Preparation of secondary amines by reductive amination with metallic magnesium

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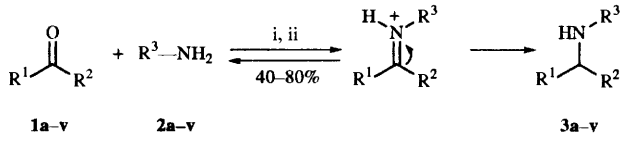
A novel and efficient method for the preparation of secondary amines by reductive amination of carbonyl compounds with primary amines has been developed. The reduction, effected with metallic magnesium in methanol, utilizing triethylamine–acetic acid as a buffer, gave pure secondary amines, mostly in good yields (65–80%). No formation of tertiary amines or alcohols was observed. Use of ammonium acetate as an amino component gave primary amines in modest yields (*ca.* 50%), together with variable amounts of secondary amines. Enamines failed to undergo reduction. The method is inexpensive, relatively rapid, operationally simple and suitable for large-scale preparations. In addition, a simple method for separation of primary amines from secondary ones has been developed.

There are numerous methods to prepare secondary amines from various precursors,[1] including a number of alkylation procedures. Simple alkylation of primary amines with various alkyl halides is severely limited owing to the formation of mixtures including tertiary amines and quaternary ammonium salts.[2] However, reductive amination utilizing carbonyl compounds and primary amines, has been used extensively.[3,4] The usual methods to effect reductive amination involve catalytic hydrogenation,[5] Leucart–Wallace reaction (formic acid),[6–8] a borane–pyridine complex[9] or certain metal hydrides.[10–17] In the last mentioned, sodium cyanoborohydride takes a prominent place, because of its wide applicability.[18]

In an earlier paper,[19] we described an efficient method for reductive amination of aromatic amines with ketones and keto esters, utilizing zinc–acetic acid as a reducing agent. However, it was entirely limited to aromatic amines, since aliphatic imines, formed *in situ*, failed to undergo reduction. In this research, we have searched for a novel reducing system, based upon dissolving metals, which should satisfy several conditions: (a) be powerful enough to reduce aliphatic imines/enamines relatively rapidly, under mild conditions; (b) be unable to reduce ketones or aldehydes; (c) permit relatively rapid formation of the corresponding imine under the reaction conditions; (d) be inexpensive and relatively nontoxic; and (e) allow a simple and efficient work-up of the reaction mixture. Those considerations led us to examine metallic magnesium, as a potential reducing agent.

Magnesium is a powerful reducing agent: it is used in the preparation of Grignard reagents[20] and for reduction of various alkyl and aryl halides in protic solvents;[21] it also readily reduces conjugated double bonds of esters,[22] nitriles,[23] amides,[24,25] and diaryl disubstituted ethylenes[26] in methanol, as well as α,β-acetylenic esters and triple bonds conjugated to two aromatic rings.[27] Under the same conditions, unactivated double and triple bonds are reduced in the presence of Pd–C,[28] while desulfonation was also effected with magnesium in methanol.[29] In aprotic solvents magnesium effects pinacol reductive coupling of aldehydes and ketones.[30] To our knowledge, however, it has never been used for reductive amination of carbonyl compounds, nor for reduction of preformed imines.



1a–v **2a–v** **3a–v**

R^1 = alkyl, R^2 = H, alkyl, R^3 = H, alkyl, aryl

Scheme 1 *Reagents and conditions:* i, Et_3N (3.0 equiv.), AcOH (4.0 equiv.), Mg (4.5 equiv.), MeOH, reflux, 2 h; ii, AcOH (4.0 equiv.), reflux, 2–4 h; or room temp., 12–24 h

