*Bull Soc Chim Fr* (1996) 133, 7-13


# Synthesis of pentasubstituted benzamides via orthometallation: base and substituent effects

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(Received 17 July 1995; accepted 24 October 1995)

**Summary** – The synthesis of diversely substituted *ortho*-methyl *N,N*-diethylbenzamides using the orthometallation concept is described. A dramatic effect of the substituents and the additive TMEDA is observed during metallation *ortho* to the *N,N*-diethylcarboxamido group. Molecular modeling confirms the conformational effect of substituents. A role for the TMEDA additive is proposed.

**orthometallation / molecular modeling / *ortho*-methyl *N,N*-diethylbenzamide**

**Résumé – Synthèse d'*ortho*-benzamides pentasubstitués via l'orthométalation: effets des bases et des substituants.** *La synthèse d'*ortho*-méthylbenzamides substitués, fondée sur le concept d'orthométalation est décrite. Un effet important des substituants et de l'additif TMEDA est observé au cours de la métalation en* ortho *du groupe* N,N*-diéthyl carboxamide. La modélisation confirme un effet conformationnel des substituants. Un rôle pour l'additif TMEDA est proposé.*

**orthométalation / modélisation / *ortho*-méthyl *N,N*-diéthylbenzamide**

## Introduction

In the course of our programme aimed at the synthesis of antitumor agents based on naturally occurring bioactive compounds, we needed highly substituted benzoic acid derivatives. Our planned synthesis required the use of benzylic anions *ortho* to a carboxylic group. According to the orthometallation concept, tertiary amides were attractive targets [1, 2]. Indeed, it should be possible to use this principle to introduce a methyl group at the *ortho* position of the amide by an orthometallation–methylation sequence. Obviously, the tertiary amide group would facilitate lateral lithiation on the methyl group to secure the formation of the required benzylic anions [3]. Although some representatives of highly substituted tetra- or pentabenzamides have been described, we had to find new routes to the other examples. In the course of these investigations, we were faced with some problems of regioselectivity in the metallation processes. Moreover, surprising results were obtained using different basic systems. We report here the results of these investigations, which shed the light on the role which could be played by *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as an additive and by the substitution pattern of the aromatic ring. Molecular modeling has also been used and could afford a plausible explanation in terms of conformational effects.

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## Results

### *Synthesis of tetrasubstituted benzamides*

In order to test the importance of the substituents on the aromatic ring on the biological activity, we envisioned the preparation of 3,4-methylenedioxy* and 3,4-dimethoxy benzamides, which could be further substituted at position 2 by a methoxy group (compounds **III**, fig 1) or leave unsubstituted (compounds **IV**). In the latter case, this position must be protected before introduction of the 6-methyl group (compounds **II**). Thus the task was to prepare tetrasubstituted benzamides **3**, **4**, **6** and **7** and then to introduce the methyl group.

Amide **3** was prepared in two ways by modification of literature procedures starting from either piperonal (1,3-benzodioxole-5-carbaldehyde) via the corresponding cyclohexylimine [4] or from piperonilic acid (piperidine-2-carboxylic acid). In each case the copper-catalyzed methoxylation at position 2 was performed from the corresponding iodo derivative **2** obtained via orthometallation and iodination of **1**. The route from piperonilic acid was the most efficient in terms of yields

* For sake of homogeneity in the discussion, we use a nomenclature based on substituted benzamides rather than the correct IUPAC nomenclature based on benzodioxole compounds, which is used in the *Experimental section*.

**Table I.** Orthometallation and methylation of tetrasubstituted aromatics **3**, **4**, **6** and **7**.

| *Entry* | *Starting compound* | *RLi/additive* | *Solvent* | *Yield %* | *Product* | *ratio* |
|---|---|---|---|---|---|---|
| 1 | **3** | *sec*-BuLi[a] or *sec*-BuLi/TMEDA[b] | THF | 90 | **8** (100) | – |
| 2 | **4** | *sec*-BuLi[a] | THF | 88 | **9** (40) | **10** (60) |
| 3 | **4** | *sec*-BuLi[a] | Hexane/$Et_2O$ 1:1 | 78 | **9** (30) | **10** (70) |
| 4 | **4** | *sec*-BuLi then TMEDA[c] | THF | 87 | **9** (40) | **10** (60) |
| 5 | **4** | *sec*-BuLi/TMEDA[b] | THF | 81 | **9** (83) | **10** (17) |
| 6 | **4** | *sec*-BuLi/TMEDA[d] | THF | 90 | **9** (85) | **10** (15) |
| 7 | **6** | *sec*-BuLi or *sec*-BuLi/TMEDA | THF | 70 | **11** (100) | – |
| 8 | **7** | *sec*-BuLi/TMEDA[b] | THF | 90 | **12** (100) | – |
| 9 | **7** | *sec*-BuLi[a] | THF | 90 | **12** (100) | – |

a) According to *Procedure A*; b) according to *Procedure B*; c) *sec*-BuLi was added to a solution of amide **4**, then TMEDA was added; d) *sec*-BuLi was added to a solution of amide **4** and TMEDA.

