Synthesis of Tertiary α-Cyanoenamines (2-Dialkylamino-2-alkenenitriles)

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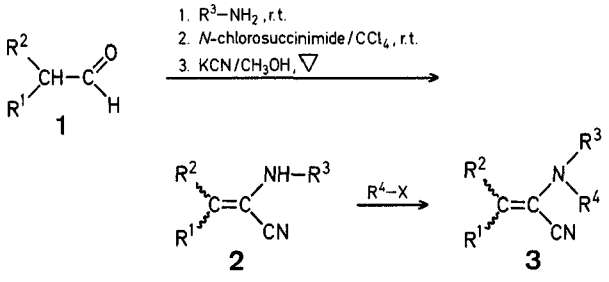
2-Amino-2-alkenenitriles (α-cyanoenamines) have in recent years received considerable attention as starting materials for the synthesis of a variety of compounds. Tertiary α-cyanoenamines (**3**, R^3, $R^4 \neq H$) have been synthesized from 2-alkenals[1], α-chloroenamines[2], α-haloaldehydes[3-6], carboxamides[7], and, more recently, from the addition of cyanogen bromide to enamines[4]. Secondary α-cyanoenamines (**2**) have hitherto exclusively been obtained from α-chloroaldimines and potassium cyanide in methanol[8]. The synthetic utility of α-cyanoenamines was demonstrated by their conversion into α-diones[2] and by their intermediacy in the transformation of aldehydes into carboxamides[9]. The reaction of tertiary α-cyanoenamines (**3**) with organolithium reagents provides possibilities for, e.g. (depending on the organometallic reagent used), selective deprotonations, additions to the nitrile moiety, or Michael additions[2,3,4], thus allowing carbon-chain elongations with the aid of electrophiles. It has been reported that the N-groups in the title compounds play a determinative role in the these reactions[4].

Tertiary α-cyanoenamines (**3**) having bulky substituents have hitherto not been reported. We have now prepared these compounds by alkylation of secondary α-cyanoenamines (**2**). Compounds **2** having bulky substituents, e.g. *t*-butyl, are easily accessible from aliphatic aldehydes (**1**) and primary amines via α-chloroaldimines[8]. Alkylation with alkyl halides or alkyl tosylates did not work; therefore, stronger alkylating agents, i.e., dialkyl sulfates, alkyl fluorosulfonates, and triethyloxonium tetrafluoroborate were used.



R^4–X = R^4–O–SO_2F , R^4–O–SO_2–O–R^4 , $(C_2H_5)_3O^{\oplus}BF_4^{\ominus}$

The reaction of compounds **2** with dimethyl sulfate (1.5 equivalents) in dry acetone in the presence of potassium carbonate (Method A) required a reflux time of 22–48 h. The analogous reaction of diethyl sulfate with 2-*t*-butylamino-3-methyl-2-butenenitrile (**2**, $R^1 = R^2 = CH_3$; $R^3 = t$-C_4H_9) proceeded more slowly, complete conversion (using 4 equivalents of diethyl sulfate) only being obtained after a reflux period of 90 h. The tertiary α-cyanoenamine **3e** could not be obtained free from excess diethyl sulfate by distillation.

A more efficient procedure consisted of the use of powerful alkylating agents such as methyl and ethyl fluorosulfon-

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Table 1. Synthesis of 2-Dialkylamino-2-alkenenitriles (Tertiary α-Cyanoenamines, 3)

