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Synthesis of α,β-Unsaturated and Other Reactive Acyl Cyanides[1)]

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Synthesen von α,β-ungesättigten und anderen reaktiven Acylcyaniden[1)]

Reaktive aliphatische Acylcyanide (**1** – **10**, siehe Tab. 1) werden aus Acylchloriden, Natriumiodid und Kupfer(I)-cyanid unter verschiedenen Bedingungen dargestellt. Die Reaktion verläuft über die Acyliodide.

Among the large class of acyl cyanides α,β-unsaturated acyl cyanides have probably been studied least, and only a few representatives have been reported in the literature[2)]. As it has turned out in our work, they also rank among the most reactive, and from the point of view of synthesis, the most interesting acyl cyanides. We here describe a number of sensitive acyl cyanides which have been obtained from preformed acyl iodides or acyl iodides generated *in situ*, and copper(I) cyanide.

Results

Acyl iodides were prepared from acyl chlorides and sodium iodide in acetonitrile and were isolated in our low-temperature reactor-extractor:

$$RCOCl + NaI \xrightarrow{MeCN} RCOI + NaCl\ ^{3)}$$

The pure acyl iodides were converted into acyl cyanides by reaction with CuCN. We have used dichloromethane (method A1) or acetonitrile (method A2) as a solvent for this transformation:

$$RCOI + CuCN \xrightarrow[MeCN]{CH_2Cl_2\ or} RCOCN + CuI$$

Although the reaction proceeds more slowly in dichloromethane than in acetonitrile, dichloromethane can be removed more readily. Methods B1 and B2 refer to one-pot procedures, with solvent acetonitrile. If the boiling point of acetonitrile (81.6°C) lies well below that of the product, work up is fairly simple because acetonitrile can be evaporated (method B1). If, however, the boiling point of the product is close to that of acetonitrile, distillative work up is more lengthy (method B2), also due to formation of azeotropes, and either losses of product are inevitable or the product is incompletely purified.

In their recent review *Hünig* and *Schaller* indicate very high yields, in fact often quantitative, for the preparation of acyl cyanides from acyl chlorides and cyanotrimethylsilane[2a)]. There is little doubt that the *Hünig*-[2a)] *Simchen*[4)] procedure (method D) for preparing acyl cyanides is

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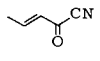
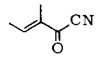
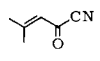
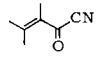
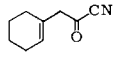
Table 1. Preparation of Acyl Cyanides

		b. p. [°C/torr]	Method[a]	Yield [%]
	**1**	–	B2	28[b]
	**2**	ca. 80/12	A2	27[c]
			B2	45[d]
	**3**	70-80/12	B2	69
			D	40 plus forerun
	**4**	64/8	C	51
	**5**	ca. 60/0.5	A1	73[e] (57[f])
			D	65
PhCH=CHCOCN	**6**	m. p. 115	A2	53
	**7**	55/12	A1	62
			D	30[g]
	**8**	60/0.05	D	45[g]
$PhCH_2COCN$	**9**	100-120/3	A2	50[h]
$4\text{-}FC_6H_4COCN$	**10**	70-80/1	B1	60[h]

[a] Method A1: Preformed acyl iodide, CuCN, solvent CH_2Cl_2
A2: Preformed acyl iodide, CuCN, solvent MeCN
B1: Acyl iodide formed *in situ*, CuCN, work up by evaporation of MeCN (b.p. of RCOCN well above that of MeCN)
B2: As B1, but modified work up (b.p. of RCOCN similar to that of MeCN)
C: Acyl chloride, CuCN, solvent benzene, P_4O_{10}, refluxing
D: Acyl chloride, Me_3SiCN, ZnI_2 according to *Hünig-Simchen*[2a,4].

[b] Evaporation of acetonitrile at 0°C at the water pump gives a solution of up to 68% of **1** in acetonitrile (GC). Fractionation of this solution with a Widmer column at normal pressure leads to formation of the Diels-Alder dimer in 80% yield. – [c] Extraction of the acetonitrile mother liquor with pentane for 48 h. – [d] Fractionation entails losses. – [e] Yield with respect to acyl chloride. – [f] Yield with respect to acyl iodide. – [g] Refers to purified material. Fractionation entails losses. – [h] Acetonitrile easily removable by distillation.

