

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

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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 similarly to the known anthelmintics 2-methoxycarbonylamino benzimidazoles. 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 satisfactory⁷ 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, reactions where the reagent was generated *in situ* were preferred. Condensation of methoxycarbonyl isothiocyanate (1) (0.01 mole) with 2,4,5-triamino-6-benzyloxypyrimidine¹¹ (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, -OCH₃), 5.48 (s, 2H, -OCH₂), 6.17 [bs, 2H, NH₂ (exchangeable with D₂O)], 11.40 [bs, 1H, NH (exchangeable with D₂O)]; Anal. Calcd. for C₁₄H₁₄N₆O₃: 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-

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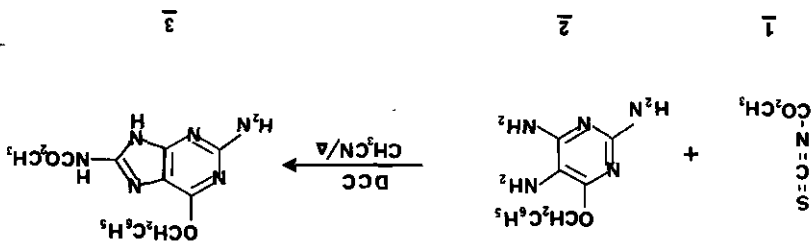
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The above example illustrates the versatility of methoxycarbonyl isothiocyanate for heterocyclic synthesis and additional studies in this area are in progress in our laboratory.



¹² For the condensation of aryl isothiocyanates with various α -phenylenediamines. A thio-ureido derivative is believed to be initially formed which in the presence of N,N'-dicyclohexyl-carbodiimide is converted to an unstable diimide intermediate which subsequently cyclizes to the