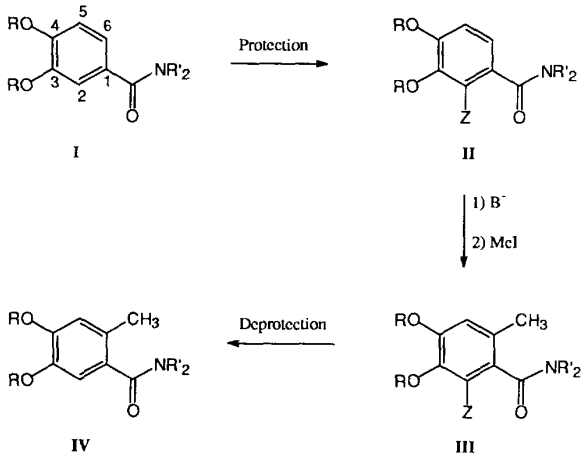


**Fig 1**

and shortness. The trimethoxy derivative **6** was prepared from the corresponding acid via standard procedures.

The second set of tetrasubstituted aromatics needed the introduction of a removable substituent at position 2. It is well known that this proton, which located in between two powerful *ortho*-directing groups (ether and carboxamide), is abstracted first. Thus, taking advantage of this fact, the silyl-protecting group has been introduced by several groups [5, 6]. Orthometallation of the amides **1** and **5** followed by quenching with chlorotrimethylsilane gave the known derivatives **4** and **7**.

*Methylation of tetrasubstituted benzamides*

Orthometallation is often performed using butyllithium or *sec*-butyllithium in tetrahydrofuran in the presence of the additive TMEDA. Although the role of this additive is still a matter of debate, TMEDA is postulated to be a good ligand of lithium and is known to accelerate metallation reactions. Thus, we can assume that TMEDA can be added to lithiation reaction with good results, if any. For several reasons, we attempted to use *sec*-butyllithium alone to perform orthometallation. Accordingly, compounds **3**, **4**, **6** and **7** were treated with *sec*-butyllithium in tetrahydrofuran at −78 °C for 15 min and methyl iodide was added. The reaction proceeded uneventfully with compounds **3**, **6** and **7** giving the expected 6-methyl derivatives **8**, **11** and **12**, respectively. However, to our surprise, compound **4** gave a mixture of two compounds **9** and **10** in a 2:3 ratio. Because orthometallation of **4** using TMEDA as an additive has been described by Kallmerten to give only compound **9** [6], we decided to further investigate this reaction in more detail under different conditions. As seen from table I, changing the solvent from THF to the less chelating hexane/ether mixture led essentially to the same results, compound **10** being the major product (compare entries 2 and 3). Addition of *sec*-butyllithium to a solution of the tertiary amide **4** and addition of TMEDA a few minutes after, did not affect the product ratio (entry 4). Finally addition of a preformed 1:1 mixture of *sec*-butyllithium and TMEDA to the amide, a technique often used in the field, led to the formation of **9** and **10** as a 83:17 mixture (entry 5). Identical results were obtained when adding *sec*-butyllithium to a preformed solution of the amide **4** and TMEDA (entry 6). Another intriguing fact was the 'normal' behavior of compound **7** which can be metallated and methylated using either *sec*-butyllithium/TMEDA [5]

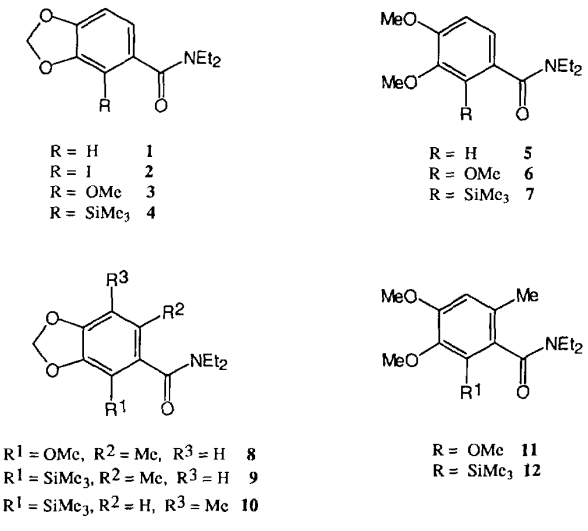


**Fig 2**

or *sec*-butyllithium alone (compare entries 8 and 9) in excellent yields.

