Application of the *ortho*-Lithiation-Cyclization Strategy to *N*-Benzyl- and *N*-Phenethylamine Derivatives

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The *ortho*-lithiation-cyclization of iodinated *N,N*-diacylphenethylamines provides a convenient method for the preparation of 2-(2-acetoamidoethyl)acetophenones and 2-(2-benzamidoethyl)benzophenones, which could be easily transformed into dihydroisoquinolines. By contrast, the *N*-ethylamino, *N*-acetylamino, and *N*-trimethylsilylamino moieties studied as *ortho*-directing groups provide poor assistance to the metalation of *N*-benzyl- and *N*-phenethylamines and the corresponding isoindolone or isoquinolone derivatives are obtained in low yields.

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Aromatic lithiation reactions permit the selective functionalization of an aromatic ring *ortho* to a directing group and the preparation of polysubstituted aromatic compounds, which are not readily available through electrophilic substitutions. The utility of this reaction has been demonstrated by applications to the synthesis of carbocycles and heterocycles [1]. However, few examples are reported for the construction of the isoindole/phthalimidine [2-6] or isoquinoline [4,7-12] ring systems by the *ortho*-lithiation-cyclization sequence. These nitrogen heterocycles are of interest as synthons in natural product chemistry and have also attracted some attention because of their biological activity [4,9,13]. In the present paper we describe the reactivity of several *N*-benzyl- and *N*-phenethylamine derivatives towards organolithium reagents in order to obtain isoindole and isoquinoline derivatives. The results of the study on these *ortho*-lithiation-cyclization reactions are described below.

Metalation of *N*-Benzyl and *N*-Phenethylamines.

A previous report from Castedo *et al.* [9] indicated that 3,4-dialkoxy-β-phenethylamines could be regioselectively lithiated with *n*-butyllithium and quenched with electrophiles to afford 7,8-dioxygenated tetrahydroisoquinolines. It seemed reasonable that *ortho*-lithiation-cyclization of 3,4-dimethoxybenzylamine should be possible under similar conditions. In the above procedure, protection of the amine with the trimethylsilyl group during the metalation is required to avoid the *N*-addition. However, we thought it was possible to circumvent this problem using the strategy developed by Barluenga [14] for the synthesis of α,β-butyrolactams by successive treatment of allylamines with *n*-butyllithium, *tert*-butyllithium and diethyl carbonate at temperatures ranging from -50° and 20°. Therefore, we decided to investigate the reactivity of *N*-benzylamine and amide derivatives **1** towards organolithium reagents (*n*-butyllithium and *tert*-butyllithium). The metalation was accomplished by metal-hydrogen exchange and the organometallic intermediates were reacted with external electrophiles (diethyl carbonate, ethyl chloroformate).

We began to explore the synthesis of isoindolone derivatives **2** through *ortho*-lithiation-cyclization of *N*-benzylamines **1a** and **1b**. The starting *N*-ethyl-3,4-dimethoxybenzylamine (**1b**) was prepared by acetylation (acetyl chloride, triethylamine, DMAP) of veratrylamine (**1a**), followed by reduction with lithium aluminium hydride of the so-obtained acetamide **1c**. Then, we first studied the 3,4-dimethoxybenzylamine (**1a**), which was protected by treatment with *n*-butyllithium (2.2 equivalents) and trimethylsilylchloride at 0° for 20 minutes in THF. Metalation with *n*-butyllithium (1.1 equivalents) (0°, 4 hours) and quenching with diethyl carbonate (1.5 equivalents) afforded, after acidic work-up, a 23% yield of 6,7-dimethoxyisoindol-1-(2*H*)-one (**2a**).

Although a variety of experimental conditions were tested, the yield of the desired isoindolone **2a** could not be improved. It is worth noting that when the reactions were performed without protection of the amine, *N*-acylation took place and the corresponding carbamate **3a** was obtained, although diethyl carbonate is known to favor *C-versus N*-carbonation [14]. The application of this methodology to *N*-ethyl-3,4-dimethoxybenzylamine (**1b**) always led to the carbamate **3b** and no cyclization product or reaction at the benzylic position was observed (Scheme I). Similar results were obtained when **1b** was silylated at the nitrogen before proceeding with the lithiation reaction. The results of these reactions are summarized in the Table I. Thus, isoindolone **2b** only could be synthesized by alkylation of **2a** with ethyl iodide.

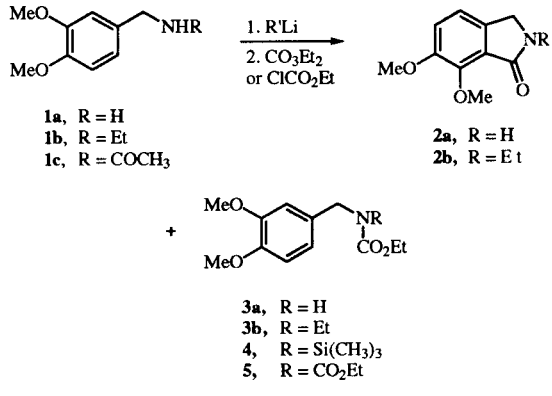
These results prompted us to apply this methodology to *N*-ethyl-3,4-dimethoxyphenethylamine (**6b**) in order to compare it with the synthesis of isoquinolone **7a** reported by Castedo *et al.* [9]. Thus, starting from amine **6b**, prepared from **6a** in a similar way as **1b**, ethyl *N*-ethoxycarbonyl-*N*-3,4-dimethoxyphenethylcarbamate (**8**) and 3',4'-dimethoxystyrene (**9**) were the major products,

Table 1
Metalation of *N*-Benzylamines **1**

Entry	Substrate	Method [a]	Metalation Conditions	Carbonating Conditions [b]	Products (yield %) 2	3 [c]
1	**1a**	A	*n*-BuLi (1.1), 0°-rt, overnight	$(EtO)_2CO$ (2), 0°-rt, 1.5 h	**2a**, 21	—
2	**1a**	A	*n*-BuLi (1.1), 0°, 4 h	$(EtO)_2CO$ (1.5), 0°, 1.5 h	**2a**, 23	—
3	**1a**	A	*n*-BuLi (2.2), 0°, 4 h	$(EtO)_2CO$ (3), 0°C-rt, 1.5 h	**2a**, 15	—
4	**1a** [d]	A	*n*-BuLi (1.1), -20°, 1 h	$(EtO)_2CO$ (1.5), 0°; 1 h, rt, 0.5 h	**2a**, 11	**3a**, 23
5	**1a** [e]	A	*n*-BuLi (2.2), -78°, 4 h	$(EtO)_2CO$ (1.5), -78°; 1 h, rt, 2 h	—	**3a**, 15
6	**1a** [f]	B	*n*-BuLi (1.1), 0°-rt, 4 h	$ClCO_2Et$ (2), 0°-rt, 2 h	—	**3a**, 45
7	**1b**	A	*n*-BuLi (1.1), 0°-rt, 4 h	$ClCO_2Et$ (2), 0°-rt, 1 h	—	**3b**, 75
8	**1b**	B	*t*-BuLi (1.1), -60°-rt, 4 h	$(EtO)_2CO$ (1.5), -60°-rt, overnight		**7b**, 50

[a] Method A: protection of the nitrogen atom [*n*-BuLi (2.2 equivalents) and TMSCl (2 equivalents) added to **1a** in THF at 0°], followed by metalation. Method B: Deprotonation of nitrogen atom [*n*-BuLi (2.2 equivalents] added to **1a** in THF at -20°), followed by metalation. [b] Quenching agent: H_2O (entries 1 and 5-8); HCl (entries 2-4). [c] Yields of isolated products are given. [d] The *N*-trimethylsilylcarbamate **4** was also isolated (35%). [e] The *N*-trimethylsilylcarbamate **4** was also isolated (57%). [f] The *N*-ethoxycarbonylcarbamate **5** was also isolated (23%).

