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# Synthesis of α-Cyanoenamines by Cyanation of α-Bromoimmonium Bromides and Dehydrobromination of β-Bromo-α-(dialkylamino)nitriles

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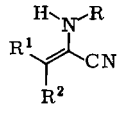
The reaction of α-bromoimmonium bromides **4** with potassium cyanide in dimethylformamide gave rise to β-bromo-α-(dialkylamino)nitriles **5**, which were dehydrobrominated in various base-solvent systems to afford (*E*)- and (*Z*)-α-cyanoenamines **2**. An adaption of a previously published preparation of α-cyanoenamines starting from aldehydes *via* enamines led to an improved, efficient and fast synthesis of the title compounds.

**Synthese von α-Cyanenaminen durch Cyanierung von α-Bromimmonium-bromiden und Dehydrobromierung von β-Brom-α-(dialkylamino)nitrilen**

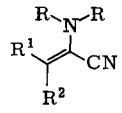
Die Reaktion der α-Bromimmonium-bromide **4** mit Kaliumcyanid in Dimethylformamid gibt β-Brom-α-(dialkylamino)nitrile **5**, die in verschiedenen Base-Lösungsmittel-Systemen zu (*E*)- und (*Z*)-α-Cyanenaminen **2** dehydrobromiert werden. Eine Modifizierung einer kürzlich veröffentlichten Synthese von α-Cyanenaminen **2** aus Aldehyden über Enamine führte zu einer verbesserten und schnellen Methode für die Darstellung der Titelverbindungen.

α-Cyanoenamines (**1**, **2**) are a group of functionalized olefins which contain a $sp^2$ carbon atom, geminally substituted with an electron-withdrawing and electron-donating substituent.

Scheme I



**1**



**2**

Especially during the last decade efforts have been undertaken for the synthesis of α-cyanoenamines, which were shown to be valuable synthons in synthetic organic chemistry (vide infra). A variety of synthetic methods are now available to synthesize secondary α-cyanoenamines **1** and tertiary α-cyanoenamines **2**. Secondary α-cyanoenamines **1** are synthesized by reaction of α-chloroaldimines with potassium cyanide[2-4] or, to a lesser extent, by dehydrohalogenation of appropriate β-halo-α-(alkylamino)nitriles[5-7].

Only in the former case are secondary α-cyanoenamines **1** generally accessible, while in the latter case an additional isomerism to the tautomeric imidoyl cyanides prohibits isolation of pure α-cyanoenamines.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Functionalized primary α-cyanoenamines **1** (R = H) are available from cyanide addition to dihaloacetonitrile[8,9]. Tertiary α-cyanoenamines **2** are synthesized by reaction of cyanide with α-chloroenamines[10], amide chlorides[10], thioimidate salts[11] and ynamines[12], while other general synthetic methods involved dehydrohalogenation of β-halo-α-(dialkylamino)nitriles, the latter being obtained from α-haloaldehydes[13-16] or enamines[16,17]. Alternative valuable entries to α-cyanoenamines are *N*-alkylation of secondary α-cyanoenamines[18], condensation of carbonyl compounds with the anion derived from diethyl 1-cyano-1-(dimethylamino)methanephosphonate[19] or α-(*N*-methylanilino)-α-(trimethylsilyl)acetonitrile[20]. Less general examples of syntheses of α-cyanoenamines involved isomerization of α-cyanoallylic amines[21-23], reaction of α-chloroacrylonitrile with secondary amines[24] and thermolysis of α,α-dicyanoamines[25]. Finally, the literature contains a great variety of reports dealing with β-functionalized α-cyanoenamines but lack of space does not permit to go into detail here (examples of functional groups in the β-position are: cyano, amino, halo, alkoxycarbonyl, etc.)[26].

