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EFFICIENT SYNTHESIS OF 4-METHYL-1,10-PHENANTHROLINE STARTING FROM 8-AMINOLEPIDINE

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Abstract : 8-aminolepidine **2** reacted with glycerol **3** in presence of sodium iodide and gave 4-methyl-1,10-phenanthroline **1** with a 66 % yield.

Recently, we have studied synthesis of 1,3,4-oxadiazoles, in presence of palladium(0), starting from N,N'-diacylhydrazines[1]. To study the influence of the metal's coordination on the reaction's course, we produced 4-methyl-1,10-phenanthroline **1**, potential ligand of palladium(0), by a new synthesic way.

First synthesis of 4-methyl-1,10-phenanthroline **1** was published by Case[2]. He prepared this compound, in a 15 % yield, starting from 8-aminolepidine **2** and glycerol **3** in presence of arsenic pentoxyde. Later, other processes have been described with yields not higher than 50 %[2,3,4,5]. Bernhard and co-workers have synthetized phenanthroline **1**, in a 51 % yield, using 8-aminoquinoline **4** and methylvinylketone **5** in presence of sodium iodide[6]. as catalyst[7] (FIG. 1). During this reaction, methylvinylketone **5** may be partially polymerized in agreement

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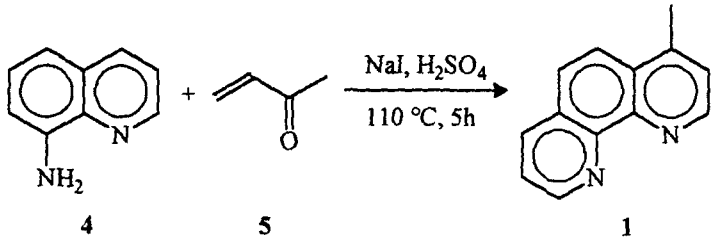
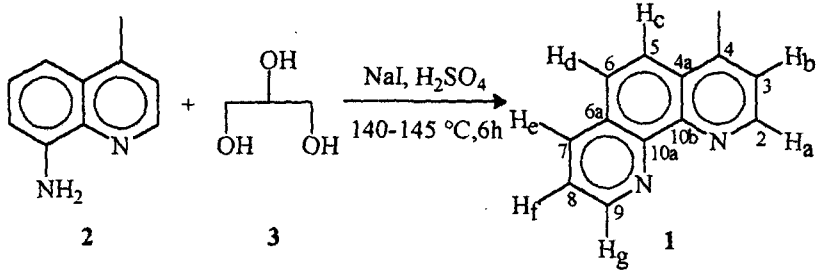
with the works of Campbell and Schaffner[8]. To avoid it, we produced phenanthroline **1** starting from 8-aminolepidine **2** and glycerol **3**. The product was isolated in a 66 % yield (FIG. 2).



4 **5** **1**

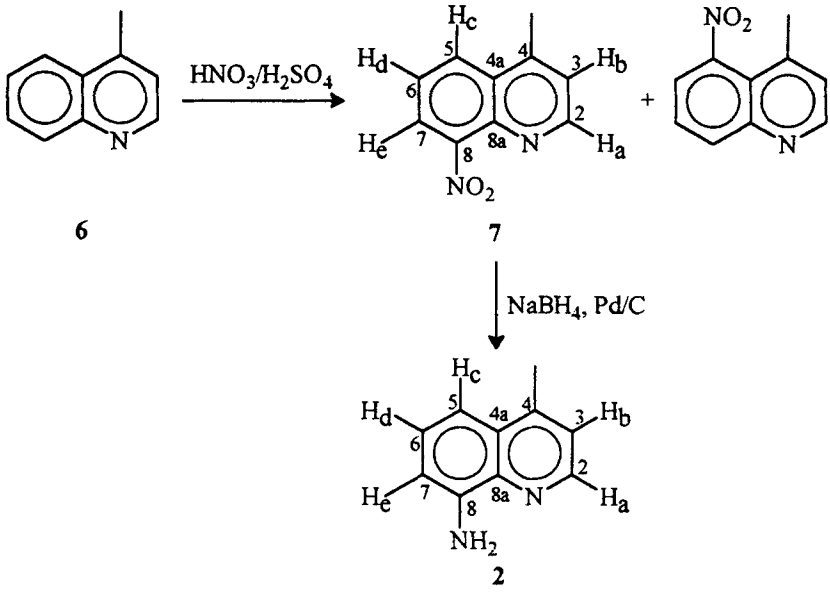
FIG. 1
Synthesis of 4-methyl-1,10-phenanthroline **1** starting from 8-aminoquinoline **4** and methylvinylketone **5**.



2 **3** **1**

FIG. 2
Synthesis of 4-methyl-1,10-phenanthroline **1** starting from 8-aminolépidine **2** and glycerol **3**.

8-Aminolepidine **2** was synthetized by a two steps process. Lepidine **6** is first nitrated by a sulfonitric mixture[9,10]. 8-Nitrolepidine **7** was isolated from the reaction's media, in a 50 % yield, by recristallization. Generally, nitrated compounds were reduced into amines using several reagents : Fe/HCl, Sn/HCl, H_2/metal, hydrides,...[3,11] We reduced 8-nitrolepidine **7** into 8-aminolepidine **2** using sodiumborohydride in a 98 % yield (FIG. 3). It was the first time that this compound was obtained by this reduction's reaction.



6 7 2

FIG. 3
Two steps synthesis of 8-aminolepidine **2** starting from lepidine **6**.