Scheme I



1a, R = H
1b, R = Et
1c, R = $COCH_3$

2a, R = H
2b, R = Et

+

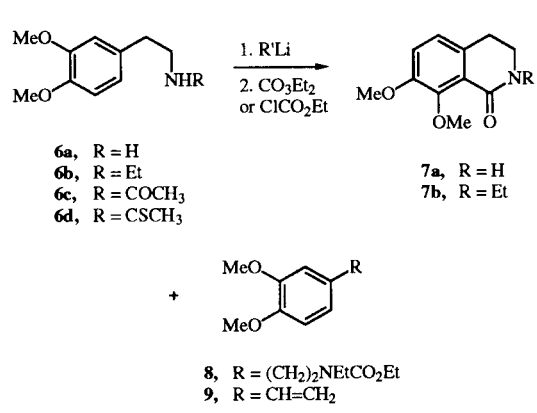
3a, R = H
3b, R = Et
4, R = $Si(CH_3)_3$
5, R = CO_2Et

which were obtained in varying yields depending on the reaction conditions (Scheme II). For instance, deprotonation of **6b** [*n*-butyllithium (1.1 equivalents), THF, -50°, 0.5 hours], followed by metalation with *tert*-butyllithium (1.1 equivalents, -30° to rt, 5 hours) and subsequent addition of diethyl carbonate (3 equivalents, 0° to rt, 3 hours) afforded the carbamate **8** (65% yield) and the styrene **9** (13%), after aqueous hydrochloric acid work-up and purification by medium pressure column chromatography. However, when metalation was performed with *n*-butyllithium (1.1 equivalents, 0° to rt, 5 hours), only the styrene **9** was obtained in a 42% yield (conversion 60%). In these cases, small amounts (5-7%) of the *N*-ethyl-7,8-dimethoxyisoquinol-1-one (**7b**) was detected (^1H nmr), but the compound could not be isolated from the reaction mixture and hence it was not fully characterized.

Metalation of *N*-Benzyl and *N*-Phenethylamides.

On the other hand, Schlosser and Simig [6] have shown that the *N*-pivaloylaminomethyl moiety provides more powerful and specific neighboring assistance to metalation that the dimethylamino group does. In fact, they have developed an efficient method to synthesize isoindolone and isoquinolone derivatives [6,10], based on the *ortho* selective lithiation of *N*-pivaloylbenzyl- and phenethylamines, respectively. Therefore, we decided to try the *ortho*-directing ability of other amides. Thus, we undertook the *ortho*-lithiation-cyclization of the *N*-benzylacetamide **1c** and the *N*-phenethylacetamide **6c** and we found that the deprotonated *N*-acetamido substituent is a weak *ortho*-directing group in hydrogen-metal exchange reac-

Scheme II



6a, R = H
6b, R = Et
6c, R = $COCH_3$
6d, R = $CSCH_3$

7a, R = H
7b, R = Et

+

8, R = $(CH_2)_2NEtCO_2Et$
9, R = $CH{=}CH_2$

tions. Thus, one of the best experiments is described as follows: treatment of **6c** in THF with excess (2.5 equivalents) of *n*-butyllithium at 0° for 4 hours, followed by addition of diethyl carbonate (3 equivalents, 0° to rt, 3 hours) afforded the 7,8-dimethoxyisoquinol-1-one **7a** [9] in 40% yield (conversion 60%), after aqueous hydrochloric acid work-up and purification by medium pressure column chromatography. When the *N*-benzylacetamide **1c** was treated under similar reaction conditions [*n*-butyllithium (2.5 equivalents), 0°, 4 hours; then diethyl carbonate (3 equivalents), 0°-rt, 3 hours], the isoindolone **2a** was obtained in low yield (30%) (conversion 55%). The use of the thioacetamide **6d**, synthesized by treatment of the acetamide **6c** with Lawesson's reagent [15] gave even poorer results and in most cases the starting material was recovered (see Scheme II).

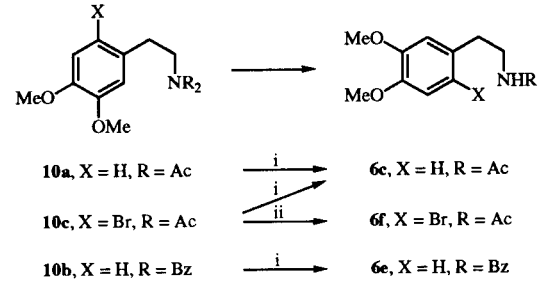
Metalation of *N*-Phenethylimides.

In our previous study [11] on cyclization of *N*-phenethylsuccinimides using organolithium reagents, we reported new and convenient entries to 8,9-dialkoxypyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones, being a carbophilic addition-cyclization *via* *N*-acyliminium ions and Parham-type cyclizations the key steps. However, we have found [12] that these strategies can not be extended to preparation of pyrroloisoindolone derivatives and we attribute the failure to the fact that in this case both types of cyclization reactions are unfavored according to Baldwin's rules [16]. Thus, we examined the reaction of *N,N*-diacetyl- and *N,N*-dibenzoyl-3,4-dimethoxyphenethylamines **10** with organolithium reagents. In this case, the generated organolithium intermediate will possess an electrophilic center and there will be no need to add external electrophiles.

The substrates **10a** and **10b** were prepared by acetylation (acetyl chloride, acetic anhydride, reflux, 1 hour) and benzoylation (benzoyl chloride, triethylamine, DMAP, dichloromethane, rt, overnight) of the 2-(3,4-dimethoxyphenyl)ethylamine respectively, while the halogenated derivatives **10c-f** were obtained by halogenation of the acetamide **6c** or benzamide **6e** and subsequent acylation. It should be noted that we were obliged to halogenate first, since these *N,N*-diacylamines suffered from deacylation under the bromination or iodination conditions used.

We have attempted the *ortho*-lithiation-cyclization sequence on the *N,N*-diacylamines **10a-c** using the standardized metalation conditions (1.2 equivalents, *n*-butyllithium, THF, -78°, 4 hours) and quenching with acid (12*M* hydrochloric acid or TFA) or water. However, we could not observe the cyclization similar to that of the corresponding succinimides [11], instead, the undesired deacylation reaction took place and the corresponding amides **6c-e** were isolated (Scheme III). The fact that deacylation always takes place before debromination confirms that metalation of the aromatic ring always occurs after carbophilic addition of the alkyllithium to the carbonyl group of the imide.

