HETEROCYCLES, Vol. 14, No. 10, 1980

THE USE OF TETRA-N-BUTYLAMMONIUM BOROHYDRIDE FOR THE REDUCTION OF INDOLES TO INDOLINES IN DICHLOROMETHANE

Takeshi Wakamatsu,* Harumi Inaki, Akemi Ogawa, Masako Watanabe, and
Yoshio Ban
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060,
Japan

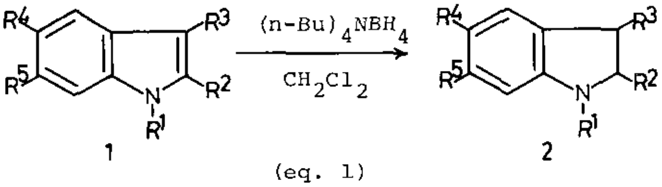
Abstract — Several indole compounds were reduced with tetra-n-butylammonium borohydride in dichloromethane to the corresponding indolines under mild conditions, in which solvent most of indole compounds are easily soluble.

The reduction of indoles to indolines is known to be an important transformation in the field of indole alkaloid synthesis. Although extensive studies on the reduction of indoles to indolines have been reported,[1] these older methods involve reduction in strong acid medium either with dissolving metals[2] or with catalytic hydrogenation.[3] Recently, several new methods for the reduction of indoles with various boron hydrides[4-9] and with alkylsilane[10] have been reported.

In the preceding paper,[11] we have described the use of tetra-n-butylammonium borohydride[12] as a mild and selective reagent for an efficient reduction of nitriles and amides to the corresponding amines.

We wish now to report a new convenient method for the reduction of indoles to indolines with tetra-n-butylammonium borohydride in dichloromethane without a proton source (eq. 1).

The results obtained in this way are compiled in Table 1. Of these indole derivatives, 3-methylindole (Entry No. 1d) remained unaffected by the reduction under these conditions and most of starting indole were recovered.



(eq. 1)

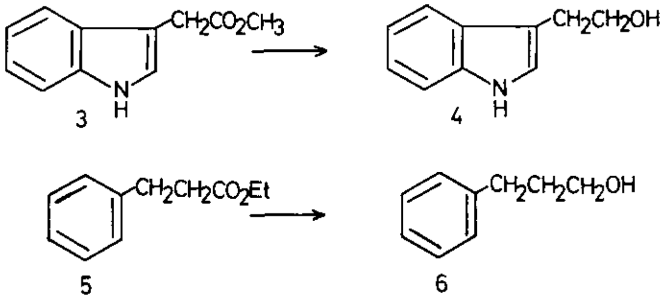
Table 1 Reduction of indoles with tetra-n-butylammonium borohydride

Substrate No.	R^1	R^2	R^3	R^4	R^5	Yield(%) of 2
1a	H	H	H	H	H	48(40)
1b	H	CH_3	H	H	H	66(27)
1c	CH_3	CH_3	H	H	H	44(38)
1d	H	H	CH_3	H	H	6(87)
1e	H	H	H	OCH_3	H	63(37)
1f	H	H	H	H	OCH_3	69(5)
1g	H	$-(CH_2)_4-$		H	H	57(40)
1h	H	$R^2-CO(CH_2)_3-R^3$		H	H	70

Numbers in parenthesis are yield(%) of recovered indoles

When indole derivative(3) was subjected to this reduction, the ester group was easily reduced faster than indole double bond to give alcohol(4) in 69% yield. On the result of this observation, ethyl 3-phenylpropionate(5) was treated with tetra-n-butylammonium borohydride in dichloromethane to afford 3-phenylpropanol in quantitative yield.[13]

These results indicate that the aliphatic ester is readily reduced rather than indole double bond and aromatic ester.[11]



Thus, the features of this reagent are demonstrated in the following: The reagent is readily soluble in dichloromethane; The reduction can be operated in dichloromethane, in which solvent most of organic compounds are easily soluble; The chemospecificity of the reagent is observed. For example, the nitrile and amide groups are easily reduced, while the ester, nitro, and halogen attached to the aromatic ring are intact; The work-up of reaction is very easy and convenient ; The reduction can be done without a proton source.

The typical procedure is described in the following:

Reduction of 6-methoxyindole(1f) with tetra-n-butylammonium borohydride to 6-methoxyindoline: To a solution of 441mg(3mmol) of 6-methoxyindole in 20ml of dichloromethane was added 2.315g(9mmol) of tetra-n-butylammonium borohydride. The whole mixture was vigorously refluxed with stirring for 10h. After removal of the solvent, asolution of 10% hydrochloric acid(15ml) was added to the residue and the mixture was stirred at room temperature for 30min. The starting indole was isolated by ether extraction, affording 23mg(5%) of 6-methoxyindole. An acidic solution was made alkaline with solid sodium hydroxide followed by extraction with ether. Evaporation of the solvent dried over magnesium sulfate gave 310mg(69%) of 6-methoxyindoline, which was converted into its hydrochloride, mp 208-222°C. (Found: C,58.17; H,6.64; N,7.73. $C_9H_{12}ClNO$ requires C,58.19; H,6.47; N,7.54%).

Acknowledgement: This work was supported by a Grant-in-Aid for Scientific Research (No. 387145) from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

References and Notes

1. B. Robinson, Chem. Rev., 1969, 785.
2. L. J. Dolby and G. W. Gribble, J. Heterocycl. Chem., 1966, **3**, 124.
3. (a) A. Smith and J. H. F. Utley, Chem. Commun., 1965, 427; (b) J. Chem. Soc., C, 1970, 1.
4. S. A. Monti and R. R. Schmidt III, Tetrahedron, 1971, **27**, 3331.
5. J. G. Berger, Synthesis, 1974, 508.
6. (a) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, J. Am. Chem. Soc., 1974, **96**, 8712; (b) G. W. Gribble and J. H. Hoffman, Synthesis, 1977, 859.
7. (a) Y. Kikugawa, J. Chem. Research(S), 1977, 212; (b) Chem. Pharm. Bull., 1978, **26**, 108; (c) J. Chem. Research(S), 1978, 184.
8. J. G. Berger, S. R. Teller, C. D. Adams, and L. J. Guggenberger, Tetrahedron Letters, 1975, 1807.
9. B. E. Maryanoff and D. F. McComsey, J. Org. Chem., 1978, **43**, 2733.
10. A. E. Lanzilotti, R. Littel, W. J. Fanshawe, T. M. McKenzie, and F. M. Lovell, J. Org. Chem., 1979, **44**, 4809.
11. T. Wakamatsu, H. Inaki, A. Ogawa, M. Watanabe, and Y. Ban, Heterocycles, preceding paper, 1980.
12. This reducing reagent commercially available from Tokyo Kasei Kogyo Co., LTD. was prepared in this experiment by the method described in the following literature; A. Brandström, U. Juggren, and B. Lamm, Tetrahedron Letters, 1972, 3173.
13. D. J. Raber and W. C. Guida, J. Org. Chem., 1976, **41**, 690.

Received, 19th June, 1980