DEOXYGENATION OF 2,3-DISUBSTITUTED QUINOXALINE 1,4-DIOXIDES

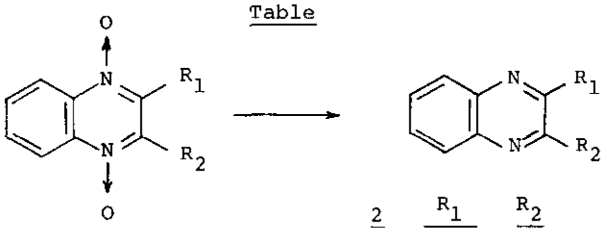
Fadia R. Homaidan and C.H. Issidorides*

Chemistry Department, American University of Beirut, Beirut,
Lebanon

Abstract - The title compounds can be deoxygenated under very mild conditions by hexachlorodisilane, iodotrimethylsilane, trifluoroacetic anhydride-sodium iodide, and titanium tetrachloride-zinc dust.

Deoxygenation of heteroaromatic N-oxides may be effected by a variety of long-established methods such as catalytic hydrogenation, complex metal hydrides, electrolysis, dissolving metals, trivalent phosphorus compounds, and various sulfur-containing compounds[1,2,3]. A number of new deoxygenating reagents have been introduced recently, including sulfoxide[4], titanium trichloride[5], chromous chloride[6], titanium tetrachloride-sodium borohydride[7], molybdenum(III) species[8], di-n-propyl sulfoxylate[9], and sulfur monoxide generated in situ[10]. However, not all these reagents are suitable for deoxygenating quinoxaline 1,4-dioxides (QNO's) to the corresponding quinoxalines, owing to the tendency of the substrates to undergo under-reduction to monoxides or over-reduction to dihydro (or tetrahydro) quinoxalines. In a previous paper[11] we reported the deoxygenation of 2,3-disubstituted QNO's by phosphorus trichloride and by sodium dithionite. More recently, titanium trichloride[12] and trimethyl phosphite[13] have been introduced, the former for dideoxygenations and the latter for selective monodeoxygenations. We now report the deoxygenation, under very mild conditions, of 2,3-disubstituted QNO's to the corresponding quinoxalines by hexachlorodisilane, iodotrimethylsilane, trifluoroacetic anhydride-sodium iodide, and titanium tetrachloride-zinc dust (Table). These reagents have recently found important applications: hexachlorodisilane in the deoxygenation of phosphine oxides[14], aliphatic amine oxides[14], azoxyalkanes[15], and nitrones[16]; iodotrimethylsilane in the deoxygenation of sulfoxides[17], oxiranes[18], and α-ketols[19]; trifluoroacetic anhydride-sodium iodide[20] as well as titanium tetrachloride-zinc dust[21] in the deoxygenation of sulfoxides.

Table



2	R_1	R_2
A	CH_2Ph	Ph
B	COPh	Ph
C	$COCH_3$	CH_3
D	CO_2Et	CH_3
E	Ph	CH_3
F	CH_3	CH_3

			% Yield[i]			
Product	M.p.	Lit.	Si_2Cl_6	Me_3SiJ	$(CF_3CO)_2O$/NaJ	$TiCl_4$/Zn
2A	96-97[b]	97[d]	57	69	50[g]	--[j]
2B	150-151[b]	150-151[e]	75	67	86	67
2C	85-86[c]	87-88[d]	48[g]	56	63[g]	54[g]
2D	72-73[c]	73-74[e]	74	85	74	47
2E	53-54[c]	53-54[e]	45[h]	76[g]	74	--[j]
2F	102-104[c]	104-106[f]	80	72	49[g]	53

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[a] For the preparation of these starting materials see reference 22.

[b] Recrystallized from methanol.

[c] Recrystallized from methanol/water.

[d] Reference 23.

[e] Reference 24.

[f] Reference 25.

[g] Purified by thick-layer chromatography on silica gel, using benzene-petroleum ether as developing solvent.

[h] Purified by column chromatography on alumina (grade II); eluted by petroleum ether.

[i] Yields refer to isolated and chromatographically pure compounds.

[j] Intractable mixture.

Deoxygenations of 2,3-disubstituted QNO's with hexachlorodisilane are carried out at room temperature in chloroform solution and are complete within a few hours. By comparison, deoxygenations with iodotrimethylsilane ($CHCl_3$) are slower, whereas those with trifluoroacetic anhydride-sodium iodide (acetone) are faster. Of the four reagents, the combination of titanium tetrachloride-zinc dust is the least convenient in practice and, in some cases, leads to intractable mixtures; the silanes, on the other hand, are particularly convenient and, therefore, highly recommended for deoxygenations. Characterization of the products (Table) is based on comparison with authentic samples (mixture m.p., IR, TLC). In general, yields are as good or better than those obtained by earlier methods[11,12]; furthermore conditions are considerably milder than those employed with phosphorus trichloride or sodium dithionite[11]. In view of the importance of reductive removal of the N-oxide oxygen in synthetic heterocyclic chemistry, the reagents described here offer an attractive alternative to earlier methods.

