Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Philippe Renaud & Inès Bétrisey (1995) Radical Reductive Alkylation of Enamines: Conversion of the Products into Alkenes and Primary Amines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:21, 3479-3491, DOI: 10.1080/00397919508013872

To link to this article: http://dx.doi.org/10.1080/00397919508013872

SYNTHETIC COMMUNICATIONS, 25(21), 3479-3491 (1995)

RADICAL REDUCTIVE ALKYLATION OF ENAMINES: CONVERSION OF THE PRODUCTS INTO ALKENES AND PRIMARY AMINES.

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Abstract. Procedures for the conversion of tertiary amines, obtained by radical reductive alkylation of enamines, into alkenes (Cope reaction) and primary amines (double β-elimination reaction) are presented.

Recently, we developed a radical mediated reductive alkylation of enamines **1** which gives tertiary amines **2** in good yields and high stereoselectivities for cyclic and acyclic systems (FIG. 1).[1-4] For instance, the alkylation of 1-

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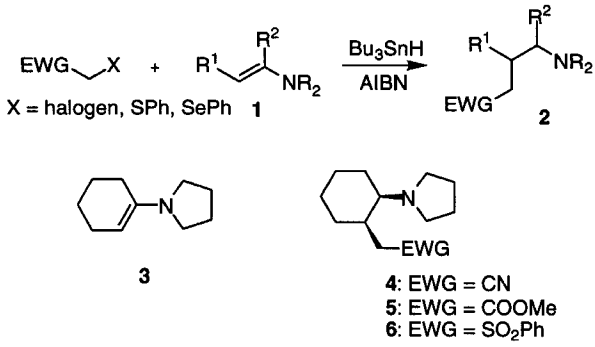

FIG. 1

pyrrolidinocyclohexene **3** gave the *cis* configured amines **4-6** in 57 % to 88 % yield.

The synthetic scope of this method is limited by the fact that only tertiary amines can be prepared. We decided to investigate the conversion of these tertiary amines into olefins via the Cope reaction as well as their dealkylation to primary amines.

The thermal decomposition of tertiary amine oxides to give alkenes (Cope reaction) is an efficient method of olefin preparation.[5] Amines **4-6** are converted into their N-oxides **7-9** by reaction with m-CPBA in nearly quantitative yields. Heating the N-oxides **7-9** at 180 °C/10^{-2} mbar in a kugelrohr allows the isolation of the cyclohexene derivatives **10** and **11** in 43% and 35% yield in a cold trap (FIG. 2). The sulfone **12** is not formed under these conditions. As expected, the elimination was completely regioselective since only one *syn* hydrogen is present as depicted in transition state **13**.

In order to convert amines of type **2** into primary amines, we have investigated amines which can easily be dealkylated. The use of enamines derived from dibenzylamine, which can be dealkylated by hydrogenolysis, is not compatible

