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A CONVENIENT SYNTHESIS OF MUSCIMOL BY A 1,3-DIPOLAR CYCLOADDITION REACTION

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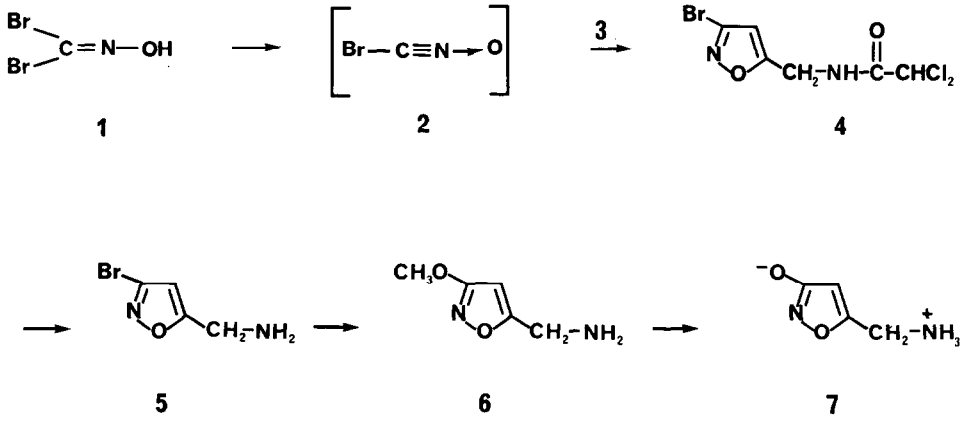
Abstract: A simple and large scale approach to the synthesis of muscimol 7 has been developed starting from the easily available dibromoformaldoxime **1**.

Muscimol 7, a semirigid analogue of γ-aminobutyric acid (GABA)[1], is a centrally active constituent of Amanita muscaria, a mushroom endowed with psychotropic effects. The preparation of muscimol derivatives has been limited by the difficult availability of muscimol 7 in gram scale.

Among the several synthetic approaches[2] described since the muscimol 7 isolation[3], the preparation reported by Gagneux and co-workers[4] is one of the most interesting routes. The limitation within this synthesis is the problematic obtainment of 5-aminomethyl-3-bromoisoxazole 5 which has been prepared starting from 4-nitro-2-butanone in poor yield[5]. Moreover Bowden and co-workers encountered difficulties in repeating this work[6].

In the present communication, we wish to report a new and simple synthesis of 5-aminomethyl-3-bromoisoxazole 5, enabling us to achieve a convenient and large scale preparation of muscimol 7. Our synthetic strategy enables us to obtain the intermediate 5 in high yield using a 1,3-dipolar cycloaddition between bromonitrile oxide 2 generated in situ from stable and easily available dibromoformaldoxime 1[7] and N-dichloroacetylpropargylamine 3[8].



The use of appropriate proceeding conditions is required to minimize the high tendency of the dipole toward dimerization to dibromofuroxan a potentially dangerous by-product[9].

In order to reconcile the low reactivity of propargylamine as dipolarophile and the short time of dimerization of nitrile oxide 2 an appropriate excess[10] of the acetylenic derivative and a low basicity of the medium are needed. The basicity necessary to (very slowly) generate the nitrile oxide is obtained using a weak base such as potassium bicarbonate in heterogenous phase. Since the presence of a base as propargylamine in homogeneous phase is sufficient to make the dipole dimerization predominant, the use of an easily removable protecting group such as dichloroacetyl is necessary.

Thus, a solution of dibromoformaldoxime 1[7] (0.5 mol) in ethyl acetate is added to a stirred mixture of N-dichloroacetylpropargylamine 3[8] (1.0 mol) and potassium bicarbonate (1.5 mol) in wet ethyl acetate. Crude intermediate 4 is treated with aqueous 36% hydrobromic acid at 120°C for 4 hours to give 5-aminomethyl-3-bromoisoxazole 5 (m.p. 170°C dec. as hydrochloride; 80%). Derivative 5 is refluxed in aqueous methanolic solution of potassium hydroxide for 48 hours to obtain 5-aminomethyl-3-methoxyisoxazole 6[4] (m.p. 175°C dec. as hydrochloride; 68%) which is heated at reflux in 33% hydrobromic acid in acetic acid for 10 minutes[6]. Muscimol 7 is obtained as a white solid by a chromatography on the ion-exchange resin IR 120 eluting with 2% aqueous ammonium hydroxide (m.p. 172-174°C dec. 64%). Analytical and spectroscopic data (NMR, UV, MS, TLC) of this substance are in complete agreement with the literature[11].

In conclusion, our synthetic route is the first applicative example of a 1,3-dipolar cycloaddition reaction in the synthesis of the isoxazole ring of muscimol 7. The simple procedure of our method makes available in large quantities muscimol 7 which is prepared in an overall yield of 35% starting from dibromoformaldoxime 1.

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