Secondary Amines from Trifluoroacetamides

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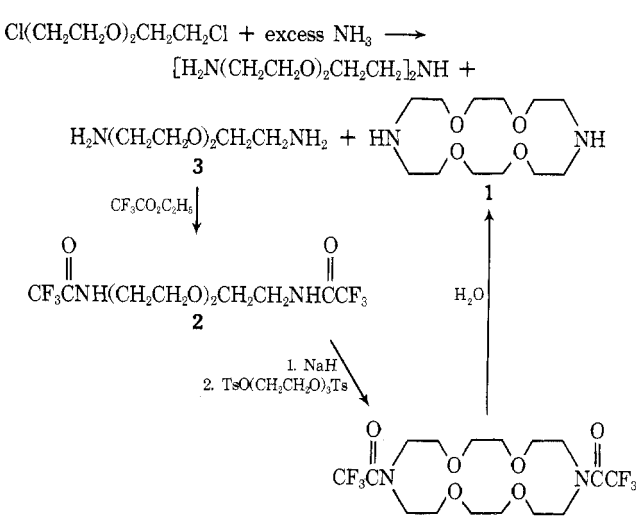
In connection with some studies of routes to bis(secondary amines) containing multiple ether functions, we investigated the alkylation of trifluoroacetamides followed by removal of the trifluoroacetyl group by basic hydrolysis. To the extent that this method is successful, it has the advantages that trifluoroacetamides are in general easily prepared in high yield from an amine and ethyl trifluoroacetate,[1] and that the trifluoroacetyl group is very readily removed after alkylation. This easy hydrolysis is in contrast to the difficulty of hydrolytic removal of arylsulfonyl groups after a synthesis by alkylation of a sulfonamide.[2] Trifluoromethanesulfonamides are similarly resistant to basic cleavage, but they are readily cleaved by hydride reduction.[3]

While our work was in progress, a report by Johnstone, *et al.*,[4] appeared on the alkylation of *N*-alkyl- and *N*-aryltrifluoroacetamides. These workers found that methyl and ethyl groups could be introduced in 80–90% yields by reaction of the trifluoroacetamides in acetone with KOH–alkyl halide. However, yields from *n*-propylation were much lower, even when a reactive propylating agent such as *O*-*n*-propyl methylsulfonate was employed.

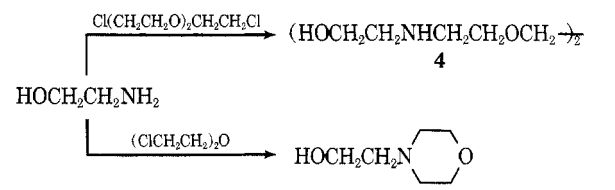
We find that the utility of the method can be extended to higher *n*-alkyl halides by the use of a dipolar aprotic medium. For example, *N*-butyltrifluoroacetamide was converted to *N,N*-dibutyltrifluoroacetamide in 62% yield by treatment of the sodium salt in dimethylformamide solution with *n*-butyl bromide. Basic hydrolysis to di-*n*-butylamine proceeded readily and in high yield.

$$CF_3CON(CH_2)_3CH_3 + Br(CH_2)_3CH_3 \xrightarrow{DMF} CF_3CON(CH_2CH_2CH_2CH_3)_2$$
$$Na^+$$

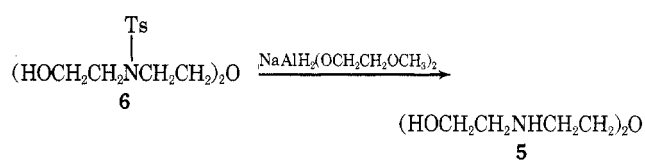
Attempts to adapt this amine synthesis to the case in which cyclic diamine **1** is formed gave at best a 3% yield. One factor responsible for the low yield is probably the reduced ability of nitrogen bearing the negative trifluoroacetyl group to participate in coordination to alkali metal ion, so that no template effect[5] is available to assist ring closure. In any event, reaction of bis(trifluoroacetamide) **2** as the disodium salt with the ditosylate of triethylene glycol in dimethylformamide gave, after basic hydrolysis, 3% of purified diamine **1**, whereas the same reaction with 1,8-dichloro-3,6-dioxaoctane in place of ditosylate gave none of diamine **1**. In contrast, the synthesis employed for the acyclic diamine **3** (given in the Experimental Section) provides **1** directly as a by-product in 4% yield.



