SHORT PAPER

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A short and expeditious regiospecific synthesis of novel pyrazoles†

S.K. Dutta Chowdhury[a], Mili Sarkar[b] and Kumar K. Mahalanabis[c]*

[a]*Jogesh Chandra Choudhuri College, Kolkata 700 033, India*

[b]*Gurudas College, Kolkata 700 054, India*

[c]*Department of Chemistry, Jadavpur University, Kolkata 700 032, India*

α-Cyano-β-enaminones, obtained by regioselective acylation of β-aminocrotononitrile, are smoothly and regiospecifically converted into substituted pyrazoles in good to excellent yields.

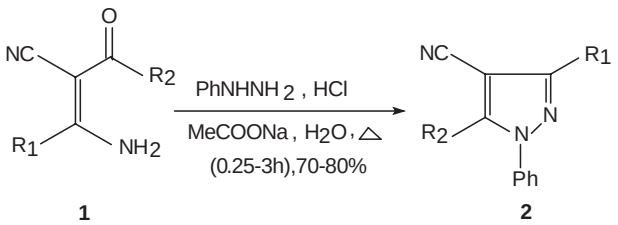
Keywords: α-cyanoenaminones, β-aminocrotononitrile, pyrazoles

Pyrazoles form an important class of 1,2-azoles[1] and they exhibit a wide range of biological activity.[2] They are used as herbicides and plant growth regulators[3] as well as insecticides[4] and nematocides.[5] Antitumor activity has been reported.[6] Some pyrazole derivatives linked to an aromatic or heteroaromatic ring have shown to exhibit antirheumatic and antipyretic properties.[7,8] These and other attributes of pyrazole derivatives make syntheses of these compounds a subject of continuing interest.

The usual methods of preparation of pyrazoles are based upon the formal addition of species containing a preformed N-N bond to an acceptor molecule at the required oxidation level.[9] The most general and widely applicable method consists of addition of hydrazine or a monosubstituted hydrazine to a 1,3-dicarbonyl compound or a precursor thereof. Unsymmetrical diketones, however, can yield isomeric pyrazoles,[10] and the formation of such mixtures is the chief disadvantage of this otherwise simple and high yielding method.

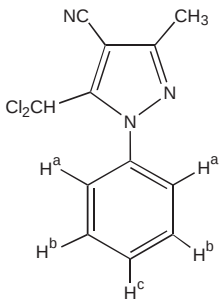
β-Acyl-enaminonitriles behave as masked 1,3-diketones and are versatile synthetic intermediates,[11] particularly in heterocyclic chemistry[12]. Preparations of enaminones are well documented.[12, 13] Recently we have developed a highly successful regioselective acylation of β-aminocrotononitrile to yield α-cyano-β-enaminones in good to excellent yields.[14] Here we report the preparation of novel 5-substituted pyrazole-4-carbonitriles via the corresponding enaminones. Thus, heating α-cyanoenaminones (**1**) with phenylhydrazine reagent in aqueous medium on a steam bath afforded a yellowish oily material which on usual work-up and purification yielded pyrazoles (**2**) (Scheme 1 and Table 1). The structures of all these compounds are supported by consistent elemental and spectral analyses. (Tables 1 and 2)

Thus, in the ^{1}H NMR spectrum of compound **2e**, the methyl signal appears at δ 2.50 ppm as a singlet, and the methine ($CHCl_2$) proton absorbs at δ 6.58 ppm. In the aromatic region a double doublet centered at δ 7.44 ppm is assigned to ArH^a (*ortho*) protons. ArH^b and ArH^c (*meta* and *para*) protons appear as a multiplet in the region δ 7.53–7.58 ppm. The synthesis is thus apparently regiospecific. In an NOE experiment, irradiation at the methine proton resonance induces enhancement of signals of the phenyl group H^a protons. Additional proof for the location of the methyl carbon at C-3 of the pyrazole ring was obtained from the ^{13}C NMR spectrum; its signal at 12.5 ppm is characteristic for this



1 **2**

Scheme 1 Formation of 1-phenylpyrazole-4-carbonitriles (**2**)



2e

position.[15] It is assumed that formation of **2** takes place via a Michael type addition of the amino group of phenylhydrazine to the double bond of **1** followed by intramolecular ring closure to the carbonyl group.

In conclusion, the ready availability of *C*-acylated enaminonitriles offers an excellent opportunity to prepare polysubstituted pyrazole derivatives with complete control of regiospecificity. In view of the inherent simplicity of the synthetic design, the substituent at the 5-position of the pyrazole ring can be alkyl (compounds **2a–2c**, **2j** and **2k**), heteroaromatic (**2i**) and halogenated alkyl (**2d** and **2e**). The last named functionalities leave wide scope for elaboration of the C-5 side chain to many other active functional groups suitable for the preparation of pyrazole-based organic molecules.[16] Variation in the nature of the 5-substituent can also occur in the form of double and triple bond unsaturation (compounds **2f–2h**) which themselves can generate new functionality. Furthermore, variation of substitution at C-3 can also be achieved by choice of an appropriate enamine (compound **2l**).