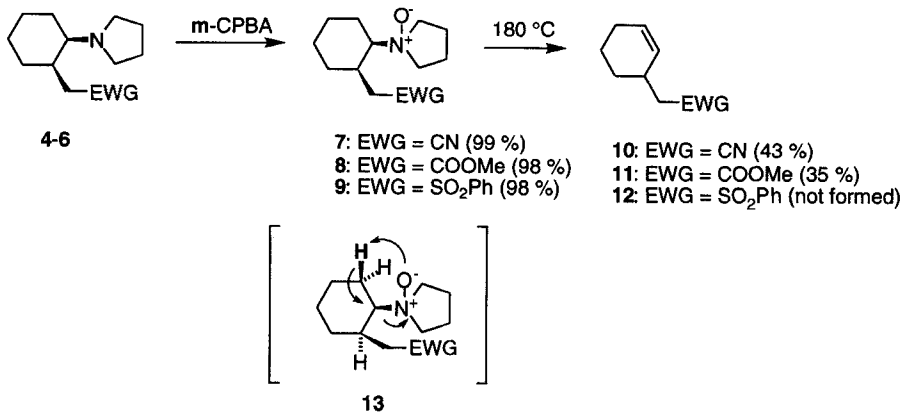

FIG. 2

with the radical reductive alkylation step due to benzylic H-abstraction by the radical intermediates. We thus turned our attention to the β-elimination reaction which represents an attractive dealkylation method. Piperidinone dimethyl or dioxolanyl acetals **14** and **15** are convenient for this purpose.[6] Preparation of enamines **17** and **18** is straightforward using acidic azeotropic water removal.[7] We already reported that enamine **16**, which is prepared from 3-methylbutanal and **15**, is alkylated to **19** in 60% yield with phenylthioacetonitrile (FIG. 3).[4] This reaction demonstrates the high reactivity of the piperidinone acetal enamines toward electrophilic radicals. Indeed, the relatively large isopropyl substituent at the β-position of the enamine was expected to hinder the radical addition. Reductive alkylation of **17** with chloromethyl phenyl sulfone gave **20** which, after hydrolysis with 3 M HCl, yields diastereomerically pure **21**. Interestingly, the alkylation of enamine **18** with chloromethyl phenyl sulfone is diastereoselective and gives **22** as a *u/l* 4.9:1 mixture. The level of stereoselectivity is similar to the one observed for the corresponding morpholino enamine. The relative configuration of the major

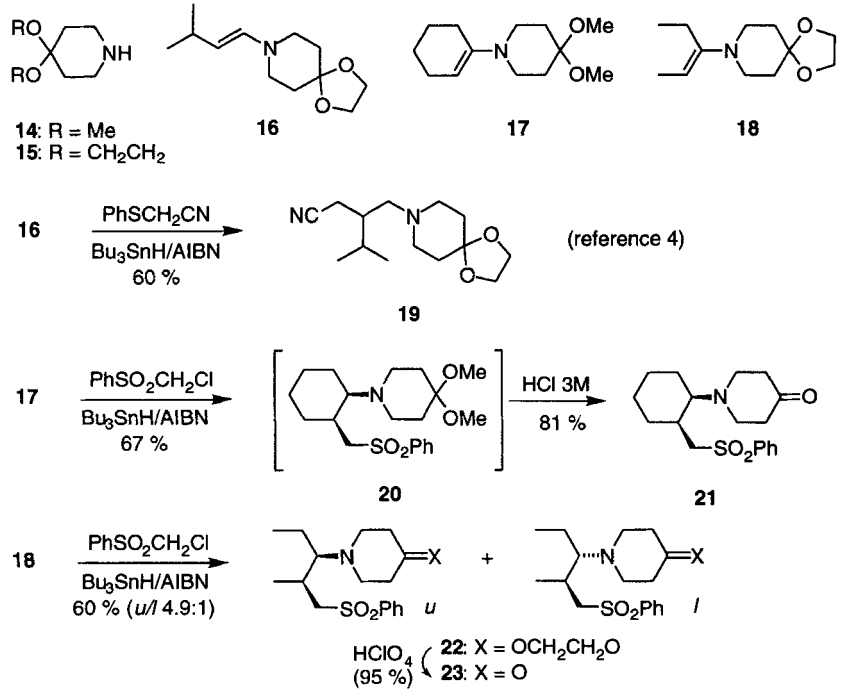

FIG. 3

isomer is attributed by analogy to this case.[4] Hydrolysis of the acetal with $HClO_4$ gives the N-substituted piperidinone **23** (95%) as an unseparable mixture of diastereoisomers.

Double dealkylation of **21** is possible by treating the hydrochloride with an excess of aniline in refluxing EtOH/water (1:1) mixture (FIG. 4).[8] The primary amine is directly converted to the benzamide for characterization purposes. The overall yield, 46%, was not satisfactory so we tested several other primary amines to carry out the dealkylation step. 2-Butylamine gives the best results in terms of conversion, yields and ease of purification of the deprotected amine. The

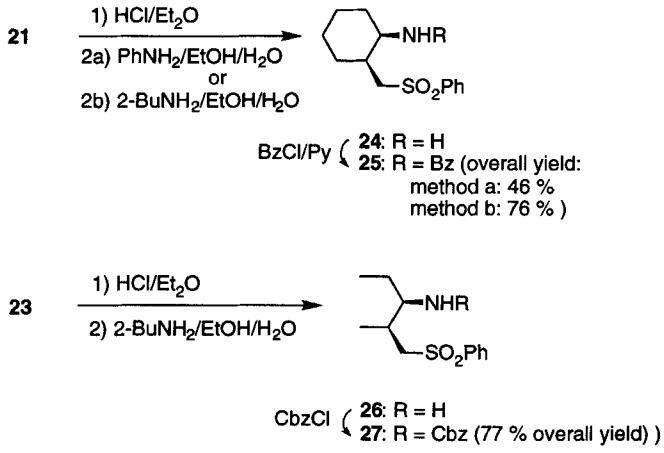

FIG. 4

deprotection step is an equilibrium reaction so that both N-phenyl-4-piperidinone and N-(but-2-yl)-4-piperidinone are formed during the reaction. Similarly, **23** is converted via **26** to the diastereomerically pure benzyloxycarbonyl (Cbz) protected primary amine **27** in 77% yield.

