Pergamon

Tetrahedron 56 (2000) 3775–3780

TETRAHEDRON

Generation and Reactivity of α-Amino-Substituted Arylmethyllithium Organometallics

Ugo Azzena,* Luciano Pilo and Elisabetta Piras

Dipartimento di Chimica e Facoltà di Farmacia, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy

Received 20 January 2000; revised 21 March 2000; accepted 6 April 2000

Abstract—Reductive cleavage of open chain and cyclic α-*N*,*N*-dialkylamino-substituted benzyl alkyl ethers **1a–f** with a dispersion of Li metal and a catalytic amount of naphthalene in THF, allowed easy access to a wide array of α-*N*,*N*-dialkylamino-substituted benzyllithium derivatives. Reaction of these organometallics with various electrophiles afforded the expected products in satisfactory yields.

Introduction

Generation of α-*N*,*N*-dialkylamino-substituted benzyllithium derivatives is a topic of current interest in organic chemistry. Indeed, besides their potential synthetic utility, there is an increasing interest in the reactivity and structural features of α-tertiary amino-substituted lithium organometallics.[1–5]

Heteroatom-facilitated α-lithiation of arylalkyl systems is usually achieved by the action of alkyllithium derivatives.[6,7] However, with *N*,*N*-dialkylbenzylamines, this is no longer the case: indeed, reaction of *N*,*N*-dimethylbenzylamine with alkyllithium derivatives led to the exclusive formation of the corresponding, thermodynamically more stable, *ortho*-Li derivative.[8–10]

Accordingly, several procedures were developed to achieve this goal: α-(dimethylamino)-benzyllithium was obtained reacting the corresponding α-sodium- or α-tributylstannyl-derivative with LiBr[10] or *n*-BuLi,[5] respectively; several other tertiary benzylic amines were successfully α-lithiated facilitating such a deprotonation by complexation with a Lewis acid.[11–13]

We elaborated a complementary approach to the generation of benzylic derivatives of alkali metals: we demonstrated that reductive cleavage of arylmethyl alkyl ethers by electron transfer from alkali metals in THF is a highly regioselective reaction resulting in the exclusive cleavage of the arylmethyl carbon–oxygen bond, thus affording a new access to a wide array of arylalkyl organometallic derivatives.[14,15] Extension of this procedure to acetals of aromatic aldehydes and ketones allowed the generation of α-alkoxy-substituted arylalkyllithium derivatives.[16]

We wish now to report that reductive cleavage of α-(*N*,*N*-dialkylamino-substituted)arylmethyl butyl ethers with an excess of Li powder and a catalytic amount of naphthalene is a useful approach to the generation of α-(*N*,*N*-dialkylamino-substituted)-arylmethyllithium derivatives.

We successfully extended this procedure to the reductive lithiation of 2-aryl-3-methyl-1,3-oxazolidines. Reductive cleavage of these cyclic derivatives with alkali metals was already reported: reduction with K metal afforded the corresponding *N*-substituted-benzylaminoalcohols in good yields, although intermediate formation of organometallics is strongly influenced by the substituent's pattern both at the benzylic carbon and the aromatic ring. Furthermore, reduction with Li wire resulted in low conversion as well as formation of dimeric by-products.[17]

Results and Discussion

α-*N*,*N*-Dialkylamino-substituted benzyl butyl ethers and 2-aryl-1,3-oxazolidines were synthesized according to known procedures: ethers **1a–c** were obtained by reaction of an aromatic aldehyde with an excess of *n*-BuOH and an amine in the presence of K_2CO_3;[18] oxazolidines **1d–f** were synthesized by reaction of the corresponding aromatic aldehyde with 2-(*N*-methyl)aminoethanol in refluxing benzene in the presence of a catalytic amount of NH_4Cl.[17]

Reductive lithiations were carried out under Ar in the presence of an excess (5–20 equiv.) of Li metal and a catalytic amount of naphthalene (5–10 mol%) in dry THF at

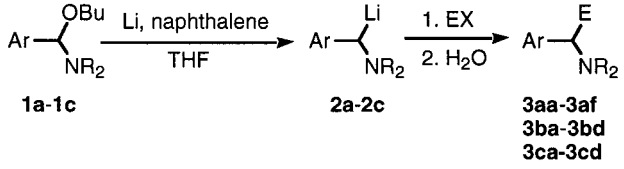
Keywords: amines; carbanions; ethers; lithium and compounds; reduction.
* Corresponding author. Tel.: +39-79-229549; fax: +39-79-229559; e-mail: ugo@ssmain.uniss.it

