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Synthesis of 2,5-difunctionalised-3,3-dimethylpiperidines via ω-halogenated imines

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Abstract—2,5-Difunctionalised-3,3-dimethylpiperidines were prepared by addition of nucleophiles to piperideinium salts, formed by electrophile-induced cyclisation of γ,δ-unsaturated imines with *N*-bromosuccinimide in alcoholic medium.

The synthesis of piperidines and piperideines has always been an important topic in synthetic organic chemistry because of their importance as substrates for alkaloid syntheses, as biologically active substances, etc.[1] Also, the 3-oxygenated piperidine nucleus[2] is found in natural products, such as canavalline,[3] leptophyllins,[3] pseudoconhydrine,[4–6] deoxocassine[7] and in some interesting therapeutic compounds, such as zamifenacin[8] and melatonergic agents.[9] Although many synthetic methodologies are known for the preparation of piperidines, the electrophile-induced cyclisation of alkenylimines was only described for the synthesis of pyrrolidines via pyrrolinium salts **3**,[10,11] for selenenylated pyrrolidines and for piperidines by ring expansion.[12]

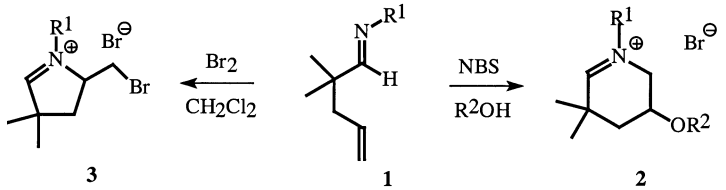
No direct electrophile-induced cyclisation towards piperidines from piperideinium salts **2** has been elaborated (Scheme 1).

In this paper, the electrophile-induced cyclisation of alkenylimines **1** was developed for the synthesis of 2,5-difunctionalised piperidines from piperideinium salts **2** via in situ formed ω-halogenated imines. This cyclisation is especially attractive because of the convenient synthesis of intermediate stable salts and because of their broad range of reactivity towards different nucleophiles.

During the systematic study of the chemistry of ω-halogenated imines[13] and their applications,[14,15] the convenient preparation of piperideinium salts came to our attention, and their reactivity towards nucleophiles, i.e. oxygenated nucleophiles, was extensively studied.

The required 4-alkenylimines **1** were prepared in two ways. A first route consisted of the alkylation of *N*-(isobutylidene)amines **4** (prepared by condensation of isobutyraldehyde and a primary amine) with allylbromide after deprotonation with LDA at 0°C (Scheme 2).

A second method consisted of the condensation of isobutyraldehyde with allyl alcohol in *p*-cymene under reflux in the presence of *p*-toluenesulfonic acid with formation of 2,2-dimethyl-4-pentenal **7** under Dean–Stark conditions,[16] followed by imination in the presence of magnesium sulfate. The preparation of pentenal **7** via the latter route, however, was sometimes problematic because of the fact that the reaction was not always reproducible and the end product **7** was not always obtained in pure form. Therefore, the first



3 1 2

Scheme 1.

Keywords: piperidines; halogenated imines; piperideinium salts.

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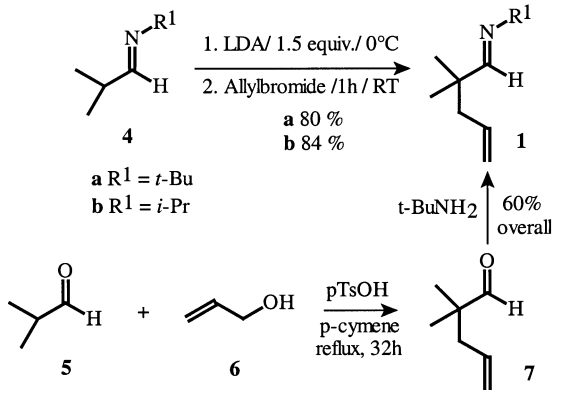


Scheme 2.

route is more reliable although the second one is more suitable for larger scale preparations (e.g. 1 mole scale).

Reaction of imines **1** with *N*-bromosuccinimide in an alcoholic solvent at room temperature during 16 h gave rise to the formation of the iminium salt **2** via the intermediate γ-alkoxy-δ-bromoimine **9**. The electrophilic addition of NBS to the non-activated double bond occurs according to the Markovnikoff rule with the solvent acting as nucleophile and leads to the reactive δ-bromoimine **9** which spontaneously cyclises to the stable piperideinium salt **2**. On the contrary, in less polar and non-nucleophilic solvents, e.g. dichloromethane, the electrophile-induced ring closure using bromine or phenylselenenyl bromide as electrophile leads regiospecifically to the formation of the corresponding pyrrolinium salts **3**.[17] Accordingly, the cyclisation process of compounds **1** is now handled in a regiospecific way so as to give rise either to pyrrolinium salts **3** or to piperideinium salts **2**, depending on the reaction conditions and the electrophile.