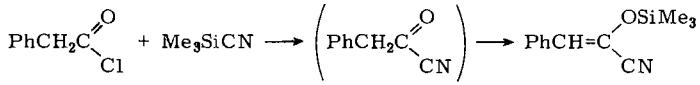
very useful. We have tested it in four cases, i. e. the preparation of **3**, **5**, **7**, and **8**. However, our *isolated* yields (Table 1) were lower than those given in the review[2a]. IR analysis may certainly suggest very high yields, but because losses are to be expected in the work up we would suggest that figures based on IR analysis[2a] be regarded as preliminary until full experimental details have appeared.

A further question concerns the optimum reaction temperature for method D: The preparation of **5** and **7** was carried out at room temperature, and no heating to 100°C was required in the

presence of catalytic amounts of zinc iodide. Any iodine formed during the reaction was removed with copper powder before distillation.

An attempt to prepare α,β-unsaturated acyl cyanide **5** from the corresponding acyl chloride and CuCN in the absence of iodide ion in solvent dichloromethane was not successful. In contrast, the acyl iodide was so reactive in this case that we could not record its ^{13}C NMR spectrum without decomposition setting in. The solution of the acyl iodide in dichloromethane reacted readily with CuCN under argon to give the desired **5**, which was also prepared conveniently from the acyl chloride by method D.

Our procedure for preparing acyl cyanides uses inexpensive starting materials and allows the preparation of sensitive derivatives such as 2-oxo-3-phenylpropanenitrile (**9**). This compound was unknown previously and could not be prepared by method D and other attempted routes: Phenylacetyl chloride and cyanotrimethylsilane yield the *O*-silylated enol of **9**[5]:



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Presumably, the relative merits of the procedures for preparing acyl cyanides will emerge more clearly in future and each preparation will have to be carefully optimized with respect to the method chosen and the experimental conditions. The *Hünig-Simchen* and our procedure are often complementary rather that competitive. For example, α-halogenated acyl cyanides[4] cannot be prepared with NaI/CuCN, because of ready nucleophilic attack of iodide ion on the activated α-halogen[6]. In the absence of such side reactions and if acetonitrile is ready separable, our procedure may be preferable.

Finally, on the basis of the ^{19}F NMR shift in *p*-fluorobenzoyl cyanide (**10**) (δ_{CFCl_3} = 94.5 ppm) the cyanocarbonyl group is a powerful π-acceptor, better than a nitro group (δ_{CFCl_3} = 99.7 ppm), but not quite as good as a diazonium group (δ_{CFCl_3} = 90 ppm) (see Table 2). We shall show elsewhere that α,β-unsaturated acyl cyanides such as **1** – **5** are useful cycloaddition reagents, e. g. for the synthesis of terpenoid compounds.

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Experimental Part

All reactions were carried out under nitrogen or argon, because acyl iodides are easily oxidized. All syntheses are summarized in Table 1.

Method A1: 2-Cyclopropyl-2-oxoethanenitrile (**7**): CuCN (1.2 g, 13 mmol) was gently refluxed in dichloromethane (15 ml) and cyclopropanecarbonyl iodide[3] (1.4 g, 7.1 mmol) was added in one batch. After being refluxed for 1 – 2 h, the mixture was filtered from CuI, and dichloromethane was removed at 0 – 5 °C. Kugelrohr distillation gave **7**[7] (420 mg, 62%). – ^1H and ^{13}C NMR: Table 2 and 3.

3,4-Dimethyl-2-oxo-3-pentenenitrile (**5**)

2,3-Dimethyl-2-butenoic acid (Trimethylacrylic acid): A solution of freshly distilled 2-bromo-3-methyl-2-butene (trimethylvinyl bromide; prepared from *tert*-amyl alcohol in 35% overall yield. *Braude* and *Evans* give 12% yield[8]) (75 g, 0.5 mol) in absol. tetrahydrofuran (50 ml) was added

Table 2. 90 MHz ^{1}H NMR ($CDCl_3$, TMS, δ, ppm) and IR ($CHCl_3$, cm^{-1}) Data of Acyl Cyanides **2** – **10**