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00303-3

Table 1. Reductive lithiation of compounds **1a–c**

Entry	Compd, R=, Ar=	Equiv. of Li	*t* (h)	EX	Product, E=	Yield (%)[a,b]
1	**1a**, CH_3, C_6H_5	5	5	H_2O	**3aa**, H	>95[c]
2	**1a**, CH_3, C_6H_5	5	5	D_2O	**3ab**, D	>95[c]
3	**1a**, CH_3, C_6H_5	5	20[d]	D_2O	**3ab**, D	75[c]
4	**1a**, CH_3, C_6H_5	5	5	$PhCH_2Cl$	**3ac**, $PhCH_2$	58
5	**1a**, CH_3, C_6H_5	5	5	acetone	**3ad**, Me_2COH	68
6	**1a**, CH_3, C_6H_5	5	5	$(CH_2)_5CO$	**3ae**, $(CH_2)_5COH$	65
7	**1a**, CH_3, C_6H_5	5	5	Me_3CCHO	**3af**, Me_3CCHOH	64[e]
8	**1b**, CH_3, 2-$(CH_3O)C_6H_4$	5	4	H_2O	**3ba**, H	>95[c]
9	**1b**, CH_3, 2-$(CH_3O)C_6H_4$	5	4	D_2O	**3bb**, D	>95[c]
10	**1b**, CH_3, 2-$(CH_3O)C_6H_4$	5	4	BuBr	**3bc**, Bu	85
11	**1b**, CH_3, 2-$(CH_3O)C_6H_4$	5	4	$(CH_3)_2CHBr$	**3bd**, $(CH_3)_2CH$	82
12	**1c**, $(CH_2)_5$, C_6H_5	5	7	H_2O	**3ca**, H	72[c,f]
13	**1c**, $(CH_2)_5$, C_6H_5	5	7	D_2O	**3cb**, D	39[c]
14	**1c**, $(CH_2)_5$, C_6H_5	20[g]	7	H_2O	**3ca**, H	>95[c]
15	**1c**, $(CH_2)_5$, C_6H_5	20[g]	7	D_2O	**3cb**, D	80[c]
16	**1c**, $(CH_2)_5$, C_6H_5	20[g]	7	BuBr	**3cc**, Bu	28
17	**1c**, $(CH_2)_5$, C_6H_5	20[g]	7	acetone	**3cd**, Me_2COH	37

[a] All reactions run at −20°C in the presence of 5 mol% of naphthalene, unless otherwise indicated.
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^1H NMR spectroscopy of the crude reaction mixture.
[d] 5 h at −20°C, then 15 h at 0°C.
[e] A Diastereoisomeric mixture (75:25, by ^1H NMR spectroscopy) was obtained.
[f] 28% of **1c** was also detected.
[g] In the presence of 10 mol% of naphthalene.



Scheme 1. Reductive lithiation of α-*N*,*N*-dialkylamino-substituted benzyl butyl ethers.

−20°C; the resulting mixtures were allowed to react with different electrophiles for 10 min before aqueous workup and purification.

Reductive lithiation of benzyl butyl ethers 1a–c

We first investigated the reductive lithiation of the α-*N*,*N*-dimethylamino-derivative **1a**. The results are reported in Table 1 (Scheme 1).

Reductive cleavage of **1a** with 5 equiv. of Li metal and 5 mol% of naphthalene was complete within 5 h; intermediate formation of the corresponding lithium derivative **2a** was evidenced by D_2O quenching (Table 1, entries 1 and 2). Under these conditions we did not observe formation of products of dimerization or cleavage of the benzylic carbon–nitrogen bond.[19]

To check the stability of **2a**, the reaction mixture was allowed to warm to 0°C and stirred for several hours before D_2O quenching; under the new conditions, α-D-*N*,*N*-dimethybenzylamine **3ab** was recovered in 75% yield (Table 1, entry 3); no isomerization to the corresponding *ortho*-Li derivative was evidenced.

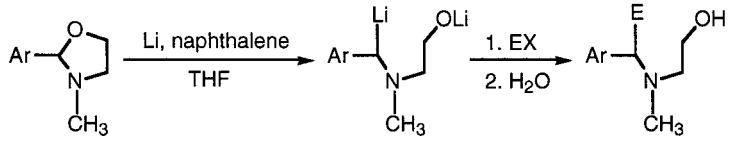
Intermediate **2a** was efficiently trapped, at −20°C, with several electrophiles; under these conditions, compounds **3ac–3af** were obtained in good to satisfactory yields (Table 1, entries 4–7).

Good results were obtained in the reductive lithiation of the *ortho*-methoxy derivative **1b**, which afforded aminoalcohol **3ba** in quantitative yield, via intermediate formation of the corresponding lithium derivative **2b**, as evidenced by D_2O quenching (Table 1, entries 8 and 9). Trapping of this organometallic with 1-BuBr and 2-propylbromide afforded aminoalcohols **3bc** and **3bd**, respectively, in good yields (Table 1, entries 10 and 11).

Under similar reaction conditions (5 equiv. of Li metal, 5 mol% of naphthalene, −20°C) cleavage of the piperidine-derivative **1c** was somewhat sluggish (28% starting material recovered after 7 h); furthermore, the intermediate organometallic **2c** was obtained in low yield (Table 1, entries 12 and 13). Better results were obtained performing the reaction in the presence of 20 equiv. of Li metal and 10 mol% of naphthalene; under these conditions the cleavage was quantitative, and the corresponding organometallic was obtained in 80% yield, as evidenced by D_2O quenching (Table 1, entries 14 and 15). Under the new conditions, reductive lithiation and subsequent electrophilic substitution with 1-BuBr or acetone afforded compounds **3cc** and **3cd**, respectively, in moderate yields (Table 1, entries 16 and 17).

