

## On the regioselectivity of 3,5-disubstituted pyrazoles derived from C-acylated- $\beta$ -enaminonitriles and esters

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Regioselectivity of 3,5-disubstituted pyrazoles derived from reaction of phenylhydrazine with  $\alpha$ -acyl- $\beta$ -aminocrotonitriles and esters is primarily deduced on the basis of spectral analyses. The present work provides direct and unambiguous evidences in support of the regioselectivity of these pyrazoles. In addition, this work also shows that  $\alpha$ -acyl- $\beta$ -enaminones derived from enaminonitriles and enaminoesters both afford 5-substituted pyrazoles in contrast to earlier observation by Benary.

**Key words:** Regioselectivity, 3,5-disubstituted pyrazoles, enaminonitriles, phenylhydrazine, aminocrotonitriles, enaminoesters, 5-substituted pyrazoles

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Enaminones are versatile synthetic intermediates particularly in heterocyclic chemistry<sup>1</sup>. Heterocycles prepared from enaminones include among others carbazolequinone alkaloids<sup>2</sup>, tricyclic benzo[*a*]quinoxalines<sup>3</sup>, benzodiazepines<sup>4</sup>, quinolines<sup>5</sup>, pyrimidines<sup>6</sup>, pyrazoles<sup>7,8</sup>, isoxazoles<sup>9</sup>, isothiazoles<sup>10</sup> and pyrroles<sup>11</sup>.

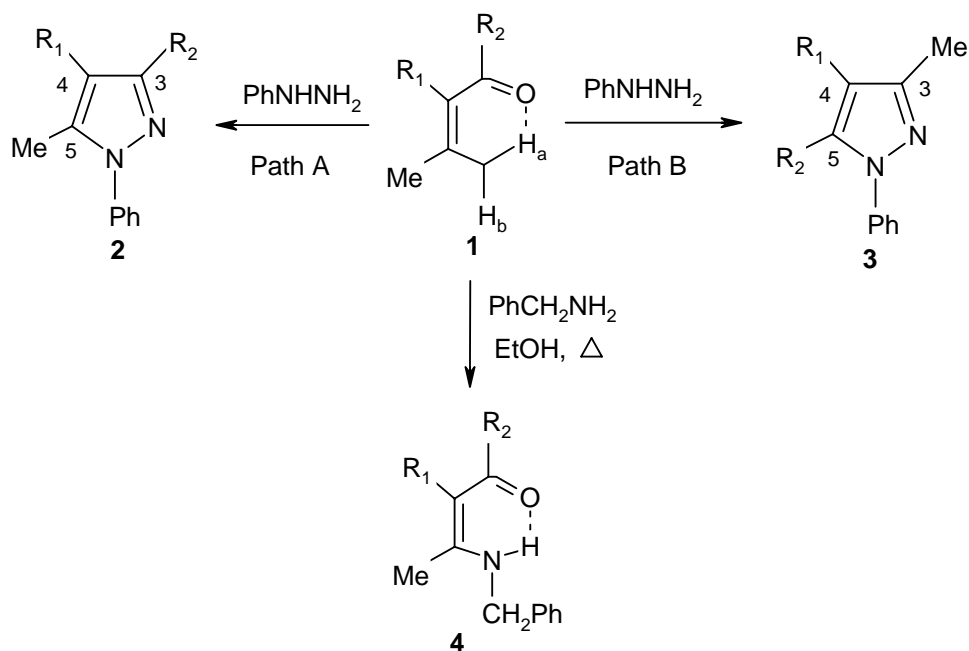
### Results and Discussion

Our continuing interest to develop a general method<sup>8-10</sup> for synthesis of 1,2-azoles centres around  $\alpha$ -cyano- $\beta$ -enaminones obtained from regioselective acylation of  $\beta$ -aminocrotonitrile<sup>12,13</sup>. However, regioselectivity of 3(5), 5(3)-disubstituted-4-cyanopyrazoles prepared from enaminones leaves scope for ambiguity as these can be formed in either of the two ways i.e. *path-A* or *path-B* (**Scheme I**). The suggested mechanism for *path-A* or *path-B* is shown in **Scheme II**. In our earlier work<sup>8</sup>, the regioselectivity of 3,5-disubstituted-4-cyanopyrazoles was deduced on the basis of NOE experiment and <sup>13</sup>C NMR spectra. In order to obtain a direct proof with regard to regioselectivity of 3,5-disubstituted pyrazoles derived from C-acylated enaminoesters and nitriles, enaminones **1a** (R<sub>1</sub>=CO<sub>2</sub>Me) and **1b** were treated with phenyl hydrazine. Pyrazole **2a/3a** was expected from **1a** (R<sub>1</sub>=CO<sub>2</sub>Me) whereas **1b** should afford either **2b/3b** depending on the reaction path followed.

