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Direct syntheses of 4-aryl-1,2,3,4-tetrahydroisoquinolines and 1-aryl-2,3,4,5-tetrahydro-3-benzoazepines via hydroamination of enol carbamates

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ABSTRACT

An efficient and simple procedure for the syntheses of 4-aryl-1,2,3,4-tetrahydroisoquinolines and 1-aryl-2,3,4,5-tetrahydro-3-benzoazepines has been developed. The approach uses easily available starting materials and requires just three steps. The hydroamination of an enol carbamate is the key step. This general and direct method has been applied to the total synthesis of the natural alkaloid cherylline and to biologically active 3-benzoazepines as well.

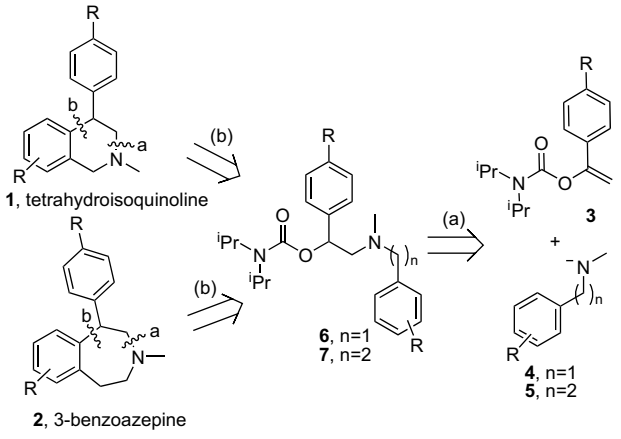
1. Introduction

Amaryllidaceae[1,2] has been one of the most studied family of plants because of its alkaloid composition. In 1970, Brossi et al.[3] isolated an alkaloid with 4-aryl-1,2,3,4-tetrahydroisoquinoline structure named cherylline (**1e**) from *Crinum Powelli.* Due to the uniqueness of its structure and owing to the potential medicinal properties of the 4-arylisoquinoline derivatives, many investigations have been carried out on this class of alkaloids. Some of them are valuable medicines with centrally stimulating, thymoleptic, and antiarrhythmic actions.[4,5] Others exhibit broad spectrum calcium antagonistic,[6] antibacterial,[7] antiplasmodial,[2,8–11] estrogen agonist/antagonist activity,[12] and serotin (5-HT) re-uptake.[13]

1-Aryl-2,3,4,5-tetrahydro-3-benzoazepines also show a wide variety of interesting biological activities. Some of them are inhibitors of 5-HT, dopamine, and norepinefrine.[14] They are also noncompetitive NMDA antagonists.[15,16] The NMDA receptors are involved in acute and chronic neurodegenerative disorders, including epilepsy, stroke, morbus Parkinson, and morbus Alzheimer;[17,18] they are important for the development of neurons and thus, for processes like learning and memory.[19,20]

The importance of these heterocyclic compounds generated a considerable number of synthetic approaches. Hence, the formation of the nitrogen-containing ring of 4-aryl-1,2,3,4-tetr ahydroisoquinolines has been achieved with several reactions such as Bischler–Napieralski,[21–23] intramolecular Horner,[24] Friedel–Crafts,[11,25–30] Pictet–Spengler,[31] and oxazoline driven chemistry[32] among others.[22,33–40] The formation of the seven-membered heterocyclic ring in 3-benzoazepines is also normally carried out by Friedel–Crafts type reactions (PPA,[41] H_2SO_4,[42] H_2SO_4–TFA,[43] HBF_4–OMe_2[44]).

Our group has been developing several efficient syntheses of bioactive compounds with microwave-assisted organic synthesis (MAOS).[45–52] Recently, we reported the preparation of enol carbamates by irradiation with microwaves under solvent-free conditions.[47] This functionality is very useful in organic synthesis since it leads to the stereoselective carbolithiation of carbon–carbon double bonds.[53] In this paper, we report on the use of enol carbamates for the construction of tetrahydroisoquinoline (**1**) and 3-benzoazepine (**2**) skeletons from the same retrosynthetic approach (Scheme 1). The key step is the formation of C–N bond *a* via hydroamination of an enol carbamate (**3**) with a lithium amide (**4** or **5**) to afford a 2-phenylethylamine (**6** or **7**), since the hydroamination of styrene derivatives with lithium or potassium amides



Scheme 1.