Reductive lithiation of *N*-methyl-2-aryl-1,3-oxazolidines 1d–f

The reductive lithiation procedure was extended to cyclic derivatives, namely *N*-methyl-2-aryl-1,3-oxazolidines **1d–f**. Interestingly, reductive lithiation of these compounds should allow the generation of α-*N*-methylamino-substituted



1d-1f **2d-2f** **3da-3df** **3ea-3ed** **3fa-3fd**

Scheme 2. Reductive lithiation of *N*-methyl-2-aryl-1,3-oxazolidines **1d–f**.

Table 2. Reductive lithiation of compounds **1d–f**

Entry	Compd, Ar=	*t* (h)	EX	Product, E=	Yield (%)[a,b]
1	**1d**, C_6H_5	2	H_2O	**3da**, H	>95[c]
2	**1d**, C_6H_5	2	D_2O	**3db**, D	>95[c]
3	**1d**, C_6H_5	17[d]	D_2O	**3db**, D	>95[c]
4	**1d**, C_6H_5	2	EtBr	**3dc**, Et	68
5	**1d**, C_6H_5	2	BuBr	**3dd**, Bu	76
6	**1d**, C_6H_5	2	acetone	**3de**, $(CH_3)_2COH$	73
7	**1d**, C_6H_5	2	Me_3CCHO	**3df**, Me_3CCHOH	89[e]
8	**1e**, 2,3-$(CH_3O)_2C_6H_3$	3	H_2O	**3ea**, H	>95[c]
9	**1e**, 2,3-$(CH_3O)_2C_6H_3$	3	D_2O	**3eb**, D	>95[c]
10	**1e**, 2,3-$(CH_3O)_2C_6H_3$	3	CH_3I	**3ec**, CH_3	61
11	**1e**, 2,3-$(CH_3O)_2C_6H_3$	3	acetone	**3ed**, $(CH_3)_2COH$	56
12	**1f**, 4-$(CH_3)_2NC_6H_4$	3.5	H_2O	**3fa**, H	>95[c]
13	**1f**, 4-$(CH_3)_2NC_6H_4$	3.5	D_2O	**3fb**, D	>95[c]
14	**1f**, 4-$(CH_3)_2NC_6H_4$	3.5	$C_6H_{13}Br$	**3fc**, C_6H_{13}	62
15	**1f**, 4-$(CH_3)_2NC_6H_4$	3.5	$(CH_2)_5CO$	**3fd**, $(CH_2)_5COH$	38

[a] All reactions run with 5 equiv. of Li metal and 5 mol% of naphthalene at −20°C unless otherwise indicated.
[b] Isolated yield, unless otherwise indicated.
[c] As determined by ^1H NMR spectroscopy of the crude reaction mixture.
[d] 2 h at −20°C, then 15 h at 0°C.
[e] A Diastereoisomeric mixture (76:24, by ^1H NMR spectroscopy) was obtained.

organometallics which are functionalized with an oxyanionic group, suitable for further elaboration (Scheme 2). The results are reported in Table 2.

Reductive cleavage of **1d** with 5 equiv. of Li metal and 5 mol% of naphthalene at −20°C afforded the corresponding aminoalcohol **3da** in quantitative yield within 2 h, via intermediate formation of the corresponding lithium derivative, **2d**, as evidenced by D_2O quenching (Table 2, entries 1 and 2). No dimerization[17] nor cleavage of the benzylic carbon–nitrogen bond[19] were observed. At variance with the organolithium derivative **2a**, intermediate **2d** can be stored at 0°C for several hours before quenching (Table 2, entry 3); this higher stability is probably due to coordination of the arylmethylithium with the alkoxy group.[20,21] Intermediate **2d** was efficiently trapped, at −20°C, with several electrophiles, like ethylbromide, 1-bromobutane, acetone and trimethylacetaldehyde, affording the corresponding adducts **3cc–3cf** in good isolated yields (Table 2, entries 4–7).

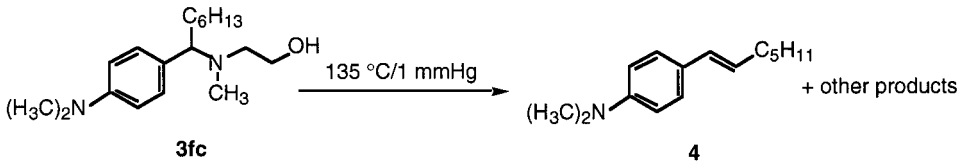
It is worth noting that, under similar reaction conditions (THF, −20°C, 6 h), K-mediated reductive cleavage of oxazolidine **1d** afforded aminoalcohol **3da** in 20% yield; only 50% deuterium incorporation in the benzylic position was obtained upon D_2O quenching.[17]

Satisfactory results were obtained in the reductive cleavage of the dimethoxy-substituted oxazolidine **1e**: reductive lithiation was achieved under the above reported reaction conditions within 4 h; quenching with D_2O showed intermediate quantitative formation of the corresponding organolithium derivative **2e** (Table 2, entries 8 and 9). Trapping of **2f** with CH_3I and acetone afforded aminoalcohols **3ec** and **3ed**, respectively, in satisfactory yields (Table 2, entries 10 and 11).

