

THE NOVEL RING OPENING OF AN OXAZOLO[5,4-d]PYRIMIDINE AND SUBSEQUENT REARRANGEMENT TO FORM AN IMIDAZO[4,5-d]PYRIMIDINE

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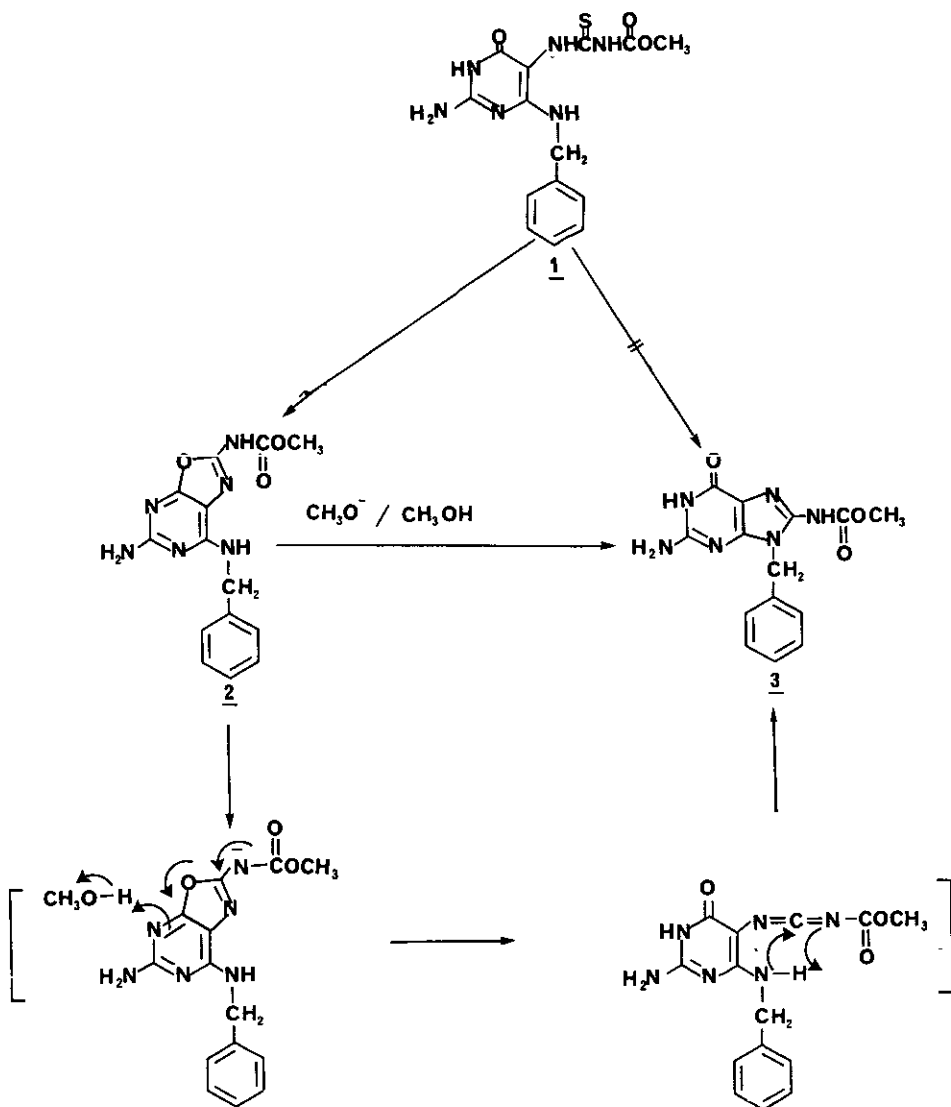
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Abstract - A novel rearrangement from methyl 6-amino-4-benzylaminooxazolo[5,4-d]pyrimidine-2-carbamate to methyl 9-benzylguanine-8-carbamate (**3**) is described.

