SYNTHESIS OF 5-[1-(3-METHOXYCARBONYL)-O-METHYLPSEUDOUREIDO]URACIL: A NOVEL METHOD FOR THE CONVERSION OF AN N,N'-DISUBSTITUTED THIOUREA INTO AN O-METHYL-N,N'-DISUBSTITUTED PSEUDOUREA

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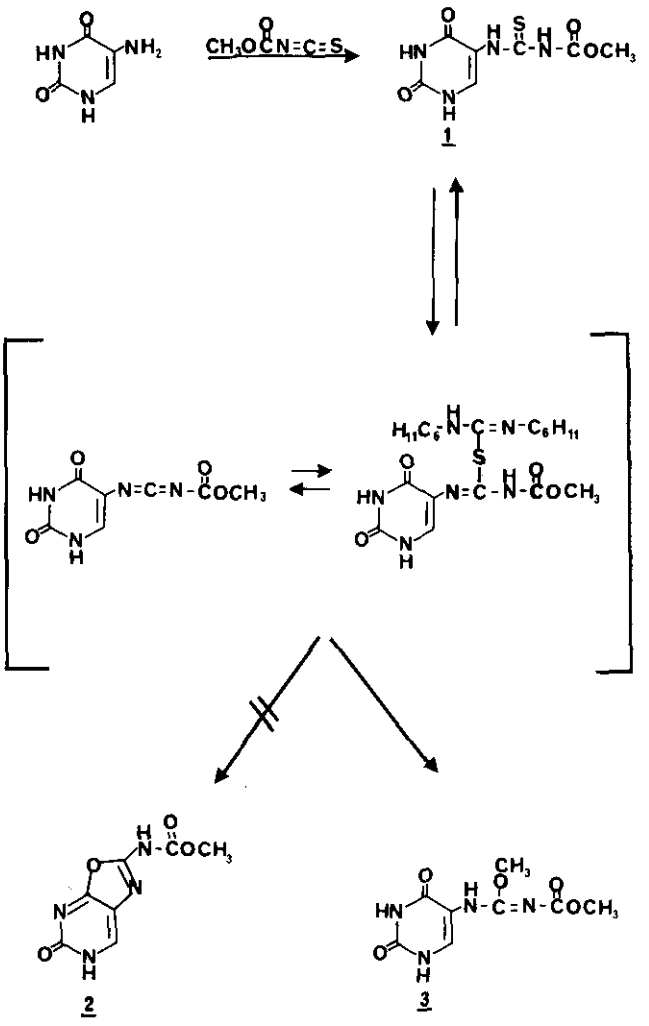
Abstract - Treatment of 5-[1-(3-methoxycarbonyl)thioureido]uracil with dicyclohexylcarbodiimide in methanol has resulted in the formation of 5-[1-(3-methoxycarbonyl)-O-methylpseudoureido]uracil.

A literature survey has revealed that several methods are available for the preparation of O-alkylpseudoureas from carbodiimides.[1,2] In the absence of catalysis, however, the reaction of carbodiimides with alcohols proceeds poorly and only under very drastic conditions, i.e., pressure and/or at high temperature.[3] It has been reported[4] that alcohols in the presence of sodium alkoxide, react exothermally with carbodiimides to afford the corresponding O-alkyl pseudoureas in near quantitative yields. Synthesis of O-alkyl pseudoureas using carbodiimide also has been accomplished with copper or zinc salts as catalysts.[5,6] However, to the best of our knowledge, the facile addition of alcohols to carbodiimides without the use of a catalyst or the aid of a sodium alkoxide, which should be of value with base sensitive compounds, has not yet been reported.

The equilibrium established between a reaction of dicyclohexylcarbodiimide (DCC) and a thiourea derivative[7], with the subsequent ring cyclization reaction of these ortho-substituted thiourea adducts to afford the various heterocyclic systems[8], has been studied. Recently, we reported on the use of DCC to accomplish the cyclodesulfurization of a 2,4-diamino-5-[1-(3-methoxycarbonyl)thioureido]pyrimidin-6-one in dimethylformamide (DMF) to furnish the oxazolo[5,4-d]-pyrimidine ring system[9]. To explore the scope of this synthetic methodology, we elected to synthesize methyl oxazolo[5,4-d]pyrimidin-6-one-2-carbamate (2) by reacting 5-[1-(3-methoxycarbonyl)thioureido]uracil (1)[10] with DCC in DMF at room temperature. However, due to the insolubility of 1 in DMF, the reaction was not successful.

