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Tetrahedron 60 (2004) 11029–11039

Kinetic versus thermodynamic access to imidazoisoindolones, benzimidazoisoindolones, and [1,4]diazepinoisoindolones: intramolecular nitrogen and π-aromatic trapping of *N*-acyliminium cation

Armelle Cul,[a] Adam Daïch,[a,*] Bernard Decroix,[a] Gérard Sanz[b] and Luc Van Hijfte[b]

[a]*Laboratoire de chimie, URCOM, EA 3221, UFR des Sciences and Techniques de l'Université du Havre, B.P: 540, 25 rue Philippe Lebon, F-76058 Le Havre Cedex, France*
[b]*Johnson & Johnson, Pharmaceutical Research & Development, Division of Janssen-Cilag, Campus de Maigremont, B.P: 615, F-27106 Val-de-Reuil Cedex, France*

Received 24 May 2004; revised 28 June 2004; accepted 5 July 2004

Available online 5 October 2004

Abstract—Efficient assembly of substituted imidazo[2,1-*a*]isoindolones **I** is reported from suitable α,β-diamine **IV** (or corresponding β-nitroamine) and phthalic anhydride (**1**) in a three- or four-step sequence in good yields. The key step of this methodology is based on an intramolecular α-aza-amidoalkylation of the *N*-acyliminium species. Furthermore, when R_2 is an aromatic moiety a competing α-amidoalkylation took place and imidazo[2,1-*a*]isoindolones (or benzimidazo[2,1-*a*]isoindolones) **I** and/or isoindolo[1,4]benzodiazepines **III** were obtained under kinetic or thermodynamic control. The chemoselectivity of these transformations is also discussed.

1. Introduction

The importance of the imidazo[2,1-*a*]isoindolone skeleton is well recognized due to its significance as a subunit of a wide panel of synthetic pharmaceutical compounds. Some of these structures are patented and have been reported to possess a wide variety of biological activities as: psychostimulant, analgesic, anti-inflammatory, antifungal, antipyretic and hypertensive,[1] blood pressure lowering, spasmolytic, anti-tussive and tranquilizer properties,[2] and use in the treatment of rheumatism.[3] Furthermore, they are useful intermediates in organic synthetic chemistry, especially in the elaboration of imidazo[2,1-*a*]isoindolol-based anorectics,[1,4a,b] central nervous system (CNS) stimulants[1,4c,d] and antidepressants,[5] respectively. Finally, this class of compounds has also demonstrated to be highly effective plant growth regulating agents[6] with effects on the plant budding process.[7] More recently related benzimidazo[2,1-*a*]isoindolones have been reported and their biological activities evaluation show Batracylin comparable anti-tumor activities[8] as well as their ability to induce unscheduled DNA synthesis in rat hepatocytes.[9]

The traditional synthesis of imidazo[2,1-*a*]isoindolones involves the reaction between a 1,2-diamine and an aromatic or non aromatic keto acid, or equivalent, under azeotropic removal of water with[10] or without[11] a catalytic amount of acid (i.e., *p*-toluenesulfonic acid). More recent methods include a reaction of a 1,2-diamine with phthalic anhydride (or dicarboxylic acid equivalent) followed by thermal cyclodehydration,[9,12] a palladium catalyzed reaction via carbonylative cyclization between an α,β-diamine and 2-bromobenzaldehyde under controlled carbon monoxide pressure,[13] an iminocyclization of *N*-azidoalkyl(or aryl) phthalimides[14a] or the *N*-(*O*-aminoaryl)phthalimides[14b] via intramolecular Aza–Wittig reaction, and finally a cationic cyclization involving *N*-acyliminium species.[15,16]

2. Results and discussion

In our laboratory we are interested in the development of synthetic methodologies towards original aza-heterocyclic systems containing imidazole, benzimidazole and benzodiazepine moieties with promising pharmaceutical activities. In association with our recent reports dealing with

Keywords: Isoindole; Imidazole; Benzimidazole; [1,4]Diazepine; *N*-Acyliminium ion; α-Aza-amidoalkylation; Kinetic versus thermodynamic control.
* Corresponding author. Tel.: +33 2 32 74 44 03; fax: +33 2 32 74 43 91; e-mail: adam.daich@univ-lehavre.fr

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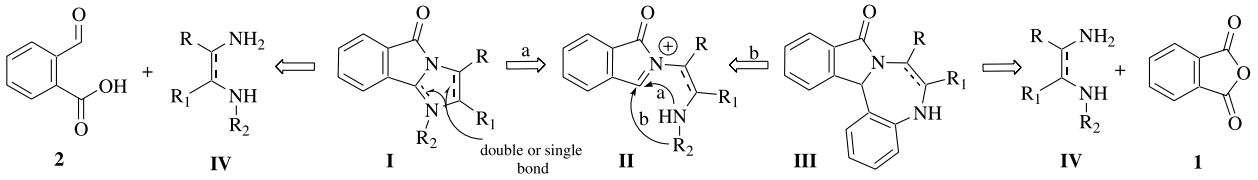
doi:10.1016/j.tet.2004.07.107



Scheme 1. Retrosynthetic scheme leading to imidazo(or benzimidazo)[2,1-*a*]isoindolones **I** and related isoindolo[1,4]benzodiazepines **III**.

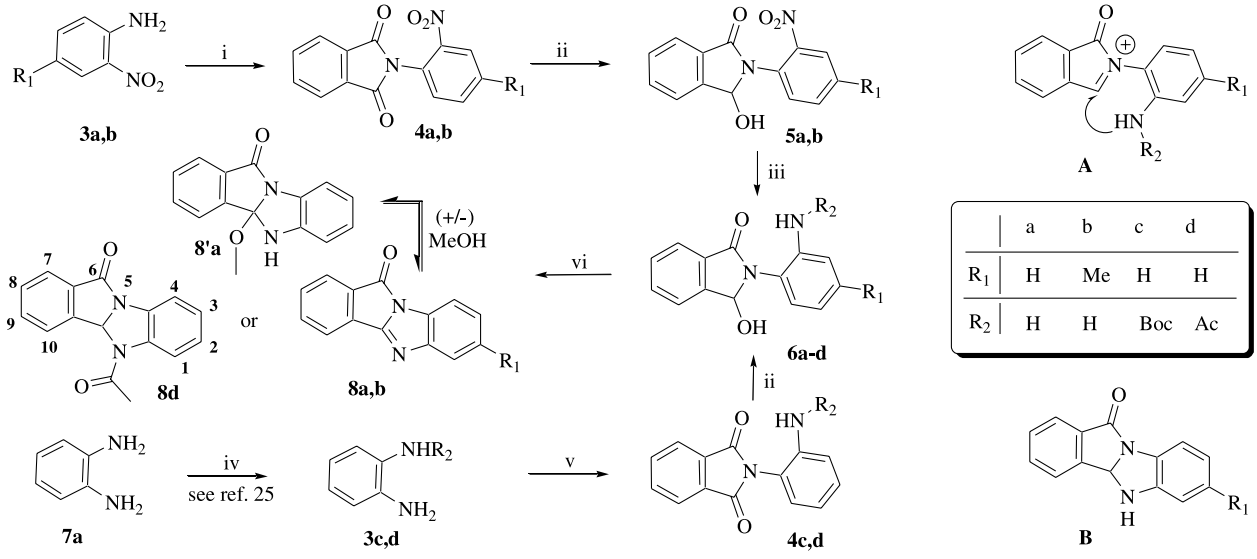
intramolecular α-thio-amidoalkylation[17] and α-oxo-amidoalkylation,[18] we reasoned that a suitably substituted *N*-acyliminium precursor of type **II** (Scheme 1) could allow a facile approach to the tricyclic derivative (**I**) or tetracyclic (**I** and **III**) cores of the title targets. The cationic cyclization using a nitrogen atom as an internal nucleophile has been mentioned first during the synthesis of 9*a*-phenyl-5,6,6*a*,11-tetrahydroisoindolo[2,1*a*]quinazoline-5,11-dione without isolation of the opened amide-hydroxylactam intermediate.[16a] Some 10 years later it was used by Speckamp et al.[16b] in the total synthesis of (±)-physostigmine ((±)-eserine), the principal alkaloid of Calabar bean. The essence of the few reports of this process concern its use in chiral version to access imidazo[2,1-*a*]isoindole-2,5-diones,[15] imidazoisoquinolinones,[16c] functionalized peptidomimetics,[16d] and azabicyclo[4.4.0]alkane amino acids.[19] To the best of our knowledge utilization of the present application in an intramolecular *N*-acyliminium mediated cyclization reaction, as depicted in Scheme 1, to form a central five- or seven-membered ring as a cyclic *N*,*N*-acetal or [1,4]diazepine structure, represents a novel illustration of this chemistry. In the intermediate **II**, cyclisation to the *N*-acyliminium cation may indeed be originated from intramolecular attack of either the nitrogen nucleophile or from the π-aromatic system, in case the latter is sufficiently activated.