From this rapid survey, it was concluded that the differences observed in the metallation of **4** and **7** should be attributed to the nature of the substitution pattern of the aromatic rings and to the base used, ie, *sec*-butyllithium with or without TMEDA additive.

## Discussion

*Role of the substituents*

One may assume that the acidities of H-6 protons are rather identical in compound **4** and **7**. This should also be true for H-5 protons. Thus, differences appearing in the orthometallation process might be related to steric hindrance rather than to the acidity of the protons. In other words, the more accessible proton should be abstracted in each case. Comparison of the normal reactivity of amide **3** and the abnormal reactivity of amide **4** using *sec*-butyllithium alone may be explained in terms of steric hindrance on H-6 due to the presence of the trimethylsilyl group in **4**. This group should induce a change in the steric surrounding of H-6 by modifying the conformation around the amide bond.

In order to find evidence of such conformational effects, nOe experiments were conducted on compounds **3** and **4**. An nOe effect of about 2% was detected between one aromatic proton, presumably H-6, and the $CH_2$ group of the $NEt_2$ substituent in **4**. No similar nOe effect can be detected for compound **3**. Accordingly, proton H-6 in **4** is relatively close to the bulky $NEt_2$ group and consequently kinetic deprotonation can occur on H-5 rather than on H-6 in amide **4**. Another possible consequence of such conformational effect in amide **4** would be that the carbonyl group which is implicated in the orthometallation process should not assume the correct orientation required for complexation with base, thus lowering the *ortho*-directing effect. This effect should no longer be present in amide **3**, where the methoxy group at C-2 should not force the amide group to adopt an unfavorable conformation for orthometallation. The influence of the geometry around the amide bond has been studied recently by Beak et al [7]. It was shown that the efficiency of the ortholithiation process should be related to the dihedral angle between the CO bond and the aromatic ring. Thus, a silyl substituent *ortho* to the tertiary amide group decreases the efficiency of ortholithiation by a factor of 1 800 compared to benzamide itself. The ground state conformation of an amide should reflect its ability to be metallated. Computations performed by Beak showed a dihedral angle of about 103° for 2-(trimethylsilyl)-*N*,*N*-diisopropylbenzamide **13** (fig 3e) with a weighted distance of 3.4 Å between the H-6 proton and the oxygen of the amide group [7]. In order to have a better knowledge of our system, we performed energy calculations on amides **3**, **4**, **6** and **7** by varying the C6-C1-C-O dihedral angle from −180° to +180° by 10° steps. As shown in a graphical form in figure 3, the total energy of the 2-trimethylsilyl derivatives **4** and **7** reaches two minima around −120° and +120°, whatever the C-3 and C-4 substituents (compare fig 3c and 3d). Almost identical results were obtained with 2-(trimethylsilyl)-*N*,*N*-diisopropylbenzamide **13**, which correlate well with Beak's calculations (see table II).

**Table II.** Dihedral angles C6-C1-C-O in energy-minimized conformations obtained from MOPAC calculations.

| *Compound* | *Dihedral angles values (°)* | | | |
|---|---|---|---|---|
| **3** | −78 | −72 | +67 | +106 |
| **4** | – | −100 | +94 | – |
| **6** | −108 | – | +66 | +111 |
| **7** | – | −97 | +103 | – |
| **13** | – | −96 | +101 | – |
| **13** in reference 7 | – | – | +103 | – |

Interestingly, the energy/dihedral angle profile of 2-methoxy derivatives **3** and **6** (fig 3a and 3b) showed four energy minima for −120°, −50°, +50° and +140° and strongly differ from that of amides **4** and **7**. In each derivative, a dihedral angle of 0° always corresponds to an energy maximum. MOPAC calculations using AM1 were then performed on these minimum conformations, which corroborate the results of energy minimization. The calculated dihedral angles are summarized in table II.