	^{1}H NMR	IR
2	7.5 (m, ^3J = 15, ^3J = 7 Hz, 1H), 6.3 (m, ^3J = 15, ^4J = 1.5 Hz, 1H), 2.2 (dd, ^3J = 7, ^4J = 1.5 Hz, 3H)	2220 (m), 1680 (br, vs), 1635 (vs), 1620 (vs), 1230 (vs), 960 (vs)
3	7.4 (m, ^3J = 7, ^4J = 1.5 Hz, 1H), 2.1 (d, ^3J = 7 Hz, 3H), 1.9 (d, ^4J = 1.5 Hz, 3H)	2220 (m), 1670 (vs), 1640 (vs)
4	6.16 (m, J = 1.5 Hz, 1H), 2.20 (d, J = 1.5 Hz, 3H), 1.98 (d, J = 1.5 Hz, 3H)	2220 (m), 1690 (s), 1640 (vs)
5	2.29 (d, J = 1.5 Hz, 3H), 2.09 (t, J = 1.5 Hz, 3H), 2.04 (s, 3H)	2220 (s), 1670 (vs), 1635 (vs), 1590 (vs), 1305 (s), 1280 (s), 1195 (s), 1020 (s)
6[a]	8.0 (d, ^3J = 15 Hz, 1H), 7.7 – 7.4 (m, 5H), 6.8 (d, ^3J = 15 Hz, 1H)	2220 (m), 1665 (vs), 1625 (vs), 1600 (vs), 1580 (s), 1450 (s), 1220 (s), 1200 (s), 980 (s) (solvent CH_2Cl_2)
7	2.0 – 2.3 (m, 1H), 1.5 – 1.55 (m, 4H)	2220 (m), 1710 (vs), 1375 (m), 1225 (m), 1075 (vs), 980 (s)
8	5.7 (m, 1H), 3.15 (s, 2H), 1.7 (m, 8H)	2220 (m), 1715 (vs)
9	7.3 – 7.5 (m, 5H), 4.0 (s, 2H)	2220 (m), 1720 (vs), 1495 (m), 1455 (m), 1210 (m), 1055 (s), 715 (s)
10	8.1 – 8.44 (m, 2H), 7.2 – 7.4 (m, 2H)	2220 (m), 1685 (vs), 1595 (vs), 1505 (s), 1415 (m), 1250 (vs), 1155 (vs), 980 (s), 850 (s)

[a] $C_{10}H_7NO$ (157.2) Calcd. C 76.42 H 4.47 N 8.91 Found C 76.04 H 4.60 N 8.65

Table 3. ^{13}C NMR Data ($CDCl_3$, TMS, δ, ppm) of Acyl Cyanides **2** – **10** ($\overset{3}{C}-\overset{2}{C}-\overset{1}{C}=O$)

	Chemical Shift			
	C-1	C-2	C-3	Other signals
2	167.3	131.4	158.2	112.5 (CN), 19.1 (CH_3)
3	169.9	138.4	153.2	112.6 (CN), 15.1, 18.3
4	169.2	123.0	164.6	115.2 (CN), 22.4, 28.4
5	168.4	127.8	159.2	114.7 (CN), 15.1, 23.7, 25.3
6	167.4	133.0	154.8	112.5 (CN), 129.5, 129.6, 132.8, 133.0 (C-arom.)
7	177.6	24.6		112.4 (CN), 12.5 (CH_2)
8	175.0	131.2	127.1	113.2 (CN), 21.7, 22.6, 25.7, 28.8, 53.3
9	174.4	50.8		113.1 (CN), 128.6, 129.1, 129.2, 130.0 (C-arom.)
10[a]	166.4			112.7 (CN), 130.2 ($^4J_{CF}$ = 2.5 Hz), 133.5 ($^3J_{CF}$ = 9.8 Hz), 177.3 ($^2J_{CF}$ = 22.6 Hz), 168.4 ($^1J_{CF}$ = 261.8 Hz)

[a] Fluorine chemical shift δ_{CFCl_3} = 94.5 ppm. For a summary of other chemical shifts of fluorine *para* to a substituent see *J. W. Emsley* and *L. Phillips*, Fluorine Chemical Shifts, Pergamon Press, Oxford 1971.