3	R^1	R^2	R^3	R^4	Method	equiv Alkylating agent/(Base)/Solvent	Reaction conditions	Yield[a] [%]	b.p./torr	Molecular formula[b]	
a	CH_3	CH_3	CH_3	C_2H_5	C	1.2/CH_2Cl_2	r.t., 1 h; ∇, 1 h	82	190°[c]	$C_8H_{14}N_2$	(138.2)
b	CH_3	CH_3	i-C_3H_7	CH_3	A	1.5/K_2CO_3/acetone	∇, 22 h	85	68–72°/12	$C_9H_{16}N_2$	(152.2)
b	CH_3	CH_3	i-C_3H_7	CH_3	B	1.05/CH_2Cl_2	∇, 2 h	73			
c	CH_3	CH_3	i-C_3H_7	C_2H_5	B	2.0/CH_2Cl_2	r.t., 22 h	78	80–82°/12	$C_{10}H_{18}N_2$	(166.3)
d	CH_3	CH_3	t-C_4H_9	CH_3	A	1.5/K_2CO_3/acetone	∇, 48 h	77	87–90°/12	$C_{10}H_{18}N_2$	(166.3)
d	CH_3	CH_3	t-C_4H_9	CH_3	B	1.05/CH_2Cl_2	∇, 2 h	90			
e	CH_3	CH_3	t-C_4H_9	C_2H_5	A	4.0/K_2CO_3/acetone	∇, 90 h	95[d]	—[d]	$C_{11}H_{20}N_2$	(180.3)
e	CH_3	CH_3	t-C_4H_9	C_2H_5	B	(1) 1.0/CH_2Cl_2; (2) 1.0/CH_2Cl_2 (consecutively)	(1) ∇, 1 h; (2) ∇, 1 h	77	90–93°/12		
e	CH_3	CH_3	t-C_4H_9	C_2H_5	C	1.2/CH_2Cl_2	r.t., 1 h; ∇, 1 h	86			
f	C_2H_5	CH_3	t-C_4H_9	CH_3	B	1.05/CH_2Cl_2	∇, 1.5 h	86	98–103°/15	$C_{11}H_{20}N_2$	(180.3)
g	C_2H_5	CH_3	t-C_4H_9	C_2H_5	B	(1) 1.5/CH_2Cl_2; (2) 1.0/CH_2Cl_2 (consecutively)	(1) ∇, 30 min; (2) r.t., overnight	62	96–99°/12	$C_{12}H_{22}N_2$	(194.3)
h	$(CH_2)_5$		t-C_4H_9	CH_3	B	1.05/CH_2Cl_2	∇, 1 h	73	144–147°/12	$C_{13}H_{22}N_2$	(206.3)
i	CH_3	CH_3	c-C_6H_{11}	CH_3	A	1.5/K_2CO_3/acetone	∇, 20 h	73	128–135°/12[e]	$C_{12}H_{20}N_2$	(192.3)
i	CH_3	CH_3	c-C_6H_{11}	CH_3	B	1.05/CH_2Cl_2	∇, 1 h	90			
j	C_2H_5	CH_3	c-C_6H_{11}	CH_3	A	1.5/K_2CO_3/acetone	∇, 48 h	70	135–142°/12	$C_{13}H_{22}N_2$	(206.3)

[a] Yield of product isolated by distillation.
[b] All compounds gave satisfactory microanalyses: C, ±0.21; H, ±0.13; N, ±0.12.
[c] Temperature of oil bath (molecular destillation).
[d] Yield estimated by G.L.C. and ^{1}H-N.M.R.; 3e and diethyl sulfate could not be sufficiently separated by distillation.
[e] Ref. [4], b.p. 58–62°/0.001 torr.

ates[10] (Method B). "Magic methyl" reacted very cleanly with the *N*-methyl derivatives (dichloromethane, reflux 1–2 h) but the reactions with ethyl fluorosulfonate needed some more care as the procedure had to be carried out stepwise. Refluxing secondary α-cyanoenamines (**2**) and ethyl fluorosulfonate in dichloromethane led only to partial conversion into the *N*-ethylated products **3c, e, g** due the thermal instability of the alkylating agent. Hence, stepwise addition of the reagent to the sterically hindered α-cyanoenamines was necessary. Less sterically hindered substrates, e.g. 2-isopropylamino-3-methyl-2-butenenitrile (**2**, $R^1=R^2=CH_3$, $R^3=i$-C_3H_7), reacted smoothly at room temperature within ~14 h (overnight).

Monitoring of the reactions by ^{1}H-N.M.R. analysis is recommended.

The tertiary α-cyanoenamines **3** obtained by alkylation of **2** with alkyl fluorosulfonates in some cases showed an impurity (~5%) of unknown structure. The impurity could not be separated from **3** by distillation but column chromatography over silica gel using pentane/tetrachloromethane (40/60) as eluent afforded analytically pure samples of the desired compounds **3**.

Triethyloxonium tetrafluoroborate in dichloromethane was found to be an even more convenient alkylating agent which reacts very smoothly and does not lead to the formation of side products.