As a starting point of our study, the α-hydroxylactam derivative **5a**, as *N*-acyliminium precursor, constituted a valuable target molecule. We expected to obtain it in a two-step sequence from phthalic anhydride (**1**) and *o*-nitro-aniline (**3a**) by thermal amino-anhydride condensation in refluxing acetic acid for 24 h,[20] followed by selective sodium borohydride reduction of one of the carbonyl functions of the imide function under mild conditions (Scheme 2). In the case of borohydride reduction of **4a**, the process led to a mixture of compounds containing none of the desired amino-alcohol product **5a**. Instead, the isoindolobenzimidazole **8a** was identified as a minor product (13%), while the major compound proved to be 10*b*-methoxyisoindolobenzimidazole **8′a** (39% yield) which resulted from the methanol

Table 1. Yields of the intermediates **4a–c**, **5a–c**, **6a–c** and the cyclized isoindolo[2,1-*a*]benzimidazole **8a**,**b**,**d** and **8′a** produced via Scheme 1

Products **4**	Yield (%)	Products **5**	Yield (%)	Products **6**	Yield (%)	Products **8**	Yield (%)[a]
4a	89	**5a**	—[b]	**6a**	—[b]	**8a**	45–61 (82)[c]
4b	91	**5b**	65	**6b**	—[b]	**8b**	63 (54)[a]
4c	91	**5c**	—	**6c**	85	**8′a**	39
4d	91	**5d**	—	**6d**	89	**8d**	91

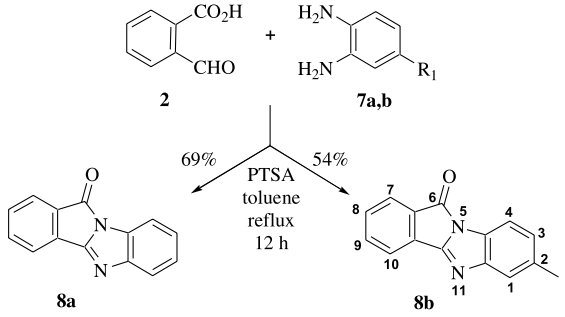
[a] After recrystallization or chromatographic purification.
[b] Product not isolated.
[c] Isolated yields after reaction of diamines **7a**,**b** and 2-formylbenzoic acid (**2**).



Scheme 2. Reagents and conditions: (i) Phthalic anhydride (**1**), AcOH, reflux, 24 h; (ii) 1.5–3 equiv of $NaBH_4$, MeOH, −5 to 0 °C, 45 min to 1 h; (iii) Fe, 50% aq. AcOH, 60 °C, 4 h or H_2/Pd-C, AcOH–H_2O (v/v), 50 psi, 6 h; (iv) see Ref. 25a for product **3c** and Ref. 25b for product **3d**; (v) **1**, toluene, reflux, NEt_3, Dean–Stark, 12 h; (vi) (a) acid hydrolysis during the work-up of the reduction of **5a**,**b** with 10% HCl or 6 M H_2SO_4; (b) For **6c**,**d**: TFA, CH_2Cl_2, rt, 4 h.

addition onto the imine function of **8a** under the protic acid activation conditions used during the reduction. Furthermore, in the presence of 2 equiv of additional nickel (II) chloride hexahydrate, the borohydride reduction reaction showed the same profile with however product **8a** obtained in larger quantity. Interestingly, treatment of **4a** with conjointly iron powder as a reductant and a 50% aqueous acetic acid as a proton source at 60 °C over 4 h,[9] provided only 6-oxoisoindolo[2,1-*a*]benzimidazole (**8a**) in 44% yield after chromatography. The product **8a** was also obtained in 61% yield, without formation of the methoxy adduct **8′a**, from **4a** via catalytic hydrogenation at 50 psi over Pd–C 10% for 6 h in ethanol in the presence of acetic acid as a proton source. Interestingly, in this case no ethoxy adduct analogous to **8′a** could be observed (Table 1).

The ease of intramolecular α-aza-amidoalkylation by the amino-ketone cyclodehydration[9,14] or the *N*-cyclization of the supposed amino–alcohol intermediate **6a**, depending of the reduction sequence, caused us to investigate additional stabilization of these species. To this end, we considered the *para*-methyl substituted series based on the idea that an electron-donating methyl group would provide some increased stability of the nitro functions in **4b** with respect to reducing agents. Interestingly, treatment of **4b** using 3 equiv of $NaBH_4$ in methanol at 0 °C during 2 h (conditions ii outlined in Scheme 2), gave successfully the nitro-hydroxylactam **5b** as a crystalline and stable product in 65% yield. This observation was in line with the fact that the reduction of the nitro-imide functionality into the nitro-alcohol was already achieved by us on related products using sodium borohydride at lower temperature.[21] Furthermore, reaction of **5b** under conditions iii as outlined above (Scheme 2), gave directly 2-methyl-6-oxoisoindolo[2,1-*a*]benzimidaz-ole (**8b**) in comparable yields (63%) after chromatography and recrystallisation from dry ethanol.



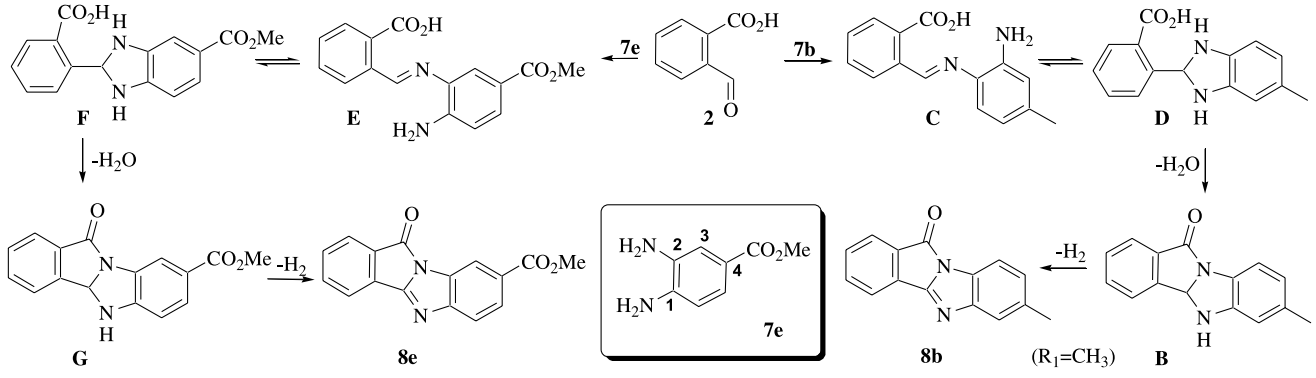
Scheme 3. Univocally 'one-pot' procedure access to 11-oxoisoindolo[2,1-*a*]-benzimidazole derivatives **8a** and **8b**.

The synthetic pathway leading to **8b** occurred through a cascade process by subsequent reduction of the nitro group of **5b** into the non isolated amino-alcohol **6b**, followed by loss of water, to form the *N*-acyliminium cation **A**, nucleophilic attack by the nitrogen atom (Scheme 2) and finally by spontaneous oxidation[22]-elimination of the resulting unstable 10*b*,11-dihydro-6-oxoisoindolo[2,1-*a*]-benzimidazole (**B**). In the case of **8a**, there was no direct evidence for the nucleophilic attack of the nitrogen atom onto the *N*-acyliminium cation since the nitro-hydroxylactam **5a** was not isolated under the set of reduction conditions.

The structure of **8a**,**b** was equally confirmed chemically, as outlined in Scheme 3, by treatment of an equimolar amount of *o*-phenylenediamine (**7a**), or 2-amino-4-methyl-aniline (**7b**) and 2-formylbenzoic acid (**2**) under azeotropic removal of water according to the classical reported procedure.[23]

It is interesting to note that this process in the case of the 4-methyl derivative **7b** proceeded in a highly regioselective manner. Scheme 4 demonstrates a plausible mechanism of the formation of the sole 2-methyl-6-oxoisoindolo[2,1-*a*] benzimidazole (**8b**). So, because the amine function at C_1 of **7b** is more nucleophilic than the one at C_2, the amino-aldehyde condensation yielded the imine **C** which then cyclized to afford the imidazoline **D**. This latter, after an intramolecular cyclodehydration into **B** followed in an ultimate step by a spontaneous oxidation/elimination reaction afforded the corresponding imidazole derivative **8b**.[24] In contrast, the opposite profile was obtained with the *o*-phenylenediamine substrate **7e**. In fact, the condensation of **2** with **7e** took another course with a more reactive amine function at C_2, giving the imine **E**. This latter intermediate, after a sequential set of reactions as outlined for **8b**, led to the product **8e** with the ester function at the C_8 position.[25]

