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Condensation of 7-Nitroindole-2-carbohydrazide Derivatives with Ethyl Acetoacetate

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Pyrazolylindolyl ketone derivatives were obtained by cyclization of the condensation products 7-nitroindole-2-carbohydrazide derivatives with ethyl acetoacetate. We have shown careful examination of spectroscopic data and the open-chain intermediate isolation as well as the identification of the formed compound structure.

Keywords: 7-Nitroindole-2-carbohydrazide, Open-chain intermediate, Pyrazolylindole, Ethyl acetoacetate.

INTRODUCTION

The indole nucleus is probably the most widely distributed heterocyclic ring system found in nature [1]. Due to the existence of a vast array of structurally diverse and biologically active indoles, it is not surprising that the indole nucleus is an important feature in many medicinal agents and the most important of all structural classes in drug discovery [2]. The synthesis and reactivity of indole derivatives have been a topic of research interest for over a century.

Compounds which contain the pyrazole functionality continue to attract great interest due to their varied and significant pharmacological effects [3]. For example, the identification of new and selective cox-2 inhibitors [4], for the relief of pain and the treatment of the symptom of arthritis and related diseases has been an important advance in modern anti-inflammatory therapy. In a related area, heterocycle-appended pyrazoles have been reported [5] to be potent and selective in inhibitors of the mitogen-activated protein kinase p38 and consequently provide a novel approach for the treatment of rheumatoid arthritis and related inflammatory diseases.

EXPERIMENTAL

All the compounds were characterized by their ^{1}H NMR and ^{13}C NMR spectra as well as by microanalysis or HRMS spectra. NMR spectra were recorded on Bruker ARX 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C) spectrometer (δ-ppm/TMS, *J*-Hz); for ^{13}C NMR, the multiplicities were determined through DEPT. Microanalysis were performed by the "Laboratoire Central de Microanalyse du UATRS" (Rabat). Mass spectra were recorded on a Varian MAT 311 spectrometer. Melting points were measured using a Köfler apparatus and were uncorrected.

Preparation of open-chain intermediates 2(a-c): A mixture of 7-nitroindole-2-carbohydrazides **1(a-c)** (4.6 mmol) and ethyl acetoacetate (35 mmol) in ethanol was heated with a steam bath at 80 °C until dissolution. The mixture was left at this temperature for 4 h. The crude product was filtered and recrystallized from ethanol.

Ethyl 3-[2-(7-nitro-1H-indole-2-cabonyl)hydrazono]-butanoate (2a): Yield = 88 %; m.p.: 192-194 °C (ethanol). ^{1}H NMR (DMSO-d_6): 1.22 (t, *J* = 7.2 Hz, 3H, CH_3); 2.08 (s, 3H, CH_3); 3.16 (s, 2H, CH_2); 4.14 (q, *J* = 7.2 Hz, 2H, CH_2); 7.33 (t, *J* = 7.8 Hz, 1H, H^5); 7.48 (dd, *J* = 2.3 Hz, *J* = 8.1 Hz, 1H, H^4); 7.54 (d, *J* = 2.1 Hz, 1H, H^3); 8.20 (dd, *J* = 2.3 Hz, *J* = 7.8 Hz, 1H, H^6); 10.87 (br s, 1H, NH); 11.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.5 (CH_3); 14.7 (CH_3); 44.6 (CH_2); 62.2 (CH_2); 107.5 (CH-5); 120.4 (CH-4); 121.8 (CH-3); 131.2 (CH-6); 129.1, 131.1; 131.2; 133.6 (ArC); 152.0 (C=N); 159.8 (CO); 169.7 (CO_2). HRMS, *m/z* 332 (M), calcd. for $C_{15}H_{16}N_4O_5$: 332.1121, found: 332.1127.