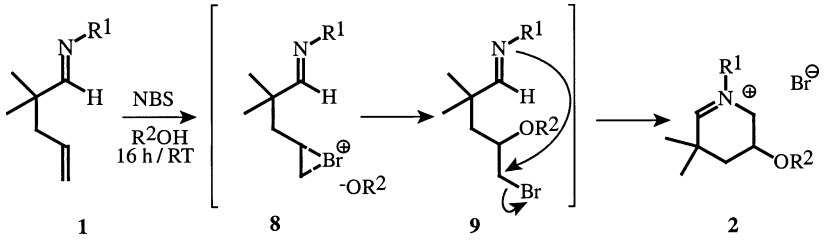
The reactions for the formation of the piperideinium salts are almost quantitative. The piperideinium salts are isolated easily by evaporation of the solvent giving a solid which contains the salt and succinimide (Scheme 3).

Succinimide can be removed completely by one or more crystallisations of the salt from a dichloromethane/diethyl ether mixture (the salts are dissolved completely in a minimum amount of dichloromethane followed by the addition of diethyl ether until slightly cloudy), in order to obtain the pure piperideinium salts **2**. The recrystallisations, however, lead mostly to an important loss of the piperideinium salts and in some cases to substantial losses (e.g. for R′=Et).

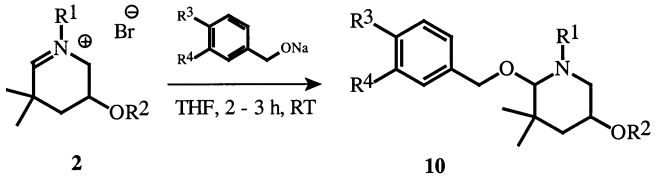
However, the use of the crude mixture of the piperideinium salts **2** does not give any problem for the following reactions since succinimide can be removed during the aqueous workup after the next reaction.

The piperideinium salts **2** were reacted with a range of benzyl alcoholates in the corresponding alcohol to give the 2,5-dialkoxypiperidines **10** in good to excellent yields. However, these derivatives could not be purified by flash chromatography due to the lability of the products during the chromatography. Although the purity of the products in the reaction mixtures was quite high (>95%), it was tried to prepare solid piperidine derivatives which could then be purified by recrystallisation. Unfortunately, none of the products synthesised was obtained as a solid (so, the reported yields refer to the crude yields). The derivative **10e**, however, was not obtained with a purity of >95%, but was contaminated with benzyl alcohol (purity: 70%). Another derivative, e.g. the 4-phenylbenzyl derivative **10d**, was not stable since the α-alkoxypiperidine decomposed again at room temperature to the alcohol and the piperideinium salt **2** after a couple of hours. The other benzyl alcohol adducts were stable and could be isolated without problems (Scheme 4).

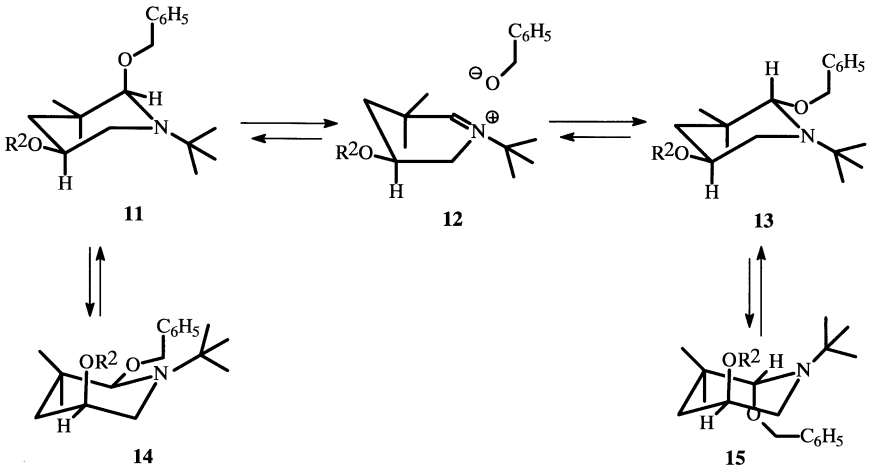
Concerning the stereochemistry, the adducts **10** were obtained as *trans* isomers (considering the 2- and 5-position) due to steric interactions during the addition



Scheme 3. 2a R^1 = *t*-Bu, R^2 = Me (95%)* (76%)**; **2b** R^1 = *t*-Bu, R^2 = Et (90%)* (20%)**; **2c** R^1 = *i*-Pr, R^2 = Me (78%)* (15%)**.
* The yields correspond to the crude products after evaporation of the solvent and taking into account the amount of succinimide (estimated by ^{1}H NMR).
** Yields after recrystallisation.



Scheme 4. 10a R^1 = *t*-Bu, R^2 = Me, R^3 = H, R^4 = H (98%); **10b** R^1 = *t*-Bu, R^2 = Me, R^3 = Br, R^4 = H (97%); **10c** R^1 = *t*-Bu, R^2 = Me, R^3 = R^4 = OMe (98%); **10d** R^1 = *t*-Bu, R^2 = Me, R^3 = Ph, R^4 = H; **10e** R^1 = *i*-Pr, R^2 = Me, R^3 = H, R^4 = H (68%); **10f** R^1 = *i*-Pr, R^2 = Me, R^3 = OMe, R^4 = H (46%, t/c; ~4/1).