However, pyrazoles thus obtained on basic hydrolysis afforded acids which were found to be identical as evidenced from extensive <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral analyses as well as from comparative IR spectra and mixed m.p. determination 178°C(lit<sup>19</sup>). This acid could be either **2c** or **3c** (**Scheme I**). In the <sup>1</sup>H NMR of **3c**, methyl proton absorbs at 2.57 ppm as a singlet and methylene protons absorb at 5.23 ppm. The aromatic protons appear as a multiplet in the region 6.88-7.56 ppm (**Table I**).

The classical pyrazole synthesis consisting of addition of hydrazine derivative to  $\alpha,\beta$ -ethynyl ketones or  $\beta$ -chlorovinyl ketones often results in the formation of mixtures of isomers since hydrazine can react either with the carbonyl group or across the unsaturation<sup>14</sup>.

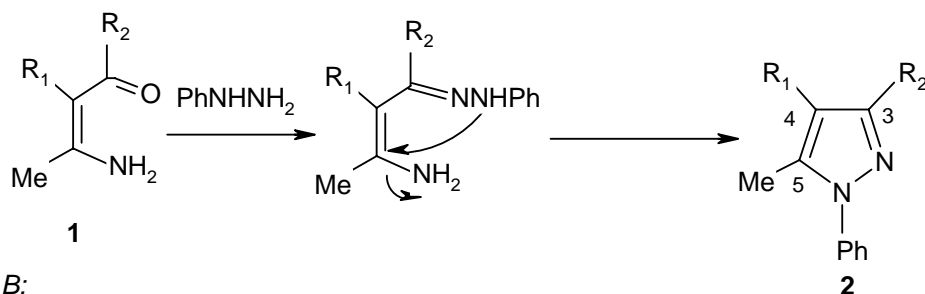
To obtain an insight to the likely course of the reaction of nucleophile with enaminones, **1c** and **1d** were treated with benzyl amine in refluxing ethyl alcohol when compounds **4a** and **4b** were obtained in excellent yields. These experiments clearly demonstrate the exclusive preference for Michael-type addition of the nucleophile to the electron-deficient unsaturated linkage present in enaminones **1c** and **1d**. In addition, these results also provide indirect support in favour of compound **3c** rather than **2c** as the most likely structure for the pyrazole acid.



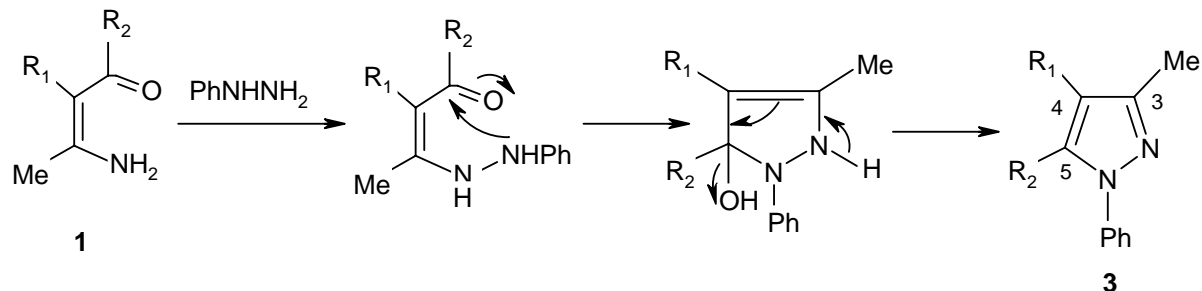
Compd	R <sub>1</sub>	R <sub>2</sub>	Compd	R <sub>1</sub>	R <sub>2</sub>
<b>1a</b>	CO <sub>2</sub> Me/CO <sub>2</sub> Et	CH <sub>2</sub> OPh	<b>3a</b>	CO <sub>2</sub> Me	CH <sub>2</sub> OPh
<b>1b</b>	CN	CH <sub>2</sub> OPh	<b>3b</b>	CN	CH <sub>2</sub> OPh
<b>1c</b>	CO <sub>2</sub> Me	CHCl <sub>2</sub>	<b>3c</b>	CO <sub>2</sub> H	CH <sub>2</sub> OPh
<b>1d</b>	CN	CHCl <sub>2</sub>	<b>3d</b>	CO <sub>2</sub> Me	CHCl <sub>2</sub>
<b>2a</b>	CO <sub>2</sub> Me	CH <sub>2</sub> OPh	<b>4a</b>	CO <sub>2</sub> Me	CHCl <sub>2</sub>
<b>2b</b>	CN	CH <sub>2</sub> OPh	<b>4b</b>	CN	CHCl <sub>2</sub>
<b>2c</b>	CO <sub>2</sub> H	CH <sub>2</sub> OPh			