Accordingly, amides **3** and **6** should be deprotonated more easily than **7** and **4** because the *ortho*-directing effect can be easier achieved on low energy conformations in which the amide carbonyl points towards the *ortho* proton. This conformation cannot be reached with 2-trimethylsilyl derivatives in which the oxygen always points towards the C-2 substituent in the more stable conformations. The question is the 'normal' behavior of amide **7** in the orthometallation. The trimethylsilyl substituent should have the same effect on the orientation of the amido group as in **4**. Nevertheless in this case, one may assume that the methoxy group at C-4 hinders the H-5 proton in such a way that kinetic deprotonation of H-5 is disfavored and thus the powerful *ortho*-directing amido group fully played its role. Indirect evidence was obtained from nOe measurements on amide **7**, which showed a strong effect (6.7%) between H-5 and the methoxy group at C-4. As a consequence deprotonation occurred only at C-6 as already shown by Snieckus [5]. It should be noted that no significant nOe was detected between H-6 and the $CH_2$ group of the amide.

*Role of TMEDA*

The role played by TMEDA in the regioselectivity of lithiation of benzamide **4** is much more difficult to rationalize. Despite a number of reported examples of metallation in the presence of TMEDA, its role is not yet clearly defined as recently summarized by Collum [8]. Nevertheless TMEDA has been reported to affect the rate of metallation [9] but also the metallation site of disubstituted aromatics [10]. Two different explanations can be envisioned. The first is that TMEDA, in complexing alkyllithium, induces deagreggation of the tetrameric butyllithium to form a more reactive dimeric form [11–13]. This smallest and more efficient base is more able to abstract even a sterically hindered proton such as H-6 in **4** [14]. Such an explanation has been

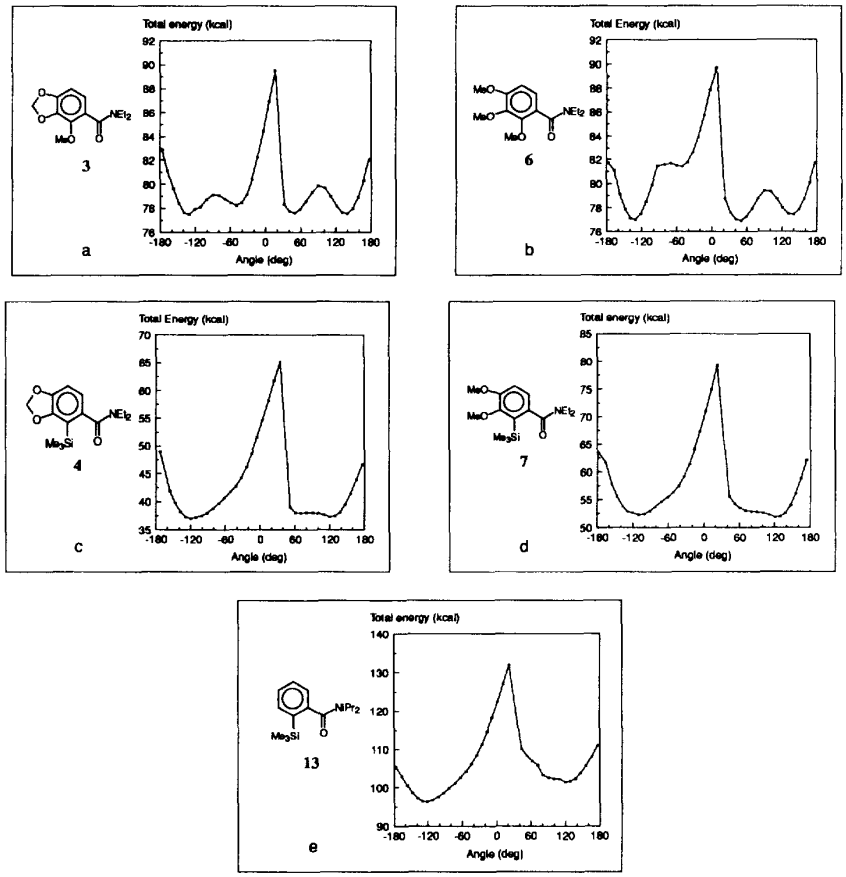


**Fig 3.** Total energy as a function of dihedral angle C-6-C-1-C-O.

proposed by Harmon and Shirley to explain the metallation of 2-methylanisole with *n*-butyllithium-TMEDA [15]. Another interesting proposal came from Slocum laboratories [10, 16] just after the disclosure of our work in a preliminary form [17]. It has been proposed that the slow step in the orthometallation process should be the complexation of the base on the heteroatom of the *ortho*-directing group. In our case, the oxygen of the amido group points in the direction of the trimethylsilyl group, thus complexation could be slow allowing kinetic deprotonation at C-5. Upon addition of TMEDA, according to Slocum hypothesis, the metallation should not proceed via complexation of the heteroatom of the DMG but rather via direct reaction of a 'overriding base' with the more acidic proton, ie, H-6 proton in compound **4**.