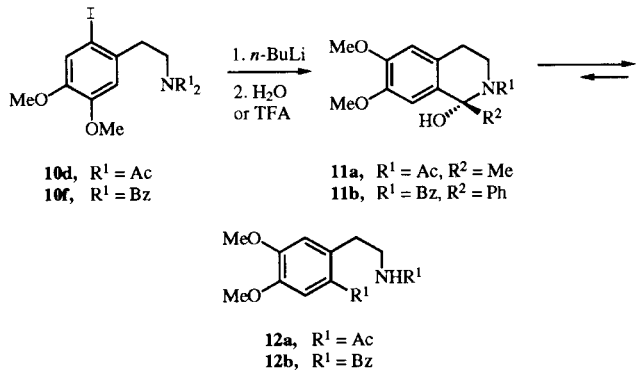
Scheme III



Reagents and conditions: i. *n*-BuLi (2.2 equivalents), THF, 0°, 75 min, rt 4 h, then H_2O; ii. *n*-BuLi or *t*-BuLi (1.2 equivalents), THF, -78°, 4 h, rt 1 h, then H_2O

As the lithium-iodine exchange is usually faster than the addition to carbonyl groups [11], we expected to obtain satisfying results applying the sequence to **10d**. As shown in Scheme IV, the metalation (2.2 equivalents, *n*-butyllithium, THF, -78°) proceeded nicely with iodinated *N,N*-diacylamine **10d**. The aryllithium intermediate then reacted with the carbonyl group of the imide and, after quenching with water or TFA, afforded the 2-(2-acetoamidoethyl)acetophenone **12a** [17]. When reacted with *n*-butyllithium, the iodinated *N,N*-dibenzoylamine **10** underwent intramolecular reaction similar to that of **10d**, leading to the 2-(2-benzamidoethyl)benzophenone **12b**. These results imply that the metalation and subsequent intramolecular cyclization takes place *via* the heterocyclic α-hydroxyamides **11**. These compounds readily tautomerize to the corresponding open-chain oxoamides **12** during the work-up procedure. This proposal is supported by nmr data. For instance, when a crude sample of the reaction of *N,N*-dibenzoylamine **10f** with *n*-butyllithium was dissolved in deuteriochloroform the ^1H nmr spectrum showed the resonances due to both compounds **11b** and **12b**. Some duplicate peaks, in particular the methoxylic

Scheme IV



and aromatic protons, were observed. The resonance due to the equatorial H-3 proton of **11b** was also observed [δ 4.02 (m)].

It should be noted that treatment of these oxoamides **12** in acidic media (*e.g.* hydrogen chloride/ethanol, reflux, 5 hours) led to the 1-methyl- or 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinolines quantitatively [17a].

A convenient approach to 2-(2-acetoamidoethyl)acetophenones and 2-(2-benzamidoethyl)benzophenones has been developed. Our strategy offers a very direct route to this type of acetophenones or benzophenones under mild conditions. It is therefore an interesting alternative to the classical sequence Bischler-Napieralski reaction-acylation [17a] or the Friedel-Crafts acylation [17b]. Besides, these ketones are useful as intermediates for preparing several types of isoquinoline derivatives, such as 1-(substituted phenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinolines [17].

On the other hand, as the photocyclization of 1-alkylidene-2-benzoyltetrahydroisoquinolines is an exceptionally facile method to prepare protoberberine alkaloids [18], we decided to apply our methodology to the *N*-acetyl-*N*-benzoylphenethylamine **10e**. However, we have found that, in this case, treatment of this imide with *n*-butyllithium under the above mentioned conditions afforded a mixture (^{1}H nmr) of the corresponding 2-(2-benzamidoethyl)acetophenone and 2-(2-acetamidoethyl)benzophenone. Therefore, no selectivity was observed in the nucleophilic addition of the aryllithium intermediate to acetyl and benzoyl groups.

Table 2

Metalation of *N,N*-Diacylamines **10**

Entry	Substrate	Metalation Conditions	Quenching Agent	Products (yield %) [a]
1	**10a**	*n*-BuLi (2.1), THF, 0°, 75 min, rt, overnight	H_2O	**6c** (94)
2	**10b**	*n*-BuLi (2.1), THF, 0°, 75 min, rt, overnight	H_2O	**6e** (92)
3	**10c**	*n*-BuLi (2.1), THF, 0°, 75 min, rt, overnight	H_2O	**6c** (95)
4	**10c**	*n*-BuLi (1.2), THF, -78°, 4 h, rt, 1 h	H_2O	**6f** (98)
5	**10d**	*n*-BuLi (2.1), THF, -78°, 4 h, rt, 1 h	H_2O	**12a** (85)
6	**10d**	*n*-BuLi (2.1), THF, -78°, 4 h, rt, 1 h	TFA	**12a** (85)
7	**10e**	*n*-BuLi (2.1), THF, -78°, 4 h, rt, 1 h	H_2O	— [b]
8	**10f**	*n*-BuLi (2.1), THF, -78°, 4 h, rt, 1 h	H_2O	**12b** (80) [c]

[a] Yields of isolated products are given. [b] An approximately 1:1 mixture (^{1}H nmr) of the corresponding 2'-(2-benzamidoethyl)acetophenone and 2'-(2-acetamidoethyl)benzophenone was obtained. [c] The *N*-[2-(2-(1-hydroxy-1-phenylpentyl)-4,5-dimethoxyphenyl]ethyl]benzamide was also isolated (17%).

It has been demonstrated that the strategy of *ortho*-lithiation-cyclization is effective for realizing selective metalations of iodinated *N,N*-diacylphenethylamines and subsequent intramolecular reaction with the imide acting as internal electrophile to aceto or benzophenone derivatives, *via* the corresponding α-hydroxytetrahydroisoquinolines. It is also shown that *N*-benzylamines need to be protected as their *N*-silyl or *N,N*-disilyl derivatives to undergo *ortho*-lithiation-cyclization and that the *N*-ethylamino, *N*-acetylamino, and *N*-thioacetylamino moieties provide less powerful assistance to metalation than other groups do, such as the *N*-pivaloylamino [6,10].

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The ir spectra were obtained by using a Perkin-Elmer 1430 spectrophotometer on potassium bromide pellets (solids) or chloroform solution (oils). The nmr spectra were recorded on a Bruker AC-250 spectrometer at 20-25°, running at 250 MHz for ^{1}H and 62.8 MHz for ^{13}C in deuteriochloroform solutions. The ^{1}H nmr chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ_{TMS} = 0.00 ppm) as internal standard. Assignments were confirmed by homonuclear spin-spin decoupling experiments. The ^{13}C nmr chemical shifts are reported in ppm downfield from TMS and referenced with respect to internal deuteriochloroform (δ = 77.04 for the center line). Assignment of individual ^{13}C resonances are supported by DEPT experiments. Elemental analyses were determined on a Perkin-Elmer 2400 CHN apparatus. Analysis (tlc) was carried out with 0.2 mm thick silica gel plates (Merck Kieselgel GF_{254}). Visualization was accomplished by uv light or by spraying with Dragendorff's reagent [19]. Flash column chromatography [20] on silica gel was performed with Merck Kieselgel 60 (230-400 mesh). All solvents used in reactions were anhydrous and purified according to standard procedures [21]. Alkyllithium reagents were purchased from Aldrich Chemical Company. Reactions were carried out under dry, deoxygenated argon atmosphere using oven- or flame-dried glassware. Transfers of solvents and solutions were performed by syringe or *via* canula [22].

General Procedure for the Synthesis of *N*-Substituted Acetamides **1c** and **6c**.

