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A CONVENIENT METHOD FOR THE SELECTIVE REDUCTION OF AMIDES TO AMINES

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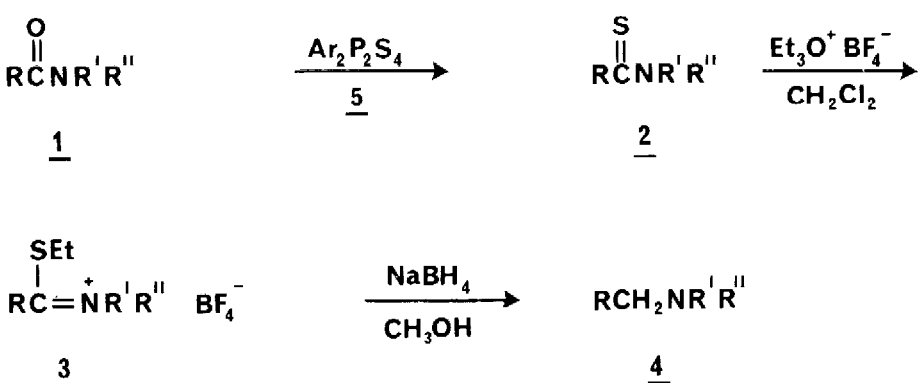
Summary: A variety of amides have been selectively reduced to the corresponding amines via conversion to their thioamides and treatment with triethyloxonium tetrafluoroborate followed by sodium borohydride. This procedure is compatible with isolated and conjugated double bonds, esters, nitro groups, and sulfonamides.

A number of methods are available for the reduction of amides to amines.[2] Several procedures which allow the selective reduction of amides in the presence of other functional groups have been reported.[3-6] The most noteworthy of these procedures include those developed by Borch[3] ($Et_3O^+ BF_4^-$; $NaBH_4$), Kornfeld[4] (P_4S_{10}; RaNi), Brown[5] (B_2H_6) and Kuehne[6] ($POCl_3$; $NaBH_4$).

Recently, in connection with projects directed toward the synthesis of indole alkaloids, we desired to selectively reduce the amide 1j[7] to the amine 4j. Attempts to utilize the procedures of Borch or Kuehne proved to be unsatisfactory for this compound, and thus we sought a viable alternative.

We now wish to report a convenient, general and selective method for the reduction of amides to amines which is compatible with other functional groups including isolated and conjugate double bonds, esters, nitro groups and sulfonamides. This procedure involves the conversion of the amide 1 to the thioamide 2, treatment of the thioamide with $Et_3O^+BF_4^-$ to give the alkylmercaptomethyleniminium salt 3,[8] and reduction of 3 with $NaBH_4$ to afford the amine 4.

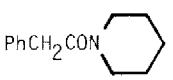
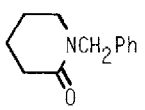
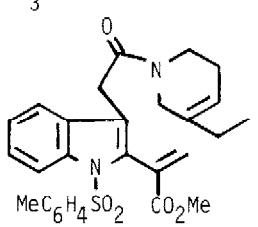


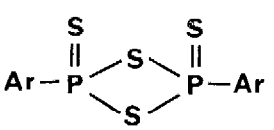
This method[9] possesses several attractive features in addition to its high selectivity and convenience. In particular, the thioamides 2 are considerably more reactive than the corresponding amides 1 toward both alkylation with $Et_3O^+BF_4^-$ and subsequent reduction with $NaBH_4$, consequently reaction times may be dramatically shortened. For example, alkylation of thioamides with $Et_3O^+BF_4^-$ typically requires less than 30 minutes at 25°, and the reduction step is complete in less than 1 hour at 25° for N,N-disubstituted thioamides. It is also noteworthy that the unsubstituted amide 1c has been transformed to the primary amine 4c via this procedure, whereas the procedure of Borch[3] affords nitriles from unsubstituted amides. The results of these studies are shown in Table I. As indicated, this procedure is applicable to a variety of amides including N,N-disubstituted-, N-substituted- and unsubstituted amides, benzamides, acetanilides, and lactams.

The thioamides 2 were prepared by treating the amides 1 with the dimer of p-methoxyphenylthionophosphine sulfide (5)[10] in toluene (85-110°, 3-5 h). This reagent was consistently superior to P_4S_{10} with respect to ease of manipulation and yields of thioamides. The thioamides were purified either by flash chromatography[11] on silica gel or by bulb-to-bulb distillation. The purified thioamides 2 were treated with $Et_3O^+BF_4^-$ (1.2 equiv) in CH_2Cl_2 (25°, 10-20 minutes), followed by addition of excess $NaBH_4$ in anhydrous methanol. The feasibility of effecting the overall transformation in a one-pot reaction without purification of the thioamides was also briefly examined (entries a, g and i). As shown in Table I, the overall yields for the one-pot procedure were somewhat lower, and thus the two-step procedure is preferable. Lower yields in the one-pot procedure may be caused by the presence of 6, the by-product of the reagent 5.[10]