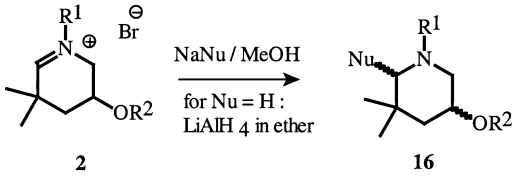


Scheme 5.

and due to the favourable 2,5-diequatorial substitution of the piperidine ring after addition as in **13**. However, for compound **10f**, a mixture of *trans* and *cis* isomers are obtained in about a 4:1 ratio (Scheme 5).

The reaction of the piperideinium salt **2** with sodium phenolates did not result in the adducts but led to complete decomposition.

Although the reaction did not succeed with phenolates, the addition of other nucleophiles to the 2-position of the piperideinium salts was general, as expected. In order to investigate this entry to 2-functionalised-5-alkoxypiperidines, the reaction was performed with hydride (e.g. lithium aluminiumhydride (1 mole equivalent in diethyl ether, reflux 2 h), sodium cyanide (3 equiv. in methanol, reflux 3 h), sodium ethylthiolate (2 equiv. in tetrahydrofuran, reflux 2 h) and sodium methoxide (2 equiv. in methanol, reflux 2 h)).



Scheme 6. **16a** R^1=*t*-Bu, R^2=Me, Nu=CN (90%, t+c); **16b** R^1=*t*-Bu, R^2=Me, Nu=OMe (76%); **16c** R^1=*t*-Bu, R^2=Me, Nu=SEt (86%); **16d** R^1=*t*-Bu, R^2=Me, Nu=H (95%); **16e** R^1=*i*-Pr, R^2=Me, Nu=CN (58%, t+c); **16f** R^1=*i*-Pr, R^2=Me, Nu=H (71%).

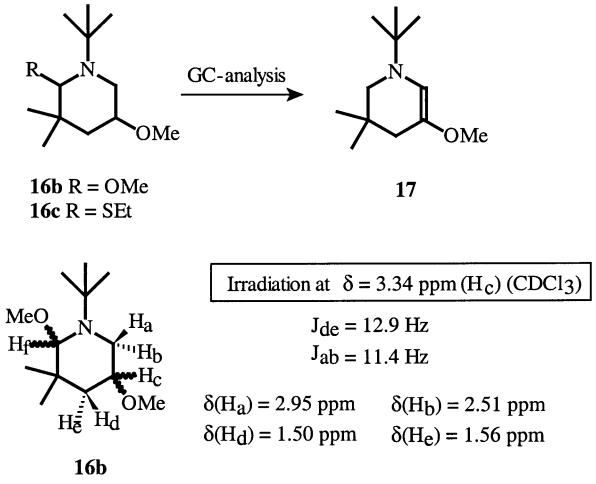
These reactions gave the adducts **16** in good yields (69–98%) without competing reactions. The derivatives with a low molecular weight could be purified by high vacuum distillation (e.g. **16a** bp: 144–145/14 mmHg, yield: 95%; **16b** bp: 55–58/14 mmHg, yield: 76%). The *N*-isopropyl derivatives **16e–f** could not be purified by flash chromatography due to decomposition of these compounds on the silica gel column (Scheme 6).

Also for the adducts **16**, the same stereochemical considerations can be formulated as for the adducts **10** (Scheme 7).

One peculiar reaction was observed during the purification of 2,5-dimethoxypiperidine **16b** and 2-ethylthio-5-methoxypiperidine **16c**. Preparative isolation during gas chromatographic analysis of the samples resulted in the formation of 5-methoxy-1,2,3,4-tetrahydropyridine **17**. This reaction was also observed when **16b** was synthesised from the corresponding pyrrolinium salt.[17] In order to prove the substitution pattern on the piperidine ring and in order to explain this remarkable elimination, double irradiation NMR experiments were conducted to assign the methoxy group to the 2-position in the starting material. Irradiating the proton at the 5-position of the piperidine ring of **16b** resulted in a simplification of the coupling systems for the protons at positions 4 and 6 of the piperidine ring. The signals became both AB-systems with J=12.9 Hz and J=11.4 Hz, respectively. This measurement proved that the second methoxy substituent was located at the 2-position and also proved this remarkable elimination.[17]

The same rearrangement was also observed during the analysis of the 2-ethylthio derivative **16c**.

In this paper, the electrophile-induced cyclisation of 4-alkenyl imines was developed and proved to be a



Scheme 7.

convenient way to synthesise a broad range of 2,5-difunctionalised piperidines in a directed way.

1. Experimental

^{1}H NMR spectra were recorded at 60 MHz (Jeol PMX 60 SI), at 270 MHz (Jeol JNM EX 270) or at 500 MHz (Brüker 500) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 20 MHz (Varian FT-80) with $CDCl_3$ as solvent. Mass spectra were obtained on a mass spectrometer (70 eV) using direct inlet or GC–MS coupling (RSL 200, 20 m capillary column, i.d. 0.53 mm, He carrier gas). Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl.