A subsequent reaction of compound 1 with DCC was performed in methanol at reflux temperature to obtain a good yield of a single product which initially appeared to be the desired product 2. This product gave ^{1}H NMR, ^{13}C NMR, UV spectral data and elemental analysis as follows: ^{1}H NMR (DMSO-d_6): δ 3.6 (s, 3 H, CH_3), 3.8 (s, 3 H, CH_3), 7.58 (s, 1 H, =C-H), 10.2 (s, 1 H, NH, D_2O exchangeable), 11.28 (br, 2 H, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 149.9 (C-2), 160.6 (C-4), 111.3 (C-5), 131.9 (C-6), 163.0 (C=N), 160.8 (C=O), 52.3 ($COOCH_3$),

55.1 (O-$\underline{CH_3}$); UV (pH) λ_{max} nm (ε x 10^4): (pH 7) 288 (1.1); (pH 1) 261 (0.85); (pH 11) 291 (1.0); Anal. Calcd. for $C_8H_{10}N_4O_5$ (242.19): C, 39.67; H, 4.16; N, 23.13; Found: C, 39.90; H, 4.21; N, 23.37; and while it was obvious that these data did not support structure 2, they did seem to be compatible with a simple methanol adduct of the desired compound 2.



This seemed like a reasonable assumption since there have been many reports[12] that Michael additions occur quite often as an intermediate step in a variety of phenomena involving pyrimidines. If a Michael addition had occurred at C-6 of compound 1, the resulting compound would be expected to possess characteristics similar to those previously reported for the addition of methanol to the 5,6-double bond of 5-diazouracil[13]. In the ^{1}H NMR spectra, this 5-diazouracil methanol adduct has demonstrated an upfield chemical shift (δ 5.72) for the C-6 proton, however, the ^{1}H NMR spectrum of our compound revealed that a downfield chemical shift

(δ 7.58) had occurred for the C-6 proton. This suggested that the C-6 proton of the uracil moiety in our target compound was still incorporated in a conjugated aromatic (uracil) electronic system. The ^{13}C NMR chemical shift observed for the uracil ring carbons of our final product remained unchanged from the shifts observed for the ring carbons of 1 and are in agreement with values previously reported.[14] Also, the mass spectrum showed an ion at M^+-32 which is characteristic for the loss of methanol, and the ions at m/z 69 and 110 can be attributed to subsequent fragmentation of the M^+-32 fragment. On the basis of these data, vide infra, we have assigned the structure of our product as 5-[1-(3-methoxycarbonyl)-O-methylpseudoureido]-uracil (3).[15]

We have now reported the first addition of an alcohol to a carbodiimide intermediate which had been generated in situ from an adduct prepared by the reaction of a thiourea derivative with DCC. This synthetic method is currently being applied to the synthesis of various 5-substituted uracils and their corresponding nucleosides in our laboratory.

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10. 5-[1-(3-Methoxycarbonyl)thioureido]uracil (1) was prepared in 94% yield by a condensation of 5-aminouracil (0.44 g, 3.5 mmoles) with methoxycarbonyl isothiocyanate[11] [methoxycarbonyl isothiocyanate was prepared by adding methyl chloroformate (0.53 mL, 6.9 mmoles) to a suspension of potassium thiocyanate (0.67 g, 6.9 mmoles) in acetonitrile (15 mL) with stirring at 70°C for 30 min] in acetonitrile at reflux temperature for 2 hours. ^{1}H NMR (DMSO-d_6): δ 3.4 (s, 3 H, CH_3), 8.9 (d, 1 H, J = 6 Hz, = C-H) 10.9 (d, 1 H, J = 6 Hz, NH, D_2exchangeable), 11.4 (s, 1 H, NH, D_2O exchangeable), 11.65 (s, 1 H, NH, D_2O exchangeable), 11.75 (s, 1 H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6): δ 149.4 (C-2), 160.7 (C-4) 113.7 (C-5), 131.1 (C-6), 176.1 (C=S), 153.9 (C=O), 53.0 ($O\underline{C}H_3$). UV (pH) λ_{max} nm (ε x 10^4): (pH 7) 259 (2.2); 311 (1.0); (pH 1) 259 (2.0); (pH 11) 260 (1.6). IR (KBr): 1780 (C=O) cm^{-1}. Anal. Calcd. for $C_7H_8N_4SO_4$ (244.22): C, 34.43; H, 3.30; N, 22.94. Found: C, 34.54; H, 3.36; N, 23.11.

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15. The exocyclic pseudourea moiety of compound 3 may exist in two tautomeric forms [$-NHC(OCH_3)=NCO_2CH_3$ and/or $-N=C(OCH_3)NHCO_2CH_3$].

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