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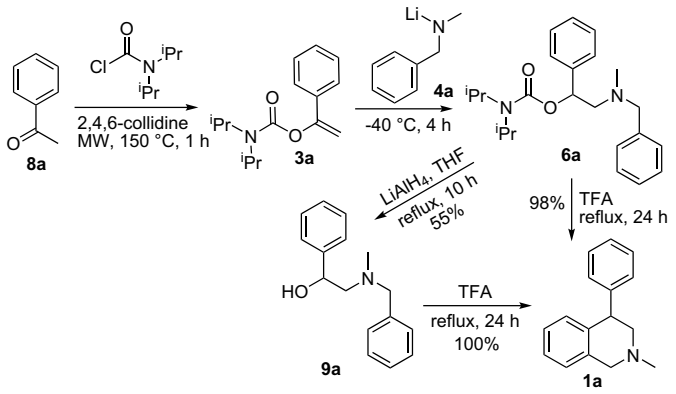
has proven to be a useful tool for the synthesis of β-phenylethylamine derivatives.[54,55] This addition might afford a 2-phenylethylamine with a carbamate group in its benzylic position, and its electrophilic character might favor the formation of C–C bond *b* via an intramolecular Friedel–Crafts type cyclization.

2. Results and discussion

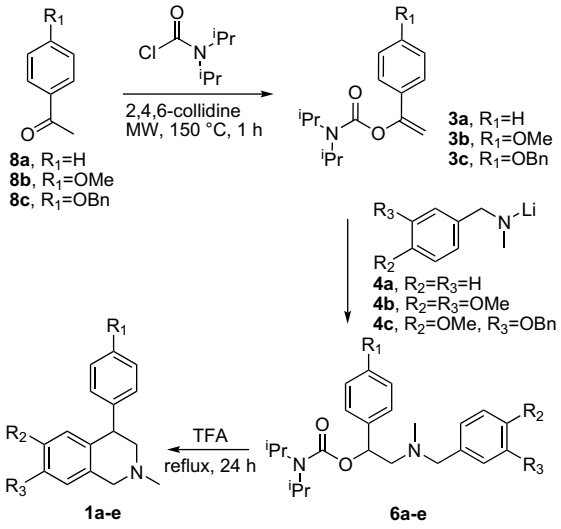
For the study of hydroamination and intramolecular cyclization steps, the synthesis of a 3-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline skeleton (**1a**) was tried; this requires acetophenone (**8a**) and *N*-methylbenzylamine as starting materials. Thus, acetophenone was converted into enol carbamate **3a** in 68% yield, using 2,4,6-collidine and *N*′,*N*′-diisopropylcarbamoyl chloride under microwave irradiation at 150 °C for 1 h with the aforementioned method.[47] The hydroamination of the double bond was performed by adding the lithium amide of *N*-methylbenzylamine (**4a**) (synthetized with *n*-BuLi in dry THF at 0 °C), dropwise to the enol carbamate **3a** at −40 °C. This operation delivered carbamate **6a** in 91% yield (Scheme 2, Table 1). To achieve the intramolecular Friedel–Crafts cyclization, first the carbamate group was reduced with lithium aluminum hydride in refluxing THF to provide the aminoalcohol **9a** in 55% yield. Then, **9a** was treated with $AlCl_3$ under similar conditions, as previously described,[56] but unfortunately no cyclization was observed. This inconvenience was overcome by refluxing in trifluoroacetic acid that yielded the tetrahydroisoquinoline **1a** quantitatively.



Scheme 2.

Because of the excellent result of the cyclization with trifluoroacetic acid, and in order to improve the moderate yield obtained in the reduction of the carbamate (55%), the deprotection and the cyclization in a single step were tested. Consequently, carbamate **6a** was treated with TFA under reflux for 24 h and gratifyingly, this operation afforded the cyclic product **1a** in excellent yield (Table 1, entry 1).