In conclusion, we have demonstrated that the products obtained by radical reductive alkylation of enamines can be used for the preparation of alkenes and primary amines in modest to good yields. Interestingly, the high degree of stereoselectivity of the reductive alkylation is either preserved (dealkylation process) or translated into a high regioselectivity (alkene formation).

Experimental

General. THF was freshly distilled from K under N_2. DME was distilled from Na/benzophenone. CH_2Cl_2 was distilled from P_2O_5. Benzene was distilled from

CaH_2 under N_2. For flash column chromatography (FC) and filtration, *Merck silical gel 60* (70-230 mesh) was used with ethyl acetate (AcOEt) and petroleum ether (PE) as solvent for elution. TLC were run on *Merck silical gel 60 F_{254}* analytical plates; detection either with UV, iodine or by spraying with a soln. of 25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2.4H_2O$, 60 mL conc. H_2SO_4 and 940 mL water with subsequent heating. Melting points (not corrected) were determined by using a *Büchi Totolli* apparatus. Bulb to bulb distillations were carried out using a *Büchi GKR-50* apparatus; boiling points refer to air bath temperature. The following apparatus were used: NMR: *Bruker AC-250 FT* (^1H/250 MHz, ^{13}C/62.9 MHz), unless otherwise indicated, spectra were recorded in $CDCl_3$ and chemical shifts are given in ppm with TMS signal at 0 ppm. IR: *Perkin-Elmer 297* spectrophotometer. MS: *Finnigan 1020* and *Nermag R10-10C* (CI: chemical ionisation with NH_3; EI: electronic ionization 70 eV). Elemental analysis: *Ilse Beetz, Mikroanalytisches Laboratorium, D-8640 Kronach, Germany.* Irradiations were conducted using a sunlamp *Osram Ultra-Vitalux 300 W.* Compounds **4-6** have been prepared according to literature procedure.[4] Chloromethyl phenyl sulfone, 4,4-dihydroxypiperidine hydrochloride and 1,4-dioxa-8-azaspiro[4.5]decan (**15**) are commercially available (Fluka).

Preparation of amine oxides:

A solution of *m*-CPBA (55 %, 7 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C to a solution of the tertiary amine (5 mmol) in CH_2Cl_2 (20 mL). After 3 h at rt, KF (0.5 g, 8.6 mmol) was added and the solution was stirred overnight. The solid was eliminated by centrifugation and the solvent was evaporated. The crude amine oxides were filtered through aluminum oxide (basic) with $CHCl_3$ as eluent and used without further purification for the pyrolysis. **7**: 1.61 g (99 %) as a white solid was obtained from **4** (1.50 g, 7.8 mmol) and *m*-CPBA (1.90 g, 10.9 mmol).

8: 2.10 g (98 %) as an orange oil was obtained from **5** (2.0 g, 8.3 mmol) and *m*-CPBA (2.0 g, 11.6 mmol). **9**: 1.0 g (98 %) as an orange oil was obtained from **6** (0.98 g, 3.2 mmol) and *m*-CPBA (0.66 g, 3.8 mmol).

General procedure 1: pyrolysis of amine oxide:

The amine oxide (2 mmol) was heated in a Kugelrohr oven at 180 °C/10^{-2} mbar for 30 min and the pyrolysis products were recuperated in a cold trap (-80 °C) and purified by FC.

