A SYNTHESIS OF CARBAMIC ACID [IMIDAZO-HETEROAROMATIC] METHYL ESTER DERIVATIVES USING METHOXYCARBONYL ISOTHIOCYANATE

Siya Ram, Dean S. Wise and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy and Department of Chemistry,

The University of Michigan, Ann Arbor, Michigan 48109

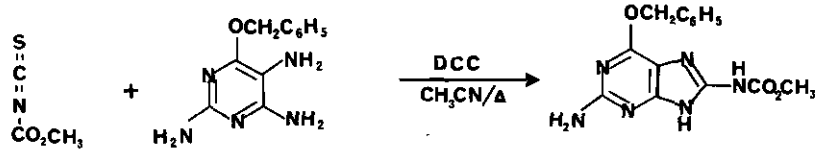
Abstract — Methoxycarbonyl isothiocyanate (1), in the presence of N,N-dicyclohexylcarbodiimide, has been found to be a versatile reagent for the one-pot synthesis of a bicyclic imidazo-heteroaromatic system.

A number of small bifunctional molecules have been used in the synthesis of heterocyclic compounds.[1-6] The search for more efficient and versatile bifunctional annulating reagents has continued to be a fertile area of research. In our program directed toward the synthesis of potential antifilarial agents, we were interested in developing a general procedure for the synthesis of various bicyclic heterocycles substituted similarily to the known anthelmentics 2-methoxycarbonylaminobenzimidazoles. Reagents, such as, cyanogen bromide, 1,3-bis(methoxycarbonyl)-S-methylisothiourea and guanidine although successful in the preparation of 2-aminobenzimidazoles have proven to be less than satisfactory[7] in the synthesis of other heterocyclic systems such as 8-aminopurines and related compounds. We now wish to describe the use of methoxycarbonyl isothiocyanate (1) as a one-pot reagent for the ring closure of an o-diaminopyrimidine derivative to afford a purine derivative possessing the methoxycarbonylamino functionality at position eight.[8]

The reagent (methoxycarbonyl isothiocyanate) was prepared[9,10] and used either *in situ* or after filtration through celite at low temperatures in order to remove the potassium chloride formed in the preparation. However, due to the volatile nature of this reagent, reac- tions where the reagent was generated *in situ* were preferred. Condensation of methoxycarbonyl isothiocyanate (1) (0.01 mole) with 2,4,5-triamino-6-benzyloxypyrimidine[11] (2) (0.01 mole), in the presence of N,N'-dicyclohexylcarbodiimide (DCC) (0.012 mole), in acetonitrile at reflux temperature gave 8-carbamic acid[2-amino-6-benzyloxypurine] methyl ester (3) in 53% yield, mp > 300°C; IR(KBr) 3400, 2960, 1730, 1660-40, 695 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.73 (s, 3H, $-OCH_3$), 5.48 (s, 2H, $-OCH_2$), 6.17 [bs, 2H, NH_2 (exchangeable with D_2O)], 11.40 [bs, 1H, NH (exchangeable with D_2O)]; Anal. Calcd. for $C_{14}H_{14}N_6O_3$; C, 53.50; H, 4.49; N, 26.74: Found: C, 53.50; H, 4.75; N, 26.63.

Formation of the cyclized product 3 presumably proceeds *via* a mechanism similar to that pro-

posed[12] for the condensation of aryl isothiocyanates with various o-phenylenediamines. A thioureido derivative is believed to be initially formed which in the presence of N,N'-dicyclohexylcarbodiimide is converted to an unstable diimide intermediate which subsequently cyclizes to the



1 2 3

desired 2-substituted benzimidazole derivative.

The above example illustrates the versatility of methoxycarbonyl isothiocyanate for heterocyclic synthesis and additional studies in this area are in progress in our laboratory.

ACKNOWLEDGEMENT

This investigation was supported by funds from the Filariasis component of the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases (I.D. 800134). The authors are also grateful to Mr. William Evans for his valuable technical assistance and to Ms Deanna VanSickle for her assistance in the preparation of this manuscript.

REFERENCES

1. K. T. Potts and C. Hirsch; J. Org. Chem., 33, 143 (1968) and references cited therein.
2. J. I. Murray, Org. Syn. Coll., Vol. 4, 744 (1963).
3. W. R. Sherman and E. C. Taylor, Jr., Org. Syn. Coll., Vol. 4, 247 (1963).
4. K. Marada and S. Suzuki, Tetrahedron Lett., 2321 (1976).
5. T. L. V. Ulbricht; T. Okuda and C. C. Price; Org. Syn. Coll., Vol. 4, 566 (1963).
6. D. G. Crosby, R. V. Berthold and H. E. Johnson, Org. Syn. Coll., Vol. 4, 566 (1963).
7. J. H. Lister in "Fused Pyrimidines, Part II, Purines," Ed. D. J. Brown, Wiley-Interscience, N.Y., Vol. 24, pp. 31-90 (1971).
8. The conditions are similar to those used in preparation of oxazolo[5,4-d]pyrimidines, Ji-wang Chern and Dean S. Wise, private communication.
9. A. E. Dixon and J. Taylor, J. Chem. Soc., 93, 648 (1908).
10. R. W. Lamon, J. Heterocyclic Chem., 5, 837 (1968).
11. M. J. Robins and R. K. Robins, J. Org. Chem., 34, 2160 (1969).
12. A. M. M. E. Omar, N. S. Habib and O. M. Aboulwafa, Synthesis, 864 (1977).

Received, 18th April, 1984