Borane–Methyl Sulfide Reductive Cyclization of ω-Ester Alkylamides: A Convenient Synthesis of *N*-Substituted Cyclic Amines[1]

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Borane–methyl sulfide (BMS) reduction of variously *N*-substituted succinamic and glutaramic esters affords the corresponding *N*-substituted pyrrolidines and piperidines in high yields. The limitations, mainly caused by steric hinderance around the amine nitrogen, and putative intermediates involved in this conversion, as detected by incomplete reaction and/or synthesis followed by BMS reduction, indicate that cyclization and amide reduction successfully compete with ester reduction to afford the *N*-substituted cyclized amines.

The preparation of *N*-substituted cyclic amines, specifically pyrrolidines and piperidines, is usually achieved by the use of cyclization reactions. These transformations are sometimes of limited application, however, owing to difficultly accessible synthetic precursors or the drastic reaction conditions required.[4–7] More convenient are procedures, which utilize the reduction of cyclic lactams and imides to the corresponding amines, since the starting materials for these transformations are more readily available.[8,9] Such reactions have, however, sometimes required lithium aluminum hydride or the like to effect the reduction.[10] The synthesis of the required succinimide can also pose potential problems in cases where the amines are not readily available. Herein, we describe a simple conversion of acyclic precursors, i.e., *N*-substituted succinamic and glutaramic esters, to the corresponding *N*-substituted pyrrolidines and piperidines, respectively, by borane–methyl sulfide (BMS)-mediated reductive cyclization. This procedure bears some resemblance to the recently reported tandem reductive amination-cyclization route to pyrrolidines, but avoids the use of both potassium tetracarbonylhydridioferrate and the easily polymerized succinaldehyde.[11]

Treatment of amines **1a–i** with the commercially available acid chloride esters **2a–c** in ether in the presence of *N,N*-dimethylaniline as base afforded the required amide esters **3a–i** in yields of 64–94% (Table 1). Reductive cyclization of **3** with 2.5 equivalents of borane-methyl sulfide complex[12] in tetrahydrofuran produced the desired *N*-substituted pyrrolidines **4a–c, e, f, h** and **i** in moderate yields (Table 2). Only the

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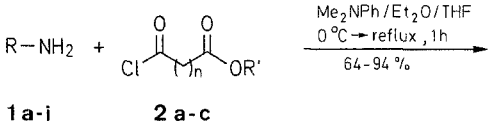
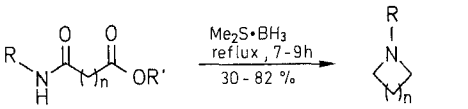
sterically hindered 2,4,6-trimethylphenyl and *tert*-butyl derivatives **3d** and **3g** failed to afford cyclized products, giving instead mixtures of the corresponding amino alcohols **5d, g** and esters **6d, g**. *N*-tert-Butylpyrrolidine has, however, been previously prepared by the lithium aluminum hydride reduction of the corresponding succinimide.[10] A somewhat lower yield of piperidine **4i** was obtained in the transformation of glutaramic ester **3i**, but even this result indicates that the method is likely amenable to generalization to the homologous series of piperidines.



1a-i **2a-c**



3a-i **4a-c,e,f,h,i**

1,3,4	R	R'	n	2	R'	n
a	Ph	Me	2	**a**	Me	2
b	4-$O_2NC_6H_4$	Me	2	**b**	Et	2
c	4-$MeOC_6H_4$	Me	2	**c**	Me	3
d	2,4,6-$Me_3C_6H_2$	Me	2			
e	4-pyridyl	Me	2			
f	2-pyridyl	Et	2			
g	*t*-Bu	Me	2			
h	*n*-C_7H_{15}	Me	2			
i	4-$O_2NC_6H_5$	Me	3			

Table 1. *N*-Substituted Amide Esters **3** Prepared

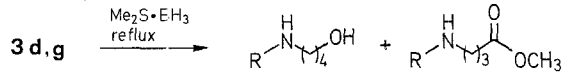
Product	Yield[a] (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr) ν (cm^{-1}) (COOR', CONHR)
3a	76	94–95	97–99[13]	1726, 1705, 1618
3b	73	185–187	$C_{11}H_{12}N_2O_5$ (252.2)	1701, 1619, 1602
3c	64	104–105	$C_{12}H_{15}NO_4$ (237.2)	1730, 1678, 1610
3d	94	132–133	$C_{14}H_{19}NO_3$ (249.3)	1742, 1655, 1612
3e	90[c]	234–236	$C_{10}H_{13}ClN_2O_3$ (244.7)	1726, 1704, 1645, 1612
3f	85[c]	156–158	$C_{11}H_{15}ClN_2O_3 \cdot 0.5H_2O$ (258.7)	1732, 1701, 1641, 1608
3g	70	76–78	$C_9H_{17}NO_3$ (187.2)	1732, 1655, 1635
3h	82	35–38	$C_{12}H_{23}NO_3$ (229.3)	1742, 1680, 1655
3i	85	148–150	$C_{12}H_{14}N_2O_5$ (266.2)	1702, 1605, 1590

[a] Yield of isolated product **3** based on **1**.
[b] Satisfactory microanalyses obtained: C ±0.13, H ±0.14, N ±0.26.
[c] Isolated as hydrochloride salt; see Experimental Section.