In this research, the reductive amination was attempted first with magnesium in methanol, ethanol or an alcohol–acetic acid mixture, where no reduction occurred, except for hydrogen evolution. Then, various buffering systems were examined, including potassium acetate–acetic acid, sodium hydrogen carbonate (with tetrabutylammonium chloride), potassium hydrogen carbonate/18-crown-6 or sodium dihydrogen phosphate, without success. However, when triethylammonium acetate was used (prepared *in situ* from triethylamine and acetic acid), reductive amination proceeded smoothly. Best results were obtained with 3 equiv. of triethylammonium acetate, with additional acetic acid added portionwise to the reaction mixture, as indicated in Scheme 1. The reaction is completed in 12–24 h at room temperature, compared to 4–6 h in boiling methanol. Interestingly, when trimethylammonium acetate was used, poor yields were observed, regardless of the temperature, probably because of the high volatility of trimethylamine. The pH of the reaction mixture is of crucial importance. If the pH is < *ca.* 7, hydrogen evolution becomes predominant, while at a pH > 9–10, the reduction does not proceed. This may be explained in terms of the reaction mechanism. Since the species which actually undergo reduction is the protonated imine (immonium ion), its concentration must be considerable in the reaction medium, which is the case at pH 7–9.

The reaction was optimized in several respects. Amount and granulation of magnesium was found to be important. Maximum yields were obtained with magnesium turnings (4.5 equiv.). while finer material (*e.g.* particle size < 0.1 mm) gave much lower yields. Chemical purity of magnesium also appears

to be important. An attempt was made to modify chemically the surface of magnesium by adding small amounts (0.1–5 mol%) of various salts: mercury(II) acetate, mercury(II) chloride, zinc chloride, ferric chloride, copper(II) sulfate and silver(I) acetate. In all instances, greatly enhanced reactivity was noted, but the product yields were negligible, since hydrogen evolution become the major reaction. Among solvents tested for the reaction, were ethanol (96% and abs.), isopropyl alcohol, formamide and tetrahydrofuran. In tetrahydrofuran the reductive amination failed to proceed, in formamide it was very slow and gelatinous, while in alcohols (ethanol, isopropyl) yields were much lower compared to methanol. Carbonyl compounds examined in the reaction were aldehydes, ketones, β-keto esters and γ-keto esters, while ammonia (ammonium acetate), primary and secondary amines were used as an amino component (see Table 1). Aliphatic ketones reacted with primary aliphatic amines, α,ω-diamines and aromatic amines in refluxing methanol affording pure secondary amines usually in good yields (**3a–l**). Heptan-3-one and pentan-3-one gave lower yields (*ca.* 45%) together with 10–15% of unchanged primary amine, regardless of the amount of magnesium used. In those instances, an efficient method to remove primary amines in the presence of secondary ones was developed. After completion of the reduction, the mixture was treated with 40 mol% of ethyl formate, thus converting primary amines into the corresponding formamides. Since secondary amines remain unaffected, they can be separated as monooxalate salts. Inexpensive and volatile amines (butylamine, methylamine) were used in excess, in place of triethylamine. However, all attempts to use secondary amines in this reaction have failed, since the enamines, slowly formed *in situ*, were resistant to reduction. Aromatic ketones gave complex mixtures with primary amines (TLC and GC) (**3m**), while β-keto esters formed stable, conjugated enamines (**3p**) and were resistant to reduction. In contrast, the γ-keto-ester, methyl levulinate, underwent smooth reduction followed by cyclization to furnish the corresponding pyrrolid-2-one (**3q**). Primary amines were obtained (**3n**, **3o**) albeit in modest yields (*ca.* 50%), when ammonium acetate was used in large excess (10 equiv.), in 70% aqueous methanol, together with the corresponding secondary amines (10–20%). When anhydrous methanol was used, secondary amines become the major product (> 50%). Interestingly, the use of ammonium chloride instead of ammonium acetate, resulted only in hydrogen evolution, probably due to the greater acidity of ammonium chloride. Aliphatic aldehydes reacted smoothly with primary amines at room temperature, to yield the corresponding secondary amines as a single product (**3s–v**) while at elevated temperature, side reactions were noted. Aromatic aldehydes, such as benzaldehyde, gave complex mixtures of products (**3r**) similar to aromatic ketones and are not useful substrates in this reaction.