(Cyclohex-2-en-1-yl)acetonitrile (10):

From **7** (0.47 g, 2.2 mmol) according to general procedure 1. FC of the crude material (AcOEt/OPE 1:10) gave **10** (118 mg, 43 %) as a colorless liquid. ^{1}H-NMR: 1.30-1.50 (m, 1 H); 1.50-1.65 (m, 1 H); 1.65-1.82 (m, 1 H); 1.85-2.08 (m, 3 H); 2.28 (A part of an ABX system, J_{AB} = 17.0, J_{AX} = 7.5, C<u>H</u>HCN); 2.35 (B part of an AB system, J_{AB} = 17.0, J_{BX} = 6.0, CH<u>H</u>CN); 2.40-2.55 (m, C<u>H</u>CH_2CN); 5.5 (dm, J = 10.0, 2.5, C=C<u>H</u>$CHCH_2$CN); 5.82 (dq, J = 10.0, 2.5, CH_2C<u>H</u>=C). ^{13}C-NMR: 20.53 (t), 23.61 (t), 24.60 (t), 28.30 (t); 32.18 (d), 118.67 (s), 127.62 (d), 130.02 (d). IR (film): 3020, 2940, 2250, 1450, 1425, 725. MS (EI): m/z (%): 121 (5, M^+), 111 (4), 81 (100), 80 (48), 66 (14), 57 (13), 53 (18). Anal. calc. for $C_8H_{11}N$ (121.18): C 79.29, H 9.15, N 11.56; found: C 78.99, H 9.23, N 11.22.

Methyl (cyclohex-2-en-1-yl)acetate (11):

From **8** (560 mg, 2.3 mmol) according to general procedure 1. FC of the crude material gave **11** (116 mg, 35 %) as a colorless liquid. ^{1}H-NMR: 1.18-1.36 (m, 1 H); 1.45-1.90 (m, 4 H); 2.00 (m, 2 H); 2.24 (A part of an ABX system, J_{AB} = 16.0, J_{AX} = 8.5, C<u>H</u>HCOOMe); 2.32 (B part of an AB system, J_{AB} = 16.0, J_{BX} = 7.5, CH<u>H</u>COOMe); 2.59 (m, 1 H, C<u>H</u>CH_2COOMe); 3.59 (s, COOMe); 5.03 (dm,

J = 10.0, C=C<u>H</u>CH); 5.21 (dq, J = 10.0, 2.5, $CH_2C\underline{H}$=C). ^{13}C-NMR: 20.91 (t), 24.95 (t), 28.74 (t), 32.18 (d), 40.53 (t), 51.42 (q), 128.13 (d), 130.01 (d), 173.23 (s). Anal. calc. for $C_9H_{14}O_2$ (121.18): C 70.10, H 9.15; found: C 70.02, H 9.08.

4,4-Dimethoxypiperidine (14):

A solution of 4,4-dihydroxypiperidine hydrochloride (2.0 g, 13 mmol) and *p*-TsOH (35 mg) in MeOH (15 mL) was heated under reflux for 4 h. After evaporation of the solvent, the residue was treated with a 1M NaOH aqu. solution (30 mL) and extracted continuously for 4 days with ether. Drying of the organic phase ($MgSO_4$), evaporation of the solvent and distillation gave **14** as a colorless liquid. B.p. 45 °C/0.1 mbar. ^{1}H-NMR: 1.4 (br., NH); 2.50-2.78 (m, $C\underline{H}_2CH_2N$); 2.60-2.95 (m, $C\underline{H}_2N$); 3.15 (s, MeO). ^{13}C-NMR: 33.51 (t), 43.00 (t) 46.80 (q), 98.23 (s). IR ($CHCl_3$): 3665, 2960, 2818, 1470, 1425, 1260, 1145, 1100, 1051. MS (EI): m/z (%): 145 (1, M^+), 130 (1), 113 (38), 98 (50), 89 (57), 85 (33), 82 (100).

1-(4,4-Dimethoxypiperidino)-1-cyclohexene (17):

A solution of **14** (0.73 g, 5.0 mmol), cyclohexanone (0.99 g, 10 mmol) and *p*-TsOH (20 mg) in benzene (10 mL) was heated under reflux (Dean-Stark) until no more H_2O was produced (12 h). The solvent was evaporated and distillation of the residue gave **17** (1.05 g, 89 %) as a colorless liquid. B.p. 125 °C/0.1 mbar. ^{1}H-NMR: 1.40-1.85 (m, 8H); 1.72 (m, 4 H, $C\underline{H}_2CH_2N$); 2.0 (m, $C\underline{H}_2C$=CH$C\underline{H}_2$); 2.77 (m, 4 H, CH_2N); 3.12 (s, MeO); 4.62 (t, J = 2.5, C=CH). ^{13}C-NMR: 22.66 (t), 23.28 (t), 24.45 (t), 27.47 (t), 31.95 (t), 44.80 (t), 47.27 (q), 98.44 (s), 100.49 (d), 144.89 (s). Anal. calc. for $C_{13}H_{23}O_2N$ (225.33): C 69.29, H 10.29, N 6.22; found: C 69.32, H 10.26, N 6.08.