To a stirred solution of the amines **1a** or **6a** (1 mmole), triethylamine (1.5 mmoles), and DMAP (0.12 mmole) in anhydrous dichloromethane (30 ml) under argon atmosphere, acetyl chloride (1.25 mmoles) was added dropwise at 0°. The reaction mixture was stirred at rt overnight, then it was poured into ice, acidified with 1*M* hydrochloric acid, and extracted with dichloromethane (3 x 30 ml). The organic extracts were dried (anhydrous sodium sulfate), the solvent evaporated, and the residues recrystallized from hexane-ethyl acetate (1:1) to leave the corresponding acetamides **1c** and **6c** in 95 and 96% yield, respectively.

N-(3,4-Dimethoxybenzyl)acetamide (**1c**).

This compound was obtained as colorless crystals, mp 90-91° [lit [23] 89-90° (benzene-hexane)]; ir: ν 3310 (NH), 1635 (C=O)

cm^{-1}; ^{1}H nmr: δ 1.95 (s, 3H, CH_3CO), 3.77 (s, 6H, 2 x OCH_3), 4.51 (d, J = 6 Hz, 2H, CH_2N), 6.42 (br s, 1H, NH), 6.80 (s, 3H, H_{arom}).

N-(3,4-Dimethoxyphenethyl)acetamide (**6c**).

This compound was obtained as colorless crystals, mp 99-100° [lit [17] 99-100° (ethyl acetate)]; ir: ν 3300 (NH), 1630 (C=O) cm^{-1}; ^{1}H nmr: 1.95 (s, 3H, CH_3CO), 2.75 (t, J = 7.0 Hz, 2H, CH_2CH_2N), 3.42-3.50 (m, 2H, CH_2CH_2N), 3.82 (s, 6H, 2 x OCH_3), 5.55 (br s, 1H, NH), 6.68-6.80 (m, 3H, H_{arom}).

General Procedure for the Synthesis of *N*-Ethylamines **1b** and **6b**.

To a stirred suspension of $LiAlH_4$ (1 mmole) in dry THF (5 ml), a solution of the acetamides **1c** and **6c** (1.3 mmoles) in dry THF (5 ml) was added dropwise and the reaction mixture was refluxed for 6 hours. Then, the mixture was cooled, water was added to destroy the excess hydride, and then was extracted with dichloromethane (3 x 30 ml). The organic extracts were dried (anhydrous sodium sulfate) and the solvent evaporated to leave the corresponding *N*-ethylamines **1b** and **6b** in 85 and 84% yields, respectively.

N-Ethyl-3,4-dimethoxybenzylamine (**1b**).

This compound was obtained as an oil; ir: ν 3320 (NH) cm^{-1}; ^{1}H nmr: δ 1.08 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 2.12 (br s, 1H, NH), 2.62 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 3.67 (s, 2H, $ArCH_2N$), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.72-6.84 (m, 3H, H_{arom}); ^{13}C nmr: δ 14.7 (NCH_2CH_3), 43.2 (NCH_2CH_3), 53.3 ($ArCH_2N$), 55.7, 55.8 (OCH_3), 110.9, 111.4, 120.3 (C_{arom}-H), 132.0 (C_{arom}-C), 148.0, 148.8 (C_{arom}-O).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.93; H, 8.64; N, 6.98.

N-Ethyl-3,4-dimethoxyphenethylamine (**6b**).

This compound was obtained as an oil; ir: ν 3320 (NH) cm^{-1}; ^{1}H nmr: δ 1.09 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 2.29 (br s, 1H, NH), 2.66 (q, J = 7.1 Hz, 2H, NCH_2CH_3), 2.73-2.78 (m, 2H, CH_2CH_2N), 2.81-2.87 (m, 2H, CH_2CH_2N), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.70-6.78 (m, 3H, H_{arom}); ^{13}C nmr: δ 15.1 (NCH_2CH_3), 36.2 ($ArCH_2CH_2N$), 43.8 (NCH_2CH_3), 49.4 ($ArCH_2CH_2N$), 55.9, 56.0 (OCH_3), 111.0, 111.8, 120.7 (C_{arom}-H), 131.0 (C_{arom}-C), 147.6, 148.8 (C_{arom}-O).

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 69.04; H, 8.96; N, 6.46.

N-3,4-Dimethoxyphenethylthioacetamide (**6d**).

To a stirred suspension of acetamide **6c** (2 g, 9 mmoles) in dry toluene (40 ml), Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (2.17 g, 5.4 mmoles) was added and the reaction mixture was refluxed for 2 hours under argon atmosphere. The toluene was removed *in vacuo*, and the residue purified by flash column chromatography (silica gel, hexane:ethyl acetate 1:1), to give 1.95 g of the thioacetamide **6d** (92%), as a solid of mp 98-100° (hexane-ethyl acetate 1:1) [24]; ^{1}H nmr: δ 2.43 (s, 3H, CH_3CS), 2.85 (t, J = 7.0 Hz, 2H, CH_2CH_2N), 3.80 (s, 6H, 2 x OCH_3), 3.78-3.89 (m, 2H, CH_2CH_2N), 6.67-6.78 (m, 3H, H_{arom}), 7.20 (br s, 1H, NH); ^{13}C nmr: δ 33.0 (CH_2CH_2N), 33.8 (CH_3CS), 46.9 (CH_2CH_2N), 55.7 (OCH_3), 111.2, 111.6, 120.4 (C_{arom}-H), 130.5 (C_{arom}-C), 147.5, 148.8 (C_{arom}-O), 200.6 (C=S).

Typical Procedure for the Metalation of Benzylamines **1a** and **1b**.

(a) Method A.

To a solution of the *N*-(3,4-dimethoxybenzyl)amine (**1a**) (500 mg, 3 mmoles) in dry THF (45 ml), cooled to 0°, *n*-butyllithium (4.5 ml of 1.51*M* in hexane, 6.6 mmoles) and trimethylsilylchloride (1 ml, 6.6 mmoles) were added. The resulting mixture was stirred for 20 minutes, then cooled to -20°, and treated with *n*-butyllithium (2.25 ml of 1.51*M* in hexane, 3.3 mmoles). After 1 hour, the solution was warmed to 0° and diethyl carbonate (0.6 ml, 4.5 mmoles) was added. The reaction mixture was further stirred for 1 hour, allowed to reach room temperature (0.5 hour), and quenched with 12*M* hydrochloric acid. Ethyl ether (15 ml) was added, the organic layer separated, and the aqueous phase extracted with dichloromethane (3 x 30 ml). The combined organic extracts were dried with sodium sulfate and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, dichloromethane:ethyl acetate 8:2) of the residue afforded the following products:

2,3-Dihydro-6,7-dimethoxyisoindol-1-one (**2a**).

This compound was obtained in a yield of 65 mg (11%), mp 135-137° (hexane-ethyl acetate 1:1) (lit [25] mp 140-141°); ir: ν 3220 (NH), 1680 (C=O) cm^{-1}; ^{1}H nmr: δ 3.89 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 4.34 (s, 2H, CH_2NH), 7.10 (s, 2H, H_{arom}), 7.66 (br s, 1H, NH); ^{13}C nmr: δ 44.7 (CH_2N), 56.5, 62.1 (OCH_3), 116.7, 118.0 (C_{arom}-H), 124.5, 137.1 (C_{arom}-C), 147.1, 151.8 (C_{arom}-O), 170.7 (C=O).

Ethyl *N*-3,4-Dimethoxybenzylcarbamate (**3a**).

