NITROIMIDAZOLES XI. SYNTHESES OF SUBSTITUTED (1-METHYL-5-NITRO-2-IMIDAZOLYL)PYRAZOLES

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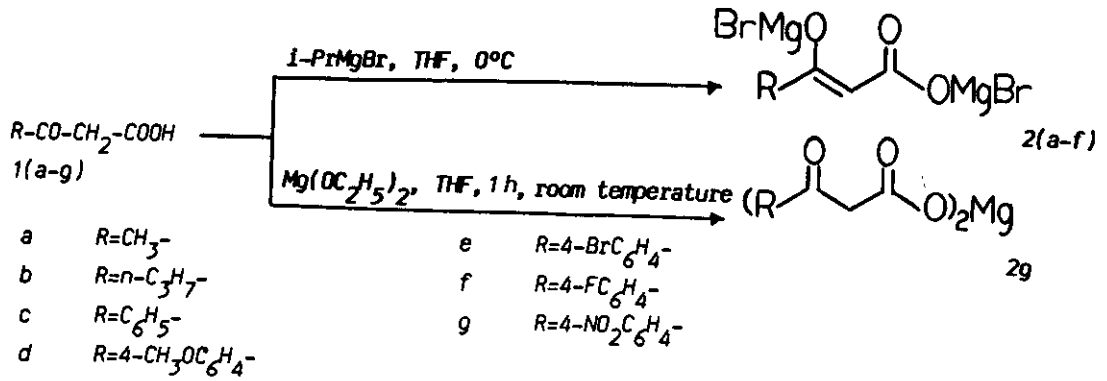
Abstract- The β-diketone derivatives of nitroimidazole were synthesized from the reaction of magnesium salt of β-keto acids (2) with imidazolide (3). The β-keto acids (1) were obtained from the hydrolysis of β-keto esters (5) or the reaction of magnesium methylcarbonate with the ketone (6). The reaction of β-diketones (4) with hydrazine afforded the pyrazoles (7), which were converted to N-methylpyrazoles (8) and (9). The latters could also be obtained from the reaction of β-diketones (4) with methylhydrazine.

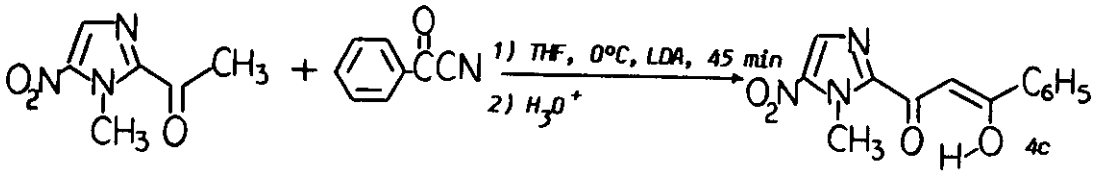
In continuation of our research program on nitroimidazole derivatives[1,2] to obtain biologically active compounds,[3] syntheses of the title compounds were undertaken. To synthesize the title compounds we needed β-diketones. The most common approaches employed to synthesize β-diketones are the condensation of a ketone with an ester,[4] with an acid chloride[5,6] or with an acyl cyanide[7] in the presence of a base, the condensation of lithium salt of a hydrazone of a ketone with an acid chloride,[8] the condensation of an enamine with an acyl chloride,[9] and the reaction of an organomagnesium halide with an acetoacetyl chloride.[10] The first three reactions either failed or gave low yield of the desired β-diketones (4) and the last reaction was not feasible because of unavailability of the starting organomagnesium halide. However, we could synthesize the β-diketones (4) from the reaction of magnesium slat (2) of β-ketocaroxylic acid (1) with imidazolide (3)[2,11] (Scheme 1).

β-Ketocarboxylic acids could be prepared by hydrolysis of the corresponding β-ketocarboxy-

late (5) or the reaction of a ketone (6) with magnesium methylcarbonate (MMC).[12] The mp, yields and analytical data of β-diketones (4) prepared by method B are given in Table 1.