After establishing the viability of the route for the synthesis of the 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton, the strategy was extended to the synthesis of a variety of poly and diversely substituted models (Scheme 3). Thus, *para*-methoxy substituted enol carbamate **3b** reacted with lithium amide of *N*-methylbenzylamine (**4a**) at −40 °C, giving **6b** in 75% yield; this was cyclized to 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-2-methylisoquinoline (**1b**) in very good yield (91%) (Table 1, entry 2). On the other hand, the influence of alkoxy groups in the lithium amide moiety was also studied (e.g., **4b**,**c**). The reaction was observed to be slower (the temperature was raised to 0 °C and the reaction time extended to 24 h). So, **4b** gave the hydroamination product **6c** in slightly higher yield (89%). This product cyclized to 1,2,3,4-tetrahydro-6,7-dimethoxy-3-methyl-4-phenylisoquinoline **1c** in 89% after refluxing in TFA (Table 1, entry 3). Similar results were obtained in the synthesis of **1d** (Table 1, entry 4), which shows the same substitution pattern as cherylline. These results confirmed that the presence of alkoxy substituents in the lithium amide moiety requires higher temperature and longer reaction time for the hydroamination than unsubstituted ones.



Scheme 3.

The method was applied to the synthesis of cherylline (**1e**), which has two phenol groups. In order to do this, both starting materials, ketone and lithium amide, were protected as benzyloxy groups due to their easy deprotection in the acidic medium employed for cyclization. Thus, the hydroamination of **3c** with the lithium amide **4c** took place though in moderate yield (51%), and the cyclization step occurred with simultaneous deprotection of both phenol groups giving cherylline (**1e**) in 72% yield (Table 1, entry 5).

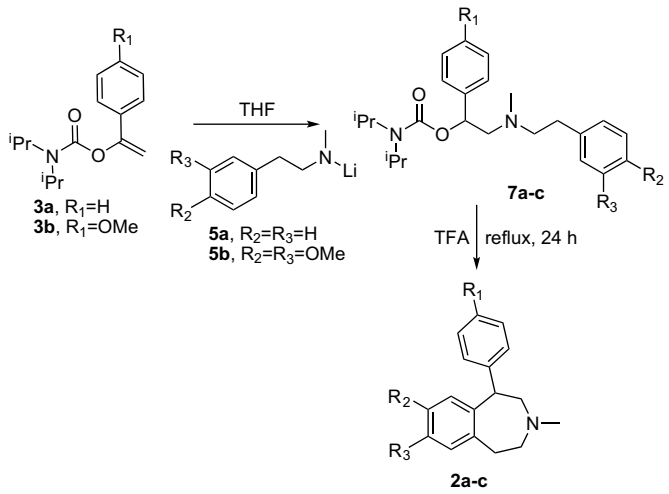
The strategy developed was also applied to the synthesis of 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzoazepines **2** (Scheme 4). The only difference lies in the cyclization step, which involves the formation of a seven-membered heterocyclic ring instead of the six-membered ring formed in the tetrahydroisoquinolines. Thus, enol carbamate **3a** was treated with lithium amide **5a** at −40 °C for 14 h, yielding the addition product **7a** in 71% (Table 1, entry 6). Under reflux in TFA this carbamate reacted sluggishly. It was only after 48 h that it furnished the aminoalcohol upon cleavage of the carbamate group, but only in 58% yield and there was no cyclization

Table 1
Yields for hydroamination and cyclization reactions

Entry	R_1	R_2	R_3	Hydroamination conditions	Hydroamination product (yield,[a] %)	Cyclization product (yield,[a] %)
1	H	H	H	−40 °C, 4 h	**6a** (91)	**1a**[57] (98)
2	OMe	H	H	−40 °C, 14 h	**6b** (75)	**1b**[58] (91)
3	H	OMe	OMe	0 °C, 24 h	**6c** (89)	**1c**[28] (89)
4	OMe	OMe	OMe	0 °C, 24 h	**6d** (68)	**1d**[59] (91)
5	OBn	OMe	OBn	0 °C, 24 h	**6e** (51)	**1e** (R_1=R_3=OH)[40] (72)
6	H	H	H	−40 °C→0 °C, 14 h	**7a** (71)	**2a**[b,60] (97)
7	OMe	H	H	−40 °C→0 °C, 16 h	**7b** (65)	**2b**[b] (88)
8	H	OMe	OMe	0 °C, 24 h	**7c** (77)	**2c**[b] (90)

[a] Isolated yields of material after chromatography.
[b] Methanesulfonic acid (20 mol%) is added to the TFA to make the cyclization more effective (24 h refluxing).

product. Fortunately, the addition of methanesulfonic acid (20 mol %) allowed to achieve the deprotection–cyclization in 24 h, and gave **2a** in very good yield (97%, Table 1, entry 6). Similar to the behavior observed in the synthesis of tetrahydroisoquinolines, when the enol carbamate has a methoxy group (**3b**) its hydroamination takes place in lower yield (**7b**, 65%), but cyclization to **2b** works very well (88%, Table 1, entry 7). Finally, the reaction of the substituted amide **5b** with enol carbamate **3a** delivered **2c** after hydroamination and subsequent cyclization (Table 1, entry 8).