## Conclusion

In fact both explanations advanced above are consistent with each other and one may propose that the role of TMEDA should be to form a strong base with butyllithium, which does not need any complexation with the DMG heteroatom to abstract the more acidic proton, *ortho* to the DMG. This is particularly true for sterically hindered proton located *ortho* to the diethylamido group. The deaggregation of polymeric alkyllithium should be the major effect of TMEDA. In our case, the other observed effect came from the presence of the bulkyl trimethylsilyl group at C-2, which induces a particular conformation around the amide bond, preventing the requisite complexation of the base to achieve *ortho* metallation at a sufficient rate.

## Experimental section

Melting points were recorded on a Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 IR FT spectrometer. $^1$H NMR spectra were obtained at 400 MHz using a Bruker Aspect 3000 spectrometer or at 250 MHz using a Bruker AC 250 spectrometer. $^{13}$C NMR spectra were obtained at 62.9 MHz using a Bruker AC 250 spectrometer. Unless otherwise stated, spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard. Mass spectra (MS) were recorded in EI mode at 70 eV on a Nermag R1010. Preparative high-pressure liquid chromatography (HPLC) used silica gel 60 H Merck, and open column chromatography used silica-gel 60 Merck 70-230 mesh. *sec*-BuLi as solution in cyclohexane purchased from Aldrich Chemicals was titrated periodically against 2,5-dimethoxybenzyl alcohol. TMEDA was dried and distilled from $CaH_2$ and stored over 4 Å molecular sieves under argon. THF and $Et_2O$ were freshly distilled from sodium benzophenone ketyl prior to use. Microanalyses were performed by the Service Central d'Analyse du CNRS at Vernaison.

*Molecular modeling*

Calculations were performed on a Silicon Graphics Indy using InsightII Biosym package. Energy minimization were performed in the Discover routine using a conjugate gradient algorithm. A constraint on the dihedral angle C6-C1-C-O was fitted and 36 conformations (−180° +180°, steps 10°) were energy minimized. Each minimized structure was then computed using the MOPAC routine (AM1 calculations) of Biosym. Final dihedral angles C6-C1-C-O are summarized in table II.

*Preparation of* N,N-*diethylbenzamides*

The desired substituted benzoic acid (10 mmol) was suspended in $SOCl_2$ (25 mL). When the solution became clear, the solvent was removed in vacuo. The resulting acyl chloride was dissolved in $CH_2Cl_2$ (40 mL), the solution was cooled to 0 °C and diethylamine (5 mL) was added dropwise at such rate that the temperature did not exceed 5 °C. After addition was complete, the reaction mixture was allowed to warm to room temperature and remain at this temperature for 3 h, then diluted with $CH_2Cl_2$ (40 mL) and HCl 3 N (3 mL). The organic layer was separated, washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography using hexane/ethyl acetate mixtures.

• N,N-*Diethyl-1,3-benzodioxole-5-carboxamide* **1**

Compound **1** (2.1 g, 95%) was obtained by treatment of piperonilic acid (1.66 g, 10 mmol) according to the general procedure. $R_f$ 0.35 (hexane/ethyl acetate 2:3). Mp 62–65 °C. Lit [18]. Bp 130–135 °C (0.5 mm Hg).

• N,N-*Diethyl-3,4-dimethoxybenzamide* **5**

Compound **5** (2.25 g, 95%) was obtained by treatment of 3,4-dimethoxybenzoic acid (1.82 g, 10 mmol) according to the general procedure. $R_f$ 0.50 (hexane/ethyl acetate 2:3). Mp 76–78 °C. Lit [5] Bp 130–132 °C (0.03 mm Hg).

• N,N-*Diethyl-2,3,4-trimethoxybenzamide* **6**

Compound **6** (2.5 g, 95%) was obtained by treatment of 2,3,4-trimethoxybenzoic acid (2.21 g, 10 mmol) according to the general procedure. $R_f$ 0.28 (hexane/ethyl acetate 2:3).

IR (film): 1 655 $cm^{-1}$.

