Fluoride ion-induced cyclization of *o*-[bis(trimethylsilyl)methyl]-*N*-acylbenzamide derivatives. New efficient synthesis of 2,3-differentially substituted 1(2*H*)-isoquinolones

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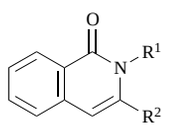
A wide variety of 2-alkyl-3-alkyl, -3-aryl and -3-heteroaryl-1(2*H*)-isoquinolones have been obtained by fluoride ion-induced intramolecular alkenation of *o*-[bis(trimethylsilyl)methyl]-*N*-acylbenzamide derivatives.

Introduction

It is well known that the 1(2*H*)-isoquinolone skeleton constitutes the framework of a wide array of plant alkaloids and drugs and that many naturally occurring or synthetic compounds based on the 1(2*H*)-isoquinolone structure exhibit great diversity in their biological activities.[1] Accordingly, synthesis of this heterobicyclic system has developed remarkably in recent years, and this is obviously linked to the synthetic potential of compounds comprising the 1-oxodihydroisoquinoline unit. Indeed, such compounds may be regarded as synthetic precursors of dihydro- and tetrahydro-isoquinoline derivatives and the importance of isoquinoline derivatives, many of which are pharmacologically active, as intermediates in the synthesis of natural products and in medicinal chemistry is particularly well documented.[2]

As part of our continuing work in this field we embarked some time ago on a programme aimed at developing new approaches to the 1(2*H*)-isoquinolone skeleton allowing incorporation of different substitution patterns at the 3- and 4-position of this heterocyclic nucleus.[3] Examination of literature data revealed the lack of general methods for the construction of 3-substituted-1(2*H*)-isoquinolones **1** and demonstrated that existing synthetic strategies are strongly influenced by the nature of the substituents linked to the six-membered heterocyclic moiety. Thus the main synthetic routes to 2-alkyl-3-aryl-1(2*H*)-isoquinolones **1** (R^2 = aryl) involve the mercury-mediated cyclization of *N*-alkylimines derived from stilbenecarbaldehydes,[4] the reaction of 2′-carboxy-2-hydroxydeoxybenzoin with primary amines,[5] the treatment of homophthalic anhydride with imidoyl chlorides[6] or the cycloaddition of benzyne to 5-phenylpyrroline-2,3-dione.[7] They are also accessible by different photochemical processes which include the electrocyclization of aromatic enamides,[3a] the photochemically induced arylation of chloroisoquinolones[8] and the $S_{RN}1$ reaction of *o*-halogenobenzamides with ketone enolates.[9] They may also be derived from the oxidation of the corresponding 3,4-dihydroisoquinolones,[10] 1,2-dihydroisoquinolines[11] or the quaternary salts of quinoline derivatives.[10,11a] However none of these methods permits the introduction of a great diversity of aromatic and even less of heteroaromatic units onto the six-membered heterocyclic moiety. On the other hand, 2,3-dialkyl-1(2*H*)-isoquinolones **1** (R^2 = alkyl) are only accessible by a few special methods such as *ortho*-thallation and subsequent palladium-promoted olefination of benzamide derivatives,[12] palladium-induced cyclization of 2-alkyl-*N*-alkylbenzamides[13] or substitution of the oxygen atom of isocoumarins by primary amines.[14] Finally, the most attractive route so far reported, which enables access to either 3-alkyl or -aryl derivatives equally well, relies upon the reaction of dilithiated *N*,2-dimethylbenzamides with alkyl and arylcarboxylic acid derivatives.[15]



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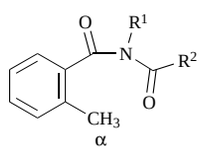

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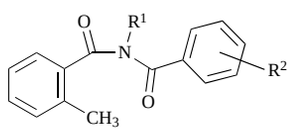
R^1 = alkyl, R^2 = alkyl, aryl, heteroaryl



R^2 = *o*-DMG, Hal, CF_3

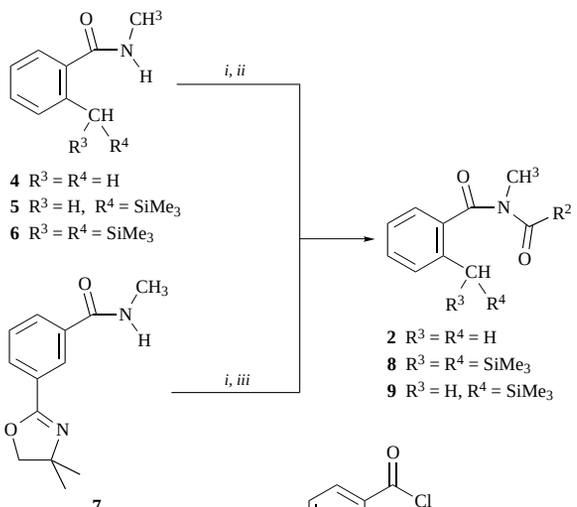
3

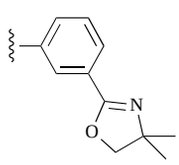
A few years ago we proposed a new methodology for the construction of this fused heterocyclic framework which hinges upon the lithiated base-induced annulation of a variety of *N*-acyl-*o*-toluamide derivatives **2**.[16] In this new cyclization process the *N*-acylbenzamide moiety plays a dual role. Indeed, it facilitates deprotonation of the adjacent benzylic α-position, an unprecedented phenomenon, and consequently enriches the repertoire of carboxylic acid derivatives promoting lateral lithiation reactions.[17] Furthermore, it is a partner in the annulation process since the resulting benzylic carbanion undergoes cyclization by intramolecular attack on the sufficiently electrophilic terminal *N*-acyl function.[18] This new concept has been successfully applied to the synthesis of 3-styryl-1(2*H*)-isoquinolones **1** (R^2 = styryl) from appropriately designed *N*-acyl-*o*-toluamides **2** (R^2 = styryl). However, attempts to extend the scope of these reactions to include the preparation of 3-alkyl and 3-heteroaryl derivatives **1** (R^2 = alkyl or heteroaryl respectively) were unrewarding, probably due to the presence of enolizable groups bearing the imidoyl moiety or to sites that can be easily deprotonated on the heterocyclic nucleus. On the other hand, even though the potential of this process has been demonstrated for the elaboration of models incorporating aromatic hydrocarbon entities, it was anticipated that problems could also arise with compounds **3** possessing on the pendant aryl unit either *ortho*-directing metallation groups (*o*-DMG)[19] at C-3 or substituents at C-4 which are known to play strong *meta*-acidifying effects, such as halogen or trifluoromethyl groups.[20] For these compounds **3** indeed lithiated base-induced deprotonation may be directed to the *ortho*-position in preference to the

benzylic α-position due to the cooperative effect of the 1,3-interrelated *o*-DMG in promoting metallation at their common *ortho* 'in-between' site and to additional inductive factors, respectively. With the aim of delineating the scope of our previously reported procedure we first examined the base-induced cyclization of the potentially problematic *N*-acyl-*o*-toluamides **2a–d**.

Results and discussion

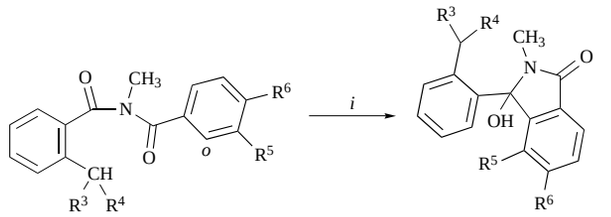
Compounds **2a–d** were easily obtained by deprotonation with butyllithium of *N*,2-dimethylbenzamide **4** and subsequent treatment with the appropriate acyl chlorides **10a–d** (Scheme 1).



2, 8, 9	R^2	8	R^2
a	3,4-$(OCH_2O)C_6H_3$	**g**	*m*-$(Me_2NSO_2)C_6H_4$
b	*m*-ClC_6H_4	**h**	
c	*p*-ClC_6H_4		
d	*p*-$CF_3C_6H_4$	**i**	2-furyl
e	Ph	**j**	cyclohexyl
f	3,4-$(MeO)_2C_6H_3$	**k**	Pr^i

Scheme 1 *Reagents and conditions:* i, BuLi, THF, 0 °C; ii, R^2COCl **10a–g**, **10i–k**, THF, −78 °C to room temp.; iii, *o*-[bis(trimethylsilyl)methyl]benzoyl chloride **11**, THF, −78 °C to room temp.

