NITROIMIDAZOLES XIII. SYNTHESIS OF SUBSTITUTED (1-METHYL-5-NITRO-2-IMIDAZOLYL) ISOXAZOLES

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ABSTRACT: *The beta-diketone derivatives of nitroimidazole were synthesized from the reaction of magnesium salt of beta-ketoacids 3 with imidazolide 4. The reaction of beta-diketones with hydroxylamine hydrochloride afforded either the isoxazoles or the 5-hydroxy-2-isoxazolines.*

KEY WORDS: *Beta-diketones, Nitroimidazole, Imidazolide, Isoxazoles, Isoxazoline.*

In continuation of our research program on nitroimidazole derivatives [1-2] and in order to expand the chemistry of these compounds, synthesis of the title compounds were considered. In the preceding paper [3], we reported the synthesis of beta-diketone derivatives of nitroimidazole and the reaction of these compounds with hydrazine for preparation of pyrazole derivatives. Here we report the condensation of beta-diketones with hydroxylamine hydrochloride for the preparation of 5-aryl-3-(1-methyl-5-nitro-2-imidazolyl) isoxazole (**1**) and 3-aryl-5-(1-methyl-5-nitro-2-imidazolyl) isoxazole (**2**) (Scheme 2).

RESULTS AND DISCUSSION

The beta-diketones **5** were synthesized from the reaction of magnesium salt **3** of beta-ketoacids **2** with imidazolide **4** [2,4] (Scheme 1).

In the preparation of isoxazole rings from diketones and hydroxylamine hydrochloride [5,6], the reaction proceeds through an oxime intermediate. If the dicarbonyl compound is symmetrical, only one product can result regardless of which carbonyl group undergoes initial attack. However, if the substrate is not symmetrical, as in our case, mixtures my result. The reaction of compound **5** with hydroxylamine hydrochloride afforded compounds **1** and **8**.

Compound **1** was formed through the intermediates **5** and **6** which could not be isolated. The structure of compound **1** in addition to ^{1}H NMR, was confirmed by its Mass spectra data. In compound **1**, the molecular ion gives $ArCO^+$ peak which confirms that the isoxazole has structure **1** rather than **2**. Similar results were observed in other isoxazoles [5].

