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SYNTHESIS OF α-CYANOENAMINES[1]

ISOLATION AND CHARACTERIZATION OF BOTH TAUTOMERIC ISOMERS: α-CYANOENAMINES AND IMIDOYLCYANIDES

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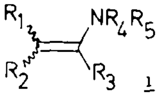
Abstract—α-Cyanoenamines have been prepared in high yield by the reaction of α-chloroaldimines with potassium cyanide in methanol. On gas chromatographic analysis, the α-cyanoenamines were partially isomerized to the tautomeric imidoylcyanides. Both isomers have been isolated and spectroscopically characterized.

Enamines are useful intermediates in organic syntheses.[3,4] Especially the reactions of enamines with electrophilic olefins involving 1,2-, 1,3- and 1,4-cycloadditions have been widely used and provide a synthetic route to a variety of compounds.[4] The electron-rich double bond of enamines is responsible for its intriguing reactivity. This can be modified by substituting the double bond with electron-attracting or electron-donating substituents. In this respect various substituted enamines have been synthesized, e.g. β-alkoxycarbonyl-,[5a] β-acyl-,[5b] β-cyano-,[5c] β-halogen-,[5d,5e] α-halogen-enamines[5f] and enediamines[5g] (Scheme 1).



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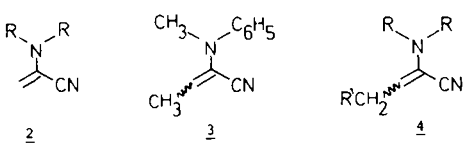
	R_1	R_2	R_3	R_4	R_5
1a	COOR	H	alkyl	alkyl	H
1b	COR	H	alkyl	alkyl	H
1c	halogen	alkyl	H	alkyl	alkyl
1d	halogen	aryl	aryl	aryl	H
1e	NR'R'	alkyl	H	alkyl	alkyl
1f	alkyl	alkyl	halogen	alkyl	alkyl
1g	CN	alkyl	alkyl	H	H

Scheme 1.

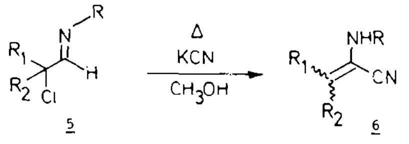


Scheme 2.

Although syntheses of enamines, substituted with various electron-attracting groups have been extensively described,[5] the chemistry of α-cyanoenamines (1: R_1, R_2 = alkyl, R_3 = CN) has been little studied. In the 1940's a licence[6] was taken out for the preparation of α-(N-substituted amino)acrylonitriles 2, following treatment of α-chloro-acetaldehyde with liquid hydrogen cyanide and two equivalents of secondary amine. The method was improved by Temin[7] and successfully extended by Ahlbrecht *et al.*[8] for the synthesis of 2-(N-methylanilino)-2-butenenitrile 3. Finally another entry into the α-cyanoenamino system was described by Yanovskaya *et al.*[9] who prepared α-cyanoenamines 4 by reaction of α,β-unsaturated aldehydes with α-(N,N-dialkylamino)-isobutyronitriles. The reaction was of limited synthetic utility since it does not apply to such ordinary alifatic α,β-unsaturated aldehydes as crotonaldehyde. Only cinnamic aldehyde, *trans*-4,4-dimethoxy-2-butenal and β-furylacrolein form 4 (respectively $R' = C_6H_5$, $R' = CH(OCH_3)_2$ and R' = furyl) in the expected way.

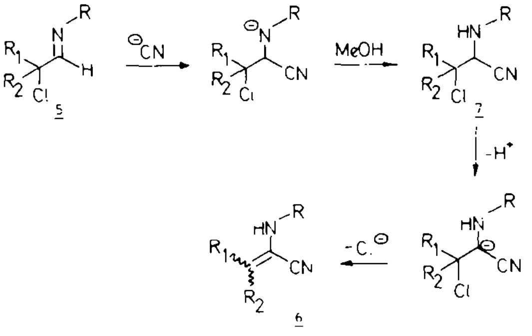
We report a convenient synthetic route to α-cyanoenamines. α-Halogenated imine chemistry has already shown a number of interesting avenues for synthetic and mechanistic studies.[10,11] Secondary[12] α-chloroaldimines 5 readily undergo rearrangement (via aziridine intermediates), elimination or substitution on treatment with nucleophilic and/or basic reagents.[1]

However, treatment of these α-chloroaldimines 5 with excess potassium cyanide in methanol under reflux has afforded high yields of α-cyanoenamines 6. The formation of compounds 6 can be rationalized in terms of an



Scheme 3.

addition of cyanide to the imino function. After proton uptake, the non isolable β-chloro-α-(N-alkylamino)nitriles **7** are dehydrochlorinated following α-proton abstraction by the base (cyanide) and chloride anion expulsion.