The work-up procedure was also fully optimized. The magnesium which reacted was precipitated completely as a basic acetate, and was filtered off. The trace amounts of magnesium ions in the filtrate were complexed with EDTA disodium salt, to prevent formation of gelatinous magnesium hydroxide upon alkalization. Triethylamine was removed under reduced pressure at room temperature, and the resulting product was precipitated as a monooxalate salt or, alternatively, distilled.

As shown in Table 1, the method is most suitable for preparation of various secondary amines, even those of considerable steric hindrance (*e.g.* **3g**). It requires approximately stoichiometric amounts of the reactants, affording usually good yields (65–80%) of pure products. Where applicable, the reductive amination with magnesium has some advantages over other methods (catalytic hydrogenation, $NaBH_3CN$, BH_3·py, Leucart–Wallace reaction). It is very inexpensive, operationally simple, rapid, relatively non-toxic and suitable for large-scale preparations, permitting maximum concentration of 0.4–0.6 mol dm^{-3} of the reactants. Since no reduction of the carbonyl group was observed (unlike with other reagents), it enables complete conversion of the carbonyl component, provided that the amino component is used in excess. This is particularly advantageous with expensive substrates. In the case of primary amines, the method is of a limited value and Leucart–Wallace reaction, oxime reduction, or other methods may be preferred. Groups which are readily reduced with metallic magnesium are not compatible with the method, in particular conjugated double and triple bonds and nitro groups.

Table 2 contains selected spectroscopic data for the products.

Experimental

A solution of $MeNH_2$ in methanol (5.4 mol dm^{-3}) was obtained by passing a stream of gaseous $MeNH_2$, generated from 40% aqueous $MeNH_2$ and solid KOH, first through a drying tube with KOH pellets and then into the methanol at 0 °C. It was standardized by acidimetric titration (HCl, Methyl Orange). Reagent quality solvents were used without further purification, and other reagents were used as supplied, by Aldrich Chemical Co., Merck Darmstadt Chemical Co. and Fluka Chemical Co. Magnesium (turnings for Grignard, 99.5%), was supplied by Merck. Melting points were taken with a Mel-Temp apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer FT IR 1725X spectrometer, ^1H NMR spectra with Bruker Spectrospin 600 MHz spectrometer and mass spectra with a Finnigan-Math instrument, model 8230. Gas chromatograms were obtained with a capillary Varian instrument, model 3400, utilizing a capillary non-polar column, DB-5. The reactions were typically performed on a 50 mmol scale while some examples, like **3a**, were also run on a 100, 150 and 200 mmol scale with essentially the same yields. In general, on the scale above, *ca.* 150 mmol, mechanical stirring was necessary. Yields refer to the pure oxalate salts unless otherwise stated, and were calculated to the corresponding amines when carbonyl compounds were used in excess. Spectroscopic and physical data are given in Tables 1 and 2. Microanalytical data for the new compounds are given in Table 3.