Although the generation of arylmethyllithium derivatives bearing strong electron donating substituents in the *para* position is a difficult task,[22] our procedure was effectively applied to the *para*-*N*,*N*-dimethylamino-substituted oxazolidine **1f**; accordingly, reductive cleavage of **1f** afforded the corresponding aminoalcohol **3fa** in quantitative yield (Table 2, entry 12). Trapping of the intermediate organometallic **2f** was efficiently achieved with different electrophiles (D_2O, 1-bromohexane, cyclohexanone) affording the corresponding products **3fb–3fd** in good to satisfactory yields (Table 2, entries 13–15). Interestingly, compound **3fc** underwent thermal decomposition upon vacuum distillation affording, as the main product (76%, as determined by ^1H NMR spectroscopy of the crude reaction mixture), the corresponding alkylstyrene, **4** (Scheme 3).

Concluding Remarks

The reported data show that Li-mediated reductive cleavage of α-(*N*,*N*-disubstituted)arylmethyl alkyl ethers and of *N*-methyl-2-aryl-1,3-oxazolidines is an efficient and simple



3fc **4**

Scheme 3. Thermal decomposition of aminoalcohol **3fc**.

procedure for the generation, in a single step, of a wide array of α-tertiary amino-substituted arylmethyllithium derivatives.

Strong electron donor substitutents do not affect the efficiency of the reaction, which can be performed under mild reaction conditions.

It is worth noting that our procedure represents an umpolung of the known reactivity of α-(*N*,*N*-disubstituted)arylmethyl alkyl ethers[18] and 2-aryl-1,3-oxazolidines[23,24] with organometallic reagents; it is therefore of interest that, under the reported reaction conditions, we did not observe formation of products of bimolecular recombination.

Experimental

General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillations is given as boiling points. Starting materials were of the highest commercial quality and were used without further purification. D_2O was 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ (unless otherwise indicated) with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of the crude mixtures and comparing the integration of the signal corresponding to the proton in the arylmethyl position with that of known signals. IR spectra were recorded on thin films, unless otherwise indicated. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Preparation of starting materials

α-*N*,*N*-Dialkylaminobenzyl butyl ethers **1a**–**1c** were prepared according to general procedures described in Ref. [18]; *N*-methyl-2-aryl-1,3-oxazolidines **1d**–**1f** were prepared according to a general procedure described in Ref. [17]. Compounds **1a**,[18] **1c**,[18] **1d**,[17] **1e**[17] and **1f**[17] are already known.

Compound **1b** was prepared according to method B described in Ref. [18] and characterized as follows.

2-Methoxy-α-(*N*,*N*-dimethylamino)benzyl butyl ether (1b). Purified by fractional distillation (75%), colourless oil; [Found: C, 70.73; H, 9.64. $C_{14}H_{23}NO_2$ requires C, 70.83; H, 9.79%]; bp 92–95°C/1 mmHg; ν_{max} 3050, 2980, 1610, 1470, 1260 cm^{-1}; δ_H 0.91 (3H, t, J=7.2 Hz, CH_3), 1.36–1.44 (2H, m, CH_2), 1.52–1.60 (2H, m, CH_2), 2.35 (6H, s, 2×CH_3N), 3.27–3.34 (2H, m, CH_2O), 3.83 (3H, s, CH_3O), 5.23 (1H, s, CH), 6.88 (1H, dd, J=7.8, 1.2 Hz, ArH), 6.96 (1H, td, J=7.8, 1.2 Hz, ArH), 7.26 (1H, td, J=7.8, 2.1 Hz, ArH), 7.43 (1H, dd, J=7.8, 2.1 Hz, ArH); δ_C (CD_3OD) 14.2, 20.0, 35.8, 40.0, 55.8, 62.7, 92.7, 111.8, 121.0, 126.7, 128.8, 130.5, 159.2; it was further characterized by acidic hydrolysis (1 N HCl/THF=1:1, rt, 3 h) to the corresponding aldehyde.

Reductive lithiation of ethers 1 and reaction with electrophiles. General procedure

Li metal (5–20 equiv. of a 30%wt. dispersion in mineral oil) was placed under Ar in a two-necked flask equipped with reflux condenser and magnetic stirrer, washed with THF (3×10 mL), and suspended in 30 mL of THF. A catalytic amount of naphthalene (5–10 mol%) was added to the suspension of the metal, and the mixture was stirred until a dark green colour appeared. The mixture was chilled to −20°C and a solution of the appropriate amino ether (5 mmol) in THF (2 mL) was added dropwise. After stirring for the reported time (Tables), a solution of the appropriate electrophile (1.1 equiv.) in THF (5 mL) was slowly added, and the mixture was stirred for 10 min. The mixture was quenched by slow dropwise addition of H_2O (10 mL, CAUTION), the cold bath removed, and the resulting mixture extracted with Et_2O (3×20 mL). The organic phase was washed with brine (10 mL), dried (K_2CO_3) and the solvent evaporated.