Scheme 4.

Table 1 gives a survey of the results.

After work up the mixture was found to consist exclusively of the enamic form **6**. Compounds **6** were characterized by NMR- and mass spectroscopy; the IR spectrum exhibited the typical stretching vibrations at 2225 cm^{-1} ($\nu_{C\equiv N}$; sharp; medium) and 1615 cm^{-1} ($\nu_{C=C}$; medium), besides the broad absorption at 3320–3360 cm^{-1} which can be attributed to the NH vibration.

All spectral data concerning α-cyanoenamines **6** are summarized in Table 2.

It was found that gas chromatographic analysis (Varian 1700; SE 30 12%; 3 meter; injector 250°C; 120°C isotherm; glass or metal column) revealed the presence of two peaks, the ratio of both peaks depending on the amount injected. The peak with the longer retention time was identified as the enamine **6**, while the first peak was established as the ketiminic form, i.e. the imidoylcyanide **8**. The structural elucidation of the ketiminic structure **8** was mainly based on NMR- and IR-spectroscopy. For example the high value (δ 1.40) for the t-Bu singlet (NMR; CCl_4) of N-t-butyl-2-ethylbutane imidoylcyanide **8e** is consistent with the C=N-t-Bu moiety (as compared with δ 1.26 for the corresponding enamine **6e**). The absence of a NH-absorption in the IR spectrum clearly supported the imino structure, as well as the C=N stretching vibration of **8e** at 1638 cm^{-1} and the very weak C≡N absorption at 2222 cm^{-1}. Further spectroscopic data are given in Table 3. As mentioned the mixture obtained immediately after work up consisted exclusively of the enaminic form **6** in high purity. Distillation *in vacuo* also gave pure α-cyanoenamine **6**, while no trace of imidoylcyanide was detected. In only one case (**6h**), a crude mixture which initially consisted of a 50/50 mixture of α-cyanoenamine and imidoylcyanide was obtained (as revealed by GC-MS coupling: see experimental conditions above).

Table 1. Synthesis of α-cyanoenamines **6**

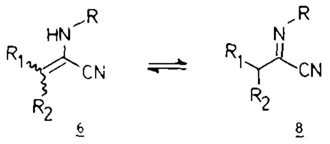
	R_1	R_2	R	Reaction time (reflux)	Yield	b.p.
6a	CH_3	CH_3	tBu	overnight	95 %	95- 96°C/12 mmHg
6b	CH_3	CH_3	iPr	6 h	83 %	112-117°C/12 mmHg
6c	CH_3	CH_3	C_6H_{11}	4 h	92 %	135-146°C/12 mmHg
6d	CH_3	Et	tBu	12 h	99 %[a,b]	-
6e	Et	Et	tBu	overnight	94 %	110-114°C/12 mmHg
6f	Et	Et	C_6H_{11}	overnight	89 %	146-157°C/12 mmHg
6g	$(CH_2)_5$		tBu	overnight	94 %[a]	-
6h	$(CH_2)_5$		C_6H_{11}	overnight	78 %	115-125°C/0,05 mmHg
6i	CH_3	C_6H_5	tBu	overnight KCN/CH_3OH	17 %[a,c]	-
6i	CH_3	C_6H_5	tBu	overnight KCN/acetone	36 %[a,d]	-

a : yield determined by glc (internal calibration).

b : 57 % Z and 42 % E isomer.

c : 17 % α-cyanoenamine 6i (14 % Z + 3 % E) along with 51 N-1-(2-methoxy-2-phenylpropylidene)tbutylamine 9.

d : low yield due to decomposition of products.



Scheme 5.