Typical procedures

***N*-(Cyclohexyl)phenethylamine 3a.** Into a 250 cm^3, two-necked flask, equipped with a reflux condenser and a dropping funnel were charged cyclohexanone (4.91 g, 5.2 cm^3, 50 mmol), phenethylamine (5.45 g, 5.65 cm^3, 45 mmol), Et_3N (15.18 g, 20.9 cm^3, 150 mmol) and MeOH (60 cm^3). The mixture was stirred magnetically and cooled (water bath), while AcOH (12.0 g, 11.45 cm^3, 200 mmol) was added with a pipette below the surface of the liquid. The dropping funnel was also charged with AcOH (12.0 g, 11.45 cm^3, 200 mmol) in MeOH (10 cm^3). Finally, Mg (5.47 g, 225 mmol) was added to the mixture which was then stirred vigorously (1200–1800 rpm, large stirring bar), under reflux, for 2 h. After this, AcOH was added, portionwise, from the dropping funnel, over a 2 h period. After a further period under reflux (1 h), the mixture was cooled to 20–25 °C and filtered with a medium porosity sinter funnel. The precipitate was removed from the funnel and stirred magnetically with MeOH (50 cm^3) for 5 min before it was again filtered. Finally, it was washed, with thorough manual stirring on the funnel, with Et_2O (70 cm^3). If the combined filtrate contained some precipitate, it was filtered through a less porous sinter funnel. A solution of K_2CO_3 (15 g) and EDTA disodium salt (3.0 g) in water (70 cm^3) was added to the filtrate, and the mixture concentrated on a rotatory evaporator (20–25 °C, 25 min). The resulting emulsion was extracted with Et_2O (3 × 70 cm^3) and the combined extracts were dried (K_2CO_3) and evaporated. The residue was dissolved in MeOH (20 cm^3) and added slowly, with magnetic stirring, to the solution of anh. oxalic acid (5.40 g, 60 mmol) in MeOH (50 cm^3). The mixture was cooled to −20 °C after which the precipitated monooxalate