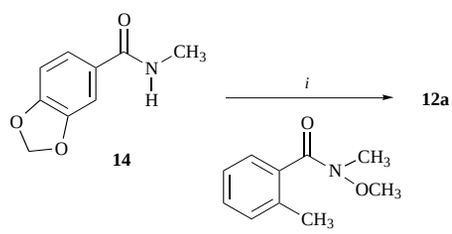
Exposure of the diacylamines **2a–d** to lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C led to the rapid disappearance of the parent compounds and to the exclusive and efficient formation of the phthalimidine derivatives with an aminal function **12a–d** (Scheme 2). The structures of compounds **12a–d** were mainly determined from IR spectra which exhibit stretching bands at 3245 and 1673 cm^{-1} characteristic of the aminal and carbonyl lactam functions. The ^1H NMR spectra further indicate the survival of the two methyl groups† at δ 2.52 (NCH_3) and 1.62 ($ArCH_3$) and the presence of a hydroxy function at δ 4.80 (deuterium exchanged). ^{13}C NMR distortionless enhancement by polarization transfer (DEPT) experiments confirm the presence of the aminal quaternary carbon centre at



	R^5	R^6
a	OCH_2O	
b	Cl	H
c	H	Cl
d	H	CF_3

Scheme 2 *Reagents and conditions:* i, LDA, THF, −30 °C, 30 min

δ_C 90.1. The structure of compound **12a** was further confirmed by the independent and unambiguous synthesis depicted in Scheme 3. Thus the piperonylic carboxamide **14** was treated



Scheme 3 *Reagents and conditions:* i, BuLi (2 mol equiv.), THF, 0 °C; then *N*-methoxy-*N*-methyl-*o*-toluamide **15**, THF, room temp., 1 h

with butyllithium (2 mol equiv.) and efficiently converted into the bis-(*N*- and *C*-*ortho*)-lithiated derivative (confirmed by D_2O quench).[21c] Subsequent treatment of the lithiated species with *N*-methoxy-*N*-methyl-*o*-toluamide **15** (Weinreb amide)[22] afforded the cyclocondensed product **12a** quantitatively. Although disappointing from a synthetic point of view‡ these reactions deserve some comment. Compounds **2a–d**, on treatment with LDA, give products resulting from exclusive *ortho*-deprotonation and subsequent intramolecular attack of the aryllithium species on the terminal acyl moiety. Now, in competitive processes involving *ortho versus* adjacent benzylic-directed lithiation of *N*,*N*-disubstituted-2-alkylbenzamides, *ortho*-lithiation is favoured over α-lithiation only with sterically hindered 2-alkyl groups[23] (*i.e.* isopropyl) and with models where steric congestion renders the α-proton inaccessible.[24] The exclusive deprotonation of the *ortho* site in the eastern part of the models **2a–d** rather than lateral α-lithiation promoted by the *N*-acylcarboxamide group of the opposite part clearly indicates the predominant influence of the cooperative effects in 1,3-related *o*-DMG and 1,4-DMG-halogen or CF_3 combinations in compounds **2a**,**b** and **2c**,**d**, respectively, even though methylenedioxy and chlorine groups only rank modestly in the hierarchy of *o*-DMGs.[19a] Another noteworthy feature is that the annulation is performed by making use of LDA as the base. Lithium dialkylamides[25] are generally of insufficient kinetic basicity for *ortho*-directed metallation reactions. However, recent reports that aromatic and heteroaromatic systems can be deprotonated with these bases, provided that the (hetero)aryl lithiated species can be trapped *in situ*,[26] afford justification for

† Values given for compound **12a**.

‡ *N*-Benzyl-substituted hydroxylactams have been used as precursors of tetracyclic indanones,[21a] of spiroindane[21b] and *o*-aroylbenzoic acid derivatives,[21c] and of 3,4-diarylisoquinoline derivatives.[21d]

the formation of the diversely substituted phthalimidine derivatives **12**. Owing to the competition between *ortho*- and α-deprotonation, which sets a limit to the applicability of the method for the elaboration of varied 2,3-disubstituted-1(2*H*)-isoquinolinones **1**, alteration of the strategy was inevitable. Owing to the erratic nature of the metallation process it was imperative to develop a methodology which forces metallation to occur at the alternative benzylic site and which tolerates a wide array of substitution patterns tethering the *N*-acyl moiety.

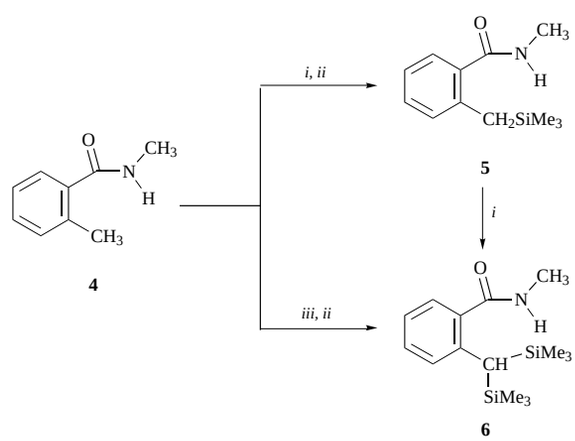
The Peterson reaction has proved to be one of the best methodologies for carbonyl olefination.[27] It conceptually involves the reaction between a carbonyl component and an α-silyl carbanion followed by elimination of the resulting β-hydroxysilane. This olefination procedure is particularly useful in the synthesis of functionalized and strained alkenes[28] and its application to heterocyclic synthesis has been reviewed.[27a] The present work originated with the following premises: (i) α,α-disilyl-*o*-toluamide should be easily derived by metallation of compound **4**,[17,29] thus permitting the incorporation of a silyl functionality into the parent diacylamines **2**, (ii) the formation of α-silyl carbanions may be promoted by fluoride ion attack on organosilicon compounds bearing two trialkylsilyl units on the same carbon atom.[30] This carbodesilylation is an effective way for the transfer of α-silyl carbanions to electrophilic centres, especially carbonyl functions.[31] The final inspiration of this work came from the possibility that this new C–C double-bond-forming process could be applied intramolecularly to systems incorporating base-sensitive electrophilic centres.[31] With these ideas in mind we undertook a study of the fluoride ion-promoted reaction of a large and significant variety of *N*-acyl-*N*-methyl-α,α-bis(trimethylsilyl)-*o*-toluamides **8a**–**k** bearing a pendant alkyl or (hetero)aromatic unit, **8j**,**k** and **8e**,**i**, respectively, and also aromatic ring systems carrying in addition diverse functional groups which disfavour the α-lateral lithiation approach (**8a**–**d** and **8f**–**h**). In the list of functionalities likely to promote undesirable *ortho*-metallation and yet liable to confer interesting properties in many aspects to the targeted annulated products the moderate methylenedioxy, dimethoxy and strong dialkylsulfonamido and oxazolino *ortho*-directing groups[19b] occupy a place of choice. Indeed the presence of dimethoxy- and methylenedioxy-aryl units connected to the 3-position of the isocarbostyril framework is observed in a wide range of alkaloids, namely in the benzo[*c*]phenanthridinone series.[32] Several patents emphasizing the pharmaceutical properties of isoquinolones bearing sulfinyl and sulfonyl substituents have been registered.[33] Finally, the oxazoline nucleus may serve as a versatile handle for further synthetic manipulation since it can be converted into a wide variety of functional groups including acids, amides, nitriles, alcohols and aldehydes.[34]

Initially the requisite disilylated toluamide **6** was prepared in high yield from the *o*-toluamide **4** either *via* the monosilylated derivative **5**[35] or directly in a one-pot procedure (Scheme 4). Deprotonation of the NH carboxamide function of product **6** with butyllithium followed by addition of the appropriate acid chlorides **10a**–**g**, **10i**–**k** proceeded uneventfully and this protocol delivered the different *N*-acyl-*o*-toluamide derivatives **8a**–**k** incorporating the disilyl functionality (Scheme 1). Owing to unpredictable difficulties associated with the synthesis of the benzoic acid chloride bearing the oxazoline moiety, compound **10h**, an alternative method was developed for the elaboration of compound **8h**. Thus the disilyl functionality was inserted *via o*-[bis(trimethylsilyl)methyl]benzoyl chloride **11**[36] (Scheme 1) which was treated with the anion of the secondary amide **7** obtained by the three-step sequence outlined in Scheme 5. Compounds **8a**–**k** were subsequently subjected to a fluoride ion source to induce benzylic carbodesilylation. Exploration of a variety of reagents, methods and conditions including CsF in dimethylformamide (DMF),[38] tris(diethylamino)sulfonium fluoride (TASF) in DMF,[39] KF-crown ether in THF or CH_3CN[40] led to the use of 'anhydrous' tetrabutylammonium fluoride (TBAF) in THF[41] as the initiator. As reported in Table 1 the reaction proceeded smoothly at room temperature, giving the expected cyclization products **1a**–**k** with moderate to high yields. This anionic carboannulation provides rapid assemblage of the 3-substituted isoquinolone framework. Since it proceeds under mild and almost neutral conditions *via* metal-free carbanionic species the reaction can be applied to compounds possessing acid- or base-sensitive functionalities such as oxazolino, heteroaromatic and alkyl groups.

