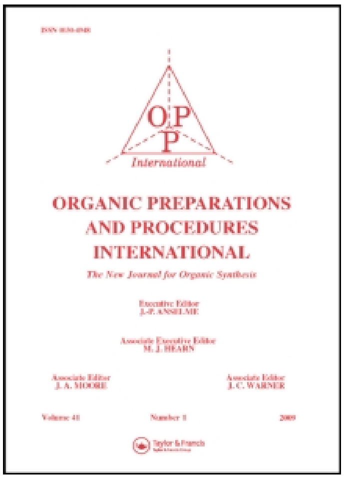

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A ONE-POT SYNTHESIS OF PYRAZOLO [3,4-b][1,4]OXAZINES

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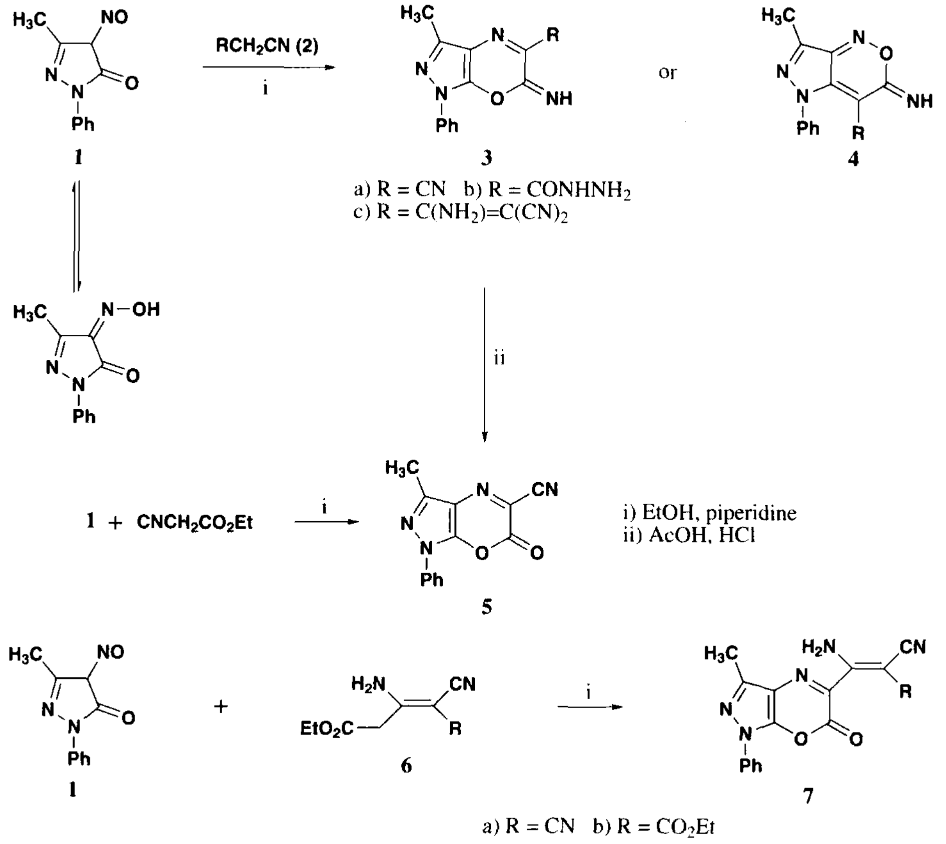
To the best of our knowledge, only a few reports for the synthesis of pyrazolo[3,4-b][1,4]oxazines have been described[1] and most of them involve many steps or give only poor to moderate yields.[2] In connection with our interest in the synthesis of condensed azines[3-7] from available laboratory materials, we report here a new efficient and simple route for the synthesis of pyrazolo[3,4-b][1,4]oxazines.

Thus, treatment of pyrazolone-4-oxime **1** with malononitrile (**2a**) in ethanol in the presence of a catalytic amount of piperidine yielded a compound of molecular formula $C_{13}H_9N_5O$ ($M^+ = 251$) which could be formulated as pyrazolo[4,3-c][1,2]oxazine derivative **4a** or its pyrazolo[3,4-b][1,4]oxazine isomer **3a**. The IR spectrum of the reaction product showed the absence of pyrazolone CO group and the presence of both NH and CN functions at 3044 and 2201 cm^{-1}, respectively. Its ^1H NMR spectrum displayed a signal at δ 8.24 that was integrated for one proton, and was assigned to exocyclic NH proton of an oxazine ring, in addition to signals for aromatic and methyl protons. The ^{13}C NMR spectra for the reaction product shows signals at δ 128.2 and 107.8 which were attributed to C-7a and C-3a of pyrazolo[3,4-b][1,4]oxazine ring. If the reaction product was **4a**, one would expect these signals at δ 136 and 144. Compound **3a** was presumably formed by condensation of the nitroso form **1** with malononitrile. Similarly, compound **1** reacts with cyanoacetic acid hydrazide (**2b**) and 1,1,3-tricyano-2-aminopropene (**2c**) to afford **3b** and **3c**. The IR spectrum of **3c** ($M+ = 317$) showed the presence of both NH_2 and NH functions at 3334 and 3045 cm^{-1} in addition to CN absorption at 2205 cm^{-1}; its ^1H NMR spectrum revealed a signal at δ 8.9 that was integrated for two protons of amino function in addition to signals for NH, phenyl and methyl functions. The ^{13}C NMR displayed signals for two cyano groups at δ 118.8 and 118.95 and two ethylenic carbons at δ 148.2 and 74.49 in addition to pyrazolo[3,4-b][1,4]-oxazine carbons. The reaction of **1** with ethyl cyanoacetate affords compound **5**, identical to the product obtained from the hydrolysis of **3a** in AcOH/HCl mixture. With **6a,b**, compound **1** reacted similarly to yield **7a,b**. Hydrolysis of **3c** led to compound **7a**.



EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded (KBr) on a Perkin-Elmer 1650 FT-IR Spectrometer. ^{1}H NMR and ^{13}C NMR were measured on a Varian (399.3 MHz) Spectrometer with DMSO-d_6 and $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are reported in d units (ppm). Mass spectra were obtained by electron impact method. Microanalytical data (C, H, N) were obtained from the Microanalytical Data Unit at Cairo University. Pyrazolone-4-oxime **1**[8]was prepared according to literature procedures.

Synthesis of Pyrazolo[3,4-b][1,4]oxazines 3a-c, 5 and 7a,b. General Procedure.- The appropriate active methylene reagent (0.01 mol) and compound **1** (0.01mol) in ethanol (30mL) in the presence of a catalytic amount of piperidine (1 mL) was heated under reflux for 4-6 h. (monitored by TLC). The solvent was then evaporated *in vacuo* and the residue was triturated with water and acidified with HCl. The solid product formed was collected and crystallized from ethanol.

TABLE 1. Analytical Data and Physical Characteristic of New Compounds

Cmpd No.	mp. (°C)	Color[a]	Yield (%)	Elemental Analysis (Calcd) C	H	N
3a[a]	164-165	orange	82	62.13	3.56	27.90
				(62.15)	(3.61)	(27.88)
3b[b]	168-169	orange	85	54.91	4.21	29.60
				(54.93)	(4.25)	(29.56)
3c	158-159	brown	87	60.53	3.46	30.80
				(60.56)	(3.49)	(30.90)
5	160-161	yellow	82	61.87	3.18	22.20
				(61.91)	(3.20)	(22.21)
7a	151-152	brown	77	60.36	3.14	26.41
				(60.38)	(3.17)	(26.40)
7b[c]	171-172	brownish yellow	79	59.15	4.11	19.18
				(59.18)	(4.14)	(19.17)

a) MS (EI), m/z = 251(M$^+$); b) MS (EI), m/z = 284(M$^+$); c) MS (EI), m/z=365(M$^+$)

TABLE 2. Spectral Data of Newly Synthesized Compounds

Cmpd No.	^{1}H NMR(δ_H)	^{13}C NMR(δ_C)	IR (cm^{-1})
3a[a]	1.24(s, 3H, CH_3); 7.12-7.91(m, 5H, C_6H_5); 8.24(s, 1H, NH).	151.8(C-3); 142.8(C-6); 139-119 (aromatic); 128.2(C-7a); 117.8 (CN); 109.4 (C-5); 107.8(C-3a); 9.4(CH_3).	3044(NH); 2201 (CN).
3b[a]	1.25(s, 3H, CH_3); 7.92-8.21(m, 7H, C_6H_5 and NH); 9.94(brs, 2H, NH_2).		3470, 3204(NH_2 and NH); 1702 (CO).
3c[b]	1.26(s, 3H, CH_3); 7.91-7.21(m, 6H, C_6H_5 and NH); 8.91(brs, 2H, NH_2).	148.2 and 74.49 (ethylenic carbons); 142.7(C-6); 125-139 (aromatic carbons); 128.7(C-7a); 118.8 and 118.95 (2CN); 109.6 (C-5); 107.7(C-3a); 9.6(CH_3).	3329(NH_2); 3183 (NH); 2203 (CN).
5[b]	1.24(s, 3H, CH_3); 7.21-7.93(m, 5H, C_6H_5).		2200 (CN); 1690 (CO).
7a	1.25(s, 3H, CH_3); 7.11-7.45(m, 5H, C_6H_5); 8.97(brs, 2H, NH_2).		3320 (NH_2); 1702 (CO).

TABLE 2. Continued...

Cmpd No.	^{1}H NMR(δ_H)	^{13}C NMR(δ_c)	IR (cm^{-1})
7b^b	1.15(s, 3H, CH_3); 1.28 (t, 3H, CH_3); 4.2(q, 2H, CH_2); 7.16-7.46(m, 5H, C_6H_5); 7.95(brs, 2H, NH_2).		3330(NH_2); 1720 (ester CO); 1700 (CO).

a) In DMSO; b) In $CDCl_3$.

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