This compound was obtained in a yield of 165 mg (23%), mp 49-51° (hexane-ethyl acetate 1:1); ir: ν 3360 (NH), 1685 (C=O) cm^{-1}; ^{1}H nmr: δ 1.22 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.26 (d, J = 6 Hz, 2H, $ArCH_2NH$), 5.05 (br s, 1H, NH), 7.79 (m, 3H, H_{arom}); ^{13}C nmr: δ 14.5 (CH_2CH_3), 44.7 (CH_2N), 56.7, 55.8 (OCH_3), 60.1 (CH_2CH_3), 110.8, 111.0, 119.6 (C_{arom}-H), 131.2 (C_{arom}-C), 148.3, 149.0 (C_{arom}-O), 156.6 (C=O).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.54; H, 7.38; N, 5.67.

Ethyl *N*-Trimethylsilyl-*N*-3,4-dimethoxybenzylcarbamate (**4**).

This compound was obtained in a yield of 330 mg (35%), mp 55-57° (hexane-ethyl acetate 1:1); ir: ν 1680 (C=O) cm^{-1}; ^{1}H nmr: δ 0.18 [s, 9H, $(CH_3)_3Si$)], 1.21 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.31 (s, 2H, $ArCH_2N$), 6.65-6.76 (m, 3H, H_{arom}); ^{13}C nmr: δ 0.4 [$(CH_3)_3Si$], 14.3 (OCH_2CH_3), 47.3 ($ArCH_2N$), 55.5, 55.6 (OCH_3), 61.0 (OCH_2CH_3), 109.6, 110.8, 118.3 (C_{arom}-H), 131.8 (C_{arom}-C), 147.5, 148.6 (C_{arom}-O), 159.1 (C=O).

Anal. Calcd. for $C_{15}H_{25}NO_4Si$: C, 57.85; H, 8.09; N, 4.50. Found: C, 58.01; H, 7.88; N, 4.39.

(b) Method B.

To a solution of the *N*-ethyl-*N*-(3,4-dimethoxybenzyl)amine (**1b**) (627 mg, 3 mmoles) in dry THF (45 ml), cooled to -20°, *n*-butyllithium (2.25 ml of 1.51*M* in hexane, 3.3 mmoles) was added. The resulting mixture was stirred for 1/2 hour, cooled to -60°, treated with *tert*-butyllithium (2.1 ml of 1.65*M* in hexane, 3.3 mmoles), and allowed to reach room temperature. After 4 hours, the solution was again cooled to -60° and diethyl carbonate (0.6 ml, 4.5 mmoles) was added. The reaction mixture was left overnight at room temperature and quenched by addition of

water. Work-up as described in Method A (*vide supra*) and flash column chromatography (silica gel, dichloromethane:ethyl acetate 8:2) of the crude material afforded 400 mg of the ethyl *N*-ethyl-*N*-3,4-dimethoxybenzylcarbamate (**3b**) (50%) as an oil; ir: ν 1690 (C=O) cm^{-1}; ^1H nmr: δ 0.98 (t, J = 6.9 Hz, 3H, NCH_2CH_3), 1.19 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.16 (m, 2H, NCH_2CH_3), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.11 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.31 (s, 2H, $ArCH_2N$), 6.71 (m, 3H, H_{arom}); ^{13}C nmr: δ 13.8 (OCH_2CH_3), 14.5 (NCH_2CH_3), 40.6 (NCH_2CH_3), 49.4 ($ArCH_2N$), 55.5, 55.6 (OCH_3), 60.9 (OCH_2CH_3), 110.8, 119.9 (C_{arom}-H), 130.6 (C_{arom}-C), 148.1, 148.9 (C_{arom}-O), 155.9 (C=O).

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.76; H, 8.10; N, 5.43.

Following these methods, several experiments were carried out on amines **1a** and **1b**, and the results are summarized in Table I. The physical and spectroscopic data of other compounds obtained are described:

Ethyl *N*-Ethoxycarbonyl-*N*-3,4-dimethoxybenzylcarbamate (**5**).

This compound had ir: ν 1670 (C=O) cm^{-1}; ^1H nmr: δ 1.22 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.23 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.18 (q, J = 7.1 Hz, 4H, 2 x OCH_2CH_3), 4.73 (s, 2H, $ArCH_2N$), 6.70-6.84 (m, 3H, H_{arom}); ^{13}C nmr: δ 14.0 (2 x OCH_2CH_3), 49.1 ($ArCH_2N$), 55.5, 55.6 (OCH_3), 62.9 (2 x OCH_2CH_3), 110.7, 111.1, 120.2 (C_{arom}-H), 130.0 (C_{arom}-C), 148.2, 148.6 (C_{arom}-O), 153.6 (C=O).

Anal. Calcd. for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 58.02; H, 6.64; N, 4.37.

N-Ethyl-2,3-dihydro-6,7-dimethoxyisoindol-1-one (**2b**).

A stirred suspension of potassium hydroxide (114 mg, 2 mmoles) in DMSO (2 ml) was stirred at room temperature for 10 minutes and then isoindolone **2a** (100 mg, 0.5 mmole), and ethyl iodide (0.08 ml, 1.02 mmoles) were added. After 1/2 hour, water (5 ml) and dichloromethane (5 ml) were added. The organic layer was separated, and the aqueous phase extracted with dichloromethane (3 x 15 ml). The combined organic extracts were dried (anhydrous sodium sulfate) and the solvent was removed *in vacuo*. Flash column chromatography (silica gel, dichloromethane:ethyl acetate 8:2) of the residue afforded 95 mg of *N*-ethyl-2,3-dihydro-6,7-dimethoxyisoindol-1-one (**2b**) (83%); ir: ν 1675 (C=O) cm^{-1}; ^1H nmr: δ 1.09 (t, J = 7.2 Hz, 3H, CH_2CH_3), 3.45 (q, J = 7.2 Hz, 2H, CH_2CH_3), 3.73 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.13 (s, 2H, CH_2N), 6.93 (s, 2H, H_{arom}); ^{13}C nmr: δ 13.1 (CH_2CH_3), 36.5 (CH_2CH_3), 47.9 (CH_2N), 56.3, 62.0 (OCH_3), 115.8, 117.5 (C_{arom}-H), 124.9, 134.1 (C_{arom}-C), 146.6, 151.8 (C_{arom}-O), 165.9 (C=O).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.46; H, 6.66; N, 6.15.

Typical Procedure for the Metalation of the *N*-Ethyl-3,4-dimethoxyphenethylamine (**6b**).

The reaction as described in Method B for metalation of benzylamines, the amine **6b** (418 mg, 2 mmoles), *n*-butyllithium (1.5 ml of 1.51*M* in hexane, 2.2 mmoles), *tert*-butyllithium (1.4 ml of 1.60*M* in hexane, 2.2 mmoles) and diethyl carbonate (0.8 ml, 6 mmoles) in THF (20 ml) afforded, after quenching with 12*M* hydrochloric acid and usual work-up, the following products:

Ethyl *N*-ethyl-*N*-3,4-dimethoxyphenethylcarbamate (**8**).

