Reactivity Studies of Ethyl(*Z*)-*N*-(2-amino-1,2-dicyanovinyl) Formimidate with Carbonyl Compounds in the Presence of Base

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Dedicated to the memory of Professor Raymond Castle

The reaction of ethyl(*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **6** with carbonyl compounds in the presence of triethylamine occurs with formation of the Schiff's base and intramolecular hydrolysis of the adjacent cyano group to give the alkylideneamino derivatives **8a-f**. When the α-carbon of the ketone has at least one proton, the prolonged contact of **8a-f** with triethylamine causes intramolecular cyclization between this carbon and the imidate carbon atom to form a seven membered ring. This is followed by cyclization of the cyano and amido groups, leading to the pyrrolo[4,3-*b*][1,4]diazepines **9**. If a strong base is used the first ring to be formed is the pyrrole ring as evidenced in the reaction of **8a** with 1,8-diazabicyclo[5.4.0]undec-7-ene leading to **14**. The subsequent addition of methyl amine to the reaction mixture, caused cleavage of the alkylideneamino unit and formation of the amidine function from the imidate (**15**). The addition of acid to the imidates **8a** and **8f** led to the diazepine compounds **10a** and **10f** respectively. A suspension of compound **8e** in ethanol and triethylamine evolved to a pyrazinone structure **12** under kinetic conditions (4 hours, room temperature) and to the pyrrolo[4,3-*b*][1,4]diazepine **9e** under thermodynamic conditions (48 hours, room temperature).

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Previous studies on the reactivity of amidines **1** (R = H) with aldehydes and ketones in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene showed that this is an efficient method for the synthesis of pyrrolo[3,4-*f*]-[1,3,5]triazepines **3** with different substituents in the 2-position [1]. The structure of compound **3** (R^1 = Ph, R^2 = H) was confirmed by X-ray crystallography and its formation must be preceded by the synthesis of an intermediate species **2**, which was never isolated under the experimental conditions used for these reactions.

All attempts to reproduce this reaction from *N*-substituted amidines **1** (R≠H) proved unsuccessful, as in this case, cyclization to the imidazole ring was a faster process, leading to compound **4**. The final product isolated, arises from the condensation of compound **4** with one or two equivalents of the carbonyl compound, leading to structure **5A** (if R^1, R^2≠H) or **5B** (if R^2=H) [1,2].

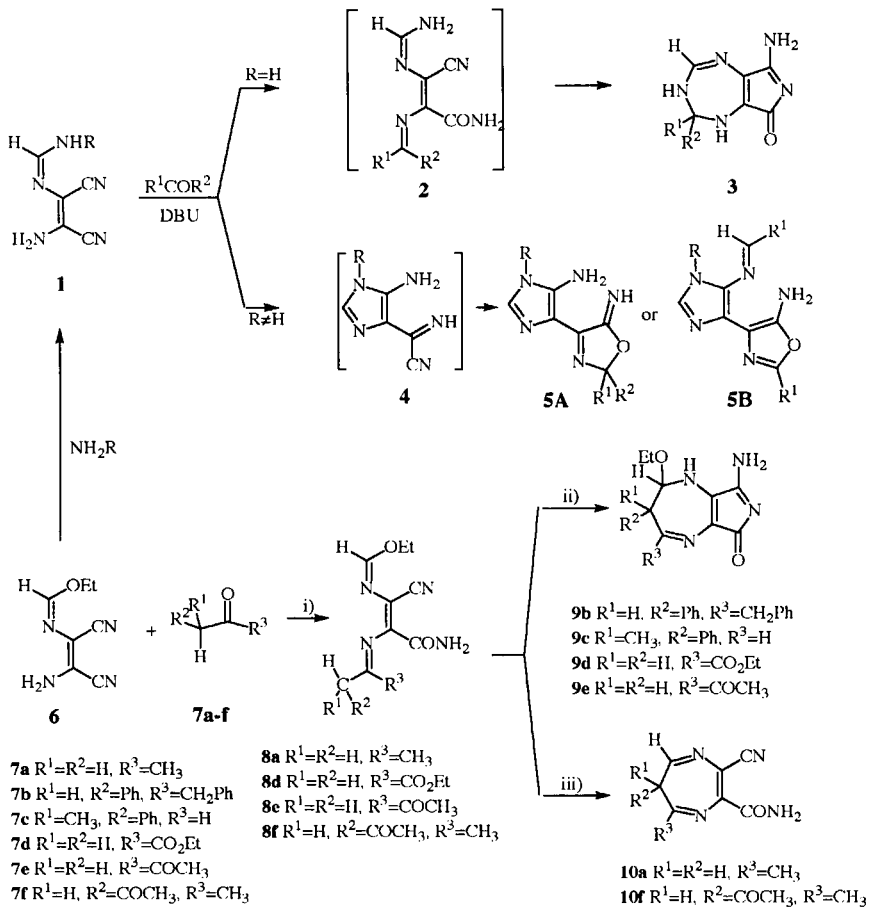
This prompted us to try a different approach to the synthesis of 3-substituted triazepines **3**. Imidate **6** [3], the precursor of amidines **1** [6], was used as the starting material in the reaction with carbonyl compounds **7**, in the presence of base. All the carbonyl compounds that were used had at least one hydrogen on the α-carbon. Dicarbonyl compounds (α- and β-dicarbonyl) were also included in this study.

