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Synthesis of Biologically Active 1-[2-(2-Methyl-5-nitroimidazol-1-yl)acetyl]-3-substituted Phenyl-4-carbaldehyde-1H-pyrazoles

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1-[2-(2-Methyl-5-nitroimidazol-1-yl)acetyl]-3-substituted phenyl-4-carbaldehyde-1H-pyrazoles (**4a-e**) have been synthesized by the cyclization of (2-methyl-5-nitroimidazol-1-yl)acetic acid (1-substituted phenylethylidine)hydrazides (**3a-e**) with phosphorous oxychloride in N,N-dimethylformamide. The pyrazoles have been characterized on the basis of analytical and spectral data and screened for biological activity.

Key Words: Synthesis, Pyrazoles, Antibacterial and Antifungal activity.

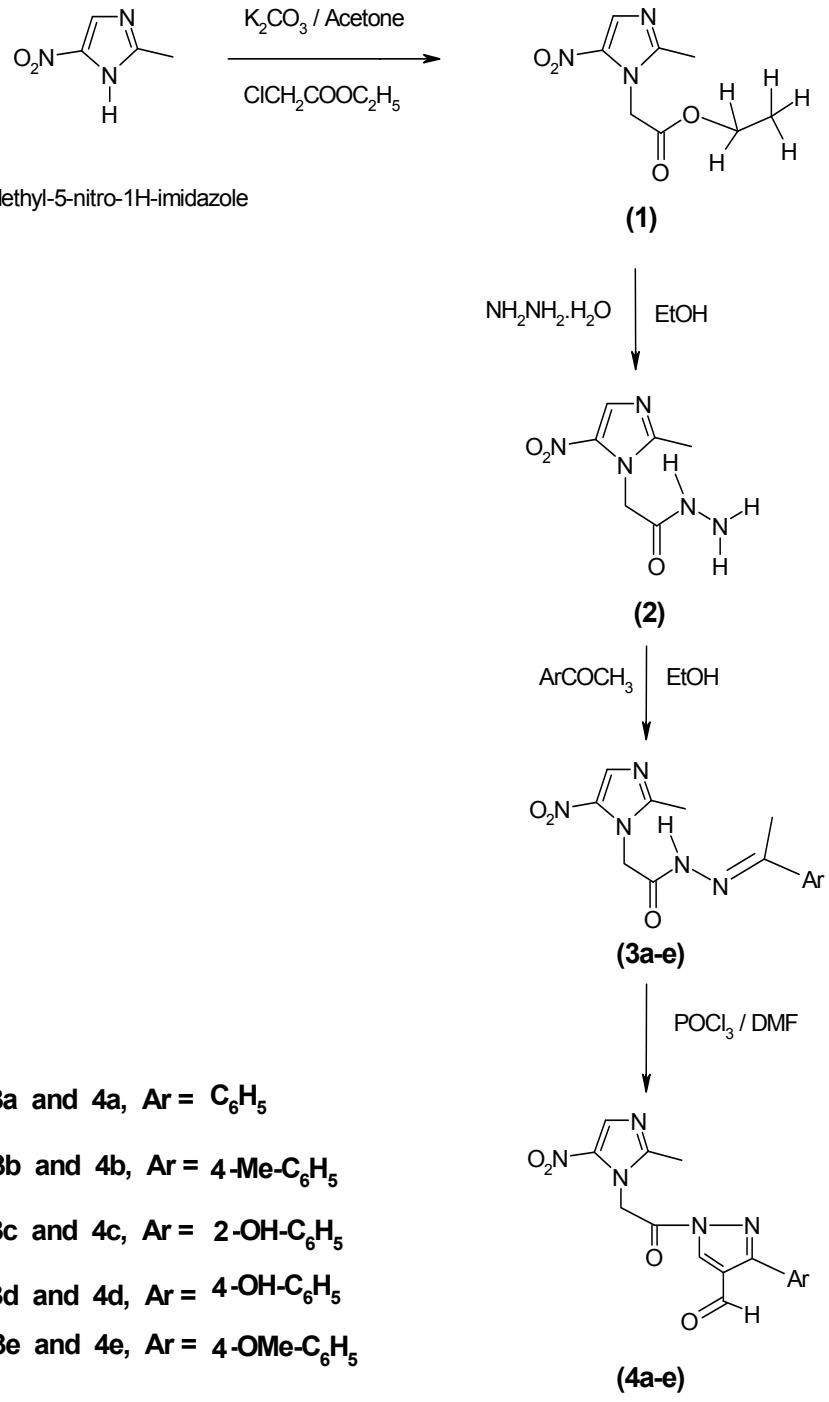
INTRODUCTION

Imidazole derivatives possess potent biological activity such as antihelmentic, antiamoebic, antiparasitic, antiprotozoal, antiinflammatory, analgesic, antifungal and antibacterial[1-3]. It is also reported that pyrazoles exhibit antibacterial[4], antifungal[5] and antiinflammatory[6] properties. In view of this, it is worthwhile to synthesize some new pyrazoles containing imidazole moiety with the objective of screening them for their biological activity.

