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A CONVENIENT AND IMPROVED PROCEDURE FOR THE CYANATION OF ENAMINES AND 1,3-DICARBONYL COMPOUNDS

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Abstract: The direct cyanation of enamines **2a-f** using acylsubstituted cyanatobenzenes **1a-c** and cyanatoanthraquinone **1d** furnishes β-cyanoenamines **3a-f** which upon hydrolysis afford the cyanoketones **4a,b**. 2-Cyano-1,3-diketones **6a-c** are obtained starting from compounds **5a-c** and **1**.

The electrophilic cyanation of enamines and enolates succeeds with various reagents, e.g. with cyanogen halides[1-4], aryl cyanates[5-7], p-toluenesulfonyl cyanide[8], chlorosulfonyl isocyanate[9,10], Viehe's reagent[11], triphenylphosphine/thiocyanogen[12,13], or cyanogen bromide/dimethylaminopyridine.[14]

Thus, the pyrrolidine, piperidine and morpholine enamines of cyclic ketones have been reacted with cyanogen halides to give the corresponding α-cyanoketones on hydrolysis.[1-3] Metallated dimethylhydrazones have been cyanated with BrCN leading to α-cyano dimethylhydrazones.[4] In some cases aryl cyanates have been used for introducing the cyano group into enamines and related compounds.[5-7] Phenyl cyanate and tosyl cyanide

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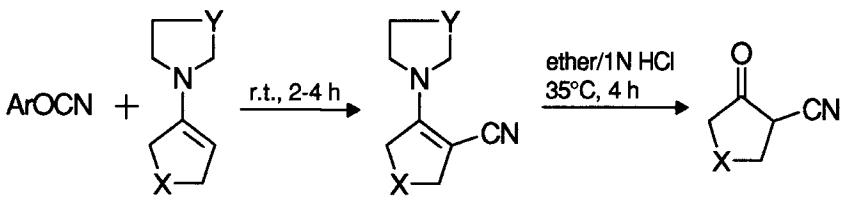
react with the anion generated by treatment of 1-(N,N-dimethylsulphamoyl)-imidazoles with butyllithium to give the corresponding 2-cyano-imidazoles.[7] 2-Cyanoimidazoles have also been prepared using cyanogen bromide/dimethylaminopyridine.[14] Kinetic cyanation of ketone enolates with tosyl cyanide provides efficient routes to β-ketonitriles.[8] The cyanation of indoles and pyrroles succeeds with a combined reagent of triphenylphosphine and thiocyanogen.[12,13] Finally, the electrophilic addition of chlorosulfonyl isocyanate to ketones or indoles affords the corresponding nitriles.[9,10] 3-Cyanoindoles have also been prepared using Viehe's reagent.[11]

Despite the usefulness of the reagents mentioned above there are several factors limiting their general application, for example toxical or irritiating activities, difficult accessibility, thermal instability, or small yields in some cases.[12,14] Recently we were able to show that the regioselective cyanation of aromatics succeeds with activated arylcyanates using $AlCl_3$/HCl.[15] We report here the cyanation of enamines **2** and ketones **5** with acylsubstituted cyanatobenzenes or cyanatoanthraquinones **1**.



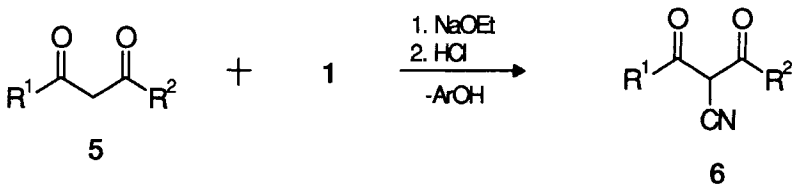
1a-g 2a-f 3a-f 4

2,3	X	Y
a	$-CH_2-$	$-CH_2-$
b	$-CH_2-CH_2-$	$-CH_2-$
c	$-CH_2-$	$-CH_2-CH_2-$
d	$-CH_2-CH_2-$	$-CH_2-CH_2-$
e	$-CH_2-$	$-O-CH_2-$
f	$-CH_2-CH_2-$	$-O-CH_2-$

