SYNTHESIS OF PYRAZOLO[4,3-*c*]QUINOLINE-5-OXIDE BY REDUCTIVE CYCLIZATION OF 4-ACETYL-5-(2-NITROPHENYL)PYRAZOLE: REVISION OF THE REPORTED STRUCTURES

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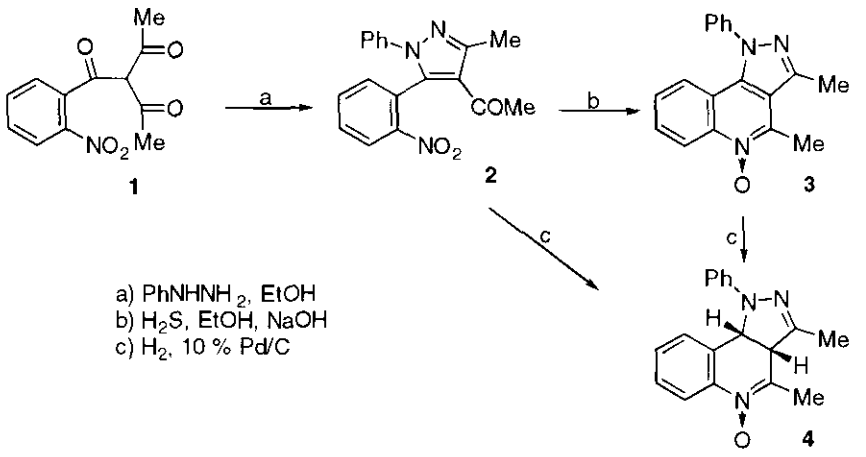
Abstract - Cyclocondensation of 3-(2-nitrobenzoyl)pentane-2,4-dione with phenylhydrazine provided 4-(2-nitrobenzoyl)-3,5-dimethyl-1-phenylpyrazole (**5**) instead of 4-acetyl-3-methyl-5-(2-nitrophenyl)-1-phenylpyrazole (**2**). Catalytic hydrogenation of **2** resulted in the stepwise formation of 3,4-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline-5-oxide (**3**), 3,4-dimethyl-1-phenyl-1*H*-pyrazolo-[4,3-*c*]quinoline (**12**), and 3,4-dimethyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (**13**). Alternate routes for reduction of **5** under different conditions and a facile synthesis of **2** are also described.

A report in literature described[1] the reaction of 3-(2-nitrobenzoyl)pentane-2,4-dione (**1**) with phenylhydrazine in ethanol in the presence of sulfuric acid to afford the alleged 4-acetyl-3-methyl-5-(2-nitrophenyl)-1-phenylpyrazole (**2**) (Scheme 1). It was also reported that reduction of **2** with H_2S in boiling mixture of ethanol and 2 *N* NaOH or with zinc dust in an aqueous ethanolic solution of ammonium chloride resulted in formation of 3,4-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline-5-oxide (**3**) and catalytic hydrogenation of compound (**2**) under usual condition over 10 % Pd/C or platinum dioxide, or catalytic hydrogenation of *N*-oxide (**3**) under usual condition gave a dihydro derivative (**4**).[1]

The standard method of synthesis of pyrazoles consists in the condensation of a β-dicarbonyl compounds with hydrazines.[2] In case of unsymmetrical reactants two isomeric pyrazoles can theoretically arise and sometimes both can be isolated from reaction mixture.[2] The most abundant isomer corresponds to the addition at the most nucleophilic nitrogen of the hydrazine to the most reactive carbonyl group of the β-dicarbonyl compound.[2] In this connection the high yield of pyrazole (**2**), the physicochemical data provided for *N*-oxide (**3**), especially low melting point of 72-73 °C and unusual behavior of these compounds under catalytic hydrogenation were somewhat troubling.[1] This prompted us to examine the reported data.