The structure of compound **8** was established

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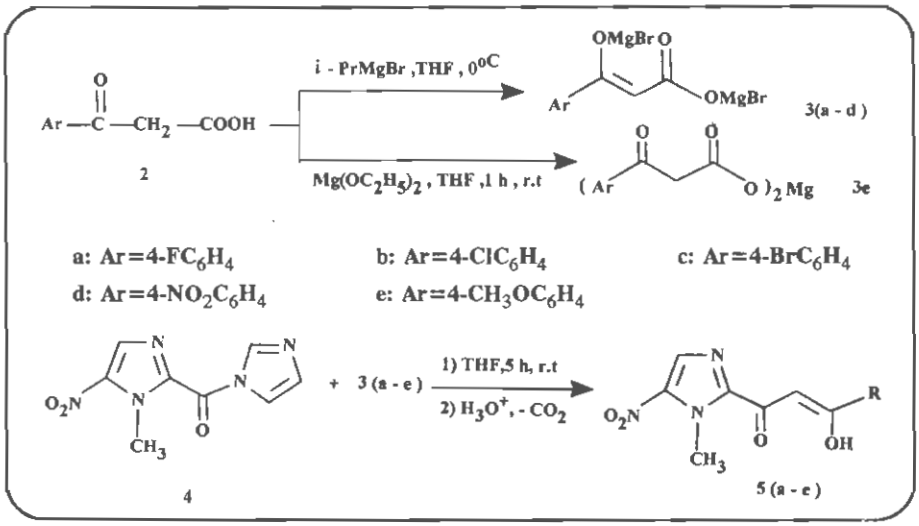
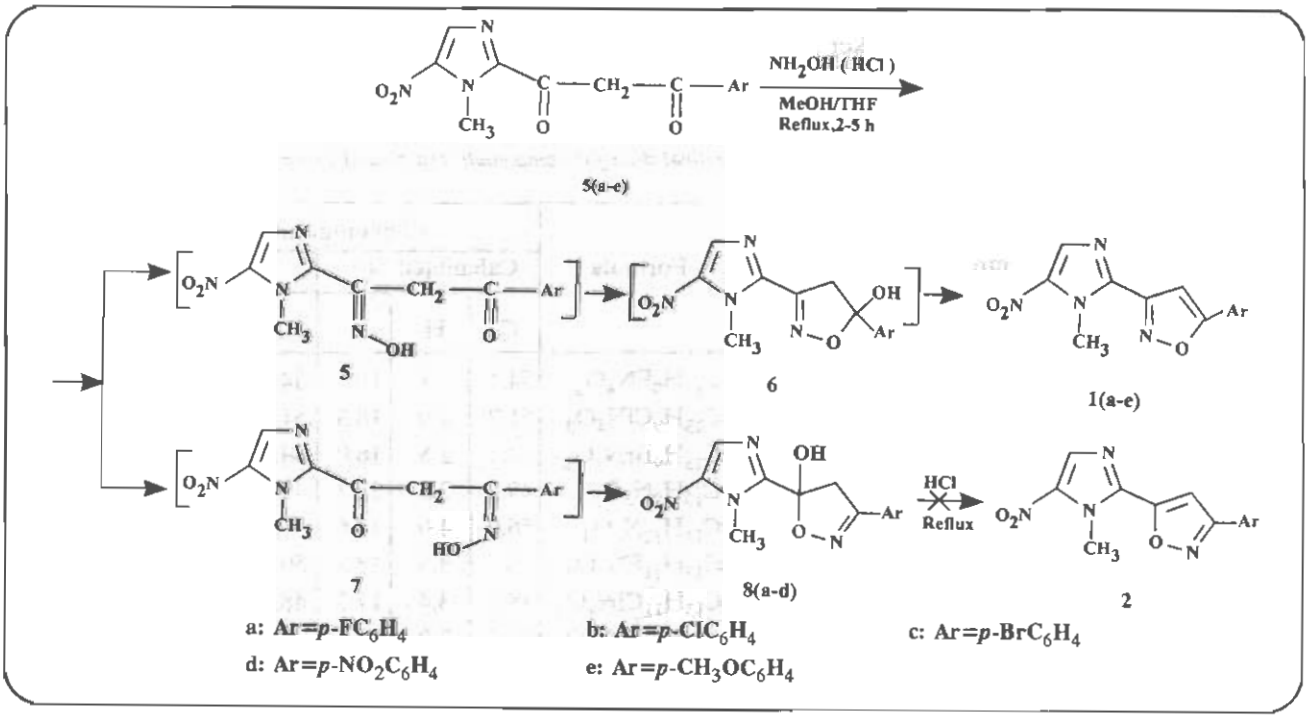


Scheme 1

through ^{1}H NMR, ^{13}C NMR and Mass spectra. In the mass spectrum of compound **8** the molecular ion first loses OH, giving the base peak (M-17) and in the next step $ArCN^{+}$ is formed (a major peak) which prove that the compound is **8** rather than **6**. In ^{1}H-NMR, CH_2 of isoxazoline gave an AB quartet with J=18 Hz. Further evidence for structure **8b** comes from the ^{13}C NMR, carbon-4 of isoxazoline is seen at δ 105.5 *ppm* in the position to be expected for a cyclic hemi-ketal [7]. Furthermore in ^{13}C NMR, 11 carbones appeared. From the DEPT spectra there were 3 CH, 1 CH_2 , and 1 CH_3 carbon atoms.

It was expected that under acidic conditions compound **8** would afford the isoxazole **2**. However under different experimental conditions it does not give the desired compound (Scheme 2).



Scheme 2

The electron withdrawing power of the group attached to carbonyl group will be a determining factor and causes oxime formation more easily from one side relative to the other. In all derivatives we prepared, one of the carbonyl groups is attached to a nitro imidazole derivative and the other carbonyl group is attached to para-substituted benzene rings. In the para-halogen benzene series, the ratio of electron releasing parameter to electronegativity plays an important role in the oxime formation.

Therefore the ratio of compounds **8** to **1** becomes greater from F to Br. Practically the ratio obtained were 0.77, 1.43, 1.60 for F, Cl and Br, respectively.

In the para-nitro analogue, a strong electron withdrawing group, the ratio was 3.84 and in para methoxy analogue, because of the electron releasing power, practically, only isoxazole **1** was formed (Scheme 2). The physical and spectra data of compounds **1** and **8** are summarized in Tables 1 and 2.