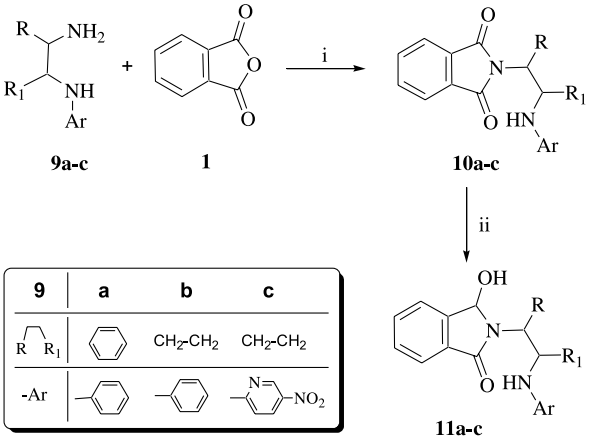
We decided next to explore another approach starting from *o*-phenylenediamine (**7a**) which was protected at one nitrogen atom with di-*t*-butyldicarbonate (Boc_2O) and acetic anhydride (Ac_2O) into carbamate **3c**[26a] and acetamide **3d**,[26b] respectively (Scheme 2). The choice of these groups was based on two considerations: first, the NHBoc and NHAc groups were rarely engaged in the intramolecular cationic cyclization, and we expected that both groups,



Scheme 4. Plausible sequential mechanism leading to 2-methyl(or 3-methoxycarbonyl)-6-oxoisoindolo[2,1-*a*]benzimidazole **8a** or **8b**.

especially the *t*-Boc, could be removed easily during[16d] or after cyclization to form the benzimidazole derivative **8a**,**b**, respectively. Second, both the *t*-butyloxy carbamate and acetyl groups are electron-withdrawing groups which could render the amino group less nucleophilic leading to the amino-alcohols **6c**,**d** as isolable intermediates. Thus, treatment of **3c**,**d** with 1 equiv of phthalic anhydride (**1**) in toluene at reflux in the presence of a catalytic amount of triethylamine over 12 h gave the imides **4c** and **4d** in 85 and 91% yields, respectively. These imides were then converted regioselectively to the *N*-acyliminium ions precursors **6c**,**d** by borohydride reduction as described above for **5b** in 85 and 89% yield.

According to our previous reports showing that trifluoroacetic acid (TFA) and acetic acid (AcOH) are good catalysts for the intramolecular α-amidoalkylation and α-heteroamidoalkylation, treatment of hydroxy-lactam **6c** with TFA in CH_2Cl_2 for 24 h or neat TFA for 4 h at room temperature afforded in both cases **8a** in about 73% yield. This product, which was identical to the one obtained from the nitro-imide **4a** (Scheme 2), resulted from an intramolecular cyclization of the *N*-acyliminium intermediate of type **A** with a nitrogen atom as nucleophile in parallel with Boc deprotection. We do have some evidence that the *t*-Boc deprotection occurs subsequently to the cyclization due to different deprotection kinetics, but this was not confirmed. Taking into account that TFA is a standard deprotecting agent for the *t*-Boc group, we decided to use a weaker acid, such as AcOH, for the cyclization process, hoping to be able to maintain the *t*.Boc protective group. Thus, α-hydroxy-lactam **6c** upon treatment with neat AcOH for 8 h or in CH_2Cl_2 for 24 h at reflux gave again **8a** in comparable yields of about 67%. In order to avoid the deprotection process, the aza-acylated α-hydroxylactam **6d** (R_2=Ac) was used as *N*-acyliminium ion precursor. In fact, the acetyl derivative **6d**, after treatment with neat TFA at rt over 4 h gave 11-acyl-6-oxoisoindolo[2,1-*a*]benzimidazo-le (**8d**) in 80% yield after recrystallization from ethanol.



Scheme 5. Sequential set leading to α-hydroxylactam precursors **11a–c**. Reagents and conditions: (i) Toluene, cat. NEt_3, reflux, Dean–Stark, 12 h; (ii) 3 equiv of $NaBH_4$, MeOH, −5 to 0 °C, aq. HCl in ethanol, 1 h.

Having established that the intramolecular α-aza-amidoalkylation route is effective for the preparation of the isoindolo[2,1-*a*]benzimidazole derivatives **8a–d**, we decided to elaborate another class of α-hydroxylactam precursors in which a nitrogen atom bear another nucleophile such as an aromatic or heteroaromatic system. Thus, as depicted in Scheme 5, the requisite α-hydroxy-lactams **11a–c** were obtained in a two-step sequence using classical procedures. Imides **10a–c** were readily prepared by amine-anhydride condensation from commercial diamines **9a–c** and phthalic anhydride (**1**) as indicated for **4c**,**d** in 76, 85 and 86%, respectively. The reaction was accelerated by adding dry triethylamine in catalytic quantity. Regioselective reduction of imides **10a–c** was accomplished with a large excess of sodium borohydride in methanol at −5 to 0 °C. In all cases, a regular addition of an ethanolic hydrogen chloride solution was necessary as already mentioned elsewhere for related structures,[17,18,21] and after 1 h of the reaction, α-hydroxylactams **11a–c** were isolated in, respectively, 80, 88 and 82% yield.

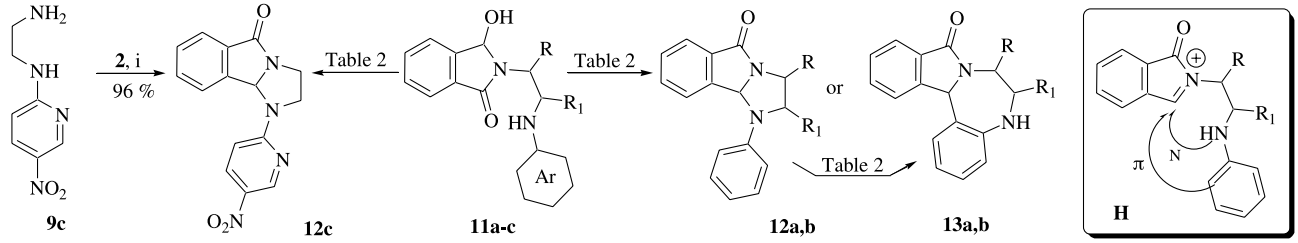
In the first set of cationic cyclizations in this series, substrate **11a** was chosen as a model for the *N*-acyl-iminium ion precursor. So, the subjection of α-hydroxy-lactam **11a** to weak AcOH (method A), weak TFA (method B) or catalytic *p*-toluenesulfonic acid (PTSA) (method C) in CH_2Cl_2 at room temperature for 12 h (Table 2, entry 1, 2 or 3) afforded only 11-phenyl-6-oxoisoindolo[2,1-*a*]benzimidazole (**12a**) in 65, 80 or 79% yield, respectively. This product resulted invariably from an intramolecular aza-cationic cyclization of the endocyclic *N*-acyliminium ion intermediate of type **H** (Scheme 6).

On the basis on our precedent work in this field and to avoid the intramolecular α-aza-amidoalkylation process to the

Table 2. Isoindolo[2,1-*a*]benzimidazole and corresponding isoindolo[1,4]dibenzodiazepine derivatives **12a**,**b** and **13a**,**b** produced via Scheme 6

	Reactant	Quantity[a] mmol	Conditions	Method	Product	Yield (%)[b]
1	**11a**	2.0	4 equiv of AcOH, CH_2Cl_2, rt, 12 h	**A**	**12a**	65
2	**11a**	2.5	4 equiv of TFA, CH_2Cl_2, rt, 12 h	**B**	**12a**	80
3	**11a**	3.0	Catalytic PTSA, CH_2Cl_2, rt, 12 h	**C**	**12a**	79
4	**11a**	4.0	Neat AcOH, rt, 12 h	**D**	**13a**	69
5	**11a**	4.0	Neat TFA, rt, 12 h	**E**	**13a**	74
6	**12a**	3.0	Neat AcOH, reflux, 24 h	**F**	**13a**	83
7	**12a**	6.0	Neat TFA, reflux, 24 h	**G**	**13a**	81
8	**12a**	5.0	Catalytic PTSA, toluene, reflux, 24 h	**H**	**13a**	90
9	**11b**	5.0	Catalytic PTSA, CH_2Cl_2, rt, 12 h	**C**	**12b**	82
10	**11b**	5.0	Neat TFA, rt, 12 h	**E**	**13b**[c]	93
11	**12b**	4.5	Neat TFA, reflux, 24 h	**G**	**13b**	89

[a] The reaction was conducted on 2–6 mmol of reactant under stirring. For entries 6–8, the isoindolo[2,1-*a*]benzimidazole **12a** was used as starting material.
[b] Isolated yield after purification by recrystallization or chromatography on silica gel column.
[c] A trace of the kinetic product **12b** were detected by ^{1}H NMR analysis and its quantity not exceed 5% of the products mixture.



Scheme 6. Reagents and conditions: (i) **2**, toluene, cat. NEt_3, reflux, Dean–Stark, 12 h; (ii) See text and Table for others procedures.