α-Cyanoenamines have proven to be of great utility in organic synthesis as demonstrated by their conversion into 1,4-diones[27], 1,2-diones[10], ketenimines[28], amides[29,30], α-haloimidoyl cyanides[3,4], acyl cyanides[7], carboxylic acids[10,19], lactones[15], and dihydropyrazines[10]. Further applications of α-cyanoenamines involve α- or γ-alkylation of their anions[15,31] and 1,2- or 1,4-addition of the latter to enones[31], a general synthesis of ketones or aldehydes[20], and their use as β-carboxylvinyl anion equivalents[11].

This introduction shows that much interest was dedicated to the chemistry of α-cyanoenamines. In connection with our previous interests in this field[2-4,18,26e,28-30] and in conjunction with our research in the field of α-halogenated imino compounds[32], we reasoned that the addition of cyanide ion to α-bromoimmonium bromides, derived from aldehydes, and subsequent dehydrobromination would constitute a viable route to tertiary α-cyanoenamines. In this report we describe our results of this strategy, which led to an efficient and fast synthesis of α-cyanoenamines starting from aldehydes.

## Results and Discussion

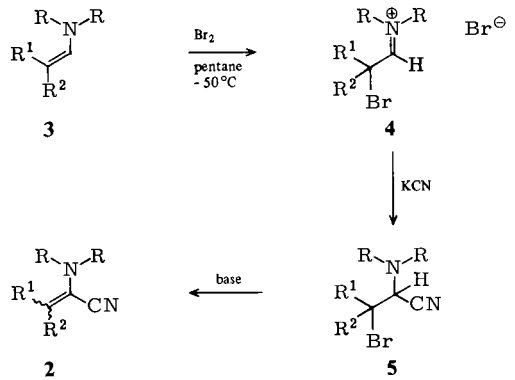
### Cyanation of α-Bromoimmonium Bromides and Dehydrobromination of β-Bromo-α-(dialkylamino)nitriles

α-Halogenated aldimines readily react with potassium cyanide in various organic solvents, e.g. methanol, dimethylformamide, dimethyl sulfoxide, to give rise to secondary α-cyanoenamines **1** by nucleophilic addition of cyanide to the imino function followed by dehydrochlorination of the resulting β-chloro-α-(alkylamino)-nitriles[2-4]. α-Halogenated immonium halides should be more reactive because of the positively charged immonium moiety. Indeed, non-halogenated immonium halides afford the corresponding α-(dialkylamino)nitriles very easily on reaction with cyanide[33]. α-Halogenated immonium halides are very reactive towards nucleophiles[32b,34] and most of these reactions are initiated by an addition of the nucleophile at the immonium function after which various reactions take place, among others rearrangement *via* aziridinium intermediates[32b]. Up to now the reaction of α-haloimmonium halides towards cyanide ion has not been described. We investigated this reaction with α-bromoimmonium bromides **4** in the hope of effecting a suitable alternative entry into the field of α-cyanoenamines.

α-Bromoimmonium bromides **4** were *in situ* prepared by reaction of bromine with enamines **3**, which were obtained from the condensation of aldehydes and secondary amines in the presence of potassium carbonate[35,36]. Our initial experiments were run with α-bromoimmonium bromides **4** which were treated with potassium cyanide under reflux (1 – 3 h) in various solvents, e.g. acetonitrile, methanol or water and gave rise to mainly the desired α-cyanoenamines besides the corresponding β-bromo-α-(dialkylamino)nitriles and some unidentified minor products. However, in some batches (especially at elevated temperature) an important side-reaction was noticed, namely the conversion of the immonium function of **4** into the corresponding α-bromodimethyl acetal. In order to get rid of the competitive reaction of the solvent, the investigation of the reaction of α-bromoimmonium bromides with potassium cyanide in dimethylformamide was undertaken. The reaction of α-bromoimmonium bromides **4** ($R^2$ = H), derived from primary aldehydes, with three molar equivalents of potassium cyanide in dimethylformamide is rather slow at room temperature and furnishes β-bromo-α-(dialkylamino)nitriles **5**, but in some cases the latter product is further dehydrobrominated to afford the corresponding α-cyanoenamine **2** (Table 1; Procedure A).

