

SOME NEW SYNTHETIC APPROACHES FOR THE PREPARATION OF PTERIDINE-3-OXIDES AND PTERIDINES

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Abstract - Starting from 2-amino-3-cyanopyrazine some new syntheses of 4-substituted pteridines and pteridine-3-oxides have been devised.

The chemistry of o-aminonitriles has been extensively investigated¹ and several useful syntheses have been elaborated in the past for the formation of bi- and polycyclic heterocycles. As a continuation of our investigations to use substituted heterocyclic amidines as synthons for new heterocycles²⁻¹² we like to report on a new and useful approach for the preparation of various 4-substituted pteridines and their 3-oxides.

As starting compound 2-amino-3-cyanopyrazine (**1**) was used. It reacted at room temperature to give the amidoxime (**2**, $R=R_1=H$) in 85% yield, mp 185-187°C (H_2O); m/e 153 (M^+) and nmr δ (DMSO- d_6) 7.40 and 7.58 (d, H_5 and H_6), 5.62 and 7.02 (broad s, NH_2), 9.64 (s, OH), $J_{5,6} = 2.4$ Hz. The amidoxime can be O-acylated and the acylation site is shown by further transformations into compound **7** ($R = COMe$). Thus, with acetic anhydride the O-acetyl compound **2** ($R_1 = H$, $R = COMe$) was obtained in almost quantitative yield, mp 170-171.5°C (EtOH), m/e 195 (M^+), and with benzoyl chloride and in the presence of triethylamine the O-benzoyl derivative **2** ($R_1 = H$, $R = CPh$) was obtained in 97% yield, mp 216-218°C (EtOH); m/e 257 (M^+). Treatment of the amidoxime **2** ($R=R_1=H$) with methyl iodide in the presence of sodium propoxide afforded the O-methyl derivative **2** ($R_1 = H$, $R = Me$) in 48% yield, mp 108-110°C (H_2O); m/e 167 (M^+) and nmr δ (DMSO- d_6) 7.23 and 7.43 (d, H_5 and H_6), 3.52 (s, Me), 5.67 and 6.80 (broad s, NH_2), $J_{5,6} = 2.4$ Hz.

On the other hand, compound **1** was transformed with N,N-dimethylformamide dimethyl acetal at room temperature into **3** ($R = NMe_2$) in 89% yield, mp 86-88°C ($CHCl_3$ and petroleum ether); m/e 175 (M^+) and nmr δ (DMSO- d_6) 8.31 (s, CH), 7.83 and 8.07 (d, H_5 and H_6), 3.06 (s, Me) 2.97 (s, Me), $J_{5,6} = 2.4$ Hz.¹³ Alternatively, from **1** and triethyl orthoformate after 15 h under reflux the ethoxymethylene derivative **3** ($R = OEt$) was obtained in 50% yield, mp 119°C (from cyclohexane); m/e 176 (M^+) and nmr δ ($CDCl_3$) 8.16 (s, CH), 8.04 (s, H_5 and H_6), 4.31 (q, OCH_2Me), 1.36 (t, OCH_2CH_3), $J_{Et} = 7.0$ Hz. The amidine **3** ($R = NMe_2$) reacted readily with free hydroxylamine at 0°C to give compound **4** in 89% yield, mp 230-233°C (conversion into **5**, $R = H$) (EtOH); m/e 196 (M^+) and nmr δ (DMSO- d_6) 7.77 and 7.86 (d, H_5 and H_6), 7.60 (d, CH), 7.77 (broad s, NH_2), 10.05 (s, OH), 10.59 (d, NH), $J_{5,6} = 2.4$, $J_{CHNH} = 9.5$ Hz.

Several attempts to obtain 4-aminopteridine-3-oxide from the above precursors should be mentioned. The reaction between 2 ($R = R_1 = H$) and triethyl orthoformate afforded the N-oxide 5 ($R = H$) in 80% yield, mp 275-278°C (H_2O); m/e 163 (M^+) and nmr δ (D_2O , 95°) 8.52 and 8.62 (d, H_6 and H_7), 8.49 (s, H_2), $J_{6,7} = 2.0$ Hz. Alternatively, the amidine 3 ($R = NMe_2$) when heated in an alcoholic solution of hydroxylamine hydrochloride for 40 min afforded a mixture of several products. The main product, which was filtered from the mixture, obtained after evaporation of the solvent and treatment of the residue with water, was the N-oxide 5 ($R = H$) (80% yield) and from the filtrate compound 2 ($R = R_1 = H$) could be isolated in 11% yield. By tlc compound 1 and 2-amino-3-pyrazinecarboxamide could be detected in the filtrate.

