A Convenient Synthesis of 2-*N*-Methoxycarbonylaminooxazolo[5,4-*d*]pyrimidines [1]

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A facile synthesis of methyl oxazolo[5,4-*d*]pyrimidine-2-carbamic acids by the cyclodesulfurization of a methoxycarbonyl thiourea with dicyclohexylcarbodiimide is described.

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As part of our synthetic study to prepare oxo and aza congeners of the anthelmintic methyl benzimidazole-2-carbamates, we were interested in preparing examples of the oxazolo[5,4-*d*]pyrimidine ring system possessing a 2-amino or protected 2-amino functionality such as a 2-*N*-alkoxycarbonylamino group as potential antifilarial agents. A perusal of the literature revealed that although numerous oxazolo[5,4-*d*]pyrimidines are known [2-4], the requisite type of compound had not been described. However, there were several reports which indicated that alkoxycarbonyl isothiocyanates should be well suited to the construction of the desired compounds [5,6], *e.g.*, the reaction of ethoxycarbonyl isothiocyanate [7] with *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol has afforded intermediate *N*-ethoxycarbonyl thiourea adducts which upon heating cyclize with the loss of hydrogen sulfide to provide 2-(*N*-ethoxycarbonylamino)benzimidazoles, benzoxazoles, and benzothiazoles respectively [8]. In addition to thermal cyclizations, the intermediate thiourea derivative has also been annulated using cupric acetate in acetic acid, [9] or by thio alkylation with an alkyl halide and subsequent thermal cyclization of the 2-alkylpseudothiourea derivative [9]. We now wish to report a convenient preparation of oxazolo[5,4-*d*]pyrimidines possessing a 2-*N*-methoxycarbonylamino moiety. The reaction involves the condensation of a 5-aminopyrimidin-4-one derivative with methoxycarbonyl isothiocyanate, isolation of the intermediate 5-*N*-methoxycarbonylthiourea derivative and subsequent cyclodesulfurization of this derivative with dicylcohexylcarbodiimide.

The free base of 6-benzylamino-2,5-diaminopyrimidin-4-one (**2a**) [10], was prepared from 2-amino-6-benzylamino-5-formamidopyrimidin-4-one (**1a**) [11]. Compound **2a** was suspended in acetonitrile, and then treated with 1.5 equivalents of methoxycarbonyl isothiocyanate [12a,12b] to afford 2-amino-6-benzylamino-5-[1-(3-methoxycarbonyl)thioureido]pyrimidin-4-one (**3a**) in 52% overall yield; ir (potassium bromide): 3490, 3390, 3330, 3230 (NH), 3030 (=C-H), 2960 (-CH_2), 1740 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.7 (s, 3H, CH_3), 4.55 (d, 2H, CH_2), 6.35 (s, 2H, NH_2, deuterium oxide exchangeable), 6.85 (t, 1H, NH, deuterium oxide exchangeable).

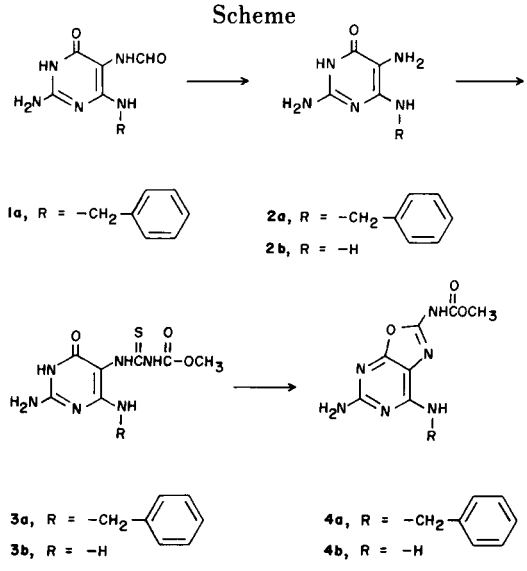
Anal. Calcd. for $C_{14}H_{16}N_6SO_3$: C, 48.27; H, 4.62; N, 24.12. Found; C, 48.15; H, 4.83; N, 23.87.