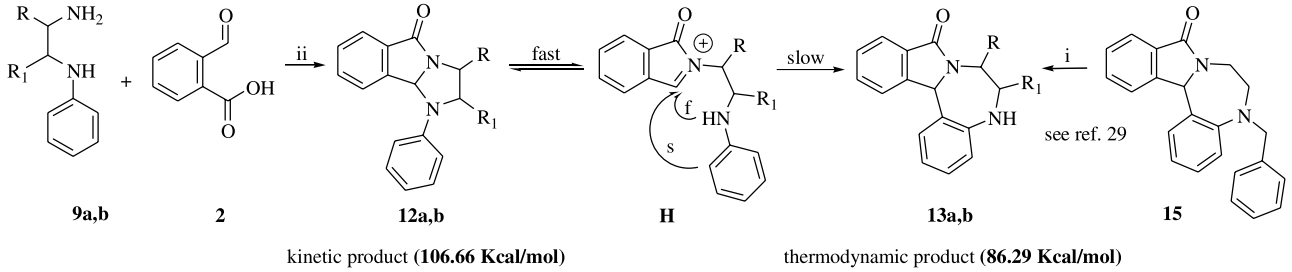
detriment of others, different reaction conditions were considered. So, the intramolecular arylation leading to isoindolo[1,4]dibenzodiazepine product **13a** as a single product occurred when neat AcOH (method D, Table 2, entry 4, 69%) or neat TFA (method E, Table 2, entry 5, 74%) was used as a proton source. Furthermore, to check the reversibility of the aza-cyclization reaction, taking into account that cyclic *N*,*N*-aminal **12a** could generate the *N*-acyliminium ion under acidic influence according to previously observations,[18c,27] we envisaged the treatment of acetal **12a** with neat AcOH (method F, Table 2, entry 6), neat TFA (method G, Table 2, entry 7) or catalytic amount of PTSA in toluene (method H, Table 2, entry 8) at reflux. Under these conditions all reactant **12a** disappeared (monitored by TLC) and the expected isoindolodibenzodiazepine product **13a** was obtained in good yield (81–90%).

The formation of these cycles **12a** and **13a** in acidic medium seems to proceed by invoking the kinetic vs thermodynamic control using the formal *N*-acyliminium ion **H** as intermediate (Schemes 6, 7). In fact, under mild conditions (methods A, B and C), the cationic intermediate **H** lead to isoindolo[2,1-*a*]benzimidazole derivative **12a** as the sole reaction product under kinetic process (fast reaction). In contrary, under stronger acidic conditions (neat acid at room temperature; methods D and E) and/or higher temperatures, the same intermediate provided in an alternate pathway isoindolo[1,4]dibenzodiazepine **13a** under thermodynamic control (slow reaction). The difference in reactivity between the two pathways can easily be contributed to the fact that the formation of **13a** requires higher activation energy due to the loss of aromaticity in the transition state. In addition, the compound **13a** proves to be about 20 kcal/mol more stable than its corresponding imidazoline **12a** according to AM1 calculations (86.29 kcal/mol vs 106.66 kcal/mol in the case of R-R_1=Ph), what clearly explains the complete conversion from **12a** to **13a** under more drastic conditions. These results confirm that the formation of the CH–N linkage of the kinetic product **12a** is reversible depending on the acidic activation. Under stronger conditions, cleavage of the CH–N bond in **12a** led back to the *N*-acyliminium ion congener **H** which in turn led to the diazepine compound **13a** as the thermodynamically more stable product.

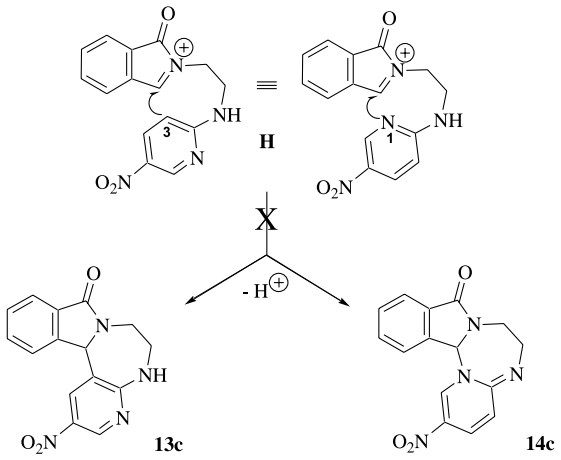
To establish the generality and versatility of this process we studied the effect of varying the nucleophilicity of the nitrogen atom which is interacts with the *N*-acyliminium ion during the cyclization process. For this purpose, two kinds of *N*-acyliminium ion precursors were considered; **11b** and **11c** in which the nitrogen atom nucleophilicity is altered with respect to the one in the reactant **11a**, and which bear a benzene or pyridine ring as a competing π-nucleophile or aza-nucleophile, respectively.

So, treatment of hydroxylactam **11b** according to method C (Table 2, entry 9), gave exclusively 1-phenyl-5-oxoisoindolo[2,1-*a*]imidazole (**12b**) under the kinetic control in 82% yield (Schemes 6 and 7). Similarly, reaction under conditions of method E, **11b** led to the cyclized thermodynamic [1,4]benzodiazepine product **13b** in excellent yield (Table 2, entry 10, 93%). During this reaction, the 1-phenyl-5-oxoisoindolo[2,1-*a*]imidazole structure **12b** was detected as a minor product but its yield did not exceed 5% in all cases.[28] As for the diazepine derivative **13a**, the product **13b** was also isolated in 89% yield starting from the kinetic product **12b** under conditions outlined in Table 2 (method G, entry 11) in a one pot procedure involving *N*-acyliminium ion intermediate **H** (Schemes 6 and 7).

In contrast, the hydroxylactam **11c**, with a reduced nucleophilicity with respect to both the N and π-aromatic nucleophilic centers due to the nitro group, afforded in all attempts with differing acidic and/or temperature conditions, the imidazoline derivative **12c** in comparable yields (85%). These results suggest that the formation of the azepine type structures **13** and **14** requires sufficiently activated aromatic systems (Scheme 8).[29]



Scheme 7. Kinetic vs thermodynamic scheme leading to imidazole and diazepine derivatives **12a**,**b** and **13a**,**b**. Reagents and conditions: (i) H_2, 10% Pd–C, AcOH–HCl, 50 °C, 6.5 h (see Ref. 30 for more details); (ii) **2**, toluene, cat. NEt_3, reflux, Dean–Stark, 12 h.



Scheme 8. Possible structures which could be resulted form a pyridine attack on the *N*-acyliminium ion intermediate **H**.

As a direct method for structural confirmation of imidazole and benzimidazole derivatives, the condensation of *o*-formylbenzoic acid (**2**) with diamines **7a**,**b** and **12a–c** under azeotropic removal of water was used successfully, thus providing isoindoloimidazoles **12b** (82%) and **12c** (96%), and isoindolobenzimidazoles **8a** (69%), **8b** (54%), and **12a** (89%) identical to the compounds obtained by the *N*-acyliminium sequence. Furthermore, the structure elucidation of these products as well as all compounds intermediates was based on their spectroscopic data (IR, ^{1}H NMR and ^{13}C NMR including NOE Difference and DEPT experiments) as well as their microanalyses.

The NMR data of the imidazole product **8a** has been previously reported in some details.[9,14b] For related compounds **8′a**, **8b**, and **8e**, the ^{1}H NMR data have a same profile globally as for **8a** with however a side chain signal corresponding to a methoxy ($\delta=3.79$ ppm), methyl ($\delta=2.47$ ppm), and methoxycarbonyl ($\delta=3.95$ ppm) groups, respectively, with an additional NH signal at $\delta=10.48$ ppm for **8′a**. No signals for the proton in position C_{4b} of the isoindole system, appearing classically at about $\delta=6.0$ ppm, was observed in theses cases.

In the imidazoisoindolones structures **12a**, **12b** and **12c**, the angular protons appear as singlets at $\delta=7.24$, 6.12, and 6.61 ppm, respectively. These latter absorb downfield compared to the same protons of their hydroxylactams congeners **11a** ($\delta=6.22$ ppm), **11b** ($\delta=5.78$ ppm), and **11c** ($\delta=5.83$ ppm), respectively. The same fact, was also observed for the diazepinoisoindolones in comparaison to their precursors, with however a little difference on the chemical shift values which are $\Delta\delta=+0.09$ ppm and $\Delta\delta=+0.05$ ppm in favour to **13a** and **13b** to the detriment of **12a** and **12b**, respectively. These observations are in agreement with the fact that C–N and C–C bonds, formed during the cyclization process, have not the same effect on the CH angular absorbance. These results are also in agreement with previous reports on analogous compounds.[15–18]

Furthermore, the key feature in the ^{13}C NMR spectra of **8′a** and **8a–d** or **8e**, was the appearance of fourteen or fifteen signals, respectively, in the aromatic region. One of these disappears in the corresponding DEPT program spectra as the consequence of the aza-amidoalkylation cyclization process. Interestingly, if the quaternary angular carbon of the C=N bond appears at $\delta=156.4$ ppm (**8a**), $\delta=152.4$ ppm (**8b**), and $\delta=155.0$ ppm (**8e**) in comparable chemical shift values reported in the literature for related products,[14b] the one of **8′a** appeared downfield with more significant deshielding at $\delta=166.7$ ppm. This fact is due to the proximity of three heteroatoms which belong to amide, amine and etheroxide functionalities, respectively. Especially diagnostic was the differentiation between the formed five-membered ring products **8b** and **12a–c** and the cyclized seven-membered ring ones **13a**,**b**.