In the reaction of imidate **6** with aldehydes or ketones **7b-e**, a mixture of ethanol and triethylamine was used as solvent. When the ketone was either acetone (**7a**) or acetylacetone (**7f**), a large excess of this reagent was used as solvent together with triethylamine for ketone **7a**. In every case, the product that is initially formed results from the condensation of the imidate with one equivalent of the aldehyde or ketone. The Schiff's base arises after intramolecular removal of water by the cyano group α to the amine function (Compounds **8a-f**). Compound **8** can only be isolated as a white or pale yellow solid if it precipitates out of solution. If this compound remains solubilized and in contact with a large excess of triethylamine, transformation occurs to give the bicyclic compound **9**. This was the case for compounds **9b** and **9c** for which the corresponding precursor could not be isolated.

The reaction of imidate **6** with ethyl pyruvate, **7d**, in triethylamine, enabled the isolation of compound **8d** when the reaction was carried out in an ice bath. When this reaction was repeated at room temperature, the orange solid that precipitates out of solution is a mixture of two compounds. The ^{1}H nmr spectrum indicates the presence of compounds **9d** and **11** in approximately 1:1 molar ratio (Scheme 2). When this mixture (**9d** and **11**) is kept stirring at room temperature, in contact with triethylamine/ethanol, a slow transformation to one of the compounds is detected by tlc, and compound **9d** is isolated in 91% yield. These observations indicate that, in triethylamine, the first mechanistic step in the formation of the fused heterocyclic structure **9** is the ring closure leading to the diazepine unit. The pyrrole ring is formed subsequently, after a prolonged contact with the non-nucleophilic base.

When a catalytic amount of sulphuric acid was added to a suspension of compound **9c** in ethanol, extensive darkening of the reaction mixture occurred even when the

Scheme 1

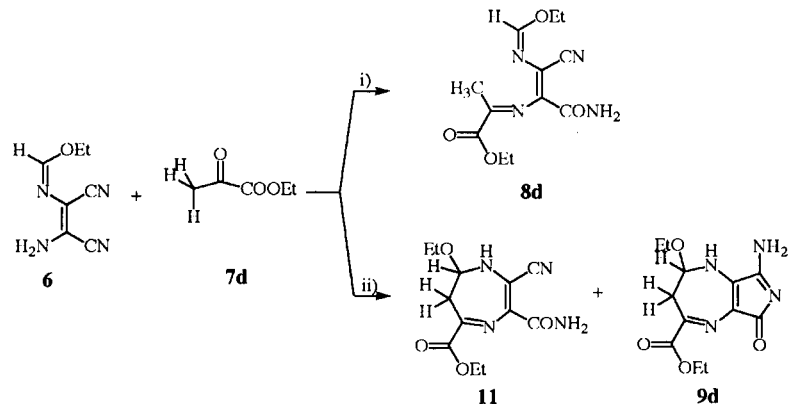


i) EtOH, NEt_3, 0 °C - rt, 25 min - 4 days; ii) EtOH, NEt_3, rt, 4 h - 2 days; iii) EtOH, $PhCO_2H$, rt, 3 h - 15 days.

reaction was carried out in an ice bath, indicating that, the elimination of ethanol is not an easy process.

When half an equivalent of benzoic acid was added separately to suspensions of **8a** and **8f** in ethanol, the diazepines **10a** and **10f** were isolated as white solids, after 2.5 hours and 15 days respectively, at room temperature. This result indicates that in the presence of acid catalyst, only the diazepine ring is formed, and in this case the

Scheme 2



i) EtOH, NEt_3, 0 °C, 75 min; ii) EtOH, NEt_3, rt, 10 min.

Table 1

Analytical and Spectroscopic data for the compounds prepared

Compound (Formula)	Mp/°C	Found (%) (Required) C	H	N	m/z
8a	147 (dec)	54.1	6.5	25.4	223 (100%, M+1$^+$)[a]
($C_{10}H_{14}N_4O_2$)		(54.1)	(6.3)	(25.2)	
8d	133.7-134.0	51.5	6.0	20.2	280 (44%, M$^+$)[c]
($C_{12}H_{16}N_4O_4$)	(dec)	(51.4)	(5.7)	(20.0)	151 (100%)
8e	132 (dec)	53.0	5.9	22.5	251 (100%, M+1$^+$)[a]
($C_{11}H_{14}N_4O_3$)		(52.8)	(5.6)	(22.4)	
8f	176 (dec)	54.3	6.0	21.2	265 (100%, M+1$^+$)[a]
($C_{12}H_{16}N_4O_3$)		(54.5)	(6.1)	(21.2)	
9b	159(dec)		374.1737		374 (25%, M$^+$)[c]
($C_{22}H_{22}N_4O_2$)			(374.1743)[b]		91 (100%)
9c	132(dec)	64.2	6.2	18.4	298 (100%, M$^+$)[c]
($C_{16}H_{18}N_4O_2$)		(64.4)	(6.0)	(18.8)	
9d	166 (dec)	51.5	6.0	20.1	280(20%, M$^+$)[c]
($C_{12}H_{16}N_4O_4$)		(51.4)	(5.7)	(20.0)	72 (100%)
9e	206.5-207.0	52.8	5.9	22.3	251(100%, M+1$^+$)[a]
($C_{11}H_{14}N_4O_3$)		(52.8)	(5.6)	(22.4)	
10a	161 (dec)		177.0775		177(100%, M+1$^+$)[a]
($C_8H_8N_4O$)			(177.07763)[b]		
10f	171 (dec)	55.2	4.5	25.5	219(100%, M+1$^+$)[a]
($C_{10}H_{10}N_4O_2$)		(55.0)	(4.6)	(25.7)	
12	192-193 (dec)	53.0	5.4	22.1	251 (100%, M+1$^+$)[a]
($C_{11}H_{14}N_4O_3$)		(52.8)	(5.6)	(22.4)	
13	150.0-150.3	53.0	6.6	18.9	297 (100%, M+1$^+$)[a]
($C_{13}H_{20}N_4O_4$)		(52.7)	(6.8)	(18.9)	
14	140 (dec)	53.9	6.5	25.0	223 (100%, M+1$^+$)[a]
($C_{10}H_{14}N_4O_2$)		(54.1)	(6.3)	(25.2)	
15	149.1-150.0		168.0883		168 (100%, M+1$^+$)[a)]
($C_6H_9N_5O$)			(168.0885) [b]		
16	158.8-159.3	42.9	5.5	41.9	167 (65%, M$^+$)[c]
($C_6H_9N_5O$)		(43.1)	(5.4)	(41.9)	123 (100%)
17	160.9-162.5	43.0	5.5	42.1	167 (89%, M$^+$)[c]
($C_6H_9N_5O$)		(43.1)	(5.4)	(41.9)	123 (100%)