Scheme 4.

3. Conclusions

In summary, a simple and efficient method for the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloids from acetophenones following a linear sequence of three chemical operations is reported. To the best of our knowledge, this is one of the shortest routes for the total synthesis of the natural alkaloid cherylline. The hydroamination of enol carbamates from acetophenones also has been used for the synthesis of 1-aryl-2,3,4,5-tetrahydro-3-benzoazepines. In addition, this paper broadens the already wide range of applications of enol carbamates in the synthesis of products with biological activities and the synthetic potential of their hydroamination in organic synthesis.

4. Experimental

4.1. General methods

Melting points were measured in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$. Mass spectra were recorded in a low-resolution spectrometer. Infrared spectra were measured on FTIR instrument (cm^{-1}).

4.2. General procedure for the hydroamination reaction

*4.2.1. Synthesis of 2-(N-benzyl-N-methylamino)-1-phenylethyl N′,N′-diisopropylcarbamate (**6a**)*

To a stirred solution of benzylamine (0.512 g, 4.2 mmol) in dry THF (10 mL) at 0 °C under nitrogen atmosphere, a solution of *n*-BuLi (1.6 M in hexane, 2.6 mL, 4.2 mmol) was added, and stirred for 15 min at this temperature. This mixture was added dropwise to a solution of 1-phenylvinyl *N′*,*N′*-diisopropylcarbamate (**3a**) (0.519 g, 2.1 mmol) in dry THF (10 mL) at −40 °C. After 4 h, the reaction was quenched with MeOH and allowed to warm to room temperature. The solvent was evaporated and the residue was partitioned between water and CH_2Cl_2. The organic layer was dried, evaporated, and purified by column chromatography (SiO_2, AcOEt/hexane, 2:8) giving 2-(*N*-benzyl-*N*-methylamino)-1-phenylethyl *N′*,*N′*-diisopropylcarbamate (**6a**) (0.706 g, 91%) as a colorless oil. IR (KBr film): 2969, 1694 (C=O), 1289 (C–O), 698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): 1.21–1.28 (m, 12H, 2×CH(CH_3)$_2$), 2.28 (s, 3H, NMe), 2.67 (dd, 1H, *J*=12.7, 5.3 Hz, CHCH_2N), 2.92 (dd, 1H, *J*=13.0, 8.2 Hz, CHCH_2N), 3.54 (d, 1H, *J*=13.2 Hz, NCH_2Ph), 3.59 (d, 1H, *J*=13.2 Hz, NCH_2Ph), 4.05 (br s, 2H, 2×C*H*(CH_3)$_2$), 5.96 (dd, 1H, *J*=5.3, 7.9 Hz, CHOCO), 7.22–7.34 (m, 10H, ArH). ^{13}C NMR (75 Hz, $CDCl_3$): *δ*=21.3, 42.7, 46.2, 62.6, 63.5, 74.0, 126.9, 127.0, 127.8, 128.3, 128.5, 129.0, 139.5, 140.9, 155.1. MS (EI): *m*/*z* (%) 223 (27), 134 (100), 91 (11). Anal. Calcd for $C_{23}H_{32}N_2O_2$: C, 74.96; H, 8.75, N, 7.60. Found: C, 74.85; H, 8.99; N, 7.61.

