Vol. 6 No. 4
Autumn 1995

NITROIMIDAZOLES XII [1]: SYNTHESES OF TRISUBSTITUTED PYRAZOLES AND SUBSTITUTED (1-METHYL-5-NITRO-2-IMIDAZOLYL) PYRIMIDINONES

B. Farzamfar, A. Ghanbarpour and A. Shafiee*

* *Department of Chemistry, Faculty of Pharmacy, The Medical Sciences University of Tehran, Tehran, Islamic Republic of Iran*

Abstract

The reaction of β-diketones **1** with phenyl hydrazine afforded 5-aryl-3-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazole (**2**) and 3-aryl-5-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazole (**3**). The reaction of diketones (**1**) with urea in the presence of *p*-toluenesulfonic acid gave 4-(or 6-)aryl-6-(or 4-)(1-methyl-5-nitro-2-imidazolyl)-2-(1H)pyrimidones (**4**). The structures of all compounds were confirmed by spectroscopic methods.

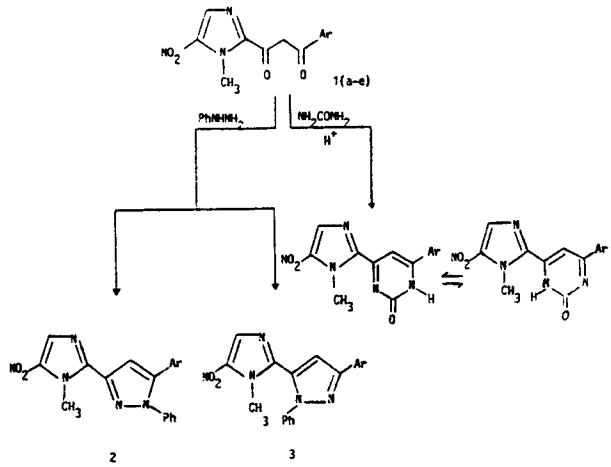
Introduction

In view of the potential activity of pyrazole [2,4] and pyrimidone ring systems [5,6] and in continuation of our research program on nitroimidazole derivatives [7,8], obtaining biologically active compounds [9] through the syntheses of the title compounds was of interest to us.

Results and Discussion

The synthesis of β-diketones (**1**) required for this work has been reported previously [1]. The reaction of compound **1** with phenylhydrazine afforded 5-aryl-3-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazole (**2**) and 3-aryl-5-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazole (**3**) [10] (Scheme 1).

Compounds **2a** and **3a** had maximum absorption at 251 and 268 nm, respectively. In compound **3a**, because of steric hindrance of N-ph of pyrazole with the imidazole ring, the latter is not coplanar with the pyrazole ring. However, the two phenyl rings are coplanar with the pyrazole ring. Therefore, the UV absorption appears at a longer wave length. The ^1H NMR is also in accordance with the suggested



a Ar = C_6H_5 -
b Ar = p - NO_2 - C_6H_4 -
c Ar = p - Br - C_6H_4 -
d Ar = p - Cl - C_6H_4 -
e Ar = p - CH_3O - C_6H_4 -

Scheme 1

Keywords: Pyrazoles; Pyrimidinones; Syntheses

structure. In compound **3a**, in which two phenyls are coplanar with the pyrazole ring, the ortho protons are deshielded by anisotropic effect of pyrazole ring and appeared at 7.50 and 7.20 ppm. The meta and para protons had resonance at 7.39 and 7.05 ppm. In compound (**2a**), only one of the phenyl rings is coplanar with the pyrazole ring, therefore, the protons of the non-coplanar phenyl appeared as a five-proton singlet at 7.37 ppm. The melting points, yields and analytical data of compounds (**2**) and (**3**) are given in Table 1.

The reaction of compound **1** with urea in boiling glacial acetic acid in the presence of *p*-toluenesulfonic acid gave 4-(or 6-)-aryl-6-(or 4-)-(1-methyl-5-nitro-2-imidazolyl)-2-(1H)pyrimidinones (**4**) [11] (Scheme 1). The melting points, yields and analytical data of compounds (**4**) are given in Table 2.

Experimental Section

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 recorded on a Nicolet-550 FT-IR. 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 Finnigan TSQ 70 spectrometer at 70 eV.

