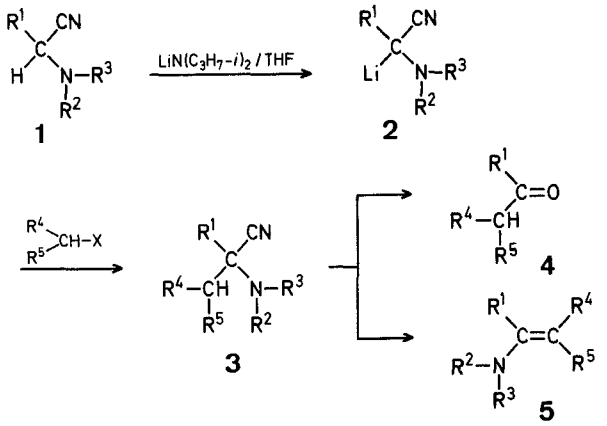
# Dehydrocyanation of α-Aminonitriles; A Versatile and Convenient Enamine and Dieneamine Synthesis

H. AHLBRECHT*, W. RAAB[1], C. VONDERHEID[2]

Fachbereich Chemie der Universität Giessen, Institut für Organische Chemie, Heinrich-Buff-Ring 58, D-6300 Lahn-Giessen 1

Deprotonation of α-aminonitriles, derived from *aromatic* aldehydes (**1**, $R^1$ = aryl), with potassium amide in liquid ammonia[3], sodium hydride in dimethylformamide[4] or even by phase-transfer catalysis[5] is a well known reaction. As we could demonstrate recently[2,6], the deprotonation can be carried out more conveniently with lithium diisopropylamide in tetrahydrofuran. This method is also applicable to α-aminonitriles derived from *aliphatic* aldehydes (**1**, $R^1$ = alkyl)[1]. Since the resulting α-lithioaminonitriles **2**[7] can be alkylated quantitatively and furthermore acid (or base) cleavage of the bis-alkylated aminonitriles **3** to carbonyl compounds **4** is achieved in excellent yields (Table 1), α-aminonitriles **1** represent highly reactive, easily available, and cheap nucleophilic acylation reagents[8].




For example, the bulky cyclohexyl group can easily be introduced, which is not possible in the case of the widely used dithianes[9], or with lower yield only in the case of the oxygen analogue of **1**[10]. Especially, bis-alkylated α-aminonitriles of type **3** with a hydrogen atom in the β-position are of remarkable synthetic value, because they are suitable substrates for the elimination of hydrogen cyanide to form enamines of type **5**.

Hauser et al. and Mąkosza et al. have already reported on the thermal or base-promoted elimination of hydrogen cyanide in the case of a *benzylic* β-hydrogen[3,5]. This has been confirmed in a recent paper on the synthesis of substituted desoxybenzoins[11].

On the other hand, elimination of hydrogen cyanide failed in cases without phenyl activation[12]. Here thermal elimination of amine is preferred[1,13]. We have now found that dehydrocyanation even in these cases proceeds smoothly, if the reaction is carried out in boiling toluene or benzene, using an excess of powdered potassium hydroxide or potassium *t*-butoxide as base (Table 2)[1]. Comparison of reaction times in Table 2, determined roughly by $^1$H-N.M.R. spectroscopy, implicates a dependence of the reaction rate on the nucleophilicity of the amino-group, the bonding character of the β-hydrogen atom, and the nature of the base used.

α-Aminonitriles with an *aliphatic* amine component react faster than those with an *aromatic* one (Table 2, entry **a**,

0039–7881/79/0232–0127 $ 03.00 

**Table 1.** Ketones **4** from α-Aminonitriles **1**[a]

| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield[b] [%] | b.p./torr m.p. (solvent) | Lit. b.p./torr m.p. |
|---|---|---|---|---|---|---|---|---|
| **4a** | $C_6H_5$ | $CH_3$ | $CH_3$ | H | H | 90[c] (96) | 85°/12 | —[h] |
| **4b** | $C_6H_5$ | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | 89[c] (94) | 74°/12 | —[h] |
| **4c** | $C_6H_5$ | $CH_3$ | $CH_3$ | $-(CH_2)_5-$ | | 85[d] (90) | 54–55° (PE) | 55–56°[h, 26] |
| **4d** | $C_6H_5$ | $CH_3$ | $CH_3$ | $CH_2CH_2-Br$ | H | 86[d, e] (89[f]) | 65° (PE) | 65–66°[27] |
| **4e** | $C_2H_5$ | $-(CH_2)_2-O-(CH_2)_2-$ | | $n$-$C_4H_9$ | H | 70[c] (90) | 62–64°/20 | 55–58°/1.5[28] |
| **4f** | $C_2H_5$ | $-(CH_2)_2-O-(CH_2)_2-$ | | $H_2C=CH$ | H | 27[c, g] (92) | 117–123°[i] | 79–82°/4[29] |

[a] **4a**: X = J; **4b–f**: X = Br.
[b] Values in brackets are yields of the alkylation step **1**→**3**.
[c] Based on **1** without isolation of **3**.
[d] Based on **3**.
[e] Formation of 1,5-diphenyl-1,5-pentandione.
[f] By reaction of $Br-(CH_2)_3-Br$ with 2 equiv. of **2**.
[g] Partial polymerisation during work-up.
[h] Identified by comparison (I.R.) with authentic material.
[i] Mixture of α,β(*E*,*Z*)- and β,γ-enone.