Table 1 Products of the reductive amination

No.	Carbonyl compd.	Amine	Product *	Yield;[a] purity (GC, %)	Molecular formula; mp (decomp., °C)[b]
1	O=C(CH$_2$)$_4$CH$_2$ **1a**[c]	PhCH$_2$CH$_2$ **2a**	Ph(CH$_2$)$_2$NH-c-Hex **3a**	79; 99[d]	$C_{14}H_{21}N$;[31] 200
2	O=C(CH$_2$)$_5$CH$_2$ **1b**	Bu **2b**[e]	BuNH-c-Hept **3b**	72; 98[d]	$C_{11}H_{23}N$; 198–9
3	(PhCH$_2$CH$_2$)$_2$C=O **1c**	Me **2c**[e]	(PhCH$_2$CH$_2$)$_2$CHNHMe **3c**	65; 98[d]	$C_{18}H_{23}N$; 147
4	PhCH$_2$COMe **1d**	Me **2d**[e]	PhCH$_2$CH(Me)NHMe **3d**	80; 99[d]	$C_{10}H_{15}N$;[32] 154
5	PhCH$_2$CH$_2$COMe **1e**	Bu **2e**[e]	Ph(CH$_2$)$_2$CH(Me)NHBu **3e**	78; 99[d]	$C_{14}H_{23}N$;[33] 153
6	PhCH$_2$CH$_2$COMe **1f**[c]	PhCH$_2$CH$_2$ **2f**	Ph(CH$_2$)$_2$CH(Me)NH(CH$_2$)$_2$Ph **3f**	70; 99[d]	$C_{18}H_{23}N$; 175
7	PhCH$_2$CH$_2$COMe **1g**[c]	CH$_2$(CH$_2$)$_4$CH– **2g**	Ph(CH$_2$)$_2$CH(Me)NH-c-Hex **3g**	65; 100[d]	$C_{16}H_{25}N$; 172
8	O=C(CH$_2$)$_4$CH$_2$ **1h**[c]	PhCH$_2$ **2h**	PhCH$_2$NH-c-Hex **3h**	65; 98[d]	$C_{13}H_{19}N$;[34] 218–9
9	O=C(CH$_2$)$_4$CH$_2$ **1i**[c]	Ph **2i**	PhNH-c-Hex **3i**	75; 97[d]	$C_{12}H_{17}N$;[19] 193
10	Et$_2$CO **1j**	PhCH$_2$CH$_2$ **2j**	Et$_2$CHNHCH$_2$CH$_2$Ph **3j**	48; 98[f]	$C_{13}H_{21}N$;[35] 184–5
11	EtCOBu **1k**	PhCH$_2$CH$_2$ **2k**	Et(Bu)CHNHCH$_2$CH$_2$Ph **3k**	45; 99[f]	$C_{15}H_{25}N$; 153
12	EtCOMe **1l**[d]	H$_2$N(CH$_2$)$_6$NH$_2$ **2l**	[Me(Et)CHNHCH$_2$CH$_2$CH$_2$]$_2$ **3l**	77; 99[g]	$C_{14}H_{32}N_2$; 207–9
13	PhCOMe **1m**	Bu **2m**[e]	Complex mixture **3m**[h]	—	—
14	PhCH$_2$COMe **1n**	NH$_3$(AcONH$_4$) **2n**[e]	PhCH$_2$CH(Me)NH$_2$ + sec. amine; (8:2)[i] **3n**	41; 100[j,k]	$C_9H_{13}N$;[36] 160
15	PhCH$_2$CH$_2$COMe **1o**	NH$_3$(AcONH$_4$) **2o**[e]	Ph(CH$_2$)$_2$CH(Me)NH$_2$ + sec. amine; (9:1)[i] **3o**	50; 99[j,k]	$C_{10}H_{15}N$;[37] 220
16	MeCOCH$_2$CO$_2$Me **1p**[c]	PhCH$_2$CH$_2$ **2p**	PhCH$_2$CH$_2$NHC(Me)=CHCO$_2$Me[l] **3p**	92; 96	$C_{13}H_{17}NO_2$
17	MeCOCH$_2$CH$_2$CO$_2$Me **1q**[c]	PhCH$_2$CH$_2$ **2q**	Ph(CH$_2$)$_2$NCH(~Me)(CH$_2$)$_2$C=O **3q**	78; 97[m]	$C_{13}H_{17}NO$
18	PhCHO **1r**[c]	CH$_2$(CH$_2$)$_4$CH– **2r**	Complex mixture of products **3r**[h]	—	—
19	Me$_2$CHCHO **1s**[c]	CH$_2$(CH$_2$)$_4$CH– **2s**	Bu^{i}NH-c-Hex **3s**	72; 98[d]	$C_{10}H_{21}N$;[34] 230
20	Me$_2$CHCHO **1t**[c]	PhCH$_2$CH$_2$ **2t**	Bu^{i}NHCH$_2$CH$_2$Ph **3t**	75; 98[d]	$C_{12}H_{19}N$;[38] 236
21	MeCH$_2$CH$_2$CHO **1u**[c]	CH$_2$(CH$_2$)$_4$CH– **2u**	BuNH-c-Hex **3u**	35; 98[d]	$C_{10}H_{21}N$;[39] 210
22	Me$_2$CHCHO **1v**[c]	Ph **2v**	Bu^{i}NHPh **3v**	46; 97[d]	$C_{10}H_{15}N$;[40] 155–6

* c-Hex and c-Hept = cyclohexyl and cycloheptyl, respectively. [a] Yields refer to crystallized oxalate salts unless otherwise stated. Free amines liberated with KOH or K_2CO_3 and purity determined with cap. GC. [b] Satisfactory microanalyses obtained for all oxalates: C ± 0.40, H ± 0.38, N ± 0.35; mp (decomp.) refer to oxalate salts. [c] Carbonyl compound used in 10–30 mol% excess. [d] Product isolated and purified as monooxalate salts. [e] Primary amines or NH_3 used instead of triethylamine. [f] Equimolar amounts of reactants used; unchanged primary amine removed with HCO_2Et; product precipitated as monooxalate salt. [g] Product isolated and purified as dioxalate salt. [h] GC and TLC. [i] Primary/secondary amine ratio in the mixture (GC). [j] Yield refers to the pure primary amine. [k] Pure primary amine obtained by fractional vacuum distillation of the mixture. [l] The crude product was not purified; structure determined by GC-MS and IR. [m] Purified by vacuum distillation; bp 130–135 °C/0.1 Torr.