The common technique of treating a large excess of primary amine with an alkylating agent to favor formation of secondary amine is effective in the preparation of bis(secondary amine) **4**, but fails in the preparation of **5** because of preferential intramolecular cyclization to *N*-(2-hydroxyethyl)morpholine.[6] Moreover, attempts to alkylate the *N*-trifluoroacetyl derivative of ethanolamine with bis(2-chloroethyl) ether, a relatively unreactive halide, gave none of **5**.



Diamine **5** was finally obtained by alkylation of the *N*-tosyl derivative of ethanolamine with bis(2-chloroethyl) ether to form **6** in 83% yield, followed by reductive removal of tosyl groups[7] to give **5**.



It therefore appears that the synthesis of secondary amines by alkylation of anions derived from trifluoroacetamides is a more generally useful method than previously reported, but that moderately reactive alkylating agents are required, even in aprotic solvents. Side reactions predominated with this method in alkylations involving cyclization to form a large ring or at elevated temperature with an alkylating agent of low reactivity.

Experimental Section[8]

Synthesis of *N*-*n*-Butyltrifluoroacetamide and Conversion to Di-*n*-butylamine. To a cold solution of 71.0 g (0.50 mol) of ethyl trifluoroacetate in 40 ml of anhydrous ether was added dropwise 36.6 g (0.50 mol) of *n*-butylamine. The mixture was stirred for 1 hr, then distilled to give 79.34 g (94%) of *N*-*n*-butyltrifluoroacetamine:[9] bp 50° (1 mm); ir (neat) 3.02 (NH), 3.35, 3.46 (saturated CH), 5.84 (C=O), 6.37 (amide II), 8–9 (CF), 13.9 μ (butyl group); ^{1}H nmr ($CDCl_3$) 7.50 (s, 1, NH), 3.25 (q, 2, NCH_2), 1.9–0.7 ppm (m, 7, $CH_2CH_2CH_3$).

To a suspension of 9.6 g (0.20 mol) of 50% NaH in 100 ml of dimethylformamide was added dropwise a solution of 33.8 g (0.20 mol) of *N*-*n*-butyltrifluoroacetamide in 50 ml of dimethylformamide. After cessation of hydrogen evolution, 27.4 g (0.20 mol) of *n*-butyl bromide was added, resulting in a mildly exothermic reaction. The mixture was stirred overnight, solvent was removed, and the residue was taken up in ether, filtered, and distilled to give 27.82 g (62%) of *N,N*-di-*n*-butyltrifluoroacetamide:[9] bp 44–47° (0.1 mm); ir (neat) 3.37, 3.47 (saturated CH), 5.93 (C=O), 8–9 μ (CF); ^{1}H nmr ($CDCl_3$) 3.7–3.2 (m, 2, NCH_2), 1.9–0.8 ppm (m, 7, $CH_2CH_2CH_3$).

Hydrolysis of *N,N*-di-*n*-butyltrifluoroacetamide to di-*n*-butylamine, bp 36° (15 mm), identified by ir, was accomplished in 95% yield by refluxing for 1 hr with ethanolic sodium hydroxide.

3,6-Dioxaoctane-1,8-diamine (3). Reaction of 524 g (2.80 mol) of 1.8-dichloro-3,6-dioxaoctane in 2.4 l. of absolute ethanol with 2380 g (140 mol) of ammonia was carried out at 125° for 20 hr in a 3-gallon autoclave. After excess ammonia had been vented from

the cooled reaction mixture, the combined liquid and solid was refluxed for 4 hr with 436 g (4.12 mol) of anhydrous sodium carbonate, filtered, and distilled to give three products. Diamine **3**, was an oil; bp 73–79° (0.10 mm); 297 g (71%); ^{1}H nmr ($CDCl_3$) 3.63 (s, 1, OCH_2CH_2O), 3.52 (rough t, J_{HH} = 5 Hz, 1, OCH_2CH_2N), 2.85 (rough t, J_{HH} = Hz, 1, OCH_2CH_2N), and 1.35 ppm (s, 1, NH_2).

Anal. Calcd for $C_6H_{16}N_2O_2$: C, 48.60; H, 10.90; N, 18.90. Found: C, 48.70; H, 10.83; N, 19.06.

A crude sample of **1**, bp 130–170° (~0.5 mm), was recrystallized from ether to give 15.0 g (4%) of pure **1**,[10] mp 112–114°, identified by nmr and mixture melting point with an authentic sample.