Method A:



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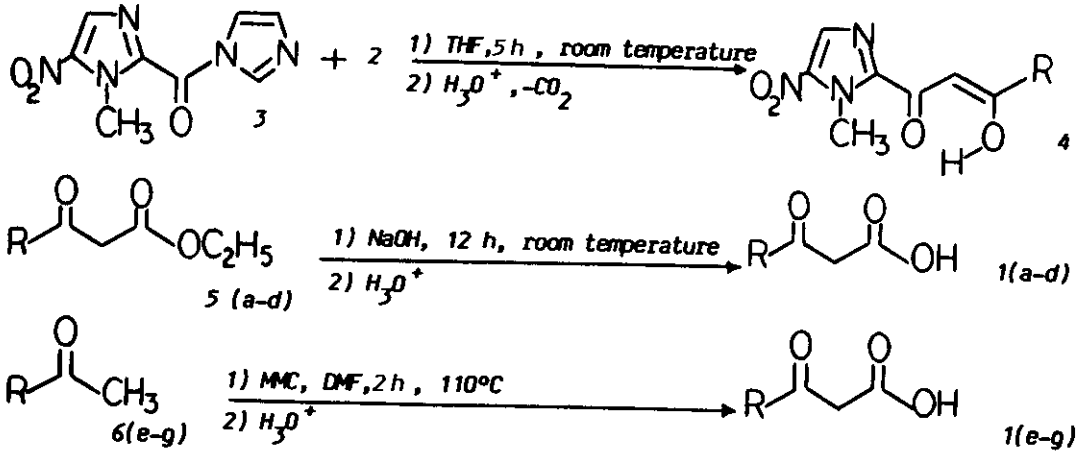


Scheme 1

Table 1. Mp, Yields and Analytical Data for β-Diketones prepared by Method B.

Compound	mp (°C[a])	Yield (%)	Formula	Elemental analysis (%)					
				Calculated			Found		
				C	H	N	C	H	N
4a	113-114[b]	35	$C_8H_9N_3O_4$	45.50	4.27	19.91	45.68	4.09	19.80
4b	47-48[b]	44	$C_{10}H_{13}N_3O_4$	50.21	5.44	17.57	50.08	5.59	17.68
4c	183-184	73	$C_{13}H_{11}N_3O_4$	57.14	4.03	15.38	57.31	4.18	15.52
4d	187-188	73	$C_{14}H_{13}N_3O_5$	55.45	4.29	13.86	55.62	4.36	13.69
4e	180-181	69	$C_{13}H_{10}N_3O_4Br$	44.32	2.84	11.93	44.50	2.66	11.77
4f	177-178	74	$C_{13}H_{10}N_3O_4F$	53.61	3.44	14.43	53.78	3.56	14.58
4g	183-184	39	$C_{13}H_{10}N_4O_6$	49.06	3.14	17.61	49.21	3.01	17.74

a: Unless otherwise mentioned the compound was crystallized from acetone. b: This compound was crystallized from ethanol.

The reaction of compound (**4**) with hydrazine afforded 3-(or 5-)(1-methyl-5-nitro-2-imidazolyl)-5-(or 3-) alkyl (or aryl)pyrazoles (7) (Scheme 2).