$^1$H NMR (250 MHz): $\delta$ 1.02 (t , $J$ = 7 Hz, 3H, C$H_3$ amide); 1.24 (t, $J$ = 7 Hz, 3H, C$H_3$ amide); 3.18 (m, 2H, C$H_2$ amide); 3.4 (m, 2H, C$H_2$ amide); 3.8–4.1 (m, 9H, 3 OC$H_3$); 6.7 (d, $J$ = 6.5 Hz, 1H, H-5); 6.89 (d, 1H, H-6).

Anal calc for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.66; H, 7.83; N, 5.37.

ortho-*Lithiation of benzamides*

• *Procedure A*

To a solution of benzamide (17 mmol) in THF (100 mL) under argon at −78 °C was added *sec*-BuLi (1.2 M in cyclohexane, 13 mL, 17 mmol). The resulting solution was stirred for 15 min and then treated with an excess of the appropriate electrophile (32 mmol, 2 equiv) in THF (20 mL). The resulting solution was then allowed to warm to room temperature. The reaction was quenched with a saturated aqueous ammonium chloride solution (10 mL) and extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography using hexane/ethyl acetate mixtures.

• *Procedure B*

A solution of TMEDA (2.5 mL, 17 mmol) in THF (100 mL) was cooled to −78 °C under argon and *sec*-BuLi (1.2 M in cyclohexane, 13 mL, 17 mmol) was added. The resulting solution was stirred for 15 min and the benzamide (16 mmol) in THF (70 mL) was added dropwise. The reaction mixture was stirred for 15 min at −78 °C and then a solution of the appropriate electrophile (32 mmol, 2 equiv) in THF (20 mL) was added. The resulting solution was then allowed to warm to room temperature and worked up as described in *Procedure A*.

• N,N-*Diethyl-4-iodo-1,3-benzodioxole-5-carboxamide* **2**

Compound **2** (2.8 g, 85%) was obtained by treatment of compound **3** (2.21 g, 10 mmol) according to *Procedure A* or *B*, using iodine as electrophile. $R_f$ 0.3 (hexane/ethyl acetate 2:3). Mp 76–78 °C.

IR (film): 1 660 $cm^{-1}$.

$^1$H NMR (250 MHz): $\delta$ 1.25 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 1.28 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 3.15 (q, $J$ = 7 Hz, 2H, $CH_2$ amide); 3.35 (b s, 2H, $CH_2$ amide); 6.05 (s, 2H, O-$CH_2$-O); 6.70 (d, $J$ = 7.5 Hz, 1H, H-7); 6.80 (d, 1H, H-6).

$^{13}$C NMR (62.9 MHz): $\delta$ 12.67, 14.04 ($CH_3$ amide); 39.12, 42.97 ($CH_2$ amide); 70.49 (C-4); 100.89 (C-2); 108.46 (C-7); 120.38 (C-6); 135.98 (C-5); 145.99, 149.81 (C-3a, C-7a); 170.51 (CO).

Anal calc for $C_{12}H_{14}INO_3$: C, 41.52; H, 4.06; N, 4.03. Found: C, 41.85; H, 4.10; N, 4.08.

• N,N-*Diethyl-4-methoxy-1,3-benzodioxole-5-carboxamide* **3**

To solution of compound **2** (13 g, 40 mmol), dissolved in anhydrous MeOH (300 mL), were added a solution of sodium methoxide (4.3 g, 190 mmol, 5 equiv) in MeOH (200 mL) and CuI (730 mg, 3.8 mmol, 0.1 equiv). The mixture was heated under reflux overnight. The solvent was removed in vacuo and the residue was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with HCl 3 N, water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Chromatography (hexane/ethyl acetate 2:3) gave compound **3** as a gum (8 g, 80%); $R_f$ 0.26 (hexane/ethyl acetate 2:3).

IR (film): 1 660 $cm^{-1}$.

$^1$H NMR (250 MHz): $\delta$ 1.05 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 1.22 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 3.20 (q, $J$ = 7 Hz, 2H, $CH_2$ amide); 3.55 (b s, 2H, $CH_2$ amide); 3.98 (s, 3H, $OCH_3$); 5.95 (s, 2H, O-$CH_2$-O); 6.52 (d, $J$ = 8 Hz, 1H, H-7); 6.67 (d, $J$ = 8 Hz, 1H, H-6).

$^{13}$C NMR (62.9 MHz): $\delta$ 12.86, 13.99 ($CH_3$ amide); 38.96, 42.93 ($CH_2$ amide); 60.04 ($OCH_3$); 101.16 (C-2); 103.05 (C-7); 120.46 (C-6); 136.39 (C-5); 139.81, 149.64 (C-3a, C-7a); 168.13 (CO).