D_2O quenching was performed by slow dropwise addition of 1 mL of the electrophile, followed by aqueous work-up as described above.

Crude products were purified by flash chromatography (petroleum ether/AcOEt/Et_3N); compounds **3aa**,[25] **3ac**,[26] **3ad**,[27] **3ae**,[10] **3ba**,[28] **3ca**,[29] **3cc**,[30] **3da**,[17] **3ea**,[17] **3fa**[17] and **4**[31] are already known.

Deuterated compounds **3ab**–**3fb** were characterized by ^1H and ^{13}C NMR spectroscopy: the resonances of the arylmethyl CHD proton appear as unresolved broad triplets shifted 0.02–0.04 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 protons; the resonances of the arylmethyl CHD carbons appear as triplets (J=19–21 Hz) shifted 0.3–0.4 ppm (δ) upfield relatively to the corresponding arylmethyl CH_2 carbons.

Other products were characterized as follows.

1-Phenyl-1-(*N*,*N*-dimethyl)amino-3,3-dimethylbutan-2-ol (3af). Purified by flash chromatography (10% Et_3N/petroleum ether), colourless oil; [Found: C, 75.79; H, 10.62.

$C_{14}H_{23}NO$ requires C, 75.95; H, 10.49]; R_f (10% Et_3N/petroleum ether) 0.61 and 0.45; bp 110°C/1 mmHg; 1st diastereoisomer solidifies upon standing, white solid: mp 71–74°C (petroleum ether); ν_{max} 3453, 2950, 1460, 1360, 1010 cm^{-1}; 1st diastereoisomer: δ_H 0.73 (9H, s, 3×CH_3), 1.60 (1H, b s, OH), 2.13 (6H, s, 2×CH_3N), 3.43 (1H, d, J=10.2 Hz, CHPh), 3.73 (1H, d, J=10.2 Hz, CHO), 7.11–7.18 (2H, m, ArH), 7.28–7.38 (3H, m, ArH); δ_C 26.9, 34.7, 40.7, 69.8, 74.3, 127.5, 127.7, 130.0, 134.6; 2nd diastereoisomer: δ_H 0.73 (9H, s, 3×CH_3), 2.20 (6H, s, 2×CH_3N), 3.14 (1H, d, J=4.0 Hz, CHPh), 3.84 (1H, d, J=4.0 Hz, CHO), 7.25–7.36 (5H, m, ArH); δ_C 26.5, 29.8, 34.3, 43.8, 72.8, 127.5, 127.9, 130.2, 138.0.

***N*,*N*-Dimethyl-1-(2′-methoxy)phenylpentylamine (3bc).** Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=8:2:1), colourless oil; [Found: C, 75.81; H, 10.58. $C_{14}H_{23}NO$ requires C, 75.95; H, 10.49]; R_f (petroleum ether/AcOEt/Et_3N=8:2:1) 0.34; bp 85°C/1 mmHg; ν_{max} 3020, 2970, 1600, 1470, 1240; δ_H 0.82 (3H, t, J=7.2 Hz, CH_3), 0.98–1.36 (4H, m, 2×CH_2), 1.65–1.89 (2H, m, CH_2), 2.17 (6H, s, 2×CH_3N), 3.81 (3H, s, CH_3O), 3.89 (1H, dd, J=9.6, 5.1 Hz, CH), 6.89 (1H, d, J=8.4 Hz, ArH), 6.95 (1H, td, J=7.5, 0.9 Hz, ArH), 7.17–7.28 (2H, m, ArH); δ_C 14.0, 22.9, 28.3, 32.0, 42.5, 55.4, 60.9, 110.5, 120.1, 127.5, 128.5, 128.8, 158.0.

***N*,*N*-Dimethyl-1-(2′-methoxy)phenyl-2-methylpropylamine (3bd).** Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=8:2:1), colourless oil; [Found: C, 75.18; H, 10.39. $C_{13}H_{21}NO$ requires C, 75.30; H, 10.23]; R_f (petroleum ether/AcOEt/Et_3N=8:2:1) 0.58; bp 70°C/1 mmHg; ν_{max} 3020, 2980, 1600, 1470, 1250; δ_H 0.71 (3H, d, J=6.6 Hz, CH_3), 1.00 (3H, d, J=6.6 Hz, CH_3), 2.10 (6H, s, 2×CH_3N), 2.15–2.23 (1H, m, CH), 3.73 (1H, d, J=9.3 Hz, CHAr), 3.79 (3H, s, CH_3O), 6.90 (1H, dd, J=8.4, 1.2 Hz, ArH), 6.95 (1H, dd, J=7.5, 1.2 Hz, ArH), 7.14–7.25 (2H, m, ArH); δ_C 19.1, 20.5, 28.7, 41.7, 55.4, 65.9, 110.5, 119.7, 126.1, 127.3, 129.1, 158.5.