A fraction, bp 171–176° (0.2 mm), was 41.7 g (11%) of 3,6,12,15-tetraoxa-9-azaheptadecane-1,17-diamine: ir (neat) 3.00, 3.05, and 6.12 (NH, NH_2), 3.49 (saturated CH), and 9.0 μ (broad COC); ^{1}H nmr ($CDCl_3$) 3.83–3.42 (m, 16, OCH_2), 3.00–2.72 (m, 8, NCH_2), and 1.4 ppm (s, 5, NH_2).

Anal. Calcd for $C_{12}H_{29}N_2O_4$: C, 51.57; H, 10.48; N, 15.04. Found: C, 51.43; H, 10.37; N, 14.80.

1,10-Diaza-4,7,13-16-tetraoxacyclooctadecane (1) from 1,8-Bis(trifluoroacetamido)-3,6-dioxaoctane (2) and 1,8-Ditosyloxy-3,6-dioxaoctane. Addition of 28.8 g (0.60 mol) of diamine **3** to 255.6 g (1.80 mol) of ethyl trifluoroacetate was carried out with external cooling, and the resulting mixture was stirred overnight at 25°. Evaporation of volatiles left 202.4 g (99%) of **2**, mp 42–44°. A sample volatilized onto a cold finger at 120–130° (1 μ) was analyzed.

Anal. Calcd for $C_{10}H_{14}F_6N_2O_4$: C, 35.31; H, 4.16; F, 33.51; N, 8.24. Found: C, 35.49; H, 4.24; F, 33.45; N, 8.23.

A solution of 68.0 g (0.20 mol) of **2** in 200 ml of dry dimethylformamide was added dropwise to a stirred suspension of 19.2 g (0.40 mol) of 50% sodium hydride in 600 ml of dimethylformamide. Then *91.7 g (0.20 mol) of 1,8-ditosyloxy-3,6-dioxaoctane*[11] was added, and the mixture was heated at 100° for 16 hr. After removal of dimethylformamide, the crude product was hydrolyzed by refluxing with aqueous NaOH for 3 hr. Concentration, continuous extraction of the residue with ether, and volatilization of the extracted product at 110° (5 μ) gave 1.48 g (3%) of **1**,[10] identified by analysis and by comparison of the nmr spectrum with that of an authentic sample.

Anal. Calcd for $C_{12}H_{26}N_2O_4$: C, 54.93; H, 10.01; N, 10.68. Found: C, 55.40; H, 10.10; N, 10.40.

6,9-Dioxa-3,12-diazatetradecane-1,14-diol (4). Two kilograms (33 mol) of ethanolamine and 374 g (2.0 mol) of 1,8-dichloro-3,6-dioxaoctane were stirred and heated at 130° for 1 day. The mixture was cooled, 163 g (4.0 mol) of NaOH pellets was added, and the mixture was then heated at 100° with stirring for 30 min. Most of the ethanolamine was then stripped off, 500 ml of tetrahydrofuran was added, and the mixture was filtered. Evaporation of the filtrate to 80° (0.5 mm) gave concentrated product **4** which was recrystallized from 1 l. of cold tetrahydrofuran to give 432.3 g (92%) of **4** as an extremely hygroscopic solid, mp 49–55°. An analytical sample was obtained by two recrystallizations from tetrahydrofuran: mp 53.5–55°; nmr [$(CD_3)_2CO$] 3.7–3.4 (m with major peak at 3.59, 3, OCH_2), 3.23 (broad, OH + NH), and 2.85–2.6 ppm (m, 2, NCH_2). Addition of D_2O moved the active H peak to 4.17 ppm (s, 1, OH + NH).

Anal. Calcd for $C_{10}H_{24}N_2O_4$: C, 50.83; H, 10.24; N, 11.86. Found: C, 51.22; H, 10.15; N, 11.67.

6-Oxa-3,9-diazaundecane-1,11-diol (5). To 611 g (10.0 mol) of ethanolamine stirred in an ice bath was added in batches 763 g (4.0 mol) of *p*-toluenesulfonyl chloride at a rate sufficient to maintain a temperature of 25–30°. After addition was complete, the ice bath was removed and an exotherm was allowed to carry the temperature to 80°. The homogeneous mixture was stirred for 1 hr and allowed to stand overnight. The resulting mixture was warmed to dissolve salts and sitrred into 4 l. of water. The oily layer was extracted with a mixture of 2 l. of water and 50 ml of concentrated HCl, the aqueous layer was extracted with 200 ml of ether, and the organic layers were combined, diluted with ether, dried over anhydrous Na_2SO_4, filtered, and evaporated to give 497.9 g (58%) of *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide, mp 55–57°.[12]