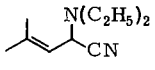
The reproducibility of these reactions is not very good because, depending on the temperature, the duration of the reaction and the scale on which the reaction is run, variable amounts of α-cyanoenamine **2** (*E* and *Z*) and β-bromo-α-(dialkylamino)-nitriles **5** were isolated.

Scheme II




**3** **4** **2** **5**

| | $R^1$, $R^2$ | NRR |
|---|---|---|
| **a** | Et, H | $NEt_2$ |
| **b** | Et, H | morpholino |
| **c** | Et, H | piperidino |
| **d** | *i*-Pr, H | $NEt_2$ |
| **e** | *i*-Pr, H | morpholino |
| **f** | *i*-Pr, H | pyrrolidino |
| **g** | *n*-Pr, H | $NEt_2$ |
| **h** | *n*-Pr, H | pyrrolidino |
| **i** | Me, Me | morpholino |
| **j** | Me, Me | pyrrolidino |



**6**

The latter, which easily crystallize from the reaction mixture, can be transformed without contamination into α-cyanoenamines **2** by base-induced dehydrobromination with potassium cyanide (1.5 equivalents) in methanol under reflux. This dehydrobromination in methanol yields (*Z*)-α-cyanoenamines **2** exclusively. The reaction in methanol requires about one hour while the dehydrobromination in dimethylformamide was executed at 80 – 90 °C during one hour, as far as $R^1$ is an unbranched substituent. The

Table 1. Conversion of Enamines **3** into β-Bromo-α-(dialkylamino)nitriles **5** or α-Cyanoenamines **2** under Various Conditions

| | $R^1$, $R^2$ | NRR | Reaction Conditions[a] | Products |
|---|---|---|---|---|
| **a** | Et, H | $NEt_2$ | 1) Procedure B<br>2) 1.5 E KCN/MeOH; Δ 1.5 h | 92% 2-(diethylamino)-2-pentenenitrile (**2a**) (*E*/*Z* 8/92); preparative GLC analysis changed the ratio *E*/*Z* to 78/22 |
| | | | 1) Procedure B<br>2) 3 E KCN/DMF; 85°C/5 h | 94% 2-(diethylamino)-2-pentenenitrile (**2a**) (crude) (*E*/*Z* 88/12); 87% (dist.) |
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | crude yield of 2-(diethylamino)-2-pentenenitrile (**2a**) (*E*/*Z* 6/94) is quantitative; distillation: 88% |
| **b** | Et, H | morpholino | 1) Procedure A<br>2) 3 E KCN/$H_2O$; RT 17 h | 40% (*E*)-2-morpholino-2-pentenenitrile (**2b**) |
| | | | **5b** + 1.5 E KCN/DMF; 1 h/90°C | 62% (*E*)-2-morpholino-2-pentenenitrile (**2b**) |
| | | | **5b** + 1.5 E KCN/MeOH; Δ 1 h | 82% (*Z*)-2-morpholino-2-pentenenitrile (**2b**) (dist.) |
| | | | **5b** + 1.5 E $Et_3N/C_6H_6$/Δ 1 h | only 20% conversion into 2-morpholino-2-pentenenitrile (**2b**) |
| **c** | Et, H | piperidino | 1) Procedure A<br>2) 2 E KCN/DMF; 85°C 1 h | 31% 2-piperidino-2-pentenenitrile (**2c**) (dist.); *E*/*Z* 25/75 |
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | 89% 2-piperidino-2-pentenenitrile (**2c**) (dist.); *E*/*Z* 9/91 |
| **d** | *i*-Pr, H | $NEt_2$ | 1) Procedure A<br>2) 3 E KCN/DMF; RT 24 h | 18% 3-bromo-2-(diethylamino)-4-methylpentanenitrile (**5d**) and 20% (*Z*)-2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**); in some batches, 2-(diethylamino)-4-methyl-3-pentenenitrile (**6**) was isolated as the major product (see text) |
| | | | **5d** + 1.5 E KCN/MeOH; Δ 1 h | 72% 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z*) |
| | | | 1) Procedure B<br>2) 2 E KCN/$CH_3CN$; Δ 22 h | ≈20% 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z* 2/1) + unidentified products |
| | | | 1) Procedure B<br>2) 3 E KCN/DMF; 90°C 20 h | 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z* 50/50); 84% crude; 75% (dist.) |
| | | | 1) Procedure B<br>2) 3 E KCN/DMF; RT 22 h | 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z* 6/94); quantitative crude yield |
| | | | 1) Procedure B<br>2) 3 E KCN/DMF; 60°C 16 h | 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z* 10/90); quantitative crude yield |
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z* 8/92); quantitative crude yield |