1-Phenyl-1-(*N*-piperidino)-2-methylpropan-2-ol (3cd). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=5:5:1), colourless oil; [Found: C, 76.93; H, 10.03. $C_{15}H_{23}NO$ requires C, 77.19; H, 9.95]; R_f (petroleum ether/AcOEt/Et_3N=5:5:1) 0.45; bp 145°C/1 mmHg; ν_{max} 3550, 3010, 2960, 1520, 1480, 1260 cm^{-1}; δ_H 1.16 (3H, s, CH_3) 1.24–1.36 (2H, m, CH_2), 1.32 (3H, s, CH_3), 1.50–1.66 (4H, m, 2×CH_2), 2.18–2.34 (2H, b s, CH_2), 2.66–2.78 (2H, b s, CH_2), 3.34 (1H, s, CH), 7.28–7.34 (5H, m, ArH); δ_C 24.2, 26.6, 26.9, 29.2, 53.9, 72.6, 79.8, 127.2, 127.7, 130.8, 135.8.

2-*N*-Methyl-*N*-(1′-phenyl)propylaminoethanol (3dc). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=5:5:1), colourless oil; [Found: C, 74.29; H, 10.09. $C_{12}H_{19}NO$ requires C, 74.55; H, 9.93]; R_f (petroleum ether/AcOEt/Et_3N=5:5:1) 0.50; bp 130°C/1 mmHg; ν_{max} 3480, 2970, 1510, 1470, 1050 cm^{-1}; δ_H 0.84 (3H, t, J=7.5 Hz, CH_3), 1.72–1.88 (1H, m, CH), 1.88–2.04 (1H, m, CH), 2.17 (3H, s, CH_3N), 2.40–2.50 (1H, m, CHN), 2.51–2.62 (1H, m, CHN), 3.42 (1H, dd, J=8.7, 6.3 Hz, CHAr), 3.47–3.64 (2H, m, CH_2O), 7.17–7.37 (5H, m, ArH); δ_C 11.6, 25.2, 37.2, 55.3, 58.3, 70.6, 127.4, 128.3, 128.9, 139.6.

2-*N*-Methyl-*N*-(1′-phenyl)pentylaminoethanol (3dd). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=3:7:1), colourless oil; [Found: C, 75.63; H, 10.69. $C_{14}H_{23}NO$ requires C, 75.95; H, 10.49]; R_f (petroleum ether/AcOEt/Et_3N=3:7:1) 0.41; bp 112°C/760 mmHg; ν_{max} 3390, 2950, 1500, 1480, 1040 cm^{-1}; δ_H 0.86 (3H, t, J=6.6 Hz, CH_3), 1.07–1.38 (4H, m, $(CH_2)_2$), 1.71–1.95 (2H, m, CH_2), 2.16 (3H, s, CH_3N), 2.40–2.48 (1H, m, CHN), 2.52–2.62 (1H, m, CHN), 3.48–3.63 (3H, m, CH_2O, CHAr), 7.18–7.36 (5H, m, ArH); δ_C 13.9, 22.7, 29.0, 31.7, 36.9, 54.9, 57.9, 68.6, 127.1, 128.0, 128.6, 139.3.

1-*N*-Methyl-*N*-(2′-hydroxyethyl)amino-1-phenyl-2-methylpropan-2-ol (3de). Purified by flash chromatography (10% Et_3N/AcOEt), colourless oil; [Found: C, 69.78; H, 9.79. $C_{13}H_{21}NO_2$ requires C, 69.90; H, 9.50]; R_f (10% Et_3N/AcOEt) 0.42; bp 126°C/1 mmHg; ν_{max} 3430, 2930, 1640, 1600, 1030 cm^{-1}; δ_H 1.18 (3H, s, CH_3), 1.41 (3H, s, CH_3), 2.26–2.37 (1H, m, CHN), 2.40 (2H, s, CH_3N), 2.91 (1H, ddd, J=13.0, 8.0, 4.5 Hz, HCN), 3.42 (1H, s, CHAr), 3.56–3.73 (2H, m, CH_2O), 7.29–7.44 (5H, m, ArH); δ_C 28.3, 29.4, 40.4, 57.1, 59.1, 74.2, 76.3, 127.3, 127.9, 130.7, 135.8.