**Table 2.** Enamines **5** from α-Aminonitriles **1**

| Product[a] | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^4$ | Yield[b] [%] | Reaction conditions Time [h][c]/ Method[d] | b.p./torr or m.p. | Lit. b.p./torr or m.p. |
|---|---|---|---|---|---|---|---|---|---|
| **5a** | $C_6H_5$ | $CH_3$ | $CH_3$ | H | H | 71 (96) | 16/A | 105°/35 | —[e] |
| **5b** | $C_6H_5$ | $C_6H_5$ | $CH_3$ | H | H | 48 (83) | 70/A | 96–98°/0.01 | 161–162°/13[20, 21] |
| **5c** | $C_6H_5$ | $CH_3$ | $CH_3$ | $CH_3$ | H | 93[f] | 14/A | 85–90°/20 | 85–90°/20[22] |
| **5d** | $C_6H_5$ | $C_6H_5$ | $CH_3$ | H | $CH_3$ | 78 (90[g]) | 167/A | 118–120°/0.05 | 106°/0.1[23] |
| | | | | | | 71 | 53/B | | |
| **5e** | $C_6H_5$ | $CH_3$ | $CH_3$ | $-(CH_2)_4-$ | | 49[h] (93) | 67/A | 78–82°/0.5 | —[e] |
| | | | | | | 68 | 4/B | | |
| **5f** | $C_6H_5$ | $CH_3$ | $CH_3$ | $-CH_2-CH=C(N(CH_3)_2)(C_6H_5)$ | H | 71[f, i] | 20/A | 48–50° | —[e] |
| **5g** | $CH_3$ | $-(CH_2)_2-O-(CH_2)_2-$ | | $CH_3$ | H | 85[j] (82) | 5/C | 75–80°/20 | 82°/15[24] |
| **5h** | $CH_3$ | $C_6H_5$ | $CH_3$ | $CH_3$ | H | 81[j] (89) | 2/C | 106–110°/20 | 84–87°/2[25] |
| **5i** | $C_6H_5$ | $CH_3$ | $CH_3$ | $H_2C=CH-$ | H | 59 (87) | 26/A | 110–115°/20 | —[e] |
| **5j** | $C_6H_5$ | $CH_3$ | $CH_3$ | $H_3C-CH=CH-$ | H | 69[f] | 23/A | 128–132°/20 | —[e] |
| **5k** | $C_6H_5$ | $C_6H_5$ | $CH_3$ | $H_3C-CH=CH-$ | H | 83 (87) | 69/A | 135–140°/0.01 | —[e] |

[a] For preparation of **5a–d, g, h** X = J; for **5e, f, i** X = Br; for **5k** X = Cl.
[b] Based on $^1$H-N.M.R.-spectroscopically pure **3**; values in brackets are for step **1**→**3**.
[c] Approximate values.
[d] Method A: KOH/toluene; Method B: $KOC_4H_9$-*t*/toluene; Method C: $KOC_4H_9$-*t*/benzene.
[e] For characterization of new enamines **5**, see Table 3.
[f] Based on pure **1**.
[g] Also thermal elimination during distillation.
[h] Contains up to 30% of ketone.
[i] By reaction of $Br-(CH_2)_3-Br$ with 2 equivalents of **2**; contains traces of **5i**.
[j] Mixture of isomers with the less substituted one dominating (~80%).

**c** compared to **b, d**). As expected, abstraction of a primary hydrogen is faster than abstraction of a secondary or a tertiary one (Table 2, entry **b** compared to **d, c** to **e**). Potassium *t*-butoxide (method B) is much more efficient than potassium hydroxide (method A).

Significant advantages of our enamine synthesis are the following:

- High versatility, resulting from the metallation-alkylation step **1**→**3**.
- High purity of the enamines **5** due to the absence of any acidic catalysts often used in other enamine syntheses[14].
- Simple synthesis of dieneamines **5i–k**, otherwise hardly available[17].
- Unusual regioselectivity – with α-aminonitriles from methyl ketones, formation of the less substituted $\Delta^1$-enamine is favoured (otherwise available by a protonation-deprotonation sequence only[18]).