Table 2. Mp, Yields and Analytical Data for 3-(or 5-)(1-methyl-5-nitro-2-imidazolyl)-pyrazoles

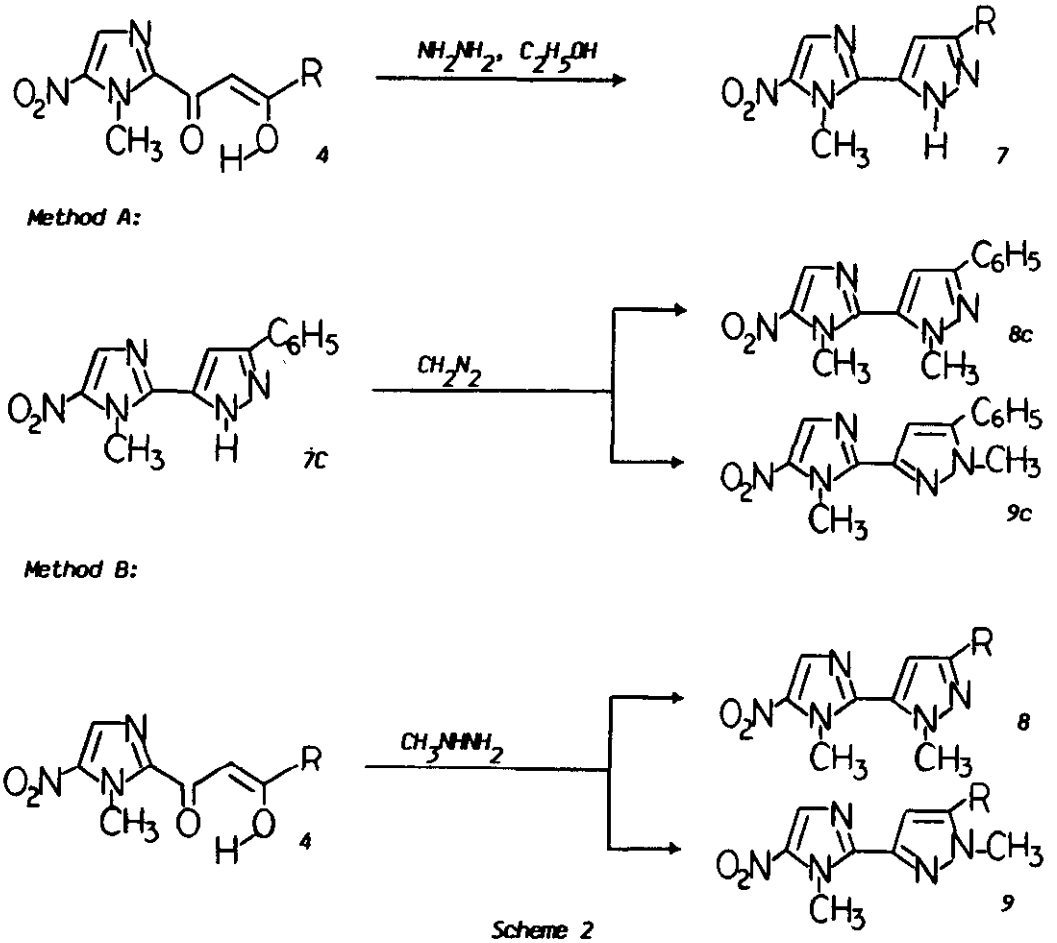
Compound	mp (°C[a])	Yield (%)	Formula	Elemental analysis (%)					
				Calculated			Found		
				C	H	N	C	H	N
7a	267-8	76	$C_8H_9N_5O_2$	46.38	4.35	33.82	46.51	4.22	33.65
7b	201-2	87	$C_{10}H_{13}N_5O_2$	51.06	5.53	29.79	51.24	5.38	29.62
7c	252-3	89	$C_{13}H_{11}N_5O_2$	57.99	4.09	26.02	57.82	4.22	26.15
7d	235-6	89	$C_{14}H_{13}N_5O_3$	56.19	4.35	23.41	56.24	4.46	23.35
7e	264-5	87	$C_{13}H_{10}N_5O_2Br$	44.83	2.87	20.11	44.67	2.69	20.22
7f	277-8	89	$C_{13}H_{10}N_5O_2F$	54.36	3.48	24.39	54.18	3.54	24.43
7g	286-7	86	$C_{13}H_{10}N_6O_4$	49.68	3.18	26.75	49.79	3.23	26.84

a: All compounds were crystallized from propanol.