This compound was obtained in a yield of 365 mg (65%); ir: ν 1690 (C=O) cm^{-1}; ^1H nmr: δ 1.08 (t, J = 7.1 Hz, 3H, NCH_2CH_3), 1.25 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.80 (br t, 2H, $ArCH_2CH_2$), 3.21 (br m, 2H, NCH_2CH_3), 3.40 (t, J = 7.4 Hz, 2H, $ArCH_2CH_2$), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.12 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 6.71-6.81 (m, 3H, H_{arom}); ^{13}C nmr: δ 13.6 (NCH_2CH_3), 14.5 (OCH_2CH_3), 29.5 ($ArCH_2CH_2$), 42.1 ($ArCH_2CH_2$), 48.8 (NCH_2CH_3), 55.6, 55.7 (OCH_3), 60.7 (OCH_2CH_3), 111.1, 111.9, 120.5 (C_{arom}-H), 131.7 (C_{arom}-C), 147.3, 148.7 (C_{arom}-O), 155.9 (C=O).

Anal. Calcd. for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.36; H, 8.01; N, 4.66.

3',4'-Dimethoxystyrene (**9**).

This compound was obtained in a yield of 43 mg (13%); ^1H nmr: δ 3.88 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.07 (dd, J = 11 and 1 Hz, 1H, $CH=CH_AH_B$), 5.50 (dd, J = 18 and 1 Hz, 1H, $CH=CH_AH_B$), 6.61 (dd, J = 18 and 11 Hz, 1H, $CH=CH_AH_B$), 6.74 (d, J = 8 Hz, 1H, $H_{5'}$), 6.85-6.91 (m, 2H, H_2 and $H_{6'}$).

N,N-Diacetyl-*N*-2-(3,4-dimethoxyphenyl)ethylamine (**10a**).

A mixture of the acetamide **6c** (2.25 g, 10 mmoles), acetic anhydride (2.1 g, 21 mmoles) and acetyl chloride (1.6 g, 20 mmoles) was refluxed for 2 hours. The reaction mixture was cooled and concentrated under reduced pressure, and the crude material purified by flash column chromatography (silica gel, hexane:ethyl acetate 4:6) to give 2.50 g (95%) of the *N,N*-diacylamine (**10a**); ir: ν_{max} 1695, 1715 (C=O) cm^{-1}; ^1H nmr: δ 2.32 (s, 6H, 2 x CH_3CO), 2.80 (t, J = 7.4 Hz, 2H, $ArCH_2CH_2$), 3.81-3.88 (m, 2H, $ArCH_2CH_2$)*, 3.85 (s, 3H, OCH_3)*, 3.87 (s, 3H, OCH_3)*, 6.70-6.73 (m, 2H, H_{arom}), 6.81 (d, 1H, H_5) (*overlapped signals); ^{13}C nmr: δ 26.4 (CH_3CO), 34.9, 47.0 ($ArCH_2CH_2N$), 55.9 (OCH_3), 111.4, 112.1, 120.8 (C_{arom}-H), 130.7 (C_{arom}-C), 147.9, 149.1 (C_{arom}-O), 173.2 (C=O).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.46; H, 7.08; N, 5.13.

N,N-Dibenzoyl-*N*-2-(3,4-dimethoxyphenyl)ethylamine (**10b**).

(a) To a stirred solution of the 2-(3,4-dimethoxyphenyl)ethylamine (**6a**) (0.55 g, 3 mmoles), triethylamine (1.25 ml, 9 mmoles), and DMAP (14.6 mg, 0.12 mmole) in anhydrous dichloromethane (30 ml) under argon atmosphere, benzoyl chloride (1.4 g, 12 mmoles) was added dropwise at 0°. The reaction mixture was stirred at rt overnight, then it was poured into ice and extracted with dichloromethane (3 x 30 ml). The organic extracts were dried (anhydrous sodium sulfate) and the solvent evaporated to dryness. Flash column chromatography (silica gel, hexane:ethyl acetate 7:3) of the crude material afforded an oil; which was recrystallized from hexane to give 200 mg (70%) of the *N*-2-(3,4-dimethoxyphenyl)ethylbenzamide (**6e**), white crystals, mp 114-116° (hexane); ir: ν 3320 (NH), 1630 (C=O) cm^{-1}; ^1H nmr: δ 2.89 (t, J = 6.85 Hz, 2H, CH_2CH_2N), 3.66-3.74 (m, 2H, CH_2CH_2N), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.13 (br s, 1H, NH), 6.75-6.85 (m, 3H, H_{arom}), 7.37-7.49 (m, 3H, H_{arom}), 7.67-7.71 (m, 2H, H_{arom}); ^{13}C nmr δ: 35.1, 41.2 ($ArCH_2CH_2N$), 55.7, 55.8 (OCH_3), 111.3, 111.9, 120.6, 126.7, 128.5, 131.2 (C_{arom}-H), 131.3, 134.5 (C_{arom}-C), 147.5, 148.9 (C_{arom}-O), 167.4 (C=O).

(b) To a stirred solution of the benzamide **6e** (3 mmoles), triethylamine (1.25 ml, 9 mmoles), and DMAP (14.6 mg, 0.12 mmole) in anhydrous dichloromethane (30 ml) under argon atmosphere, benzoyl chloride (12 mmoles) was added dropwise at

0°. After heating under reflux overnight, the reaction mixture was cooled and the solvent evaporated to dryness. Flash column chromatography (silica gel, hexane:ethyl acetate 7:3) of the crude material afforded an oil; which was recrystallized from methanol to give 705 mg (60%) of the *N,N*-dibenzoylamine **10b**, as white crystals of mp 103-105°; ir: ν 1650, 1700 (C=O) cm^{-1}; ^1H nmr: δ 3.06-3.12 (m, 2H, ArCH_2CH_2), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.24-4.30 (m, 2H, ArCH_2CH_2), 6.79-6.80 (m, 3H, H_{arom}), 7.09-7.20 (m, 4H, H_{arom}), 7.21-7.27 (m, 2H, H_{arom}), 7.31-7.35 (m, 4H, H_{arom}); ^{13}C nmr: δ 34.5, 48.5 (ArCH_2CH_2N), 55.8, 55.9 (OCH_3), 111.2, 112.2, 121.2, 128.1, 128.7, 131.7 (C_{arom}-H), 130.8, 136.6 (C_{arom}-C), 147.7, 148.8 (C_{arom}-O), 174.5 (C=O).

Anal. Calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.26; H, 5.94; N, 3.91.

N,N-Diacetyl-*N*-2-(2-bromo-4,5-dimethoxyphenyl)ethylamine (**10c**).

(a) To a well stirred solution of the acetamide **6c** (1.8 g, 8 mmoles) in glacial acetic acid (20 ml), a solution of bromine (1.28 g, 8 mmoles) in glacial acetic acid (10 ml) was added dropwise. After stirring at room temperature for 6 hours the solvent was evaporated. The residue was treated with water and the so-obtained precipitate recrystallized from methanol, thus affording 2.10 g of the *N*-2-(2-bromo-4,5-dimethoxyphenyl)ethylacetamide (**6f**) (88%), white crystals of mp 103-105°; ir: ν 3260 (NH), 1635 (C=O) cm^{-1}; ^1H nmr: δ 1.93 (s, 3H, CH_3CO), 2.87 (t, J = 7.0 Hz, 2H, CH_2CH_2N), 3.42-3.50 (m, 2H, CH$_2$CH_2N), 3.82 (s, 6H, 2 x OCH_3), 5.77 (br s, 1H, NH), 6.71 (s, 1H, H_6), 6.97 (s, 1H, H_3); ^{13}C nmr δ: 23.2 (*C*H$_3$CO), 35.3, 39.6 (Ar*C*H$_2$CH$_2$N), 56.0, 56.1 (OCH_3), 113.3, 115.5 (C_{arom}-H), 114.1 (C_{arom}-Br), 130.1 (C_{arom}-C), 148.2, 148.4 (C_{arom}-O), 170.1 (C=O).