4-Aminopteridine-3-oxide (5, $R = H$) could be reduced with aqueous solution of titanium trichloride at room temperature into 4-aminopteridine (6) in low yield (11%). The later compound is obtainable in high yield (87%) from the ethoxymethylene derivative 3 ($R = OEt$) and methanolic ammonia at room temperature after 24 h, mp 309-312°C (EtOH) (Lit. ¹⁵ gives mp 305°); m/e 147 (M^+) and nmr δ (DMSO- d_6) 8.14 (s, H_2), 8.36 and 8.63 (d, H_6 and H_7), 7.50 (broad s, NH_2), $J_{6,7} = 1.8$ Hz. In the same manner the amidine 3 ($R = NMe_2$) afforded at room temperature after 1 week 4-aminopteridine 6 in 58% yield.

4-Aminopteridine-3-oxide could be easily transformed in boiling water after 7 h into the 4-hydroxylamino compound 7 ($R = H$) in 73% yield, mp over 310°C (from H_2O); m/e 163 (M^+) and nmr δ (DMSO- d_6 , 130°) 7.33 (s, H_2), 7.96 and 8.10 (d, H_6 and H_7), $J_{6,7} = 2.3$ Hz. This transformation proceeds by ring opening at the pyrimidine ring followed by ring closure involving the former 4-amino function. This is substantiated by the presence of a small amount of compounds 1 and 2 ($R = R_1 = H$) in the filtrate. The hydroxylamino compound 7 ($R = H$) is acetylated with acetic anhydride to give the O-acetyl derivative (7, $R = COMe$) which is in turn obtained in 29% yield from the reaction between 2 ($R_1 = H$, $R = COMe$) and triethyl orthoformate after 6 h under reflux, mp 231-234°C (from H_2O); m/e 205 (M^+) and nmr δ (DMSO- d_6 , 50°) 7.52 (s, H_2), 8.15 and 8.30 (d, H_6 and H_7), 2.08 (s, Me), 3.35 (broad s, NH), $J_{6,7} = 2.2$ Hz. The O-methyl derivative can be prepared in a similar way from 2 ($R_1 = H$, $R = Me$) in 54% yield, mp 263-266°C (from EtOH); m/e 177 (M^+).

The above described reaction paths are suitable also for the synthesis of 2-substituted derivatives as exemplified in the following cases. Acetylation of 1 afforded a mixture of the monoacetyl and diacetyl derivatives in a ratio of about 2:1 and recrystallization from ethyl acetate afforded the pure monoacetyl derivative, mp 147°C, m/e 162 (M^+). The diacetyl derivative had mp 70-71°C (from H_2O). Each of these compounds reacted with free hydroxylamine at room temperature to give after 80 min the corresponding monoacetylated amidoxime (2, $R_1 = COMe$, $R = H$) in about 80% yield, mp 159-161°C (from EtOH), m/e 195 (M^+). The later compound, when heated either in the presence of glacial acetic acid for 1 h under reflux or in the presence of polyphosphoric acid at 70-80°C for 1.5 h, afforded the pteridine 5 ($R = Me$) in 79% and 40% yield, respectively, mp 278-280°C; m/e 177 (M^+).

and nmr δ (D_2O , 78°) 8.19 and 8.32 (d, H_6 and H_7), 2.60 (s, Me), $J_{6,7} = 1.8$ Hz. However, if compound 1 was acetylated with a mixture of acetic anhydride and glacial acetic acid (1:1) for 3 h, 2-acetylaminopyrazine-3-carboxamide was obtained in 50% yield, mp $219-221^\circ C$ (from EtOH); m/e 181 (M^+) (Lit. ¹⁶ gives mp $219^\circ C$). At its mp or when heated at $230-235^\circ C$ the later compound is cyclized into the pteridinone 8 (R = Me) in 52% yield, mp over $200^\circ C$ (from EtOH and N,N-dimethylformamide) (Lit. ¹⁷ gives mp over $200^\circ C$); nmr δ (DMSO- d_6) 8.66 and 8.75 (d, H_6 and H_7), 2.39 (s, Me), 3.3 (broad s, NH), $J_{6,7} = 2.1$ Hz. The analogous desmethyl analog 8 (R = H) could be prepared from the hydroxylamino compound 7 (R = H) by acid hydrolysis (hydrochloric acid, 1:1, 10 min at boiling temperature) in 28% yield, mp over $350^\circ C$ (Lit. ¹⁵ gives mp over $350^\circ C$); nmr δ (DMSO- d_6 , 115°) 8.25 (s, H_2), 8.78 and 8.95 (d, H_6 and H_7), $J_{6,7} = 2.2$ Hz.

The described reactions represent a new and versatile approach for the preparation of some functionalized pteridines. Satisfactory analyses (C,H,N) were obtained for all compounds.

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