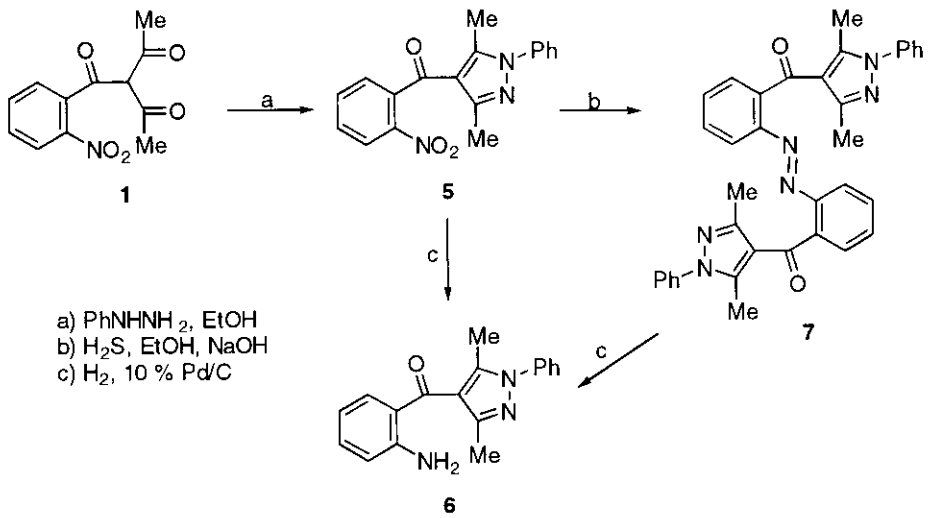
Scheme 1



We thoroughly repeated the described reactions[1] and found that cyclocondensation of 3-(2-nitrobenzoyl)pentane-2,4-dione (**1**) with phenylhydrazine yielded 4-(2-nitrobenzoyl)-3,5-dimethyl-1-phenylpyrazole (**5**) (Scheme 2) instead of pyrazole (**2**). This result is in accordance with relative activities of carbonyl groups in compound (**1**). The structure of **5** was confirmed by following chemical reactions. Catalytic hydrogenation of pyrazole (**5**) under usual condition over 10 % Pd/C gave a material with mp of 132-134 °C (lit.,[1] 135-136 °C). IR spectrum (KBr) of this compound demonstrated a carbonyl absorption at 1622 cm^{-1} and absorptions of primary amino group at 3430, 3315 cm^{-1}. Inspection of ^1H NMR (DMSO-d_6) revealed a broad, D_2O exchangeable singlet at δ 6.99 integrating for two protons which confirmed presence of amino group. The above data suggested that the structure for the product of a catalytic hydrogenation of **5** was the aminopyrazole (**6**). In addition, fragmentation of compound (**6**) under electron impact showed occurrence of ions at *m/z* 199, 171, 120, and 92 corresponding to the fragments shown in Figure 1.

When nitro derivative (**5**) dissolved in boiling mixture of ethanol and 2 *N* sodium hydroxide was allowed to react with excess of hydrogen sulfide for 30 min, a new material (mp 97-98 °C) was isolated by column chromatography in 81 % yield. The mp of 72-73 °C given in literature[1] might be due to contamination. IR spectrum (KBr) of this material showed a carbonyl absorption at 1637 cm^{-1}. The position of carbonyl absorption suggested the appearance of a substitutent with less electron-withdrawing effect than nitro group (carbonyl absorption of **5** at 1641 cm^{-1}) and with less electron-donating effect than amino group (carbonyl absorption of **6** at 1622 cm^{-1}).[3] The structural assignment was also supported by ^1H NMR spectroscopy. Nine aromatic protons of nitro compound (**5**) and amino compound (**6**) appeared at δ 8.28-7.51 and δ 7.60-6.52 respectively, whilst nine aromatic protons of a new compound were found at δ 7.74-7.04. These data coupled with analytical information suggested this product to be azo derivative (**7**).

Scheme 2



This result was in accord with mechanism of reduction of nitro derivatives under alkaline conditions.[4] The structure of **7** was proven by chemical ionization mass spectrometry, which showed molecular ion at *m/z* 578. The reduction of **5** under different conditions proved its structure beyond any doubt. Since the compounds (**7**) and (**6**) of this paper (Scheme 2) and the products (**3**) and (**4**) obtained from **2** (Scheme 1) were identical by spectral means, the *N*-oxide (**3**) and dihydro derivative (**4**) reported in original article[1] must be 2,2'-azobis[3,5-dimethyl-1-phenyl-1*H*-4-pyrazolylcarbonyl]benzene (**7**) and 4-(2-aminobenzoyl)-3,5-dimethyl-1-phenylpyrazole (**6**), respectively.