Scheme I

Path A:



Path B:



Scheme II

**Table I** — Characterization data of compounds **1a-d**, **3a-d**, **4a-b** and **5-8**

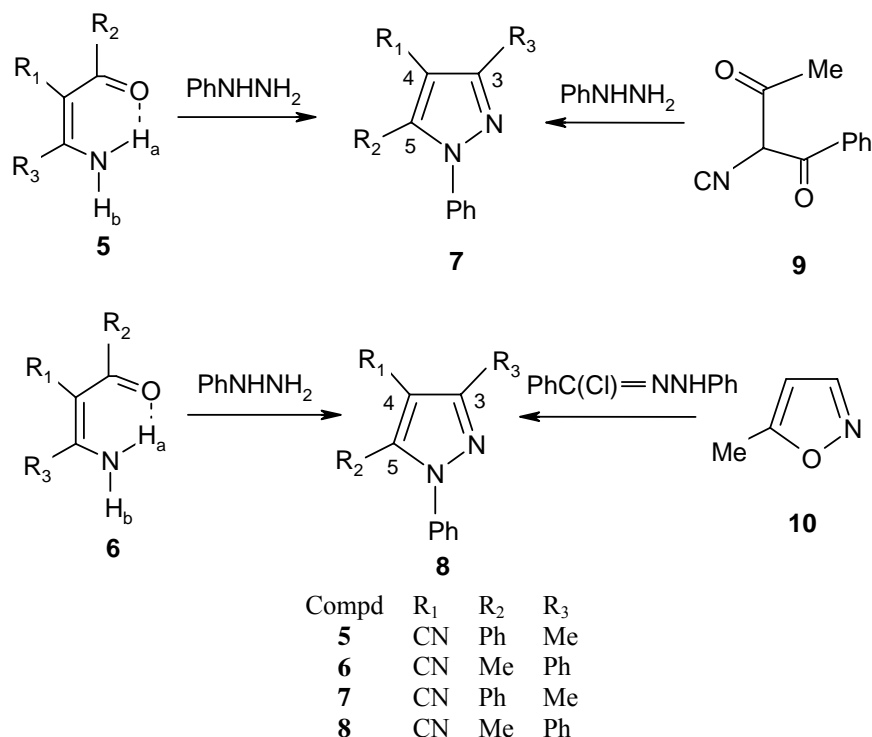
Compd	Yield (%)	m p °C	MS (M <sup>+</sup> )	UV(EtOH) $\lambda_{\max}$ (nm, $\epsilon$ )	<sup>1</sup> H NMR ( $\delta$ , ppm)
<b>1a</b> (R <sub>1</sub> =Me)	35	112-14	249	289 (8221), 240 (5323)	2.30 (3H, s, CH <sub>3</sub> ), 3.74 (3H, s, OCH <sub>3</sub> ), 4.95 (2H, s, CH <sub>2</sub> ), 6.94-7.29 (5H, m, Ar-H), 8.60 (1H, bs, NH <sub>b</sub> ), 10.61 (1H, bs, NH <sub>a</sub> )
<b>1b</b>	80	165-66	216	297 (8948), 227 (3220)	2.31 (3H, s, CH <sub>3</sub> ), 4.95 (2H, s, CH <sub>2</sub> ), 6.28 (1H, bs, NH <sub>b</sub> ), 6.91-7.31 (5H, m, Ar-H), 10.65 (1H, bs, NH <sub>a</sub> )
<b>1c</b>	85	95-96	225	301 (16769), 245 (14509)	2.36 (3H, s, CH <sub>3</sub> ), 3.80 (3H, s, OCH <sub>3</sub> ), 6.47 (1H, bs, NH <sub>b</sub> ), 7.03 (1H, s, CHCl <sub>2</sub> ), 11.20 (1H, bs, NH <sub>a</sub> )
<b>1d</b>	71	154-55	192	303 (9685), 222 (7430)	2.40 (3H, s, CH <sub>3</sub> ), 6.51 (1H, s, CHCl <sub>2</sub> ), 6.59 (1H, bs, NH <sub>b</sub> ), 10.57 (1H, bs, NH <sub>a</sub> )
<b>3a</b>	70	48-49	322	245 (18515), 215 (22958)	2.55 (3H, s, CH <sub>3</sub> ), 3.88 (3H, s, OCH <sub>3</sub> ), 5.21 (2H, s, CH <sub>2</sub> ), 6.91-7.72 (10H, m, Ar-H)
<b>3b</b>	72	70 (lit <sup>19</sup> 72-73)	289	248 (16762), 214 (19276)	2.46 (3H, s, CH <sub>3</sub> ), 5.04 (2H, s, CH <sub>2</sub> ), 6.99-7.50 (10H, m, Ar-H)
<b>3c</b>	73	178 (lit <sup>19</sup> 178)	308	251(9688)	2.57 (3H, s, CH <sub>3</sub> ), 5.23 (2H, s, CH <sub>2</sub> ), 6.88-7.56 (10H, m, Ar-H)
<b>3d</b>	75	92-93	298	247 (26013), 214 (21079)	2.40 (3H, s, CH <sub>3</sub> ), 3.86 (3H, s, OCH <sub>3</sub> ), 7.57 (5H, s, Ar-H), 7.75 (1H, s, CHCl <sub>2</sub> )
<b>4a</b>	71	63-64	315	318 (12054), 250 (9597)	2.12 (3H, s, CH <sub>3</sub> ), 3.80 (3H, s, OCH <sub>3</sub> ), 4.61 (2H, d, <i>J</i> = 6Hz, CH <sub>2</sub> ), 6.71 (1H, s, CHCl <sub>2</sub> ), 7.21 (5H, s, Ar-H), 11.20 (1H, bs, NH)
<b>4b</b>	65	semi-solid	282	314 (13057), 229 (12889)	2.41 (3H, s, CH <sub>3</sub> ), 4.62 (2H, d, <i>J</i> = 6Hz, CH <sub>2</sub> ), 6.56 (1H, s, CHCl <sub>2</sub> ), 7.28-7.51 (5H, m, Ar-H), 11.93 (1H, bs, NH)
<b>5</b>	67	150 (lit <sup>13</sup> 148)	186	234 (15190), 307 (20832)	2.37 (3H, s, CH <sub>3</sub> ), 6.36 (1H, bs, NH <sub>b</sub> ), 7.40-7.81 (5H, m, Ar-H), 11.17(1H,bs, NH <sub>a</sub> )
<b>6</b>	67	152 (lit <sup>21</sup> 152)	186	304 (10962), 212 (10701)	2.46 (3H, s, CH <sub>3</sub> ), 6.00 (1H, bs, NH <sub>b</sub> ), 7.37-7.61 (5H, m, Ar-H), 10.95 (1H, bs, NH <sub>a</sub> )
<b>7</b>	78	190 (lit <sup>15a</sup> 192)	259	322 (10826), 237 (14011)	2.50 (3H, s, CH <sub>3</sub> ), 7.24-7.52 (10H, m, Ar-H)
<b>8</b>	64	133 (lit <sup>15b</sup> 134)	259	255 (12432)	2.54 (3H, s, CH <sub>3</sub> ), 7.41-8.06 (10H, m, Ar-H)

