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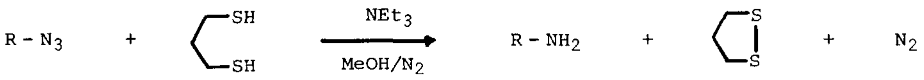
PROPANE-1,3-DITHIOL: A SELECTIVE REAGENT FOR THE EFFICIENT REDUCTION OF ALKYL AND ARYL AZIDES TO AMINES

Hagan Bayley, David N. Standring, and Jeremy R. Knowles*

Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge, MA 02138 USA

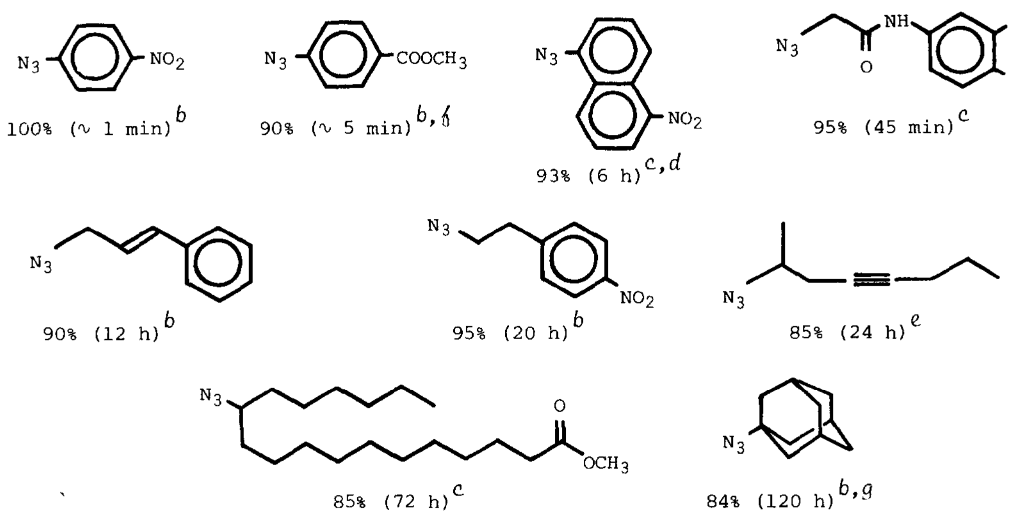
Most reducing agents reduce azides, and the product is almost invariably the amine. However, the reagents commonly employed for this purpose (e.g., $LiAlH_4$, H_2/catalyst) are rather unselective, and there is considerable interest in more selective methods. Recent examples include Cr(II)/H^+,[1] ϕ_3P/NH_4OH,[2] H_2S/pyridine/water,[3] and H_2/Lindlar catalyst.[4] We have earlier demonstrated[5,6] the facile reduction of a number of aryl azides by dithiothreitol in aqueous solution at pH 10, and we report here on the synthetic utility of propanedithiol-triethylamine for the rapid reduction of both alkyl and aryl azides at room temperature:



In the Table are listed the isolated yields for the reduction of a number of bifunctional compounds. These results demonstrate the ease and selectivity of the reduction. The procedure is also compatible with a number of other potentially sensitive functional groups. Thus, when 2-(4-nitrophenyl)ethyl azide was completely reduced in the presence of 2-hydroxypropionitrile, 2-hydroxy-3-nitrobutane, or 3-methylcyclohexanone, these materials were reisolated unchanged, in 100%, 98%, and 97% yield, respectively.[7] The rate of reduction of aryl azides depends markedly upon the substituents: electron withdrawing substituents evidently accelerate the reaction. Thus 4-nitrophenyl azide is reduced 12 times faster than methyl 4-azidobenzoate, which is reduced 11 times more rapidly than 4-methoxyphenyl azide.[8]

The reduction of azido groups with dithiols has two clear advantages over other methods. First, it is highly selective for the azido group. Azides are selectively reduced in the presence of double and triple bonds, carboxylic acids,[5] amides, esters, phosphoramidates,[5] nitro groups, haloaryl groups, aryl and alkyl nitriles, and keto groups. Secondly, the rate of reduction varies considerably with the steric and electronic environment of the azido group (see Table), which should allow the selective reduction of suitably situated azido groups in the presence of those less favorably sited.[11]

Table. Reduction of Aryl and Alkyl Azides by Propane-1,3-Dithiol.[a]



100% (∿ 1 min)[b]

90% (∿ 5 min)[b,f]

93% (6 h)[c,d]

95% (45 min)[c]

90% (12 h)[b]

95% (20 h)[b]

85% (24 h)[e]

85% (72 h)[c]

84% (120 h)[b,g]

[a] The azide was dissolved in dry freshly-distilled MeOH[9] to a concentration of 0.2 M. The vessel was purged with N_2 and a 2- to 5-fold molar excess of each of propane-1,3-dithiol[10] and NEt_3[10] was added by syringe. The solution was stirred at room temperature for the time shown in parentheses, and the product was isolated as indicated.[b,c,e] The percentage yield of isolated amine is shown beneath each azide. All products gave satisfactory spectral data, which were compared with those from authentic samples where necessary. [b] After removal of solvent, the residue was dissolved in dry benzene and the product precipitated with dry HCℓ. [c] The reaction mixture was applied to Dowex 50 (H^+ form in MeOH). Elution with MeOH removed the thiol and the product was eluted by MeOH/NEt_3 (19:1, v/v). [d] In $CH_2Cℓ_2$/MeOH (1:1, v/v). [e] After addition of aq. HCℓ and washing with ether to remove the thiol, the solution was made basic and the product extracted into ether. [f] No transesterification was observed when the reaction was done in CD_3OH. [g] At 60°C.

References and Notes

1. D.N. Kirk and M.A. Watson, J. Chem. Soc. Chem. Commun. 64 (1970); T. Kondo, H. Nakai, and T. Goto, Tetrahedron 29, 1801 (1973).
2. W.S. Mungall, G.L. Greene, G.A. Heavner, and R.L. Letsinger, J. Org. Chem. 40, 1659 (1975).
3. T. Adachi, Y. Yamada, I. Inoue, and M. Saneyoshi, Synthesis, 45 (1977).
4. E.J. Corey, K.C. Nicolaou, R.D. Balanson, and Y. Machida, Synthesis, 590 (1975).
5. J.V. Staros, H. Bayley, D.N. Standring, and J.R. Knowles, Biochem. Biophys. Res. Commun. 80, 568 (1978).
6. Cartwright, et al. [I.L. Cartwright, D.W. Hutchinson, and V.W. Armstrong, Nucleic Acids Res. 3, 2331 (1976)] first showed that 8-azido-adenine derivatives are reduced by dithiols, though these workers did not detect the reduction of phenyl azide under their reaction conditions.
7. Yields were estimated from g.l.c. of recovered materials.
8. These rates were measured either spectrophotometrically, or by g.l.c.
9. The reaction is less rapid in dimethylformamide or EtOH, is slow in $CH_2Cℓ_2$, and it does not proceed in dry pyridine. Pyridine-water (70:30, v/v) is, however, effective.
10. Dry NEt_3 was distilled from 1-napthylisocyanate. Propane-1,3-dithiol (Aldrich: 96% pure by I_2 titration) was used without purification. Although excess dithiol is used in preparative experiments, the reduction is stoichiometric. A white precipitate of thiol polymer may form, but this has no effect on the outcome of the reaction. Butane-1,4-dithiol reacts 11 times more slowly than propane-1,3-dithiol.
11. This study developed from an observation of J.V. Staros. The support of the National Institutes of Health is gratefully acknowledged.

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