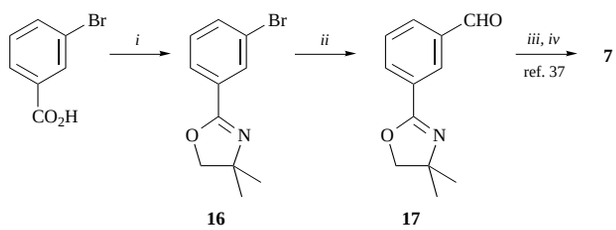
Table 1 Hydroxyphthalimidines and 2,3-disubstituted-1(2*H*)-isoquinolones

N-acyl-*o*-toluamide	Method[a]	Product (% yield)[b]
2a	A	**12a** (91)
2b	A	**12b** (88)
2c	A	**12c** (87)
2d	A	**12d** (78)
8a	B	**1a** (76)
8b	B	**1b** (75)
8c	B	**1c** (75)
8d	B	**1d** (72)
8e	B	**1e** (84)
	C	**1e** (56) + **2e** (14)
	D	**1e** (61) + **2e** (16)
	E	**1e** (64) + **2e** (15)
8f	B	**1f** (75)
8g	B	**1g** (66)
8h	B	**1h** (28)
8i	B	**1i** (59)
8j	B	**1j** (48)
8k	B	**1k** (42)
9a	A	**13a** (88)
9c	A	**13c** (79)

[a] Method: (A) LDA, THF, −30 °C; (B) Bu_4NF, THF, room temp., 5 min. Traces (yield < 5%) of desilylated *N*-acyl-*o*-toluamides were detected in the crude reaction product; (C) CsF, DMF, room temp., 0.5 h; (D) TASF, DMF, room temp., 1 h; (E) KF–crown ether, THF, 5 h. [b] Yields were evaluated before recrystallization.

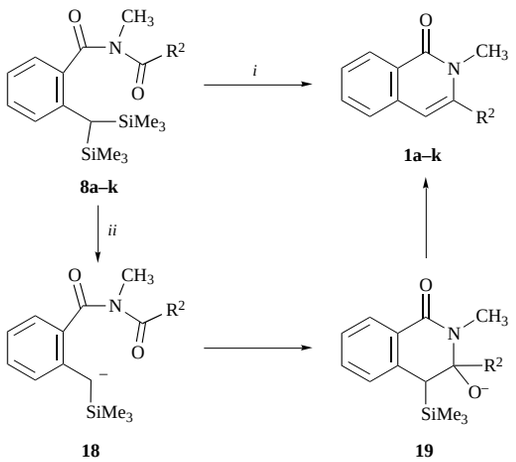


Scheme 4 *Reagents and conditions:* i, BuLi (2 mol equiv.), THF, −78 °C; then Me_3SiCl (2 mol equiv.); ii, H_3O^+; iii, BuLi (2 mol equiv.), THF, −78 °C; then Me_3SiCl (2 mol equiv.), −78 °C; then BuLi (1 mol equiv.), Me_3SiCl (1 mol equiv.), −78 °C



Scheme 5 *Reagents and conditions:* i. $SOCl_2$, 2-amino-2-methylpropan-1-ol; then $SOCl_2$; ii, BuLi, THF, −100 °C; then DMF, THF; iii, NBS, AIBN, CCl_4, reflux; iv, CH_3NH_2, 0 °C

From a mechanistic point of view we can assume that the annulation is initiated by fluoride ion to generate the α-silyl carbanion **18** which then reacts with the terminal carbonyl moiety to give the corresponding β-silylethoxide **19**. Further elimination of trimethylsilylalkoxide gives rise to the desired 2-methyl-3-alkyl, -3-aryl and -3-heteroaryl-1(2*H*)-isoquinolones **1a–k** (Scheme 6). Particularly noteworthy is the fact that



Scheme 6 *Reagents and conditions:* i, Bu_4NF, THF, room temp., 5 min; ii, F^-

attempts to generate the α-silylbenzylic carbanionic species **18** by metallation[42] of monosilylated *N*-acylamines **9**, readily accessible (Scheme 1) from *N*-methyl-α-trimethylsilyl-*o*-toluamide **5**, proved unfruitful. Indeed despite the enhanced acidity of the α-hydrogen of organosilanes relative to hydrogens of the corresponding hydrocarbons,[43] the silyl functionality is not affected by basic treatment of these compounds, as exemplified by the exclusive and efficient formation of the hydroxyphthalimidines **13a**,**c** (Scheme 2) upon treatment of monosilylated *N*-acylamides **9a**,**c** with LDA.

The reaction reported here represents therefore a tactically and conceptually new approach to the construction of the isocarbostyril framework with different substitution patterns at the 3-position of the heterocyclic nucleus. Since this process is carried out under essentially neutral conditions it complements the existent methodology based on the metallation approach and consequently is valuable for the preparation of substituted systems that cannot tolerate strongly basic conditions. These TBAF-induced desilylative cyclizations, which allow the survival of organic functions, represent a new development of the modified Peterson reaction and undoubtedly deserve further attention. The efficiency and the versatility of this intramolecular process invite futher use of this tactic for the construction of other heterocyclic frameworks.

Experimental

Mp determinations were carried out on a Reichert-Thermopan apparatus and are uncorrected. IR absorption spectra were run on a Perkin-Elmer 881 spectrometer. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, on a Bruker AM 300 spectrometer, as solutions in deuteriochloroform. Chemical shifts are referenced to tetramethylsilane and *J*-values are given in Hz and rounded to the nearest 0.1 Hz. Mass spectral analyses were performed on a Ribermag 10-10 mass spectrometer. Elemental analyses were determined by the CNRS microanalysis centre. For flash chromatography, Merck silica gel 60 (230–400 mesh ASTM) was used. THF was freshly distilled over $LiAlH_4$, and diisopropylamine over CaH_2. Dry glassware for moisture-sensitive reactions was obtained by oven-drying and assembly under Ar. An inert atmosphere was obtained with a stream of dry Ar and glassware equipped with rubber septa; transfer of reagents was performed by syringe or cannula techniques. Commercial butyllithium in hexanes (1.6 mol dm^{-3}) was titrated just before use.[44] Extracts were dried over $MgSO_4$.

Compound **5** was prepared following the reported experimental procedure.[35]

2-[Bis(trimethylsilyl)methyl]-*N*-methylbenzamide 6

A solution of butyllithium (20 mmol) was added slowly to a solution of *N*,2-dimethylbenzamide **4** (1.49 g, 10 mmol) in anhydrous THF (40 cm^3) under a stream of Ar at −78 °C. The mixture was stirred for 0.5 h at this temperature after which a solution of Me_3SiCl (2.22 g, 20 mmol) in THF (20 cm^3) was slowly transferred by way of a cannula. The mixture was stirred at −78 °C for 1 h. Butyllithium (10 mmol) was then added dropwise by way of a syringe to the mixture at −78 °C and the mixture was stirred at this temperature for an additional 0.5 h. Further solution of Me_3SiCl (1.11 g, 10 mmol) in THF (10 cm^3) was subsequently added, and the mixture was slowly warmed to room temperature and finally hydrolysed with dil. HCl (10%; 30 cm^3). The aqueous layer was extracted twice with CH_2Cl_2 (2 × 30 cm^3) and ethyl acetate (20 cm^3). The combined organic extracts were washed with brine, then dried. Removal of the solvents afforded a solid, which was finally purified by recrystallization from hexane–toluene to give *title compound* **6** (2.6 g, 89%), mp 158–159 °C (Found: C, 61.1; H, 9.5; N, 5.0; Si, 19.4. $C_{15}H_{27}NOSi_2$ requires C, 61.4; H, 9.3; N, 4.8; Si, 19.1%); δ_H 0.01 (18 H, s), 2.41 (1 H, s), 2.94 (3 H, d, *J* 4.9), 5.69 (1 H, br s), 7.02 (2 H, m) and 7.24 (2 H, m); δ_C 171.3 (CO), 142.6, 135.8, 129.3, 129.2, 127.0, 123.0, 26.6, 24.1 and 0.3; *m*/*z* 293 (M^+, 14%), 278 (88), 206 (50) and 73 (100); ν_{max}/cm^{-1} 3292 (NH) and 1631 (CO).