Table 2. *N*-Substituted Pyrrolidines **4a–h** and Piperidine **4i** Prepared

Product	Yield[a,b] (%)	mp (°C) or bp (°C)/mbar	Molecular Formula[c] and/or Lit. Data
4a	82	bp 60–65/0.3[d]	$C_{10}H_{13}N$ (147.2) bp 110–116/12[14]
4b	75	mp 163–165	$C_{10}H_{12}N_2O_2$ (192.2) mp 170[14]
4c	68	mp 46–47 bp 120–130/16[d]	$C_{11}H_{15}NO$ (177.3) mp 55–57[14]
4d	0[e]	–	–
4e	58	mp 55–57	mp 57[15]
4f	47	bp 130–140/0.5	bp 252/1 atm[14]
4g	0[e]	–	–
4h	30	oil	$C_{11}H_{23}N \cdot 0.75H_2O$ (182.8)[f]
4i	46	mp 103–104	mp 102[14]

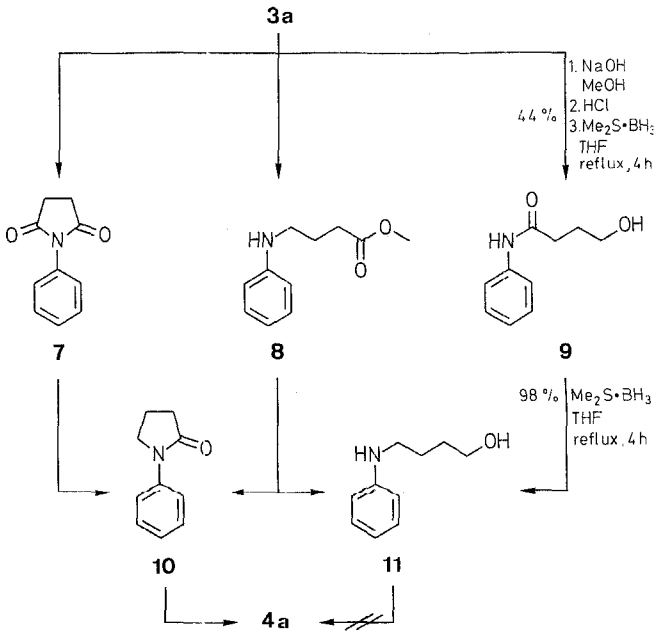
[a] Yield of isolated product **4** based on **3**.
[b] Isolated by silica gel column chromatography (CH_2Cl_2 as eluent) unless otherwise noted.
[c] Satisfactory microanalyses were obtained for the new compound **4h** and for those compounds whose mp or bp data differed from literature values: C ±0.24, H ±0.28, N ±0.05.
[d] Kugelrohr distillation.
[e] Desired product not isolated; see Experimental Section.
[f] ^{1}H-NMR data for **4h** reported in Experimental Section.



5d,g **6d,g**

5,6	R
d	2,4,6-$Me_3C_6H_2$
g	*t*-Bu

In order to determine the order of reactions involved in this multistep transformation, a number of putative intermediates in the reaction sequence were subjected to the BMS-induced reductive cyclization conditions. Of these compounds **7–11**, only **9** and **11** could not be transformed into the corresponding



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pyrrolidine **4a**. Premature quenching or use of insufficient BMS in the reductive cyclization of **3a** also demonstrated that all of **7–11** *except* **9** were present in the mixture obtained from incomplete reaction. The results of these experiments suggest that reduction of the amide group, and/or cyclization to the succinimide **7** effectively compete with reduction of the ester group, and that any diminution in overall yield likely results from the untoward reduction of **8** to the amino alcohol **11**, incapable of cyclization to **4a**.

In conclusion, the method described herein for the preparation of *N*-substituted cyclic amines from readily available synthetic precursors and reagents provides a convenient method for the synthesis of a range of pyrrolidine and piperidine derivatives. In particular, the use of BMS, a reagent of documented selectivity,[12] as the reducing agent for this reductive cyclization allows the reaction to be carried out in the presence of aromatic halo and nitro substituents, providing a useful alternative to procedures requiring preformed succinimides and less selective reducing agents,[10] thus greatly extending the scope of this procedure.