salt was filtered off, washed with Et_2O (50 cm^3), and dried (80 °C, 6 h). It may be recrystallized from hot methanol; yield 10.45 g (79%, calculated with reference to the 2-phenylethyamine used). The free amine was obtained by treatment of the oxalate salt with K_2CO_3 (20 g) in water (100 cm^3) and extraction with CH_2Cl_2 (2 × 50 cm^3). The combined extracts were dried (K_2CO_3), and evaporated (rotatory evaporator) and the residue was vacuum distilled, to afford the pure amine (6.92 g, 75%), bp 148–155 °C/12 Torr.

***N*-(Cycloheptyl)butylamine 3b.** The reaction was conducted and worked up as described for **3a**, except that butylamine was used instead of triethylamine. The following quantities were used: cycloheptanone (5.61 g, 5.90 cm^3, 50 mmol), butylamine (11.0 g, 14.8 cm^3, 150 mmol), Mg (5.47 g, 225 mmol) and AcOH (9.0 g, 8.6 cm^3, 150 mmol), followed by additional amount of AcOH (15.0 g, 14.3 cm^3, 250 mmol). The monooxalate salt was obtained with anh. oxalic acid (5.40 g, 60 mmol) in 72% yield (9.32 g).

***N*-(Cyclohexyl)isobutylamine 3s.** The same equipment was used as for **3a**. Isobutyraldehyde (3.60 g, 4.55 cm^3, 50 mmol), cyclohexylamine (4.46 g, 5.15 cm^3, 45 mmol), Et_3N (15.18 g, 20.9 cm^3, 150 mmol), Mg (5.47 g, 225 mmol) and MeOH (60 cm^3) were combined. The mixture was stirred and cooled (water bath), while AcOH (12.0 g, 11.45 cm^3, 200 mmol) was added with a pipette below the surface of the liquid. The mixture was stirred vigorously, at 20–25 °C for 3 h, after which AcOH (12.0 g, 11.45 cm^3, 200 mmol) was added, portionwise, from the dropping funnel, over a 2 h period. After being further stirred for 12 h (overnight) at 20–25 °C, the mixture was worked up as described above to afford the monooxalate salt (7.98 g, 72%).

***N*-Methyl-1,5-diphenylpentan-3-ylamine 3c.** Into a 250 cm^3, single-necked flask, were combined 1,5-diphenylpentan-3-one