The reaction of diazomethane with (**7c**) gave 1-methyl-5-(1-methyl-5-nitro-2-imidazolyl)-3-phenylpyrazole (**8c**) and 1-methyl-3-(1-methyl-5-nitro-2-imidazolyl)-5-phenylpyrazole (**9c**) in 27% and 13% respectively (Scheme 2).

Compounds (**8c**) and (**9c**) had maximum absorptions at 325 and 340 nm respectively. In compound (**8c**) because of steric hindrance of N-CH_3 of pyrazole ring with imidazole ring,

*the imidazole ring is not coplanar with pyrazole ring, while in compound (**9c**) this hindrance does not exist. Therefore, compound (**9c**) showed absorption at longer wavelength. In compound (**7c**) the imidazole and pyrazole rings are coplanar. The N-CH_3 group of imidazole is deshielded by anisotropic effect of pyrazole ring and appeared at 4.34 ppm.*



Scheme 2

*Similar effect was observed in compound (**9c**). The N-CH_3 group of imidazole appeared at 4.43 ppm. However, in compound (**8c**) the imidazole and pyrazole rings are not coplanar and the N-CH_3 group of imidazole ring is not deshielded and appeared at 4.11 ppm. Similar effect was observed in the proton position of the phenyl ring. In compound (**7c**) the phenyl and pyrazole rings are coplanar. The ortho protons are deshielded by anisotropic*

effect of pyrazole ring and appeared at 7.83 ppm. The meta and para protons had resonance at 7.46 ppm. Similar effect was observed in compound (**8c**). The ortho protons of phenyl appeared at 7.81 ppm, while meta and para protons had resonance at 7.38 ppm. In compound (**9c**) the phenyl and pyrazole rings are not coplanar. The ortho protons are not deshielded by pyrazole ring. Therefore, all phenyl protons appeared as a singlet at 7.46 ppm. Compounds (**8**) and (**9**) could also be prepared from the reaction of the diketone (**4**) with methylhydrazine (Scheme 2).

The mp, yields and analytical data of compounds (**8**) and (**9**) are given in Table 3.

Table 3. Mp, Yields and Analytical Data for 3-aryl-1-methyl-5-(1-methyl-5-nitro-2-imidazolyl)pyrazoles (8) and 5-aryl-1-methyl-3-(1-methyl-5-nitro-2-imidazolyl)pyrazoles (9) by Method B.

Compound	mp (°C[a])	Yield (%)	Formula	Elemental analysis (%)					
				Calculated			Found		
				C	H	N	C	H	N
8c	201-202	17	$C_{14}H_{13}N_5O_2$	59.36	4.59	24.73	59.52	4.63	24.91
8d	200-201	14	$C_{15}H_{15}N_5O_3$	57.51	4.79	22.36	57.64	4.63	22.52
8e	176-177	25	$C_{14}H_{12}N_5O_2Br$	46.41	3.31	19.34	46.59	3.45	19.22
8f	217-218	26	$C_{14}H_{12}N_5O_2F$	55.81	3.99	23.26	55.65	4.11	23.44
9c	180-181[b]	62	$C_{14}H_{13}N_5O_2$	59.36	4.59	22.73	59.17	4.41	22.59
9d	178-179[b]	66	$C_{15}H_{15}N_5O_3$	57.51	4.79	22.36	57.65	4.88	22.52
9e	226-227	56	$C_{14}H_{12}N_5O_2Br$	46.41	3.31	19.34	46.26	3.26	19.23
9f	192-193	53	$C_{14}H_{12}N_5O_2F$	55.81	3.99	23.26	55.68	4.07	23.37

a: Unless otherwise mentioned the compound was crystallized from ethanol. b: This compound was crystallized from n-propanol.