a: X= CH_2
b: X= CH_2-CH_2

Good to excellent yields of isolated cyanoenamines **3a-f** are obtained by treating the enamines **2a-f** with **1a-d** at room temperature for 2-4 h (Tables 1, 2). 2-Cyanopyrrole is obtained by reaction of pyrrole with **1a** at -70°C in the presence of $AlCl_3$ as catalyst. Compounds **3** may be transformed with hydrochloric acid into cyanoketones **4a,b** in yields up to 72 %. Furthermore, 2-cyano-1,3-diketones **6a-c** are prepared when the sodium salts of compounds **5** are reacted with substituted cyanatobenzenes **1** under ice cooling.

Comparative studies of the cyanation of 2-(4-morpholinyl)-1-cyclopentene (**2e**) followed by hydrolysis with HCl leading to **4a** show that yields are best with **1a-d**. Using **1d** as cyanating agent, easy separation and high yields make this procedure attractive for preparation of cyanoenamines of the type **3**. The cyanation of **2e** with 4-nitrophenylcyanate **1f** succeeds only with 55 % yield. As shown in Table 1, the dicyanates **1c,d** are able to transfer both of the cyano groups.

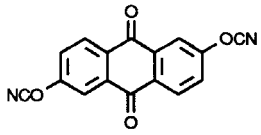


5, 6	R^1	R^2
a	CH_3	CH_3
b	C_6H_5	CH_3
c	C_6H_5	C_6H_5

Experimental

Melting points were determined on a BOËTIUS apparatus. The ^{1}H-NMR spectra were obtained on a WP-200 SY instrument (Bruker) at 200 MHz (TMS). The ^{13}C-NMR spectra were recorded on a Varian GEMINI 300

Table 1: Comparative Cyanation of Morpholino-cyclopentene-(1) (**2e**) with various Arylcyanates **1**

No	Aryl Cyanate	Sol-vent	molar ratio enamine : ArOCN	yield of **3a**[a] (%)	yield of **4a**[a] (%)
1a	4-MeCO-C_6H_4-OCN	Et_2O	1 : 1	89[b]	52
1b	4-PhCO-C_6H_4-OCN	THF	1 : 1	88	49
1c	(4-NCO-C_6H_4)$_2$CO	THF	2 : 1	78	35
1d		THF	2 : 1	82	57
1e	C_6H_5-OCN	Et_2O	1 : 1	68[b]	15
1f	4-O_2N-C_6H_4-OCN	Et_2O	1 : 1	55[b]	24
1g	4-NCO-C_6H_4-OCN	Et_2O	1 : 1	73[b]	22

[a] Isolated yields referred to starting compound **2e**.
[b] Determined by ^{1}H-NMR.

spectrometer at 75 MHz (internal standard: HMDS, δ = 1.9). Mass spectra were obtained on a Hewlett-Packard 5985-B spectrometer at 70 eV: m/e (rel. intensity). IR spectra were measured on a Specord 75 (Carl Zeiss Jena). The aryl cyanates **1** were prepared according to known procedures (cf. ref.[15] and literature cited herein).

Cyanoenamines - (General Procedure): A solution of the appropriate arylcyanate (0.05 mol) in diethyl ether or THF (20 to 50 ml) is added under stirring at room temperature to a solution of the enamine **2** (0.05 mol) in 20 ml of diethyl ether. In the cases of **1b**, **1c**, and **1d** THF is used as solvent

Table 2: Cyanoenamines **3** and Cyanoketones **6** Prepared

Aryl Cyanate	Enamine or 1,3-diketone	Cyanated Product	Yield (%)	b.p./Pa[a] or m.p.
1a	**2a**	**3a**	91	120/50-60
1d	**2b**	**3b**	81	90-120/40-50
1d	**2c**	**3c**	80	90-110/10-20
1d	**2d**	**3d**	82	80-110/5
1a	**2e**	**3e**	89	90-110/40-50
1a	**2f**	**3f**	86	90-110/30[b]
1a	**5a**	**6a**	62	51-53[c]
1e	**5a**	**6a**	28[d]	
1g	**5b**	**6b**	59	74-77
1a	**5c**	**6c**	88	158-159

[a] Kugelrohr distillation: bath temperature.
[b] Reported b.p.110-118°C/0.05 Torr (ref.[6]).
[c] Reported m.p. 53-54°C (ref.[5]).
[d] Reported yield 23 % (ref.[5]).

and the enamines are added to aryl cyanates (cf. also Table 1). Stirring is continued for 2 h, the solvent is evaporated, and the resulting oil is distilled using a Kugelrohr apparatus.