4,4-Dimethyl-2-[3-(*N*-methylcarbamoyl)phenyl]-4,5-dihydrooxazole 7

Compound **7** was prepared according to the following procedure. 3-Bromobenzoic acid was initially converted into 2-(3-bromophenyl)-4,4-dimethyl-4,5-dihydrooxazole **16** by adapting a previously reported general procedure.[45] To a solution of compound **16** (1 g, 3.9 mmol) in anhydrous THF (30 cm^3) cooled at −100 °C was added a solution of butyllithium (4.3 mmol). The mixture was stirred at −100 °C for 15 min and then was treated with a solution of DMF (1.45 g, 20 mmol) in THF (3 cm^3). The mixture was warmed to room temperature, water (50 cm^3) was added and the aqueous layer was extracted with diethyl ether (2 × 30 cm^3). The organic layer was washed successively with water and brine and finally dried over $MgSO_4$. After removal of the solvent the product **17** was purified by flash chromatography using ethyl acetate–hexane (1:1) as eluent and finally was recrystallized from hexane–toluene (0.52 g, 65%). Compound **7** was obtained from aldehyde **17** by applying a recently described procedure[37] for the conversion of an aromatic aldehyde into the corresponding carboxamide.

2-(3-*Bromophenyl*)-4,4-*dimethyl*-4,5-*dihydrooxazole* **16**. Pale yellow crystals, mp 43–44 °C (Found: C, 52.2; H, 4.6; N, 5.3. $C_{11}H_{12}BrNO$ requires C, 52.0; H, 4.75; N, 5.5%); δ_H 1.26 (6 H, s), 3.92 (2 H, s), 7.14 (1 H, m), 7.46 (1 H, d, *J* 7.6), 7.74 (1 H, d, *J* 7.6) and 8.01 (1 H, s).

2-(3-*Formylphenyl*)-4,4-*dimethyl*-4,5-*dihydrooxazole* **17**. Crystals, mp 81–82 °C (Found: C, 70.7; H, 6.7; N, 7.2. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); δ_H 1.24 (6 H, s), 4.08 (2 H, s), 7.49 (1 H, t, *J* 7.7), 7.81 (1 H, dt, *J* 1.4 and 7.6), 8.08 (1 H, dt, *J* 1.4 and 7.6), 8.35 (1 H, t, *J* 1.4) and 9.98 (1 H, s).

4,4-*Dimethyl*-2-[3-(*methylcarbamoyl*)*phenyl*]-4,5-*dihydrooxazole* **7**. Fawn crystals, mp 106–107 °C (Found: C, 66.9; H, 7.0; N, 12.4. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.1%); δ_H 1.15 (6 H, s), 2.78 (3 H, d, *J* 4.9), 3.88 (2 H, s), 7.21 (1 H, t, *J* 7.7), 7.54 (1 H, d, *J* 4.9), 7.78 (2 H, dt, 2.1 and 7.7) and 8.16 (1 H, t, *J* 2.1).

General procedure for the synthesis of the *N*-acyl-*o*-toluamide derivatives 2a–d, 8a–k and 9a,c

The *N*-lithiated derivatives of the secondary toluamides **4**, **5**, **6**, **7** were prepared by the dropwise addition of butyllithium (21 mmol) to a stirred solution of amide **4**, **5**, **6** or **7** (20 mmol) in anhydrous THF (50 cm^3) cooled at 0 °C. The appearance of a red-wine colour corresponding to the formation of the benzylic carbanion indicated the NH deprotonation end-point. The mixture was cooled to −78 °C and a solution of the appropriate carboxylic acid chloride **10a–d**, **10a–g**,**i–k** and **10a**, **10c** and **11** respectively (20 mmol) in THF (10 cm^3) was added dropwise with the internal temperature maintained at below −50 °C. The cooling bath was removed and the mixture was warmed to room temperature and stirred for 1 h. Aq. $NaHCO_3$ was added and the organic layer was separated. The aqueous solution was extracted with ethyl acetate (2 × 50 cm^3) and the combined organic layers were washed successively with water and brine and finally dried over $MgSO_4$. Evaporation of the solvent furnished an oily product, which was purified by flash column chromatography using ethyl acetate–hexane (2:3) as eluent.

N,2-Dimethyl-*N*-(3,4-methylenedioxybenzoyl)benzamide **2a**. Crystals, mp 78–79 °C (lit.,[3c] 79 °C); δ_H 2.34 (3 H, s), 3.46 (3 H, s), 5.91 (2 H, s), 6.62 (1 H, d, *J* 8.3), 6.87 (1 H, s) and 6.97–7.46 (5 H, m); δ_C 173.5 (CO), 173.4 (CO), 150.4, 147.4, 147.3, 136.4, 136.1, 130.6, 130.2, 127.2, 125.0, 123.6, 108.2, 107.2, 101.4 (OCH_2O), 33.2 and 19.3; *m*/*z* 297 (M^+, 24%), 149 (83) and 119 (100); ν_{max}/cm^{-1} 1695 and 1652 (CO).

N-(m-*Chlorobenzoyl*-N,2-*dimethylbenzamide* **2b.** Crystals, mp 75–76 °C (Found: C, 67.0; H, 5.1; N, 5.0. $C_{16}H_{14}ClNO_2$ requires C, 66.8; H, 4.9; N, 4.9%); δ_H 2.26 (3 H, s), 3.44 (3 H, s), 6.89 (1 H, d, *J* 7.4), 6.96 (1 H, d, *J* 7.4), 7.03–7.18 (5 H, m) and 7.26 (1 H, s); δ_C 173.6 (CO), 173.1 (CO), 138.5, 137.1, 135.9, 133.9, 131.3, 131.0, 130.8, 129.6, 129.4, 127.8, 125.9, 125.4, 33.3 and 19.6; *m*/*z* 289 (M^+, 2%), 287 (M^+, 5) and 119 (100); ν_{max}/cm^{-1} 1694 and 1653 (CO).

N-(*p*-Chlorobenzoyl)-*N*,2-dimethylbenzamide **2c.** Crystals, mp 74–75 °C (lit.,[3c] 75 °C); δ_H 2.20 (3 H, s), 3.36 (3 H, s), 6.87–6.96 (2 H, m), 7.00–7.07 (4 H, m) and 7.22 (2 H, d, *J* 8.4); δ_C 173.9 (CO), 173.7 (CO), 138.0, 137.1, 136.2, 135.3, 131.3, 131.0, 129.5, 128.5, 128.0, 125.7, 33.6 and 19.8; *m*/*z* 289 (M^+, 1%), 287 (M^+, 3), 141 (5), 139 (13) and 119 (100); ν_{max}/cm^{-1} 1696 and 1668 (CO).