2-Methyl-5-nitro-1H-imidazole[7] on electrophilic substitution with ethyl chloroacetate gave (2-methyl-5-nitro-imidazol-1-yl)acetic acid ethyl ester (**1**) which on amination with hydrazine hydrate afforded (2-methyl-5-nitroimidazol-1-yl)acetic acid hydrazide (**2**). Condensation of the compound **2** with various aromatic acetophenones gave (2-methyl-5-nitroimidazol-1-yl)acetic acid (1-substituted phenylethylidene)hydrazide (**3a-e**) which on cyclization with Vilsmeier-Haack reagent yielded the title compounds (**4a-e**) (**Scheme-I**).

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Jasco 410 plus FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian 300 MHz and Bruker



3a and 4a, Ar = C_6H_5

3b and 4b, Ar = 4-Me-C_6H_5

3c and 4c, Ar = 2-OH-C_6H_5

3d and 4d, Ar = 4-OH-C_6H_5

3e and 4e, Ar = 4-OMe-C_6H_5

Scheme-I

Avance 500 MHz NMR spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts in δ ppm). The purity of the compounds was monitored by thin layer chromatography.

(2-Methyl-5-nitroimidazol-1-yl)acetic acid ethyl ester (1): A solution of 2-methyl-5-nitro-1H-imidazole (12.7 g, 0.1 mol) in 100 mL dry acetone was heated with ethyl chloroacetate (12.3 mL, 0.1 mol) on a water bath for 3 h in presence of anhydrous potassium carbonate (7 g). The reaction mixture was cooled and filtered to separate potassium carbonate. Acetone was removed under vacuum and the product isolated was recrystallized from methanol and water (7:3), yield (18.3 g, 86 %), m.p. 106 °C; IR (KBr, cm^{-1}) 1730 ν(C=O str. ester), 1460 ν(C-N str.), 1341 ν(C-NO_2). [Found: N, 19.78 $C_8H_{11}N_3O_4$ requires N, 19.72 %].

(2-Methyl-5-nitroimidazol-1-yl)acetic acid hydrazide (2): A mixture of compound **1** (2.13 g, 0.01 mol) and 80 % hydrazine hydrate (1 mL, 0.025 mol) in methanol was refluxed for about 3 h. The reaction mixture was then allowed to cool to room temperature. The separated white coloured crystalline solid was filtered, washed with methanol and crystallized from aqueous ethanol, yield (1.71 g, 86 %), m.p. 193 °C ; IR (KBr, cm^{-1}) 3342 ν(N-H str.), 3242 ν(-NH_2 str.), 1689 ν(C=O str. amide), 1600 ν(C=N str.), 1334 ν(C-NO_2); ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 3H, -CH_3), 4.38 (s, 2H, -NH_2), 4.71 (s, 2H, -CH_2), 8.26 (s, 1H, -CH of imidazole), 9.43 (s, 1H, -NH), [Found : N, 35.26 $C_6H_9N_5O_3$ requires N, 35.18 %].

(2-methyl-5-nitroimidazol-1-yl)acetic acid (1-phenylethylidene)-hydrazide (3a): (2-Methyl-5-nitroimidazol-1-yl)acetic acid hydrazide (**2**) (1.99 g, 0.01 mol) was dissolved in 1:1 ethanol and water containing few drops of glacial acetic acid, to which was added acetophenone (0.011 mol). The reaction mixture was refluxed for 3 h and then cooled in an ice-bath. The product separated on cooling was filtered, washed with cold methanol and recrystallized from methanol. **3a:** IR (KBr, cm^{-1}) 3360 ν(N-H str.), 3073 ν(C-H, aromatic), 2925 ν(C-H str.), 1683 ν(C=O str. amide), 1611 ν(C=N str.), 1541, 1487, 1456, ν(C=C, aromatic), 1323 ν(C-NO_2), 1040 ν(C-N str.); ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3H, -CH_3), 2.31 (s, 3H, -CH_3), 5.44 (s, 2H, -CH_2), 7.44-7.88 (m, 5H, ArH), 8.30 (s, 1H, -CH of imidazole), 11.14 (s, 1H, -NH). The compounds **3b-e** were prepared similarly.