EXPERIMENTAL

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 (KBr disks). The ^{1}H-NMR spectra were recorded on a Bruker FT-80 spectrophotometer. Chemical shifts are reported in *ppm* from TMS as an internal standard and are in δ units. The Mass spectra were run on a Varian model MAT MS-311 spectrometer at 70 ev.

3-(1-Methyl-5-nitro-2-imidazolyl)-5-(4-chlorophenyl) isoxazole (**1b**) and 3-(4-chlorophenyl)-5-(1-methyl-5-nitro-2-imidazolyl)-5- hydroxy-2-isoxazoline (**8**b)

To a stirring warm solution of compound **5**b (370 mg, 1.2 mmol) in MeOH (40 mL) and THF (20 mL) was added a solution of hydroxylamine hydrochloride (166 mg, 2.4 mmol) in water (1 mL). The mixture was heated under reflux for 3 hours. The solvent was evaporated and the residue was purified by preparative TLC on silica gel using chloroform-ethyl acetate (1:1) as the eluent.

The fast moving fraction was crystallized from ethanol to give **1b** (136 mg, 37%) mp 220-221°C.
IR(KBr disk): ν_{max}(cm^{-1}), 3120, 1620, 1560, 1370.
^{1}H NMR(DMSO-d_6): δ(*ppm*), 8.28(s, 1H, H_4 -imidazole), 7.89(s, 1H, H_4 -isoxazole), 7.84(2d, 4H, aromatic), 4.23(s, 3H, NCH_3).
MS: *m/z*(%), 304(M^+, 80), 178(50), 139(30), 121(80), 111(50), 95(25), 69(100), UV(CH_3OH): λ_{max}(nm), 317(log ε= 4.10), 245(log ε= 4.26).

The slow moving fraction was crystallized from ethanol to give **8b** (205 mg, 53%), mp 160-161°C (decomp.). IR(KBr disk): ν_{max}(cm^{-1}) 3200-2900(br), 1600, 1550, 1360.
^{1}H NMR(DMSO-d_6): δ(*ppm*), 8.58(s, 1H, OH, exchan-

Table 1: M. ps., Yields and analytical data for compounds 1(a-e) and 8(a-d)

Compound	mp (°C)[a]	Yield (%)	Formula	Elemental analysis					
				Calculated(%)			Found(%)		
				C	H	N	C	H	N
1a	193-194	52	$C_{13}H_9FN_4O_3$	54.1	3.1	19.4	54.3	3.2	19.1
1b	220-221	37	$C_{13}H_9ClN_4O_3$	51.2	2.9	18.3	51.4	3.1	18.1
1c	236-237	35	$C_{13}H_9BrN_4O_3$	44.7	2.5	16.0	44.9	2.6	15.7
1d	250-251	19	$C_{13}H_9N_5O_5$	49.5	2.8	22.2	49.8	3.0	22.0
1e	120-121	96	$C_{14}H_{12}N_4O_4$	56.0	4.0	18.6	55.7	3.8	19.0
8a	169-170(decomp.)	40	$C_{13}H_{11}FN_4O_4$	50.9	3.5	18.3	50.7	3.3	18.1
8b	160-161(decomp.)	53	$C_{13}H_{11}ClN_4O_4$	48.3	3.4	17.3	48.7	3.5	17.6
8c	157-158(decomp.)	56	$C_{13}H_{11}BrN_4O_4$	42.5	3.0	15.2	42.4	2.8	14.9
8d	191-192	73	$C_{13}H_{11}N_5O_6$	46.8	3.3	21.0	46.5	3.2	21.1

a: All compounds were crystallized from ethanol.