***N*-Alkylation of α-Cyanoenamines (2, 2-Alkylamino-2-alkenenitriles); Typical Procedures:**

Method A; *N*-Alkylation with Dialkyl Sulfates; Synthesis of 2-(Isopropylmethylamino)-3-methyl-2-butenenitrile (**3b**): To a stirred solution of 2-isopropylamino-3-methyl-2-butenenitrile (**2**, $R^1=R^2=CH_3$, $R^3=i$-C_3H_7; 4.14 g (0.03 mol) in dry acetone (60 ml) is added dry potassium carbonate (6.62 g, 0.048 mol) and dimethyl sulfate (5.67 g, 0.045 mol). The mixture is refluxed with vigorous stirring for 22 h. The solvent is then evaporated in vacuo, the residue is stirred with water (100 ml), and the mixture is extracted with dichloromethane (3 × 50 ml). The organic extract is dried with magnesium sulfate for 15 min, evaporated in vacuo, and the residual pale yellow oil distilled in vacuo; yield of colorless **3b**: 3.9 g (85%); b.p. 68–72°/12 torr.

Method B; *N*-Alkylation with Alkyl Fluorosulfonates; Synthesis of 2-(*t*-Butylmethylamino)-3-methyl-2-butenenitrile (**3d**): Methyl fluorosulfonate (*Caution!*[10]; 11.97 g, 0.105 mol) is added to a stirred solution of 2-*t*-butylamino-3-methyl-2-butenenitrile (**2**; $R^1=R^2=CH_3$, $R^3=t$-C_4H_9; 15.2 g, 0.1 mol) in dry dichloromethane (150 ml). The mixture becomes warm after a few minutes, is then refluxed for 2 h, and allowed to cool. 2 Normal aqueous sodium hydroxide (150 ml) is added and the layers are thoroughly mixed by stirring for 30 min. The organic layer is separated and the aqueous layer extracted with dichloromethane (1 × 40 ml). The combined organic layers are washed with saturated aqueous sodium chloride, dried with magnesium sulfate for 30 min, and evaporated. The residual pale yellow oil is distilled in vacuo to give colorless **3d**; yield: 14.9 g (90%); b.p. 87–90°/12 torr.

All alkylations by Method B are monitored by ^{1}H-N.M.R. analysis of samples of the reaction mixture before work-up. In some cases, an impurity (<5%) of unknown structure has to be removed by passing the distilled products **3** through a 20 cm column of silica gel using pentane/ tetrachloromethane (40/60) as eluent.

Method C; *N*-Alkylation with Triethyloxonium Tetrafluoroborate; Synthesis of 2-(*t*-Butylethylamino)-3-methyl-2-butenenitrile (**3e**): A solution of 2-(*t*-butylamino)-3-methyl-2-butenenitrile (**2**, $R^1=R^2=CH_3$, $R^3=t$-C_4H_9; 6.08 g, 0.04 mol) in dry dichloromethane (6 ml) is added to a 0.85 normal solution (56.4 ml, 0.048 mol) of triethyloxonium tetrafluoroborate in dichloromethane. The mixture is allowed to stand at room temperature for 1 h and is then refluxed for 1 h. The cooled mixture is stirred with 1 normal aqueous sodium hydroxide (120 ml) for 5 min; the organic phase is then separated and the aqueous phase extracted once with dichloromethane. The combined organic extracts are washed with saturated

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Table 2. Spectrometric Data of Compounds **3**

