Reactivity of α-Acylated β-Enamino Ketones and Esters: Synthesis of Pyrazoles

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The reactivity of the enamino compounds 4-amino-3-phenylamino(thio)carbonyl-3-penten-2-one **1** and **2** and ethyl 3-amino-2-phenylamino(thio)carbonyl-2-butyrate **7** and **8** was studied using the reaction with hydrazine hydrate and hydrazine hydrochloride to evaluate the 1,3 electrophilic center of the compounds by the formation of the pyrazole rings. The pyrazoles **3, 4, 5, 9, 11** and **13** were obtained depending on the reaction conditions employed.

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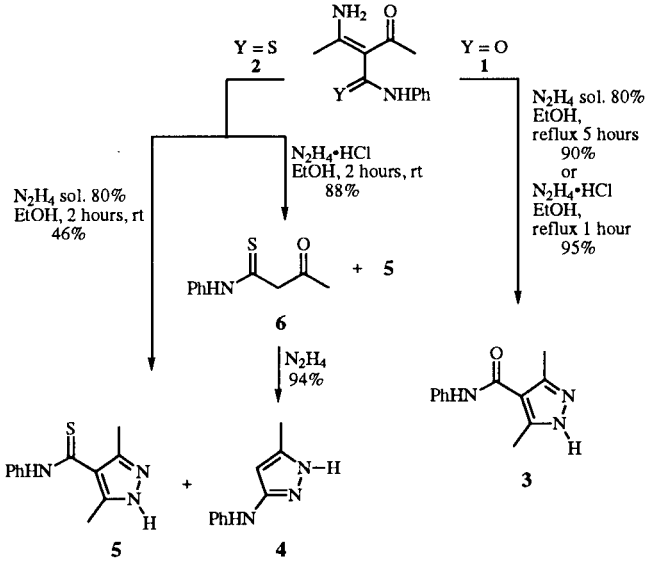
β-Amino α,β-unsaturated ketones and esters are important building blocks for the construction of a variety of heterocyclic compounds [1-4] as well as useful precursors for liquid crystals [5]. We have recently reported the selective synthesis of α-acylated β-enamino compounds using suitable methodologies with montmorillonite as solid support [6]. In order to study the reactivity of electrophilic centers the β-enamino α-phenylamino(thio)carbonyl compounds, we wish now to report the reaction of these compounds with hydrazine to afford pyrazoles. The usual preparation of pyrazoles involves the direct reaction of β-dicarbonyl compounds with hydrazine [7]. The acylation of β-dicarbonylic can lead to a mixture of *C* and *O*-products [8]. The relative amount of *C*- to *O*-acylation depends on the various factors such as the polarity of the solvent whereas, with K-10, the acylation of β-enamino compounds with phenyl isocyanate and isothiocyanate without solvent gave *C*-acylated products selectively in good yield [6] making this a versatile system for the synthesis of substituted pyrazoles. The reaction of 4-amino-3-phenylaminocarbonyl-3-penten-2-one **1** with hydrazine was carried out under reflux in ethanol for 5 hours (1 hour when hydrazine hydrochloride was employed) to give 3,5-dimethyl-4-phenylaminocarbonyl)-1*H*-pyrazole **3** in good yield. However when 4-amino-3-phenylaminothiocarbonyl-3-penten-2-one **2** was treated with hydrazine in ethanol at room temperature for 2 hours, a mixture of **4** and **5** was isolated in a ratio of 6:1, respectively; indicating that after the attack of hydrazine to C-β the cleavage takes place in a ratio larger than that of the cyclization, while with hydrazine hydrochloride the pyrazole **5** was obtained together with a small amount of **6** (See Scheme I), which could be readily separated by chromatography to give **5** (81%) and **6** (7%). The compound **6** was obtained from the cleavage of **2** after the attack of hydrazine to C4. This was confirmed when **2** was treated with *p*-toluenesulfonic acid for 24 hours, followed by neutralization with aqueous sodium bicarbonate afforded **6** quantitatively. The formation of **4** was unexpected; it