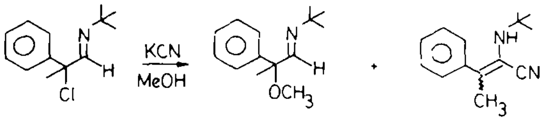
In the case of **6c,e,f,g,h** gas chromatographic analysis (see conditions given above) eluted ketiminic isomers **8**. Imidoylcyanides **8** were isolated by preparative gas chromatography and were stable colourless liquids for at least 10 hr. On prolonged standing in carbon tetrachloride solution at room temperature, they were slowly isomerized within 3 days to enamines **6**. No trace of tautomerization was found in the case of **6a,b,d,i**. On the other hand, on-column-injection of crude α-cyanoenamine (Pye Unicam 104 coupled with MS 20 mass spectrometer; glass column, 5% SE 30) exclusively α-cyanoenamines **6** were found. The spectroscopic data of N-alkyl imidoylcyanides **8** are given in Table 3. Imidoylcyanides lacking α-hydrogens are known, for example phenyl benzimidoylchloride when treated with potassium cyanide afforded the corresponding phenyl benzimidoylcyanide in which no tautomerism was possible.[13] In our opinion, we describe the first report dealing with the isolation of imidoylcyanides possessing α-hydrogens.

However, it was reported[9] that the reaction of some α,β-unsaturated aldehydes with α-(N-monoalkylamino) isobutyronitriles or acetone cyanohydrine and primary amines also lead to imidoylcyanides. The latter paper was limited in scope and experimental details, while no tautomerism was reported.

The absence of tautomerism for **6a,b,d,i**, as compared with the other representatives, is still an open question except for **6i**, i.e. 2-(N-t-butylamino)-3-phenyl-2-butenenitrile, the enaminic form being favoured by resonance stabilization. The low yield of **6i** (17%) was due to the reaction of N-1-(2-chloro-2-phenylpropylidene) t-butylamine **5i** with methanol, producing N-1-(2-methoxy-2-phenylpropylidene) t-butylamine **9**. This α-substitution involving a S_N1 process has been described in

Table 2. Spectroscopic properties of α-cyanoenamines **6**

Compound	I.R. (NaCl ; cm^{-1})			N.M.R. (CCl_4 ; δ)	Mass spectrum m/e (%)
	$\nu_{C\equiv N}$	$\nu_{C=C}$	ν_{NH}		
6a	2225	1632	3360	1.20 (9H, s, tBu) ; 1.78 (3H, s, CH_3 trans with respect to C≡N) ; 2.00 (3H, s, CH_3 cis with respect to C≡N) ; 2.3 (1H, s broad, NH)	m/e 152(M^+ ; 16 %) ; 137(18 %) ; 122(3 %) ; 121(2 %) ; 120(2 %) ; 96(100 %) ; 95(8 %) ; 81(67 %) ; 69(13 %) ; 68(6 %) ; 57(97 %) ; 56(4 %) ; 55(4 %) ; 54(4 %) ; 53(8 %) ; 42 (16 %) ; 41(48 %)