*4.2.2. Synthesis of 2-(N-benzyl-N-methylamino)-1-phenylethanol (**9a**)*

To a suspension of $LiAlH_4$ (1.519 g, 40.0 mmol) in dry THF (20 mL) under nitrogen atmosphere, a solution of 2-(*N*-benzyl-*N*-methylamino)-1-phenylethyl *N′*,*N′*-diisopropylcarbamate (**5a**) (2.444 g, 6.6 mmol) was added dropwise in dry THF (15 mL), and refluxed for 1 day. The reaction mixture was poured into an aqueous saturated solution of Na_2SO_4 (75 mL) and extracted with AcOEt (3×30 mL). The organic layer was dried, evaporated, and purified by column chromatography (SiO_2, AcOEt/hexane 4:6) giving 2-(*N*-benzyl-*N*-methylamino)-1-phenylethanol (**9a**) (0.875 g, 55%) as a colorless oil. IR (KBr film): 3433 (OH), 1453, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 2.36 (s, 3H, NMe), 2.54–2.69 (m, 2H, CHCH_2N), 3.58 (d, 1H, *J*=13.2 Hz, NCH_2Ph), 3.78 (d, 1H, *J*=12.7 Hz, NCH_2Ph), 4.04 (br s, 1H, OH), 4.80 (dd, 1H, *J*=10.1, 4.0 Hz, C*H*OH), 7.25–7.42 (m, 10H, ArH). ^{13}C NMR ($CDCl_3$) *δ* 42.0, 62.6, 65.8, 69.6, 126.2, 127.6, 127.7, 128.6, 128.7, 129.3, 138.5, 142.5. MS (EI): *m*/*z* (%) 241 (M^+, 4), 135 (100), 114 (29), 106 (17). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94, N, 5.80. Found: C, 79.45; H, 8.09; N, 5.66.

4.3. General procedure for the cyclization

*4.3.1. Synthesis of 1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline (**1a**)*

A solution of 2-(*N*-benzyl-*N*-methylamino)-1-phenylethyl *N′*,*N′*-diisopropylcarbamate (**6a**) (0.135 g, 0.4 mmol) in TFA (3.5 mL) was refluxed for 44 h. The reaction mixture was evaporated, dissolved in CH_2Cl_2 (30 mL), and washed with 10% aq NaOH (3×10 mL). The organic extracts were dried and evaporated, giving 1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline (**1a**) (0.081 g, 99%) as an oil.[57]

4.4. Data of previously unreported compounds

*4.4.1. 2-(N-Benzyl-N-methylamino)-1-(4-methoxyphenyl)ethyl N′,N′-diisopropylcarbamate (**6b**)*

Yield 75%. Oil. IR (KBr film): 1688 (C=O), 1288 (C–O), 1247 cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 1.20–1.25 (m, 12H, 2×CH(CH_3)$_2$), 2.28 (s, 3H, NMe), 2.66 (dd, 1H, *J*=13.0, 5.5 Hz, CHCH_2N), 2.92 (dd, 1H, *J*=13.2, 7.9 Hz, CHCH_2N), 3.57 (s, 2H, NCH_2Ph), 3.80 (s, 3H, OMe), 3,97 (br s, 2H, 2×C*H*(CH_3)$_2$), 5.92 (dd, 1H, *J*=5.5, 7.7 Hz, CHOCO), 6.87 (d, 2H, *J*=8.8 Hz, Ar–H), 7.20–7.28 (m, 7H, Ar–H). ^{13}C NMR ($CDCl_3$) *δ* 21.4, 42.4, 46.1, 55.1, 62.3, 62.9, 73.3, 113.6, 126.7, 128.0, 128.7, 132.7, 139.2, 154.9, 159.0. MS (EI): *m*/*z* (%) 254 (21), 253 (52), 134 ($PhCH_2NCH_3CH_2^+$, 100), 91 (21). Anal. Calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 72.15; H, 8.46; N, 6.90.

*4.4.2. 2-(N-(3,4-Dimethoxybenzyl)-N-methylamino)-1-phenylethyl N′,N′-diisopropylcarbamate (**6c**)*

Yield 89%. Oil. IR (KBr film): 1689 (C=O), 1288 (C–O) cm^{-1}. ^{1}H NMR ($CDCl_3$) *δ* 1.18–1.20 (m, 12H, 2×CH(CH_3)$_2$), 2.27 (s, 3H, NMe),

2.71 (dd, 1H, J=12.9, 5.9 Hz, CHCH_2N), 2.91 (dd, 1H, J=13.2, 7.5 Hz, CHCH_2N), 3.46 (d, 1H, J=13.2 Hz, NCH_2Ar), 3.52 (d, 1H, J=13.2 Hz, NCH_2Ar), 3.77 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.93 (br s, 2H, 2×CH(CH$_3$)$_2$), 5.94 (dd, 1H, J=7.3, 5.9 Hz, CHOCO), 6.74–6.72 (m, 3H, ArH), 7.26–7.32 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$) δ 21.5, 42.7, 46.3, 56.0, 56.1, 62.4, 62.9, 74.2, 110.8, 112.1, 121.1, 127.0, 127.8, 128.4, 132.1, 140.9, 148.1, 149.0, 155.1. MS (EI): m/z (%) 248 (7), 247 (45), 150 (100). Anal. Calcd for $C_{25}H_{36}N_2O_4$: C, 70.06; H, 8.47; N, 6.54. Found: C, 70.13; H, 8.56; N, 6.51.