(E)-3-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)pent-2-ene (18):

A solution of **15** (1.43 g, 10 mmol), pentan-3-one (0.86 g, 10 mmol) and *p*-TsOH (20 mg) in benzene (10 mL) was heated under reflux (Dean-Stark) until no more H_2O was produced (12 h). The solvent was evaporated and distillation of the residue gave **18** (1.60 g, 76 %) as a colorless liquid. B.p. 120 °C/0.1 mbar. ^{1}H-NMR: 0.92 (t, J = 7.5, $C\underline{H}_3CH_2$); 1.51 (d, J = 7.0, $C\underline{H}_3CH$=C); 1.63 (m, $CH_2\underline{CH}_2N$); 2.10 (q, J = 7.5, $CH_3C\underline{H}_2$); 2.79 (m, CH_2N); 3.88 (s, CH_2O); 4.37 (q, J = 7.0, C=CH). ^{13}C-NMR: 12.42 (q), 12.88 (q); 21.60 (t); 34.62 (t), 46.59 (t), 63.96 (t), 97.99 (d), 107.19 (s), 149.95 (s). Compound **18** was not stable enough to be submitted for elemental analysis.

cis-4-Oxo-1-{2-[(phenylsulfonyl)methyl]cyclohexyl}piperidine (21):

To a refluxing solution of **17** (1.10 g, 5.0 mmol) and chloromethyl phenyl sulfone (1.9 g, 10 mmol) in benzene was added over 6 h a solution of Bu_3SnH (3.6 g, 12 mmol) and AIBN (60 mg) in benzene (15 mL). The reaction mixture was heated for 2 h under reflux, cooled and poured into Et_2O (50 mL). The organic phase was extracted with 1M HCl (2 x 20 mL). The aqueous phase was washed with Et_2O (2 x 20 mL), neutralized with 3M NaOH and extracted with CH_2Cl_2 (3 x 30 mL). Drying ($MgSO_4$) and evaporation of the solvent gave the crude **20** (1.3 g) which was dissolved in 3M HCl and stirred for 12 h at rt. The reaction mixture was neutralized with 3M NaOH and extracted with Et_2O (3 x 30 mL). Drying ($MgSO_4$) and evaporation of the solvent gave a yellow solid. Recrystallization from Et_2O/PE gave **21** (0.91, 55 %) as white crystals. M.p. 92.5-94 °C. ^{1}H-NMR: 0.78-0.95 (m, 1 H); 1.05-1.50 (m, 4 H); 1.70 (m, 2 H); 1.95 (dm, J = 12, 1 H); 2.20 (m, 5 H, CHN, CH_2C=O); 2.60 (m, 5 H, $C\underline{H}CH_2SO_2$, CH_2N); 3.08 (dd, J = 14.0, 10.0, $C\underline{H}HSO_2$); 3.60 (d, J = 14.0, $CH\underline{H}SO_2$); 7.45-7.64 (m, 3 arom. H); 7.88 (m, 2 arom. H). ^{13}C-NMR: 19.15 (t), 24.81 (t), 25.21 (t), 27.48 (t), 30.63 (d), 40.93 (t), 49.24 (t), 52.74 (t), 62.53 (d), 127.66 (d), 129.11 (d), 133.40 (d),

139.77 (s), 209.24 (s). IR (KBr): 3060, 2930, 1720, 1410, 1300, 1290, 1230, 1150, 1090, 750, 720, 695. MS (EI): m/z (%): 194 (19), 112 (5), 97 (5), 95 (16), 82 (14), 77 (100), 70 (8), 68 (16), 55 (27), 51 (31). Anal. calc. for $C_{18}H_{25}NO_3S$ (335.47): C 64.45, H 7.51, N 4.18, S 9.56; found: C 64.52, H 7.65, N 4.16, S 9.57.