[a] Fast Atom Bombardment; [b] High Resolution Mass Spectroscopy; [c] Electron Impact.

elimination of ethanol occurs easily leading to compounds of type **10**. In the presence of triethylamine, both cyclizations occur (the diazepine and pyrrole rings are formed) and ethanol is not eliminated from the product **9**.

The structure of compounds **8**, **9** and **10** were assigned on the basis of elemental analyses (Table 1) and spectroscopic data (Tables 2, 3 and 4). In the ir spectra of compounds of type **8** the stretching vibration corresponding to the cyano group is visible in the 2200-2210 cm^{-1} region as a medium intensity band. The amide carbonyl is an intense band in the 1680-1700 cm^{-1} region. In the dicarbonyl compounds, the other carbonyl group is always visible at higher wave numbers (above 1700 cm^{-1}) with the exception of **8f**, where the absence of a second C=O vibration suggests that the enol form must predominate in the solid state. This also seems to be the case in deuterated dimethylsulfoxide solution, as the ^{1}H nmr shows a singlet at δ 5.51 ppm which integrates for one proton and can be assigned to the C-H and another singlet at δ 12.61 ppm for the N-H/O-H proton. All these compounds show the imidate C-H around δ 8.2 ppm. The amide protons always appear as two singlets, each integrating for one proton, at δ 7.6-7.8 ppm and δ 7.2-7.4 ppm. In the ^{13}C nmr, the signals for C4 and C5 are typical of the open chain compound and are present respectively at δ 85-106 ppm and δ 140-144 ppm. All the pyrrolodiazepines **9** show ir spectra that confirm the absence of the cyano group. The intense band in the 1700-1715 cm^{-1} region can be assigned to the C=O stretching vibration of the 2-oxo substituent in the pyrrole ring. The ^{1}H nmr spectra of these compounds were determined in deuterated dimethylsulfoxide solution and show only one set of bands, with the exception of **9c**, where two sets of bands were always present. This duplication was assigned to the presence of two different tautomers in solution. When the same sample of **9c** was dissolved in deuterated chloroform, the ^{1}H nmr spectrum showed that a single compound was present. For compounds **9b** and **9c** (see Table 2 and 4), the proton on C2 (δ 5.12 ppm for **9b** and δ 5.29 ppm for **9c**) is coupled to the adjacent N-H (δ 8.55 ppm,

Table 2

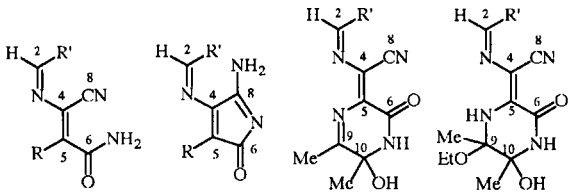
^{1}H NMR Spectroscopic Data for the Compounds Prepared.