In fact, for the isoindolobenzimidazole **8b** the appearance of the C=N signal at $\delta=152.4$ ppm constitutes the consequence of the intramolecular cyclization of **4b**. This value is similar to those obtained for related structures.[14] Interestingly, it can be seen that the aza-cyclization process of **11a**,**b** into **12a**,**b** induces a weak variation in the carbon angular absorbance which is $\Delta\delta=+1.2$ ppm and $\Delta\delta=+7.3$ while the π-cyclization into **13a**,**b** of **11a**,**b** shifted dramatically the absorbance of the angular carbon to higher fields. In these case, an important deshielding of $\Delta\delta=+21.2$ ppm and $\Delta\delta=+20.5$ ppm was observed.

3. Conclusion

In summary, we have shown that *N*-acyliminium ion precursors **6a–d** could be generated in two pathways from nitro-hydroxylactams **5a**,**b** or corresponding amino-imides **4c**,**d** by regioselective reduction processes using iron/acetic acid or sodium borohydride/methanol, respectively. The *N*-acyliminium ion in turn furnished via an intramolecular α-aza-amidoalkylation with a nitrogen atom as nucleophile various and new 6-oxoisoindolo[2,1-*a*]benzimidazole products **8a–d** in good yields. In some cases, the amino-hydroxylactam intermediates **6** were not isolated but cyclized directly into product **8**.

Similar α-hydroxylactams **11a**,**b**, under the same process, produced efficiently under thermodynamic control the expected isoindolo[1,4]benzodiazepines **13a**,**b** in good yields and excellent regiocontrol. These latter were also obtained starting from isoindoloimidazoles **12a**,**b**, which turned out to be the kinetically formed products from cyclization of the nitrogen onto the iminium ion species produced by acid treatment of the α-hydroxylactams **11a**,**b**. The hydroxylactam **11c** only gave rise to the imidazoline derivative **12c**, clearly demonstrating the influence of electronic factors in the π-aromatic attack. Finally, the structures of the isoindoloimidazole derivatives **8a**,**b** and **12a**,**b** as well as **12c** was confirmed chemically by an alternative synthesis from *o*-formylbenzoic acid (**2**) and corresponding diamines **7a**,**b** or **9a–c** in an one pot procedure. For full exploitation of this route which provides a novel synthesis of imidazole, benzimidazole and diazepine derivatives and which is short, facile, general and more competitive, further work is currently underway to enlarge the scope of this application by accessing a wider variety of these structures.

4. Experimental

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualised using an ultraviolet lamp or iodine vapour. Mass spectral measurements were recorded on a AEI MS 902 S spectrophotometer. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France.

4.2. General procedure for synthesis of imides (4a,b)

A mixture of powdered phthalic anhydride (**1**, 1.48 g, 10 mmol) and *o*-nitroaniline (**3a**, 1.38 g, 10 mmol) or 4-methyl-2-nitroaniline (**3b**, 1.52 g, 10 mmol) in 100 mL of glacial acetic acid was heated at reflux for 24 h. After cooling, the precipitate formed was collected by filtration, washed with cyclohexane, diethyl ether and air dried. The resulting products were purified by recrystallization from ethanol to give imides **4a** and **4b** as yellow needles.

4.2.1. *N*-(*o*-Nitrophenyl)phthalimide (4a). This product was isolated as yellow solid in 89% yield; mp = 190–195 °C (lit.,[31] mp = 202–203 °C); IR (KBr) v 3093, 1715, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H, $1H_{benzene}$, J = 7.8 Hz), 7.61 (t, 1H, $1H_{benzene}$, J = 7.8, 7.0 Hz), 7.74–7.83 (m, 3H, $1H_{benzene}$ and $2H_{phthalimide}$), 7.93–7.98 (m, 2H, $2H_{phthalimide}$), 8.18 (d, 1H, $1H_{benzene}$, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 124 (2CH), 125.6 (Cq), 125.9 (CH), 129.8 (CH), 131.0 (CH), 131.9 (Cq), 134.3 (CH), 134.9 (2CH), 145.8 (2Cq), 166.5 (2CO); Anal. Calcd for $C_{14}H_8N_2O_4$ (268.22): C, 62.69; H, 3.01; N, 10.44. Found: C, 62.48; H, 2.95; N, 10.22.

4.2.2. *N*-(4′-Methyl-*o*-nitrophenyl)phthalimide (4b). This product was isolated as yellow needles in 91% yield; mp = 181 °C (lit.,[32] mp = 187 °C); IR (KBr) v 3082, 1716, 1534, 1383 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 2.50 (s, 3H, CH_3), 7.67 (d, 1H, $1H_{benzene}$, J = 7.6 Hz), 7.77 (d, 1H, $1H_{benzene}$, J = 7.6 Hz), 7.94–8.08 (m, 2H, $1H_{benzene}$ and $4H_{phthalimide}$); ^{13}C NMR (DMSO d_6) δ 19.8 (CH_3), 121.4 (Cq), 123.4 (2CH), 125.0 (CH), 130.3 (CH), 130.6 (Cq), 134.6 (CH), 134.8 (2CH), 140.6 (Cq), 144.6 (2Cq), 165.8 (2CO); Anal. Calcd for $C_{15}H_{10}N_2O_4$ (282.25): C, 63.83; H, 3.57; N, 9.93. Found: C, 63.66; H, 3.28; N, 9.87.

4.3. General procedure for synthesis of imides (4c,d) and (10a–c)

A mixture of α,β-diamine **4c**, **4d**, **9a**, **9b**, or **9c** (10 mmol), phthalic anhydride (**1**) (1.48 g, 10 mmol) and triethylamine (0.5 mL, 3.6 mmol) in toluene (50 mL) was refluxed with a Dean–stark apparatus for 12 h. The reaction mixture was cooled, then concentrated under reduced pressure. The residue was dissolved into dichloromethane, washed with 5% hydrochloric acid solution then with a 5% sodium hydrogenocarbonate solution. The organic layer was dried over magnesium sulfate, concentrated under vacuo, and recrystallization of the residue gave the expected imides **4c**,**d** or **10a**–**c** in good yields.

4.3.1. *N*-(*o*-*Tert*-butoxycarbonylamidophenyl)phthalimide (4c). This product was isolated as white crystals in 91% yield; mp = 269 °C (decomposition); IR (KBr) v 3417, 3034, 2990, 1731, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 9H, $3CH_3$), 7.12–7.53 (m, 4H, $4H_{benzene}$), 7.61–7.82 (m, 2H, $2H_{phthalimide}$), 7.90–7.98 (m, 2H, $2H_{phthalimide}$), 8.15 (s broad, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.9 ($3CH_3$), 80.1 (Cq), 123.4 (Cq), 124.8 (2CH), 125.6 (CH), 127.3 (CH), 129.6 (Cq), 131.1 (CH), 142.3 (CH), 134.4 (2CH), 140.6 (2Cq), 164.8 (CO), 167.2 (2CO); Anal. Calcd for $C_{19}H_{18}N_2O_4$ (338.36): C, 67.44; H, 5.36; N, 8.28. Found: C, 67.18; H, 5.22; N, 8.31.

4.3.2. *N*-(*o*-Acetamidophenyl)phthalimide (4d). This product was isolated as white crystals in 91% yield; mp = 200 °C; IR (KBr) v 3244, 3038, 1720, 1657 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, $COCH_3$), 7.24–7.31 (m, 2H, $1H_{benzene}$ and NH, exchangeable with D_2O), 7.36–7.58 (m, 2H, $2H_{benzene}$), 7.77–7.86 (m, 3H, $1H_{benzene}$ and $2H_{phthalimide}$), 7.89–7.96 (m, 2H, $2H_{phthalimide}$); ^{13}C NMR ($CDCl_3$) δ 24.3 (CH_3), 124.0 (Cq), 124.2 (2CH), 125.9 (CH), 126.0 (CH), 128.6 (CH), 129.7 (CH), 131.8 (Cq), 133.9 (2Cq), 134.8 (2CH), 167.4 (2CO), 168.6 (CO); Anal. Calcd for $C_{16}H_{12}N_2O_3$ (280.28): C, 68.56; H, 4.32; N, 9.99. Found: C, 68.39; H, 4.25; N, 10.05.

4.3.3. *N*-(*o*-Phenylaminophenyl)phthalimide (10a). This product was isolated as a yellow solid in 76% yield; mp = 200 °C (ethanol); IR (KBr) ν 3320, 3006, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.04 (s, 1H, NH, exchangeable with D_2O), 7.08–7.27 (m, 4H, $4H_{benzene}$), 7.37–7.80 (m, 5H, $5H_{benzene}$), 8.01–8.12 (m, 2H, $2H_{phthalimide}$), 8.17–8.26 (m, 2H, $2H_{phthalimide}$); ^{13}C NMR ($CDCl_3$) δ 118.5 (2CH), 121.4 (CH), 121.7 (CH), 123.3 (Cq), 123.9 (CH), 124.2 (2CH), 129.6 (2CH), 129.7 (CH), 130.2 (CH), 132.3 (2Cq), 134.8 (2CH), 140.8 (Cq), 143.4 (Cq), 167.7 (2CO); Anal. Calcd for $C_{20}H_{14}N_2O_2$ (314.34): C, 76.42; H, 4.49; N, 8.91. Found: C, 76.09; H, 4.25; N, 8.71.