A mixture of 107.5 g (0.50 mol) of the above product and 500 ml of purified dimethylformamide was treated with 58 g (0.52 mol) of potassium *tert*-butoxide with stirring and cooling to keep the temperature below 40°. The mixture was stirred overnight and then to it was added 35.8 g (0.25 mol) of bis(chloroethyl) ether. The reaction mixture was stirred and heated at 100–105° for 1 day, cooled, and poured into 2.5 l. of water. The resulting mixture was stirred until the oil crystallized, then triturated thoroughly and filtered. The dried solid **6**, mp 90.5–91.5°, weighed 104.1 g (83%).

A sample was recrystallized twice from tetrahydrofuran–ether for analysis: mp 91.5–92.5°; ir (KBr) 2.95 and 3.00 (OH), 3.26 (unsaturated CH), 3.41 and 3.47 (saturated CH), 6.26, 6.69, and 6.73 (aromatic C=C), 7.46 and 8.61 (NSO_2), and 9 μ (broad, COC, COH); ^{1}H nmr [$(CD_3)_2SO$] main bands of AA'BB' at 470, 461, 450, and 441 Hz (4, aromatic CH) and 4.73 (t, J_{HH} = 5 Hz, 1, OH), 3.7–3.1 (m, 8, OCH_2CH_2N), and 2.40 ppm (s, 3, CH_3).

Anal. Calcd for $C_{22}H_{32}N_2O_7S_2$: C, 52.78; H, 6.44; N, 5.60; S, 12.81. Found: C, 52.55; H, 6.61; N, 5.53; S, 12.92.

The tosyl groups were removed from **6** by a reductive procedure adapted from that reported in ref 7.

Benzene (400 ml) and 50.1 g (0.10 mol) of **6** were stirred under nitrogen while 288 g (~1.0 mol) of 70% sodium bis(2-methoxyethoxy)aluminum hydride in benzene was added dropwise. The mixture was refluxed for 1 day, and 300 ml of water and then 100 ml (1.0 mol) of concentrated HCl were added. The mixture was stirred for 1 hr and filtered through Celite, and the filter cake was washed with 600 ml of water. The combined washings and filtrate were acidified with 25 ml of concentrated HCl and the benzene layer was removed. The aqueous layer was extracted twice with 250 ml of ether, then basified with 12.0 g (0.30 mol) of sodium hydroxide, evaporated to low volume, treated with 25 g of anhydrous Na_2CO_3, and evaporated to 50° (0.5 mm). The residue was stirred well with 300 ml of absolute ethanol and filtered, and the filter cake was extracted with 150 ml of absolute ethanol. The filtrate was evaporated to give 25 g of viscous oil which was distilled in a molecular still to give 12.0 g (62%) of 6-oxa-3,9-diazaundecane-1,11-diol (**5**), bp 127–130° (0.3 μ), $n^{25}D$ 1.4891. On standing, crystals, mp 41.5–43°, formed slowly: ir (neat) 3.03 (broad, OH, NH), 8.7–9.6 μ (COC, COH); ^{1}H nmr [$(CD_3)_2CO$] 3.51, 3.42, and 3.33 (skewed t, 2, OCH_2), 3.11 (s, broad and shifted to lower field by D_2O, 1, OH + NH), and 2.73, 2.64, 2.55, and 2.46 ppm (skewed q, 2, NCH_2).

Anal. Calcd for $C_8H_{20}N_2O_3$: C, 49.98; H, 10.49; N, 14.57. Found: C, 50.56; H, 9.99; N, 14.40.

Registry No.—**1**, 23978-55-4; **2**, 50977-91-8; **3**, 929-59-9; **4**, 50977-92-9; **5**, 50977-93-0; **6**, 50977-94-1; *N*-*n*-butyltrifluoroacetamide, 400-59-9; di-*n*-butylamine, 111-92-2; ethyl trifluoroacetate, 383-63-1; *n*-butylamine, 109-73-9; *N*,*N*-di-*n*-butyltrifluoroacetamide, 313-32-6; 1,8-dichloro-3,6-dioxaoctane, 112-26-5; 3,6,12,15-tetraoxa-9-azaheptadecane-1,17-diamine, 50977-95-2; 1,8-ditosyloxy-3,6-dioxaoctane, 19249-03-7; *p*-toluenesulfonyl chloride, 98-59-9; *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide, 14316-14-4.

References and Notes

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