Table 2 : Spectral data for compounds 1(a-e) and 8(a-d)

Product	^{1}H NMR(DMSO-d_6) δ(ppm)	MS(70 ev) m/z(%)	λ_{max}(log ε) ethanol
1a	8.04(s, 1H, H_4 -imi.), 7.89(s, 1H, H_4 -Oxa.)7.22 (2d, 4H, Ar) and 4.47 *ppm*(s, 3H, NCH_3).	288(M^+, 35), 162(46), 137(10), 123 (100), 95(75).	319(4.14), 237(4.26).
1c	8.31(s, 1H, H_4 -imi), 7.88(s, 1H, H_4 -Oxa.)7.85 (2d, 4H, Ar) and 4.16 *ppm*(s, 3H, NCH_3).	348(M^+, 100), 252(95), 224(48), 185(15). 169(12), 157(20).	323(4.25), 249(4.44).
1d	8.36(s, 1H, H_4 -imi), 7.83(s, 1H, H_4 -Oxa.) 8.20 (2d, 4H, Ph) and 4.48 *ppm*(s, 3H, NCH_3).	315(M^+, 100), 189(85), 157(12), 150(5), 143(75), 115(38), 76(64).	304(4.36).
1e	8.16(s, 1H, H_4 -imi.), 7.65(s, 1H, H_4 -Oxa.) 7.45 (2d, 4H, Ar), 4.21(s, 3H, NCH_3) and 3.83 *ppm*(s, 3H, OCH_3).	300(M^+, 100), 266(11), 173(42), 158(21), 146(37), 135(38), 77(100).	315(4.24), 261(4.37).
8a	8.48(brs, 1H, OH, exchangeable with D_2O), 8.03 (s, 1H, H_4 -imi.), 7.68(2d, 4H, Ar), 4.12(s, 3H, NCH_3) and 4.05(ABq, 2H, CH_2 , J= 18.4 Hz).	306(M^+, 53), 289(100), 179(23), 169(30), 162(23), 154(25), 139(75), 135(85), 121(60), 95(70).	301(4.02), 255(4.18).
8c	8.52(brs, 1H, OH, exchangeable with D_2O), 8.03 (s, 1H, H_4 -imi.), 7.70(2d, 4H, Ar), 4.16(s, 3H, NCH3) and 4.13(ABq, 2H, CH_2 , J= 18 2 Hz).	366(M^+, 13), 348(7), 241(15), 208 (20), 183(10), 171(21), 128(100), 102(95), 86(57).	265(4.56), 307(4.21).
8d	8.36(brs, 1H, OH, exchangeable with D_2O), 8.09 (s, 1H, H_4 -imi.), 8.09(2d, 4H, Ar), 4.31(s, 3H, NCH_3) and 4.11(ABq, 2H, CH_2 , J= 18.2 Hz).	333(M^+, 2), 316(5), 154(30), 148 (18), 127(38), 121(50), 108(38), 102 (100), 91(60), 76(92).	307(4.21).

geable with D_2O), 8.03(s, 1H, H_4 -imidazole), 7.67 (2d, 4H, aromatic) 4.12(s, 3H, NCH_3), 4.08(ABq, 2H, $-CH_2-$, J= 18.4 Hz).

^{13}C NMR(DMSO-d_6): δ(ppm), 156.3(C), 148.2(C), 140.1(C), 135.1(C), 130.2(CH), 128.9(CH), 128.5 (CH), 127.7(C), 105.5(C), 44.7(CH_2), 34.8(CH_3).

MS: m/z(%), 322(M^+, 23), 305(58), 291(38), 195(64), 178(10), 167(28), 151(35), 137(90), 127(100), 111(54).

UV(CH_3OH):λ_{max}(nm), 295(log ε= 4.03), 262(log ε= 4.23).

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REFERENCES

[1] Shafiee, A., Parang, K., Khazen, M. and Ghasemian, F., *J. Heterocycl. Chem.*, **29,** 1859 (1992).

[2] Shafiee, A., Pirouzzadeh, B., Ghasemian, F. and Parang, K., *J. Heterocycl. Chem.*, **29,** 1021(1992) and references cited therein.

[3] Karimi-Khoozani, R., Ghanbarpour, A. and Shafiee, A., *Heterocycles,* **38,** 503(1994).

[4] Ohta, S., Tsujimura, A. and Okamoto, M., *Chem. Pharm. Bull.* **29,** 2762(1981).

[5] Mitchell, A. D. and Nonhebel, D. C., *Tetrahedron,* **32,** 2437(1967).

[6] Larkin, J., Murray, M. G. and Nonhebel, D. C., *J. Chem. Soc. Sect(c).*, 9479(1970).

[7] Anjaneyulu, A. S. R., Jaganmohan Rao, K., Kameswara Rao, V., Ramachandra Row, L. and Subrahmanyan, C., *Tetrahedron,* **31,** 1277(1975).