3	M.S. (70 eV) *m/e* (relative intensity)	I.R. (NaCl) $\nu_{C\equiv N}$ [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
a	138 (M^+, 20); 123 (100); 109 (11); 68 (12); 67 (24); 53 (13); 42 (32); 41 (14)	2210	0.97 (t, 3H, J=6.5 Hz, H_3C–C–N); 2.36 (s, 3H, N–CH_3); 2.47 (q broadened, 2H, CH_2–N); 1.98 (s, 3H, –C–CH_3 *cis*[a]); 1.87 (s, 3H, –C–CH_3 *trans*)
b	152 (M^+, 16); 137 (100); 95 (12); 83 (8); 82 (8); 69 (8); 68 (8); 67 (16); 56 (8); 53 (8); 43 (12); 42 (24); 41 (24)	2208	1.04 [d, 6H, J=6.5 Hz, $(CH_3)_2$C–N]; 2.00 (s, 3H, –C–CH_3 *cis*); 1.90 (s, 3H, –C–CH_3 *trans*); 2.80 (septet, 1H, J=6.5 Hz, CH–N); 2.38 (s, 3H, NCH_3)
c	166 (M^+, 10); 151 (100); 123 (6); 109 (17); 96 (16); 82 (13); 81 (7); 69 (12); 68 (11); 55 (6); 54 (7); 53 (12); 43 (21); 42 (21); 41 (35); 39 (12); 29 (21)	2209	1.03 [d, 6H, J=7 Hz, $(CH_3)_2$C–N]; 2.04 (s, 3H, CH_3 *cis*); 1.89 (s, 3H, CH_3 *trans*); 0.92 (t, 3H, J=6.5 Hz); 2.72 (q, 2H, J=6.5 Hz); ~2.8 (septet, overlap, 1H, CH–N)
d	166 (M^+, 15); 151 (100); 136 (4); 110 (29); 109 (8); 96 (11); 95 (38); 83 (34); 82 (11); 81 (7); 68 (8); 67 (7); 57 (77); 56 (14); 55 (4); 53 (5); 42 (15); 41 (32)	2202	1.12 (s, 9H, t-C_4H_9); 2.43 (s, 3H, N–CH_3); 2.01 (s, 3H, –C–CH_3 *cis*); 1.92 (s, 3H, –C–CH_3 *trans*)
e	180 (M^+, 11); 165 (100); 109 (35); 97 (22); 96 (28); 81 (22); 69 (14); 57 (80); 56 (11); 55 (8); 53 (8); 42 (16); 41 (46)	2202	1.11 (s, 9H, t-C_4H_9); 0.88 (t, 3H, J=6.5 Hz, H_3C–C–N); 2.75 (m, 2H, CH_2–N); 2.04 (s, 3H, –C–CH_3 *cis*); 1.90 (s, 3H, –C–CH_3 *trans*)
f	180 (M^+, 16); 165 (100); 124 (16); 123 (10); 109 (60); 97 (22); 82 (23); 57 (8); 42 (16); 41 (30)	2202	1.13 (s, 9H, t-C_4H_9); 0.98 (t, 3H, J=7 Hz); 2.3 (covered, 2H, CH_2–C–); 1.97, 1.89 (55% and 45% of H_3C–C–, *cis* and *trans* with respect to C–N); 2.43 (s, 3H, N–CH_3)
g	194 (M^+, 0.4); 179 (7); 123 (3); 111 (2); 96 (2); 68 (32); 57 (100); 56 (1); 55 (2); 41 (8); 39 (2); 29 (8)	2208	1.10 (s, 9H, t-C_4H_9); 0.9–1.1 (overlapped signals, 6H, H_3C–C–C, H_3C–C–N); 2.4 (overlap, 2H, CH_2–C–); 2.7 (overlap, 2H, CH_2–N); 2.01, 1.90 (55% and 45% of H_3C–C–, *cis* and *trans* with respect to C–N)
h	206 (M^+, 13); 191 (100); 150 (22); 149 (15); 123 (24); 82 (20); 57 (57); 42 (17); 41 (28)	2202	1.13 (s, 9H, t-C_4H_9); 2.43 (s, 3H, N–CH_3); 2.2–2.6 (m, 4H, CH_2–CH_2–C–); 1.3–2.0 [m, 6H, $(CH_2)_3$]
i	192 (M^+, 24); 177 (5); 149 (100); 135 (7); 123 (6); 121 (15); 111 (9); 95 (6); 83 (17); 82 (11); 68 (5); 67 (9); 55 (20); 53 (6); 42 (16); 41 (21)	2208	1–2 [m, 10H, $(CH_2)_5$]; 1.98 (s, 3H, –C–CH_3 *cis*); 1.87 (s, 3H, –C–CH_3 *trans*); 2.36 (s, 3H, H_3C–N); 2.4 (m, 1H, N–CH)
j	206 (M^+, 22); 191 (7); 177 (10); 163 (100); 135 (37); 125 (10); 123 (15); 121 (7); 109 (10); 97 (7); 82 (22); 67 (12); 55 (30); 42 (24); 41 (30)	2208	0.9 (t, 3H, J=7 Hz); 2.3 (covered, 2H, CH_2–C–C); 2.33 (s, 3H, N–CH_3); ~2.3 (covered, 1H, N–CH); 1.93, 1.83 (54% and 46% of H_3C–C–, *cis* and *trans* with respect to C–N); 1–2 [m, 10H, $(CH_2)_5$]

[a] *cis* with respect to the nitrile function, and vice versa for *trans*.

aqueous sodium hydroxide solution, dried with magnesium sulfate (10 min), and evaporated. The residual clear oil is distilled in vacuo; yield of **3e**: 6.2 g (86%); b.p. 90–93°/12 torr.

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[10] **Caution!** Alkyl fluorosulfonates should only be handled in a well-ventilated hood as they are know as potentially carcinogeneous agents. Inhalation of methyl fluorosulfonate has been reported to be lethal: D. M. W. Van Den Ham, D. Van Der Meer, *Chem. Br.* **12**, 362 (1976).

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