Melting points were obtained on a Thomas-Hoover melting point apparatus, and are uncorrected. ^{1}H-NMR spectra were obtained on either an EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instrument as solutions in $CDCl_3$ using TMS as internal standard. Infrared spectra were recorded as KBr pellets with a Perkin-Elmer 237 grating spectrophotometer. Mass spectra were determined on an Atlas CH-7 instrument. Elemental analyses were performed by either Atlantic Microlabs, Atlanta, GA, or by the Analytical and Environmental Research Department, Syntex Research, on samples dried 24 h at ambient temperature and high vacuum. Column chromatography at ambient pressure was carried out using Silica gel 60A (70–230 mesh) obtained from American Scientific Products. TLC was routinely used to monitor reactions, and was carried out using Analtech 250 micron silica gel plates. Amines **1a–i**, acid chlorides **2a–c**, 1-phenyl-2-pyrrolidinone **(10)**, *N,N*-dimethylaniline and borane–methyl sulfide complex (10 M in THF) were purchased from Aldrich Chemical Co., Milwaukee, WI; *N*-phenylsuccinimide **(7)** was purchased from Pfaltz and Bauer, Inc., Waterbury, CT and were used as received. Methyl 4-(phenylamino)butyrate **(8)** was prepared by literature procedure.[16] THF for acylation and BMS reduction reactions was freshly distilled from sodium-benzophenone ketyl immediately prior to use. All organic extracts were dried over Na_2SO_4 prior to evaporation.

N-Substituted Succinamic and Glutaramic Esters 3; General Procedure:
A solution of **1** (0.2 mol) and *N,N*-dimethylaniline (25.3 mL, 0.2 mol) in ether (250 mL) is cooled to 0–5 °C, and then treated with a solution of **2** (0.22 mol) in THF (50 mL) dropwise over 30 min. When the addition is complete, the cooling is removed, and the resulting mixture is brought to reflux for 1 h to complete the reaction. The solvent is removed by evaporation, and the residue is suspended in water. The resulting precipitate is collected by filtration and washed with water, 2 N H_2SO_4 sat. aq. $NaHCO_3$ (200 ml each), and finally with water until the washings were neutral. The crude product is recrystallized from aqueous acetone and dried at 80 °C *in vacuo* to afford **3** (Table 1).

For amides **3e, f**, the addition of *N,N*-dimethylaniline is eliminated, and the products are isolated by filtration, washing with anhydrous ether, and drying of the precipitate formed in the reaction, to give the hydrochloride salts of **3e, f**.

Borane–Methyl Sulfide Reductive Cyclization of 3 to 4; General Procedure:
A solution of **3** (20 mmol) in THF (50 mL) in a 100 mL round-bottomed flack equipped with a side-arm septum inlet and reflux condenser under a blanket of nitrogen is treated dropwise via syringe with a 10 M THF solution of borane–methyl sulfide complex (5.0 mL, 50 mmol). The mixture is then brought to reflux for 7–9 h, after which it is cooled, and treated with CH_3OH or 2 N NaOH to quench the remaining BMS. The solvent is evaporated, and the residue is purified by either silica gel chromatography with CH_2Cl_2 as eluent, or by Kugelrohr distillation, as noted in Table 2.

Physical and analytical data for **4a–i** prepared by this method are reported in Table 2. All compounds have been previously reported, with the exception of **4h**, for which the following additional spectral data are reported:

4h:

IR: ν = 2900 (CH); 1450 cm^{-1}.

^{1}H-NMR: δ = 0.85 (t, 3 H, J = 7.0 Hz, CH_3); 1.20 (br s, 6 H, $3CH_2$); 1.50–2.25 (m, 8 H, $4CH_2$); 2.50–3.25 (m, 6 H, CH_2N).

Attempted reductive cyclization of amide **3d**, followed by work-up as described, affords only amino alcohol **5d** and amino ester **6d**, isolated column chromatography on silica gel with CH_2Cl_2 as eluent:

5d; yield: 1.05 g (45%); bp 120 °C/13 mbar (Kugelrohr distillation).

$C_{13}H_{21}NO$	calc.	C 75.32	H 10.21	N 6.76
(207.3)	found	75.04	10.00	6.57

IR: ν = 3350 (OH + NH); 1585 cm^{-1}.