2-Pyrrolidino-1-cyclopentene-1-carbonitrile (**3a**): m.p.: 69-72°C. - ^{13}C-NMR (DMSO): δ = 160.04, 122.77(CN), 67.53, 49.33, 34.80, 33.08, 25.45, 22.13. - ^{1}H-NMR (DMSO): δ = 3.4 (m, 4H, CH_2), 2.5 (m, 4H, CH_2), 1.8 (m, 6H, CH_2). - MS: 162 (55) [M^+], 161 (100), 147 (13), 133 (21), 119 (43), 107 (18), 92 (29), 79 (32), 65 (61). - IR (KBr): ν = 2150, 1590 cm^{-1}. Anal. calcd. for $C_{10}H_{14}N_2$ (162.25): C, 74.03; H, 8.70; N, 17.27. Found: C, 74.04; H, 8.88; N, 17.26.

2-Pyrrolidino-1-cyclohexene-1-carbonitrile (**3b**): ^{13}C-NMR ($CDCl_3$): δ = 155.19, 125.00 (CN), 69.68, 49.44, 29.16, 28.56, 25.40, 22.48, 22.38. - ^{1}H-NMR ($CDCl_3$): δ = 3.5 (m, 4H, CH_2), 2.2 (m, 4H, CH_2), 1.8 (m, 4H, CH_2), 1.4-1.6 (m, 4H, CH_2).

2-Piperidino-1-cyclopentene-1-carbonitrile (**3c**): ^{13}C-NMR ($CDCl_3$): δ = 160.61, 121.32(CN), 68.95, 48.87, 33.77, 32.93, 25.27, 23.60, 21.01. - ^{1}H-NMR ($CDCl_3$): δ = 3.4 (m, 4H, CH_2), 2.4-2.6 (m, 4H, CH_2), 1.7-1.9 (m, 2H, CH_2) 1.5 (m, 6H, CH_2). - IR (neat): ν = 2170, 1590 cm^{-1}.

2-Piperidino-1-cyclohexene-1-carbonitrile (**3d**): ^{13}C-NMR ($CDCl_3$): δ = 158.81, 122.95 (CN), 77.38, 49.64, 28.19, 27.76, 26.07, 24.16, 22.22, 21.90. - ^{1}H-NMR ($CDCl_3$): δ = 3.3 (m, 4H, CH_2), 2.0-2.2 (m, 4H, CH_2), 1.5 (m, 10H, CH_2). - IR (neat): ν = 2170, 1580 cm^{-1}.

2-(4-Morpholinyl)-1-cyclopentene-1-carbonitrile (**3e**): ^{1}H-NMR (DMSO): δ = 3.6 (m, 4H, OCH_2), 3.4 (m, 4H, NCH_2), 2.4-2.6 (m, 4H, CH_2), 1.8 (m, 2H, CH_2). - MS: 178 (100) [M^+], 177 (78). - IR (neat): ν = 2170, 1670, 1590 cm^{-1}.

2-(4-Morpholinyl)-1-cyclohexene-1-carbonitrile (**3f**): ^{1}H-NMR (DMSO): δ = 3.6 (m, 4H, OCH_2), 3.3 (m, 4H, NCH_2), 2.1-2.3 (m,4 H, CH_2), 1.5-1.7 (m, 4H, CH_2).

Cyanoketones from Cyanoenamines - (General Procedure): A mixture of the appropriate cyanoenamine in diethyl ether (50 ml) and hydrochloric acid (1N, 60 ml) is stirred at 35-40°C for 4 h. The organic layer is separated and washed with a little water. Then the aqueous phase is rendered to pH 6 and several times extracted with diethyl ether. The combined ether phase is dried over Na_2SO_4 and fractionally distilled.