Ethyl 3-[2-(5-methyl-7-nitro-1H-indole-2-cabonyl)-hydrazono]butanoate (2b): Yield = 81 %; m.p.: 176-178 °C (Ethanol). ^{1}H NMR (DMSO-d_6): 1.20 (t, *J* = 6.9 Hz, 3H, CH_3); 2.06 (s, 3H, CH_3); 2.46 (s, 3H, CH_3); 3.33 (s, 2H, CH_2); 4.12 (q, *J* = 6.9 Hz, 2H, CH_2); 7.38 (dd, *J* = 8.8, *J* = 3.1 Hz, 1H, H^3); 7.98 (d, *J* = 8.8 Hz, 1H, H^4); 8.05 (d, *J* = 3.1 Hz, 1H, H^6); 10.91 (br s, 1H, NH); 11.40 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 14.5 (CH_3); 16.4 (CH_3); 20.8 (CH_3); 44.5 (CH_2); 61.3 (CH_2); 107.1 (CH-3); 122.8 (CH-6); 131.0 (CH-4); 128.0, 129.9, 131.0, 131.4, 133.0 (ArC); 159.2 (C=N); 162.8 (C-O); 168.0 (CO_2). HRMS, *m/z* 346 (M), calcd. for $C_{16}H_{18}N_4O_5$: 346.1277, found: 346.1272.

Ethyl 3-[2-(5-methoxy-7-nitro-1H-indole-2-cabonyl)-hydrazono]butanoate (2c): Yield = 78 %; m.p.: 126-128 °C (Ethanol). ^{1}H NMR (DMSO-d_6): 1.22 (t, *J* = 7.0 Hz, 3H, CH_3); 2.07 (s, 3H, CH_3); 3.17 (s, 2H, CH_2); 3.87 (s, 3H, OCH_3); 4.14 (q, *J* = 7.0 Hz, 2H, CH_2); 7.44 (dd, *J* = 9.3, *J* = 3.0 Hz, 1H, H^3); 7.56 (d, *J* = 3.0 Hz, 1H, H^6); 7.85 (d, *J* = 9.3 Hz, 1H, H^4); 10.94 (s, 1H, NH); 11.23 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 11.9 (CH_3); 14.6 (CH_3); 44.6 (CH_2); 56.3 (OCH_3); 61.4 (CH_2); 107.4 (CH-3); 118.2 (CH-6); 126.4 (CH-4); 107.3, 117.5, 126.3, 133.0, 135.3 (ArC); 153.4 (C=N); 159.8 (C-O); 169.7 (CO_2). HRMS, *m/z*: 362 (M), calcd. for $C_{16}H_{18}N_4O_6$: 362.1226, found: 362.1235.

Cyclization of open-chain intermediates 2(a-c) with ethyl acetoacetate: The open-chain intermediates **2(a-c)** (2.4 mmol) and ethyl acetoacetate (3.6 mmol) were heated under reflux for 5 h. After cooling, the obtained solid product was filtred off, then recrystallized from ethanol.

(5-Hydroxy-3-methylpyrazol-1-yl)(7-nitro-1H-indol-2-yl)ketone (3a): Yield = 76 %; m.p.: 250-252 °C. ^{1}H NMR (DMSO-d_6): 2.14 (s, 3H, CH_3); 7.35 (t, *J* = 8.8 Hz, 1H, H^5); 7.45 (dd, *J* = 2.5 Hz, *J* = 8.8 Hz, 1H, H^4); 7.57 (d, *J* = 2.2 Hz, 1H, H^3); 8.22 (dd, *J* = 2.5 Hz, *J* = 8.8 Hz, 1H, H^6); 8.64 (s, CH pyrazolic); 10,72 (s, 1H, NH); 11.87 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): 14.5 (CH_3); 85.0 (CH pyrazolic); 107,7 (CH-5); 120.6 (CH-4); 121.8 (CH-3); 131.2 (CH-6); 129.5, 131.4; 131.3; 133.5 (ArC); 158.7 (C=N); 163.0 (C-O); 168.0 (C=O). HRMS, *m/z* 286 (M), calcd. for $C_{13}H_{10}N_4O_4$: 286.0702, found: 286.0704.

(5-Hydroxy-3-methylpyrazol-1-yl)(5-methyl-7-nitro-1H-indol-2-yl)ketone (3b): Yield = 66 %; m.p.: 246-248 °C. ^{1}H NMR (DMSO-d_6): 1.87 (s, 3H, CH_3); 2.24 (s, 3H, CH_3); 2.65 (s, 3H, CH_3); 7.32 (dd, *J* = 8.3, *J* = 2.6 Hz, 1H, H^3); 7.97 (d, *J* = 8.3 Hz, 1H, H^4); 8.06 (d, *J* = 2.6 Hz, 1H, H^6); 8.80 (s, 1H, CH pyrazolic); 10,79 (s, 1H, NH) ; 11.55 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): 16.4 (CH_3); 20.8 (CH_3); 84.5 (CH pyrazolic); 107.6 (CH-3); 123.0 (CH-6); 131.1 (CH-4); 130.1, 130.9, 131.3, 132.7, 133.2 (ArC); 159.9 (C=N); 162.8 (C-O); 169.2 (C=O). HRMS, *m/z*: 300 (M), calcd. for $C_{14}H_{12}N_4O_4$: 300.0859, found: 300.0906.