6b	2215	1635	3340	1.14 (6H, d, J 6Hz, $(CH_3)_2CH$) ; 1.73 (3H, s, CH_3) ; 1.97 (3H, s, CH_3) ; 2.32 (1H, s broad, NH) ; 4.40 (1H, septet, J 6Hz, NCH)	m/e 138(M^- ; 20 %) ; 123(100 %) ; 109(2 %) ; 108(3 %) ; 107(4 %) ; 100(5 %) ; 96(8 %) ; 95(5 %) ; 81(17 %) ; 69(12 %) ; 60(6 %) ; 58(6 %) ; 43(11 %) ; 42(7 %) ; 41(11 %)
6c	2222	1640	3360	1.73 (3H, s, CH_3 trans with respect to C≡N) ; 1.97 (3H, s, CH_3 cis with respect to C≡N) ; 1-2 (10H, m, $(CH_2)_5$) ; 3.00 (1H, m, N-CH)	m/e 178(M^+ ; 46 %) ; 163(1.5 %) ; 150(3 %) ; 137(100 %) ; 124(3 %) ; 123(5 %) ; 111(10 %) 109(9 %) ; 97(70 %) ; 83(21 %) ; 81(32 %) ; 69(28 %) ; 55(46 %)
6d	2220	1625	3320	1.02 (3H, t, J 6.9Hz, CH_3-C-C=) ; 1.23 (9H, s, tBu) ; 1.80 (s, CH_3 trans with respect to C≡N, 40 %) ; 2.00 (s, CH_3 with respect to C≡N, 60 %) ; 2.30 (2H, m, CH_2)	m/e 166(M^+ ; 19 %) ; 151(14 %) ; 110(61 %) ; 95(100 %) ; 83(9 %) ; 68(13 %) ; 57(94 %)
6e	2225	1615	3360	1.00 (6H, degenerated, $2xCH_3$) ; 2.3 (4H, m, $2xCH_2$) ; 1.26 (9H, s, $(CH_3)_3$)	m/e 180(28 %) ; 165(24 %) ; 124(55 %) ; 109 (81 %) ; 95(82 %) ; 82(29 %) ; 68(4 %) ; 57 (100 %) ; 56(4 %) ; 55(9 %) ; 53(5 %) ; 41(42%)
6f	2222	1630	3360	δ 1.03 (6H, degenerated, $2xCH_3$) ; 1-2 (10H, m, $(CH_2)_5$) ; 2.2 (4H, m, $(CH_2)_2$) ; 3.0 (1H, m, N-CH) ; NH invisible	m/e 206(M^+ ; 56 %) ; 191(43 %) ; 178(13 %) ; 163(100 %) ; 149(6 %) ; 135(24 %) ; 124(31 %) 123(20 %) ; 109(93 %) ; 97(28 %) ; 95(46 %) ; 83(46 %) ; 82(39 %) ; 68(9 %) ; 67(13 %) ; 55 (80 %) ; 54(9 %) ; 53(13 %) ; 41(74 %)
6g	2220	1622	3350	δ 1.24 (9H, s, tBu) ; 1.4-1.9 (6H, m, $(CH_2)_3$) ; 2.1-2.7 (4H, m, $(CH_2)_2$)	-
6h	2220	1635	3350	δ 1-2.6 (20H, m) ; 3.6 (1H, m, N-CH) ; NH invisible	m/e 218(69 %) ; 189(6 %) ; 176(6 %) ; 175 (100 %) ; 162(6 %) ; 161(7 %) ; 147(22 %) ; 136(32 %) ; 135(14 %) ; 110(8 %) ; 109(26 %) 108(15 %) ; 94(10 %) ; 83(10 %) ; 83(22 %) ; 82(16 %) ; 81(20 %) ; 70(11 %) ; 69(13 %) ; 68(27 %) ; 67(21 %) ; 56(12 %) ; 55(53 %) ; 54(9 %) ; 53(11 %) ; 41(55 %)
6i	2230	1608	3370	δ 1.20 (9H, s, tBu) ; 2.26 and 2.11 (3H, 2xs, resp. CH_3 cis and trans with respect to C≡N) ; 3.1 (1H, s broad, NH) ; 7.0-7.6 (5H, m, C_6H_5)	m/e 214(M^+ ; 15 %) ; 199(10 %) ; 157(100 %) ; 156(15 %) ; 143(4 %) ; 142(3 %) ; 141(4 %) ; 140(2 %) ; 131(16 %) ; 130(7 %) ; 116(5 %) ; 104(5 %) ; 103(7 %) ; 77(8 %) ; 57(51 %) ; 41(23 %)