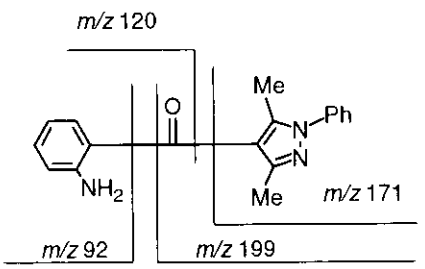
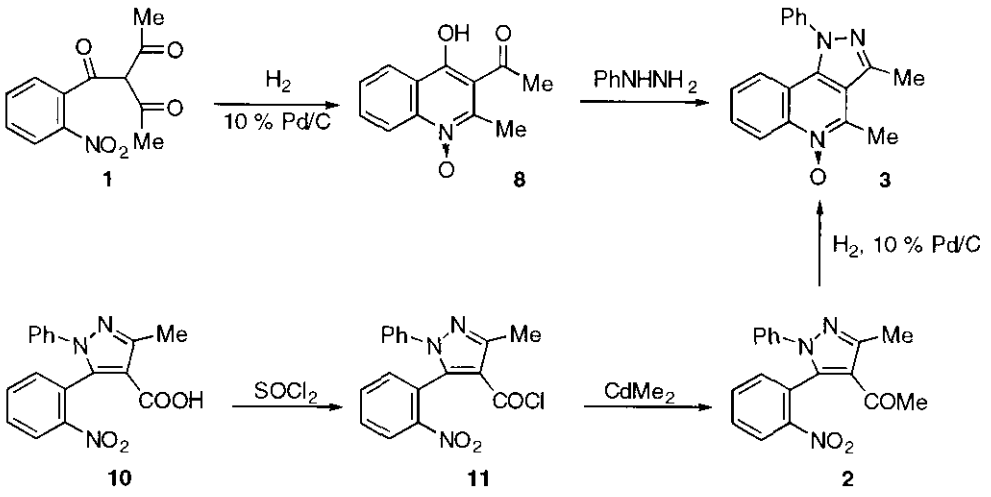


Figure 1. MS Fragmentation of **6**

A synthesis of the *N*-oxide (**3**) was required in order to complete this reinvestigation. With compound (**1**) in our hands we synthesized *N*-oxide (**8**) (Scheme 3) according to Sicker *et al.*[5] Reaction of **8** with phenylhydrazine in boiling acetic acid gave *N*-oxide (**3**). It was also suggested that reductive cyclization of nitro ketone (**2**) resulted in the formation of 3,4-dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline-5-oxide.[1]

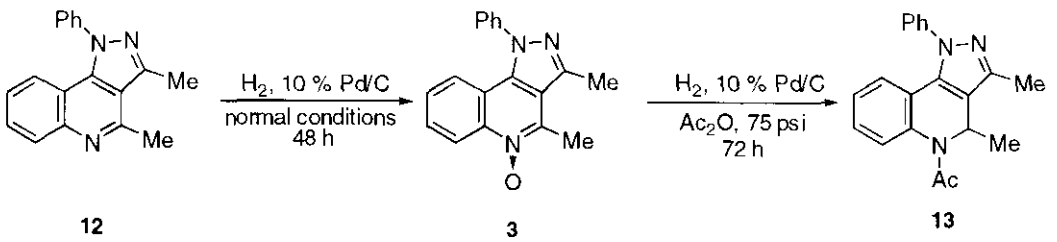
The actual nitro ketone (**2**) was synthesized starting from nitro acid (**10**).[6] Reaction of **10** with an excess of thionyl chloride followed by treatment with dimethylcadmium in boiling benzene provided **2**. Under catalytic hydrogenation it produced compound with identical physicochemical properties to *N*-oxide (**3**).

Scheme 3



When **3** was hydrogenated for 48 h under usual conditions over 10 % Pd/C (Scheme 4) pyrazoloquinoline (**12**) was formed as expected. Earlier we[7] found that hydrogenation of 2-substituted pyrazolo[4,3-*c*]quinoline led to the formation of 2-substituted 4,5-dihydropyrazolo[4,3-*c*]quinoline, which was unstable and spontaneously oxidized back to the pyrazolo[4,3-*c*]quinoline. Acetylation of NH-group resulted in stabilization of dihydro structure. Catalytic hydrogenation of *N*-oxide (**3**) at higher pressure for 72 h over 10 % Pd/C in ethyl acetate in the presence of acetic anhydride gave *N*-acetyl-4,5-dihydro derivative (**13**).

Scheme 4



EXPERIMENTAL

Melting points were taken on the Mel-Temp apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu IR-435 spectrophotometer. NMR spectra were recorded on a Varian Gemini-200 MHz spectrometer with tetramethylsilane as internal standard. MS spectra were obtained on a Shimadzu QP 100 GC/MS mass spectrometer and JEOL JMS-DX 305 high-resolution mass spectrometer. Elemental analyses were carried out by Chemical Analysis Laboratory at the Korea Research Institute of Chemical Technology.