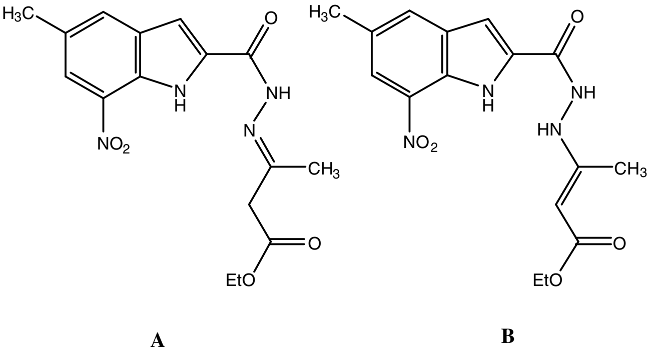
(5-Hydroxy-3-methylpyrazol-1-yl)(5-methoxy-7-nitro-1H-indol-2-yl)ketone (3c): Yield = 56 %; m.p.: 224-226 °C. ^{1}H NMR (DMSO-d_6): 2.25 (s, 3H, CH_3); 3.65 (s, 3H, OCH_3); 7.38 (dd, *J* = 9.0, *J* = 2.7 Hz, 1H, H^3); 7.55 (d, *J* = 2.7 Hz, 1H, H^6); 7.87 (d, *J* = 9.0 Hz, 1H, H^4); 8.62 (s, 1H, CH pyrazolic); 10,84 (s, 1H, NH) ; 11.76 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): 18.5 (CH_3); 58.1 (OCH_3); 85.0 (CH pyrazolic); 105.05 (CH-3); 106.9 (CH-6); 109.4 (CH-4); 109.4, 114.1, 125.1, 131.9, 134.7 (ArC); 153.5 (C=N); 159.2 (C-O); 169.2 (C=O). HRMS, *m/z*: 316 (M), calcd. for $C_{14}H_{12}N_4O_5$: 316.0808, found: 316.0901.

RESULTS AND DISCUSSION

Due to the potent biological activity exhibited by various indoles derivatives, there is a continuous demand for novel synthetic procedures in this area. In 1990s, it has attracted much attention, as it employs simple and readily available starting materials. In previous papers [6-8], we have reported some reactions of 7-aminoindoles and the condensation of the 7-nitroindole-2-carbohydrazides **1(a-c)** with acetylacetone. We report now a synthesis of (5-hydroxy-3-methyl-1H-pyrazol-1-yl)(7-nitro-1H-indol-2-yl)ketone derivatives **3(a-c)** by 7-nitroindole-2-carbohydrazides **1(a-c)** condensation with ethyl acetoacetate following by cyclization of the open chain intermediates **2(a-c)** (**Scheme-I**).

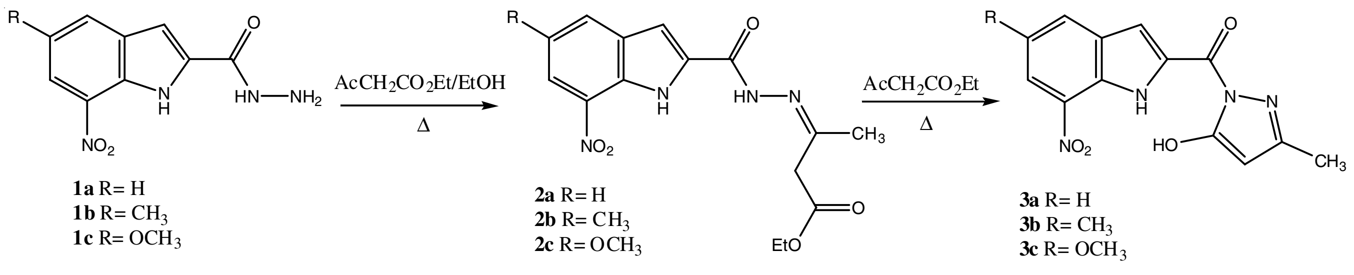
Preparation of substituted open-chain intermediates 2(a-c): The condensation of 7-nitroindole-2-carbohydrazides **1(a-c)** with ethyl acetoacetate in ethanol lead to the open-chain intermediates **2(a-c)**. The synthesis of the starting reagents carbohydrazides was reported in our recent work [7]. The identification of the open-chain intermediates **2(a-c)** structure was based on spectroscopic data (NMR, mass and X Ray). In NMR spectra, we observed the principal signal corresponding to methylene proton and the signals of ethyl group.