4.4.3. 2-(N-(3,4-Dimethoxybenzyl)-N-methylamino)-1-(4-methoxyphenyl)ethyl N′,N′-diisopropylcarbamate (**6d**)

Yield 68%. Oil. IR (KBr film): 1687 (C=O), 1514, 1250 (C–O) cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 1.16–1.25 (m, 12H, 2×CH(CH_3)$_2$), 2.25 (s, 3H, NMe), 2.68 (dd, 1H, J=12.7, 6.2 Hz, CHCH_2N), 2.86 (dd, 1H, J=13.0, 7.3 Hz, CHCH_2N), 3.43 (d, 1H, J=13.2 Hz, NCH_2Ar), 3.51 (d, 1H, J=12.7 Hz, NCH_2Ar), 3.76 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.86 (br s, 2H, 2×CH(CH$_3$)$_2$), 5.80 (t, 1H, J=6.6 Hz, CHOCO), 6.72 (br s, 3H, ArH), 6.83 (d, 2H, J=8.8 Hz, ArH), 7.24 (d, 2H, J=8.8 Hz, ArH). ^{13}C NMR (CDCl$_3$) δ 21.5, 42.7, 46.1, 55.4, 55.9, 56.0, 62.4, 62.6, 73.8, 110.8, 112.1, 113.8, 121.1, 132.1, 133.0, 148.1, 149.0, 155.0, 159.2. MS (EI): m/z (%) 459 (M$^+$+1, 5), 314 (30), 197 (37), 151 (100). Anal. Calcd for $C_{26}H_{38}N_2O_5$: C, 68.10; H, 8.35; N, 6.11. Found: C, 68.34; H, 8.36; N, 6.24.

4.4.4. 2-(N-(3-(Benzyloxy)-4-methoxybenzyl)-N-methylamino)-1-(4-(benzyloxy)phenyl)ethyl N′,N′-diisopropylcarbamate (**6e**)

Yield 51%. Oil. IR (KBr film): 1686 (C=O), 1512, 1260 (C–O) cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 1.19–1.29 (m, 12H, 2×CH(CH_3)$_2$), 2.23 (s, 3H, NMe), 2.71 (dd, 1H, J=13.2, 6.2 Hz, CHCH_2N), 2.89 (dd, 1H, J=12.7, 7.5 Hz, CHCH_2N), 3.44 (d, 1H, J=13.2 Hz, NCH_2Ar), 3.52 (d, 1H, J=12.7 Hz, NCH_2Ar), 3.86 (s, 3H, OMe), 3.88 (br s, 2H, 2×CH(CH$_3$)$_2$), 5.01 (s, 2H, OCH$_2$Ph), 5.04 (s, 2H, OCH$_2$Ph), 5.90 (t, 1H, J=6.6 Hz, CHOCO), 6.78–6.98 (m, 5H, ArH), 7.25–7.47 (m, 12H, ArH). ^{13}C NMR (CDCl$_3$) δ 21.6, 22.0, 42.6, 46.4, 56.3, 62.2, 62.6, 70.2, 71.1, 73.7, 111.7, 114.8, 127.7, 127.8, 128.2, 128.5, 128.7, 128.8, 128.9, 133.2, 137.3, 148.1, 148.3, 148.9, 155.2, 158.6. MS (EI): m/z (%) 270 (23), 228 (30), 227 (100). Anal. Calcd for $C_{38}H_{46}N_2O_5$: C, 74.72; H, 7.59; N, 4.59. Found: C, 74.89; H, 7.56; N, 4.71.

4.4.5. 2-(N-Methyl-N-phenylethylamino)-1-phenylethyl N′,N′-diisopropylcarbamate (**7a**)