1.1. General procedure for the synthesis of piperideinium salts 2

To 0.02 M of alkenylimine **1** in 40 ml of absolute alcohol (methanol or ethanol), 0.021 M (1.05 equiv.) of *N*-bromosuccinimide was added. The mixture was stirred for 16 h at room temperature and the mixture was protected from humidity in the air by a calcium chloride tube. The solvent was then evaporated leaving a sticky mixture. Dry diethyl ether was added and the product was well scratched and stirred with a glass rod in order to obtain a crystalline product mixture. The ether was removed by filtration and the whole procedure was repeated another time. After a second filtration the product was dried under vacuum. The piperideinium salt (in the presence of succinimide) can be used as such in the next reaction step. In order to purify the piperideinium salt from the succinimide, the piperideinium salt was dissolved in a minimum amount of boiling dichloromethane, and diethyl ether was added untill the mixture got slightly cloudy. The mixture was then placed in a refrigerator for the piperideinium salt to recrystallise. The piperideinium salt **2** was obtained pure after filtration and drying in vacuo.

1.1.1. 1-*t*-Butyl-3,3-dimethyl-5-methoxy-1-piperideinium bromide 2a. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.39 (3H, s, Me); 1.51 (3H, s, Me); 1.59 (9H, s, *t*-Bu); 1.93 and 1.99 (2H, 2x br d, AB, J_{AB}=14.5 Hz, J<1 Hz, CH_2); 3.28 (3H, s, OMe); 3.92 (1H, br s, C*H*OMe); 3.91 and 4.37 (2H, 2x br d, AB, J_{AB}=12.6, J<1 Hz, CH_2N); 8.77 (1H, br s, CH=N). ^{13}C NMR ($CDCl_3$) δ: 27.25 (q, Me_3), 27.99 (q, Me_3), 33.67 (t, *C*H_2CHOMe); 37.05 (s, CMe_2), 50.96 (t, CH_2N), 56.64 (q, OMe), 69.70 (s, *C*Me_3), 71.10 (d, *C*HOMe), 179.96 (d, C=N). IR (KBr, cm^{-1}) 1705 (ν C=N). White solid, mp 182°C. Yield 95% (crude yield). Anal. Calcd for $C_{12}H_{24}BrNO$: C, 51.80%; H, 8.69%. Found: C, 51.72%; H, 8.78%.

1.1.2. 1-*t*-Butyl-3,3-dimethyl-5-ethoxy-1-piperideinium bromide 2b. ^{1}H NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz, Me); 1.53 (3H, s, Me), 1.61 (3H, s, Me), 1.73 (9H, s, *t*-Bu); 1.9–2.1 (2H, m, CH_2CMe$_2$); 3.61 (2H, q, J=7 Hz, OCH_2CH$_3$); 4.0–4.5 (2H, m, CH_2N); 9.10 (1H, br s, CH=N). ^{13}C NMR ($CDCl_3$) δ: 15.25 (q, *Me*CH_2), 27.31 (q, Me), 27.83 (q, *Me*$_3$), 29.78 (q, Me), 34.50 (t, *C*H_2); 37.04 (s, *C*Me$_2$), 51.24 (t, CH_2N), 64.42 (t, OCH_2), 69.24 (d, OCH), 69.28 (s, *C*Me$_3$), 178.36 (d, C=N). IR (KBr, cm^{-1}) 1712 (ν C=N). White solid, tentative mp 178°C (due to traces of succinimide). Yield: 90% (crude yield). Anal. Calcd for $C_{13}H_{26}BrNO$: C, 53.43%; H, 8.97%. Found: C, 53.60%; H, 8.84%.

1.1.3. 1-Isopropyl-3,3-dimethyl-5-methoxy-1-piperideinium bromide 2c. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 1.44 (3H, s, Me); 1.55 (6H, m, *i*-Pr); 1.56 (3H, s, Me); 2.00 (2H, m, CH_2); 3.37 (3H, s, OMe); 3.74 and 4.29 (2H, 2x d, AB, J_{AB}=15 Hz, CH_2N); 3.96 (1H, br s, C*H*OMe); 4.80 (1H, sept, J=6.9 Hz, $CHMe_2$); 9.31(1H, s, CH=N). ^{13}C NMR ($CDCl_3$) δ: 19.87 (q, Me), 20.70 (q, Me), 26.85 (t, Me); 27.98 (Me), 33.60 (t, CH_2), 36.39 (s, CMe_2), 50.37 (t, CH_2N), 56.60 (q, OMe), 64.40 (s, N*C*HMe_2), 70.64 (d, *C*HOMe), 181.52 (d, C=N). IR (KBr, cm^{-1}) 1678 (ν C=N). Beige solid, mp 157–159°C. Yield: 78% (crude yield). Anal. Calcd for $C_{11}H_{22}BrNO$: C, 50.01%; H, 8.39%. Found: C, 49.78%; H, 8.76%.