3-(or 5-)(1-methyl-5-nitro-2-imidazolyl)-5-(or 3-)phenylpyrazole (2a, 3a)

Phenyl hydrazine (1.08 g, 0.01 mole) in anhydrous ethanol (20 ml) was slowly stirred into a solution of compound **1a** (2.73 g, 0.01 mole) in anhydrous ethanol (20 ml). The resulting solution was refluxed for 10

Table 1. Melting points, yields and analytical data for 5-aryl-3-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazoles (**2**) and 3-aryl-5-(1-methyl-5-nitro-2-imidazolyl)-1-phenylpyrazoles (**3**)

Compound	MP (°C)[a]	Yield (%)	Formula	Elemental analysis (%)					
				Calculated			Found		
				C	H	N	C	H	N
2a	140-143	40	$C_{19}H_{15}N_5O_2$	66.09	4.35	20.29	66.25	4.54	20.46
2b	153-155	44	$C_{19}H_{14}N_6O_4$	58.46	3.59	21.54	58.32	3.64	21.67
2c	140-142	40	$C_{19}H_{14}BrN_5O_2$	53.77	3.30	16.51	53.89	3.15	16.34
2d	135-138	36	$C_{19}H_{14}ClN_5O_2$	60.08	3.70	18.45	60.23	3.85	18.63
2e	130-133	44	$C_{20}H_{17}N_5O_3$	64.00	4.53	18.67	64.18	4.71	18.49
3a	150-152	24	$C_{19}H_{15}N_5O_2$	66.09	4.35	20.29	65.91	4.16	20.14
3b	165-168	16	$C_{19}H_{14}N_6O_4$	58.46	3.59	21.54	58.59	3.43	21.72
3c	142-145	24	$C_{19}H_{14}BrN_5O_2$	53.77	3.30	16.51	53.92	3.45	16.66
3d	140-142	20	$C_{19}H_{14}ClN_5O_2$	60.08	3.70	18.45	60.22	3.84	18.63
3e	140-142	20	$C_{20}H_{17}N_5O_3$	64.00	4.53	18.67	64.11	4.39	18.54

[a] All compounds were crystallized from ethanol.

Table 2. Melting points, yields and analytical data for 6-(or 4-)aryl-4-(or 6-)(1-methyl-5-nitro-2-imidazolyl)-2(1H) pyrimidinones (**4**)

Compound	MP (°C)[a]	Yield (%)	Formula	Elemental analysis (%)					
				Calculated			Found		
				C	H	N	C	H	N
4a	235-237	27	$C_{14}H_{11}N_5O_3$	56.57	3.70	23.57	56.62	3.81	23.39
4b	247-248	26	$C_{14}H_{10}N_6O_5$	49.12	2.92	24.56	49.25	2.78	24.37
4c	232-235	25	$C_{14}H_{10}BrN_5O_3$	44.63	2.66	18.62	44.83	2.51	18.45
4d	212-215	25	$C_{14}H_{10}ClN_5O_3$	50.68	3.02	21.12	50.49	2.91	21.35
4e	152-155	22	$C_{15}H_{13}N_5O_4$	55.05	3.98	21.41	55.22	3.81	21.32

[a] All compounds were crystallized from ethanol.

hours and evaporated under reduced pressure. The residue was treated with water (20 ml) and extracted twice with chloroform. The chloroform was washed with a saturated solution of sodium hydrogen carbonate and then with water, dried (magnesium sulfate) and evaporated under reduced pressure to give a residue which was separated by preparative TLC on silica gel using chloroform:ethyl acetate (9:1) as the eluent.

The slow moving fraction (R_f=0.55) was crystallized from ethanol to give 0.83 g (24%) of **3a**; m.p. 153-155°C; UV (ethanol): λ_{max} 268 nm (log ε = 4.27); IR (potassium bromide): ν 3100 (H-C_4 imidazole), 1560 and 1355 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$): 7.66 (s, 1H, H_4-imidazole), 7.50 (m, 2H, arom), 7.39 (m, 3H, arom), 7.20 (m, 2H, arom), 7.10 (s, 1H, H_4-pyrazole), 7.05 (m, 3H, arom) and 3.60 ppm (s, 3H, NCH_3); ms: m/z (%) 345 (M^+, 15), 330 (93), 328 (100), 326 (96), 281 (93), 279 (84), 267 (13), 204 (95), 126 (99) and 77 (13).