4.3.4. *N*-(*o*-Phenylaminoethyl)phthalimide (10b). This product was isolated as a white solid in 85% yield; mp = 100 °C (ethanol); IR (KBr) ν 3345, 3010, 2989, 1712; ^{1}H NMR ($CDCl_3$) δ 3.42 (t, 2H, CH_2, J = 6.3 Hz), 3.96 (t, 2H, CH_2, J = 6.3 Hz), 6.57–6.72 (m, 3H, $3H_{benzene}$), 7.08–7.19 (m, 2H, $2H_{benzene}$), 7.66–7.75 (m, 2H, $2H_{phthalimide}$), 7.77–7.87 (m, 2H, $2H_{phthalimide}$); ^{13}C NMR ($CDCl_3$) δ 37.7 (CH_2), 43.3 (CH_2), 112.9 (2CH), 117.9 (CH), 123.7 (2CH), 129.6 (2CH), 132.3 (2Cq), 134.4 (2CH), 147.9 (Cq), 169 (2CO); Anal. Calcd for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.02; H, 5.15; N, 10.41.

4.3.5. *N*-(2-(5′-Nitropyridin-2′-ylamino)ethyl)phthalimide (10c). This product was isolated as a white solid in 86% yield; mp = 191 °C (ethanol); IR (KBr) ν 3242, 3005, 2950, 1710, 1503, 1396; ^{1}H NMR (DMSO d_6) δ 3.37–3.76

(m, 4H, $2CH_2$), 6.42 (d, 1H, $H_{pyridine}$, $J=8.6$ Hz), 7.79–7.85 (m, 2H, $2H_{phthalimide}$), 8.04 (d, 1H, $H_{pyridine}$, $J=8.6$ Hz), 8.12–8.24 (m, 2H, $2H_{phthalimide}$), 8.71 (s, 1H, $H_{pyridine}$), 8.90 (t, 1H, NH, $J=2.4$ Hz, exchangeable with D_2O); ^{13}C NMR (DMSO d_6) δ 36.9 (CH_2), 38.5 (CH_2), 108.5 (CH), 122.6 (2CH), 131.4 (CH), 131.6 (Cq), 133.9 (2CH), 134.4 (2Cq), 146.1 (CH), 161.4 (Cq), 167.8 (2CO); Anal. Calcd for $C_{15}H_{12}N_4O_4$ (312.09): C, 57.69; H, 3.87; N, 17.94. Found: C, 57.51; H, 3.66; N, 17.63.

4.4. General procedure for reduction of imides (4a–d) and (10a–c)

To a mixture of 5 mmol of imide **4a** (**4b**, **4c**, **4d**, **10a**, **10b** or **10c**) in dry methanol (40 mL) at −5 to 0 °C was added sodium borohydride (283–565 mg, 7.5–15 mmol) by portions during 5 min. To this mixture was added 5 drops of ethanolic hydrochloric acid solution (prepared by addition of nine drops of concentrated hydrochloric acid into 9 mL of dry ethanol) at regular intervals of 10 min. The reaction was monitored by TLC using CH_2Cl_2 as eluent (CH_2Cl_2/MeOH (9/1) in the case of **10c**). After the end of the reaction (45 min to 1 h), the excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10% hydrochloric acid until pH 4. Sodium hydrogen carbonate was added and the solvent was evaporated. The resulting residue was triturated with water and dichloromethane and the organic layer was separated, washed with water, brine, dried and concentrated in vacuo. The resulting product was purified by chromatography on silica gel column or by recrystallization to give in appreciable yield **5b**, **6c**, **6d**, **8a**, **8′a**, **11a**, **11b** or **11c**, respectively.

4.4.1. 3-Hydroxy-2,3-dihydro-2-(*o*-nitrophenyl)isoindol-1-one (5a). This product was not isolated but react immediately in situ to give the cyclised product **8′a** and/or **8a**.

4.4.2. 6-Oxoisoindolo[2,1-*a*]benzimidazole (8a). This product was obtained in a range of 45–61% yield and have same characteristics to that reported in literature (lit.,[9] mp > 290 °C, 39% yield).

4.4.3. 10*b*-Methoxy-10*b*,11-dihydrobenzo[4,5]imidazo[2,1-*a*]isoindol-6-one (8′a). This product was isolated as orange crystals in 39% yield after chromatography on silica gel column using a mixture of dichloromethane/cyclohexane (7:3) as eluent; mp = 128 °C; IR (KBr) v 3246, 3023, 2958, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, OCH_3), 7.16 (t, 1H, $1H_{isoindole}$, $J=7.8$, 7.0 Hz), 7.46–7.57 (m, 3H, $3H_{benzene}$), 7.65 (t, 1H, $1H_{isoindole}$, $J=7.8$, 7.0 Hz), 7.91 (d, 1H, $1H_{benzene}$, $J=7.0$ Hz), 8.17 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz), 8.84 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz), 10.45 (s, 3H, NH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 52.8 (OCH_3), 122.6 (CH), 123.8 (CH), 125.9 (CH), 127.3 (CH), 129.2 (Cq), 130.6 (CH), 130.7 (CH), 132.6 (CH), 134.7 (Cq), 136.3 (CH), 136.8 (Cq), 137.9 (Cq), 166.8 (CO), 167.9 (Cq); Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.27): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.64; N, 11.01.

4.4.4. 3-Hydroxy-2,3-dihydro-2-(4′-methyl-*o*-nitrophen-yl)isoindol-1-one (5b). This product was isolated as a yellow solid in 65% yield; mp = 158 °C; IR (KBr) v 3351, 3082, 1690, 1532, 1383 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 3.59 (d, 1H, OH, $J=11.7$ Hz, exchangeable with D_2O), 6.17 (d, 1H, CH, $J=11.7$ Hz), 7.35–7.55 (m, 3H, $1H_{benzene}$ and $2H_{isoindole}$), 7.56–7.75 (m, 3H, $1H_{benzene}$ and $2H_{isoindole}$), 7.84 (d, 1H, $1H_{benzene}$, $J=10.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 83.9 (CH), 123.8 (CH), 124.6 (CH), 125.9 (CH), 127.5 (Cq), 130.2 (CH), 130.6 (CH), 130.8 (Cq), 134.0 (CH), 135.4 (CH), 139.7 (Cq), 145.4 (Cq), 146.7 (Cq), 166.9 (CO); Anal. Calcd for $C_{15}H_{12}N_2O_4$ (284.27): C, 63.38; H, 4.25; N, 9.85. Found: C, 63.21; H, 4.08; N, 9.71.

4.4.5. 3-Hydroxy-2,3-dihydro-2-(*o*-*tert*-butoxycarbonylamidophenyl)isoindol-1-one (6c). This product was isolated as a white solid in 85% yield; mp = 188 °C; IR (KBr) v 3446, 3280, 3010, 2970, 1736, 1663 cm^{-1}; ^1H NMR (DMSO d_6) δ 1.39 (s, 9H, $3CH_3$), 6.23 (d, 1H, OH, $J=7.1$ Hz, exchangeable with D_2O), 6.77 (d, 1H, CH, $J=7.1$ Hz), 7.14 (t, 1H, $1H_{benzene}$, $J=7.8$, 7.0 Hz), 7.34 (t, 2H, $1H_{benzene}$ and $1H_{isoindole}$, $J=7.8$, 7.8 Hz), 7.58–7.88 (m, 5H, $2H_{benzene}$ and $3H_{isoindole}$), 8.35 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO d_6) δ 28.1 ($3CH_3$), 79.5 (Cq), 83.6 (CH), 122.2 (CH), 122.9 (CH), 123.5 (CH), 123.7 (CH), 127.5 (Cq), 128.0 (CH), 129.2 (CH), 129.6 (CH), 131.4 (Cq), 132.6 (Cq), 136.6 (Cq), 145.8 (Cq), 152.9 (CO), 165.8 (CO); Anal. Calcd for $C_{19}H_{20}N_2O_4$ (340.37): C, 67.05; H, 5.92; N, 8.23. Found: C, 67.12; H, 5.81; N, 8.09.

4.4.6. 3-Hydroxy-2,3-dihydro-2-(*o*-acetamidophenyl)-isoindol-1-one (6d). This product was isolated as a white solid in 89% yield; mp = 185 °C (ethanol); IR (KBr) v 3439, 3247, 3006, 2923, 1689, 1673 cm^{-1}; ^1H NMR (DMSO d_6) δ 1.98 (s, 9H, CH_3), 6.17 (s, 1H, CH), 6.65 (s broad, 1H, OH, exchangeable with D_2O), 7.11–7.34 (m, 3H, $3H_{benzene}$), 7.46–7.56 (m, 1H, $1H_{benzene}$), 7.60–7.62 (m, 2H, $2H_{isoindole}$), 7.79 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz), 8.03 (d, 1H, $1H_{isoindole}$, $J=7.8$ Hz),$_{isoindole}$), 8.48 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO d_6) δ 24.3 (CH_3), 84.6 (CH), 123.5 (2CH), 124.1 (CH), 125.0 (CH), 127.7 (CH), 128.4 (CH), 129.7 (CH), 131.0 (Cq), 132.7 (CH), 135.8 (Cq), 141.3 (Cq), 144.9 (Cq), 170.1 (CO), 174.9 (CO); Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282.29): C, 68,07; H, 5,00; N, 9,92. Found: C, 67,98; H, 4,81; N, 9,84.