MS $m/z$ 251 ($M^+$), 220, 179, 164, 149, 134, 121, 106, 94, 78, 65, 63, 53, 42.

Anal calc for $C_{13}H_{17}NO_4$: C, 62.12; H, 6.82; N, 5.58. Found: C, 62.03; H, 6.78; N, 5.61.

• N,N-*Diethyl-4-trimethylsilyl-1,3-benzodioxole-5-carboxamide* **4**

Compound **4** (2.81 g, 96%) was obtained by treatment of compound **1** (2.21 g, 10 mmol) according to *Procedure A* or *B*, using TMSCl as electrophile. $R_f$ 0.7 (hexane/ethyl acetate 3:2). Lit [6].

• N,N-*Diethyl-3,4-dimethoxy-2-(trimethylsilyl)-benzamide* **7**

Compound **7** (2.88 g, 93%) was obtained upon treatment of compound **5** (2.51 g, 10 mmol) according to *Procedure A* or *B*, using TMSCl as an electrophile. $R_f$ 0.70 (hexane/ethyl acetate 1:3). Mp 56.5–57 °C (hexane/ether). Lit [5]. Mp 57–58 °C.

IR (film): 1 615 $cm^{-1}$.

$^1H$ NMR (250 MHz): $\delta$ 0.28 (s, 9H, $Si(CH_3)_3$); 1.08 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 1.25 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 3.21 (b s, 2H, $CH_2$ amide); 3.51 (b s, 2H, $CH_2$ amide); 3.90 (s, 6H, $OCH_3$); 6.90 (s, 2H, H-5, H-6).

*Methylation of amides* **3**, **4**, **6** *and* **7**

• N,N-*Diethyl-4-methoxy-6-methyl-1,3-benzodioxole-5-carboxamide* **8**

Compound **8** (2.3 g, 90%) was obtained by treatment of compound **3** (2.5 g, 10 mmol) according to *Procedure A* or *B*, using methyl iodide as an electrophile. $R_f$ 0.3 (hexane/ethyl acetate 2:3).

IR (film): 1 660 $cm^{-1}$.

$^1H$ NMR (250 MHz): $\delta$ 1.05 (t, $J$ = 7.5 Hz, 3H, $CH_3$ amide); 1.24 (t, $J$ = 7.5 Hz, 3H, $CH_3$ amide); 2.13 (s, 3H, $CH_3$ benzylic); 3.15 (q, $J$ = 7.5 Hz, 2H, $CH_2$ amide); 3.42, 3.70 (2m, 2H, $CH_2$ amide); 3.95 (s, 3H, $OCH_3$); 5.95 (AB, $J$ = 1.5 Hz, 2H, O-$CH_2$-O); 6.40 (s, 1H, H-7).

$^{13}C$ NMR (62.9 MHz): $\delta$ 12.76, 13.85 ($CH_3$ amide); 18.68 ($CH_3$ benzylic); 38.66, 42.56 ($CH_2$ amide); 59.85 ($CH_3$ methoxy); 100.90 (C-2); 104.61 (C-7); 123.11 (C-4); 128.56 (C-6); 134.05 (C-5); 139.33, 149.09 (C-3a, C-7a); 167.83 (CO).

MS: $m/z$ 265 ($M^+$), 250, 193, 178, 163, 77.

Anal calc for $C_{14}H_{19}NO_4$: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.06; H, 7.33; N, 5.47.

• N,N-*Diethyl-6-methyl-4-(trimethylsilyl)-1,3-benzodioxole-5-carboxamide* **9**

Compound **4** treated according to *Procedure A* gave a mixture of two compounds **9** and **10** in 2:3 ratio in 88% yield, which were separated by preparative HPLC (hexane/ethyl acetate 1:7).

Compound **4** treated according to *Procedure B* gave a mixture of two compounds **9** and **10** in 83:17 ratio in 81% yield which were separated by preparative HPLC (hexane/ethyl acetate 1:7). $R_f$ 0.30 (hexane/ethyl acetate 2:3).

IR (film): 1 660 $cm^{-1}$.

$^1H$ NMR (250 MHz): $\delta$ 0.25 (s, 9H, $Si(CH_3)_3$); 1.00 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 1.22 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 2.12 (s, 3H, $CH_3$ benzylic); 3.12 (m, 3H, $CH_2$ amide); 3.90 (m, 1H, $CH_2$ amide); 5.75 (AB, $J$ = 1.5 Hz, 2H, O-$CH_2$-O); 6.60 (s, 1H, H-7).