dropwise to a well stirred suspension of lithium powder (10 g, 1.4 mol as a 30% dispersion in mineral oil) in absol. tetrahydrofuran (150 ml) under dry argon[9] cooled to −15 °C. As soon as the reaction had started (observed by a rise in temperature) the reaction mixture was cooled to and maintained at −30 °C throughout the addition. After completion of addition (1.5 h) the tempera-

ture was allowed to rise to −5 °C until most of the lithium powder had disappeared. The reddish-brown mixture was then cooled to −78 °C and an excess of dry, finely powdered carbon dioxide was added. After being warmed to 0 °C the mixture was hydrolysed with ice-water and extracted with pentane (the pentane phase was rejected). The aqueous layer was acidified with hydrochloric acid and the lipophilic trimethylacrylic acid was extracted with pentane. The organic phase was dried and the solvent was removed to leave light yellow crystals (19.5 g, 34.2%) of 2,3-dimethyl-2-butenoic acid, m. p. 71 °C. – IR ($CHCl_3$): 1630 (C=C), 1682 (C=O) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.86 (s, 6H), 2.12 (d, *J* = 1.5 Hz, 3H), 11.1 (br, 1H). – ^{13}C NMR ($CDCl_3$): δ = 15.5, 23.38, 23.51, 121.86, 148.18, 175.26.

2,3-Dimethyl-2-butenoyl chloride (Trimethylacryloyl chloride): Trimethylacrylic acid (6.4 g, 56 mmol) in dichloromethane (10 ml) was slowly dropped into a solution of oxalyl chloride (10.9 g, 90 mmol) in dichloromethane (30 ml) containing solid K_2CO_3 and maintained at room temperature. In order to minimize contact of the carboxylic acid with gaseous hydrogen chloride (brown coloration) during addition we used argon as protective gas. After completion of addition the mixture was stirred for 4 h at room temperature, filtered and the solvent was removed to leave an oily residue which was distilled (Kugelrohr), b. p. 60 °C/0.5 torr, yield 4.2 g (56.5%). – IR (film): 1608, 1768 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.9 (s, 3H), 2.03 (s, 6H). – ^{13}C NMR ($CDCl_3$): δ = 16.66, 23.35, 127.22, 149.06, 168.20.

2,3-Dimethyl-2-butenoyl iodide (Trimethylacryloyl iodide): This preparation followed our standard procedure[3], 4.0 g of the acyl chloride giving 5.3 g (78%) of light-yellow acyl iodide after extraction of the reaction mixture with pentane for 2 h at −20 °C. The acyl iodide was highly reactive and after evaporation of pentane was dissolved in dichloromethane.

5: Copper(I)-cyanide (2.2 g, 24.5 mmol) was suspended in boiling dichloromethane (20 ml) and 5.0 g (22.3 mmol) of trimethylacryloyl iodide in absol. dichloromethane (10 ml) was added in one batch. After a few seconds an exothermic reaction ensued. After refluxing for 2 h, insoluble CuI was filtered off, the solvent was removed and the residue was distilled at 60 °C/0.5 torr (Kugelrohr) to give 2.0 g (73%) of **5**. – IR (film): 1595 (br), 1635 (C=C), 1670 (C=O), 2215 (C≡N) cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.04 (s, 3H), 2.09 (t, 3H, *J* = 1.5 Hz), 2.30 (d, 3H, *J* = 1.5 Hz). – ^{13}C NMR: Table 3.

5 was also prepared conveniently from trimethylacryloyl chloride (1.325 g, 10 mmol), cyanotrimethylsilane (equimolar) and catalytic amounts of zinc iodide at room temperature in the absence of solvent, following the procedure of *Hünig* and *Simchen*[4]. After a reaction time of 20 h, 800 mg (65%) of the desired product was obtained.

