,9-dimethoxy-2,8-dioxo-1-azaspiro[4.5]-deca-6,9-dien-1-yl)carbamate 11g and methyl (5-bromo-6,7,8-trimethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12g. Obtained from **4Bg** (200 mg, 0.51 mmol) after PTLC; product **11g** was isolated in 70% yield (134 mg) as a colourless solid; mp 225–230 °C (decomp.) (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3240, 1752, 1712, 1676, 1652; δ_H 2.39 (1H, m), 2.50 (1H, m), 2.73 (2H, m), 3.70 (3H, s), 3.73 (3H, s), 3.90 (3H, s), 6.15 (1H, s), 6.40 (1H, br s) (Calc. for $C_{13}H_{15}BrN_2O_6$: C, 41.62; H, 4.03; N, 7.47. Found: C, 41.41; H, 3.98; N, 7.53%). Product **12g** (12 mg, 6%) crystallised as a colourless solid, mp 155–158 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3250, 1740, 1696; δ_H 2.60 (1H, m), 2.78 (1H, m), 3.95 (1H, m), 3.16 (1H, m), 3.76 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 3.91 (3H, s), 7.37 (1H, br s) (Calc. for $C_{14}H_{17}BrN_2O_6$: *M*, 388.0270. Found: M$^+$, 388.0259).

Dienone–phenol rearrangement of 11e to methyl (6-hydroxy-7-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-1-yl)carbamate 12k. A mixture of **11e** (50 mg, 0.19 mmol), H_2SO_4–HOAc (10 cm^3; 0.5 M) and CH_2Cl_2 (10 cm^3) was heated under reflux (16 h). The organic phase was separated, washed successively with aq. $NaHCO_3$ (5%) and water, and dried. Usual work-up gave a product which was purified by PTLC (CH_2Cl_2–acetone; 8 : 2). The phenol **12k** (46 mg, 91%) had mp 215–218 °C (from acetone); ν_{max}/cm^{-1} 3470, 3170, 1736, 1660; δ_H (CD_3CN) 2.63 (2H, t, *J* 7.3), 2.85 (2H, t, *J* 7.3), 3.71 (3H, s), 3.81 (3H, s), 6.54 (1H, s), 6.63 (1H, s), 6.81 (1H, s), 7.66 (1H, br s) (Calc. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.83; H, 5.18; N, 10.52%).

Methylation of 12k to 12e. The phenol **12k** (25 mg, 0.094 mmol) in MeOH (1 cm^3) was treated with an excess of CH_2N_2 at 0 °C and the solution was kept at this temperature for an additional hour. Evaporation of the solution followed by crystallisation of the residue (from EtOAc–hexane) gave a sample (23 mg, 87%) identical with **12e** in all aspects (mp, TLC, IR).

Preparation of *N*-amino derivatives of quinolones, benzazepinones and benzazocinones from the corresponding phenyl carbamates 12h, 15c and 18b. General procedure

A mixture of the appropriate phenyl carbamate and 10% aq. KOH (30 equiv./mmol carbamate) in 1,4-dioxane (15 cm^3/mmol carbamate) was kept at rt (6–15 h) with stirring under nitrogen. It was then neutralised with 5% aq. HCl, diluted with water, and extracted with CH_2Cl_2. The extract was washed with brine and dried. Evaporation of the solution and purification of the resulting residue by PTLC gave the compounds described below.

1-Amino-6,8-dimethoxy-3,4-dihydroquinolin-2(1*H*)-one 13b. Obtained from phenyl carbamate **12h** (100 mg, 0.29 mmol) after 15 h; purification by PTLC (CH_2Cl_2–MeOH; 95 : 5) gave the title compound in 96% yield (62 mg); mp 118–120 °C (from CH_2Cl_2–hexane); ν_{max}/cm^{-1} 3350, 1656; δ_H 2.63 (2H, t, *J* 6.9), 2.84 (2H, t, *J* 6.9), 3.79 (3H, s), 3.88 (3H, s), 5.37 (2H, br s), 6.33 (1H, d, *J* 2.4), 6.43 (1H, d, *J* 2.4) (Calc. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.14; H, 6.02; N, 12.36%).