Compound	δH (ppm) in DMSO-d_6
8a[a]	1.39 (3H, t, J = 7.2 Hz, Me), 1.92 (3H, s, Me), 2.26 (3H, s, Me), 4.22 (2H, q, J = 7.2 Hz, CH_2), 6.03 (1H, brs, NH), 6.43 (1H, brs, NH) 8.26 (1H, s, CH)
8d	1.20 (3H, t, J = 6.3 Hz, Me), 1.26 (3H, m, Me), 1.97, 2.35 (3H, 2 brs, Me), 4.22 (2H, m, CH_2), 7.36 (1H, brs, NH), 7.77 (1H, brs, NH), 8.13 (1H, brs, CH)
8e	1.19 (3H, t, J = 7.2 Hz, Me), 1.84 (3H, s, Me), 2.41 (3H, s, Me), 4.06 (2H, q, J = 7.2 Hz, CH_2), 7.42 (1H, s, NH), 7.80 (1H, s, NH), 8.16 (1H, s, CH)
8f	1.38 (3H, t, J = 7 Hz, Me), 2.15 (6H, s, 2xMe), 4.50 (2H, q, J = 7 Hz, CH_2), 5.51 (1H, s, CH), 8.24 (1H, s, NH), 8.62 (1H, s, NH), 8.18 (1H, s, CH), 12.61 (1H, s, NH)
9b	1.05 (3H, t, J = 7 Hz, Me), 3.40 (2H, s, $\underline{CH_2}$Ph), 3.45 (2H, m, OCH_2), 3.55 (1H, s, H_{3a}), 5.12 (1H, d, J = 4.8 Hz, H_2), 6.83 (2H, m, Ar), 7.08 (3H, m, Ar), 7.31 (5H, s, Ph), 8.25 (1H, brs, NH), 8.55 (1H, d, J = 4.8 Hz, NH), 10.0 (1H, brs, NH)
9c[b]	**A**: 1.08 (3H, t, J = 6.9 Hz, $OCH_2\underline{CH_3}$), 1.67 (3H, s, Me), 3.50 (2H, m, OCH_2), 5.29 (1H, d, J = 3.9 Hz, H_2), 7.00-7.20 (5H, m, Ar), 7.38 (1H, s, CH), 8.90 (1H, d, J = 4.5 Hz, NH), 9.31 (1H, brs, NH), 9.70 (1H, brs, NH) **B**: 1.07 (3H, t, J = 6.9 Hz, $OCH_2\underline{CH_3}$), 1.64 (3H, s, Me), 3.50 (2H, m, OCH_2), 5.22 (1H, d, J = 3.9 Hz, H_2), 7.00-7.20 (5H, m, Ar), 7.38 (1H, s, CH), 8.14 (1H, s, NH), 8.70 (1H, d, J = 4.5 Hz, NH), 8.97 (1H, s, NH)
9c[a]	1.17 (3H, t, J = 6.9 Hz, $OCH_2\underline{CH_3}$), 1.79 (3H, s, Me), 3.50 (1H, m, OCH_2), 3.70 (1H, m, OCH_2), 5.17 (1H, s, H_2), 7.02 (2H, m, Ar), 7.20 (2H, m, Ar), 7.30 (1H, m, Ar), 7.64 (1H, s, CH), 8.0-8.4 (>1H, brs, NH)
9d	0.95 (3H, m, Me), 1.25 (3H, t, J = 7 Hz, $OCH_2\underline{CH_3}$), 1.75 (1H, d, J = 13 Hz, H_{3a}), 3.40 (2H, m, OCH_2), 3.95 (1H, dd, J = 6.0 Hz and J = 13 Hz, H_{3b}), 4.20 (2H, q, J = 7 Hz, OCH_2), 5.27 (1H, d, J = 6 Hz, H_2), 8.39 (1H, brs, NH), 9.15 (1H, brs, NH), 9.35 (1H, brs, NH)
9e	0.93 (3H, t, J = 7.2 Hz, Me), 1.52, (1H, d, J = 12 Hz, H_{3a}), 2.45 (3H, s, COMe), 3.45 (2H, m, OCH_2), 4.00 (1H, dd, J = 12 Hz, J = 6 Hz, H_{3b}), 5.2 (1H, d, J = 6 Hz, Hc), 8.60 (1H, s, NH), 9.42 (1H, s, NH), 9.60 (1H, s, NH)
10a	1.64, (1H, brs, H_{3a}), 2.25 (3H, s, Me), 4.50 (1H, brs, H_{3b}), 6.91 (1H, t, J = 4.8 Hz, H_2), 7.78 (1H, brs, NH), 7.81 (1H, brs, NH)
10f	2.27 (3H, s, Me), 2.54 (3H, s, COMe), 6.74 (1H, s, H_3), 7.70 (1H, brs, NH), 7.85 (1H, brs, NH), 8.45 (1H, s, H_2)
12	1.30 (3H, t, J = 7.2 Hz, Me), 1.43, (3H, s, Me), 2.14 (3H, s, Me), 4.28 (2H, q, J = 7.2 Hz, CH_2), 6.56 (1H, s, OH), 8.04 (1H, s, CH)
13	1.00 (3H, t, J = 7.2 Hz, Me), 1.29, (3H, t, J = 7.2 Hz, Me), 1.32 (3H, s, Me), 1.44 (3H, s, Me), 3.36 (2H, m, CH_2), 4.33 (2H, m, CH_2), 5.98 (1H, s, NH), 6.63 (1H, s, NH), 7.99 (1H, s, CH), 8.78 (1H, s, NH)
14	1.40 (3H, t, J = 7.2 Hz, Me), 1.99, (3H, s, Me), 2.25 (3H, s, Me), 4.38 (2H, q, J = 7.2 Hz, CH_2), 8.05 (1H, s, CH), 8.61 (1H, brs, NH), 8.80-9.80 (1H, brs, NH)
15	2.76 (3H, s, Me), 5.10 (2H, s, NH_2), 7.19 (2H, brs, CH+NH), 8.07 (1H, s, NH), 9.10-9.80 (1H, brs, NH)
16	2.76 (3H, d, J = 4.2 Hz, Me), 5.49 (2H, brs, NH_2), 7.16 (1H, brs, NH), 7.50 (2H, brs, NH_2), 7.68 (1H, d, J = 3.3 Hz, CH)
17	3.46 (3H, s, Me), 6.78 (2H, brs, NH_2), 7.26 (1H, s, CH), 8.05 (1H, brs, CONH), 9.80 (1H, brs, CONH), 10.01 (1H, s, NH)

[a] $CDCl_3$ as solvent, [b] Mixture of two tautomers A and B in the ratio of 1:1.