1-*N*-Methyl-*N*-(2′-hydroxyethyl)amino-1-phenyl-3,3-dimethylbutan-2-ol (3df). Purified by flash chromatography (10% Et_3N/AcOEt), colourless oil; [Found: C, 71.43; H, 10.35. $C_{15}H_{25}NO_2$ requires C, 71.66; H, 10.04]; R_f (10% Et_3N/AcOEt) 0.40 and 0.39; bp 140°C/1 mmHg; ν_{max} 3360, 2950, 1475, 1450, 1360 cm^{-1}; 1st diastereoisomer: δ_H 0.75 (9H, s, 3×CH_3), 2.18 (3H, s, CH_3N), 2.30–2.45 (1H, m, CHN), 2.55–2.66 (1H, m, CHN), 3.59 (1H, d, J=9.6 Hz, CHAr), 3.69–3.75 (2H, m, CH_2O), 3.80 (1H, d, J=9.6 Hz, CHO), 7.15–7.22 (2H, m, ArH), 7.28–7.38 (3H, m, ArH); 2nd diastereoisomer: not obtained in a sufficiently pure form to unambiguously assign its ^1H NMR resonances; 1st diastereoisomer: δ_C 26.9, 34.8, 37.5, 55.4, 59.6, 69.3, 74.4, 127.6, 127.9, 129.8, 135.2; 2nd diastereoisomer: δ_C 26.6, 35.1, 38.4, 56.1, 58.7, 70.8, 78.2, 127.2, 128.0, 130.6, 136.3.

2-*N*-[1′-(2′,3′-Dimethoxy)phenyl]ethyl-*N*-methylaminoethanol (3ec). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=0.5:9.5:1), colourless oil; [Found: C, 65.17; H, 9.01. $C_{13}H_{21}NO_3$ requires C, 65.23; H, 8.86]; R_f (petroleum ether/AcOEt/Et_3N=0.5:9.5:1) 0.34; bp 125°C/1 mmHg; ν_{max} 3320, 2970, 1580, 1450, 1210 cm^{-1}; δ_H 1.34 (3H, d, J=6.9 Hz, CH_3), 2.18 (3H, s, CH_3N), 2.53–2.64 (2H, m, CH_2N), 3.49–3.61 (2H, m, CH_2O), 3.83 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 4.18 (1H, q, J=6.9 Hz, CH), 6.83 (1H, dd, J=7.8, 1.5 Hz, ArH), 6.93 (1H, dd, J=7.8, 1.5 Hz, ArH), 7.05 (1H, t, J=7.8 Hz, ArH); δ_C 17.3, 37.1, 55.2, 55.4, 55.6, 58.3, 60.7, 110.8, 119.5, 123.7, 136.7, 147.0, 152.7.

1-*N*-(2′-Hydroxy)ethyl-*N*-methyl-1-(2′,3′-dimethoxy)-phenyl-2-methylpropan-2-ol (3ed). Purified by flash chromatography (10% Et_3N/AcOEt), white solid; [Found: C, 63.31; H, 9.12. $C_{15}H_{25}NO_4$ requires C, 63.57; H, 8.91]; R_f (10% Et_3N/AcOEt) 0.51; mp 91–93°C (Et_2O/pentane); ν_{max} (KBr) 3410, 2990, 1610, 1460, 1270 cm^{-1}; δ_H 1.17 (3H, s, CH_3), 1.44 (3H, s, CH_3), 2.37 (3H, s, CH_3N), 2.38–2.48 (1H, m, CHN), 2.64 (2H, b s, OH), 2.76–2.85 (1H, m, CHN), 3.55–3.62 (1H, m, CHO), 3.64–3.72 (1H, m, CHO), 3.82

(3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.11 (1H, s, CH), 6.87 (1H, dd, J=8.1, 1.2 Hz, ArH), 7.04 (1H, t, J=8.1 Hz, ArH), 7.32 (1H, dd, J=8.1, 1.2 Hz, ArH); δ_C 28.5, 29.5, 40.2, 55.5, 57.3, 59.1, 60.6, 65.6, 74.5, 110.9, 122.8, 122.8, 129.9, 148.2, 152.6.

2-*N*-[1′-*para*-(*N*′,*N*′-Dimethylamino)phenylhepthyl]-*N*-methylaminoethanol (3fc). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=4:6:1), colourless oil; [Found: C, 73.78; H, 11.32. $C_{18}H_{32}N_2O$ requires C, 73.90; H, 11.05]; R_f (petroleum ether/AcOEt/Et_3N=4:6:1) 0.46; bp 135°C/1 mmHg (decomposition); ν_{max} 3420, 2970, 1600, 1520, 1360 cm^{-1}; δ_H 0.85 (3H, t, J=7.0 Hz, CH_3), 1.10–1.35 (8H, m, 4×CH_2), 1.67–1.92 (2H, m, CH_2), 2.14 (3H, s, CH_3N), 2.37–2.47 (1H, m, CHN), 2.49–2.61 (1H, m, CHN), 2.94 (6H, s, 2×CH_3N), 3.40 (1H, dd, J=8.7, 6.3 Hz, CHO), 3.48–3.61 (2H, m, CHAr, CHO), 6.66–6.73 (2H, m, ArH), 7.03–7.10 (2H, m, ArH); δ_C 14.1, 22.6, 27.0, 29.4, 31.8, 32.0, 36.6, 40.6, 54.8, 57.8, 67.7, 111.9, 127.0, 129.4, 149.6.