EXPERIMENTAL

Hexachlorodisilane - The QNO (2.5 mmol) was dissolved in chloroform (7 ml). Hexachlorodisilane (6 mmol) was added dropwise to the solution, which was kept at 0-5° in a stoppered flask. When the addition was complete, the ice-bath was removed and the reaction mixture was stirred for 3 to 4 hr in a water bath at room temperature. The reaction mixture was then cooled in an ice-bath and an excess of 20% aqueous sodium hydroxide was added with rapid stirring. The organic phase was washed with saturated sodium chloride solution and dried over magnesium sulfate. The solvent was then removed under reduced pressure and the product was collected and purified (Table).

Iodotrimethylsilane - The QNO (2 mmol) was dissolved in chloroform (7 ml) in a stoppered flask. Iodotrimethylsilane (10 mmol) was added dropwise by means of a syringe, and the mixture was allowed to stand at room temperature for 48 hr, after which it was quenched with 10% aqueous sodium thiosulfate and extracted with chloroform. The organic phase was washed first with 5% aqueous sodium thiosulfate and then with water. The dried extract (magnesium sulfate) was evaporated to dryness and the product collected and purified (Table).

Trifluoroacetic anhydride-sodium iodide - The QNO (1.25 mmol) and sodium iodide (6 mmol) were magnetically stirred with acetone (5-7 ml) in a round-bottomed flask. An acetone solution of trifluoroacetic anhydride (6.5 mmol) was slowly added with stirring. The extremely rapid reaction was followed by TLC and, when complete, the acetone was evaporated under reduced pressure and water was added. The mixture was then extracted with ether and the organic phase was washed first with 5% aqueous sodium thiosulfate and then with water. The ether was removed from the dried (magnesium sulfate) extract and the product collected and purified (Table).

Titanium tetrachloride-zinc dust - The QNO (1 mmol) was dissolved in ether in a round-bottomed flask immersed in a water bath kept at room temperature. Titanium(IV) chloride (4 mmol) was added rapidly to the magnetically stirred solution, followed by zinc dust (8 mmol) in small portions. After one hr water (50 ml) was added and the organic phase was separated. The aqueous layer was extracted with ether and the combined ether layers were washed with water and dried over magnesium sulfate. The solvent was then removed and the product collected and purified (Table).

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REFERENCES:

1. A.R. Katritzky and J.M. Lagowski, Chemistry of the Heterocyclic N-Oxides, p. 166, Academic Press, London, 1971.
2. E. Ochiai, Aromatic Amine Oxides, p. 184, Elsevier Publishing Co., New York, 1967.
3. R.A. Abramovitch (Ed), Pyridine and its Derivatives, Heterocyclic Compounds, Vol. 14, Suppl. Pt 2, John Wiley, New York, 1974.
4. M.E.C. Biffin, G. Bocksteiner, J. Miller, and D.B. Paul, Aust. J. Chem., 1974, **27**, 789.
5. J.M. McCall and R.E. TenBrink, Synthesis, 1975, 335.
6. Y. Akita, K. Misu, T. Watanabe, and A. Ohta, Chem. Pharm. Bull., 1976, **24**, 1839.
7. S. Kano, Y. Tanaka, S. Hibino, Heterocycles, 1980, **14**, 39.
8. S. Polanc, B. Stanovnik, and M. Tisler, Synthesis, 1980, 129.
9. H. Kagami and S. Motoki, J. Org. Chem., 1978, **43**, 1267.
10. B.F. Bonini, G. Maccagnani, G. Mazzanti, and P. Pedrini, Tetrahedron Letters, 1979, 1799.

11. M.J. Haddadin, G.E. Zahr, T.N. Rawdah, N.C. Chelhot, and C.H. Issidorides, Tetrahedron, 1974, **30**, 659.

12. B.W. Cue, J.P. Dirlam, and E.A. Glazer, Organic Preparations and Procedures Int., 1977, **9**, 263.

13. J.P. Dirlam and J.W. McFarland, J. Org. Chem., 1977, **42**, 1360.

14. K. Naumann, G. Zon, and K. Mislow, J. Am. Chem. Soc., 1969, **91**, 7012; K.E. DeBruin, G. Zon, K. Naumann, and K. Mislow, J. Am. Chem. Soc., 1969, **91**, 7027.

15. J.P. Snyder, L. Lee, V.T. Bandurco, C.Y. Yu, and R.J. Boyd, J. Am. Chem. Soc., 1972, **94**, 3260.

16. A.G. Hortmann, J.Y. Koo, and C.C. Yu, J. Org. Chem., 1978, **43**, 2289.

17. G.A. Olah, B.G.B. Gupta, and S.C. Narang, Synthesis, 1977, 583.

18. J.N. Denis, R. Magnane, M. Von Eenoo, and A. Krief, Nouveau J. Chim., 1979, **3**, 705.

19. T.L. Ho, Synthetic Commun., 1979, **9**, 665.

20. J. Drabowicz and S. Oae, Synthesis, 1977, 404.

21. J. Drabowicz and M. Mikolajczyk, Synthesis, 1978, 138.

22. M.J. Haddadin and C.H. Issidorides, Heterocycles, 1976, **4**, 767.

23. J.C.E. Simpson, The Chemistry of Heterocyclic Compounds, Condensed Pyridazine and Pyrazine Rings, Interscience Publishers Inc., New York, 1953.

24. T.N. Rawdah, M.S. Thesis, American University of Beirut, Beirut, Lebanon, 1972.

25. R.W. Bost and E.F. Towell, J. Am. Chem. Soc., 1948, **70**, 903.

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