4.4.7. 3-Hydroxy-2,3-dihydro-2-(*o*-phenylaminophenyl)-1*H*-isoindol-1-one (11a). This product was isolated as a yellow solid in 80% after recrystallization from ethanol; mp = 73 °C; IR (KBr) ν 3381, 3333, 3038, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.22 (s, 1H, CH), 7.17–7.36 (m, 9H, $9H_{benzene}$), 6.65–7.64 (m, 12H, $9H_{benzene}$ and $3H_{isoindole}$), 7.80–7.89 (m, 1H, $1H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 84.5 (CH), 118.5 (2CH), 120.5 (CH), 121.2 (CH), 122.5 (CH), 123.8 (CH), 124.2 (CH), 127.0 (Cq), 128.3 (CH), 129.1 (CH), 129.6 (2CH), 130.5 (CH), 131.3 (Cq), 133.1 (CH), 141.5 (Cq), 143.6 (Cq), 144.3 (Cq), 167.2 (CO); Anal. Calcd for $C_{20}H_{16}N_2O_2$ (316.35): C, 75.93; H, 5.10; N, 8.86. Found: C, 75.80; H, 5.02; N, 8.65.

4.4.8. 3-Hydroxy-2,3-dihydro-2-(*o*-phenylaminoethyl)-1*H*-isoindol-1-one (11b). This product was isolated as a white solid in 88% after recrystallization from ethanol; mp = 76 °C; IR (KBr) ν 3363, 3009, 2988, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (t, 2H, CH_2, $J=5.5$ Hz), 3.51–3.67 (m, 1H, CH_2), 3.72–3.88 (m, 1H, CH_2), 4.09 (s large, 1H,

NH, exchangeable with D_2O), 5.78 (s, 1H, CH), 6,58 (d, 2H, $J=7.8$ Hz), 6,69 (t, 1H, $J=7.1$ Hz), 7.12 (t, 2H, $J=7.8$ Hz), 7.39–7.57 (m, 3H, $3H_{isoindole}$), 7.66 (d, 1H, $1H_{isoindole}$, $J=7.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 40.3 (CH_2), 43.4 (CH_2), 83 (CH), 113.5 (2CH), 118.3 (CH), 123.5 (2CH), 129.6 (2CH), 130.1 (CH), 131.5 (Cq), 132.7 (CH), 144.1 (Cq), 147.9 (Cq), 168.6 (CO); Anal. Calcd for $C_{16}H_{16}N_2O_2$ (268.31): C, 75.93; H, 5.10; N, 8.86. Found: C, 75.80; H, 5.02; N, 8.65.

4.4.9. 3-Hydroxy-2,3-dihydro-2-[2-(5′-nitropyridin-2′-ylamino)ethyl]-1*H*-isoindol-1-one (11c). This product was isolated as a yellow solid in 82% after recrystallization from dry ethanol; mp = 120 °C (decomposition); IR (KBr) ν 3467, 3307, 3093, 2935, 1704, 1504, 1337 cm^{-1}; ^1H NMR ($CDCl_3$, this product is no stable in the solution) δ 3.08 (s broad, 1H, NH, exchangeable with D_2O), 3.28–3.71 (m, 3H, CH_2–CH_2), 4.13–4.18 (m, 1H, CH_2–CH_2), 3.08 (s broad, 1H, OH, exchangeable with D_2O), 5.83 (s, 1H, CH), 6.37 (d, 1H, $1H_{pyridine}$, $J=9.4$ Hz), 7.29–7.43 (m, 1H, $1H_{benzene}$), 7.47–7.57 (m, 3H, $3H_{benzene}$), 7.99 (d, 1H, $1H_{pyridine}$, $J=9.4$ Hz), 8.58 (s, 1H, $1H_{pyridine}$); Anal. Calcd for $C_{15}H_{14}N_4O_4$ (314.30): C, 57.32; H, 4.49; N, 17.83. Found: C, 57.18; H, 4.27; N, 17.65.

4.5. Procedure for the reductive cyclization of nitro-hydroxylactam 5b

To a solution of 6 mmol of nitro-hydroxylactam **5b** in dry methanol (40 mL) at −5 to 0 °C was added sodium borohydride (679 mg, 18 mmol) by portions during 10 min. To this mixture was added 5 drops of ethanolic hydrochloric acid solution (as prepared above) at regular intervals of 5 min. The reaction was monitored by TLC using CH_2Cl_2 as eluent. After the end of the reaction (2 h), the excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10% hydrochloric or H_2SO_4 acid until pH 4. After sodium hydrogen carbonate was added and the solvent was evaporated. The resulting residue was triturated with water and dichloromethane and the organic layer was separated, washed with water, brine, dried and concentrated in vacuo.

4.5.1. 2-Methyl-6-oxoisoindolo[2,1-*a*]benzimidazole (8b). This product was obtained as a white powder in 63% after recrystallization from absolute ethanol; mp = 238 °C; IR (KBr) ν 3025, 2952, 1719, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H, CH_3), 7.1 (d, 1H, $1H_{benzene}$, $J=8.1$ Hz), 7.41 (s, 1H, $1H_{benzene}$), 7.49 (d, 1H, $1H_{benzene}$, $J=8.1$ Hz), 7.57–7.94 (m, 4H, $4H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 22.8 (CH_3), 115.8 (CH), 116.6 (CH), 125.4 (CH), 131.2 (Cq), 131.4 (2CH), 131.7 (CH), 132.7 (Cq), 133.3 (CH), 134.6 (Cq), 138.4 (Cq), 139.6 (Cq), 152.4 (Cq), 170.4 (CO); Anal. Calcd for $C_{15}H_{10}N_2O$ (234.26): C, 76.91; H, 4.30; N, 11.96. Found: C, 76.81; H, 4.09; N, 12.05.

4.6. General procedure for acid cyclization of hydroxy-lactams (6c,b) and (11a–c)

The procedure is general and concerns the use of neat or weak TFA, AcOH or catalytic PTSA at rt or reflux without or with a solvent as CH_2Cl_2 or toluene. For more details see Table 2. A stirred solution of 6 mmol of amino-hydroxy-lactams **6c**,**d** (or hydroxy-lactams **11a–c**) in 10 mL of appropriate acid or catalytic amount (in the case of PTSA) was left to react at room temperature or reflux in the presence or not of the solvent (For details see Table 2). After the required time, the solvent was evaporated in vacuo, and the residue was diluted with dichloromethane (10 mL) and treated with a saturated solution of hydrogenocarbonate. After separation, the organic layer was washed with water, brine, dried and concentrated in vacuo. The resulting residue was purified either by recrystallisation from ethanol or through a silica gel column.

4.6.1. 6-Oxoisoindolo[2,1-*a*]benzimidazole (8c). This product is identical to **8a** described above.

4.6.2. 11-Acetyl-10*b*,11-dihydrobenzo[4,5]imidazo[2,1-*a*]isoindol-6-one (8d). This product was isolated as a white-yellow crystals after chromatography on silica gel column using a mixture of chloroform/cyclohaxane (2:3) as eluent in 91% yield; mp = 168 °C; IR (KBr) v 3021, 2943, 1732, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, CH_3), 6.93 (s, 1H, CH), 7.05–7.19 (m, 3H, $3H_{benzene}$), 7.49–7.64 (m, 2H, $1H_{benzene}$ and $1H_{isoindole}$), 7.66–7.75 (m, 1H, $1H_{isoindole}$), 7.85 (d, 1H, $1H_{isoindole}$, $J=7.0$ Hz), 8.25 (d, 1H, $1H_{isoindole}$, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_3), 79.4 (CH), 113.1 (CH), 117.2 (CH), 124.1 (CH), 124.5 (CH), 124.9 (CH), 128.3 (CH), 130.3 (CH), 132.1 (Cq), 132.8 (Cq), 133.7 (CH), 136.0 (Cq), 145.0 (Cq), 169.3 (CO), 171.6 (CO); Anal. Calcd for $C_{16}H_{12}N_2O_2$ (264.28): C, 72.72; H, 4.58; N, 10.60. Found: C, 72.59; H, 4.32; N, 10.28.

