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AN IMPROVED SYNTHESIS OF MUSCIMOL

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Abstract: A regiospecific 1,3-dipolar cycloaddition/elimination is the key-step of a convenient, gram-scale synthesis of the GABA-agonist muscimol (**1**).

Muscimol (**1**), a structural analogue of γ-aminobutyric acid (GABA) first isolated from mushrooms of the genus *Amanita*[1], has been the subject in recent years of considerable pharmacological interest[2] and synthetic effort[3]. Among several synthetic approaches, the formation of the isoxazole moiety by a 1,3-dipolar cycloadditive process has been shown to be convenient and suitable for large scale preparations[4]. We report an improved synthesis of muscimol which exploits the regiospecific[5]

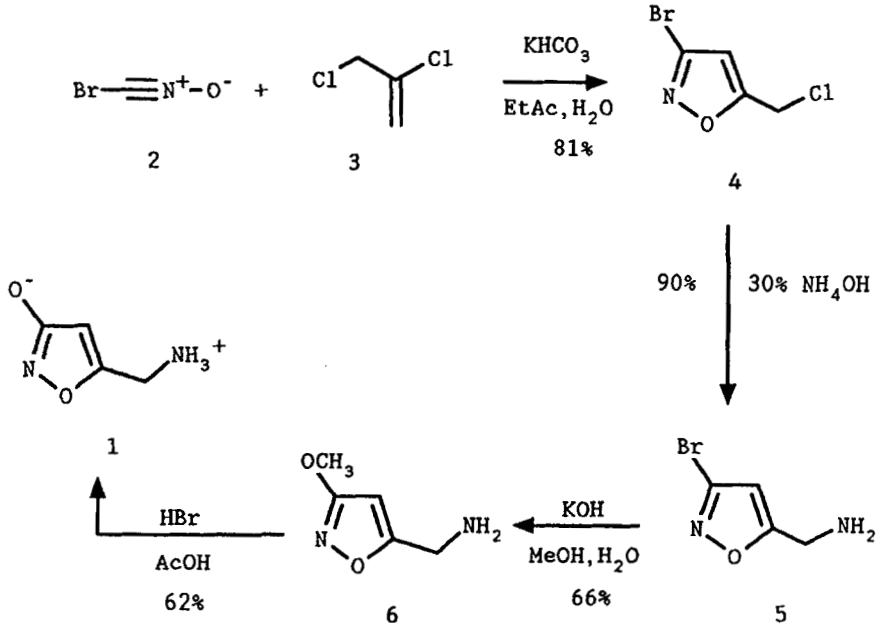

FIG. 1

1,3-dipolar cycloaddition/elimination[6] of bromonitrileoxide (**2**)[7] to commercially available 2,3-dichloro-1-butene (**3**)(**FIG 1**).

While this synthesis is almost equivalent to the previous 1,3-dipolar cycloaddition procedure[4] in terms of yields, the starting dipolarophile (**3**) is less expensive than propargylamine and can be used as such. Thus one can avoid the necessity of protecting the dipolarophile and spare one step. Furthermore, reaction conditions required to obtain the common

intermediate (**5**) from the cycloadduct are milder than those reported in the previous work (4h/NH_4OH/r.t. vs. 4h/HBr 48%/130 °C).

As far as other short synthetic procedures[3e,f,h] are considered, this method provides an useful alternative because no anhydrous conditions are required at any stage of the synthesis and very low-cost reagents, except dipolarophile (**3**), are employed.

Attempts to carry out a "one-pot" synthesis gave lower total yields (8-9 vs. 30% in the four-step synthesis) and gave rise to problems in isolating muscimol from a complex mixture.

The whole process can be carried out without any chromatographic separation or crystallisation, up to compound (**6**).

Experimental

Melting points are uncorrected. IR-spectra were recorded on a Perkin-Elmer 297. ^{1}H-NMR spectra were acquired on a Bruker WP 80 SY or AT 200, respectively at 80 and 200 Mhz. Chemical shifts are reported in ppm relative to internal Me_4Si. MS spectra were recorded on a CH-7 Varian MAT spectrometer at 70 eV.

Elemental analyses were performed by our analytical laboratories and agreed with theoretical values within 0.4%. Common reagent grade chemicals and starting materials were purchased from commercial sources and used as received.

1. 5-Chloromethyl-3-bromoisoxazole (4)

2,3-Dichloro-1-propene (24.4 g, 0.238 mol) was dissolved in ethyl acetate (320 ml); 23.8 g (0.238 mol) of potassium hydrogen carbonate and 32 ml of water were added and the mixture stirred at r.t. for 1 hour. To this suspension, 24.1 g (0.119 mol) of dibromoformaldoxime[6] in ethyl acetate (32 ml) were added dropwise within 4 hours. The mixture was allowed to stand overnight after which water (100 ml) was added. Extraction with ethyl acetate (2x100 ml), drying over sodium sulfate and evaporation gave (4) as a pale-yellow oily residue (22.2 g;81%) which was pure enough to be used in the next step. For analytical purpose, a sample was further purified by distillation (b.p. 110 °C/20mm; colourless liquid).

