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SIMPLE SYNTHESIS OF γ-CARBOLINES

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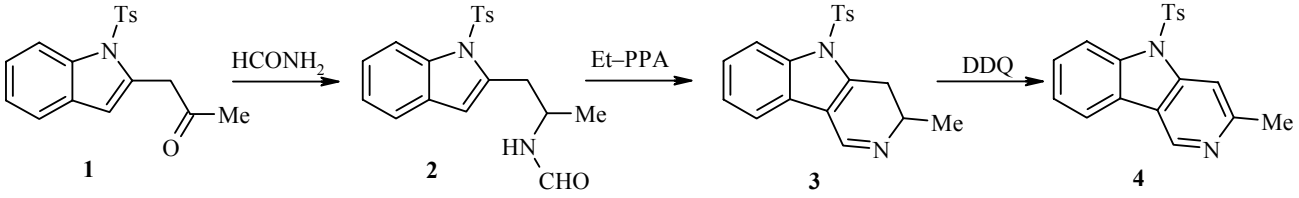
γ-Carboline derivatives and their hydrogenated analogs are less popular than the structurally isomeric β-carbolines [1]. None the less, γ-carbolines are of interest pharmacologically since compounds having various forms of biological activity are found in this class [2-5] and so the development of novel routes of synthesizing the γ-carboline framework is timely. Thanks to the availability of tryptamine derivatives, electrophilic cyclizations of the Pictet-Spengler, Bischler-Napieralski and related type processes are widely used for the synthesis of β-carbolines [1]. Analogous reactions amongst methods for preparing γ-carbolines [2, 6-9] occupy a modest placement [10, 11] and this is likely related to the lesser availability of the corresponding amines.

In this work we report preliminary data regarding a novel synthesis of γ-carbolines in which the key stage is a Bischler-Napieralski reaction. As a result of a Leuckart-Wallach type reductive amination the indole **1** [12] gave the amide **2**. Refluxing compound **2** in ethyl polyphosphate led to the dihydro-γ-carboline **3** which we were unable to separate in a pure state. TLC analysis of the reaction mixture after work up showed the basic product **3** and, unexpectedly, compound **4** was also formed, likely through a disproportionation reaction. Work up of this mixture with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave the γ-carboline **4** in 38% yield for the two stages.



^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 instrument (300 and 75 MHz respectively) using $CDCl_3$ with TMS as internal standard. IR spectra were taken on a Shimadzu IR Prestige-21 instrument for KBr tablets.

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N-[1-(Tosyl-1H-indol-2-yl)-2-propyl]formamide (2). A mixture of compound **1** (5 g, 15 mmol) in formamide (100 ml) was refluxed for 40 min (TLC monitoring). The reaction mixture was poured into water (1 litre). The precipitate formed was filtered off and recrystallized from a mixture of dichloromethane and hexane. Yield 4 g (75%) as a white powder. The compound obtained was used in the subsequent stage without further purification.

3-Methyl-5-tosyl-5H-pyrido[4,3-*b*]indole (4). A mixture of compound **2** (2 g, 5.6 mmol) in ethyl polyphosphate (Et-PPA) (40 ml) was refluxed for 4 h (TLC monitoring). The reaction mixture was poured into water (300 ml), neutralized with $NaHCO_3$, and extracted with ethyl acetate (3×50 ml). The extract was dried over Na_2SO_4, filtered, treated with carbon, and the solvent was removed *in vacuo*. DDQ (0.2 g) was added and the product was refluxed for 5-7 min (TLC monitoring). The reaction mixture was then poured into water (100 ml) and extracted with ethyl acetate (3×30 ml). Solvent was removed *in vacuo* and the residue was column chromatographed using benzene–hexane (1:3). Yield 0.72 g (38%) as a light-cream powder; mp 173-174ºC (mixture of benzene and hexane). IR spectrum, ν, cm^{-1}: 1596, 1456, 1366, 1175, 1153, 980, 708. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.27 (3H, s, CH_3); 2.74 (3H, s, CH_3); 7.14 (2H, d, *J* = 8.1, H Ts); 7.34-7.39 (1H, m, H Ar); 7.46-7.52 (1H, m, H Ar); 7.73 (2H, d, *J* = 8.1, H Ts); 7.92-7.94 (1H, m, H Ar); 8.05 (1H, s, H Py); 8.23-8.26 (1H, m, H Ar); 9.05 (1H, s, Py). ^{13}C NMR spectrum, δ, ppm: 21.5, 25.1, 108.4, 114.7, 120.0, 120.1, 124.0, 124.4, 126.5 (2C); 127.8, 129.9 (2C); 134.7, 137.9, 141.8, 144.3, 145.5, 156.5. Found, %: C 67.98; H 4.57; N 8.12. $C_{19}H_{16}N_2O_2S$. Calculated, %: C 67.84; H 4.79; N 8.33.

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