Scheme I



can be considered to proceed by the initial formation of **6**, followed by cyclization. To prove the proposed intermediate, the compound **6** was reacted with hydrazine to give **4** in 94% yield. The structures of **4, 5** and **6** were confirmed on the basis of their spectral data and microanalyses (see Table). Under similar conditions, the reaction of ethyl 3-amino-2-phenylaminocarbonyl-2-butyrate **7** with hydrazine afforded the expected pyrazolone **9**. When **7** was reacted with hydrazine hydrochloride, a mixture of **9** and β-dicarbonylic compound **10** was obtained, which could be separated to give **9** in 70% and **10** in 10%. The reaction of ethyl 3-amino-2-phenylaminothiocarbonyl-2-butyrate **8** with hydrazine hydrochloride gave a 1:2 mixture, respectively, of β-thioxo ester **12** and pyrazole **13**, (Scheme II). When hydrazine hydrate was employed, the only product isolated was the pyrazolone **11**. This reaction involves initial cleavage of **8** with subsequent nucleophilic attack of hydrazine, followed by loss of hydrogen sulfide (detected by qualitative test with lead acetate), to give **11**. The reactivity of **1** and **7** with

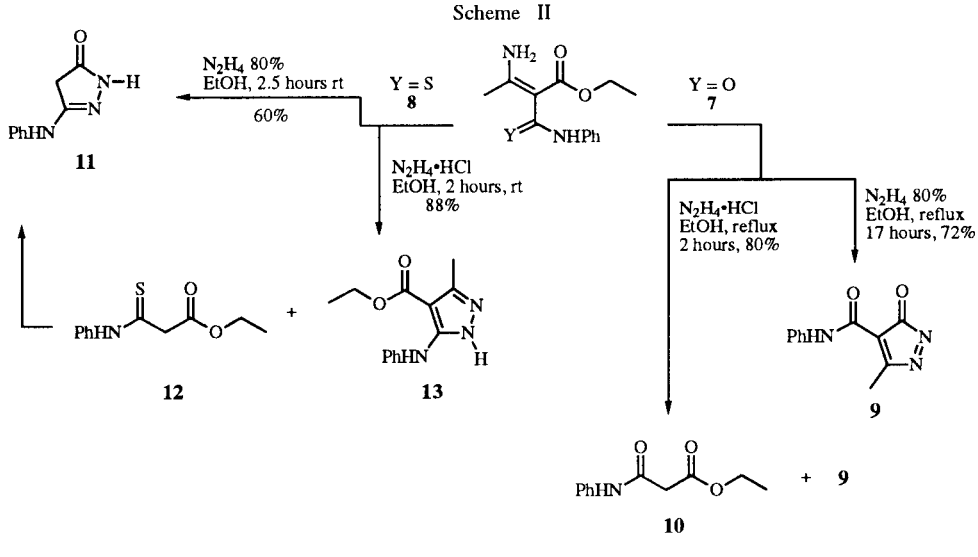
Table 1

Selected Physical and Spectral [a] Data of compounds **3-6** and **9-13**

No.	Yield [b] (%)	Mp [c] °C	Molecular Formula	Analysis (%) Calcd./Found C	H	N	^{1}H-NMR δ, J (Hz)	^{13}C-NMR δ
3	95	234	$C_{12}H_{13}N_3O$ 215.25	66.96 66.51	6.09 6.06	19.52 19.58	2.31 (s, 6H, CH_3), 6.92-7.69 (m, 5H arom), 9.39 (br s, 1H, NH)	11.7, 114.0 (C-4), 119.8 123.2, 128.6, 139.5, 143.6 (C-3,5), 163.4
4	40	117-119	$C_{10}H_{11}N_3$ 173.22	69.34 69.21	6.40 6.29	24.26 24.12	2.16 (s, 3H, CH_3), 5.59 (s, 1H, CH), 6.56-7.35 (m, 5H arom), 8.16 (br s, 1H, NH), 11.59 (br s, 1H, NH)	10.7, 93.0 (C-4), 114.5, 117.6, 128.6, 138.7, 144.2 (C-3), 151.2 (C-5)
5	81[d]	160-162	$C_{12}H_{13}N_3S$ 231.31	62.31 62.42	5.66 5.71	18.17 17.98	2.28 (s, 6H, CH_3), 7.18-7.81 (m, 5H arom), 11.0 (br, 1H, NH)	14.7, 122.1 (C-4), 123.3, 125.5, 128.3, 139.9, 142.0 (C-3,5), 191.6