Yield 71%. Oil. IR (KBr film): 1686 (C=O), 1287 (C–O), 1047, 698 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 1.21–1.25 (m, 12H, 2×CH(CH_3)$_2$), 2.40 (s, 3H, NMe), 2.69–2.77 (m, 5H, CH_2NCH_2CH_2), 2.96 (dd, 1H, J=13.4, 7.7 Hz, CHCH_2N), 3.95 (br s, 2H, 2×CH(CH$_3$)$_2$), 5.90 (dd, 1H, J=7.9, 5.3 Hz, CHOCO), 7.14–7.36 (m, 10H, ArH). ^{13}C NMR (CDCl$_3$) δ 21.3, 34.2, 42.8, 46.2, 60.1, 63.5, 74.2, 126.1, 126.9, 127.8, 128.6, 129.0, 140.7, 140.9, 155.0. MS (EI): m/z (%) 291 (M$^+$−PhCH$_2$, 27), 148 (M$^+$−PhCHOCb, 100), 105 (PhCH$_2$CH$_2^+$, 35). Anal. Calcd for $C_{24}H_{34}N_2O_2$: C, 75.35; H, 8.96; N, 7.32. Found: C, 74.98; H, 8.96; N, 7.55.

4.4.6. 1-(4-Methoxyphenyl)-2-(N-methyl-N-phenylethylamino)ethyl N′,N′-diisopropylcarbamate (**7b**)

Yield 65%. Oil. IR (KBr film): 2973, 2933, 1685 (C=O), 1510, 1260, 1044, 733, 701 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 1.18–1.27 (m, 12H, 2×CH(CH_3)$_2$), 2.37 (s, 3H, NMe), 2.68–2.74 (m, 5H, CH_2NCH_2CH_2), 2.93 (dd, 1H, J=12.8, 7.5 Hz, CHCH_2N), 3.80 (s, 3H, OMe), 3.90 (br s, 2H, 2×CH(CH$_3$)$_2$), 5.84 (t, 1H, J=6.6 Hz, CHOCO), 6.86–6.88 (m, 2H, ArH), 7.14–7.29 (m, 7H, ArH). ^{13}C NMR (CDCl$_3$) δ 21.4, 34.2, 42.9, 46.0, 55.4, 60.2, 63.3, 73.9, 114.0, 126.1, 128.3, 128.5, 129.0, 133.1, 140.8, 155.2, 159.3. MS (EI): m/z (%)148 (M$^+$−OCH$_3$PhCHOCb, 100), 105 (PhCH$_2$CH$_2^+$, 51). Anal. Calcd for $C_{25}H_{36}N_2O_3$: C, 72.78; H, 8.80; N, 6.79. Found: C, 72.87; H, 8.88; N, 6.64.

4.4.7. 2-(N-3,4-Dimethoxyphenethyl-N-methylamino)-1-phenylethyl N′,N′-diisopropylcarbamate (**7c**)

Yield 77%. Oil. IR (Golden-Gate): 2938, 1684 (C=O), 1515, 1438, 1261, 1137, 1047, 1029, 734, 699 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 1.20–1.24 (m, 12H, 2×CH–(CH_3)$_2$), 2.37 (s, 3H, NCH$_3$), 2.64–2.66 (m, 4H, NCH_2CH_2), 2.72 (dd, 1H, J=13.3, 5.4 Hz, OCHCH_2), 2.94 (dd, 1H, J=13.3, 7.6 Hz, OCHCH_2), 3.83 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 3.94 (br s, 2H, 2×CH(CH$_3$)$_2$), 5.89 (dd, 1H, J=7.6, 5.4 Hz, OCH), 6.67–6.70 (m, 2H, ArH), 6.76 (d, 1H, J=8.7 Hz, ArH), 7.22–7.35 (m, 5H, ArH). ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.3, 33.9, 42.9, 46.1, 56.1, 56.2, 60.2, 63.5, 74.3, 111.8, 112.6, 120.8, 126.9, 127.7, 128.5, 133.5, 141.0, 147.6, 149.2, 155.0. MS (EI): m/z (%) 443 (M$^+$+1, 1), 297 (31), 291 (76), 248 (54), 208 ($C_{12}H_{18}NO_2$, 100), 165 (84), 146 (63), 128 (25), 104 (47), 86 (57), 57 (47), 43 (72). Anal. Calcd for $C_{26}H_{38}N_2O_4$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.33; H, 8.78; N, 6.31.