When compared with literature documented methods[16] for the preparation of pyrazole derivatives, the present procedure offers an extremely simple and highly regiospecific synthesis of pyrazoles with novel variants at C-5 position which are otherwise difficult to prepare, in good to excellent yields.

* To receive any correspondence. E-mail: kkmahalanabis@yahoo.co.in

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Preparation, and physical and analytical data of compounds **2a–2l**

Compd	R_1	R_2	Yield (%)	M.p./*b.p.* (°C)	Mol. formula	Found (%) C	H	N	Calc. (%) C	H	N
2a	Me	Me	71	88[a]	$C_{12}H_{11}N_3$	72.92	5.70	21.26	73.07	5.62	21.30
2b	Me	Et	70	*140–142/4mm*	$C_{13}H_{13}N_3$	73.65	6.26	20.01	73.90	6.20	19.89
2c	Me	Pr	78	*150–152/8mm*	$C_{14}H_{15}N_3$	74.52	6.74	18.71	74.62	6.71	18.65
2d	Me	CH_2Cl	75	126–127	$C_{12}H_{10}ClN_3$	61.91	4.37	18.02	62.21	4.35	18.14
2e	Me	$CHCl_2$	74	122	$C_{12}H_9Cl_2N_3$	53.94	3.44	15.69	54.16	3.41	15.79
2f	Me	CH=CHPh	70	131[b]	$C_{19}H_{15}N_3$	79.75	5.32	14.80	79.97	5.30	14.72
2g	Me	C≡CPh	72	115	$C_{19}H_{13}N_3$	79.90	4.66	14.92	80.54	4.62	14.83
2h	Me	$(CH=CH)_2Ph$	71	144–145	$C_{21}H_{17}N_3$	81.21	5.53	13.42	81.00	5.50	13.49
2i	Me	2-furyl	80	177–178	$C_{15}H_{11}N_3O$	72.02	4.47	16.92	72.22	4.44	16.84
2j	Me	CH_2CH_2Ph	72	*190–191/6mm*	$C_{19}H_{17}N_3$	79.53	5.98	14.66	79.41	5.96	14.62
2k	Me	$CH_2OC_6H_3Cl_2(2,4)$	73	115–116	$C_{18}H_{13}Cl_2N_3O$	59.98	3.68	11.80	60.35	3.66	11.73
2l	$C_6H_4OMe(4)$	Me	75	112–123	$C_{18}H_{15}N_3O$	74.63	5.24	14.50	74.72	5.22	14.52

[a]Lit.[15] 90-91 °C; [b]Lit.[20] 134 °C

Table 2 ^{1}H NMR spectral data of pyrazoles **2a–l** (δ, $CDCl_3$; *J* / Hz)

Compd	NMR
2a	2.40 (s, 3 H, 3-CH_3), 2.44 (s, 3H, 5- CH_3), 7.36–7.64 (m, 5H, Ar-H)
2b	1.23 (t, *J* 7.2, 3H, CH_2CH_3), 2.41 (s, 3H, 3-CH_3), 2.80 (q, *J* 7.2, CH_2CH_3), 7.39 (5H, Ar-H)
2c	0.88 (t, *J* 7.2, 3H, $CH_2CH_2CH_3$), 1.52 (sextet, *J* 7.2, $CH_2CH_2CH_3$), 2.40 (s, 3H, 3- CH_3), 2.75 (t, *J* 7.2, 2H, $CH_2CH_2CH_3$), 7.45(5H, Ar-H)
2d	2.44 (s, 3H, 3-CH_3), 4.58 (s, 2H, CH_2Cl), 7.53 (5H, Ar-H)
2e	2.50 (s, 3 H, 3-CH_3), 6.58 (s, 1H, $CHCl_2$), 7.41-7.48 (m, 2H, Ar-2′H), 7.53–7.58 (m,3H, Ar-3′H and Ar-4′H)
2f	2.46 (s, 3 H, 3-CH_3), 6.77 (d, *J* 16, 1H, CH=CH-Ph), 7.07–7.79 (m, 6H, Ar-H and =CH-Ph),
2g	2.47 (s, 3 H, 3-CH_3), 7.43 (5H, Ar-H)
2h	2.45 (s, 3 H, 3-CH_3), 6.36 (d, *J* 16, 1H, CH=CH-CH=CH-Ph), 6.76–6.87 (m, 2H, =CH-CH=), 7.26–7.50 (m, 6H, Ar-H and =CH-Ph)
2i	2.46 (s, 3 H, 3-CH_3), 6.40 (dd, *J* 2 and 2.5, 1H, partial overlap with signal at 6.43, β-H of furan ring), 6.43 (d, *J* 2.5, 1H, β′H of furan ring), 7.25–7.60 (m, Ar-H and α-H of furan ring)
2j	2.40 (s, 3 H, 3-CH_3), 2.97 (s, 4H, $(CH_2)_{2)}$, 7.05–7.44 (m, 10H, Ar-H)
2k	2.47 (s, 3 H, 3-CH_3), 5.03 (s, 2H, CH_2), 6.99–7.60 (m, 8H, Ar-H)
2l	2.50 (s, 3 H, 3-CH_3), 3.82 (s, 3H, OCH_3), 6.83–7.91 (m, 9H, Ar-H)

