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Studies on β-enaminonitriles: Part III†—Reaction of β-aminocrotononitrile with unsaturated acid chlorides : Benary revisited

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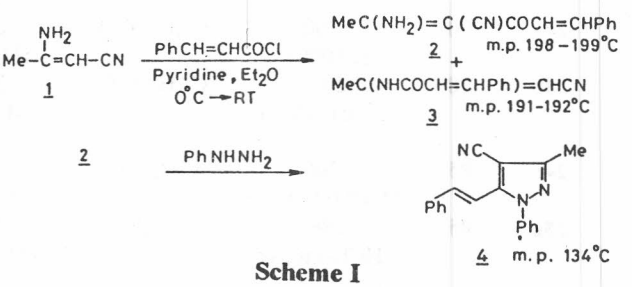
Acylation of β-aminocrotononitrile with cinnamoyl chloride when carried out in the presence of pyridine affords, according to Benary, a mixture of *C*- and *N*-acylated products. Reinvestigation of this reaction now firmly establish through extensive spectral analyses and comparison with authentic sample that Benary. designated *N*-acylated product is, in fact, 5-cyano-6-methyl-4-phenyl-3,4-dihydropyridin-2 (1*H*)-one **5** formed via *in situ* cyclisation of the corresponding *N*-acylated enaminonitrile. Interestingly, when this reaction is tried with other classes of unsaturated acid chlorides having triple bond or extended conjugation, exclusive preference for *C*-acylation of β-aminocrotononitrile is observed.

While working towards a general route for facile and efficient synthesis of isothiazolo[5,4-*b*]pyridines[3] we became interested in exploring the chemistry of primary enaminonitriles, particularly that of β-aminocrotononitrile **1**. Literature examples are known[4] where acylation of enamines with α,β-unsaturated acid chlorides were reported. However, most of these studies involved primarily cyclic tertiary enamines. In sharp contrast, much less work is reported with acyclic enaminonitriles with acid chlorides[5], esters[6], and amides[7]. It is worth mentioning here that as early as 1922 Benary *et al.*[8], could recognise the importance of enamononitriles and their derivatives for the synthesis of heterocyclic compounds and was able to isolate *C*- and *N*-acylated products **2** and **3** in equal amounts from the reaction of **1** with cinnamoyl chloride in the presence of pyridine as an added organic base (Scheme I).

When the reaction of β-aminocrotononitrile **1** with cinnamoyl chloride was carried out in the presence of triethylamine a highly crystalline material, m.p. 189 °C, was obtained in excellent yield. Careful examination of the TLC and ^{1}H NMR spectrum of the crude reaction mixture showed the presence of only one compound thereby ensuring its homogeneity. Surprised by this observation we felt it necessary to repeat this reaction under Benary condition and were able to

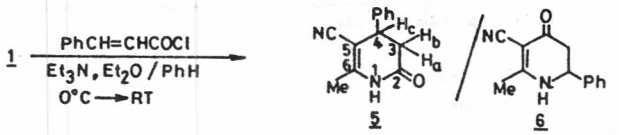


Scheme I

isolate, on chromatographic separation, two products in equal amounts.

One of these products was found to be the *C*-acylated compound **2** and its structural assignment was based on ^{1}H NMR spectral analysis and conversion to pyrazole **4** (Scheme I). The most notable feature in the ^{1}H NMR spectrum of **2** is the signals for the NH protons which appeared at two regions at δ 6.19 and 11.16 ppm respectively. These values for NH protons were found to be in complete agreement with the observation of a Japanese group[9] who found that all the ^{1}H NMR spectra of α-cyano-β-amino-β-alkylacrylic acid ester **7** showed two broad signals with an equal intensity in the region δ 9.20-10.02 and 5.85-6.10 ppm respectively. The signal appearing in the lower field could not be the NH protons of the other isomer (*E*) since the fine signal of the β-alkyl protons suggests the existence of only one species. Presumably, this low field absorption of one of the NH protons is to be attributed to the non equivalence of two protons on nitrogen atom

†For Parts I and II, see refs. 1 and 2.