Table 3

^{13}C nmr Spectroscopic Data for the Compounds

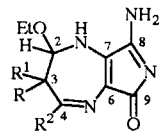


8, 16 **15** **12** **13**

Compound	δC (ppm) in DMSO-d_6 C2	C4	C5	C6	C8	R'	R
8a [a]	160.1	105.8	143.9	164.5	113.9	63.5; 13.9	174.4 (C=N); 27.8 (Me); 23.5 (Me)
8d	163.0	85.0	141.5	163.3 [b]	113.0	64.1; 13.9	163.5 (CO)[b]; 161.6 (C=N); 20.0 (Me); 62.6 (OCH_2); 14.0 (Me);
8e	160.4	104.3	143.8	168.0	113.7	63.4; 13.8	198.3 (CO); 161.5 (=C); 24.8 (Me); 16.2 (Me)
8f	157.5	100.0	140.0	164.4	114.1	63.5; 14.0	197.3 (CO); 102.7 (CH); 29.7 (Me); 19.0 (Me)
12	158.6	119.3	133.1	172.1	116.7	63.9; 14.3	162.4 (C9); 80.0 (C10); 26.9 (Me); 21.7 (Me)
13	156.5	93.8	138.3	158.8	115.5	63.4; 14.1	84.8 and 81.9 (C9 and C10); 55.8 (OCH_2); 22.5 (Me); 17.7 (Me); 15.6 (Me)
15	153.1	118.0 (br)	125.0 (br)	173.0 (br)	164.5 (br)	26.7 (Me)	-------
16	149.7	96.8	140.5	164.4	116.7	27.5 (Me)	-------
17	130.6	114.3	145.2	-------	-------	-------	161.8 (CO); 159.6 (C=NH); 29.8 (Me)

[a] $CDCl_3$ as solvent . [b] These bands may be assigned to C6 or CO.

Table 4
^{13}C nmr Spectroscopic Data for the Compounds



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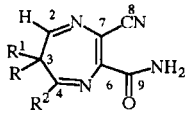

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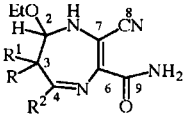

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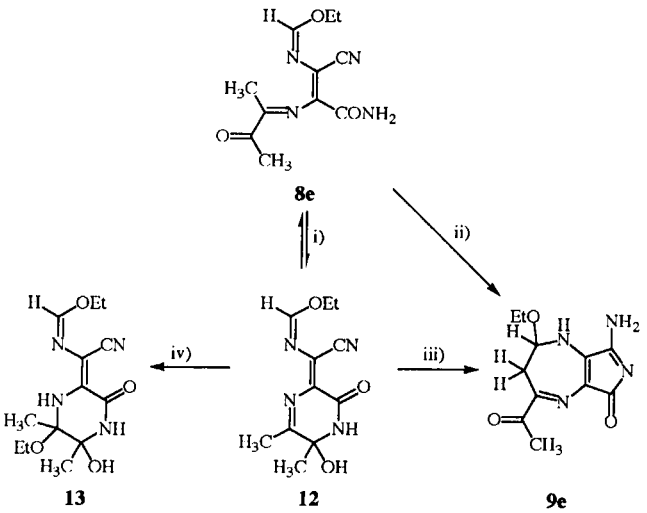
Compound	δC (ppm) in DMSO-d_6 C2	C3	C4	C6	C7	C8	C9	OEt	R, R^1, R^2
9b	86.7	44.1	165.2	130.4	115.4	168.1	170.6	60.9; 14.8	139.1 (C'); 137.7 (C'); 129.1 (CH);128.9 (CH); 127.5 (CH); 127.2 (CH); 125.6 (CH); 58.9 ($\underline{CH_2}$Ph);
9c	86.4; 66.3	57.3; 57.0	161.5 161.1	142.4; 142.1	115.9; 115.2	169.3; 154.1	170.3; 157.3	62.0; 61.9; 14.8(br)	137.5 (C'); 132.6 (C'); 128.4 (CH); 128.3 (CH); 126.5 (CH); 126.4 (CH); 125.8 (CH); 125.7 (CH); 29.3 (Me); 28.7 (Me)
9d	81.21; 81.1(w)	37.7; 37.5(w)	147.8	137.5	114.2	164.4	173.0	61.6 61.6(w) 14.7	163.6 (CO); 60.9 (OCH_2); 61.0 (OCH_2(w)); 14.2 (Me)
9e	80.7	34.1	153.6	139.0	114.3	174.7	175.8	61.8; 14.9	198.0 (CO); 24.4 (Me)
10a	144.3	45.0	151.6	140.8	116.8[a]	114.9[a]	164.1	-------	26.7 (Me)
10f	140.3	75.3	145.8	142.8	123.1	110.7	161.0	-------	197.5 (CO); 31.9 ($\underline{Me}$CO); 17.9 (Me)
11	83.7	37.7	150.8	122.6	116.3[a]	115.7[a]	165.9	61.5[b]; 14.7[b]	163.6 (CO); 61.3[b] (OCH_2); 14.0[b] (Me)

[a] These signals may be assigned to C7 or C8; [b] These signals may be assigned to OEt or R^2.

J = 4.8 Hz for **9b** and δ 8.90 ppm, J = 4.5 Hz for **9c**). No coupling is observed with the proton on C3 (δ 3.55 ppm for **9b**) suggesting a dihedral angle of about 90° between these two bonds. For compounds **9d** and **9e**, no coupling is observed between the proton on C2 (δ 5.27 ppm for **9d** and δ 5.20 ppm for **9e**) and the adjacent N-H (δ 8.39 ppm for **9d** and δ 8.60 ppm for **9e**). On the contrary, coupling is observed between the proton on C2 and one of the protons on C3 (δ 3.97 ppm, J = 6 Hz for **9d** and δ 4.00 ppm, J = 6 Hz for **9e**). The coupling constant indicates a dihedral angle of about 30° between these two bonds. For all these compounds, the protons of the NH_2 group on C8 appear as two broad singlets in the δ 9.35-10.00 ppm and δ 8.25-9.40 ppm regions. For the diazepines **10** it is possible to see the signal for the cyano stretching vibration in the ir spectrum, as a medium intensity band at ν 2226 cm^{-1} (**10a**) and 2240 cm^{-1} (**10f**). The amide carbonyl is an intense band at ν 1664 cm^{-1} (**10a**) and 1687 cm^{-1} (**10f**). In the ^1H nmr spectrum, the amide NH_2 protons are non-equivalent and are registered as two singlets in the δ 7.8-7.9 ppm and δ 7.7-7.8 ppm region. The imine C-H in compound **10a** (δ 6.91 ppm) is coupled with the adjacent protons, with a coupling constant of 4.8 Hz. The two protons on C3 show up in the spectrum as two broad bands (δ 4.50 and 1.67 ppm). Similar chemical shifts were reported for analogous diazepine structures [4]. For compound **10f**, the proton on C3 originates a singlet at δ 6.74 ppm, indicative of its high acidity. In the ^{13}C nmr spectrum it is possible to identify the signal for the cyano carbon atom (δ 114.9 ppm for **10a** and δ 110.7 ppm for **10f**). The difference observed in the ^{13}C chemical shift of C3 of δ 45.0 ppm for **10a** and δ 75.3 ppm for **10f** is evidence for the electron-withdrawing effect of the $COCH_3$ substituent in **10f**, and this is reflected in the low field shift of the proton on C3 to δ 6.74 ppm.