^{1}H-NMR (δ $CDCl_3$): 4.59 (s,2H,CH_2Cl); 6.39 (s,1H,H-4).

MS (m/z eV): 195 ($M^{+\cdot}$), 160, 146 (100%).

IR (ν-cm^{-1}) 1595, 1435, 1360, 1290, 1270, 1150, 995, 955, 800, 740.

TLC: R_f 0.58 (Cyclohexane/Ethyl acetate;90/10).

Anal. for $C_4H_3BrClNO$ (C,H,N,Br,Cl).

2. 5-Aminomethyl-3-bromoisoxazole (5)

6.6 g (0.0283 mol) of (**4**) were dissolved in dioxane (75 ml) while cooling the reaction mixture in an ice-bath at 0-5 °C. 200 ml of 30% NH_4OH were dropped to this solution at a flow-rate of 5 ml/min. Stirring was continued for 1/2 hour at 0-5 °C and 4 hs at r.t.. The mixture was concentrated to about 100 ml and extracted with ethyl acetate (3x75 ml) and ethyl acetate/n-butanol (1:1; 1x50 ml) to give, after drying and evaporation, 4.5 g (90%) of (**5**) as a brownish fluid. A sample was transformed into its hydrochloride for comparison with literature data. [m.p. 180 °C (dec.); lit.: 175 °C (dec.)[3a]]

^{1}H-NMR (δ DMSO): 4.29 (s,2H,$CH_2NH_3^+$), 6.95 (s,1H,H-4), 8.82 (bs,3H,NH_3^+).

MS (m/z eV): 176 ($M^{+\cdot}$), 175, 97 (100%).

IR (ν-cm^{-1})3420, 3130, 1610, 1510, 1370, 1235, 1080, 960, 910, 840.

TLC: R_f 0.31 ($CHCl_3$:CH_3OH:30%NH_4OH;95:5:0.5)

Anal. for $C_4H_5BrN_2O \cdot HCl$ (C,H,N,Br,Cl).

3. 5-Aminomethyl-3-methoxyisoxazole (6)

3 g of (**5**)(0.0169 mol) were dissolved in methanol (60 ml) and 4.73 g (0.0845 mol; 5 eq) of potassium hydroxide in 6 ml of water were added. The mixture was heated 24 h at reflux, under nitrogen. A further 4.73 g of base (tot: 0.169 mol; 10 eq) were added and heating continued for 24 h. After evaporation, the residue was taken up with ethyl acetate and extracted (3x50 ml) to give (**6**) as a colourless fluid (1.43 g; 66%), which was purified by flash-chromatography (eluant: $CHCl_3$:CH_3OH;95:5).An analytical sample was transformed into its hydrochloride [m.p. 175 °C(dec.); lit:175 °C (dec.)[3a,4]].

^{1}H-NMR (δ D_2O): 3.95 (s,3H,OCH_3), 4.31 (s,2H,CH_2N), 6.25 (s,1H,H-4).

MS (m/z eV): 128 ($M^{+\cdot}$),112,97.

IR (ν-cm^{-1}): 3400, 3150, 1625, 1505, 1250, 1150, 1070, 1025, 960, 935, 720.

TLC :R_f: 0.29 ($CHCl_3$:CH_3OH:30%NH_4OH;95:5.0.5).

Anal. for $C_5H_8N_2O_2$.HCl (C,H,N,Cl).

4. 5-Aminomethyl-3-hydroxyisoxazole (muscimol;1)

A solution of derivative (**6**)(2.0 g; 0.0156 mol) was treated with 50 ml of 33% HBr in AcOH and refluxed for 15 min. After cooling, the solution was mixed with cyclohexane (3x50 ml) and evaporated three times. The pale brown solid residue was dissolved in water and purified on Dowex W50X8-200 mesh (H^+-form) eluting with water and then with 2% NH_4OH. Evaporation gave muscimol (**1**) as a white solid (1.1 g; 62%; lit. 64%[4]);(m.p. 175°C (dec.); lit.: values range from 170 to 175 °C[3a-d,f-h]; 176-178 °C[3e]). ^{1}H-NMR, MS, IR and TLC were in agreement with literature[3g,1f].

Anal. for $C_4H_6N_2O_2.\frac{1}{2}H_2O$ (C,H,N,H_2O).

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