Scheme II

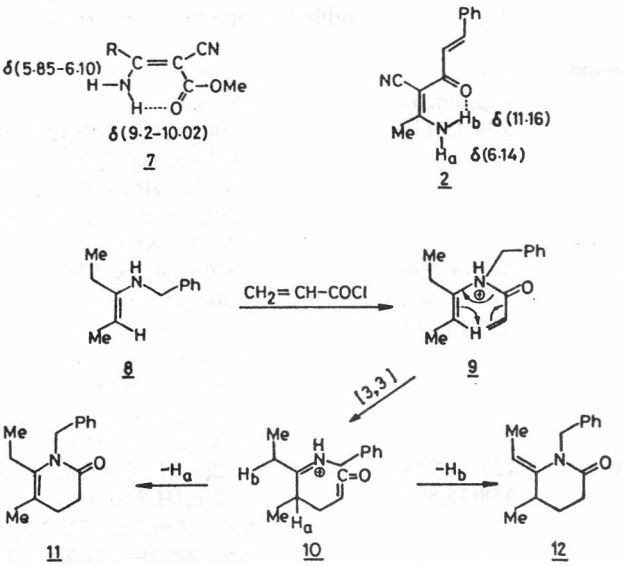
resulting from restricted rotation about C-N single bond. The *C*-acylated product **2** thus exists exclusively in the *Z* form at least in solution. This characteristic feature of ^{1}H NMR spectrum of the *C*-acylated acyclic primary enamine thus provides an extremely useful diagnostic information in analysing the composition of products in such acylation reaction.

The other product obtained from the reaction mixture was found to be identical with the compound **5/6** (Scheme II) previously obtained by us as the sole product during acylation of **1** with cinnamoyl chloride in the presence of triethylamine. The present work clearly demonstrates the influence of the added organic base in directing the site of acylation in enaminonitrile **1**.

Since enamines are ambident nucleophiles the reaction with electrophiles can occur at the nitrogen or at the β-carbon atom. *N*-Acyl enamine, if formed, has an alternative reaction path available namely, [3,3] sigmatropic rearrangement to give a ketene intermediate. Cyclisation of the regenerated enamine system on to the ketene then affords an enolate anion which is subsequently protonated to yield a heterocyclic compound. This postulation finds adequate support from the work of Hickmott *et al.*[10] who investigated acylation of enamine **8** with acryloyl chloride and isolated double bond isomers of 2-oxo-tetrahydropyridine **11** and **12**. These compounds were formed through cyclisation of *N*-acyl derivative **9** via ketene **10** (Scheme III). Structure of these compounds were firmly secured on UV and IR spectral analyses.

However, in our case structural assignment for compound **5** or **6** on the basis of spectral analyses (Table I) appeared to be somewhat unreliable and therefore leaves scope for error[11]. The basic enamino moiety remaining intact in both **5** and **6**, a comparison based on UV and IR data for their structural elucidation as described in the literature should not be taken for granted.

In the ^{1}H NMR spectra, both **5** and **6** are expected to exhibit similar proton signal patterns allowing only recognition of their gross structure.



Scheme III

Analysis of ^{1}H NMR spectrum (500 MHz) of **5** or **6** coupled with nOe experiments showed a singlet at δ 2.24 ppm assigned to 6-methyl protons, a pair of double doublets centred at δ 2.78 (J=5.7, 16.7 Hz) were assigned to 3-H_a, H_b protons. 4-H_c proton appeared at δ 3.89 ppm as a double doublet (J=5.7 and 7.7 Hz) and the aromatic protons appeared as multiplet centred at δ 7.35 ppm. A broad signal at δ 7.92 ppm was assigned to –NH protons. Based on these observations it could be concluded, with a fair degree of certainty, that compound **5/6** represents a dihydro pyridone ring with a H-C-H group at C-3 rather than *N*-acylated compound **3** as reported by Benary. The H_a and H_b methylene protons being non equivalent constitute a geminal pair adjacent to carbonyl group and therefore exhibit the expected proton signals characteristic of ABX system. In order to settle unequivocally the structure in favour of either compound **5** or **6**, a close examination of their structural features reveals that ^{13}C NMR spectrum should be highly informative. Thus, in compound **5** the C-4 is expected to appear around δ 26-30 ppm whereas in compound **6** the C-2 should appear at a much higher field (50-55 ppm)[12]. Furthermore, the carbonyl carbon signal position of **5** and **6** should also differ considerably[13]. ^{13}C NMR spectrum(pyridine-d_5) analysis of **5/6** (Table I) showed among other signals, a doublet at δ 40.0 ppm corresponding to C-4 and a singlet appearing at 169.3 ppm was assigned to –NHCO- group.