Our attempt to synthesize methyl 9-benzylguanine-8-carbamate (**3**) by a direct cyclodesulfurization of 2-amino-4-benzylamino-5-[1-(3-methoxycarbonyl)thioureido]pyrimidin-6-one (**1**) with dicyclohexylcarbodiimide was unsuccessful. Using the reaction conditions which were specifically designed to effect a direct conversion of **1** to **3**, we have obtained only 6-amino-4-benzylaminooxazolo[5,4-d]pyrimidine-2-carbamate (**2**). However, we have now developed reaction conditions which effect a novel ring opening of compound **2** followed by a rearrangement and recyclization to afford compound **3**. In essence, this represents a facile conversion of compound **1** into compound **3**. It has been well documented that various 1,2,4-oxadiazoles undergo a mononuclear heterocyclic rearrangement to various heterocyclic compounds under experimental conditions such as heating or treatment with a base, *i.e.*, potassium hydroxide or sodium methoxide in methanol^{2,3}. Also numerous 7-aminooxazolo[5,4-d]pyrimidines are known to undergo an intramolecular rearrangement to imidazo[4,5-d]pyrimidin-6-ones by heating in formamide or dilute sodium hydroxide^{4,5}. The mechanism postulated for the rearrangement of these oxazolo[5,4-d]pyrimidines to an imidazo[4,5-d]pyrimidine assumes that an initial nucleophilic substitution occurs at the carbon atom of the oxazole ring effecting a ring opening to an intermediate 5-acylamino-4-amino-6-oxopyrimidine anion. Subsequent annulation through nucleophilic attack of the C-4 amino group on the acyl carbonyl carbon then affords the imidazo[4,5-d]pyrimidine ring system. To the best of our knowledge, an intramolecular ring-opening-recyclization of a 7-aminooxazolo[5,4-d]pyrimidine which proceeds through a carbodiimide intermediate to an imidazo[4,5-d]pyrimidine has not been described. We now wish to report a facile synthetic procedure for the synthesis of compound **3** from compound **2** through a presumed carbodiimide intermediate.

A mixture of compound **2**¹ (2.45 g, 7.8 mmoles), anhydrous potassium carbonate (2.2 g, 15.6 mmoles) in anhydrous methanol (50 mL) was heated under reflux for 5 hours. The solvent was

removed in vacuo and the resulting solid was dissolved in water (20 mL). Upon the addition of an aqueous ammonium chloride solution [1.68 g, (31.2 mmoles) in water (20 mL)] the solid which had precipitated was collected by filtration. The solid was washed with cold water (10 mL) and then



methanol (5 mL) to furnish 2.13 g (87%) of crude compound **3**. The solid was recrystallized from a DMF and methanol mixture (1:1); mp 321-322° dec.; ir (KBr): 3450, 3280, 2920, 1740 cm^{-1} ;

^1H NMR (DMSO-d_6): δ 3.4 (s, 3 H, CH_3), 5.1 (s, 2 H, CH_2), 6.58 (s, 2 H, NH_2 , D_2O exchangeable), 7.3 (m, 5 H, Ar-H), 9.8 (br, 1 H, NH, D_2O exchangeable), 10.7 (s, 1 H, NH, D_2O exchangeable); uv: $\lambda_{\text{max}}^{\text{pH } 7}$ 266 nm (ϵ 1.7×10^4), $\lambda_{\text{max}}^{\text{pH } 1}$ 259 nm (ϵ 1.8×10^4), $\lambda_{\text{max}}^{\text{pH } 11}$ 264 nm (ϵ 1.4×10^4), 273 nm (ϵ 1.3×10^4), 289 nm (ϵ 1.4×10^4). A reasonable mechanism for this reaction involves the initial abstraction of a proton from the 2-carbamoyl moiety of compound 2, followed by an opening of the oxazole ring to give a carbodiimide intermediate. Subsequent addition of the C-4-amino nucleophile to the carbon atom of the carbodiimide, then furnishes the imidazo[5,4-d]pyrimidin-6-one derivative 3.

The mechanism of this facile rearrangement and its application to the synthesis of other heterocyclic systems is under further investigation in our laboratory.

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