The reaction of imidate **6** with diacetyl (**7e**) which led to the isolation of compound **8e** in 52% yield after 25

Scheme 3

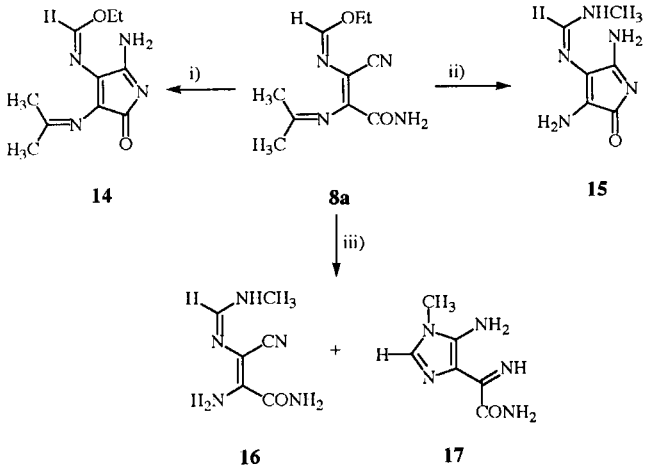


i) EtOH, NEt_3, rt, 4 h; ii) EtOH, NEt_3, rt, 48 h; iii) EtOH, NEt_3, rt, 26 h; iv) EtOH, $PhNH_3^+ Cl^-$ cat., rt, 2.5 h.

minutes at 5 °C, gave also a small amount of another compound, isolated from the mother liquor and identified as structure **12** (8%). This observation prompted us to study this reaction in more detail (Scheme 3). When a suspension of imidate **8e** in ethanol and triethylamine was stirred at room temperature, the white solid that was isolated after 4 hours had structure **12** (79%). If the previous reaction mixture is allowed to stir at room temperature for a total of 48 hours, the white solid of **12** goes into solution, which gradually turns orange and **9e** (61%) can be isolated. This suggests that there is an equilibrium between **8e** and **12** (the kinetic product) that leads to the thermodynamically more stable compund **9e**. A suspension of **12** in ethanol in the presence of a catalytic amount of anilinium chloride, generates **13**, isolated in 49% yield.

The structures of compounds **12** and **13** were confirmed by elemental analysis and spectroscopic data. They both show ir spectra with several bands in the N-H/O-H region (ν 3400-3100 cm^{-1}). The cyano group stretching vibration is a medium/intense band at ν 2204 (**12**) and 2200 cm^{-1} (**13**). The C=O stretching vibration gives an intense band at 1686 cm^{-1} in both compounds. A significant difference is detected in the ^1H nmr spectra for the signals of the two methyl groups. For compound **12** these two singlets appear at δ 1.43 and 2.14 ppm, the latter indicative of a CH_3 bonded to an sp^2 carbon atom. For compound **13** the two singlets are at δ 1.44 and 1.32 ppm indicating that both are bound to sp^3 carbon atoms. The signal corresponding to the C-H of the imidate group is a singlet, for both compounds, at δ 8.0 ppm. The ^{13}C nmr spectra confirms the presence of two sp^3 carbon atoms in compound **13** (δ 84.8 and 81.9 ppm) while the corresponding carbon signals for structure **12** were identified at δ 162.4 and 80.0 ppm. All the other signals show no major differences, with the exception of the carbonyl groups (at δ 172.1 ppm for **12** and δ 158.8 ppm for **13**).

Scheme 4



i) EtOH, $CHCl_3$, 1:1,1,8-diazabicyclo[5.4.0]undec-7-ene, 5 °C, 1 h; ii) 1. $CHCl_3$, 1,8-diazabicyclo[5.4.0]undec-7-ene, rt, 3 h; 2. NH_2CH_3, 5°C, 15 min; iii) $CHCl_3$, NH_2CH_3, 5°C, 75 min.

Compound **8a** was used as the starting material in order to investigate the possibility of preparing 3-*N*-substituted pyrrolo[1,3,5]triazepines **3**. When a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene was added to a suspension of **8a** in ethanol and chloroform, at 5 °C, compound **14** was isolated in 23% yield and extensive darkening was noted in the mother liquor, preventing the isolation of other products. Similar extensive decomposition was observed when compound **14** was solubilized in deuterated dimethylsulfoxide, which prevented its characterisation by ^{13}C nmr . Its empirical formula was determined by elemental analysis and mass spectrometry.

