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SYNTHESIS OF 4-METHYL-1H-IMIDAZO[4,5-c]QUINOLINE

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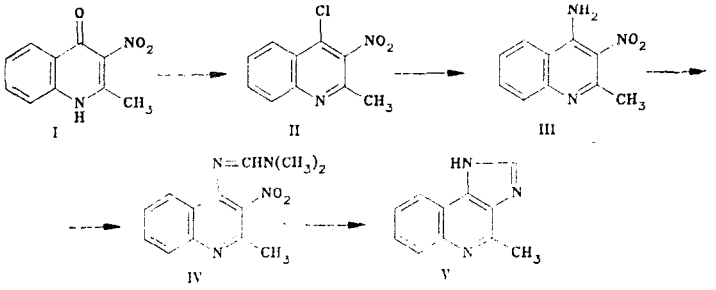
A four-step synthesis of 4-methyl-1H-imidazo[4,5-c]quinoline from 2-methyl-3-nitro-4-oxo-1,4-dihydroquinoline is developed.

Synthesis of imidazo[4,5-c]quinolines based on the reaction of N-substituted 3,4-diaminoquinolines with formic acid or orthoesters [1, 2] is known.

We developed a new synthetic method for 4-methyl-1H-imidazo[4,5-c]quinoline V from 2-methyl-3-nitro-4-oxo-1,4-dihydroquinoline I [3]. Chloroquinoline II, which upon reaction with an alcoholic solution of ammonia forms the aminoquinoline III with quantitative yield, is obtained by treatment of quinoline I with $POCl_3$ in the presence of triethylamine. Condensation of III with the diethylacetal of dimethylformamide gives the formamidine IV, reductive cyclization of which with zinc in acetic acid leads to imidazo[4,5-c]quinoline V.



EXPERIMENTAL

Melting points were determined on a Kofler block (GDR). IR spectra were recorded on a Perkin-Elmer 599 instrument in vaseline, UV spectra were recorded on Perkin-Elmer 575 and Specord M-40 instruments in ethanol. PMR spectra were recorded on Varian XL-100 and XL-200 instruments with working frequencies of 100 and 200 MHz, respectively, and an internal standard of TMS. Mass spectra were taken on a Varian MAT-112 spectrometer with ionization energy of 70 eV and a source temperature of 180°C.

Elemental analysis for C, H, N, and Cl corresponded to those calculated.

2-Methyl-3-nitro-4-chloroquinoline (II, $C_{10}H_7ClN_2O_2$). To a suspension of 6.7 g (33 mmole) quinoline I in 6.7 g (9.2 ml, 66 mmole) triethylamine at room temperature were added dropwise with stirring 58.6 g (35 ml, 383 mmole) $POCl_3$. The reaction mixture was heated at 110°C for 1 h and cooled to room temperature. Excess $POCl_3$ was removed in vacuum. To the residue were added 100 ml chloroform and the solution was poured onto ice with ammonia. The mixture was extracted with chloroform (4 × 50 ml), the chloroform extract was washed with water (2 × 35 ml), dried over Na_2SO_4 and evaporated. The solid residue was dried in vacuum. Yield 6.3 g (86%), mp 79-82°C (from ethanol). IR spectrum: 1610, 1600, 1550, 1535 (C=C, C=N, NO_2), 1330 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 210 (4.41), 232 nm (4.47). PMR spectrum (DMSO-D_6): 2.69 (3H, s, CH_3); 7.85-8.26 ppm (m, 4H arom.). Mass spectrum, m/z: 222 (M^+), 176 $[M - NO_2]^+$.

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2-Methyl-3-nitro-4-aminoquinoline (III), $C_{10}H_9N_3O_2$). A mixture of 3 g (14 mmole) chloroquinoline II and 35 ml 12% alcoholic ammonia was heated at 100°C for 5 h in an autoclave. After cooling the mixture, the precipitate was filtered and dried in vacuum. Yield 2.68 g (99%), mp 201.5-204°C (from ethanol). IR spectrum: 3380, 3260 (NH), 3070 (C–H), 1610, 1585, 1550, 1525 (C=C, C=N, NO_2), 1335 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 227 (4.40), 268.4 (4.10), 290.5 (4.01), 382.6 nm (3.67). PMR spectrum (DMSO-D_6): 2.64 (3H, s, CH_3); 7.52 (1H, m); 7.76 (2H, m); 8.43 (1H, d, arom.); 8.18 ppm (2H, br.s., NH_2). Mass spectrum, m/z: 203 (M^+), 157 $[M - NO_2]^+$.

N,N-Dimethylamino-N'-(2-methyl-3-nitroquinolyl-4)formamidine (IV, $C_{13}H_{14}N_4O_2$). To a solution of 0.35 g (2 mmole) aminoquinoline III in 10 ml ethanol at 50°C were added 1 ml diethylacetal of DMF. The mixture was boiled for 5 h and cooled. The precipitate was filtered, the mother solution was evaporated, and the residue was recrystallized with cooling. Yield 0.15 g (34%), mp 113-114°C (from ethanol). IR spectrum: 1635, 1570, 1515 (C=C, C=N, NO_2), 1315 cm^{-1} (NO_2). UV spectrum, λ_{max} (log ε): 223 (4.47), 310 (4.42), 375 nm (4.18). PMR spectrum (DMSO-D_6): 2.56 (3H, s, CH_3); 3.02 (3H, s, NCH_3); 3.09 (3H, s, NCH_3). 7.58 (1H, t); 7.80 (1H, t); 7.93 (1H, d); 8.02 (1H, d, arom.); 7.82 ppm (1H, s, =CH). Mass spectrum, m/z: 258 (M^+).

4-Methyl-1H-imidazo[4,5-c]quinoline (V, $C_{11}H_9N_3$). To a solution of 1 g (4 mmole) amidine IV in 25 ml glacial acetic acid at 65°C was added in portions with rapid stirring 10 g zinc dust. The reaction mixture was held at 110°C for 2 h. After cooling, the precipitate was filtered, washed with 50 ml acetic acid, and the filtrate evaporated. The residue was basicified with an aqueous solution of ammonia to pH 10. The precipitate was filtered, washed with water, and dried in vacuum. Yield 0.45 g (64%), mp 257-260°C (from ethylacetate). IR spectrum: 1690, 1590, 1520 cm^{-1} (C=C, C=N). UV spectrum, λ_{max} (log ε): 237 (4.53), 308 (3.52), 320 nm (3.49). PMR spectrum (DMSO-D_6): 2.52 (3H, s, CH_3); 7.61 (2H, m); 8.03 (1H, d); 8.33 (1H, d, arom.); 8.44 ppm (1H, s, 2-CH). Mass spectrum, m/z: 183 (M^+), 156 $[M - HCN]^+$.

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