Table 1 (*Continued*)

| | $R^1$, $R^2$ | NRR | Reaction Conditions[a] | Products |
|---|---|---|---|---|
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; RT 4 h | 2-(diethylamino)-4-methyl-2-pentenenitrile (**2d**) (*E*/*Z* 6/94); quantitative crude yield |
| **e** | *i*-Pr, H | morpholino | 1) Procedure A<br>2) 3 E KCN/DMF; RT 16 h | 35% 3-bromo-4-methyl-2-morpholinopentanenitrile (**5e**), m.p. 132 °C[b] |
| | | | **5e** + 1.5 E KCN/MeOH; Δ 1 h | 72% (*Z*)-4-methyl-2-morpholino-2-pentenenitrile (**2e**) (dist.) |
| | | | **5e** + 2 E KCN/DMF; 115 °C/6 h | 80% 4-methyl-2-morpholino-2-pentenenitrile (**2e**) (*E*/*Z* 90/10) + unidentified products |
| **f** | *i*-Pr, H | pyrrolidino | 1) Procedure B<br>2) 3 E KCN/DMF; 80 °C/4 h | 92% (*E*)-4-methyl-2-pyrrolidino-2-pentenenitrile (**2f**) |
| | | | 1) Procedure B<br>2) 1.5 E KCN/MeOH; Δ 45 min | quantitative yield of 4-methyl-2-pyrrolidino-2-pentenenitrile (**2f**) (crude); *E*/*Z* 21/79; on preparative GLC analysis the *E*/*Z* ratio changed to 91/9 |
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | quantitative yield of 4-methyl-2-pyrrolidino-2-pentenenitrile (**2f**) (crude); *E*/*Z* 9/91; 90% (dist.) |
| **g** | *n*-Pr,H | $NEt_2$ | 1) Procedure B<br>2) 3 E KCN/DMF; 80 °C/8 h | 86% 2-(diethylamino)-2-hexenenitrile (**2g**) (dist.); *E*/*Z* 6/94 |
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | 90% 2-(diethylamino)-2-hexenenitrile (**2g**) (crude); *E*/*Z* 16/84 |
| **h** | *n*-Pr, H | pyrrolidino | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | 71% 2-pyrrolidino-2-hexenenitrile (**2h**) (dist.); *E*/*Z* 15/85 |
| **i** | Me, Me | morpholino | 1) Procedure A<br>2) 1.5 E KCN/DMF; 1 h RT + 1 h 85 °C | 38% 3-methyl-2-morpholino-2-butenenitrile (**2i**) |
| | | | 1) Procedure B<br>2) 1.2 E NaOMe/MeOH 2 N; Δ 20 min | 78% 3-methyl-2-morpholino-2-butenenitrile (**2i**) (dist.) |
| **j** | Me, Me | pyrrolidino | 1) Procedure A<br>2) 3 E KCN/MeOH; RT 3 h + Δ 1.5 h | 80% 3-methyl-2-pyrrolidino-2-butenenitrile (**2j**) (GLC) + 10% 3-bromo-3-methyl-2-pyrrolidinobutanenitrile (**5j**) |
| | | | 1) Procedure A<br>2) 3 E KCN/$H_2O$; RT 1 h | 55% 3-methyl-2-pyrrolidino-2-butenenitrile (**2j**) + 15% 3-bromo-3-methyl-2-pyrrolidinobutanenitrile (**5j**) + unidentified products |