**α-Aminonitriles 1 from Aldehydes[19]:**
The aldehyde is added slowly to a stirred, concentrated aqueous solution of sodium hydrogen sulfite at about 0–10°. When the adduct has formed, one equivalent of amine is added at room temperature with stirring continued. In the case of *N*-methylaniline and morpholine it is necessary to warm the reaction mixture at ~80° for 6–10 h. A concentrated solution of potassium cyanide

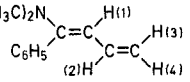
**Table 3.** Characterization of New Enamines **5**

| Product | $n_D^{20}$ | Molecular formula[a] | $^1$H-N.M.R. ($CCl_4$)[b] $\delta$ [ppm] |
|---|---|---|---|
| **5a** | 1.5405 | $C_{10}H_{13}N$ (147.1) | 2.60 (s, 6H, N—$CH_3$); 4.06, 4.18 (s+s, 1H+1H, =$CH_2$); 7.3–7.66 (m, 5$H_{arom}$) |
| **5e** | 1.5456 | $C_{14}H_{19}N$ (201.2) | 1.12–2.30 [m, 8H, —$(CH_2)_4$—]; 2.49 (s, 6H, N—$CH_3$); 7.16–7.45 (m, 5$H_{arom}$) |
| **5f** | — | $C_{21}H_{26}N_2$ (306.2) | 2.44 (s, 12H, N—$CH_3$); 2.44 (2H, =CH—$CH_2$—)[c]; 4.31 (t, 2H, $J$=7 Hz, =CH—); 7.16 (s, 10$H_{arom}$) |
| **5i** | 1.5928 | $C_{12}H_{15}N$ (173.1) | 2.62 (s, 6H, N—$CH_3$); 4.52 [dd, 1H, $J_{2,4}$=11 Hz, $J_{3,4}$=2.5 Hz, H(4)]; 4.87 [dd, 1H, $J_{2,3}$=17.5 Hz, $J_{3,4}$=2.5 Hz, H(3)]; 5.3 [d, 1H, $J_{1,2}$=11 Hz, H(1)]; 6.07 [dt, 1H, $J_{2,3}$=17.5 Hz, $J_{2,4}$=11 Hz, $J_{1,2}$=11 Hz, H(2)]; 7.36 (s, 5$H_{arom}$)[d] |
| **5j** | 1.5856 | $C_{13}H_{17}N$ (187.1) | 1.62 (dd, 3H, $J$=7 Hz, 1 Hz, =C—$CH_3$)[c]; 1.73 (dd, 3H, $J$=7 Hz, 1.5 Hz, =C—$CH_3$); 2.61, 2.65 (s, 3H, N—$CH_3$); 4.9–6.04 (m, 6H, =CH—CH=CH—); 7.42 (s, 5$H_{arom}$) |
| **5k** | 1.6355 | $C_{18}H_{19}N$ (249.2) | 1.72 (dd, 3H, $J$=7 Hz, 1 Hz, $CH_3$)[c]; 1.82 (dd, 3H, $J$=7 Hz, 1.5 Hz, $CH_3$); 3.09 (s, 3H, N—$CH_3$); 5.31–6.47 (m, 3H, =CH—CH=CH—); 6.47–7.43 (m, 10$H_{arom}$) |

[a] All products gave satisfactory microanalyses (C ±0.51, H ±0.12, N ±0.26).

[b] Measured at 100 MHz on a Jeol JNM-MH-100 spectrometer; shifts downfield from internal TMS.

[c] Signal hidden by N—$CH_3$ singlet.

[d] 


[e] Predominant isomer.

(1 equiv) in water is then added at room temperature and the reaction mixture is now kept at 60–80° for 5–10 h again. Extraction with ether and distillation in vacuo yield the desired product.

**α-Aminonitriles 3 from α-Aminonitriles 1:**

In a three-necked flask (argon inlet, serum cap) a solution of lithium diisopropylamide in tetrahydrofuran (1 mmol/ml) is prepared under argon in the usual manner and cooled to −78°. A solution of the aminonitrile **1** (1 mmol/ml) in dry tetrahydrofuran is then added dropwise into the stirred solution. The mixture is stirred for 2 h at −78° (metallation at 0° is also possible) and then quenched with the alkylating reagents. Subsequent aqueous work-up, i.e. treatment with concentrated ammonium chloride solution followed by ether extraction yields crude bis-alkylated aminonitriles **3**, which may be used in the next step without further purification.

**Ketones 4 from α-Aminonitriles 3:**

A stirred mixture of aminonitrile **3** (10 mmol) and 2 normal hydrochloric acid (25 ml) is heated at 80° for 3 h (in the case of **3a**: 5 ml 2 normal potassium hydroxide/100°/5 h). After cooling to room temperature the mixture is extracted with ether, the organic phase is separated and dried with magnesium sulfate. After removal of the solvent the residue is distilled or recrystallized.