4-(2-Nitrobenzoyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**5**). 3-(2-Nitrobenzoyl)pentane-2,4-dione (**1**, 2.49 g, 10 mmol) and phenylhydrazine (1.08 g, 10 mmol) were refluxed in ethanol (25 mL) with 96 % sulfuric acid (0.05 g) for 3 h. Pyrazole (**5**) was precipitated as crystals (2.95 g, 92 %): mp 175-177 °C (from ethanol); ^{1}H NMR (DMSO-d_6) δ 8.28-7.51 (m, 9H, aromatics), 2.23 (s, 3H, Me), 2.04 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 188.2, 150.2, 146.3, 144.7, 138.2, 137.3, 135.0, 131.3, 129.5, 128.9, 128.5, 125.7, 125.0, 118.3, 13.9, 12.6; IR (KBr) 1641 cm^{-1} (C=O); MS (EI) *m/z* (%) 321 (M$^+$, 3), 275 (3), 199 (8), 187 (28), 118 (100), 77 (55).

4-(2-Aminobenzoyl)-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**6**). Compound (**5**, 1.07 g, 3.3 mmol) was hydrogenated under usual conditions over 10 % Pd-C (0.1 g) or platinum dioxide (0.1 g) until no more hydrogen was consumed. After separation from catalyst, **6** was obtained as yellow oil which was crystallized on standing (1.0 g, 93 %): mp 132-134 °C (from methanol); ^{1}H NMR (DMSO-d_6) δ 7.60-7.55 (m, 5H, Ph), 7.49 (m, 1H, ArH), 7.39 (m, 1H, ArH), 6.99 (br s, D_2O exchangeable, 2H, NH_2), 6.83 (d, 1H, J = 7.9 Hz, ArH), 6.56 (t, 1H, J = 7.5 Hz, ArH), 2.18 (s, 3H, Me), 2.16 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 193.3, 151.1, 148.2, 140.4, 139.0, 134.2, 133.6, 129.4, 128.2, 125.2, 120.9, 118.8, 116.9, 114.8, 13.3, 12.4; IR (KBr) 3430, 3315, 1622 (C=O) cm^{-1}; MS (EI) *m/z* (%) 291 (M$^+$, 66), 276 (53), 274 (98), 199 (54), 171 (26), 120 (94), 92 (46), 77 (100).

2,2'-Azobis[(3,5-dimethyl-1-phenyl-1*H*-4-pyrazolylcarbonyl]benzene (**7**). Hydrogen sulfide was passed through a solution of pyrazole (**5**, 1.07 g, 3.3 mmol) in boiling ethanol (83 mL) and 2 *N* sodium hydroxide (8.3 mL) for 30 min. After cooling and acidification with dilute HCl, the reaction mixture was partitioned between ethyl acetate and water. Elemental sulfur was filtered off and organic layer was separated, washed with water, dried over sodium sulfate and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate : hexane, 1:3) to afford 0.78 g (81 %) of **7**: mp 97-98 °C (from methanol); ^{1}H NMR (DMSO-d_6) δ 7.74-7.04 (m, 9H, aromatics), 2.40 (s, 3H, Me), 2.35 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 160.8, 157.0, 147.8, 139.8, 138.9, 131.5, 129.5, 128.3, 125.0, 124.0, 121.2, 114.8, 108.3, 13.1, 12.3; IR (KBr) 1637 cm^{-1}; MS (CI) 578 (M$^+$); HRMS Calcd for $C_{36}H_{30}N_6O_2$ 578.2432, Found 578.2431.

3,4-Dimethyl-1-phenylpyrazolo[4,3-*c*]quinoline-5-oxide (3)

Method A. Compound (**8**,[4] 0.217 g, 1.0 mmol) and phenylhydrazine (0.108 g, 1.0 mmol) in acetic acid (20 mL) was refluxed for 1 h. Reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate - methanol, 10:1) yielding **3** as a white solid (0.27 g, 67 %): mp 216-219 °C (decomp, from MeOH-H_2O); ^{1}H NMR (DMSO-d_6) δ 8.95 (d, 1H, J = 8.4 Hz, ArH), 7.77-7.26 (m, 8H, ArH), 3.07 (s, 3H, Me), 2.79 (s, 3H, Me); ^{13}C NMR (DMSO-d_6) δ 144.2, 141.8, 140.1, 139.6, 133.3, 129.9, 129.8, 129.7, 127.5, 126.9, 122.0, 121.5, 115.8, 15.0, 14.9; MS (EI) *m/z* (%) 289 (M^+, 44), 273 (M^+-O, 100).

Anal. Calcd for $C_{18}H_{15}N_3O \cdot H_2O$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.41; H, 5.71; N, 13.52.