EXPERIMENTAL

All commercially available reagents were used as received from the suppliers. Melting points were determined with a Mettler FP1 and are uncorrected. ^{1}H and ^{13}C spectra were recorded on a Brucker AC300 spectrometer operating at, respectively, 300.133 and 75.47 MHz. Chemical shifts are given in part per million positive values down field from internal TMS (^{1}H and ^{13}C). Coupling constants are given in Hz.

Synthesis of 8-nitrolepidine 7

Lepidine **6** (50 g, 0.350 mole) was dissolved, at 10 °C, in concentrated sulfuric acid (76 mL). A mixture of concentrated sulfuric acid (13 mL) and fuming nitric acid (37 mL, 0.775 mole) was added, slowly, at -5 °C. The mixture was stirred

and held at 0 °C for two hours after all of the nitric acid has been added, then at room temperature for one night. The reaction's media was poured on ice and the solution made alkaline with 11M ammonia (400 mL, 4.40 mole) to precipitate the product. After filtering and washing the solid, pure 8-nitrolepidine **7** was obtained by two fractional recrystallizations from ethanol (2x135 mL) with application of charcoal (32.6 g, 50 %).

^{1}H NMR (DMSO d6) : δ = 2.70 (d, 3H, J = 0.9), 7.52 (dd, 1H, J = 0.9/4.4, H_b), 7.73 (dd, 1H, J = 7.6/8.5, H_d), 8.21 (dd, 1H, J = 1.3/7.6, H_c), 8.31 (dd, 1H, J = 1.3/8.5, H_e), 8.83 (d, 1H, J = 4.4, H_a); ^{13}C NMR (DMSO d6) : δ = 18.3 (-CH_3), 122.5 (C_3), 123.59 (C_7), 125.5 (C_6), 128.12 (C_5), 128.4 (C_{4a}), 138.22 (C_{8a}), 145.2 (C_4), 148.6 (C_8), 152.2 (C_2); m.p. = 126 °C (126 °C[9])

Synthesis of 8-aminolepidine 2

Under N_2 atmosphere, a solution of 8-nitrolepidine **7** (32 g, 0.17 mole) in methanol (1000 mL) was poured into a mixture of 10 % palladium on charcoal (1.17 g) in methanol (200 mL). Sodium borohydride (13 g, 0.342 mole) was added. The reaction's media was stirred for 30 minutes. The reaction's media is acidified by 2M chlorhydric acid (300 mL), neutralized by 1M sodium hydroxyde (100 mL) and concentrated under reduced pression. The resulting mixture was extracted by $CHCl_3$ (4x150 mL). The combined organic layers were dried over magnesium sulfate and evaporated under reduced pression. The resulting solid was recristallized in a mixture of water and ethanol (7:3, 260 mL) and filtered. We have obtained pure 8-aminolepidine **2** (26.3 g, 98 %).

^{1}H NMR ($CDCl_3$) : δ = 2.63 (d, 3H, J = 0.7), 5.00 (s, 2H), 6.92 (dd, 1H, J =

1.7/7.1, H_e), 7.19 (dd, 1H, J = 0.7/4.3, H_b), 7.28 (dd, 1H, J = 1.7/8.3, H_c), 7.34 (dd, 1H, J = 7.1/8.3, H_d), 8.95 (d, 1H, J = 4.3, H_a); ^{13}C NMR ($CDCl_3$) : δ = 18.5 ($-CH_3$), 108.6 (C_7), 109.81 (C_5), 121.9 (C_3), 127.31 (C_6), 128.5 (C_{4a}), 137.1 (C_{8a}), 143.7 (C_4), 145.7 (C_8), 146.40 (C_2); m.p. = 82 °C (80-81 °C[6])

Synthesis of 4-methyl-1,10-phenanthroline 1

A stirred solution of sodium iodide (0.23g, 1.53 mmole), 8-aminolepidine **2** (25.5g, 0.166 mole) and concentrated sulfuric acid (88.5g, 0.728 mole) was heated at 140 °C. Glycerol **3** (14.1 mL, 0.192 mole) was added over 6 hours. Then, temperature was raised up to 145 °C to distill water formed. After cooling, the dark brown reaction mixture was poured into 1M Na_2CO_3 (1000 mL) and extracted with CH_2Cl_2 (4x500 mL). The organic mixture layers was treated with 12M HCl (6x100 mL), the acidic solution was neutralized by 1M Na_2CO_3 (500 mL) and 7M NaOH (700 mL) and extracted with CH_2Cl_2 (4x300 mL). Removal of the solvent in vacuo afforded crude 4-methyl-1,10-phenanthroline. The product was recrystallized into a mixture of toluene and hexane (3:1, 170 mL). We have isolated 4-methyl-1,10-phenanthroline **1** (20g, 66 %).

^1H NMR ($CDCl_3$) : δ = 2.65 (d, 3H, J = 0.9), 7.34 (dd, 1H, J = 0.9/4.5, H_b), 7.50 (dd, 1H, J = 4.4/8.1, H_f), 7.66 (d, 1H, J = 9.1, H_c), 7.85 (d, 1H, J = 9.1, H_d), 8.11 (dd, 1H, J = 1.7/8.1, H_e), 8.95 (d, 1H, J = 4.5, H_a), 9.10 (dd, 1H, J = 1.7/4.4, H_g); ^{13}C NMR ($CDCl_3$) : δ = 19.0 ($-CH_3$), 122.4 (C_6), 122.8 (C_8), 124.1 (C_3), 125.9 (C_5), 128.0 (C_{4a} and C_{6a}), 135.8 (C_7), 144.2 (C_4), 145.9 (C_{10b}), 146.5 (C_{10a}), 149.8 (C_2), 150.2 (C_9); m.p. = 145 °C (146-150 °C[6]).

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