Table 3 UV and IR spectra of pyrazoles **2a–l**

Compd	UV[a]	IR[b]
2a	245 (13.1)	2216, 1594, 1554, 1506, 1482, 1426, 1394, 762, 690
2b	242 (10.3)	2220, 1596, 1546, 1504, 1460, 1440, 1396, 1072, 1020, 764, 696
2c	241 (11.3)	2224, 1596, 1546, 1502, 1468, 1454, 1396, 768, 696
2d	235 (40.8), 274 (10.9)	2224, 1594, 1556, 1500, 1484, 1446, 766, 694
2e	253 (7.07)	2220, 1594, 1554, 1498, 1434, 770, 696
2f	226 (18.3), 336 (26.8)	2220, 1594, 1536, 1498, 1430, 958, 770, 690
2g	293 (27.0)	2212, 1594, 1536, 1495, 1438, 1382, 758, 690
2h	228 (19.2), 342 (38.2)	2920, 2216, 1613, 1594, 1534, 1498, 1452, 1036, 988, 776, 700
2i	282 (21.9)	2224, 1612, 1596, 1522, 1510, 1442, 1288, 1022, 780, 706
2j	235 (10.1)	3056, 3020, 2220, 1600, 1546, 1502, 1452, 752, 696
2k	231 (17.0), 249 (12.6)	2224, 1504, 1486, 1452, 1286, 1246, 1060, 1006, 808, 764
2l	269 (27.4)	3208, 2216, 1598, 1530, 1502, 1454, 1248, 1172, 772

[a]in EtOH, λ_{max}, nm ($\varepsilon \times 10^{-3}$) [b]$\nu_{max}$, cm^{-1}, KBr or as oil

Experimental

Melting points were determined in open capillaries. UV spectra were taken on a Hitachi U-2000 spectrometer; IR spectra on a Hitachi 270-30 spectrometer, and 1H NMR spectra in $CDCl_3$ on Hitachi R-600, Bruker-AC 200, AM 250 and AM 360 spectrometers. Elemental analyses were performed using a Perkin–Elmer 240C elemental analyser.

β-Aminocrotononitrile[17] and acid chlorides[18] were prepared according to literature procedures.

General procedure for the preparation of **1**: α-Cyanoenaminones **1** were prepared by reaction of β-aminocrotononitrile with suitable acid chlorides in dry benzene.[14] The acid chloride (24 mmol) in dry benzene (10 ml) was added dropwise under ice cold conditions to a magnetically stirred solution of β-aminocrotononitrile (1.64 g, 20 mmol) in dry benzene (15 ml) and pyridine (4 g). The reaction mixture was allowed to attain room temperature and it was then poured onto ice-water and extracted with ethyl acetate (3 × 25 ml). Excess of pyridine was removed from the organic layer by washing with cold HCl (2N) and then made neutral by washing with sodium bicarbonate solution and finally with brine. The organic layer was then dried over anhydrous Na_2SO_4. Removal of the solvent afforded solid materials which on subsequent crystallization from suitable solvents furnished pure acylated products **1.**

Preparation of phenylhydrazine reagent: Phenylhydrazine reagent[19] was prepared by dissolving colourless phenylhydrazine hydrochloride (2.5 g) in water (25 ml). Crystallised sodium acetate (4.5 g) was added with shaking to the above prepared cold solution until dissolved. Decolourising carbon (0.05 g) was added to the mixture and the solution was filtered into a dark bottle after shaking the solution thoroughly.

General procedure for the preparation of **2**: A mixture of α-cyanoenaminone (**1**) (3 mmol) and phenylhydrazine reagent (9 mmol) was heated on a steam bath for 20 to 45 min, during which a yellow oily material separated. The reaction mixture was acidified with acetic acid (50%) followed by neutralization with solid $NaHCO_3$ in the cold. It was then extracted with diethyl ether or ethyl acetate (3 × 20 ml). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude material obtained on removal of the solvent was purified by crystallisation from a suitable solvent or by column chromatography (silica gel, 60–120 mesh; 5% ethyl acetate-pet ether).

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