1-Amino-7-methoxy-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one 17a. Obtained from **15c** (130 mg, 0.40 mmol) after 6 h (TLC control; AcOEt–hexane; 7 : 3). Work-up followed by PTLC (AcOEt–hexane; 7 : 3) yielded the title compound in 50% yield (41 mg), as a pale pink solid; mp 117–117.5 °C (from AcOEt–hexane); ν_{max}/cm^{-1} 3330, 3210, 1644; δ_H 2.20 (2H, quintet, *J* 7.1), 2.34 (2H, t, *J* 7.1), 2.68 (2H, t, *J* 7.1), 3.82 (3H, s), 4.73 (2H, s, exchangeable with D_2O), 6.71 (1H, d, *J* 2.8), 6.85 (1H, dd, *J* 8.8, *J* 2.8), 7.40 (1H, d, *J* 8.8); *m*/*z* 206 (M$^+$, 100%), 191 (3), 178 (22), 163 (63), 162 (66), 135 (38), 91 (28) (Calc. for $C_{11}H_{14}N_2O_2$: *M*, 206.1055. Found: M$^+$, 206.1068).

1-Amino-8-methoxy-3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one 19a. Obtained from **18b** (55 mg, 0.16 mmol) after 6 h (TLC control; CH_2Cl_2–MeOH; 95 : 5). Work-up and purification by PTLC (AcOEt–hexane; 7 : 3) yielded the title compound in 81% yield (28.7 mg) as a colourless oil that crystallised on storage; mp 82–93 °C; ν_{max}(film)/cm^{-1} 3305, 3195, 1644; δ_H 1.40 (1H, m), 1.77 (1H, m), 1.93 (1H, m), 2.03 (1H, m), 2.13 (1H, m), 2.34 (1H, m), 2.37 (1H, m), 2.76 (1H, m), 3.82 (3H, s), 4.83 (2H, s,

exchangeable with D_2O), 6.74 (1H, d, *J* 2.9), 6.82 (1H, dd, *J* 8.8, *J* 2.9), 7.30 (1H, d, *J* 8.8); *m*/*z* 220 (M^+, 71%), 205 (50), 149 (100), 91 (25), 57 (75) (Calc. for $C_{12}H_{16}N_2O_2$: *M*, 220.1212. Found: M^+, 220.1211).

1-Amino-3,4-dihydroquinolin-2(1*H*)-one 13a. A mixture of **12a** (60 mg, 0.27 mmol) and conc. hydrochloric acid was heated under reflux (24 h). Excess of acid was removed under reduced pressure and the resulting residue on crystallisation (from water) gave the title compound **13a** (42 mg, 96%), mp 139–141 °C (lit.,[12] 143.5–144 °C).

Deamination of *N*-amino derivatives of quinolones, benzazepinones and benzazocinones. Method A. General procedure

To the appropriate *N*-amino derivative in acetic acid (20 cm^3/mmol *N*-amino compound) at rt was added, with stirring, sodium nitrite (1.5 equiv./mmol *N*-amino compound) in water (7.5 cm^3/mmol $NaNO_2$) and the mixture was stirred for an additional hour; TLC control (AcOEt–hexane; 7 : 3) showed the completion of the reaction. The mixture was then diluted with water, basified with 10% aq. NaOH, and extracted with CH_2Cl_2; the extract was washed with water and dried. Evaporation of the solution furnished a solid, which was purified by PTLC to give the compounds described below.

6,8-Dimethoxy-3,4-dihydroquinolin-2(1*H*)-one 13c. Obtained from the amine **13b** (20 mg, 0.09 mmol) in 75% yield (13.9 mg) after PTLC (Et_2O–hexane; 8 : 2); mp 104–105 °C; no depression in the mp was observed on admixture with an authentic sample (mp 103–105 °C) prepared by the literature procedure.[10] In addition the IR and ^1H NMR spectra of the two samples were identical.