To effect cyclization, compound **3a** (0.37 g, 1.06 mmoles) was dissolved in 20 ml of dimethylformamide and treated with dicyclohexylcarbodiimide (0.62 g, 3.18 mmoles) to furnish methyl 6-amino-4-benzylaminooxazolo-[5,4-*d*]pyrimidine-2-carbamate (**4a**) in 87% (mp 250° softening, 278-280° dec); ir (potassium bromide): 3500, 3420, 3300 (NH), 3180 (NH_2), 3080 (=CH), 2950 (-CH_2-), 1770 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.70 (s, 3H, CH_3), 4.65 (d, 2H, CH_2), 6.20 (s, 2H, NH_2, deuterium oxide exchangeable), 7.32 (s, 5H, Ar-H), 7.9 (t, 1H, NH, deuterium oxide exchangeable), 11.08 (s, 1H, NH, deuterium oxide exchangeable); uv: (*p*H 7) λ max, nm ($\epsilon \times 10^4$), 284 (2.2); (*p*H 1), 268 (2.5), 306 (1.4); (*p*H 11), 297 (2.5).

Anal. Calcd. for $C_{14}H_{14}N_6O_3$: C, 53.50; H, 4.49; N, 26.74. Found: C, 53.53; H, 4.64; N, 26.63.

Under similar reaction conditions, treatment of 2,4,5-triaminopyrimidin-6-one (**2b**) [13] with methoxycarbonyl isothiocyanate, furnished 2,4-diamino-5-[1-(3-methoxycarbonyl)thiourea]pyrimidin-6-one (**3b**) (mp > 360°) in 63% yield. Subsequent treatment of **3b** with dicyclohexylcarbodiimide in dimethylformamide gave methyl 4,6-diaminooxazolo[5,4-*d*]pyrimidine-2-carbamate (**4b**) in 84% yield

Scheme



(mp > 300°); ^{1}H nmr (DMSO-d_6): δ 3.7 (s, 3H, CH_3), 6.10 (s, 2H, NH_2, deuterium oxide exchangeable), 6.90 (s, 2H, NH_2, deuterium oxide exchangeable), 11.10 (br, 1H, NH, deuterium oxide exchangeable); uv: (*p*H 7) λ max nm (ε × 10^4), 269 (1.8); (*p*H 1), 264 (2.2); (*p*H 11), 282 (1.0), 296 (2.1).

Anal. Calcd. for $C_7H_8N_6O_3 \cdot H_2O$: C, 34.71; H, 4.16; N, 34.70. Found: C, 34.97; H, 4.25; N, 34.85.

That the oxazolo[5,4-*d*]pyrimidine derivative was indeed isolated from the reaction; rather than a possible 8-aminopurine derivative, was substantiated by the ^{1}H nmr spectra of **4a**. The triplet observed for the 4-NH and the doublet observed for the methylene of the benzylamino moiety confirms the formation of an oxazolo[5,4-*d*]pyrimidine ring system as the product of the reaction. Under deuterium exchange conditions the methylene splitting pattern collapses to a singlet. In addition, an oxazolopyrimidine to purine rearrangement could be accomplished by treatment of the oxazolo[5,4-*d*]pyrimidine **4a** with potassium bicarbonate in methanol under reflux and anhydrous conditions to effect the rearrangement to the purine (methyl 9-benzylguanine-8-carbamate) in 87% yield (mp 321-322° dec); uv: (*p*H 7) λ max nm (ε × 10^4), 266 (3.4); (*p*H 1), 259 (3.6); (*p*H 11), 264 (2.8), 273 (2.6), 289 (2.7).

Anal. Calcd. for $C_{14}H_{14}N_6O_3$: C, 53.50; H, 4.49; N, 26.74. Found: C, 53.21; H, 4.57; N, 26.60.

The cyclization is believed to proceed *via* formation of a reactive carbodiimide intermediate, similar to that reported for the cyclization of *o*-aminophenyl aryl and alkyl thioureas [14]. That the purine ring system was not formed in these reactions may be due to the delocalization of the lone pair of electrons on the 4-amino group decreasing the basicity and nucleophilicity of this moiety. This procedure for the cyclodesulfurization of the methoxycarbonyl-thioureido adduct should be adaptable to the synthesis of other bicyclic heterocyclic systems such as, purines or thiazolopyrimidines and additional studies in this area are in progress.

REFERENCES AND NOTES

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