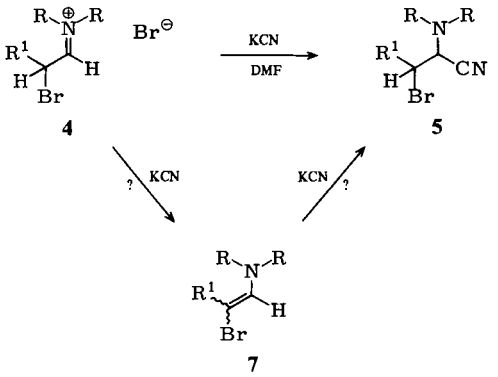
[a] Procedure A: enamine **3** + $Br_2$/pentane/ − 50 °C/15 min; Procedure B: enamine **3** + BrCN/acetonitrile/RT/5 min; Δ = reflux; RT = room temperature; E = equivalents. − [b] Lit. m.p. 132 − 133 °C (ref.[16]).

dehydrobromination of the more branched 3-bromo-4-methyl-2-morpholinopentanenitrile (**5e**) with potassium cyanide (2 equivalents) in dimethylformamide required heating at 115 °C during six hours. On the other hand, reaction of the same substrate **5e** with potassium cyanide in methanol proceeds smoothly over a period of one hour.

It is worthnoting that some experiments with 1-(diethylamino)-3-methyl-1-butene **3d** gave deviating results. After reaction of this enamine with bromine in pentane and subsequent treatment with potassium cyanide in dimethylformamide (40 °C/15 h) the deconjugated product **6** was isolated as the major product. Attempts to isomerize this allylic amine **6** to the conjugated α-cyanoenamine **2d** with potassium cyanide in methanol under reflux (2 h) was only partially successful (yield ≈30%). It should be pointed out that the strategy *via* α-bromoimmonium bromides and subsequent conversion into α-cyanoenamines has been applied in one heterocyclic case, namely for the synthesis of 1,3-dimethyl-2-cyano-4-(3-methoxyphenyl)-1,4,5,6-tetrahydropyridine[37].

Concerning the mechanism of the conversion with potassium cyanide in dimethylformamide of *in situ* prepared α-bromoimmonium bromides **4** into β-bromo-α-(dialkylamino)nitriles **5**, it should be emphasized that this reaction is possible either by a more plausible direct addition of cyanide at the immonium function or, alternatively, by deprotonation of the α-bromoimmonium compound by cyanide to afford the corresponding β-bromoenamine **7** (Scheme III). The latter can undergo addition of cyanide at the more electrophilic carbon (1-position) to furnish β-bromo-α-(dialkylamino)nitriles **5**.

Scheme III



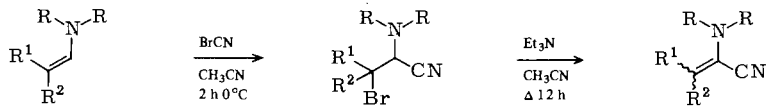

Of course, this reasoning is only valid for α-bromoimmonium bromides **4** having an α-hydrogen ($R^2$ = H in the general scheme), but it does not exclude that both routes, as outlined in scheme V, are operative.

### Addition of Cyanogen Bromide to Enamines and Subsequent Dehydrobromination into α-Cyanoenamines

The elegant synthesis of α-cyanoenamines **2**, starting from the addition of cyanogen bromide to enamines **3** and subsequent dehydrobromination, recently described by *Ahlbrecht* et al. (Scheme IV)[16], proceeds parallel to the strategy developed in the final

part of the present report (i.e. Procedure A and subsequent dehydrobromination). Both strategies employ the same starting material and make use of a dehydrobromination as the final step. Only the reaction sequence from **3** to **5** is different, but the direct addition of cyanogen bromide, as described by the above mentioned authors[16] is far more convenient than the two-step-approach *via* bromination and cyanide addition. Therefore we decided to combine the published work of *Ahlbrecht* et al.[16] with our findings discussed above. As a result, this combination together with some considerable improvements led to an efficient, fast, and high-yield synthesis of tertiary α-cyanoenamines starting from enamines **3** (or more essentially from their precursors, i.e. aldehydes) (Table 1).