Considering that 1,8-diazabicyclo[5.4.0]undec-7-ene was simply leading to the formation of the pyrrole ring, the previous reaction was repeated in chloroform, at room temperature. When the starting material **8a** was no longer present in solution (evidence by tlc), methylamine was bubbled for 15 minutes through the solution, cooled in an ice bath. The product isolated proved to be compound **15** (76%), where the imidate had been replaced by the amidine function, as expected, but the imine had been cleaved by methylamine, a reasonably strong nucleophile.

Considering that methylamine can equally behave as a base, a suspension of **8a** in chloroform, kept in an ice bath, was simply combined with methylamine, which was bubbled through the solution for 35 minutes. A dark reaction mixture was obtained, from which the amidine **16** (31%) and the imidazole **17** (17%) were isolated. Imidazole **17** is the result of intramolecular cyclization of **16**, which is known to occur in the presence of base [6].

EXPERIMENTAL

^1H Nmr spectra were recorded on Varian Unity Plus 300 (300 MHz) or Bruker XL300 (300 MHz) instruments, ^{13}C nmr spectra (with DEPT 135) on a Bruker WP80 or XL 300 instrument, and ir spectra on a Perkin Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on a Kratos Concept instrument. Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

Reactions of Ethyl (Z)-*N*-(2-Amino-1,2-dicyanovinyl)-formimidate **6** .

With **7a**.

A suspension of imidate **6** (0.93 g, 5.7 mmole) in acetone (1.5 ml) and triethylamine (1 ml) was stirred efficiently at room temperature. After 26 hours, the tlc showed no evidence for the presence of the starting material and the white solid suspension was filtered and washed with cold acetone and diethyl ether. The product was identified as compound **8a** (0.73 g, 3.3 mmoles, 58%) by elemental analysis and spectroscopic data (Tables 1, 2 and 3).

With **7b**.

1,3-Diphenyl acetone (0.66 g, 3.15 mmoles) was added to a solution of imidate **6** (0.52 g, 3.15 mmoles) in ethanol (3 ml)

and triethylamine (2 ml). The brown solution was stirred at room temperature for 4 days. The yellow suspension was concentrated in the rotary evaporator and the solid was filtered and washed with ethanol and diethyl ether. The product was identified as compound **9b** (0.48 g, 1.27 mmoles, 40%) (Tables 1, 2 and 4).

With **7c**.

The aldehyde **7c** (0.88 g, 0.87 ml, 6.60 mmoles) was added to a solution of imidate **6** (0.54 g, 3.28 mmoles) in ethanol (2 ml) and triethylamine (2 ml). A yellow-orange solution was obtained after a slightly exothermic reaction and the mixture was stirred at room temperature. After 30 minutes, a thick yellow suspension formed and more ethanol (2 ml) was added. After a total of 75 minutes, the tlc indicated the absence of the starting material and the yellow solid was filtered and washed with ethanol, acetonitrile and diethyl ether. The product was identified as compound **9c** (0.57 g, 1.29 mmole, 59%) (Tables 1, 2 and 4)

With **7d**.

Method A: Ethyl pyruvate (0.43 g, 0.43 ml, 3.7 mmoles) was added to a suspension of imidate **6** (0.61 g, 3.7 mmoles) in ethanol (2 ml) and triethylamine (2 ml), kept stirring in an ice bath. A dark yellow solution was obtained immediately and a green solid precipitated out. After 75 minutes, tlc indicated the absence of the starting material, and the solid was filtered and washed with ethanol and diethyl ether. The product was identified as compound **8d** (0.83 g, 2.97 mmoles, 80%) (Tables 1, 2 and 3). The mother liquor was left at room temperature and after 14 days the orange suspension was filtered and washed with ethanol and diethyl ether giving **9d** (0.05 g, 0.14 mmole, 4%) (Tables 1, 2 and 4).

Method B: Ethyl pyruvate (0.36 ml, 0.38 g, 3.28 mmoles) was added to a solution of imidate **6** (0.54 g, 3.28 mmoles) in ethanol (2 ml) and triethylamine (2 ml), at room temperature. A yellow solution was obtained after a slightly exothermic reaction. Cooling in an ice bath led to an orange solid that was filtered and washed with ethanol and diethyl ether. The solid was identified as a mixture of **9d** and **11** in an approximately 1:1 molar ratio, as evidenced by ^{1}H nmr (0.60 g, 2.14 mmole, 65%). Part of the previous mixture (0.09 g, 0.33 mmole) was stirred at room temperature, as a suspension in ethanol (1 ml) and triethylamine (1 ml). After 3 days, the tlc indicated the presence of a single product, which was filtered and washed with diethyl ether. The product was identified as compound **9d** (0.08 g, 0.30 mmole, 91%).

With **7e**.

Diacetyl (0.15 ml, 1.69 mmoles) was added to a suspension of imidate **6** (0.28 g, 1.69 mmoles) in ethanol (0.5 ml) and triethylamine (1 ml). The yellow homogeneous solution was stirred at 5 °C for 25 minutes, when the tlc indicated the absence of any starting material. The yellow solid suspension was filtered and washed with a 1:1 mixture of ethanol and diethyl ether. The product was identified as having structure **8e** (0.22 g, 0.88 mmole, 52%) by elemental analysis and spectroscopic data. A off-white solid was isolated from the mother liquor and was identified as compound **12** (0.03 g, 0.13 mmole, 8%) (Tables 1, 2 and 3).

With **7f**.

A suspension of imidate **6** (1.99 g, 10.27 mmoles) in acetylacetone (5 ml) was stirred at room temperature. After two days, a cream solid started to precipitate from the yellow reaction mixture. The reaction was completed after a total of 4 days. Ethanol was added to the thick reaction mixture and the cream solid was filtered and washed with cold diethyl ether. The product was identified as compound **8f** (1.59 g, 6.02 mmoles, 59%) (Tables 1, 2 and 3).