N,2-*Dimethyl*-N-[p-(*trifluoromethyl*)*benzoyl*]*benzamide* **2d.** Crystals, mp 61–62 °C (Found: C, 63.4; H, 4.3; N, 4.1. $C_{17}H_{14}F_3NO_2$ requires C, 63.5; H, 4.4; N, 4.4%); δ_H 2.26 (3 H, s), 3.47 (3 H, s), 6.86–7.18 (4 H, m) and 7.43 (4 H, s); δ_C 173.7 (CO), 173.2 (CO), 140.1, 137.0, 135.8, 131.1, 130.0, 128.7 (CF_3, d, *J* 240), 128.0, 125.6, 125.0, 33.4 and 19.6; *m*/*z* 321 (M^+, 36%), 173 (14), 119 (100) and 91 (97); ν_{max}/cm^{-1} 1653 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-*methyl*-N-(3,4-*methylenedioxybenzoyl*)*benzamide* **8a.** Crystals, mp 143–144 °C (Found: C, 62.7; H, 6.9; N, 3.1; Si, 12.5. $C_{23}H_{31}NO_4Si_2$ requires C, 62.5; H, 7.1; N, 3.2; Si, 12.7%); δ_H 0.03 (18 H, s), 2.36 (1 H, s), 3.24 (3 H, s), 6.02 (2 H, s), 6.81 (1 H, d, *J* 8.1), 7.05–7.12 (2 H, m), 7.17 (1 H, d, *J* 1.7), 7.29 (2 H, dd, *J* 1.7 and 8.1) and 7.39–7.42 (1 H, m); δ_C 174.2 (CO), 173.3 (CO), 151.0, 147.8, 145.2, 132.8, 130.3, 130.0, 128.9, 128.5, 124.3, 123.0, 109.1, 108.1, 101.8 (OCH_2O), 35.3, 24.3 and 0.5; *m*/*z* 441 (M^+, 1%), 292 (34), 278 (100) and 73 (91); ν_{max}/cm^{-1} 1697 and 1654 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-(m-*chlorobenzoyl*)-N-*methylbenzamide* **8b.** Crystals, mp 63–64 °C (Found: C, 61.3; H, 6.8; N, 3.0; Si, 13.3. $C_{22}H_{30}ClNO_2Si_2$ requires C, 61.1; H, 7.0; N, 3.2; Si, 13.0%); δ_H 0.04 (18 H, s), 2.35 (1 H, s), 3.25 (3 H, s), 7.14 (2 H, d, *J* 7.6), 7.34 (2 H, d, *J* 7.6), 7.40–7.54 (3 H, m) and 7.66 (1 H, s); δ_C 174.3 (CO), 172.8 (CO), 145.7, 137.4, 134.7, 132.4, 131.7, 130.9, 130.3, 129.8, 128.8, 128.6, 126.2, 122.1, 35.3, 24.7 and 0.6; *m*/*z* 431 (M^+, 3%), 342 (47), 320 (41), 152 (59), 139 (41) and 73 (100); ν_{max}/cm^{-1} 1676 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-(p-*chlorobenzoyl*)-N-*methylbenzamide* **8c.** Yellow oil (Found: C, 61.4; H, 7.2; N, 3.5; Si, 12.7%); 0.04 (18 H, s), 2.37 (1 H, s), 3.25 (3 H, s), 7.08–7.32 (3 H, m), 7.37 (2 H, d, *J* 8.3), 7.43–7.51 (1 H, m) and 7.62 (2 H, d, *J* 8.3); δ_C 174.4 (CO), 172.1 (CO), 145.8, 138.0, 134.0, 132.4, 131.1, 130.9, 130.4, 129.2, 128.9, 123.4, 35.3, 24.6 and 0.7; *m*/*z* (M^+, 3%), 342 (45), 320 (68), 152 (65), 139 (37) and 73 (100); ν_{max}/cm^{-1} 1680 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-*methyl*-N-[p-(*trifluoromethyl*)*benzoyl*]*benzamide* **8d.** Yellow oil (Found: C, 59.0; H, 6.5; N, 3.3; Si, 12.2. $C_{23}H_{30}F_3NO_2Si_2$ requires C, 59.3; H, 6.5; N, 3.0; Si, 12.1%); δ_H 0.00 (18 H, s), 2.36 (1 H, s), 3.27 (3 H, s) and 7.09–7.57 (4 H, m), 7.65 (2 H, d, *J* 8.0) and 7.76 (2 H, d, *J* 8.0); δ_C 173.8 (CO), 172.4 (CO), 145.5, 135.8 (CF_3, d, *J* 295), 132.2, 131.7, 130.5, 129.9, 129.6, 128.4, 128.0, 125.0, 122.9, 34.7, 24.2 and −0.1; *m*/*z* 465 (M^+, 4%), 376 (59), 320 (52), 186 (94), 173 (44), 145 (49) and 73 (100); ν_{max}/cm^{-1} 1685 (CO).

N-*Benzoyl*-2-[*bis*(*trimethylsilyl*)*methyl*]-N-*methylbenzamide* **8e.** Crystals, mp 73–74 °C (Found: C, 66.2; H, 8.0; N, 3.3; Si, 14.3. $C_{22}H_{31}NO_2Si_2$ requires C, 66.4; H, 7.9; N, 3.5; Si, 14.1%); δ_H 0.03 (18 H, s), 2.37 (1 H, s), 3.26 (3 H, s) 7.06–7.13 (2 H, m), 7.30–7.49 (5 H, m) and 7.66–7.70 (2 H, m); δ_C 174.2 (CO), 174.0 (CO), 145.3, 135.2, 131.8, 130.4, 130.0, 128.8, 128.4, 123.1, 35.1, 24.3 and 0.5; *m*/*z* 397 (M^+, 9%), 118 (100), 105 (91) and 73 (71); ν_{max}/cm^{-1} 1689 and 1670 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-(3,4-*dimethoxybenzoyl*)-N-*methylbenzamide* **8f.** Crystals, mp 102–103 °C (Found: C, 62.8; H, 7.9; N, 2.9; Si, 12.5. $C_{24}H_{35}NO_4Si_2$ requires C, 63.0; H, 7.7; N, 3.1; Si, 12.3%); δ_H 0.02 (18 H, s), 2.42 (1 H, s), 3.26 (3 H, s), 3.84 (3 H, s), 3.89 (3 H, s), 6.82 (1 H, d, *J* 8.3), 6.97–7.06 (1 H, m), 7.09 (1 H, d, *J* 8.0), 7.19–7.37 (3 H, m) and 7.43 (1 H, d, *J* 8.0); δ_C 174.3 (CO), 173.6 (CO), 152.4, 145.3, 142.5, 130.3, 130.0, 129.1, 128.6, 127.0, 122.9, 122.7, 111.9, 110.2, 56.0, 55.9, 35.3, 24.2 and 0.8; *m*/*z* 457 (M^+, 1%), 292 (27), 278 (100) and 73 (95); ν_{max}/cm^{-1} 1675 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-[3-(*dimethylsulfamoyl*)*benzoyl*]-N-*methylbenzamide* **8g.** Crystals, mp 110–111 °C (Found: C, 56.9; H, 6.9; N, 5.7; Si, 11.05. $C_{24}H_{36}N_2O_4SSi_2$ requires C, 57.1; H, 7.2; N, 5.55; Si, 11.1%); δ_H 0.11 (18 H, s), 2.22 (1 H, s), 2.54 (6 H, s), 3.24 (3 H, s), 7.13 (1 H, d, *J* 7.8), 7.15 (1 H, t, *J* 7.4), 7.37 (1 H, t, *J* 7.8), 7.57 (1, H, d, *J* 7.8), 7.62 (1 H, t, *J* 7.8), 7.86 (1 H, d, *J* 7.8) and 7.92–7.96 (2 H, m); δ_C 174.3 (CO), 171.6 (CO), 146.4, 135.2, 134.3, 132.2, 131.4, 131.1, 130.3, 130.1, 129.4, 128.3, 126.7, 123.4, 37.9, 35.2, 24.4 and 0.4; *m*/*z* 504 (M^+, 5%), 212 (73), 278 (91) and 73 (100); ν_{max}/cm^{-1} 1678 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-[3-(4,4-*dimethyl*-4,5-*dihydrooxazol*-2-*yl*)*benzoyl*]-N-*methylbenzamide* **8h.** From compounds **7** and **11**,[36] a yellow oil (Found: C, 65.3; H, 8.0; N, 5.85; Si, 11.5. $C_{27}H_{38}N_2O_3Si_2$ requires C, 65.5; H, 7.8; N, 5.7; Si, 11.35%); δ_H 0.01 (18 H, s), 1.34 (6 H, s), 2.33 (1 H, s), 3.24 (3 H, s), 4.07 (2 H, s), 7.02–7.48 (5 H, m), 7.71 (1 H, d, *J* 7.6), 8.0 (1 H, d, *J* 7.6) and 8.20 (1 H, s); δ_C 173.7 (CO), 172.8 (CO), 160.8, 144.8, 135.3, 132.2, 131.0, 130.3, 130.0, 129.6, 128.3, 128.0, 127.8, 122.7, 78.9, 67.4, 34.7, 28.0, 24.0 and 0.0; *m*/*z* 494 (M^+, 11%), 405 (38), 320 (100), 215 (74) and 73 (91); ν_{max}/cm^{-1} 1690 and 1650 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-(2-*furoyl*)-N-*methylbenzamide* **8i.** Crystals, mp 51–52 °C (Found: C, 62.05; H, 7.4; N, 3.8; Si, 14.2. $C_{20}H_{29}NO_3Si_2$ requires C, 62.0; H, 7.55; N, 3.6; Si, 14.5%); δ_H 0.03 (18 H, s), 2.35 (1 H, s), 3.25 (3 H, s), 6.49 (1 H, dd, *J* 1.7 and 3.6), 7.05–7.11 (2 H, m), 7.18 (1 H, dd, *J* 0.7 and 3.6) and 7.26–7.47 (3 H, m); δ_C 173.7 (CO), 162.6 (CO), 147.6, 144.9, 144.2, 132.7, 130.0, 129.5, 122.8, 117.9, 111.9, 33.7, 24.0 and 0.2; *m*/*z* 387 (M^+, 2%), 108 (100) and 73 (81); ν_{max}/cm^{-1} 1677 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-(*cyclohexylcarbonyl*)-N-*methylbenzamide* **8j.** Crystals, mp 44–45 °C (Found: C, 65.7; H, 9.4; N, 3.2; Si, 13.7. $C_{22}H_{37}NO_2Si_2$ requires C, 65.4; H, 9.25; N, 3.5; Si, 13.9%); δ_H 0.04 (18 H, s), 1.23–1.94 (11 H, m), 2.10 (1 H, s), 3.00 (3 H, s) and 7.04–7.33 (4 H, m); δ_C 180.6 (CO), 173.7 (CO), 144.4, 134.4, 130.0, 129.7, 127.9, 123.2, 44.8, 34.7, 29.8,