EXPERIMENTAL

General Methods. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded on a Perkin Elmer 550 SE spectrophotometer. The ir spectra were obtained on a Perkin Elmer 267 spectrophotometer (potassium bromide disks). The nmr spectra were recorded on a Bruker FT-80 spectrometer. Chemical Shifts are reported in ppm from TMS as an internal standard and are given in δ units. The mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

2-Benzoylacetyl-1-methyl-5-nitroimidazole (4c).

Method A: 2-Acetyl-1-methyl-5-nitroimidazole (406 mg, 2.4 mmol)[2] was added to a stirring solution of lithium diisopropylamide (2.6 mmol) in tetrahydrofuran (5 ml) at 0°C. After 5 min benzoyl cyanide (0.3 ml, 2.4 mmol) was added and stirring was continued for 45 min. The mixture was added to 4% hydrochloric acid (4.5 ml). The mixture was extracted with ethyl acetate (2x20 ml). The ogranic layer was separated, dried over sodium sulfate and the solvent was evaporated under vacuum. The residue was crystallized from acetone to give **4c** (236 mg, 36%): mp 183-184°C; uv λ_{max} (ethanol): 372 (log ε=4.47), 294 (log ε= 3.90) and 240 nm (log ε=3.99); ir : 1605 (C=O), 1535 and 1360 cm^{-1} (NO_2); ^{1}H-nmr ($CDCl_3$): 15.85 (broad, 1H, enol-OH), 8.03 (s, 1H, H_4 imidazole), 7.98 (m, 2H, phenyl), 7.49 (m, 3H, phenyl), 7.35 (s, 1H, =CHCO) and 4.45 (s, 3H, NCH_3); ms m/z (%) 273 (M^+, 30), 245 (18), 186 (11), 168 (24), 154 (30), 147 (10), 143 (19), 130 (11), 118 (12), 105 (97), 103 (17), 102 (100), 91 (16), 77 (78), 69 (47), 54 (7) and 51 (15).

Method B: Thionyl chloride (475 mg, 4 mmol) was added to a stirred solution of imidazole (1.09 g, 16 mmol) in anhydrous THF (15 ml). After 15 min the suspension was filtered and washed with THF (3 ml). To the filtrate was added 1-methyl-5-nitro-imidazole-2-carboxylic acid (684 mg, 4 mmol). The mixture was stirred for 15 min. To the stirred suspension was added magnesium banzoylacetate (1.48 g, 4 mmol)[11] in THF (10 ml). The mixture was stirred for 5 h at room temperature. It was acidified with 4% hydrochloric acid. The mixture was extracted with ethyl acetate (3x20 ml). The organic layer was dried with sodium sulfate. The solvent was evaporated and the residue was crystallized from acetone to give **4c** (797 mg, 73%); mp 183-184°C.

Other β-diketones (**4a-4g**) were prepared similarly (Table 1).

3-(or 5-)(1-Methyl-5-nitro-2-imidazolyl)-5-(or 3-)phenylpyrazole (7c).

To a refluxing solution of compound (**4c**) (273 mg, 1 mmol) in ethanol (12 ml) and THF (3 ml) was added a solution of hydrazine hydrochloride (75 mg, 1.1 mmol) and sodium acetate (90 mg, 1.1 mmol) in water (0.5 ml). The refluxing was continued for 2 h. The solvent was evaporated. To the residue was added water (5 ml). The precipitate was filtered and crystallized from propanol to give **7c** (239.5 mg, 89%); mp 252-253°C; uv λ_{max} (ethanol): 338 (log ε=4.10) and 248 nm (log ε=4.36); ir: 3200 (NH), 1535 and 1320 cm^{-1}

(NO_2); ^{1}H-nmr (DMSO-d_6) 13.92 (broad, 1H, NH) 8.17 (s, 1H, H_4 imidazole) 7.83 (m, 2H, phenyl), 7.46 (m, 3H, phenyl), 7.26 (s, 1H, H_4 pyrazole) and 4.34 (s, 3H, N-CH_3); ms m/z (%) 269 (M^+, 40), 240 (7), 239 (19), 223 (13), 184 (10), 183 (19), 182 (100), 171 (28), 170 (24), 169 (19), 153 (12), 140 (25), 126 (18), 117 (10), 116 (17), 114 (20), 104 (35), 87 (12), 77 (35), 74 (52), 71 (10) and 57 (16).