Table 2 Spectroscopic data for novel products

Product	^{1}H NMR ($CDCl_3$/TMS) δ(*J* Hz)	Mass spectra mass (% intensities)
3b	0.90 (t, *J* 7.3, CH_3), 1.30–1.37 (m, 4 H), 1.41–1.45 (m, 4 H), 1.49–1.54 (m, 4 H), 1.62–1.64 (m, 2 H), 1.79–1.82 (m, 2 H), 2.55–2.60 (m, 3 H)	169 (M^+, 7)
3c	1.55 (br s, NH), 1.73–1.82 (m, 2 CH_2), 2.41 (s, CH_3), 2.52–2.56 (quint, *J* 7.3, CH), 2.64–2.69 (m, 2 CH_2), 7.19–7.22 (m, 3 ArH), 7.26–7.30 (m, 2 ArH)	253 (M^+, 3)
3f	1.09 (d, *J* 6.0, CH_3), 1.58–1.64 (m, 1 H), 1.73–1.79 (m, 1 H), 2.54–2.60 (m, 2 H), 2.65–2.68 (sext, *J* 6.2, 1 H), 2.77–2.84 (m, 3 H), 2.90–2.94 (m, 1 H), 7.12–7.32 (m, 10 ArH)	253 (M^+, 0.6)
3g	0.97–1.06 (m, 2 H), 1.08 (d, *J* 6.0, CH_3), 1.12–1.15 (m, 2 H), 1.20–1.26 (m, 2 H), 1.58–1.62 (m, 2 H), 1.70–1.76 (m, 4 H), 1.82–1.86 (m, 2 H), 2.47–2.51 (m, CH), 2.59–2.67 (m, CH_2), 2.82 (sext, *J* 6.2, CH), 7.17–7.20 (m, 3 ArH), 7.26–7.29 (m, 2 ArH)	231 (M^+, 6)
3k	0.83 (t, *J* 7.8, CH_3), 0.89 (t, *J* 7.2, CH_3), 1.18–1.22 (m, CH_2), 1.28 (hept, *J* 6.6, CH_2), 1.35–1.40 (m, CH_2), 1.42 (quint, *J* 7.2, CH_2), 2.42 (quint, *J* 6.0, CH), 2.81 (q, *J* 6.8, CH_2), 2.83–2.90 (m, CH_2), 7.21–7.24 (m, 3 ArH), 7.27–7.32 (m, 2 ArH)	219 (M^+, 1)
3l	0.88 (t, *J* 7.4, 2 CH_3), 1.02 (d, *J* 6.4, 2 CH_3), 1.33–1.37 (m, 6 H), 1.45–1.52 (m, 6 H), 2.51–2.56 (m, 2 CH_2), 2.59–2.63 (m, 2 CH)	228 (M^+, 6)
3q	1.16 (d, *J* 6.6, CH_3), 1.51–1.57 (m, 1 H), 2.09–2.15 (m, 1 H), 2.26–2.32 (m, 1 H), 2.37–2.42 (m, 1 H), 2.74–2.79 (m, 1 H), 2.85–2.90 (m, 1 H), 3.12–3.17 (m, 1 H), 3.53 (sext, *J* 6.9, CH), 3.80–3.85 (m, 1 H), 7.20–7.22 (m, 3 ArH), 7.26–7.31 (m, 2 ArH)	203 (M^+, 16)

Table 3 Elemental microanalyses for the new compounds

Compd.	Formula	Found (%)	Calculated[a] (%)
3b	$C_{13}H_{25}NO_4$: *M*, 259.35	C, 59.9; H, 9.75; N, 5.3	C, 60.20; H, 9.72; N, 5.40
3c	$C_{20}H_{25}NO_4$: *M*, 343.43	C, 70.3; H, 7.5; N, 3.8	C, 69.95; H, 7.34; N, 4.08
3f	$C_{20}H_{25}NO_4$: *M*, 343.43	C, 70.2; H, 7.3; N, 4.4	C, 69.95; H, 7.34; N, 4.08
3g	$C_{18}H_{27}NO_4$: *M*, 321.42	C, 66.9; H, 8.3; N, 4.5	C, 67.26; H, 8.47; N, 4.36
3k	$C_{17}H_{27}NO_4$: *M*, 309.41	C, 66.4; H, 8.7; N, 4.6	C, 66.00; H, 8.80; N, 4.52
3l	$C_{18}H_{36}N_2O_8$: *M*, 408.486	C, 52.6; H, 8.7; N, 6.6	C, 52.93; H, 8.88; N, 6.85
3q	$C_{13}H_{17}NO$: *M*, 203.279	C, 76.65; H, 8.7; N, 7.0	C, 76.81; H, 8.43, N, 6.89

[a] All elemental microanalytical data refer to the monooxalate salts, except for the **3l** which is a dioxalate salt and **3q** which is a neutral compound.