6	7	60-62	$C_{10}H_{11}NSO$ 193.26	62.15 62.27	5.74 5.73	7.25 7.32	1.97 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.02 (s, 2H, CH_2), 7.22-7.90 (m, 5H arom), 11.06 (br s, 1H, NH)	29.5 (C-4), 61.5 (C-2), 122.8, 124.4, 126.0, 128.4, 189.6 (C-1), 201.8 (C-3)
9	72	197-199	$C_{11}H_9N_3O_2$ 215.21	61.39 61.54	4.22 4.38	19.53 19.32	2.42 (s, 3H, CH_3), 6.91-7.67 (m, 5H arom), 10.11 (br s, 1H, NH)	11.9, 97.5 (C-4), 119.2, 122.9, 128.9, 139.1, 146.8 (C-5), 165.0 (C-3), 166.0
10	10	oil	$C_{11}H_{13}NO_3$ 207.23	63.74 63.49	6.32 6.28	6.76 6.62	1.31 (t, 3H, J = 7.1, CH_3), 3.46 (s, 2H, CH_2), 4.25 (q, 2H, J = 7.1, CH_2), 7.09-7.59 (m, 5H arom), 9.21 (br s, 1H, NH)	13.9 (C-5), 43.6 (C-2), 60.6 (C-4), 119.2, 123.5, 128.7, 138.8, 164.0 (C-1), 167.6 (C-3)
11	60	271-273	$C_9H_9N_3O$ 175.19	61.69 61.32	5.18 5.20	23.99 23.89	3.42 (s, 2H, CH_2), 7.15-7.51 (m, 5H arom), 9.16 (br s, 1H, NHPh), 10.37 (br s, 1H, NH)	37.1 (C-4), 117.0, 120.6, 128.8, 140.8 152.6 (C-3), 171.0 (C-5)
12	32	oil	$C_{11}H_{13}NSO_2$ 223.29	59.17 59.44	5.87 5.86	6.27 6.30	1.19 (t, 3H, J = 7.2, CH_3), 3.85 (s, 2H CH_2), 4.12 (q, 2H, J = 7 2, CH_2), 7.14-7.67 (m, 5H arom), 10.75 (br s, 1H, NHPh)	13.4 (C-5), 52.2 (C-4), 60.1 (C-2), 122.3, 125.6, 128.0, 138.8, 164.8 (C-3), 192.8 (C-1)
13	55	164-166	$C_{13}H_{15}N_3O_2$ 245.28	63.64 63.39	6.17 6.18	17.13 16.91	1.30 (t, 3H, J = 7.12, CH_3), 2.39 (s, 3H, CH_3), 4.24 (q, 2H, J = 7.12, CH_2), 6.81-7.59 (m, 5H arom), 8.13 (br s, 1H, NHPh), 12.42 (br s, 1H, NH)	11.5, 14.2, 59.4, 95.9 (C-4), 116.3, 119.7, 128.8, 141.5, 142.7 (C-3), 142.7 (C-5), 164.8

[a] The nmr spectra were recorded on a Bruker AC 80 (^{1}H at 80 MHz and ^{13}C at 20 MHz) in DMSO-d_6/TMS. [b] Yields given for pure isolated products. [c] Melting points were determined with a Microquímica APF-301 apparatus and are uncorrected. [d] Yield obtained of reaction with hydrazine hydrochloride.