The Cyclization of **8a** in the Presence of Benzoic Acid.

Benzoic acid (0.08 g, 0.65 mmole) was added to a suspension of imidate **8a** (0.29 g, 1.29 mmoles) in ethanol (2 ml). The suspension was stirred at room temperature and the reaction was completed after 2.5 hours (evidence by tlc). The white solid suspension was filtered, washed with ethanol and diethyl ether, and identified as the diazepine **10a** (0.06 g, 0.35 mmole, 27%) (Tables 1, 2 and 4).

The Cyclization of **8f** in the Presence of Benzoic Acid.

Benzoic acid (0.03 g, 0.21 mmole) was added to a suspension of imidate **8f** (0.11 g, 0.42 mmole) in ethanol (3 ml). The suspension was stirred at room temperature for 15 days, during which time the yellow suspension became cream. The mixture was concentrated in the rotary evaporator and addition of diethyl ether led to a cream solid that was filtered and washed with diethyl ether. The product was identified as the diazepine **10f** (0.05 g, 0.22 mmole, 52%) (Tables 1, 2 and 4).

The Reaction of **8e** with Triethylamine.

Method A: A suspension of compound **8e** (0.40 g, 1.60 mmoles) in ethanol (2.5 ml) and triethylamine (5 ml) was stirred at room temperature for 4 hours. The reaction was completed (evidence by tlc) and the white solid was filtered and washed with cold ethanol and diethyl ether. The product was identified as compound **12** (0.32 g, 1.26 mmoles, 79%) (Tables 1, 2 and 3).

Method B: A suspension of compound **8e** (0.51 g, 2.06 mmoles) in ethanol (2.5 ml) and triethylamine (5 ml), was stirred at room temperature. After 4 hours, a white solid had been formed, and the reaction mixture was kept stirring at room temperature for a further 44 hours. During this time, the solid was gradually solubilized, leading to an orange solution, followed by the formation of an orange solid. The solid was filtered and washed with ethanol and diethyl ether leading to **9e** (0.31 g, 1.25 mmoles, 61%) (Tables 1, 2 and 4).

The Reaction of **12** with Triethylamine.

A suspension of compound **12** (0.17 g, 0.67 mmole) in ethanol (1 ml) and triethylamine (1 ml) was stirred at room temperature to give, after 26 hours, an orange suspension. This was filtered and washed with diethyl ether. The product was identified as **9e** (0.05 g, 0.18 mmole, 27%) by comparison of its ir spectrum with that of a previously identified sample.

The Reaction of **12** with Ethanol.

A catalytic amount of anilinium chloride was added to a suspension of compound **12** (0.16 g, 0.66 mmole) in ethanol (2.5 ml). The mixture was stirred at room temperature, and the reaction was completed after 2.5 hours at room temperature (evidenced by tlc). The cream solid was filtered and washed with ethanol and diethyl ether. The product was identified as **13** (0.09 , 0.32 mmole, 49%) (Tables 1, 2 and 3).

The Reaction of **8a** with 1,8-Diazabicyclo[5.4.0]undec-7-ene.

1,8-Diazabicyclo[5.4.0]undec-7-ene (10 µl, 0.07 mmole) was added to a suspension of compound **8a** (0.31 g, 1.40 mmoles) in

a 1:1 mixture of chloroform and ethanol (4 ml). The reaction mixture was stirred at 5 °C and after 1 hour a brownish color had developed and tlc indicated the absence of starting material. The solution was concentrated on the rotary evaporator and addition of cold ethanol and diethyl ether led to a yellow solid that was filtered and washed with cold diethyl ether. The product was identified as having structure **14** (0.07 g, 0.32 mmole, 23%) (Tables 1 and 2).

The Reaction of **8a** with 1,8-Diazabicyclo[5.4.0]undec-7-ene and Methylamine.

1,8-Diazabicyclo[5.4.0]undec-7-ene (15 µl, 0.09 mmole) was added to a suspension of compound **8a** (0.36 g, 1.64 mmoles) in chloroform (3 ml). The suspension was stirred at room temperature leading to a yellow and then a geenish solution after 3 hours. All the starting material had been consumed (evidence by tlc) and the flask was equipped with a serum cap and cooled in an ice bath followed by bubbling methylamine, with a syringe needle, for 15 minutes. A yellow solid precipitated from the orange solution and the suspension was concentrated in the rotary evaporator. Addition of chloroform to the residue led to a yellow solid that was filtered and washed with chloroform and diethyl ether. The product was identified as having structure **15** (0.21 g, 1.25 mmoles, 76%) (Tables 1, 2 and 3).

The Reaction of **8a** with Methylamine.

A suspension of compound **8a** (0.26 g, 1.18 mmoles) in chloroform (3 ml) kept in a flask equipped with a serum cap, was stirred efficiently in an ice bath. Methylamine was bubbled, with a syringe needle, through the suspension for 35 minutes. A brownish homogeneous solution was obtained and tlc indicated the absence of the starting material after another 40 minutes. The solution was concentrated in the rotary evaporator. Addition of ethanol and chloroform to the dark residue led to a white solid which was filtered and washed with chloroform. The product was identified as having structure **16** (0.06 g, 0.37 mmole, 31%) (Tables 1, 2 and 3). A different product was isolated from the mother liquor, by addition of acetone. The product was identified as compound **17** (0.03 g, 0.37 mmole, 17%) (Tables 1, 2 and 3).

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