4.6.3. 11-Phenyl-6(10*bH*)-oxoisoindolo[2,1-*a*]benzimidazole (12a). This product was obtained as white crystals in 79% after recrystallization from ethanol; mp = 208–210 °C (decomposition); IR (KBr) ν 3015, 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03–7.12 (m, 1H, H benzene), 7.24 (s, 1H, CH), 7.26–7.42 (m, 2H, $2H_{benzene}$), 7.64–8.03 (m, 9H, $9H_{benzene}$), 8.28–8.37 (m, 1H, $1H_{benzene}$); ^{13}C NMR ($CDCl_3$) δ 83.3 (CH), 108.6 (CH), 116.9 (CH), 120.4 (CH), 124.2 (CH), 124.8 (2CH), 125.3 (CH), 125.6 (CH), 126.4 (CH), 130.2 (2CH), 130.4 (CH), 131.5 (Cq), 133.1 (CH), 133.9 (Cq), 141.9 (Cq), 144.1 (Cq), 146.3 (Cq), 170.7 (CO); Anal. Calcd for $C_{20}H_{14}N_2O$ (298.34): C, 80.52; H, 4.73; N, 9.39. Found: C, 80.42; H, 4.59; N, 9.19.

4.6.4. 5-Phenyl-4*b*,5,6,7-tetrahydroimidazo[2,1-*a*]isoindol-9-one (12b). This product was obtained as a white powder in 82% after recrystallization from absolute ethanol; mp = 143 °C; IR (KBr) ν 3005, 2992, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.39–3.68 (m, 2H, CH_2), 3.77–3.92 (m, 1H, CH_2), 4.26–4.39 (m, 1H, CH_2), 6.12 (s, 1H, CH), 6.87–7.28 (m, 3H, $3H_{benzene}$), 7.29–7.41 (m, 2H, $2H_{benzene}$), 7.44–7.54 (m, 2H, $2H_{isoindole}$), 7.71–7.86 (m, 2H, $2H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 42.4 (CH_2), 53.3 (CH_2), 75.7 (CH), 114.7 (2CH), 119.3 (CH), 124.6 (2CH), 129.7 (2CH), 130.0 (CH), 132.9 (CH), 133.3 (Cq), 145.7 (Cq), 146.8 (Cq), 173.1 (CO); Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.84; H, 5.48; N, 11.27.

4.6.5. 2-(1-Benzyl-1*H*-benzimidazol-2-yl)-3-hydroxy-2,3-dihydroisoindol-1-one (12c). This product was obtained as a yellow orange powder in 85% after recrystallization from absolute ethanol; mp = 234 °C; IR (KBr) ν 3079, 2963, 1699, 1513, 1327 cm^{-1}; ^1H NMR (DMSO d_6) δ 3.50–3.82

(m, 2H, CH_2), 3.87–3.99 (m, 1H, CH_2), 4.33 (dd, 1H, CH_2, J=6.4, 10.7 Hz), 6.61 (s, 1H, CH), 6.78 (d, 1H, $1H_{pyridine}$, J=9.1 Hz), 7.56–7.82 (m, 3H, $3H_{isoindole}$), 8.30–8.44 (m, 2H, $2H_{isoindole}$ and $1H_{pyridine}$), 9.26 (d, 1H, $1H_{pyridine}$, J=2.7 Hz); ^{13}C NMR (DMSO d_6) δ 42.8 (CH_2), 50.4 (CH_2), 76.2 (CH), 108.6 (CH), 124.3 (CH), 128.2 (CH), 131.2 (CH), 133.2 (Cq), 134.0 (2CH), 136.6 (Cq), 145.3 (Cq), 146.8 (CH), 159.5 (Cq), 173.1 (Cq); Anal. Calcd for $C_{15}H_{12}N_4O_3$ (296.28): C, 60.81; H, 4.08; N, 18.91. Found: C, 60.70; H, 4.10; N, 18.69.

4.6.6. 5,15*b*-Dihydro-11*H*-isoindolo[2,1-*d*]dibenzo[*b*,*f*]-[1,4]diazepin-11-one (13a). This product was obtained as a yellow powder in 81–91% after recrystallization from absolute ethanol; mp=248 °C; IR (KBr) ν 3346, 3013, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.13 (s, 1H, CH), 6.61–6.83 (m, 3H, $3H_{benzene}$), 6.88–7.16 (m, 4H, $4H_{benzene}$), 7.32 (s, 1H, NH, exchangeable with D_2O), 7.42–7.68 (m, 1H, $1H_{isoindole}$), 8.2 (m, 1H, $1H_{isoindole}$); ^{13}C NMR ($CDCl_3$) δ 63.3 (CH), 118.9 (CH), 119.3 (CH), 119.5 (CH), 120.1 (CH), 122.7 (CH), 124.2 (CH), 124.4 (CH), 125.3 (CH), 126.1 (Cq), 126.2 (CH), 127.2 (Cq), 128.6 (CH), 129.1 (CH), 131.1 (Cq), 133.1 (Cq), 135.2 (Cq), 142.0 (Cq), 144.1 (Cq), 166.9 (CO); Anal. Calcd for $C_{20}H_{14}N_2O$ (298.34): C, 80.52; H, 4.73; N, 9.39. Found: C, 80.41; H, 4.59; N, 9.21.

4.6.7. 5,6,7,13*b*-Tetrahydroisoindolo[2,1-*d*][1,4]benzodiazepin-9-one (13b). This product was obtained as a white solid in 89–93% after chromatography over silica gel column using a mixture of CH_2Cl_2/hexane (9.5/0.5) as eluent and recrystallization from absolute ethanol; mp=139 °C (lit.,[29] mp=135–137 °C); IR (KBr) ν 3336, 3013, 2986, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.03–3.19 (m, 1H, CH_2), 3.49–3.68 (m, 2H, CH_2), 4.0 (s br, 1H, NH, exchangeable with D_2O), 4.25–4.39 (m, 1H, CH_2), 5.73 (s, 1H, CH), 6.77–6.92 (m, 2H, $2H_{benzene}$), 7.03 (d, 1H, $1H_{benzene}$, J=7.1 Hz), 7.16–7.25 (t, 1H, $1H_{benzene}$, J=7.1 Hz), 7.47–7.68 (m, 3H, $3H_{isoindole}$), 7.94 (d, 1H, $1H_{isoindole}$, J=7.2, Hz); ^{13}C NMR ($CDCl_3$) δ 44.3 (CH_2), 47.5 (CH_2), 62.5 (CH), 120.7 (CH), 121.8 (CH), 124.6 (CH), 125.4 (CH), 127.3 (Cq), 127.7 (CH), 128.9 (CH), 129.3 (CH), 131.2 (CH), 133.5 (Cq), 143.1 (Cq), 150.0 (Cq), 168.6 (CO); Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.59; H, 5.61; N, 11.08.

4.7. General procedure for acidic transformation of isoindoloimidazoles (12a,b) into isoindolobenzodiazepines (13a,b)

4.7.1. Products 13a and 12b. All chemicals and physicals characteristics of these products are identical to that described above in Sections 4.6.6 and 4.6.7, respectively.

4.8. General procedure for keto acids/diamines cyclodehydration into isoindoloimidazole derivatives (8a,b,e), and (12a–c)

To a solution of 2-carboxybenz-aldehyde (**2**, 1.5 g, 10 mmol) in anhydrous toluene with or without addition of PTSA (50 mg), was added 10 mmol of diamine **7a**, **7b**, **7e**, **9a**, **9b** or **9c**. The reaction mixture was refluxed for 12 h with a Dean–Stark apparatus. After cooling and removal of the solvent in vacuo, the residue was purified by recrystallization from ethanol to yield the expected isoindolobenzimidazoles **8a** (82%), **8b** (54%), **8e** (51%) or **12a** (91%), or isoindoloimidazoles **12b** (82%) or **12c** (96%), respectively, as crystals.

4.8.1. Products 8a,b and 12a–c. All chemicals and physicals characteristics of these products **8a**,**b** and **12a–c** are identical to that reported above.

4.8.2. 3-Methoxycarbonyl-6-oxoisoindolo[2,1-*a*]benzimidazole (8e). This product was isolated as white crystals in 51% yield; mp=269 °C; IR (KBr) ν 3009, 1709, 1698, 1635 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 3.95 (s, 3H, CH_3), 7.64–7.98 (m, 6H, $3H_{benzene}$ and $3H_{isoindole}$), 8.12 (s, 1H, $H_{isoindole}$); ^{13}C NMR (DMSO d_6) δ 53.0 (CH_3), 115.7 (CH), 118.0 (CH), 124.1 (CH and Cq), 130.5 (CH), 131.1 (CH and Cq), 131.4 (CH), 132.1 (CH), 134.0 (Cq), 140.1 (Cq), 143.3 (Cq), 155.1 (Cq), 167.7 (CO), 169.4 (CO); Anal. Calcd for $C_{16}H_{10}N_2O_3$ (278.27): C, 69.06; H, 3.62; N, 10.07. Found: C, 68.98; H, 3.51; N, 10.01.

Acknowledgements

We acknowledge the Johnson and Johnson Pharmaceutical Research and Development, Division of Janssen–Cilag, for scientific and financial support of this program. We thank also the Region of 'Haute Normandie' for a 'Regional-Industrial Graduate Fellowship' (BRI), 1998–2001, attributed to A. Cul. We also thank C. Meyer, from J&J PRD, a division of Janssen-Cilag, for the AM1 calculations.

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