$^{13}C$ NMR (62.9 MHz): $\delta$ −0.17 ($Si(CH_3)_3$); 12.69, 13.58 ($CH_3$ amide); 19.04 ($CH_3$ benzylic); 38.99, 43.03 ($CH_3$ amide); 100.23 (C-2); 111.16 (C-7); 116.16 (C-4); 127.21 (C-6); 134.19 (C-5); 145.89, 151.27 (C-3a, C-7a); 170.99 (CO).

MS: $m/z$ 307 ($M^+$), 292, 278, 235, 163, 84, 49.

Anal calc for $C_{16}H_{15}NO_3Si$: C, 62.50; H, 8.20; N, 4.56. Found: C, 62.37; H, 8.38; N, 4.51.

• N,N-*Diethyl-7-methyl 4-(trimethylsilyl)-1,3-benzodioxole-5-carboxamide* **10**

$R_f$ 0.26 (hexane/ethyl acetate 2:3). Mp 70–72 °C.

IR (film): 1 660 $cm^{-1}$.

$^1H$ NMR (250 MHz): $\delta$ 0.25 (s, 9H, $Si(CH_3)_3$); 1.06 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 1.21 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 2.16 (s, 3H, $CH_3$ benzylic); 3.21 (q, $J$ = 7 Hz, 2H, $CH_2$ amide); 3.60 (q, $J$ = 7 Hz, 2H, $CH_2$ amide); 5.90 (s, 2H, O-$CH_2$-O); 6.49 (s, 1H, H-6).

$^{13}C$ NMR (62.9 MHz): $\delta$ 0.64, 0.41, 0.21 ($Si(CH_3)_3$); 12.42, 12.64 ($CH_3$ amide); 14.35 ($CH_3$ benzylic); 38.99, 43.44 ($CH_2$ amide); 99.97 (C-2); 113.93 (C-7); 119.02 (C-4); 121.60 (C-6); 135.68 (C-5); 144.39, 152.48 (C-3a, C-7a); 171.74 (CO).

MS: $m/z$ = 307 ($M^+$), 292, 235, 177, 163, 73, 43.

Anal calc for $C_{16}H_{15}NO_3Si$: C, 62.50; H, 8.20; N, 4.56. Found: C, 62.43; H, 8.27; N, 4.51.

• N,N-*Diethyl-6-methyl-2,3,4-trimethoxy-benzamide* **11**

Compound **11** (1.97 g, 70%) was obtained by treatment of compound **6** (2.67 g, 10 mmol) according to *Procedure A* or *B*, using methyl iodide as electrophile. $R_f$ 0.34 (hexane/ethyl acetate 2:3).

IR (film): 1 630 $cm^{-1}$.

$^1H$ NMR (400 MHz): $\delta$ 1.05 (t, $J$ = 7.5 Hz, 3H, $CH_3$ amide); 1.26 (t, $J$ = 7.5 Hz, 3H, $CH_3$ amide); 2.2 (s, 3H, $CH_3$); 3.13 (m, 2H, $CH_2$ amide); 3.58 (m, 2H, $CH_2$ amide); 3.87 (s, 6H, $OCH_3$); 3.92 (s, 3H, $OCH_3$); 6.5 (s, 1H, H-5).

MS: $m/z$ 281 ($M^+$), 265, 209, 166, 151, 72, 42.

Anal calc for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.17; H, 8.32; N, 4.92.

• N,N-*Diethyl-3,4-dimethoxy-6-methyl-2-(trimethylsilyl)benzamide* **12**

Compound **12** (2.9 g, 90%) was obtained by treatment of compound **7** (3.09 g, 10 mmol) according to *Procedure A* or *B*, using methyl iodide as electrophile. $R_f$ 0.70 (hexane/ethyl acetate 1:3). Lit [5].

IR (film): 1 617 $cm^{-1}$.

$^1H$ NMR (250 MHz): $\delta$ 0.24 (s, 9H, $Si(CH_3)_3$); 1.02 (t, $J$ = 7 Hz, 3H, $CH_3$ amide); 1.24 (t, $J$ = 7 Hz, 3H, 3H, $CH_3$ amide); 2.17 (s, 3H, $CH_3$ benzylic); 2.9–3.2 (m, 4H, $CH_2$ amide); 3.90 (s, 6H, $OCH_3$); 6.72 (s, 1H, H-7).

## Acknowledgments

We gratefully acknowledge Bernard Maigret and Miklos Szerco, Université Henri-Poincaré-Nancy I, URA CNRS 510 for their advice and help regarding molecular modeling.

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