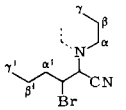
Scheme IV




**3** **5** **2**

The first improvement of the above mentioned sequence (Scheme IV) was based on the observation that the reaction of enamines **3** with cyanogen bromide (1.0 molar equivalents) in acetonitrile is complete after five minutes and that simple evaporative removal of the solvent yields the crude β-bromo-α-(dialkylamino)nitrile **5** in nearly quantitative yield (Procedure B). The $^{13}C$ NMR data of these compounds are compiled in Table 2.

Table 2. $^{13}C$ NMR Spectral Data (δ, $CDCl_3$) of β-Bromo-α-(dialkylamino)nitriles **5**

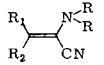


**5**

| | NRR | $R^1$ | $C_\alpha$ | $C_\beta$ | $C_\gamma$ | C≡N | C–C≡N | C–Br | $C_{\alpha'}$ | $C_{\beta'}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | $NEt_2$ | Et | 45.65 | 13.02 | – | 115.50 | 60.61 | 54.81 | 28.51 | 11.66 |
| **5b** | morpholino | Et | 50.25 | 66.46 | – | 113.97 | 63.79 | 52.12 | 28.58 | 11.50 |
| **5c** | piperidino | Et | 51.33 | 25.76 | 23.98 | 114.46 | 64.53 | 52.96 | 28.77 | 11.58 |
| **5d** | $NEt_2$ | *i*-Pr | 45.62 | 13.14 | – | 115.49 | 61.37 | 59.73 | 30.80 | 22.38<br>16.26 |
| **5e** | morpholino | *i*-Pr | 50.01 | 66.54 | – | 113.86 | 62.87 | 58.70 | 30.73 | 22.18<br>16.40 |
| **5f** | pyrrolidino | *i*-Pr | 49.84 | 23.75 | – | 114.87 | 61.37 | 59.73 | 30.96 | 22.10<br>16.54 |

The second improvement deals with the dehydrohalogenation step[16] which, according to *Ahlbrecht's* method, required a reflux period of twelve hours with triethylamine in acetonitrile, but for sterically more hindered derivatives, such as 3-bromo-4-methyl-2-morpholinopentanenitrile (**5e**), the reflux period mounted to two days. While the