25.9, 25.6, 24.7 and 0.5; *m*/*z* 403 (M^+, 1%), 320 (100) and 73 (93); ν_{max}/cm^{-1} 1688 (CO).

2-[*Bis*(*trimethylsilyl*)*methyl*]-N-*methyl*-N-(2-*methylpropanoyl*)*benzamide* **8k.** Yellow oil (Found: C, 62.8; H, 9.0; N, 3.7; Si, 15.6. $C_{19}H_{33}NO_2Si_2$ requires C, 62.7; H, 9.2; N, 3.85; Si, 15.4%); δ_H 0.03 (18 H, s), 1.16 (6 H, d, *J* 6.7), 2.13 (1 H, s), 3.03 (3 H, s), 3.46 (1 H, sept, *J* 6.7) and 7.03–7.30 (4 H, m); δ_C 182.0 (CO), 173.9 (CO), 143.9, 133.9, 130.2, 129.3, 127.5, 124.3, 35.2, 34.7, 24.6, 19.7 and 0.4; *m*/*z* 363 (M^+, 5%), 320 (88), 278 (63) and 73 (100); ν_{max}/cm^{-1} 1689 and 1656 (CO).

N-*Methyl*-N-(3,4-*methylenedioxybenzoyl*)-2-[(*trimethylsilyl*)*methyl*]*benzamide* **9a.** Yellow oil (Found: C, 64.8; H, 6.0; N, 3.7; Si, 7.8. $C_{20}H_{23}NO_4Si$ requires C, 65.0; H, 6.3; N, 3.8; Si, 7.6%); δ_H 0.18 (9 H, s), 2.09 (2 H, s), 3.48 (3 H, s), 6.04 (2 H, s), 6.57 (1 H, d, *J* 8.1), 6.77–6.96 (2 H, m), 7.03–7.13 (2 H, m), 7.43 (1 H, t, *J* 1.6) and 7.61 (1 H, dd, *J* 1.6 and 8.2); δ_C 175.0 (CO), 174.1 (CO), 151.3, 148.3, 141.8, 135.2, 131.1, 130.3, 129.1, 126.0, 124.6, 124.4, 109.1, 108.1, 102.4 (OCH_2O), 33.9, 24.6 and −1.3; *m*/*z* 369 (M^+, 3%), 220 (55), 149 (85) and 73 (100); ν_{max}/cm^{-1} 1709 and 1654 (CO).

N-(p-*Chlorobenzoyl*)-N-*methyl*-2-[(*trimethylsilyl*)*methyl*]-*benzamide* **9c.** Mp 64–65 °C (Found: C, 63.7; H, 5.9; N, 4.2; Si, 7.6. $C_{19}H_{22}ClNO_2Si$ requires C, 63.5; H, 6.2; N, 3.9; Si, 7.8%); δ_H 0.04 (9 H, s), 2.09 (2 H, s), 3.48 (3 H, s), 6.83 (1 H, d, *J* 7.6), 6.94 (1 H, d, *J* 7.6) and 7.08–7.32 (6 H, m); δ_C 173.9 (CO), 173.8 (CO), 141.3, 137.4, 135.2, 134.0, 130.7, 129.7, 129.2, 128.7, 128.2, 123.8, 33.6, 24.5 and 0.4; *m*/*z* 361 (M^+, 8%), 360 (11), 359 (M^+, 21), 152 (61), 139 (98), 119 (63), 118 (56) and 73 (100); ν_{max}/cm^{-1} 1697 and 1649 (CO).

General procedure for the synthesis of the hydroxyphthalimidine derivatives 12a–d and 13a,c

To a solution of diisopropylamine (0.47 cm^3, 3.36 mmol) in THF (10 cm^3) at −78 °C and under Ar was added butyllithium (3.36 mmol). After being stirred for 0.5 h at −78 °C the solution was warmed to −30 °C and a solution of the *N*-acyl-*o*-toluamide **2a**–**d** and **9a**,**c** (3.36 mmol) in THF (10 cm^3) was added dropwise during 5 min, then the reaction mixture was allowed to come to room temperature over a period of 1 h. After this, several drops of dil. HCl (10%), water (10 cm^3) and diethyl ether (2 × 30 cm^3) were added. The organic layer was separated, rinsed with brine, dried ($MgSO_4$) and concentrated to dryness. The crude product was finally purified by flash chromatography using ethyl acetate–hexane (1:1) as eluent and finally was recrystallized from ethanol.

Alternative procedure for the synthesis of compound 12a

Compound **12a** was also prepared in the following manner. To a solution of *N*-methyl-3,4-methylenedioxybenzamide **14** (0.90 g, 5.5 mmol) in THF (20 cm^3) was added butyllithium (11 mmol) under Ar at 0 °C. The mixture was maintained at this temperature for 0.5 h after which a solution of *N*-methoxy-*N*-methyl-*o*-toluamide **15** (0.98 g, 5.5 mmol), readily obtained from the corresponding acid chloride,[22] in THF (5 cm^3) was added dropwise during 5 min. The mixture was stirred for an additional 1 h and the usual work-up afforded a crude product which was purified by flash column chromatography using ethyl acetate–hexane (7:3) as eluent and recrystallized from ethanol.

3-*Hydroxy*-2-*methyl*-4,5-*methylenedioxy*-3-(2-*methylphenyl*)-1-*isoindolone* **12a.** Crystals, mp 157–158 °C (Found: C, 68.7; H, 5.3; N, 4.8. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); δ_H 1.62 (3 H, br s), 2.52 (3 H, s), 4.80 (1 H, s), 5.90 (1 H, d, *J* 1.0), 6.00 (1 H, d, *J* 1.0), 6.81 (1 H, d, *J* 7.9), 7.05 (1 H, m), 7.17 (1 H, d, *J* 7.9), 7.25–7.35 (2 H, m) and 8.22 (1 H, m); δ_C 167.7 (CO), 152.5, 141.7, 134.6, 132.4, 129.2, 128.7, 126.6, 126.4, 118.0, 109.3, 102.9 (OCH_2O), 90.1 (C-3), 24.1 and 19.9; *m*/*z* 297 (M^+, 23%), 280 (27) and 206 (100); ν_{max}/cm^{-1} 3245 (OH) and 1673 (CO).