4.4.8. 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-4-phenylisoquinoline (**1c**)

Yield 89%. Mp 79–81 °C. IR (KBr film): 1514, 1265 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.42 (s, 3H, NMe), 2.54 (dd, 1H, J=11.4, 8.8 Hz, CHCH_2N), 3.02 (ddd, 1H, J=11.4, 5.7, 1.3 Hz, CHCH_2N), 3.58 (d, 1H, J=14.5 Hz, NCH_2Ar), 3.63 (s, 3H, OMe), 3.68 (d, 1H, J=14.5 Hz, NCH_2Ar), 3.85 (s, 3H, OMe), 4.22 (t, 1H, J=6.8 Hz, CH$_2$CHPh), 6.34 (s, 1H, ArH), 6.56 (s, 1H, ArH), 7.17–7.30 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$) δ 45.6, 46.0, 56.0, 56.1, 58.2, 62.1, 109.0, 112.2, 126.7, 127.4, 128.6, 130.0, 130.1, 137.8, 144.8. MS (EI): m/z (%) 284 (M$^+$+1, 10), 283 (M$^+$, 62), 282 (21), 240 (87), 209 (100). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.43; H, 7.55; N, 5.02.

4.4.9. 2,3,4,5-Tetrahydro-3-methyl-1-phenyl-1H-3-benzoazepine (**2a**)[60]

Yield 97%. Mp 73–75 °C. IR (KBr film): 2940, 1679, 1486, 1438, 1131, 754, 700 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.41–2.44 (m, 1H, CH$_2$), 2.43 (s, 3H, NMe), 2.87–2.96 (m, 3H, CH_2), 3.11–3.23 (m, 2H, CH$_2$), 4.40 (d, 1H, J=8.8 Hz, CHPh), 6.70 (d, 1H, J=7.5 Hz, ArH), 7.15–7.41 (m, 8H, ArH). ^{13}C NMR (CDCl$_3$) δ 36.7, 47.9, 50.1, 57.4, 63.2, 126.47, 126.59, 126.62, 128.4, 128.7, 128.8, 129.7, 141.6, 143.4, 144.6. MS (EI): m/z (%) 238 (M$^+$+1, 34), 237 (M$^+$, 21), 180 ($C_{14}H_{12}^+$, 100), 147 ($C_{10}H_{13}N^+$, 62), 133 ($C_9H_{11}N^+$, 84), 115 (72). Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.35; H, 7.99; N, 5.82.

4.4.10. 2,3,4,5-Tetrahydro-1-(4-methoxyphenyl)-3-methyl-1H-3-benzoazepine (**2b**)

Yield 88%. Mp 78–80 °C. IR (KBr film): 2933, 1502, 1363, 1148, 868, 518 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.40 (s, 3H, NMe), 2.48 (m, 1H, CH$_2$), 2.78–2.88 (m, 2H, CH_2), 2.98–3.10 (m, 3H, CH_2), 3.16 (s, 3H, OCH$_3$), 4.35 (t, 1H, J=4.6 Hz, CH$_2$CHPh), 6.69 (d, 1H, J=7.5 Hz, ArH), 7.07–7.28 (m, 7H, ArH). ^{13}C NMR (CDCl$_3$) δ 36.5, 37.6, 48.0, 49.7, 57.4, 62.6, 122.2, 126.6, 127.0, 128.6, 130.0, 130.2, 141.5, 142.7, 143.6, 147.8. MS (EI): m/z (%) 252 (M$^+$−CH$_3$, 89), 165 (77), 146 (88), 115 (98), 57 (100). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.99; H, 7.98; N, 5.22.

4.4.11. 2,3,4,5-Tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1H-3-benzoazepine (**2c**)[61]

Yield 90%. Mp 80–81 °C (lit.[62] 103–105 °C). IR (Golden-Gate): 2938, 1513, 1448, 1271, 1216, 1098, 1013, 732, 701 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.40–2.47 (m, 4H, NCH$_3$, CH$_2$), 2.75–3.11 (m, 5H, CH$_2$, CH$_2$), 3.61 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), 4.30 (d, 1H, J=7.8 Hz, OCH), 6.26 (s, 1H, ArH), 6.68 (s, 1H, ArH), 6.92–7.58 (m, 5H, ArH). ^{13}C NMR (CDCl$_3$) δ 36.1, 47.9, 49.8, 56.1, 56.3, 57.6, 63.2, 113.4, 113.9, 126.6, 128.6, 128.7, 133.8, 136.7, 143.5, 147.1, 147.2. MS (EI): m/z (%) 298 (M$^+$+1, 1), 297 (M$^+$, 91), 282 (25), 253 (18), 241 (60), 240 (78), 223 (23), 206 (100), 193 (63), 178 (29), 165 (36), 57 (17), 42 (21). Anal.

Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.38; H, 8.01; N, 4.79.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for all previously unreported compounds are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.098.

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