(b) A mixture of the so-obtained brominated acetamide **6f** (1.5 g, 5 mmoles), acetic anhydride (1.05 g, 10.5 mmoles) and acetyl chloride (0.80 g, 10 mmoles) was refluxed for 1 hour. Then, the reaction mixture was cooled and concentrated under reduced pressure, and the so-obtained precipitate recrystallized from methanol to give 1.40 g (82%) of the brominated *N,N*-diacylamine **10c**, mp 85-87°; ir: ν 1675, 1705 (C=O) cm^{-1}; ^1H nmr δ: 2.34 (s, 6H, 2 x CH_3CO), 2.90 (t, J = 7.5 Hz, 2H, ArCH_2CH$_2$), 3.78-3.84 (m, 2H, ArCH$_2$CH_2)*, 3.82 (s, 6H, 2 x OCH_3)*, 6.69 (s, 1H, H_6), 6.96 (s, 1H, H_3) (*overlapped signals); ^{13}C nmr: δ 26.3 (*C*H$_3$CO), 34.8, 45.1 (Ar*C*H$_2$*C*H$_2$N), 56.0, 56.1 (OCH_3), 113.9 (C_{arom}-Br), 113.6, 115.3 (C_{arom}-H), 129.4 (C_{arom}-C), 148.5, 148.6 (C_{arom}-O), 173.3 (C=O).

Anal. Calcd. for $C_{14}H_{18}BrNO_4$: C, 48.85; H, 5.27; N, 4.07. Found: C, 49.04; H, 5.21; N, 4.25.

General Procedure for the Synthesis of Iodinated *N,N*-Diacylphenethylamines.

(a) To a well stirred solution of the acetamide **6c** or the benzamide **6e** (6 mmoles) in glacial acetic acid (25 ml), a solution of iodine monochloride (1.13 g, 7 mmoles) in glacial acetic acid (10 ml) was added dropwise. After stirring at room temperature for 2 hours, the reaction mixture was concentrated and the residue dissolved in dichloromethane. The solution was treated with 10% aqueous sodium thiosulfate, and then extracted with dichloromethane (3 x 30 ml). The combined organic extracts were dried with sodium sulfate and the solvent was removed under reduced pressure. The so-obtained precipitate was recrystallized, thus affording the corresponding iodinated acetamide **6g** and benzamide **6h** in 90% and 96% yield, respectively.

N-2-(2-Iodo-4,5-dimethoxyphenyl)ethylacetamide (**6g**).

This compound was obtained as white crystals, mp 110-111° (dichloromethane); ir: ν 3300 (NH), 1635 (C=O) cm^{-1}; ^1H nmr: δ 1.95 (s, 3H, CH_3CO), 2.87 (t, J = 7.0 Hz, 2H, CH_2CH$_2$N), 3.41-3.49 (m, 2H, CH$_2$CH_2N), 3.83 (s, 6H, 2 x OCH_3), 5.65 (br s, 1H, NH), 6.73 (s, 1H, H_6), 7.19 (s, 1H, H_3); ^{13}C nmr: δ 22.9 (*C*H$_3$CO), 39.4, 39.5 (Ar*C*H$_2$*C*H$_2$N), 55.7, 55.9 (OCH_3), 87.9 (C_{arom}-I), 112.3, 121.4 (C_{arom}-H), 133.7 (C_{arom}-C), 147.9, 149.1 (C_{arom}-O), 170.2 (C=O).

N-2-(2-Iodo-4,5-dimethoxyphenyl)ethylbenzamide (**6h**).

This compound was obtained as white crystals, mp 144-146° (ethyl acetate); ir: ν 3320 (NH), 1630 (C=O) cm^{-1}; ^1H nmr: δ 3.01 (t, J = 6.9 Hz, 2H, CH_2CH$_2$N), 3.64-3.72 (m, 2H, CH$_2$CH_2N), 3.74 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.38 (br s, 1H, NH), 6.75 (s, 1H, H_6), 7.20 (s, 1H, H_3), 7.36-7.45 (m, 3H, H_{arom}), 7.73-7.76 (m, 2H, H_{arom}); ^{13}C nmr: δ 39.5, 40.2 (Ar*C*H$_2$*C*H$_2$N), 55.8, 56.1 (OCH_3), 88.0 (C_{arom}-I), 112.7, 121.6, 126.8, 128.5, 131.4 (C_{arom}-H), 133.9, 134.3 (C_{arom}-C), 148.2, 149.4 (C_{arom}-O), 167.7 (C=O).

(b) To a stirred solution of the iodinated acetamide **6g** or benzamide **6h** (3 mmoles), triethylamine (1.25 ml, 9 mmoles), and DMAP (0.12 mmole) in anhydrous dichloromethane (30 ml) under argon atmosphere, acetyl or benzoyl chloride (12 mmoles) was added dropwise at 0°. The reaction mixture was stirred at rt (for the acetamide) or under reflux (for the benzamide) overnight, then it was concentrated. Flash column chromatography (silica gel, hexane:ethyl acetate 7:3) of the crude material afforded the corresponding *N,N*-diacylamines.

N,N-Diacetyl-*N*-2-(2-iodo-4,5-dimethoxyphenyl)ethylamine (**10d**).

This compound was obtained as white crystals (1.03 g, 88%), mp 97-99° (hexane-ethyl acetate, 1:1); ir: ν 1680, 1720 (C=O) cm^{-1}; ^1H nmr: δ 2.34 (s, 6H, 2 x CH_3CO), 2.90 (t, J = 7.5 Hz, 2H, ArCH_2CH$_2$), 3.75-3.80 (m, 2H, ArCH$_2$CH_2)*, 3.80 (s, 6H, 2 x OCH_3)*, 6.69 (s, 1H, H_6), 7.15 (s, 1H, H_3) (*overlapped signals); ^{13}C nmr: δ 26.4 (*C*H$_3$CO), 39.1, 45.2 (Ar*C*H$_2$*C*H$_2$N), 55.8, 56.0 (OCH_3), 87.6 (C_{arom}-I), 112.8, 121.4 (C_{arom}-H), 133.8 (C_{arom}-C), 148.4, 149.5 (C_{arom}-O), 173.2 (C=O).

Anal. Calcd. for $C_{14}H_{18}INO_4$: C, 42.98; H, 4.64; N, 3.58. Found: C, 43.12; H, 4.48; N, 3.40.

N-Acetyl-*N*-benzoyl-*N*-2-(2-iodo-4,5-dimethoxyphenyl)ethylamine (**10e**).