4-Oxo-1-{2-[(phenylsulfonyl)methyl]pent-3-yl}piperidine (23):

To a refluxing solution of **18** (1.05 g, 5.0 mmol) and chloromethyl phenyl sulfone (1.9 g, 10 mmol) in benzene was added over 6 h a solution of Bu_3SnH (3.6 g, 12 mmol) and AIBN (60 mg) in benzene (15 mL). The reaction mixture was heated for 2 h under reflux, cooled and poured into Et_2O (50 mL). The organic phase was extracted with 1M HCl (2 x 20 mL). The aqueous phase was washed with Et_2O (2 x 20 mL), neutralized with 3M NaOH and extracted with CH_2Cl_2 (3 x 30 mL). Drying ($MgSO_4$), evaporation of the solvent and filtration through silicagel (AcOEt/PE 1:2) of the residue gave **22** (1.11 g, 60 %) as an unseparable *u/l* 4.9:1 mixture of diastereoisomers. ^{1}H-NMR: isomer *u*: 0.97 (d, J = 7.5, $C\underline{H}_3CH$); isomer *l*: 1.09 (d, J = 7.5, $C\underline{H}_3CH$). A solution of 3.5 M perchloric acid (10 mL) was added to **22** (1.0 g, 2.7 mmol) and the mixture was stirred for 12 h, poured into H_2O (20 mL), neutralized with 3M NaOH and extracted with Et_2O (3 x 20 mL). Drying ($MgSO_4$) of the organic phase, evaporation of the solvent and FC (AcOEt/PE 1:1) of the residue gave **23** (0.81 g, 92 %) as an unseparable *u/l* 4.9:1 mixture of diastereoisomers. Colorless oil. ^{1}H-NMR (isomer *u*): 0.85 (t, J = 7.0, CH_3CH_2); 0.98 (d, J = 7.0, CH_3CH); 1.25-1.55 (m, 2 H); 2.25 (m, 5 H); 2.52 (m, 1 H); 2.60-3.0 (m, 5 H, $C\underline{H}HSO_2$, CH_2N); 3.42 (dd, J = 14.0, 5.0, $CH\underline{H}SO_2$); 7.45-7.65 (m, 3 arom. H); 7.86 (m, 2 arom. H). ^{13}C-NMR (isomer *u*): 12.45 (q); 16.01 (q), 19.89 (t), 31.10 (d), 42.12 (t), 50.27 (t), 60.00 (t), 67.54 (d), 127.53 (d), 129.11 (d), 133.43 (d), 139.82 (s), 209.06 (s). IR (film):

2940, 2800, 1710, 1445, 1300, 1215, 1150, 1090, 750. Anal. calc for $C_{17}H_{25}NO_3S$ (323.45): C 63.13, H 7.79, N 4.33; found: C 62.18, H 7.60, N 4.36.

General procedure 2: amine dealkylation:

With aniline: HCl gas was bubbled through a solution of the amine (3 mmol) in 50 mL dry Et_2O. The white precipitate of amine hydrochloride was isolated in quantitative yield after washing with Et_2O and drying under vacuum. A solution of the hydrochloride (3 mmol) and aniline (1.40 g, 15 mmol) in CH_3CN (30 mL) was heated under reflux for 24 h. The solvent was evaporated under vacuum, the residue was treated with 1M NaOH (30 mL) and the solution was extracted with Et_2O (3 x 20 mL). Drying (MgSO4) and evaporation of the solvent gave the crude primary amine which was purified by FC.

With 2-butylamine: the same prodedure as above was used excepted that 2-butylamine (1.10 g, 15 mmol) was used instead of aniline. The N-(2-butyl)piperidinone which was formed was eliminated by distillation in a Kugelrohr (100 °C/0.01 mbar) before FC.

cis-N-benzyl-2-[(phenylsulfonyl)methyl]cyclohexylamine (25):