2-*N*-Methyl-*N*-[α-(1′-hydroxycyclohexyl)-*para*-(*N*′,*N*′-dimethylamino)]-phenyl-methylaminoethanol (3fd). Purified by flash chromatography (petroleum ether/AcOEt/Et_3N=1:9:1), colourless oil; [Found: C, 70.46; H, 9.96. $C_{18}H_{30}N_2O_2$ requires C, 70.53; H, 9.88]; R_f (petroleum ether/AcOEt/Et_3N=1:9:1) 0.54; bp 210°C/1 mmHg; ν_{max} 3440, 2960, 1600, 1520, 1340 cm^{-1}; δ_H 1.10–1.75 (10H, m, 5×CH_2), 2.28–2.37 (1H, m, CHN), 2.38 (3H, s, CH_3N), 2.75–2.86 (1H, m, CHN), 2.95 (6H, s, 2×CH_3N), 3.31 (1H, s, CHAr), 3.51–3.68 (2H, m, CH_2O), 6.68–6.72 (2H, m ArH), 7.21–7.30 (2H, m, ArH); δ_C 21.8, 22.2, 25.7, 36.3, 36.4, 40.0, 40.4, 57.2, 58.9, 74.7, 75.1, 111.6, 123.2, 131.8, 149.5.

Acknowledgements

Financial support from MURST, Roma (60 and 40% funds) and from Regione Autonoma della Sardegna (R.A.S.) are gratefully acknowledged. L. P. thanks R.A.S. for a fellowship.

References

1. Weston, J.; Ahlbrecht, H. *Tetrahedron* **1999**, *55*, 2289–2306.
2. Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342–12343.
3. Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089–6096.
4. Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887–1894.
5. Ahlbrecht, H.; Harbach, J.; Hauck, T.; Kalinowski, H.-O. *Chem. Ber.* **1992**, *125*, 1753–1762.
6. Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1–314.
7. Azzena, U.; Pilo, L.; Sechi, A. *Tetrahedron* **1998**, *54*, 12389–12398 (and references therein).
8. Jones, F. N.; Vaulx, R. L.; Hauser, C. R. *J. Org. Chem.* **1963**, *28*, 3461–3465 (and references therein).
9. van Koten, G.; Jastrzebski, J. T. B. H. *Tetrahedron* **1989**, *45*, 569–578.
10. Puterbaugh, W. H.; Hauser, C. H. *J. Am. Chem. Soc.* **1963**, *85*, 2467–2470.
11. Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Singh, K. N. *J. Chem. Soc., Chem. Commun.* **1991**, 568–570.
12. Harmata, M.; Carter, K. W.; Jones, D. E.; Kahraman, M. *Tetrahedron Lett.* **1996**, *37*, 6267–6270.
13. Kessar, S. V.; Singh, P. *Chem. Rev.* **1997**, *97*, 721–737 (and references therein).
14. Azzena, U. *Trends in Organic Chemistry* **1997**, *6*, 55–65 (and references therein).
15. Azzena, U.; Carta, S.; Melloni, G.; Sechi, A. *Tetrahedron* **1997**, *53*, 16205–16212.
16. Azzena, U.; Melloni, G.; Pisano, L.; Sechi, B. *Tetrahedron Lett.* **1994**, *35*, 6759–6762.
17. Azzena, U.; Melloni, G.; Nigra, C. *J. Org. Chem.* **1993**, *58*, 6707–6711.
18. Stewart, A. T.; Hauser, C. R. *J. Am. Chem. Soc.* **1955**, *77*, 1098–1103.
19. Reductive lithiation of some *N*,*N*-dialkylbenzylamines was reported: Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1996,** *52* 8545–8564.
20. Kato, T.; Marumoto, S.; Sato, T.; Kuwajima, I. *Synlett* **1990**, 671.
21. Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501–1523.
22. Schlosser, M.; Maccaroni, P.; Marzi, E. *Tetrahedron* **1998**, *54*, 2763–2777 (and references therein).
23. Wu, M. -J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340–1344.
24. Napolitano, E.; Morsani, M.; Fiaschi, R. *Gazz. Chim. Ital.* **1991**, *121*, 249–255.
25. Skita, A.; Keil, F. *Chem. Ber.* **1930**, *63*, 34–50.
26. Lepley, A. R.; Giumanini, A. G. *J. Org. Chem.* **1967**, *32*, 1706–1713.
27. Puterbaugh, W. H.; Hauser, C. H. *J. Org. Chem.* **1963**, *28*, 3465–3467.
28. Jones, F. N.; Hauser, C. R. *J. Org. Chem.* **1962**, *27*, 4020–4024.
29. Pollak, I. E.; Trifunac, A. D.; Grillot, G. F. *J. Org. Chem.* **1967**, *32*, 272–275.
30. Haury, H. *Arch. Pharm.* **1962,** *295*, 728–735; *Chem. Abs.* **1963,** *58*, 6822h.
31. Ueda, T.; Nakata, I.; Toyoshima, S. *Pharm. Bull.* **1953**, *1*, 383–385.