Method B. Nitro ketone (**2**, 0.321 g, 1.0 mmol) in methanol (50 mL) was hydrogenated under usual conditions over 10 % Pd-C (0.3 g) for 1.5 h. After separation of the catalyst and purification by column chromatography (silica gel, ethyl acetate : methanol, 10:1) **3** was obtained as a white solid (0.34 g, 96 %).

3-Methyl-5-(2-nitrophenyl)-1-phenyl-1*H*-4-pyrazolylcarbonyl chloride (11). A mixture of 3-methyl-5-(2-nitrophenyl)-1-phenyl-1*H*-4-pyrazolecarboxylic acid (**10**[5], 1.29 g, 4.0 mmol), freshly distilled thionyl chloride (15 mL, 205 mmol) and 1 drop of DMF was refluxed for 1 h. Excess thionyl chloride was removed completely *in vacuo*, then 5 mL of benzene were added and also removed *in vacuo*. The residue was treated with 5 mL of petroleum ether, leaving 1.3 g (96 %) of acid chloride, which was satisfactory for the following preparation. It may be recrystallized from mixture of benzene - petroleum ether: mp 101-103 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (m, 1H, ArH), 7.59 (m, 2H, ArH), 7.26 (m, 6H, ArH), 2.63 (s, 3H, Me).

4-Acetyl-3-methyl-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole (2). A mixture of acid chloride (**11**, 0.68 g, 2.0 mmol) and dimethylcadmium (0.50 g, 3.5 mmol) in benzene (50 mL) was refluxed for 1 h. After cooling, ice and 5 mL of 2 *N* hydrochloric acid were added. The mixture was stirred for about 20 min and extracted with ethyl acetate. Organic layer was washed with water, dried over sodium sulfate and evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate : hexane, 2:1). The nitro ketone (**2**) was obtained as an oil (0.50 g, 79 %) which crystallized upon treatment with 3 mL of hexane: mp 112-113 °C (from hexane); ^{1}H NMR ($CDCl_3$) δ 8.11 (m, 1H, ArH), 7.56 (m, 2H, ArH), 7.24 (m, 6H, ArH), 2.62 (s, 3H, 3-Me), 2.19 (s, 3H, MeCO); IR (KBr) 1654 cm^{-1}; MS (EI) *m/z* (%) 321 (M^+, 4), 306 (6), 275 (84), 259 (25), 77 (100); HRMS Calcd for $C_{18}H_{15}N_3O_3$ 321.1113, Found 321.1109.

3,4-Dimethyl-1-phenyl-1*H*-pyrazolo[4,3-*c*]quinoline (12). *N*-Oxide (**3**, 0.29 g, 1.0 mmol) in 50 mL of methanol was hydrogenated under usual conditions over 10 % Pd/C (0.1 g) for 48 h. The catalyst was filtered off and filtrate was evaporated to give a solid. Purification by column chromatography (silica gel, ethyl acetate : hexane, 2:3) gave **12** (0.24 g, 88 %): mp 174-176 °C (from ethyl acetate - hexane): ^{1}H NMR ($CDCl_3$) δ 8.12-7.24 (m, 9H, ArH), 3.00 (s, 3H, 4-Me), 2.81 (s, 3H, 3-Me); MS (EI) *m/z* (%) 273 (M^+, 100); HRMS Calcd for $C_{18}H_{15}N_3$ 273.1256, Found 273.1261.

5-Acetyl-3,4-dimetyl-1-phenyl-4,5-dihydro-1*H*-pyrazolo[4,3-*c*]quinoline (13). *N*-Oxide (**3**, 0.29 g, 1.0 mmol) was dissolved in a mixture of ethyl acetate (50 mL) and acetic anhydride (5 mL) and hydrogenated at 75 *psi* for 72 h. The catalyst was filtered off and filtrate was evaporated. The residue was purified by column chromatography (silica gel, ethyl acetate : hexane) yielding **13** as an oil (0.05 g, 33 %), which was crystallized on standing: mp 153-156 °C (from ethyl acetate - hexane): ^{1}H NMR ($CDCl_3$) δ 7.55-6.95 (m, 9H, aromatics), 6.09 (br s, 1H, 4-H), 2.35 (s, 3H, 3-Me), 2.28 (s, 3H, MeCO), 1.18 (d, 3H, *J* = Hz, 4-Me); MS (EI) 317 (M^+, 11), 302 (44), 260 (100); HRMS Calcd for $C_{20}H_{19}N_3O$ 317.1504, Found 317.1516.

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