Method A2: 2-Oxo-3-phenylpropanenitrile (**9**)[10]: A suspension of CuCN (1.2 g, 13 mmol) in anhydrous acetonitrile (100 ml) was warmed to 40–60 °C and phenylacetyl iodide[3] (2.5 g, 10 mmol) was added in one batch. After 2–3 min a yellow, almost clear solution resulted. The solution was stirred for 1 h, and the acetonitrile was removed using a rotary evaporator. The product was dissolved in dichloromethane and CuI filtered off. After evaporation of dichloromethane the residue was distilled twice (Kugelrohr), b. p. 100–120 °C/3 torr, giving pure **9** (730 mg, 50%). – IR (CCl_4): 2220 (m), 1720 (vs), 1495 (m), 1455 (m), 1210 (m), 1055 (s), 715 (s) cm^{-1}. – 60 MHz ^1H NMR ($CDCl_3$): δ = 4.00 (s, 2H), 7.3–7.5 (m, 5H). – ^{13}C NMR: Table 3.

Method B: CuCN (7.2 g, 80 mmol) and dry sodium iodide (23 g, 150 mmol) were stirred briefly with absol. acetonitrile (180 ml). The resulting almost clear solution was mixed with the appropriate acyl chloride (75 mmol) and stirred for 30 min at room temperature. The work up depends on the volatility of the product.

Variant B1 (for acyl cyanides boiling at a sufficiently higher temperature than acetonitrile): The reaction mixture is filtered and acetonitrile is removed using a rotary evaporator. The residue is

taken up in dichloromethane with precipitation of CuI, which is filtered off. After removal of the solvent the product is obtained by Kugelrohr distillation.

Variant B2 (for acyl cyanides boiling close to acetonitrile): At the end of the reaction all volatile products and solvent are distilled into a trap cooled to −78 °C using a water pump. The residue is treated with a little dichloromethane and filtered. The combined solutions are distilled in a Widmer column which allows the separation of the bulk of the volatile components (dichloromethane, acetonitrile). The final separation is carried out by Kugelrohr distillation and if necessary, the forerun is redistilled several times. Some product is usually lost at this stage. The purity of the product is monitored by GC and is generally higher than 95%.

Method C: 4-Methyl-2-oxo-3-pentenenitrile (**4**): CuCN (19 g, 212 mmol) was introduced into a round-bottomed three-necked flask and just covered with benzene. The mixture was refluxed and 3-methyl-2-butenoyl chloride (10 g, 85 mmol) was added rapidly. Refluxing was continued for 6 h, whilst phosphorous pentoxide was added in four portions (4 × 0.5 g). The mixture was allowed to cool, diluted with ether (150 ml), filtered and the resulting solution was washed with a cold aqueous solution of 10% $NaHCO_3$ and dried ($MgSO_4$). After removal of the solvent using a rotary evaporator the residue was distilled at 64−66 °C/8 torr, giving **4** (4.7 g, 51%). − IR (film): 2220, 1670, 1650, 1442, 1375 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 2.08 (d, *J* = 1.5 Hz, 3H), 2.3 (d, *J* = 1.5 Hz, 3H), 6.24 (m, *J* = 1.5 Hz, 1H). − ^{13}C NMR: Table 3.

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1) Reactive Iodine Compounds, 6; Part 5: *K. Belsner* and *H. M. R. Hoffmann*, Synthesis **1982**, 239.
2) [2a] *S. Hünig* and *R. Schaller*, Angew. Chem. **94**, 1 (1982); Angew. Chem., Int. Ed. Engl. **21**, 36 (1982). − [2b] See also *A. Jellal* and *M. Santelli*, Tetrahedron Lett. **1980**, 4487.
3) *H. M. R. Hoffmann* and *K. Haase*, Synthesis **1981**, 715.
4) *K. Hermann* and *G. Simchen*, Synthesis **1979**, 204; see also *U. Hertenstein, S. Hünig, H. Reichelt*, and *R. Schaller*, Chem. Ber. **115**, 261 (1982).
5) Ref.[2a], p. 38.
6) See e. g. *M. R. Ashcroft* and *H. M. R. Hoffmann*, Org. Synth. **58**, 17 (1978).
7) *E. Zbiral* and *L. Fenz*, Monatsh. Chem. **96**, 1983 (1965).
8) *E. A. Braude* and *E. A. Evans*, J. Chem. Soc. **1955**, 3331.
9) *G. L. Closs* and *L. E. Closs*, J. Am. Chem. Soc. **85**, 99 (1963).
10) *K. Haase* and *H. M. R. Hoffmann*, Angew. Chem. **94**, 80 (1982); Angew. Chem., Int. Ed. Engl. **21**, 83 (1982).

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