(7.15 g, 30 mmol), a solution of $MeNH_2$ in MeOH (5.4 mol dm^{-3}, 44.5 cm^3, 240 mmol), and Mg (3.28 g, 135 mmol). AcOH (14.4 g, 13.75 cm^3, 240 mmol) was added as above, and the flask capped with a mercury-filled bubbler, to reduce escape of $MeNH_2$. The mixture was stirred vigorously, at 20–25 °C, for 12 h. If the reaction was incomplete (TLC), additional Mg (0.73 g, 30 mmol), $MeNH_2$ solution (11.1 cm^3, 60 mmol) and AcOH (3.6 g, 3.4 cm^3, 60 mmol) were added and the stirring continued until completion (3–6 h). Work-up afforded the monooxalate salt (6.72 g, 65%).

1-Methyl-3-phenylpropylamine 3o. In a 250 cm^3, single-necked flask were combined 4-phenylbutan-2-one (7.41 g, 50 mmol), $AcONH_4$ (38.54 g, 500 mmol), Mg (6.08 g, 250 mmol) and 70% aqueous MeOH (100 cm^3). The flask was capped with a mercury-filled bubbler, to reduce escape of NH_3, and the mixture was stirred at 20–25 °C, for 12 h. If the reaction was not complete (TLC), additional AcOH (6.0 g, 5.70 cm^3, 100 mmol) and Mg (2.43 g, 100 mmol) were added and the stirring continued for an additional 12 h. The mixture was poured into water (600 cm^3) to which $NaHCO_3$ (50 g) was then added; the whole was then internally steam distilled until 500 cm^3 of the distillate collected. It was made alkaline (pH > 12) with 50% aq. NaOH, and extracted with CH_2Cl_2 (3 × 50 cm^3). The combined extracts were dried (K_2CO_3), filtered and evaporated on a rotatory evaporator. The residue was dissolved in MeOH (20 cm^3) and added slowly, with stirring, to a solution of anh. oxalic acid (5.40 g, 60 mmol) in MeOH. Complete precipitation was effected by adding Et_2O (50 cm^3) to the mixture and cooling it to −20 °C. The yield of the mixed monooxalate salt was 8.63 g. An analytical sample of the free amine was obtained as for **3a**: purity (GC): 90% of the primary amine and 10% of the secondary amine. The pure primary amine was obtained by vacuum fractional distillation: bp 90–95 °C/10 Torr; yield 3.71 g (50%).

***N*-(Phenethyl)heptan-3-ylamine 3k.** The procedure adopted was the same as that for **3a** except that stoichiometric amounts of the reactants were used: heptan-3-one (50 mmol, 5.71 g, 7.0 cm^3) and phenethylamine (50 mmol, 6.06 g, 6.30 cm^3). After completion of the reduction (6 h), ethyl formate (20 mmol, 1.48 g, 1.62 cm^3) was added to the mixture and heating discontinued. After 1.5 h of stirring, the mixture was worked up as for **3a**; yield of the monooxalate salt: 6.95 g (45%).

***N,N'*-Di(butan-2-yl)hexane-1,6-diamine 3l.** The procedure adopted was the same as that for **3a** with the following reactants: ethyl methyl ketone (10.82 g, 13.4 cm^3, 150 mmol), hexane-1,6-diamine (5.81 g, 50 mmol), Et_3N (30.36 g, 41.8 cm^3, 300 mmol), Mg (10.94 g, 450 mmol), AcOH (24 g, 22.9 cm^3, 400 mmol) followed by portionwise addition of AcOH (24 g, 22.9 cm^3, 400 mmol). The product was precipitated as the dioxalate salt: 15.81 g (77%).

5-Methyl-*N*-(phenethyl)-2-pyrrolidone 3q. The procedure adopted was the same as that for **3a** with the following reactants: methyl levulinate (8.46 g, 8.3 cm^3, 65 mmol) and phenethylamine (6.06 g, 6.3 cm^3, 50 mmol). In the work-up, the ether extract was washed with 5% aqueous oxalic acid to remove basic components, dried ($MgSO_4$), and evaporated. Vacuum distillation gave a pale yellow oil, bp 130–135 °C/0.1 Torr; yield 7.95 g (78%).

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