<sup>13</sup>C NMR: **1c**: 24.66, 51.63, 69.61, 98.05, 168.10, 171.79, 185.32; **3c**: 14.18, 59.13, 111.70, 114.99, 121.58, 125.18, 128.85, 129.22, 129.49, 138.41, 142.39, 152.71, 157.85, 169.26; **3d**: 13.75, 51.85, 59.04, 109.54, 127.01, 129.05, 129.82, 138.84, 142.11, 149.82, 162.87; **4a**: 17.95, 48.05, 51.75, 69.64, 127.20, 128.23, 129.15, 135.15, 168.64, 171.27; **7**: 12.58, 93.71, 114.30, 125.15, 126.89, 128.87, 128.94, 129.11, 129.88, 131.46, 138.62, 147.78, 152.64; **8**: 11.96, 91.31, 115.01, 125.14, 126.67, 128.88, 129.12, 129.42, 129.52, 130.67, 138.38, 147.32, 152.52

Direct proof regarding regiospecificity of 3,5-disubstituted-4-cyanopyrazoles was obtained from the unambiguous synthesis of pyrazoles **7** and **8** from enaminones<sup>13</sup> **5** and **6**, respectively (**Table I**). The preparations of **7** (ref. 15a) from **9** and **8** (ref. 15b) from **10** were previously described in the literature and the positions of C-3 and C-5 substituents are firmly secured in both the cases (**Scheme III**).