The fast moving fraction (R_f = 0.65) was crystallized from n-propanol to give 1.39 g (27%) of **2a**; m.p. 140-143°C; UV (ethanol): λ_{max} 251 nm (log ε = 4.37); IR (potassium bromide: ν 3120 (H-C_4 imidazole), 1555 and 1360 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$): 8.12 (s, 1H, H_4-imidazole), 7.67 (m, 2H, arom) 7.40 (m, 3H, arom), 7.37 (s, 5H, arom) and 3.60 ppm (s, 3H, NCH_3).

Other compounds (**2** and **3 b-e**) were prepared similarly (Table 1).

4-(or 6-)(1-methyl-5-nitro-2-imidazolyl)-6-(or 4-) phenyl-2-(1H)pyrimidinone (4a)

Compound **1a** urea (90 mg, 1.5 mmoles), *p*-toluenesulfonic acid (260 mg, 1.5 mmole) and glacial acetic acid (15 ml) were heated under reflux for 48 hours and neutralized with aqueous sodium hydroxide (12%). The product was collected, washed with water, dried and crystallized from ethanol to give 80 mg (27%) of **4a**; m.p. 232-237°C; UV (ethanol): λ_{max} 292 (log ε = 3.69) and 231 nm (log ε = 3.74); IR (potassium bromide): ν 3365 (NH), 3130 (H-C_4, imidazole), 1550 and 1360 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$); 8.00 (s, 1H, H_4-imidazole), 7.56 (m, 2H, phenyl), 7.46 (m, 3H, phenyl), 6.65 (s, 1H, CH, of pyrimidinone) and 4.43 ppm (s, 3H, NCH_3); ms: m/z (%) 297 (M^+, 8), 279 (15), 272 (49), 255 (19), 244 (18), 220 (16), 167 (36), 149 (100), 126 (26) and 111 (41).

Other compounds **4 (b-e)** were prepared similarly (Table 2).

References

1. For Nitroimidazole XI see R. Karimi-Khoozani, A. Ghanbarpour and A. Shafiee, *Heterocycles*, **38**, 503, (1994).
2. Dusza, J. P., Joseph, J. P. and Bernstein, S. *U. S.*, **4**, 360, 680, (1982); *Chem. Abstr.*, **98**, 72090a, (1983).
3. Bondavelli, F., Bruno, O., Ranise, A., Schenone, P., Donnoli, D., Cenicola, M. L., Matera, C., Russo, S. and Marmo, E. *Farmaco*, **44**, 655, (1989); *Chem. Abstr.*, **112**, 151256v, (1990).
4. Menozzi, G., Most, L., Schenone, P., Donnoli, D., Schiariti, F. and Marmo, E. *Farmaco*, **45**, 167, (1990); *Chem. Abstr.*, **113**, 184198b, (1990).
5. Clough, J. M., Godfrey, C. R. A., Streeting, I. T. and Bacon, D. P. *Eur. Pat. Appl. E. P.*, **430**, 471, (1991); *Chem. Abstr.*, **115**, 136117u, (1991).
6. Ikeda, M. and Okabe, S. *Eur. Pat. Appl. E. P.*, **257**, 850, (1988); *Chem. Abstr.*, **109**, 6543v, (1988).
7. Shafiee, A., Parang, K., Khazan, M. and Ghasemian, F. *J. Heterocyclic Chem.*, **29**, 1859, (1992).
8. Shafiee, A., Pirouzzadeh, B., Ghasemian, F. and Parang, K. *Ibid.*, **29**, 1021, (1992) and references cited therein.
9. Seaborg, G. T. *Science*, **223**, 9, (1984).
10. Menozzi, G., Mosti, L. and Schenone, P. *J. Heterocyclic Chem.*, **24**, 1669, (1987).
11. Katrizky, A. R., Salgado, H. J., Chermprapai, A. and Ponkshe, N. K. *J. Chem. Soc. Perkin Trans*, **1**, 153, (1982).