4a (prepared from **3e**): yield: 72 %, b.p.: 80°C/40-50 Pa (ref.[5] b.p.: 135-137°C/13 Torr).

4b (prepared from **3d**): yield: 66 %, b.p.: 95-105°C/100 Pa (ref.[5] b.p.: 130-135°C/13 Torr).

2-Cyanopyrrole: $AlCl_3$ (0.1 mol) is suspended in 50 ml of $CHCl_3$. To this suspension a solution of pyrrole (0.1 mol) in $CHCl_3$ (25 ml) is added at

-70°C. Then 0.1 mol of 4-cyanatoacetophenone in $CHCl_3$ (50-100 ml) is added dropwise to the stirred suspension. After stirring at 0°C for 6 h, a stream of dry NH_3 is passed through to render the mixture basic. The precipitate is collected by suction and washed thoroughly with $CHCl_3$. The combined filtrate is washed several times with brine, dried over Na_2SO_4, and distilled. Yield: 50 %, b.p. 115-120°C/1.7kPa. ^{13}C-NMR ($CDCl_3$): δ = 124.10, 120.26, 115.02 (CN), 109.91, 100.29. - IR (neat): ν_{CN}= 2215 cm^{-1}.

2-Cyano-1,3-diketones - (General Procedure): 0.05 mol of the diketone in diethyl ether (40 ml) are added under stirring and ice cooling to a solution of 0.05 mol sodium in absolute ethanol (20 ml). To this solution 0.05 mol of the appropriate aryl cyanate in THF (50 ml) are added dropwise and stirred for 1 h. Then the ice cooling is removed and stirring continued for 5 h at room temperature. After standing overnight, the ether phase is reduced by evaporation, 150 ml of diethyl ether is added under stirring, the sodium salt obtained is isolated, and poured into ice / 2N HCl. Then the precipitate is isolated by suction and recrystallized.

3-Cyano-2,4-pentanedione (**6a**): m.p.: 51-53°C (from heptane; ref.[5] m.p.: 53-54°C). - ^{13}C-NMR ($CDCl_3$): δ = 197.05, 116.46 (CN), 90.81, 24.55 . - ^{1}H-NMR ($CDCl_3$): δ = 16.8 (s, 1H, O-H···O), 2.3 (s, 6H, CH_3). - MS: 125 (100) [M^+], 83 (45). - IR (KBr): ν_{CN} = 2215 cm^{-1}.

2-Cyano-1-phenyl-1,3-butanedione (**6b**): m.p.: 74-77°C (from diethyl ether). - ^{13}C-NMR ($CDCl_3$): δ = 200.23, 189.91, 133.72, 133.01, 128.68, 117.63 (CN), 88.08, 25.58. - 1H-NMR ($CDCl_3$): δ = 17.6 (s, 1H, O-H···O), 7.9-8.0 (m, 2H, arom. H), 7.4-7.6 (m, 3H, arom. H), 2.5 (s, 3H, CH_3). - MS: 187 (95) [M^+], 186 (93), 105 (100), 77 (35). - IR (KBr): ν_{CN} = 2200 cm^{-1}. Anal. calcd. for $C_{11}H_9NO_2$ (187.21): C, 70.58; H, 4.85; N, 7.48. Found: C, 70.76; H, 4.89; N, 7.39.

2-Cyano-1,3-diphenyl-1,3-propanedione (**6c**): m.p.: 158-159°C (from ethyl acetate). - ^{13}C-NMR (DMSO): δ = 191.50, 134.14, 133.28, 128.62, 128.50, 118.23 (CN), 87.30. - ^{1}H-NMR ($CDCl_3$): δ = 18.2 (s, 1H, O-H···O), 8.0 (m,

4H, arom. H), 7.5 (m, 6H, arom. H). - MS: 249 (85) [M^+], 248 (69), 105 (100), 77 (59). - IR (KBr): ν_{CN} = 2200 cm^{-1}. Anal. calcd. for $C_{16}H_{11}NO_2$ (249.28): C, 77.10; H, 4.45; N, 5.62. Found: C, 77.18; H, 4.44; N, 5.53.

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