1.2. General procedure for the synthesis of the adducts 10 and 16

To 4 mmol of piperideinium salt **2** in 20 ml of dry tetrahydrofuran, 4 mmol of nucleophile (sodium alcoholate, prepared from the corresponding alcohol and sodium hydride, sodium metal or sodium methoxide) in 10 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred at room temperature for 3 h and then poured into 30 ml of NaOH (1 M). The mixture was extracted three times with diethyl ether (3×20 ml) and the combined organic layers were dried over magnesium sulfate. After filtration of the drying agent, the solvent was evaporated in vacuo yielding the 2-substituted-5-alkoxypiperidines **10**.

A similar procedure was used for the preparation of the adducts **16**. For **16a**, **16e** the reaction was performed in dry methanol with 3 equiv. of KCN and the reaction mixture was refluxed for 3 h. For **16b**, **16c** 2 equiv. of sodium alkoxide and sodium thiolate (prepared from sodium methoxide and ethylthiol) were used during 2 h of reflux. The reactions using lithium aluminium hydride (1 mole equiv.) were performed in dry diethyl ether and the mixture was refluxed during 2 h for the preparation of **16d** and **16f**.

1.2.1. 2-Benzyloxy-1-*t*-butyl-3,3-dimethyl-5-methoxypiperidine 10a. ^{1}H NMR ($CDCl_3$) δ: 1.00 (3H, s, Me); 1.13 (3H, s, Me), 1.13 (9H, s, *t*-Bu); 1.5–1.9 (2H, m, CH_2); 2.6–3.0 (2H, m, CH_2N); 3.1–3.5 (1H, m, C*H*OMe), 3.36 (3H, s, OMe); 4.13 (1H, s, OC*H*N), 4.60 and 4.72 (2H, 2xd, AB, J_{AB}=12 Hz, CH_2O), 7.36 (5H, s, Ph). ^{13}C NMR ($CDCl_3$) δ: 26.79 (q, Me), 27.91 (q, Me), 28.57 (q, *Me*$_3$), 37.75 (s, *C*Me$_2$), 38.99 (t, *C*H_2CMe$_2$), 43.08 (t, CH_2N), 53.28 (s, *C*Me$_3$), 55.57 (q, OMe), 71.13 (t, OCH_2), 75.00 (d, *C*HOMe), 92.72 (d, O*C*HN), 126.68 (d, CH), 126.85 (d, CH), 128.07 (d, CH), 139.64 (s, C_{quat}). IR (NaCl) ν_{max} (cm^{-1}): 2975, 1455, 1360, 1105. MS (*m*/*z*) direct inlet: 305 (M^+, 13); 290 (13); 250 (13); 199 (56); 191 (13); 184 (6); 182 (6); 158 (19); 142 (44); 126 (31); 108 (31); 107 (38); 102 (44); 91 (100); 79 (38); 77 (25); 57 (56); 41 (56). Yellowish oil; Yield: 98%.

1.2.2. 2-(4-Bromobenzyloxy)-1-*t*-butyl-3,3-dimethyl-5-methoxypiperidine 10b. ^{1}H NMR ($CDCl_3$) δ: 0.98 (3H,

s, Me); 1.15 (12H, s, Me, *t*-Bu); 1.3–1.8 (2H, m, CH_2); 2.3–2.9 (2H, m, CH_2N); 2.9–3.6 (1H, m, C*H*OMe), 3.35 (3H, s, OMe); 4.08 (1H, s, OC*H*N), 4.49 and 4.63 (2H, 2xd, AB, J_{AB}=12 Hz, CH_2O), 7.14 (2H, d, J=9 Hz, 2× CH), 7.39 (2H, d, J=9 Hz, 2×CH). ^{13}C NMR ($CDCl_3$) δ: 26.75 (q, Me), 27.88 (q, Me), 28.56 (q, Me_3), 37.71 (s, *C*Me_2), 38.97 (t, *C*H_2CMe_2), 43.06 (t, CH_2N), 53.27 (s, *C*Me_3), 55.62 (q, OMe), 70.27 (t, OCH_2), 74.88 (d, C*H*OMe), 92.91 (d, O*C*HN), 120.59 (s, CCH_2), 128.40 (d, CH), 131.19 (d, CH), 138.72 (s, C_{quat}). IR (NaCl) ν_{max} (cm^{-1}): 2920, 1592, 1485, 1385, 1360. MS (*m*/*z*) direct inlet: 198 ($M^+-BrC_6H_4CH_2O$, 13); 185/87 (46); 183/85 (22); 157 (17); 142 (11); 126 (23); 106 (89); 90 (11); 89 (13); 86 (13); 79 (89); 78 (44); 77(100); 76 (13); 75 (17); 57 (89); 51 (29); 50 (27). Yellowish oil; Yield: 97%.

