Department of Pharmaceutical Chemistry, The University of Mississippi

Dimethylformamide in the Preparation of 2-Dimethylaminobenzoxazole (1)

Joseph Sam and Shyam B. Advani

In an attempt to prepare various *N*-substituted-2-aminobenzoxazoles it was observed that the reaction of 2-chlorobenzoxazole (I) with amines (example, diphenylamine, amino acids) in dimethylformamide (DMF) yielded only 2-dimethylaminobenzoxazole (II). Refluxing 2-chlorobenzoxazole with DMF in the absence of amines also yielded II. A by-product in this reaction was dimethylamine hydrochloride. This was not unexpected since it is known that DMF on standing in the presence of acid or base slowly decomposes to dimethylamine (2). On refluxing a solution of DMF with hydrogen chloride dimethylamine hydrochloride was obtained.

Dimethylformamide has been used in a number of cases to introduce into the molecule the dimethylamino substituent. Coppinger (3) used DMF to prepare *N*,*N*-dimethylbenzamide from benzoyl chloride, and *N*,*N*-dimethylbenzylamine from benzyl chloride. It was shown by Schmerling (4) that haloaromatic compounds in the presence of monoalkylformamides at elevated temperature and pressure give monoalkylaminoaromatic compounds. Similar results have been reported by Wakae and Hamano (5) and Deorha and Sharma (6) in replacing the halogen in halonitrobenzenes by the dimethylamino group.

More recently it has been reported that 2-chlorobenzothiazole (7) and 2-chlorobenzimidazole (8) react in a similar manner to give the respective 2-dimethylamino compounds. The mechanism of formation of 2-dimethylaminobenzoxazole from 2-chlorobenzoxazole and DMF is probably similar to that proposed by D'Amico *et al.* (7).

EXPERIMENTAL (9)

2-Dimethylaminobenzoxazole (II). Method A.

A solution of 4.25 g. (0.05 mole) of piperidine and 7.7 g. (0.05 mole) of 2-chlorobenzoxazole in 100 ml. of DMF was refluxed for 48 hours and then allowed to remain at room temperature for 2 hours. Dimethylamine hydrochloride was removed by filtration and the filtrate was concentrated *in vacuo*. The residual solid was recrystallized from petroleum ether (30-60°) to give 5.9 g. (73%) of product, m.p. 82-83°. The infrared absorption spectrum showed strong absorption at 2930, 2850, 1650, 1390, 940 and 740 cm^{-1} characteristic of benzoxazole and 2-amino or *N*-substituted 2-aminobenzoxazoles (10).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.66; H, 6.17; N, 17.28. Found: C, 66.26; H, 6.13; N, 16.76.

Method B.

A solution of 8.45 g. (0.05 mole) of diphenylamine and 7.7 g. (0.05 mole) of 2-chlorobenzoxazole in 100 ml. of DMF was refluxed for 48 hours and then allowed to remain at room temperature for six hours. The reaction mixture was treated as above; 7.2 g. (89%) of product melting at 83-84° was obtained.

Method C.

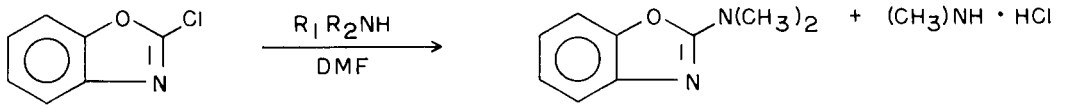
A solution of 7.7 g. (0.05 mole) of 2-chlorobenzoxazole in 100 ml. of DMF was refluxed for 48 hours. The solution was concentrated *in vacuo* to a syrup and then allowed to cool. This material was treated with 50 ml. of acetone and filtered to remove dimethylamine hydrochloride. The filtrate was then concentrated *in vacuo*. The residual solid was recrystallized from petroleum ether (30-60°) to give 5.6 g. (72%) of product, m.p. 82-83°.

Method D.

A mixture of 7.7 g. (0.05 mole) of 2-chlorobenzoxazole, 4.0 g. (0.05 mole) of dimethylamine hydrochloride, 10.0 g. (0.1 mole) of triethylamine and 100 ml. of toluene was refluxed for 24 hours and then allowed to remain at room temperature for 6 hours. The mixture was treated as in Method A; 7.9 g. (98%) of product was obtained, m.p. 83-84°.

Method E.

A solution of 4.0 g. (0.025 mole) of 2-chlorobenzoxazole and 5.0 g.



I II

of diethyl glutamate in 100 ml. of DMF was refluxed for 48 hours. The mixture thereafter was treated as in Method C; 2.1 g. (50%) of product was obtained, m.p. 82-83°. Mixture melting points of the products above showed no depression. The infrared spectra were identical.

Dimethylamine hydrochloride.

A solution of hydrogen chloride in 20 ml. of DMF was refluxed for 24 hours. The solution was concentrated *in vacuo*; the residual syrup was treated with 50 ml. of acetone to yield 13.1 g. (75%) of dimethylamine hydrochloride, m.p. 169-170° (lit. (11) m.p. 170-171°).

REFERENCES

(1) This work was supported by research grant CA 07857 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Maryland.

(2a) Ya. I. Tur'yan, V. G. Baranove and V. A. Aliferova, *Zh. Analit. Khim.*, 18, 121 (1963); *Chem. Abstr.*, 59, 29b (1963). (b) Du Pont Product Information Bulletin, "DMF," Industrial and Biochemical Department, E. I. du Pont de Nemours and Co., Inc., Wilmington, Delaware, p. 4.

(3) G. M. Coppinger, *J. Am. Chem. Soc.*, 76, 1372 (1954).

(4) L. Schmerling, U. S. Patent 2,887,514 (May 19, 1959); *Chem. Abstr.*, 54, 22631 (1960).

(5) M. Wakae and K. Hamano, *Bull. Chem. Soc. Japan*, 36, 230 (1963); *Chem. Abstr.*, 59, 1508e (1963).

(6) D. S. Deorha and H. L. Sharma, *J. Indian Chem. Soc.*, 40, 689 (1963); *Chem. Abstr.*, 59, 13855e (1963).

(7) J. J. D'Amico, S. T. Webster, R. H. Campbell and C. E. Twine, *J. Org. Chem.*, 30, 3618 (1965).

(8) L. Joseph and A. H. Albert, *J. Heterocyclic Chem.*, 3, 107 (1966).

(9) All melting points were taken in a Thomas-Hoover melting point apparatus and are uncorrected.

(10) J. Sam, J. N. Plampin and G. I. Poos, *J. Org. Chem.*, 23, 1500 (1958).

(11) N. A. Lange, Ed., Handbook of Chemistry, Ninth Edition, Handbook Publishers, Inc., Ohio, 1956, p. 512.

Received September 28, 1966 University, Mississippi 38677