From **21** (1.62 g, 4.2 mmol) according to general procedure 2 with aniline. FC of the residue gave the primary amine **24** (0.62 g, 56 %) as a yellow oil. Similar reaction conducted with 2-butylamine gave **24** (0.90 g, 84 %). For characterization purposes, **24** was benzoylated: a solution of benzoyl chloride (0.5 mL, 4.3 mmol) in benzene (10 mL) was added to a solution of **24** (0.5 g, 2.0 mmol) in pyridine (5 mL). The reaction mixture was heated for 30 min under reflux and poured into 100 mL water. Extraction with CH_2Cl_2 (3 x 20 mL), washing with 5 % H_2SO_4 and water gave, after drying ($MgSO_4$) and evaporation of the solvent, crude **25**. Recrystallization from CH_2Cl_2/AcOEt) gave pure **25** (0.66 g, 92 %) as a white

solid. M.p. 164-165 °C. ^{1}H-NMR: 1.35-2.10 (m, 8 H); 2.50 (m, C<u>H</u>CH$_2$SO$_2$); 3.0 (dd, J = 14.5, 8.0, C<u>H</u>HSO$_2$); 3.38 (dd, J = 14.5, 3.5, CH<u>H</u>SO$_2$); 4.22 (m, CHN); 6.71 (d, J = 8.0, NH); 7.30-8.00 (m, 10 arom. H). ^{13}C-NMR: 22.11 (t), 23.01 (t), 28.77 (t), 29.65 (t), 34.59 (d), 49.39 (d), 57.99 (t), 126.96 (d), 127.87 (d), 128.57 (d), 129.37 (d), 131.60 (d), 133.78 (d), 134.34 (s), 139.34 (s), 167.09 (s). IR (KBr): 3310, 3070, 2940, 2880, 1630, 1535, 1305, 1150, 1090, 820, 755, 690, 610. MS (EI): m/z (%): 357 (0.7, M$^+$), 216 (15), 202 (1), 122 (6), 105 (100), 77 (51), 51 (8). Anal calc. for $C_{20}H_{23}NO_3S$ (357.47): C 67.20, H 6.49, N 3.92, S 8.97; found: C 67.04, H 6.35, N 3.96, S 8.58.

N-Benzyloxycarbonyl-2-[(phenylsulfonyl)methyl]pent-3-ylamine (27).

From **23** (1.61 g, 5.0 mmol) according to general procedure 2 with 2-butylamine. FC of the residue gave the primary amine **26** (1.02 g, 85 %) as a yellow oil. For characterization purposes, **26** was N-protected with a benzyloxycarbonyl (Cbz) group: A 2M Na_2CO_3 solution (2 mL) was added to **26** (0.24 g, 1.0 mmol) followed by CbzCl (0.34 g, 2 mmol) and the solution was stirred for 12 h, poured into CH_2Cl_2, washed successively with H_2O, 1M HCl and H_2O before drying ($MgSO_4$) and evaporation of the solvent. Purification by FC gave **27** (0.35 g, 93 %) as a colorless oil (*u/l* 7:1 mixture of diastereoisomers). ^{1}H-NMR (diastereomer *u*): 0.85 (t, J = 7.0, C<u>H</u>$_3$CH$_2$); 1.05 (d, J = 7.0, C<u>H</u>$_3$CH); 1.40 (m, C<u>H</u>$_2$CH$_3$), 2.36 (m, C<u>H</u>CH$_2$SO$_2$); 2.90 (dd, J = 14.0, 8.0, C<u>H</u>HSO2); 3.30 (dd, J = 14.0, 3.0, CH<u>H</u>SO$_2$); 3.54 (m, CHN); 4.80 (d, J = 9.5, NH); 5.00 and 5.06 (AB system, J_{AB} = 13.0, OC<u>H</u>$_2$C$_6$H$_5$); 7.30 (m, 5 arom. H); 7.45-7.70 (m, 3 arom. H); 7.90 (m, 2 arom. H). ^{13}C-NMR (diastereoisomer *u*): 10.75 (q), 14.04 (q), 25.29 (t), 32.14 (d), 56.74 (d), 60.09 (t), 66.62 (t), 127.71 (d), 127.82 (d), 128.02 (d), 128.40 (d), 129.17 (d), 133.51 (d), 136.22 (s), 139.67 (s), 156.37

(s). Anal. calc. for $C_{20}H_{25}NO_4S$ (375.48): C 63.98, H 6.71, N 3.73, S 8.54; found: C 64.60, H 6.78, N 3.71, S 8.42.

We are very grateful to the Swiss National Science Foundation for funding. P.R. thanks the Stiftung für Stipendien auf dem Gebiete der Chemie for the Alfred Werner stipend.

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(Received in The Netherlands 05 April 1995)