1.2.3. 2-(3,4-Dimethoxybenzyloxy)-1-*t*-butyl-3,3-dimethyl-5-methoxypiperidine 10c. ^{1}H NMR ($CDCl_3$) δ: 1.00 (3H, s, Me); 1.13 (3H, s, Me); 1.16 (9H, s, *t*-Bu); 1.58 (2H, m, C*H*$_2$CHOMe); 2.4–3.3 (3H, m, C*H*$_2$N, C*H*OMe); 3.36 (3H, s, OMe); 3.86 (3H, s, OMe); 3.88 (3H, s, OMe); 4.11 (1H, s, OC*H*); 4.52 and 4.67 (2H, 2xd, AB, J_{AB}=11.2 Hz, CH_2O), 6.8–7.0 (3H, m, C_6H_3). ^{13}C NMR ($CDCl_3$) δ: 26.82 (q, Me), 28.00 (q, Me), 28.58 (q, Me_3), 37.75 (s,*C*Me_2), 39.02 (t, CH_2), 43.08 (t, CH_2N), 53.31 (s, *C*Me_3), 55.68 (q, OMe), 55.82 (q, OMe), 55.94 (q, OMe), 70.97 (t, OCH_2), 75.01 (d, C*H*OMe), 92.70 (d, OC*H*N), 110.86 (d,CH), 111.48 (d,CH), 119.11 (d,CH), 132.55 (s, *C*CH_2), 148.34 (s, *C*OMe), 149.12 (s, *C*OMe). IR (NaCl) ν_{max} (cm^{-1}): 1592, 1515, 1465, 1265. MS (*m*/*z*) direct inlet: 213 ($M^+-(MeO)_2C_6H_3CH_2$, 3); 198 (47); 197 (20); 182 (47); 168 (40); 151 (47); 142 (27); 138 (13); 134 (10); 126 (100); 94 (16); 57 (40). Yellowish oil; Yield: 98%.

1.2.4. 1-*t*-Butyl-2-(4-phenylbenzyloxy)-3,3-dimethyl-5-methoxypiperidine 10d. No structural assignment could be performed due to the fast decomposition of the compound after synthesis.

1.2.5. 2-Benzyloxy-3,3-dimethyl-1-isopropyl-5-methoxypiperidine 10e. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.99 (3H, s, Me); 1.01 (3H, s, Me); 1.05 (3H, d, J=6.6 Hz, *i*-Pr); 1.09 (3H, d, J=6.6 Hz, *i*-Pr); 1.58 (2H, m, C*H*$_2$); 2.65 (1H, m, CH_2); 2.83 (1H, m, C*H*OMe), 3.05 (1H, sept., J=6.6 Hz, C*H*Me_2); 3.35 (3H, s, OMe); 4.5–4.7 (2H, m, $OCH_2C_6H_5$); 7.3–7.36 (5H, m, Ph). ^{13}C NMR ($CDCl_3$) δ: 19.19, 21.65, 26.31, 27.35, 37.00, 38.38, 43.68, 53.15, 55.45, 71.80, 74.41, 96.89, 126.59, 128.03, 139.15, 140.93. IR (NaCl) ν_{max} (cm^{-1}): 1496, 1206, 1382, 1361. MS (*m*/*z*) direct inlet: 292 (M^++1, 12); 185 (82); 173 (13); 169 (24); 145 (28); 108 (100); 107 (82); 91 (60); 86 (19); 84 (30); 79 (86); 77 (56); 51 (29); 49 (29). Yellowish oil. Yield: 68%.

1.2.6. 2-(4-Methoxybenzyloxy)-3,3-dimethyl-1-isopropyl-5-methoxypiperidine 10f. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.98 (3H, s, Me); 1.00 (3H, s, Me); 1.05 (3H, d, J=6.6 Hz, *i*-Pr); 1.09 (3H, d, J=6.6 Hz, *i*-Pr); 1.55 (1H, m, C*H*$_2$); 2.69 (1H, t, J=10.6 Hz, CH); 2.80 (1H, m, C*H*OMe), 3.02 (1H, m, C*H*Me_2); 3.34 (3H, s, OMe); 3.35 (2H, m, CH_2), 3.78 (s, 3H, PhOMe), 4.47 and 4.58 (2H, d, AB, J_{AB}=12.2 Hz); 6.86 and 7.25 (4H, m, C_6H_4). ^{13}C NMR ($CDCl_3$) major+(minor) δ: 19.71 (20.43) (*i*-Pr); 21.56 (25.36) (*i*-Pr); 26.20 (26.97) (Me); 27.26 (27.55) (Me); 36.84 (37.72) (*C*Me_2); 38.28 (38.51) (*C*H_2CMe_2); 43.49 (43.86) (*C*H_2N); 53.03 (50.00) (CH); 54.65 (55.31) (OMe); 63.81 (65.39) (ArOMe); 71.48 (70.96) (ArCH_2O); 74.27 (74.54) (*C*HOMe); 96.71 (97.34) (OCHN); 113.26 (113.15); 128.05 (128.05); 133.15 (131.18); 158.47 (158.76). IR (NaCl) ν_{max} (cm^{-1}): 1610, 1510, 1460. MS (*m*/*z*) direct inlet: 321 (M^+, 0.2); 137 (100) 136 (66); 121 (48); 109 (70); 107 (24); 105 (13); 94 (25); 79 (13); 77(40); 78 (11); 65 (11). Yellowish oil; Yield: 98%.