7-Methoxy-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one 17b. Obtained from **17a** (30 mg, 0.145 mmol) as a colourless solid in 61% yield (16.8 mg) after PTLC (AcOEt–hexane; 7 : 3); mp 143–144 °C (lit.,[13] 141–142 °C); ν_{max}/cm^{-1} 3175, 1674; δ_H 2.21 (2H, quintet, *J* 7.1), 2.33 (2H, t, *J* 7.1), 2.77 (2H, t, *J* 7.1), 3.81 (3H, s), 6.79–6.73 (2H, m), 6.89 (1H, d, *J* 8.2), 7.06 (1H, br s, exchangeable with D_2O); *m*/*z* 191 (M^+, 59%), 162 (28), 148 (13), 136 (100).

8-Methoxy-3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one 19b. Obtained from **19a** (19.8 mg, 0.09 mmol) as a colourless solid in 80% yield (14.8 mg) after PTLC (AcOEt–hexane; 7 : 3); mp 144–146 °C (lit.,[14] 145–146 °C); ν_{max}/cm^{-1} 3200, 1666; δ_H 1.43 (1H, m), 2.00–1.65 (2H, m), 2.42–2.00 (3H, m), 2.91–2.42 (2H, m), 3.82 (3H, s), 6.75 (1H, dd, *J* 8.6, *J* 2.8), 6.79 (1H, d, *J* 2.8), 7.00 (1H, d, *J* 8.6), 7.21 (1H, br s, exchangeable with D_2O); *m*/*z* 205 (M^+, 100%), 162 (28), 149 (61), 136 (58), 57 (37).

Method B

The amine **13b** (20 mg, 0.09 mmol) and *N*-nitrosodiphenylamine (17.8 mg, 0.09 mmol) were heated in benzene (2 cm^3) under reflux for 3 h. The residue obtained on evaporation of the solution was purified by PTLC (Et_2O–hexane; 8 : 2) to give the deaminated product **13c** (13.9 mg, 75%), identical with that obtained by *method A*.

Supplementary reactions

Carbamate 12d from amine 13b. A suspension of the amine **13b** (10 mg, 0.045 mmol) and $NaHCO_3$ (4.9 mg, 0.058 mmol) in CH_2Cl_2 (2 cm^3) was treated with methyl chloroformate (5.1 mm^3, 0.066 mmol) and the mixture was stirred at rt for 14 h. Work-up in the usual manner led to a solid, which as purified by crystallisation from CH_2Cl_2–hexane to furnish a product (10 mg, 79%) identical in all respects (IR, ^1H NMR, TLC, mp and mixed mp) with carbamate **12d**.

Carbamate 12h from amine 13b. Similarly, the amine **13b** (10 mg, 0.045 mmol) provided carbamate **12h** on acylation with phenyl chloroformate in nearly quantitative yield.

Acknowledgements

We thank Fundação para a Ciência e a Tecnologia (Portugal) for partial financial support. Our thanks are also due to Dr S. N. Swami (Pfizer, UK) and Prof. W. B. Motherwell (University College, London, UK) for their interest shown. Two of us (D.-T. S. C. and I. M.) are grateful for the awards of research fellowships.