Other substituted pyrazoles (**7a-7g**) were prepared similarly (Table 2).

1-Methyl-5-(1-methyl-5-nitro-2-imidazolyl)-3-phenylpyrazole (8c) and 1-Methyl-3-(1-methyl-5-nitro-2-imidazolyl)-5-phenylpyrazole (9c).

Method A: To a stirring solution of compound (**7c**) (269 mg, 1 mmol) in ether (20 ml) was added diazomethane (excess). The stirring was continued and the progress of the reaction was followed by tlc (silica gel, chloroform: ethyl acetate, **8:2**). After the reaction was complete, the solvent was evaporated and the residue was separated by preparative tlc on silica gel using chloroform: ethyl acetate (**8:2**) as the eluent. The slow moving fraction (R_f =0.42) was crystallized from ethanol to give **8c** (77 mg, 27%); mp 201-202°C; uv λ_{max} (ethanol): 325 (log ε=4.03) and 245 nm (log ε=4.39); ^{1}H-nmr ($CDCl_3$) 8.12 (s, 1H, H_4 imidazole), 7.81 (m, 2H, phenyl), 7.38 (m, 3H, phenyl), 6.78 (s, 1H, H_4 pyrazole), 4.11 (s, 3H, N-CH_3 imidazole) and 4.08 (s, 3H, N-CH_3 pyrazole); ms m/z (%) 283 (M^+, 91), 282 (45), 253 (20), 236 (19), 209 (11), 197 (15), 196 (100), 185 (33), 183 (40), 182 (36), 180 (33), 163 (30), 152 (25), 142 (10), 140 (13), 126 (18), 118 (12), 116 (13), 106 (24), 104 (18), 103 (17), 99 (11), 80 (15), 77 (74), 67 (14), 66 (99) and 54 (40).

The fast moving fraction (R_f=0.52) was crystallized from propanol to give **9c** (37 mg, 13%); mp 180-181°C; uv λ_{max} (ethanol): 340 (log ε=4.14) and 239 nm (log ε=4.39); ^{1}H-nmr ($CDCl_3$) 8.08 (s, 1H, H_4 imidazole), 7.46 (s, 5H, phenyl), 6.97 (s, 1H, H_4 pyrazole), 4.43 (s, 3H, N-CH_3 imidazole) and 3.97 (s, 3H, N-CH_3 pyrazole); ms m/z (%) 283 (M^+, 100), 268 (38), 267 (58), 253 (35), 237 (25), 223 (12), 198 (15), 197 (15), 196 (99), 185 (48), 184 (19), 182 (10), 140 (13), 118 (77), 103 (12), 91 (19), 77 (48), 63 (13) and 54 (19).

Method B: To a stirring warm solution of compound (**4c**) (273 mg, 1 mmol) in ethanol (10 ml) and THF (2 ml) was added a solution of methylhydrazine monoacetate (117 mg, 1.1 mmol) in water (1 ml). The mixture was heated under reflux for 2 h. The solvent was evaporated and

*the residue was separated by preparative tlc on silica gel using chloroform: ethyl acetate (**8:2**) as the eluent. The slow moving fraction was crystallized from ethanol to give **8c** (48 mg, 17%); mp 201-202°C. The fast moving fraction was crystallized from propanol to give **9c** (176 mg, 62%); mp 180-181°C.*

*Compounds (**8d-8f**) and (**9d-9f**) were prepared similarly (Table 3).*

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