^{1}H-NMR: δ = 1.70 (m, 4 H, CH_2CH_2); 2.20 (s, 3 H, *p*-CH_3); 2.25 (s, 6 H, 2 *m*-CH_3); 2.85 (m, 2 H, CH_2N); 3.05 (s, 2 H, OH + NH); 3.60 (m, 2 H, CH_2O); 6.90 (s, 3 H_{arom}).

MS: m/z = 207 (M^+).

6d; yield: 0.88 g (40%); bp 110 °C/13 mbar (Kugelrohr distillation).

IR: ν = 3380 (NH); 1735 cm^{-1} (CO).

^{1}H-NMR: δ = 1.95 (q, 2 H, J = 6.9 Hz, CCH_2C); 2.20 (s, 9 H, $3CH_3$); 2.50 (t, 2 H, J = 6.8 Hz, CCH_2CO); 2.80 (s, 1 H, NH); 3.00 (t, 2 H, J = 6.9 Hz, CCH_2N); 3.70 (s, 3 H, $COOCH_3$); 6.90 (s, 3 H_{arom}).

Similar results are obtained upon attempted reduction of **3g**, but the product mixture was not further characterized.

4-Hydroxy-*N*-phenylbutyramide (9):

N-Phenylsuccinamic Acid: A solution of **3a** (4.15 g, 20 mmol) and NaOH (1.60 g, 40 mmol) in CH_3OH (35 mL) and water (15 mL) is stirred at room temperature for 1 h. CH_3OH is then removed by evaporation, the solution is diluted with water (35 mL), and extracted with EtOAc (2 × 50 mL). The organic extract is discarded, and the aqueous solution is acidified with 1 M HCl (50 mL) to give a precipitate, which is collected by filtration and dried at 50 °C *in vacuo* to give *N*-phenylsuccinamic acid; yield: 2.3 g (60%); mp 148–149 °C (Lit.[10] mp 147–148 °C).

BMS Reduction of N-Phenylsuccinamic Acid to **9**: A solution of *N*-phenylsuccinamic acid (1.93 g, 10 mmol) in THF (50 mL) is treated dropwise at room temperature with 10 M BMS in THF (1.5 mL, 15 mmol). The mixture is heated to reflux for 4 h, then is cooled and treated with CH_3OH (10 mL). The solvent is evaporated, and the residue is purified by column chromatography on silica gel (5% CH_3OH in CH_2Cl_2 as eluent) to afford **9**, which solidifies *in vacuo*; yield: 1.3 g (73%); mp 60–63 °C (Lit.[17] 83–84 °C after crystallization from ether).

$C_{10}H_{13}NO_2$	calc.	C 67.02	H 7.31	N 7.82
(179.2)	found	66.89	7.32	7.77

IR: ν = 3300 (OH); 3250 (NH); 1650, 1605 cm^{-1} (NCO).

^{1}H-NMR: δ = 1.95 (m, 2 H, CCH_2C); 2.45 (t, 2 H, J = 7.0 Hz, CH_2CO); 3.75 (br m, 2 H, CH_2O); 3.95 (br t, 1 H, OH); 6.95–7.60 (m, 5 H_{arom}); 8.70 (br s, 1 H, NH).

4-(Phenylamino)butanol (11):
A solution of **9** (0.82 g, 4.6 mmol) in THF (5 mL) is treated with 10 M BMS in THF (1.15 mL, 11.5 mmol) at room temperature, then is brought to reflux for 4 h. After cooling and quenching with additional CH_3OH (5 mL), TLC (silica gel, 5% CH_3OH in CH_2Cl_2) shows no evidence of formation of **4a**. Evaporation of the solvent and chromatography of the residue over silica gel (0–10% CH_3OH gradient in CH_2Cl_2) affords **11**; yield: 0.74 g (98%); bp 130–140 °C/0.7 mbar (Kugelrohr distillation) Lit.[10] bp 134 °C/0.9 mbar.

$C_{10}H_{15}NO$	calc.	C 72.60	H 9.15	N 8.48
(165.2)	found	72.34	9.27	8.31

IR: ν = 3350 (br, OH, NH); 1602, 1500 cm^{-1} (Ph).

^{1}H-NMR: δ = 1.65 (m, 4 H, CH_2CH_2); 3.10 (m, 2 H, CH_2N); 3.30 (s, 2 H, NH + OH); 3.65 (m, 2 H, CH_2O); 6.65–7.30 (m, 5 H_{arom}).

Reductive Cyclization of Putative Reaction Intermediates:
Borane–methyl sulfide reduction of *N*-phenylsuccinimide **(7)**, methyl 4-(phenylamino)butyrate **(8)** or 1-phenyl-2-pyrrolidone **(10)** according to

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the above procedure affords **4a** *in 67–89% yields, with only traces of* **11** detectable by TLC, as compared with authentic samples prepared above.

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