Scheme II



hydrazine hydrate is comparable to that β-dicarbonyl compounds [9] and enol ethers [10] which are known to be susceptible to attack by hydrazine to give pyrazoles derivatives. When the α-acyl group is replaced by a α-thioacyl group, the enamino esters **7** and **8** showed different reactivity. For the compound **7** (Y = O), the reaction with hydrazine involves initial nucleophilic attack at the C-β site, followed by cyclization to give the pyrazolone **9**. For

the compound **8** (Y = S), occurs the attack at the C-β site and cleavage to afford cyclic compound **11**. The pyrazoles obtained from cyclization of the α-acylated enamino compounds with hydrazine (hydrate or hydrochloride) depend on the reaction media employed as well as the α-substituent, carbonyl or thiocarbonyl group.

EXPERIMENTAL

Melting points were determined using a Microquímica APF-301 apparatus and are uncorrected. The nmr spectra were recorded on a Bruker AC-80 spectrometer. (^{1}H at 80 MHz with TMS as internal standard and ^{13}C at 20 MHz). Elemental analyses were carried out on a Vario CHN elemental analyser. α-Acylated β-amino ketones and esters **1** and **2** were prepared according to the known procedure [6].

3,5-Dimethyl-4-phenylaminocarbonyl-1*H*-pyrazole **3** and 4-Phenylaminocarbonyl-5-methylpyrazol-3-one **9**.

General Procedure.

Hydrazine hydrochloride for **1** or hydrazine hydrate (80%) for **7** (1.5 mmoles) was added dropwise to a stirred solution of the α-acylated β-enamino ketone **1** or α-acylated β-enamino ester **7** (1 mmole) in ethanol (2 ml). The mixture was stirred and heated under reflux for 1 hour (17 hours for **7**). The solvent was evaporated in a rotary evaporator under vacuum, the crystals were washed with water, separated by filtration and dried *in vacuo* to give **3** (95%) or **9** (72%) from **1** or **7**, respectively. Adding hydrazine hydrochloride to **7** and refluxing for 2 hours, gave a mixture of **9** and **10**. These were purified by column chromatography on silica gel (Aldrich, 230-400 mesh) using dichloromethane/methanol as eluent (98:2) resulting **9** in 68% and **10** in 10%.

3,5-Dimethyl-4-(*N*-phenylaminothiocarbonyl)-1*H*-pyrazole **5** and 4-Ethoxycarbonyl-5(3)-methyl-3(5)-phenylaminocarbonyl-1*H*-pyrazole **13**.

Hydrazine hydrochloride (1.5 mmoles) was added dropwise to a stirred solution of the α-acylated β-enamino compounds **2** or **8** (1 mmole) in ethanol (2 ml). The mixture was stirred and refluxed for 2 hours then neutralized with sodium bicarbonate. The product was extracted with ethyl acetate (3 x 10 ml). The solution was dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to yield the crude products. The products were purified by column chromatography on silica gel (Aldrich, 230-400 mesh) using dichloromethane/methanol as eluent, resulting **5** (81%), **6** (7%), **13** (55%) and **12** (32%).

Under the same conditions employing hydrazine hydrate (80%), **5** was isolated in 6% and 5-methyl-3-(*N*-phenylamino)-1*H*-pyrazole, **4**, in 40%.

1,4-Dihydro-3-(*N*-phenylamino)pyrazol-5-one **11**.

Hydrazine hydrate (80%) (1.5 mmoles) was added dropwise to a stirred solution of the ethyl 3-amino-2-phenylaminothiocarbonyl-2-butyrate, **8**, (1 mmole) in ethanol (2 ml). The mixture was stirred at room temperature for 2 hours after which the solvent was evaporated by rotary evaporation. The crude product was washed with water, separated by filtration and dried *in vacuo* to give **11** (60%).

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