References

1 O. Diels, *Justus Liebig's Ann. Chem.*, 1922, **429**, 1; R. B. Carlin and M. S. Moores, *J. Am. Chem. Soc.*, 1962, **84**, 4107; S. H. Schroeter, *J. Org. Chem.*, 1969, **34**, 4012.
2 I. Zaltsgendler, Y. Leblanc and M. A. Bernstein, *Tetrahedron Lett.*, 1993, **34**, 2441.
3 R. Lenarsic, M. Kocevar and S. Polanc, *J. Org. Chem.*, 1999, **64**, 2558.
4 (*a*) D.-T. Clemente, A. M. Lobo, S. Prabhakar and M. J. Marcelo-Curto, *Tetrahedron Lett.*, 1994, **35**, 2043; for two similar approaches to *N*-alkoxydihydroquinolin-2-ones involving *N*-alkoxy-*N*-acylnitrenium ions as reactive intermediates see:; (*b*) S. A. Glover, A. Goosen, C. W. McCleland and J. L. Schoonraad, *Tetrahedron*, 1987, **43**, 2577; (*c*) M. Kawase, T. Kitamura and Y. Kikugawa, *J. Org. Chem.*, 1989, **54**, 3394.
5 A preliminary account of this work was presented at the 1st Organic Chemistry Division Meeting of the Portuguese Chemical Society, Braga, July, 1995.
6 L. A. Carpino, P. H. Terry and P. J. Crowley, *J. Org. Chem.*, 1961, **26**, 3673.
7 R. M. Moriarty, I. Prakash and R. Penmasta, *Synth. Commun.*, 1987, **17**, 409.
8 M. Fetizon, M. Golfier, R. Milcent and I. Papadakis, *Tetrahedron*, 1975, **31**, 165.
9 C. W. Bird, *J. Chem. Soc.*, 1963, 674.
10 R. S. Mali and V. J. Yadav, *Synthesis*, 1984, 862.
11 C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 1969, 756.
12 H. E. Baumgarten, P. L. Creger and R. L. Zey, *J. Am. Chem. Soc.*, 1960, **82**, 3977.
13 M. Tomita, S. Minami and S. Uyeo, *J. Chem. Soc. C*, 1969, 183.
14 Y. Sawa, T. Kato, T. Masuda, M. Hori and H. Fujimura, *Chem. Pharm. Bull.*, 1975, **23**, 1917.
15 E. Fahr and H. Lind, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 372.
16 R. Zey, *J. Heterocycl. Chem.*, 1987, **24**, 1261.
17 S. E. Denmark. *Nazarov and Related Cationic Cyclizations*, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, pp. 751–784.
18 T. Curtius and J. Boetzelen, *J. Prakt. Chem.* 1900, [2], **64**, 312 (*Beilstein*, H **9**, 446).
19 J. J. Ares and R. J. Messier, *J. Heterocycl. Chem.*, 1991, **28**, 1197.
20 J. Shavel Jr., F. Leonard, F. H. McMillan and J. A. King, *J. Am. Pharm. Assoc.*, 1953, **42**, 402 (*Chem. Abstr.*, 1954, **48**, 9325e).
21 W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, 1955, **9**, 1498.
22 K. Tanaka, K. Matsuo, A. Nakanashi, T. Hatano, H. Izeki, Y. Ishida and W. Mori, *Chem. Pharm. Bull.*, 1983, **31**, 2810.
23 S. Kakimoto, I. Sekikawa and K. Yamamoto, *J. Pharm. Soc. Jpn.*, 1955, **75**, 353 (*Chem. Abstr.*, 1956, **50**, 1663d).
24 H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, *J. Am. Chem. Soc.*, 1953, **75**, 1933.
25 P. Pfeiffer and E. Heinrich, *J. Prakt. Chem.*, 1940, **156**, 241 (*Chem. Abstr.*, 1941, **35**, 1793[1]).
26 (*a*) O. Diels and P. Fritzsche, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 3018; (*b*) F. Eloy and C. Moussebois, *Bull. Soc. Chim. Belg.*, 1959, **68**, 409 (*Chem. Abstr.*, 1960, **54**, 3179g).
27 (*a*) T. Horaguchi, E. Hasegawa, T. Shimizu, K. Tanemura and T. Susuki, *J. Heterocycl. Chem.*, 1989, **26**, 365; (*b*) P. D. Gardner, W. J. Horton, G. Thompson and R. R. Twelves, *J. Am. Chem. Soc.*, 1952, **74**, 5527.
28 A. T. Nielson, *J. Heterocycl. Chem.*, 1975, **12**, 1233.
29 H. W. Thompson, *J. Chem. Soc.*, 1932, 2310 (*Chem. Abstr.*, 1932, **26**, 5941).
30 R. Willstätter and F. Müller, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 2171.