**Enamines 5 from α-Aminonitriles 3:**

In a three-necked flask (argon inlet, reflux condenser), the aminonitrile **3** (30 mmol) is dissolved in toluene or benzene (30 ml). Dry powdered potassium hydroxide (or potassium *t*-butoxide; 60 mmol) is added and the reaction mixture is heated with stirring under argon for the tabulated time. After cooling to room temperature, the solid is filtered off and extracted several times with absolute solvent. After removal of the solvent the residue is distilled under reduced pressure.

*We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.*

Received: August 4, 1978
(Revised form: October 16, 1978)

* Author to whom correspondence should be addressed.

[1] W. Raab, *Dissertation*, Universität Giessen, in preparation.
[2] C. Vonderheid, *Dissertation*, Universität Giessen, 1976.
[3] C. R. Hauser, H. M. Taylor, T. G. Ledford, *J. Am. Chem. Soc.* **82**, 1786 (1960).
[4] D. J. Bennet, G. W. Kirby, V. A. Moss, *J. Chem. Soc. Chem. Commun.* **1967**, 218; *J. Chem. Soc.* [C] **1970**, 2049.
[5] M. Mąkosza, B. Serafinowa, T. Boleslawska, *Roczn. Chem.* **42**, 817 (1968); *C. A.* **69**, 106174 (1968).
J. Dockx, *Synthesis* **1973**, 442.
[6] H. Ahlbrecht, K. Pfaff, *Synthesis* **1978**, 897.
[7] The structure of these intermediates is not yet established.
[8] B. Gröbel, D. Seebach, *Synthesis* **1977**, 357.
[9] D. Seebach, *Synthesis* **1969**, 17.
[10] G. Stork, L. Maldonado, *J. Am. Chem. Soc.* **93**, 5286 (1971).
[11] S. F. Dyke, E. P. Tiley, A. W. C. White, D. P. Gale, *Tetrahedron* **31**, 1219 (1975).
[12] H. M. Taylor, C. R. Hauser, *J. Am. Chem. Soc.* **82**, 1960 (1960); *J. Org. Chem.* **27**, 465 (1962).
[13] E. Vedejs, D. A. Engler, *Tetrahedron Lett.* **1977**, 1241.
[14] Enamine formation from ketone/amine in the presence of acid catalysts often leads to side reactions and aldol-type by products[15], mainly in the case of the rather unreactive *N*-methylaniline. This enamine type attracts our interest in another context[16].
[15] S. L. W. Haynes in *Enamines: Synthesis, Structure and Reactions*, A. Cook, Ed., M. Dekker, New York, 1969, p. 55.
[16] H. Ahlbrecht, *Chimia* **31**, 391 (1977).
[17] O. Cervinka, A. Fábryová, *Chem. Listy* **70**, 1266 (1976); *C. A.* **86**, 70958 (1977).
[18] R. Carlson, L. Nilson, C. Rappe, A. Babadjamian, J. Metzger, *Acta Chem. Scand.* [B] **32**, 85 (1978).
[19] P. Kurtz in Houben-Weyl, *Methoden der organischen Chemie*, 4th Edit., E. Müller, Ed., Vol. 8, Georg Thieme Verlag, Stuttgart, 1952, p. 279ff.
[20] J. Hoch, *Compt. rend.* **200**, 938 (1935); *Chem. Zentralbl.* **1935**, I, 3922.
[21] R. Fusco, S. Rossi, G. Bianchetti, *Gazz. Chim. Ital.* **91**, 841 (1961); *C. A.* **56**, 14019 (1962).
[22] L. Duhamel, P. Duhamel, S. Combrisson, P. Siret, *Tetrahedron Lett.* **1972**, 3603.
[23] H. Ahlbrecht, G. Rauchschwalbe, *Synthesis* **1973**, 417.
[24] D. Pocar, G. Bianchetti, P. Ferruti, *Gazz. Chim. Ital.* **97**, 597 (1967); *C. A.* **68**, 12927 (1968).
[25] D. Pocar, R. Stradi, B. Gioia, *Gazz. Chim. Ital.* **98**, 958 (1968); *C. A.* **70**, 28587 (1969).
[26] D. H. Hey, O. C. Musgrave, *J. Chem. Soc.* **1949**, 3156.
[27] L. A. Wiles, F. C. Baughan, *J. Chem. Soc.* **1953**, 933.
[28] P. G. Gassmann, G. D. Richmond, *J. Org. Chem.* **31**, 2355 (1966).
[29] P. W. Hickmott, B. J. Hopkins, C. T. Yoxall, *J. Chem. Soc.* [B] **1971**, 205.