This compound was obtained as white crystals (0.85 g, 63%), mp 111-113° (methanol); ir: ν 1680, 1720 (C=O) cm^{-1}; ^1H nmr: δ 2.27 (s, 3H, CH_3CO), 2.93 (t, J = 7.0 Hz, 2H, ArCH_2CH$_2$), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.96 (t, J = 7.0 Hz, 2H, ArCH$_2$CH_2), 6.63 (s, 1H, H_6), 7.11 (s, 1H, H_3), 7.35-7.49 (m, 5H, H_{arom}); ^{13}C nmr: δ 26.1 (*C*H$_3$CO), 39.3, 46.6 (Ar*C*H$_2$*C*H$_2$N), 55.8, 56.1 (OCH_3), 88.2 (C_{arom}-I), 113.1, 121.6, 128.3, 128.6, 132.2 (C_{arom}-H), 133.3, 135.1 (C_{arom}-C), 148.3, 149.3 (C_{arom}-O), 173.6, 174.1 (C=O).

Anal. Calcd. for $C_{19}H_{20}INO_4$: C, 50.35; H, 4.45; N, 3.09. Found: C, 50.64; H, 4.21; N, 2.85.

N,N-Dibenzoyl-*N*-2-(2-iodo-4,5-dimethoxyphenyl)ethylamine (**10f**).

This compound was obtained as white crystals (1.25 g, 80%), mp 128-129° (hexane-ethyl acetate, 9:1); ir: ν 1670, 1695 (C=O) cm^{-1}; ^1H nmr: δ 3.19 (t, J = 7.6 Hz, 2H, ArCH_2CH$_2$), 3.80 (s,

3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.22 (t, J = 7.6 Hz, 2H, $ArCH_2CH_2$), 6.82 (s, 1H, H_6), 7.15-7.44 (m, 11H, H_3 and H_{arom}); ^{13}C nmr: δ 39.3, 47.2 ($ArCH_2CH_2N$), 55.9, 56.2 (OCH_3), 88.1 (C_{arom}-I), 113.0, 121.7, 128.3, 128.8, 131.9 (C_{arom}-H), 133.4, 136.2 (C_{arom}-C), 148.3, 149.4 (C_{arom}-O), 174.3 (C=O).

Anal. Calcd. for $C_{24}H_{22}INO_4$: C, 55.94; H, 4.30; N, 2.72. Found: C, 56.12; H, 4.18; N, 2.59.

General Procedure for the Metalation of Iodinated *N,N*-Diacylamines **10**.

To a solution of the iodinated imide **10** (1 mmoles) in dry THF (20 ml), cooled to -78°, *n*-butyllithium (1.5 ml of 1.51*M* in hexane, 2.2 mmoles) was added. The resulting mixture was stirred at -78° for 4 hours, and then quenched with water or TFA. The solution was allowed to reach room temperature. Ethyl ether (15 ml) was added, the organic layer separated, and the aqueous phase extracted with dichloromethane (3 x 30 ml). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography, thus affording the ketones **12**.

2'-(2-Acetoamidoethyl)-4',5'-dimethoxyacetophenone (**12a**).

In this case, column chromatography (silica gel, dichloromethane:methanol 9.5:0.5) of the crude afforded the acetophenone **12a** as white crystals (225 mg, 85%), mp 123-124° (hexane-ethyl acetate, 1:1) (lit [17b] 124-125°); ir: ν 3320 (NH), 1670 (C=O) cm^{-1}; ^1H nmr: 1.90 (s, 3H, CH_3COAr), 2.59 (s, 3H, CH_3CON), 2.94-3.01 (m, 2H, $ArCH_2CH_2N$), 3.46-3.54 (m, 2H, $ArCH_2CH_2N$), 3.92 (s, 6H, 2 x OCH_3), 6.68 (br s, 1H, NH), 6.75 (s, 1H, H_6), 7.17 (s, 1H, H_3); ^{13}C nmr: δ 23.2 (CH_3COAr), 29.5 (CH_3CON), 32.6 ($ArCH_2CH_2N$), 41.8 ($ArCH_2CH_2N$), 56.0, 56.2 (OCH_3), 112.7, 114.0 (C_{arom}-H), 130.0, 134.4 (C_{arom}-C), 146.8, 152.1 (C_{arom}-O), 170.4 (C=O amide), 202.5 (C=O ketone).

2'-(2-Benzamidoethyl)-4',5'-dimethoxybenzophenone **12b**.

In this case, flash column chromatography (silica gel, dichloromethane:methanol 9.5:0.5) of the crude gave benzophenone **12b** as an oil (311 mg, 80%); ir: ν 3320 (NH), 1640 (C=O) cm^{-1}; ^1H nmr: δ 2.96-3.01 (m, 2H, $ArCH_2CH_2N$), 3.75 (s, 3H, OCH_3)*, 3.74-3.81 (m, 2H, $ArCH_2CH_2N$)*, 3.93 (s, 3H, OCH_3), 6.82 (s, 1H, H_6), 6.91 (s, 1H, H_3), 7.36-7.52 (m, 6H, H_{arom}), 7.82-7.88 (m, 4H, H_{arom}), 7.99 (br s, 1H, NH) (*overlapped signals); ^{13}C nmr: δ 31.3 ($ArCH_2CH_2N$), 41.5 ($ArCH_2CH_2N$), 56.0, 56.1 (OCH_3), 113.0, 113.2, 127.1, 128.3, 128.4, 130.6, 131.1, 133.3 (C_{arom}-H), 130.1, 133.7, 134.5, 137.9 (C_{arom}-C), 146.3, 151.5 (C_{arom}-O), 167.5 (C=O amide), 198.2 (C=O ketone).

Anal. Calcd. for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 74.32; H, 6.04; N, 3.49.

N-[2-(2-(1-Hydroxy-1-phenylpentyl)-4,5-dimethoxyphenyl]-ethyl]benzamide.

This compound was also obtained from the above chromatographic separation as an oil (75 mg, 17%); ir: ν 3200-3500 (NH, OH), 1730 (C=O) cm^{-1}; ^1H nmr: δ 0.88 [t, J = 7.0 Hz, 3H, $CH_3(CH_2)_3$], 1.28-1.38 [m, 4H, $CH_3(CH_2)_2CH_2$], 1.68 (br s, 1H, OH), 2.20-2.29 [m, 2H, $CH_3(CH_2)_2CH_2$], 2.70-2.81 (m, 2H, $ArCH_2CH_2N$), 3.13-3.21 (m, 1H, $ArCH_2CH_aH_bN$), 3.28-3.40 (m, 1H, $ArCH_2CH_aH_bN$), 3.81 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.43 (br s, 1H, NH), 6.72 (s, 1H, $H_{6'}$), 7.12 (s, 1H, $H_{3'}$), 7.18-7.49 (m, 8H, H_{arom}), 7.62-7.70 (m, 2H, H_{arom}); ^{13}C nmr: δ 14.1 [$CH_3(CH_2)_3$], 23.1 [$CH_3CH_2(CH_2)_2$], 26.2 [$CH_3CH_2CH_2CH_2$], 32.0 [$CH_3(CH_2)_2CH_2$], 41.3, 43.5 ($ArCH_2CH_2N$), 55.8, 56.2 (OCH_3),78.8 (C-OH), 111.2, 114.6, 125.9, 126.6, 126.8, 127.9, 128.4, 131.2 (C_{arom}-H), 131.0, 134.7, 136.7, 146.2 (C_{arom}-C), 148.0, 148.1 (C_{arom}-O), 167.5 (C=O).

Anal. Calcd. for $C_{28}H_{33}NO_4$: C, 75.14; H, 7.43; N, 3.13. Found: C, 75.46; H, 7.15; N, 3.35.

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