5i 9 6i

Scheme 6.

detail.[1] In order to avoid the undesirable solvolysis, the reaction of **5i** with KCN was carried out in acetone. Owing to decomposition the yield of **6i** could be improved only to 36%. Compound **6i** existed as two geometrical isomers E and Z. The E/Z ratio was calculated from the NMR spectrum by means of integration of the Me signals (in β-position with respect to C≡N). The NMR data of the dimethyl derivative **6a** allowed us to distinguish between E and Z isomers since the δ-values of the Me signals were used as reference material. The Me singlet at higher δ-value (~2.0 ppm) was attributed to the one *cis* with respect to the nitrile function (and *vice versa* for the singlet at δ ~ 1.8 ppm). This argument was based on the

Table 3. Spectroscopic data of N-alkyl imidoylcyanides **8**

	R_1	R_2	R	I.R. (NaCl) (cm^{-1}) $\nu_{C\equiv N}$	I.R. (NaCl) (cm^{-1}) $\nu_{C=N}$	N.M.R. (CCl_4) δ (ppm)	Mass spectrum m/e (%)
8c	CH_3	CH_3	C_6H_{11}	2220	1638	δ 1.22 (6H, d, J 6.5Hz, $(CH_3)_2$) ; 1-2 (10H, m, $(CH_2)_5$) ; 2.70 (1H, septet, J 6.5Hz, C$\underline{H}$-C=N) ; 3.56 (1H, m, C$\underline{H}$-N)	m/e 178(M^+ ; 70 %) ; 163(33 %) ; 137 (100 %) ; 83(60 %) ; 67(66 %) ; 55(22 %) 41(36 %)
8e	Et	Et	tBu	2222	1638	δ 1.40 (9H, s, tBu) ; 0,91 (6H, t, J 6.5Hz, $(CH_3)_2$) ; 1.5(4H, m, $(CH_2)_2$) ; 2.33 (1H, quintet, J 7Hz, C$\underline{H}$-C=N)	m/e 180(M^+ ; 2 %) ; 165(6 %) ; 152(4 %) 151(1 %) ; 137(2 %) ; 125(3 %) ; 124 (5 %) ; 123(10 %) ; 109(2 %) ; 96(15 %) 95(10 %) ; 82(3 %) ; 81(3 %) ; 69(1 %) ; 68(1 %) ; 57(100 %) ; 41(15 %)
8f	Et	Et	C_6H_{11}	2220	1638	δ 0.90 (6H, t, J 6Hz, $(CH_3)_2$) ; 1.2-2 (14H, m, $(CH_2)_5$ and $(CH_2)_2$) ; 2.30 (1H, quintet, J 6.5Hz, C$\underline{H}$-C=N) 3.60 (1H, m, N-C$\underline{H}$)	m/e 206(M^+ ; 12 %) ; 191(7 %) ; 178(40 %) 177(63 %) ; 163(50 %) ; 150(6 %) ; 149 (6 %) ; 135(33 %) ; 125(8 %) ; 123(10 %) 121(5 %) ; 110(20 %) ; 109(13 %) ; 98 (10 %) ; 97(17 %) ; 96(18 %) ; 95(40 %) 83(53 %) ; 82(50 %) ; 81(30 %) ; 70(8 %) 69(15 %) ; 68(13 %) ; 67(42 %) ; 55 (100 %) ; 54(50 %) ; 53(18 %) ; 43 (22 %) 41(77 %)
8g	$(CH_2)_5$		tBu	2220	1642	δ 1.36 (9H, s, tBu) ; 1-2 (10H, m, $(CH_2)_5$) ; 2.4 (1H, m, C$\underline{H}$-C=N)	-
8h	$(CH_2)_5$		C_6H_{11}	2220	1670	δ 1.0-2.6 (22H, m)	m/e 218(M^+ ; 63 %) ; 189(15 %) ; 176 (19 %) ; 175(100 %) ; 163(12 %) ; 162 (11 %) ; 161(10 %) ; 147(10 %) ; 137 (23 %) ; 121(12 %) ; 110(51 %) ; 109 (12 %) ; 108(12 %) ; 94(9 %) ; 93(10 %) 83(50 %) ; 82(25 %) ; 81(47 %) ; 70 (11 %) ; 69(12 %) ; 68(17 %) ; 67(35 %) 56(22 %) ; 55(97 %) ; 54(24 %) ; 53 (18 %) ; 41(84 %)

anisotropy effect of the C≡N grouping.[14] The E/Z ratio of **6i** was found to be 18/82. In a similar way, 2-t-butylamino-3-methyl-2-pentenenitrile **6d** showed a E/Z ratio of 58/42.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer spectrophotometer model 257. NMR spectra were measured on a Varian T-60 NMR spectrometer. Mass spectra were obtained from GC-MS couplings using a A.E.I. MS 20 mass spectrometer connected to a Pye Unicam 104 gas chromatograph (SE 30 5%; glass; 1.5 m). Preparative gas chromatographic analyses were performed with a Varian 1700 gas chromatograph. A metal as well as a glass column were used: SE 30 12%; 3 m. N-1-(2-chloroalkylidene) amines **5** were prepared as previously described.[1]

Preparation of 2-N-*alkylamino-2-alkenenitriles* **6** (α-cyanoenamines). In a typical experiment, **5e** (10.0 g; 0.052 moles) was dissolved in 150 ml dry MeOH. KCN (10.3 g; 0.156 moles) was added under vigourous stirring and the soln refluxed overnight. The solvent was half evaporated under reduced pressure, after which the mixture was poured into 200 ml water, extracted three times with ether, dried ($MgSO_4$), filtered and evaporated. The remaining clear liquid contained pure **6e** as shown by NMR spectroscopy. Injection of 5 μl of crude **6e** in the gaschromatograph (metal column) afforded two peaks (1 : 1 ratio). Injection of increasing quantities changed the ratio at the expense of the first peak. Both peaks were isolated: the first peak was shown to be **8e**, while the second one was found to be **6e**. GC-MS coupling of the crude mixture showed only **6e**. Distillation of the crude mixture provided 9.0 g of pure **6e** (yield 94%): b.p. 110–114°/12 mmHg.

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