Table I — Spectral Characteristics of compounds **5, 14a, 14b** and **14c**

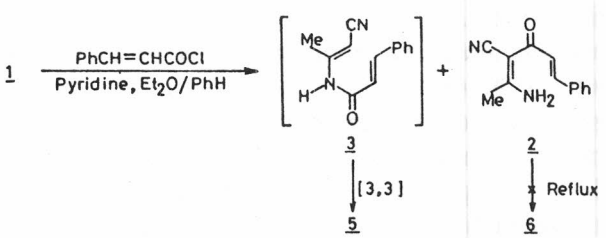
Compd	UV λ_{max}(nm, ε)	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)	M^+ (m/z)
5	274(15,117)	2.24(s, CH_3), 2.78 (dd, *J*=5.7 & 16.7 Hz, Ha), 2.94 (dd, *J*=7.7 & 16.7 Hz, Hb), 3.89 (dd, *J*=5.7 & 7.7 Hz, Hc); 7.22-7.36 (m, Ar-H), 7.92 (bs, NH)	18.6 (q, 6-CH_3), 38.2 (t,C-3); 40.0(d, C-4), 88.0(s,C-5); 119.3 (s, CN); 127.4(s); 127.9(s); 129.4(s); 141.8(s, C-6), 150.2(s), 169.3(s,C=O)	212
14a	242 (8,254) 287 (12.443) 335(19,113)	1.87(d,3H,*J*=4.5 Hz), 2.30(s,3H), 6.15 (dd,1H,*J*=5 & 12), 6.26 (dd, 1H,*J*=7 & 12 Hz), 6.48(bs,1H,NHa), 6.72(d,1H,*J*=12 Hz); 7.25 (dd, 1H, *J*=3 & 7 Hz), 11.3 (bs, 1H, NH_b)	18.86, 22.64,120,208 124.6, 130.49, 140.25, 142.98, 170.97, 187.23	176
14b	235(12,773) 358(35,833)	2.32(s,3H); 6.08(bs,1H,NHa); 6.92(d,1H,*J*=16 Hz); 6.8-7.16(m,2H), 7.2-7.6(m, 6H, ArH, ArCH=), 11.20(bs,1H, NH_b)	18.86, 22.64, 84.04, 120.20, 124.60, 130.49, 140.25, 142.98, 170.97 187.23	238
14c	283(11,382) 334(26,292)	2.36(s,3H), 6.52(bs,NH_a); 7.58-7.70 (m,3H, ArH), 7.88(dd, 2H, *J*=2 & 7Hz, ArH); 10.76 (bs,1H,NH_b)		210

*Recorded in pyridine-d_5 for compound **5**

These results clearly demonstrated the fine structure of the dihydropyridone in favour of **5**.

Further proof regarding the correctness of the assigned structure was obtained from the preparation of an authentic sample[14] found to be identical in all respects (mmp, UV, IR, MS) with **5**. Acylation of **1** under Benary condition showed, in the crude reaction mixture, unmistakable presence of *C*-acylated product **2** along with compound **5** easily detected through characteristic ^{1}H NMR spectrum. Analysis of this spectrum provided invaluable information with regard to the participating intermediate species responsible for formation of **5**. Thus, the presence of *C*-acylated product **2** in the crude reaction mixture precluded its participation in the cyclization process leading to the formation of the corresponding dihydropyridone **6** under the reaction conditions employed. It was further noted that the compound **2** failed to cyclise even at elevated temperature in refluxing diphenyl ether (Scheme IV). In view of these observations it can be safely concluded that the formation of **5** must have resulted from *in situ* cyclization of *N*-acylenamine **3** via [3,3]sigmatropic rearrangement (Scheme IV).

The present work, therefore, not only confirmed the structure of the Benary product **3** but also demonstrated the importance of the added organic base vis-à-vis pyridine and triethylamine in



Scheme IV

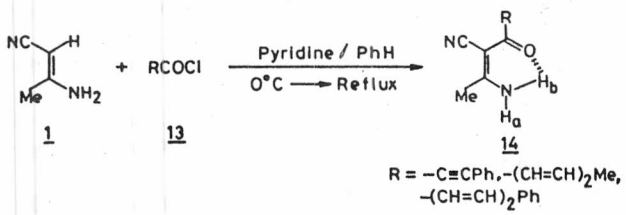
controlling the acylation site of the enaminonitrile **1**.

While generality of this enamine reactivity to produce cleanly the corresponding 3,4-dihydropyridin-2(1*H*)-one in the presence of triethylamine has been found to be well documented[2] with α,β-unsaturated acid chlorides, a complete reversal of regioselectivity was observed with acid chlorides obtained from 2,4-hexadienoic acid and phenyl propiolic acid **13a-c**. Thus, when enaminonitrile **1** was reacted with **13a-c**, *C*-acylated products **14a-c** were obtained exclusively in excellent yield (Scheme V, Table II).