1.2.7. 1-*t*-Butyl-2-cyano-3,3-dimethyl-5-methoxypiperidine 16a. Mixture of stereoisomers, major+(minor); ratio ~4:1. ^{1}H NMR ($CDCl_3$) δ: 1.13 (6H, s, Me_2); 1.18 (9H, s, *t*-Bu); 1.5–2.0 (2H, m, CH_2); 2.0–2.7 (2H, m, CH_2N); 3.33 (3H, s, OMe); 3.0–3.5 (1H, m, C*H*OMe); 3.56 (1H, br s, CHCN). ^{13}C NMR ($CDCl_3$): major+(minor) δ: 25.54 (q, Me), 27.09 (q, *Me*$_3$), 28.18 (28.71) (q, Me), 34.82 (33.81) (s, *C*Me_2), 40.34 (36.75) (t, *C*H_2), 46.46 (43.93) (t, CH_2N), 54.46 (54.25) (s, *C*Me_3), 55.83 (q, OMe), 56.98 (57.79) (d, *C*HCN), 73.96 (74.71) (d, C*H*OMe), 118.15 (118.37) (s, CN). IR (NaCl) ν (cm^{-1}): 2820 (OMe), 2220 (CN). MS (*m*/*z*): 224 (M^+, 7); 209 (100); 182 (8); 177 (4); 141(4); 126 (10); 111 (4); 99 (4); 96 (4); 83 (11); 82 (15); 71 (8); 68 (8); 58 (23); 57 (20); 56 (23); 55 (20); 41 (57); 40 (30); 39(17). Colorless oil; Yield: 90%, bp 144–145°C/14 mmHg. Anal. Calcd for $C_{13}H_{24}N_2O$: C, 69.60%; H, 10.78%. Found: C, 69.43%; H, 10.64%.

1.2.8. 1-*t*-Butyl-3,3-dimethyl-2,5-dimethoxypiperidine 16b. ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 0.95 (3H, s, Me); 0.96 (3H, s, Me), 1.13 (9H, s, *t*-Bu); 1.2–1.8 (2H, m, C*H*$_2$); 2.51 (1H, dxd, J=12.9, 9.5 Hz, NC*H*CHOMe); 2.95 (1H, dxd, J=11.4, 4.9 Hz, NC*H*CHOMe); 3.3–3.4 (1H, m, C*H*OMe), 3.34 (3H, s, OMe); 3.41 (3H, s, OMe); 3.80 (1H, s, OC*H*N). ^{13}C NMR ($CDCl_3$) δ: 26.83 (q, Me), 27.74 (q, Me), 28.36 (q, Me_3), 37.66 (s, CMe_2), 38.74 (t, *C*H_2CMe_2), 43.00 (t, CH_2N), 53.29 (s, *C*Me_3), 55.74 (q, OMe), 58.04 (q, OMe), 74.89 (d, C*H*OMe), 95.13 (d, MeOC*H*N). IR (NaCl) ν_{max} (cm^{-1}): 2820 (OMe). MS (*m*/*z*): an appropriate mass spectrum could not be obtained due to spontaneous loss of methanol. Colorless oil; Yield: 76%, bp 55−58°C/0.05 mmHg. Anal. Calcd for $C_{13}H_{27}NO_2$: C, 68.08%; H, 11.87%. Found: C, 67.93%; H, 11.98%.

1.2.9. 1-*t*-Butyl-3,3-dimethyl-2-ethylthio-5-methoxypiperidine 16c. ^{1}H NMR ($CDCl_3$) δ: 1.10 (3H, s, Me); 1.11 (3H, s, Me), 1.18 (9H, s, *t*-Bu); 1.2–1.8 (2H, m, C*H*$_2$); 1.26 (3H, t, J=7.3 Hz, CH_2CH_3); 2.66 (2H, q, J=7.3 Hz, CH_2CH_3); 3.2–3.5 (3H, m, C*H*OMe, CH_2N); 3.38 (3H, s, OMe); 4.00 (1H, brs, C*H*SEt). ^{13}C NMR ($CDCl_3$, 68 MHz) δ: 15.77 (q,Me), 27.83 (q, *Me*$_3$), 27.83 (t, Me*C*H_2), 29.05 (q, Me), 38.94 (s, CMe_2), 39.51 (t, *C*H_2CMe_2), 46.11 (t, CH_2N), 54.34 (s, *C*Me_3), 55.72 (q, OMe), 74.78 (d, C*H*OMe), 79.13 (d, CHS). IR (NaCl) ν_{max} (cm^{-1}): 2970, 1960, 1455, 1380. MS (*m*/*z*): an appropriate spectrum could not be obtained due to spontaneous loss of ethanethiol. Brown oil; Yield: 86%.