4-*Chloro*-3-*hydroxy*-2-*methyl*-3-(2-*methylphenyl*)-1-*isoindolone* **12b.** Crystals, mp 190–191 °C (Found: C, 67.1; H, 4.8; N, 5.0. $C_{16}H_{14}ClNO_2$ requires C, 66.9; H, 4.9; N, 4.9%); δ_H 1.47 (3 H, s), 2.54 (3 H, s), 47.0 (1 H, s), 7.01 (1 H, d, *J* 7.2), 7.24–7.42 (4 H, m), 7.48 (1 H, d, *J* 7.2) and 8.28 (1 H, d, *J* 7.6); δ_C 166.8 (CO), 143.6, 134.5, 133.9, 133.5, 133.3, 131.8, 130.9, 129.7, 129.6, 129.0, 126.1, 121.6, 90.0 (C-3), 23.9 and 19.4; *m*/*z* 289 (M^+, 6%), 287 (M^+, 17), 221 (100), 198 (22) and 196 (65); ν_{max}/cm^{-1} 3250 (OH) and 1688 (CO).

5-*Chloro*-3-*hydroxy*-2-*methyl*-3-(2-*methylphenyl*)-1-*isoindolone* **12c.** Crystals, mp 199–200 °C (Found: C, 66.7; H, 4.7; N, 5.2%); 1.52 (3 H, s), 2.61 (3 H, s), 4.40 (1 H, s), 7.03 (1 H, d, *J* 7.6), 7.18–7.47 (5 H, m) and 8.23 (1 H, d, *J* 7.6); δ_C 166.7 (CO), 149.2, 138.7, 134.8, 134.0, 132.0, 129.5, 128.8, 128.0, 126.1, 123.8, 123.0, 89.6 (C-3), 23.6 and 19.0; *m*/*z* 289 (M^+, 7%), 287 (M^+, 20), 287 (20), 119 (100) and 91 (63); ν_{max}/cm^{-1} 3275 (OH) and 1665 (CO).

3-*Hydroxy*-2-*methyl*-3-(2-*methylphenyl*)-5-*trifluoromethyl*-1-*isoindolone* **12d.** Crystals, mp 146–147 °C (Found: C, 63.8; H, 4.3; N, 4.5. $C_{17}H_{14}F_3NO_2$ requires C, 63.55; H, 4.4; N, 5.35%); δ_H 1.48 (3 H, s), 2.65 (3 H, s), 4.84 (1 H, s), 7.03 (1 H, d, *J* 6.5), 7.25–7.60 (5 H, m) and 8.26 (1 H, d, *J* 6.5); δ_C 168.7 (CO), 148.3, 134.8, 134.4, 133.9, 130.6 (CF_3, d, *J* 263), 129.4, 128.5, 126.7, 126.6, 123.3, 119.9, 90.1 (C-3), 24.1 and 19.8; *m*/*z* 321 (M^+, 54%), 176 (25), 118 (100) and 90 (35); ν_{max}/cm^{-1} 3215 (OH) and 1667 (CO).

3-*Hydroxy*-2-*methyl*-4,5-*methylenedioxy*-3-{2-[(*trimethylsilyl*)*methyl*]*phenyl*}-1-*isoindolone* **13a.** Crystals, mp 175–176 °C (Found: C, 65.2; H, 6.2; N, 4.0; Si, 7.7. $C_{20}H_{23}NO_4Si$ requires C, 65.0; H, 6.3; N, 3.8; Si, 7.6%); δ_H, two rotamers A and B (2:1), −0.35 (9 H, s, A), 0.07 (9 H, s, B), 1.47 and 1.65 (2 H, 2 d, *J* 15.5, A), 2.31 and 3.27 (2 H, 2 d, *J* 11.5, B), 2.53 (3 H, s, A), 2.68 (3 H, s, B), 4.50 (1 H, s, A), 4.61 (1 H, s, B), 5.60 and 6.03 (2 H + 2 H, m, A + B), 6.63–7.25 (5 H + 6 H, m, A + B) and 8.23 (1 H, br s, A); δ_C, two rotamers, 166.3 (2 CO), 152.6, 148.8, 147.5, 142.3, 140.5, 139.8, 135.6, 133.8, 129.5, 128.4, 128.1, 126.0, 125.8, 124.7, 124.2, 116.3, 115.9, 108.9, 102.2, 101.9, 91.2 (C-3), 89.7 (C-3), 25.8, 24.3, 24.1, 20.7 and 0.4; *m*/*z* 369 (M^+, 37%), 354 (24), 311 (61) and 73 (100); ν_{max}/cm^{-1} 3268 (OH) and 1678 (CO).

5-*Chloro*-3-*hydroxy*-2-*methyl*-3-{2-[(*trimethylsilyl*)*methyl*]-*phenyl*}-1-*isoindolone* **13c.** Crystals, mp 163–164 °C (Found: C, 63.3; H, 6.4; N, 3.8; Si, 8.1. $C_{19}H_{22}ClNO_2Si$ requires C, 63.5; H, 6.2; N, 3.9; Si, 7.8%); δ_H, two rotamers A and B (1:1), −0.37 (9 H, s, A), 0.11 (9 H, s, B), 1.31 and 1.49 (2 H, 2 d, *J* 14.6, A), 2.44 and 3.29 (2 H, 2 d, *J* 12.2, B), 2.57 (3 H, s, A), 2.75 (3 H, s, B), 5.05 (1 H, s, A), 5.16 (1 H, s, B), 6.54 (1 H, d, *J* 8.0, A), 6.85–7.48 (5 H + 7 H, m, A + B) and 8.24 (1 H, m, A); δ_C, two rotamers, 167.1 (2 CO), 151.8, 151.0, 141.2, 139.2, 138.8, 138.7, 132.7, 132.3, 132.1, 130.5, 129.6, 129.4, 129.1, 128.8, 128.2, 127.6, 126.5, 124.6, 124.3, 124.2, 123.8, 123.2, 93.9 (C-3), 89.9 (C-3), 26.6, 24.5, 24.3, 20.8 and −1.0; *m*/*z* 359 (M^+, 8%), 358 (11), 357 (5), 344 (21), 234 (25) and 73 (100); ν_{max}/cm^{-1} 3215 (OH) and 1669 (CO).

General procedure for the synthesis of the 2,3-disubstituted 1(2*H*)-isoquinolones 1a–k

Commercial TBAF·$3H_2O$ (500 mg) was placed in a 25 cm^3 two-necked, round-bottom flask equipped with a rubber septum. The mixture was heated and stirred under reduced pressure (0.05 mmHg) at 45 °C for 48 h and during that time the sample liquefied. The product was maintained under vacuum and anhydrous THF (5 cm^3) was added by way of a syringe, followed by the slow addition of a solution of the appropriate disilyl derivatives **8a**–**k** (1.57 mmol) in THF (10 cm^3). The mixture was then stirred for 5 min. Dil. HCl (10%; 20 cm^3) was added and the mixture was extracted with ethyl acetate (2 × 20 cm^3). The organic layer was washed with water, rinsed with brine and dried ($MgSO_4$). The crude reaction mixture was purified by flash column chromatography using ethyl acetate–hexane (3:2) as eluent to give the cyclized products **1a**–**k** which were finally recrystallized from hexane–toluene.

2-Methyl-3-(3,4-methylenedioxyphenyl)-1(2*H*)-isoquinolone **1a.** Crystals, mp 114–115 °C (lit.,[3c] 115 °C); δ_H 3.45 (3 H, s), 6.06 (2 H, s), 6.45 (1 H, s), 6.84–6.89 (3 H, m), 7.44–7.49 (2 H, m), 7.59–7.65 (1 H, m) and 8.45 (1 H, d, *J* 7.5); δ_C 163.4 (CO), 148.2, 147.7, 143.5, 136.3, 132.2, 129.9, 127.8, 126.5, 125.7, 124.9, 122.7, 109.3, 108.4, 107.5, 101.5 (OCH_2O) and 34.0; *m*/*z* 279 (M^+, 100%), 278 (94), 248 (20) and 220 (21); ν_{max}/cm^{-1} 1653 and 1616 (CO).