Structure of all these compounds were firmly secured on elemental and spectral analyses (Table I). Currently we are looking into different factors responsible for reversal of terminal selection of β-aminocrotononitrile **1** in these acylation reactions[15]. Such unique regioselection offers unlimited

Table II — Physical data of compounds **14a-c**

Compd	R	mp °C	yield (%)	Found % (Calcd) C	H	N
14a	$(-CH=CH)_2Me$	138	73	67.93 (68.16	6.88 6.86	16.01 15.90)
14b	$(-CH=CH)_2Ph$	227	76	74.73 (75.63	5.89 5.88	11.42 11.75)
14c	-C≡C-Ph	175	80	74.11 (74.26	4.48 4.80	13.41 13.32)



Scheme V

opportunities to achieve synthesis of various novel heterocyclic compounds.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. Progress of reactions was monitored by TLC. UV spectra were taken in ethyl alcohol on a Hitachi U-200 spectrophotometer. IR spectra were recorded in KBr discs on a Hitachi 270-30 spectrophotometer, NMR spectra in $CDCl_3$ on Hitachi R-600. JEOL EX 90, JEOL FX 100, Bruker AC 200, AM 250, AM-360 and Brucker Advance 500 FT NMR spectrometers with TMS as internal reference. Mass spectra were recorded on Hitachi RMU GL and JMS-AX 505H mass spectrometer at 70 eV. Micro analyses were performed in Perkin Elmer 240C elemental analyser. Solvents and reagents were dried by conventional methods. β-Aminocrotononitrile[16] and the unsaturated acid chlorides were prepared according to literature procedures[17,18].

Acylation of β-aminocrotononitrile 1 with cinnamoyl chloride : Preparation of 5-cyano-6-methyl-4-phenyl-3,4-dihydropyridin-2 (1*H*)-one 5. Freshly prepared cinnampoyl chloride (20 mmoles) in dry ether or benzene (20 mL) was added dropwise to a magnetically stirred solution of β-aminocrotononitrile (**1**, 20 mmoles) and triethylamine (60 mmoles) in dry ether or benzene (20 mL) at 0°C. The reaction mixture was allowed to attain room temperature and then poured into crushed ice, acidified with hydrochloric acid (2*N*) and extracted with ether (3×20 mL). Removal of the solvent and crystallisation from ethyl acetate-benzene afforded compound **5**, m.p 189 °C (lit[14]. 189-90 °C), yield 80%. Anal. Found : C,73.69; H, 5.64; N, 13.27. Calc. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20%.

Acylation of β-aminocrotononitrile 1 with cinnamoyl chloride in the presence of pyridine : Preparation of 5 and α-cinnamoyl-β-aminocrotononitrile 2. To a magnetically stirred solution of β-aminocrotononitrile (**1**, 20 mmoles) and dry pyridine (60 mmoles) in dry ether at 0°C was added cinnamoyl chloride (20 mmoles) in dry ether (10 mL). The reaction mixture was allowed to attain ambient temperature. Usual work-up and column chromatography (10% ethyl acetate-pet ether as eluent) afforded, after crystallisation, compound **2** in 38% yield mp 197 °C (lit.[14]. 198-99 °C); UV: 230 (ε 10, 206), 340 nm (ε 2665); IR : 3348, 3188, 2188, 1646, 1590, 1466, 1336, 1214 and 972 cm^{-1}; ^1H NMR : 2.36 (s, 3H, $-CH_3$), 6.19 (bs, 1H, $-NH_a$), 7.07 (d, 1H, *J*=16 Hz, -C*H*=CH-Ph), 7.19-7.79 (m, 6H, Ar- and CH=C*H*-Ph), 11.16 ppm, (bs, 1H, $-NH_b$).MS : M^+ (m/z) 212. Anal. Found: C, 73.60; H, 5.44; N, 13.35. Calc. for $C_{13}H_{12}N_2O$: C, 73.57; H, 5.66; N, 13.20%.

20% Ethyl acetate-pet. ether fractions afforded a solid material, mp 189 °C in 39% yield which was found to be identical in all respects with compound **5**.

Preparation of 4-cyano-3-methyl-5-styryl-1-phenylpyrazole 4. A mixture of **2** (3 mmoles) and phenylhydrazine reagent[18c] (9 mmoles) was heated on a steam-bath for 40 min. when a yellowish oily liquid was separated. The mixture was cooled and acidified with acetic acid (50%) followed by neutralisation with sodium bicarbonate. Recrystallisation from ethyl acetate-petroleum ether afforded **4** as white needles in 70% yield, mp

132 °C (lit[8]. Mp 134 °C); UV : 225 (ε 18,293), 336 nm (ε 26,807); IR : 2220, 1594, 1536, 1498, 1430, 958, 770, 690 cm^{-1}; ^1H NMR: 2.40 (s, 3H, 3-CH_3), 6.77 (d, 1H, *J*=16 Hz), -C*H*=CH-Ph), 7.07-7.79 (m, 11H, Ar-H and –CH=C*H*-Ph).

General procedure for the preparation of compounds 14a-c. These compounds were prepared by the reaction of β-aminocrotononitrile (**1**, 20 mmoles) with appropriate acid chlorides (20 mmoles) in dry benzene (20 mL) and pyridine (60 mmoles) at 0 °C. Usual work-up afforded the corresponding C-acylated products **14a-c** in excellent yield.

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