Additional proof in support of correctness of the assigned structure for 3,5-disubstituted pyrazoles also results from the HMBC and HSQC experiments of compound **3d** as well as from the observation that

methyl carbon at C-3 of pyrazole showed signal at  $\delta$  13.75 in conformity with the literature observation<sup>16</sup>. On the other hand, methyl carbon at C-5 of pyrazole **8** showed signal at  $\delta$  11.96 ppm which is in agreement with the literature reported value<sup>17</sup>. HSQC spectrum correlates <sup>1</sup>H and <sup>13</sup>C resonance of directly attached nuclei whereas HMBC spectrum correlates <sup>1</sup>H and <sup>13</sup>C resonance of nuclei separated by two or three bonds. In HMBC of compound **3d**, methyl proton correlates with C-3 ( $\delta$  149.82 ppm, two-bond separation) and C-4 ( $\delta$  109.54 ppm, three-bond separation) whereas CHCl<sub>2</sub> correlates with C-5



Scheme III

( $\delta$  142.11 ppm, two-bond separation) and C-4 ( $\delta$  109.54 ppm, three-bond separation). If  $\text{CHCl}_2$  is at C-3 position, it would have correlated with C-3 ( $\delta$  149.82 ppm, two-bond separation) and C-4 ( $\delta$  109.54 ppm, three-bond separation) (Table I). All these  $\delta$  values for carbons are in consistent with literature<sup>18</sup> reported values. Thus, the structure of the compound **3d** was unequivocally established by HMBC and HSQC. In this connection it may be mentioned that Benary<sup>19</sup> as early as 1922 investigated reaction of phenylhydrazine with ethyl  $\alpha$ -phenoxyacetyl- $\beta$ -aminocrotonate **1a** ( $\text{R}_1=\text{CO}_2\text{Et}$ ) and  $\alpha$ -phenoxyacetyl- $\beta$ -aminocrotononitrile **1b** and reported isolation of pyrazoles **2c** and **3b**. Our investigation however, shows conclusively that Benary assigned structure of **2c** was incorrect and should correspond to **3c**.

In conclusion, it can be said with certainty that reaction of phenylhydrazine with  $\alpha$ -acyl- $\beta$ -aminocrotononitriles as well as esters 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 yielding 5-substituted pyrazoles (*path B*, Scheme II).

### Experimental Section

Melting points were determined in open capillaries and are uncorrected. UV spectra ( $\lambda_{\text{max}}$  in nm,  $\epsilon$  in

parentheses) in ethanol were taken on a Hitachi U-2000 spectrometer; IR spectra (KBr) on a Hitachi 270-30 spectrometer; <sup>1</sup>H NMR spectra on a dpx 400, dpx 500 and Bruker AC-300 spectrometers using  $\text{CDCl}_3$  as the solvent (chemical shifts in  $\delta$ , ppm relative to TMS); and mass spectra in Thermo Finnigan LCQ DUO. Elemental analyses were performed using a Perkin-Elmer 240C elemental analyser. All compounds were purified either by crystallization from ethyl acetate-pet. ether or by column filtration (silica gel, 60-120 mesh). Homogeneity of compound **4b** was established by HPLC (1: 3; ethyl acetate-pet. ether).

**General method of acylation**<sup>13</sup>. Acid chloride (0.024 mole) in dry benzene (10 mL) was added dropwise under ice-cold condition to a magnetically stirred solution of  $\beta$ -aminocrotononitrile (1.64 g, 0.02 mole) in dry benzene (15 mL) and pyridine (4 g). The reaction was allowed to attain room temperature and it was poured onto ice water and extracted with ethyl acetate (3 $\times$ 25 mL). Excess pyridine was removed from organic layer by washing with cold hydrochloric acid (2*N*) and then made neutral by washing with saturated bicarbonate solution and finally washed with brine. The organic layer was then dried over anhydrous sodium sulphate. Removal of the solvent afforded solid materials which on subsequent

crystallization from suitable solvent furnished pure acylated products.

#### Preparation of phenylhydrazine reagent.

Phenylhydrazine reagent<sup>20</sup> 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 (0.05g) was added to the mixture and the solution was filtered into a dark bottle after shaking the solution thoroughly.

**General method of pyrazole preparation<sup>8</sup>.** A mixture of C-acylated enaminonitrile (0.003 mole) and phenylhydrazine reagent (13 mL, 0.009 mole) was heated on a steam-bath for a period of 20-45 min, when a yellowish oily material was separated. The reaction mixture was cooled and acidified with acetic acid (50%) followed by neutralization with solid sodium bicarbonate in cold condition. It was extracted with ethyl acetate (3 $\times$ 20 mL). The organic layer was washed with brine and dried over anhydrous sodium sulphate. The solid material obtained on removal of the solvent was purified by crystallization with suitable solvent or by column filtration.

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