A typical experimental procedure for the preparation of N,N-dimethyl-2-phenylethylamine follows.[12] A mixture of N,N-dimethyl phenylacetamide (1e) (652 mg, 4.00 mmol), $Ar_2P_2S_4$ (5) (984 mg, 2.4 mmol) and dry toluene (5 mL) was heated at 100° for 4 hours in an atmosphere of argon. The toluene was removed in vacuo, and the residue was purified by flash chromatography[11] on silica gel 60 (40-63 μm) with methylene chloride to give N,N-dimethyl phenylthioacetamide (2e)[13]: (640 mg, 3.60 mmol, 90%). ^1H NMR ($CDCl_3$) δ 3.08 (s, 3), 3.37 (s, 3), 4.23 (s, 2), 7.30 (s, 5H). To a solution of the thioamide 2e (550 mg, 3.07 mmol) in methylene chloride (3 mL) cooled to 0° under argon was added a 1 M solution of $Et_3O^+BF_4^-$ in methylene chloride (3.7 mL, 3.7 mmol, 1.2 equiv). The reaction mixture was stirred at 0° for 5 min, the cooling bath was removed, and stirring was continued for 45 min. The methylene chloride was removed in vacuo, the residue was dissolved in anhydrous methanol (5 mL) and the resulting solution was cooled at 0°. Excess $NaBH_4$ (300 mg, 8 mmol) was added in portions over 5 minutes. Since ethanethiol is formed in this step, the reaction should be carried out in an efficient fume hood. The reaction mixture was stirred at 0° for an additional 5 min, the cooling bath was removed and stirring was continued for 2 hours. The reaction mixture was treated with 10% aqueous HCl (5 mL), stirred for 5 min, and basified with 10% aqueous NaOH to pH ~ 10. The mixture was extracted with ether (3 x 25 mL), the ether extracts were washed with brine, dried (Na_2SO_4), and the ether was removed in vacuo and purified by bulb-to-bulb distillation to give N,N-dimethy-2-phenylethylamine 4e: (458 mg, 3.0 mmol, 100%). ^1H NMR ($CDCl_3$) δ 2.20 (s, 6), 2.6 (m, 4), 7.16 (s, 5).

TABLE I. YIELDS FOR CONVERSION OF AMIDES TO AMINES

entry	$RCONR'R''$ Amide (1)	$RCSNR'R''$ Thioamide (2)	$RCH_2NR'R''$ Amine (4)	one pot procedure
a	$PhCONMe_2$	89%	93%	58%
b	$p\text{-}O_2NC_6H_4CONMe_2$	90%	100%	--
c	$PhCH_2CONH_2$	63%	88%	--
d	$PhCH_2CONHMe$	98%	98%	--
e	$PhCH_2CONMe_2$	90%	100%	--
f		75%	98%	--
g		93%	90%	53%
h	$CH_3CONHPh$	91%	70%	--
i	$CH_3CONMePh$	86%	80%	56%
j		70%	94%	--



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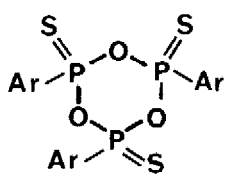

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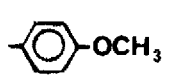
Ar = 

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(6) M. E. Kuehne and P. J. Shannon, J. Org. Chem., 42, 2082 (1977).

(7) A procedure for the preparation of 1j will be detailed shortly: S. Raucher and R. F. Lawrence, research in progress.

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(9) An isolated example involving the reduction of a thioamide by this procedure has recently been reported: W. R. Roush, J. Am. Chem. Soc., 102, 1390 (1980). We have also been informed by Professor R. J. Sundberg of a method developed in his laboratories which involves the alkylation of thioamides with methyl iodide, and reduction of the resulting iminium salts with $NaBH_3CN$

(10) S. Scheibye, B. S. Pedersen, and S. O. Lawesson, Bull. Soc. Chim. Belg. 87, 229 (1978).

(11) W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978).

(12) Yields refer to isolated compounds purified either by flash chromatography[11] on silica gel 60 (40-63 μm) with hexane/methylene chloride (2b, 2d, 2e, 2g, 2i, 2j, 4j), or hexane/ether (2c), or by bulb-to-bulb distillation (2a, 2h). The amines prepared in the two-step procedure were purified by bulb-to-bulb distillation, whereas those prepared in the one-pot reaction were isolated as their hydrochloride salts. Spectral data were in full accord for the structures of all compounds and were identical to those available for known samples. Several of the thioamides were also prepared utilizing P_4S_{10} or were commercially available. Formation of the thioamides was followed by TLC, and in all cases the Rf of the thioamide was greater than that of the amide. The reduction of the salts 3 was allowed to go for 1-2 hours for 3a, 3b, 3e, 3f, 3g, 3c, and 3j; for 2-3 hours for 3d, and 3h, and for 4-5 hours for 3c. For an extensive list of references for the preparation of thioamides, see Ref. 14.

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