3-(m-*Chlorophenyl*)-2-*methyl*-1-(2H)-*isoquinolone* **1b.** Crystals, mp 119–120 °C (Found: C, 71.05; H, 4.7; N, 5.1. $C_{16}H_{12}ClNO$ requires C, 71.2; H, 4.5; N, 5.2%); δ_H 3.38 (3 H, s), 6.45 (1 H, s), 7.28–7.69 (7 H, m) and 8.46 (1 H, d, *J* 7.9); δ_C 163.4 (CO), 142.6, 138.0, 136.2, 134.9, 132.5, 130.1, 129.3, 129.1, 128.1, 127.2, 127.1, 126.1, 125.3, 108.0 and 34.3; *m*/*z* 271 (M^+, 26%), 270 (43), 269 (M^+, 78) and 268 (100); ν_{max}/cm^{-1} 1644 and 1618 (CO).

3-(*p*-Chlorophenyl)-2-methyl-1(2*H*)-isoquinolone **1c.** Crystals, mp 142–143 °C (lit.,[3c] 142 °C); δ_H 3.42 (3 H, s), 6.44 (1 H, s), 7.28–7.57 (7 H, m) and 8.46 (1 H, d, *J* 7.7); δ_C 163.3 (CO), 142.6, 136.1, 135.1, 134.6, 132.4, 130.1, 127.9, 128.9, 126.9, 125.9, 125.0, 107.5 and 34.1; *m*/*z* 271 (M^+, 28%) and 269 (100); ν_{max}/cm^{-1} 1645 and 1616 (CO).

2-*Methyl*-3-[p-(*trifluoromethyl*)*phenyl*]-1(2H)-*isoquinolone* **1d.** Crystals, mp 154–155 °C (Found: C, 67.0; H, 4.3; N, 4.5. $C_{17}H_{12}F_3NO$ requires C, 67.3; H, 4.0; N, 4.6%); δ_H 3.43 (3 H, s), 6.47 (1 H, s), 7.49–7.79 (7 H, m) and 8.47 (1 H, d, *J* 8.6); δ_C 163.2 (CO), 142.4, 139.7, 136.1, 134.8, 132.5, 129.5 (CF_3, d, *J* 290), 129.3, 127.9, 127.1, 125.8, 125.7, 125.2, 108.0 and 34.1; *m*/*z* 303 (M^+, 80%), 302 (100) and 284 (19); ν_{max}/cm^{-1} 1643 and 1621 (CO).

2-Methyl-3-phenyl-1(2*H*)-isoquinolone **1e**. Crystals, mp 62–63 °C (lit.,[46] 59–60 °C or lit.,[6b] 68.5–70.5 °C); δ_H 3.42 (3 H, s), 6.45 (1 H, s), 7.26–7.61 (8 H, m) and 8.45 (1 H, d, *J* 7.5); δ_C 164.1 (CO), 143.9, 136.4, 136.2, 132.2, 128.9, 128.8, 128.6, 127.9, 126.6, 125.8, 124.9, 107.5 and 34.1; *m*/*z* 235 (M^+, 88%) and 234 (100); ν_{max}/cm^{-1} 1651 and 1617 (CO).

3-(3,4-*Dimethoxyphenyl*)-2-*methyl*-1(2H)-*isoquinolone* **1f.** Crystals, mp 172–173 °C (Found: C, 73.4; H, 6.0; N, 4.6. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%); δ_H 3.43 (3 H, s), 3.90 (3 H, s), 3.94 (3 H, s), 6.46 (1 H, s), 6.88–6.96 (3 H, m), 7.44–7.49 (2 H, m), 7.59–7.66 (1 H, m) and 8.43 (1 H, d, *J* 7.8); δ_C 163.5 (CO), 149.7, 149.1, 143.9, 136.5, 132.3, 128.9, 127.9, 126.6, 125.8, 124.9, 121.6, 112.2, 111.3, 107.5, 56.1 and 34.2; *m*/*z* 295 (M^+, 100%) and 294 (68); ν_{max}/cm^{-1} 1647 and 1620 (CO).

3-[(*Dimethylsulfamoyl*)*phenyl*]-2-*methyl*-1(2H)-*isoquinolone* **1g**. Crystals, mp 182–183 °C (Found: C, 62.9; H, 5.5; N, 8.15. $C_{18}H_{18}N_2O_3S$ requires C, 63.1; H, 5.3; N, 8.2%); δ_H 2.77 (6 H, s), 3.42 (3 H, s), 6.47 (1 H, s), 7.49–7.55 (2 H, m), 7.63–7.70 (3 H, m), 7.84–7.92 (2 H, m) and 8.46 (1 H, d, *J* 7.5); δ_C 168.3 (CO), 141.4, 137.6, 135.3, 132.9, 132.5, 129.5, 128.1, 127.9, 127.8, 127.2, 126.2, 126.0, 108.3, 37.9 and 34.2; *m*/*z* 342 (M^+, 100%); ν_{max}/cm^{-1} 1644 and 1618 (CO).

3-[3-(4,4-*Dimethyl*-4,5-*dihydrooxazol*-2-*yl*)*phenyl*]-2-*methyl*-1(2H)-*isoquinolone* **1h**. Crystals, mp 101–102 °C (Found: C, 76.2; H, 6.4; N, 8.2. $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.1; N, 8.4%); δ_H 1.26 (6 H, s), 3.38 (3 H, s), 4.02 (2 H, s), 6.41 (1 H, s), 7.23–7.51 (5 H, m), 7.62–7.73 (2 H, m) and 8.41 (1 H, d, *J* 7.9); δ_C 163.9 (CO), 158.5, 143.7, 135.2, 134.3, 132.0, 130.6, 130.1, 129.8, 129.3, 129.0, 128.5, 123.6, 107.6, 79.1, 68.1, 34.5 and 28.1; *m*/*z* 332 (M^+, 100%) and 331 (76); ν_{max}/cm^{-1} 1646 and 1620 (CO).

3-(2-*Furyl*)-2-*methyl*-1(2H)-*isoquinolone* **1i**. Crystals, mp 68–69 °C (Found: C, 74.8; H, 5.0; N, 6.05. $C_{14}H_{11}NO_2$ requires C, 74.65; H, 4.9; N, 6.2%); δ_H 3.60 (3 H, s), 6.52 (1 H, dd, *J* 1.8 and 3.4), 6.65 (1 H, dd, *J* 0.6 and 3.4), 6.74 (1 H, s), 7.48–7.53 (2 H, m), 7.57 (1 H, dd, *J* 0.6 and 1.8), 7.61–7.64 (1 H, m) and 8.43 (1 H, d, *J* 7.8); δ_C 162.7 (CO), 148.2, 143.2, 135.6, 133.4, 132.3, 127.9, 127.2, 125.8, 124.3, 111.3, 111.2, 108.0 and 33.2; *m*/*z* 225 (M^+, 100%); ν_{max}/cm^{-1} 1647 and 1619 (CO).

3-*Cyclohexyl*-2-*methyl*-1(2H)-*isoquinolone* **1j.** Crystals, mp 86–87 °C (Found: C, 79.8; H, 8.1; N, 6.05. $C_{16}H_{19}NO$ requires C, 79.6; H, 7.9; N, 5.8%); δ_H 1.24–1.45 (5 H, m), 1.78–2.00 (5 H, m), 2.59–2.65 (1 H, m), 3.64 (3 H, s), 6.34 (1 H, s), 7.36–7.44 (2 H, m), 7.57 (1 H, d, *J* 7.0) and 8.36 (1 H, d, *J* 8.0); δ_C 163.7 (CO), 148.3, 136.6, 132.0, 127.8, 125.8, 125.4, 124.2, 102.5, 40.5, 33.1, 30.3, 26.7 and 26.1; *m*/*z* 241 (M^+, 100%); ν_{max}/cm^{-1} 1648 and 1617 (CO).

3-Isopropyl-2-methyl-1(2*H*)-isoquinolone **1k**. Crystals, mp 83–84 °C (lit.,[3c] 84 °C); δ_H 1.31 (6 H, d, *J* 6.6), 3.08 (1 H, sept, *J* 6.6), 3.65 (3 H, s), 6.40 (1 H, s), 7.37 (1 H, t, *J* 7.9), 7.43 (1 H, d, *J* 7.9), 7.58 (1 H, t, *J* 7.9) and 8.39 (1 H, d, *J* 7.9); δ_C 163.2 (CO), 149.1, 136.2, 131.6, 127.3, 125.5, 125.1, 123.8, 101.3, 29.9, 29.6 and 21.9; *m*/*z* 201 (M^+, 74%) and 186 (100); ν_{max}/cm^{-1} 1645 and 1616 (CO).

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