In order to confirm which tautomere was obtained, X-ray analysis is performed [9] (Fig. 1). The data of this analysis showed that the open-chain intermediate is present in the methylene group (Figs. 1 and 2).



A **B**

Fig. 1. Possible structure of the open chain intermediate



Scheme-I: Synthesis of pyrolylindolylketone derivatives

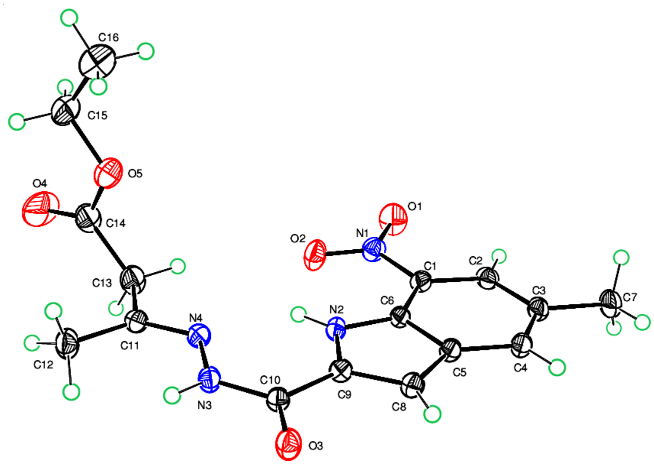
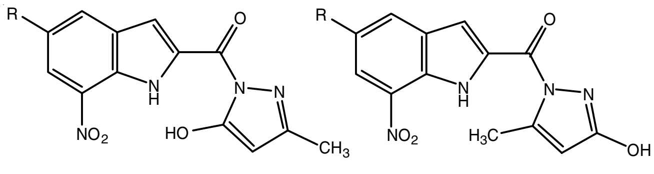


Fig. 2. Crystal structure of Z-ethyl 3-(5-methyl-7-nitro-1H-indole-2-carboylimino)butanoate

The isolation of such open-chain intermediates was very interesting to confirm the structure of the pyrazole moiety (C or D) Fig. 3.



C **D**

Fig. 3. Possible structure of the pyrazolylindolyle ketone

Open-chain intermediates cyclization 3(a-c): Acid-catalyzed substitution reactions on indole derivatives containing only 7-nitro substituent in the benzene ring, in general, are prohibited by the acid lability of the indole nucleus and in those cases where these reactions are possible, the substituent orientation and the remaining functionality are not always the most desired. Ready access has provided the impetus to investigate synthetic schemes that might be expected to provide various indole-substituted by pyrazole moiety [10-14]. This work describes general procedure used in our recent work [15] by which (5-hydroxy-3-methyl-1H-pyrazol-1-yl)(7-nitro-1H-indol-2-yl)ketone derivatives **3(a-c)** may be conveniently prepared in neutral medium by the cyclization of the open-chain intermediates **2(a-c)** with ethyl acetoacetate.

The establishment of the structure of these compounds **3(a-c)** has been confirmed by spectroscopic data. The ^{1}H NMR spectra of the compound **3a** showed the presence of the singlet at 2.14 ppm due to protons of methyl group of pyrazole moiety and the pyrazolic proton appeared at 8.64 ppm. The ^{13}C NMR spectra of **3a** exhibited one signal at 24.2 ppm assignable to carbon of methyl group and another at 85.0 ppm for the pyrazolic carbon. The molecular ion peak at *m/z* 300 was observed in the mass spectrum of **3a**. These spectra data and elemental analysis supported the structure of **3a**.

Conclusion

In this work, we report the condensation of 7-nitroindole-2-carbohydrate derivatives with ethyl acetylacetate leading to new (5-hydroxy-3-methylpyrazol-1-yl)(7-nitro-1H-indol-2-yl)ketones after isolation the open-chain intermediates. The structures of obtained products were established with spectroscopic data of ^{1}H NMR and ^{13}C NMR, mass and X ray.

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