The melting points, yields and analytical data of compounds **3a-e** are given in Table-1.

1-[2-(2-Methyl-5-nitroimidazol-1-yl)acetyl]-3-phenyl-4-carbaldehyde-1H-pyrazole (4a): The compound **3a** (0.004 mol) was added to the mixture of Vilsmeier-Haack reagent, prepared by dropwise addition of phosphorous oxychloride (0.012 mol) to an ice-cold solution of N,N-dimethylformamide (5 mL). The reaction mixture was warmed in a water bath for 2 h, then poured into ice-cold water and neutralized using an

TABLE-1
PHYSICAL DATA OF COMPOUNDS

Compd.	Ar	m.p. (ºC)	Yield (%)	m.f.	N %	
					Requires	Found
3a	C_6H_5	259	86	$C_{14}H_{15}N_5O_3$	23.26	23.22
3b	4-CH_3-C_6H_5	255	92	$C_{15}H_{17}N_5O_3$	22.22	22.28
3c	2-OH-C_6H_5	244	85	$C_{14}H_{15}N_5O_4$	22.08	22.12
3d	4-OH-C_6H_5	259	88	$C_{14}H_{15}N_5O_4$	22.08	22.02
3e	4-OCH_3-C_6H_5	252	81	$C_{15}H_{17}N_5O_4$	21.15	21.23
4a	C_6H_5	162	62	$C_{16}H_{13}N_5O_4$	20.65	20.70
4b	4-CH_3-C_6H_5	188	56	$C_{17}H_{15}N_5O_4$	19.94	19.96
4c	2-OH-C_6H_5	144	60	$C_{16}H_{13}N_5O_5$	19.72	19.80
4d	4-OH-C_6H_5	173	69	$C_{16}H_{13}N_5O_5$	19.72	19.74
4e	4-OCH_3-C_6H_5	196	58	$C_{17}H_{15}N_5O_5$	18.97	18.90

excess of sodium bicarbonate solution. The product obtained was filtered, washed with water and recrystallized from ethyl acetate. **4a:** IR (KBr, cm^{-1}) 3161ν(C-H, aromatic), 2958 ν(C-H str.), 1642 ν(C=O str.), 1582 ν(C=N str.), 1530, 1482, 1446 ν(C=C, aromatic), 1321 ν(C-NO_2), 1153-825 ν(C-C str.), 1074 ν(C-N str.); ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3H, -CH_3), 3.57 (s, 2H, -CH_2), 7.9-8.04 (m, 5H, ArH), 8.30 (s, 1H, -CH of imidazole), 8.75 (s, 1H, -CH of pyrazole), 10.1 (s, 1H, -CHO). The compounds **4b-e** were prepared similarly. The characterization data of compounds **4a-e** have been given in Table-1.

RESULTS AND DISCUSSION

Biological activity: The pyrazoles (**4a-e**) synthesized were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique[8] and for antifungal activity against *Aspergillus niger, Candida albicans, Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper-disc diffusion method[9] using concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for both antibacterial and antifungal activity.

The antibacterial and antifungal activities displayed by compounds **4a-e** have been listed in Table-2.

TABLE-2
BIOLOGICAL ACTIVITY DATA OF PYRAZOLES

Compd.	Antibacterial activity							
	S. aureus		*E. coli*		*B. subtilis*		*S. typhosa*	
	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL
4a	+	++	+	+	+	++	-	+
4b	+	++	+	+	-	++	-	+
4c	-	++	-	+	+	+	-	+
4d	+	+	-	+	-	+	-	-
4e	-	+	+	++	-	+	+	+
	Antifungal Activity							
	A. niger		*C. albicans*		*C. neoformans*		*T. paradoxa*	
	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL
4a	+	+	-	+	+	++	-	+
4b	-	+	-	+	+	+	-	+
4c	+	+	-	+	-	+	+	++
4d	-	+	-	-	-	+	-	+
4e	-	+	+	+	+	+	+	++

Inhibition zone diameter in mm: (-) < 11 mm, (+) 11-14 mm, (++) 15-18 mm

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