1.2.10. 1-*t*-Butyl-3,3-dimethyl-5-methoxypiperidine[18] 16d. ^{1}H NMR ($CDCl_3$; 500 MHz) δ: 0.86 (3H, s, Me); 0.93 (3H, s, Me); 1.00 (9H, s, *t*-Bu); 1.5–1.9 (2H, m, C*H*$_2$); 2.3–2.7 (4H, m, CH_2NCH_2); 3.30 (3H, s, OMe); 3.1–3.3 (1H, m,

C*H*OMe). ^{13}C NMR ($CDCl_3$) δ: 26.31 (q, Me), 26.46 (q, *Me*$_3$), 29.83 (q, Me), 31.50 (s, *C*Me$_2$), 44.04 (t, *C*H$_2$), 51.53 (t, CH$_2$N), 53.18 (s, *C*Me$_3$), 55.87 (q, OMe), 58.44 (t, *C*H$_2$N), 75.57 (d, C*H*OMe). IR (NaCl) ν_{max} (cm^{-1}): 2985, 2790, 1105, 738. MS (*m*/*z*): 199 (M$^+$, 10); 184 (100); 152 (10); 144 (5); 96 (5); 95 (10); 70 (10); 58 (14); 57 (24); 56 (14); 55 (19); 44 (14); 43 (5); 42 (14); 41 (33); 40 (57); 39 (10). Yield: 95%.

1.2.11. 2-Cyano-3,3-dimethyl-1-isopopyl-5-methoxypiperidine 16e. ^{1}H NMR ($CDCl_3$): mixture of 2-stereoisomers: major+(minor); ratio ~4:1; δ: 1.11 (0.90) (6H, s, Me$_2$); 1.11 (3H, d, *J*=6.9 Hz, Me); 1.13 (3H, d, *J*=6.3 Hz, Me); 1.2–1.4 (1.4–1.5) (2H, m, C*H*$_2$); 1.6–1.8 (1.6–1.7) (1H, m); 2.24 (2.5–2.6) (1H, t, *J*=10.9 Hz), 2.81 (sept., 1H, *J*=6.6 Hz, NCHMe$_2$), 3.12–3.18 (3.0–3.1) (1H, m, C*H*OMe); 3.32 (1H, s, CHCN), 3.36 (3H, s, OMe). ^{13}C NMR ($CDCl_3$) major+(minor); ratio ~4:1; δ: 19.44 (16.74) (q, Me), 19.82 (20.22) (q, Me), 25.18 (26.10) (q, Me), 28.02 (27.05) (q, Me), 34.22 (33.73) (s, *C*Me$_2$), 39.82 (38.67) (t, *C*H$_2$), 48.86 (47.64) (t, CH$_2$N), 53.50 (52.71) (s, *C*Me$_3$), 55.78 (55.78) (q, OMe), 59.64 (61.06) (d, *C*HCN), 73.10 (73.68) (d, C*H*OMe), 117.00 (117.25) (s, CN). IR (NaCl) ν_{max} (cm^{-1}): 2220 (CN), 1464, 1388, 1367. MS (*m*/*z*): 211 (M$^+$+1, 7); 196 (100); 167 (10); 164 (13); 59 (49); 57 (10); 43 (17). Yellowish oil; Purified by flash chromatography (Hexanes/EtOAc:70/30) R_f=0.56. Yield: 69%. Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53%; H, 10.54%. Found: C, 68.62%; H, 10.39%.

1.2.12. 3,3-Dimethyl-1-isopropyl-5-methoxypiperidine 16f. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.91 (3H, s, Me); 0.98 (3H, s, Me); 0.97 (3H, d, *J*=6.6 Hz, Me); 1.00 (3H, d, *J*=6.6 Hz, Me); 1.08–1.16 (1H, m, *H*CHCHOMe); 1.75 (1H, ddt, *J*=12.5, 4.62, 1.65 Hz, HC*H*CHOMe); 1.85 (1H, d, *J*=10.9 Hz, CMe$_2$*H*CHN); 1.86 (1H, d, *J*=9.9 Hz, N*H*CHCH); 2.26 (1H, dt, *J*=10.9, 1.65 Hz); 2.76 (1H, sept., *J*=6.6 Hz, C*H*Me$_2$); 3.03 (1H, ddt, *J*=9.9, 4.62, 1.65 Hz, NC*H*CH); 3.35 (3H, s, OMe); 3.36–3.45 (1H, m, C*H*OMe). ^{13}C NMR ($CDCl_3$) δ: 17.12 (q, Me),18.74 (q, Me), 25.88 (q, Me), 29.78 (q, Me), 31.37 (s, *C*Me$_2$), 43.99 (t, *C*H$_2$), 54.37 (t, CH$_2$N), 54.64 (s, *C*Me$_2$), 56.12 (q, OMe), 59.64 (t, *C*H$_2$N), 75.22 (d, C*H*OMe). IR (NaCl) ν_{max} (cm^{-1}): 2940, 1460, 1360, 1050. MS (*m*/*z*): 185 (M$^+$, 8); 170 (100); 138 (12); 71 (10); 58 (14); 56 (29); 44 (13); 43 (16); 41 (22). Purified by flash chromatography (Hexanes/EtOAc: 95:5) R_f=0.17. Yield: 71%. Yellowish oil. Anal. Calcd for $C_{11}H_{23}NO$; C, 71.30%; H, 12.51%. Found: C, 71.04%; H, 12.65%.

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