Table 3. Physical and Spectral Data of α-Cyanoenamines **2**



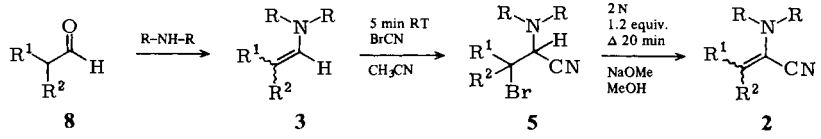
| | $R^1$ | $R^2$ | NRR | B.p. °C/Torr | Yield [a] | IR (NaCl; $cm^{-1}$) $\nu_{C\equiv N}$ | IR (NaCl; $cm^{-1}$) $\nu_{C=C}$ | $^1$H-NMR (δ; $CCl_4$) $CH=C$ | N-Analyses (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | Et | H | $NEt_2$ | 85 – 87/12 | 88% [b] | 2210 | 1610 – 1615 | 6.10 (t, $J$ = 8 Hz) | Calcd. | 18.40 |
| | H | Et | | | | 2225 | 1610 – 1615 | 5.11 (t, $J$ = 8 Hz) | Found | 18.49 |
| **2b** | Et | H | morpholino | 120 – 122/12 | 82% [c] | 2220 | 1620 | 5.90 (t, $J$ = 7.5 Hz) | Calcd. | 16.85 |
| | H | Et | | | | | | 5.17 (t, $J$ = 7.5 Hz) | Found | 16.92 |
| **2c** | Et | H | piperidino | 112 – 120/15 | 89% | 2205 | 1615 – 1630 | 5.71 (t, $J$ = 7 Hz) | Calcd. | 17.06 |
| | H | Et | | | | | | 5.08 (t, $J$ = 7 Hz) | Found | 16.95 |
| **2d** | *i*-Pr | H | $NEt_2$ | 88 – 95/12 | 75% | 2215 | 1615 | 5.91 (d, $J$ = 10 Hz) | Calcd. | 16.85 |
| | H | *i*-Pr | | | | 2230 | 1615 | 4.91 (d, $J$ = 10 Hz) | Found | 16.90 |
| **2e** | *i*-Pr | H | morpholino | 123 – 124/10 | 72% [d] | 2220 | 1620 – 1640 | 5.79 (d, $J$ = 10 Hz) | Calcd. | – |
| | H | *i*Pr | | | | 2230 | 1620 | 5.00 (d, $J$ = 10.5 Hz) | Found | – |
| **2f** | *i*-Pr | H | pyrrolidino | 108 – 113/12 | 90% | 2218 | 1615 | 5.25 (d, $J$ = 10 Hz) | Calcd. | 17.06 |
| | H | *i*-Pr | | | | 2224 | 1612 | 4.66 (d, $J$ = 10 Hz) | Found | 17.01 |
| **2g** | *n*-Pr | H | $Et_2N$ | 98 – 108/12 | 86% | 2208 | 1610 | 6.10 (d, $J$ = 7 Hz) | Calcd. | 16.85 |
| | H | *n*-Pr | | | | | | 5.13 (d, $J$ = 7.5 Hz) | Found | 16.96 |
| **2h** | *n*-Pr | H | pyrrolidino | 43 – 47/0.01 | 71% | 2220 | 1612 | 5.33 (t, $J$ = 7.5 Hz) | Calcd. | 17.06 |
| | H | *n*-Pr | | | | | | 4.73 (t, $J$ = 7.5 Hz) | Found | 17.19 |
| **2i** | Me | Me | morpholino | 114 – 122/12 [e] | 78% | 2205 | 1650 | – | Calcd. | – |
| | | | | | | | | | Found | – |
| **2j** | Me | Me | pyrrolidino | – | – [f] | 2205 | 1650 | – | Calcd. | – |
| | | | | | | | | | Found | – |

[a] Yields refer to the improved route described in this paper, i.e. reaction of enamines **3** with cyanogen bromide and subsequent reaction with sodium methoxide in methanol (two-step-sequence). – [b] Known compound (ref.[31]); yield 75%; no physical data given). – [c] Compound **2b** was obtained from **5b** and KCN (1.5 equiv.) in methanol under reflux for one hour (100% *Z*). – [d] Compound **2e** was obtained from **5e** and KCN (1.5 equiv.) in methanol under reflux for one hour (100% *Z*); reported b.p. 53 – 55 °C/0.001 Torr (ref.[16]). – [e] Reported b.p. 116 – 119 °C/20 Torr (ref.[16]). – [f] See Table 1.

dehydrobromination of **5** worked nicely with potassium cyanide in methanol or dimethylformamide, we found that sodium methoxide in methanol (2 N solution; 1.2 equivalents) cleanly (and nearly quantitatively) converted compounds **5** into α-cyanoenamines **2** after a reflux period of twenty minutes. The crude reaction mixture consisted of essentially pure α-cyanoenamines. This reaction can even be run at room temperature (4 h).

Combining all improving factors results in an excellent synthesis of α-cyanoenamines according to a sequence in which an aldehyde **8** is converted (by known methods) to an enamine, which is treated with cyanogen bromide in acetonitrile at room temperature during five minutes and, after evaporation of the solvent, the resulting β-bromo-α-(dialkylamino)nitrile **5** is reacted with sodium methoxide in methanol (2 N; 1.2 equivalents; reflux 20 min) to afford α-cyanoenamines **2** in 71 – 90% yield (two steps) (Table 3; Scheme V; recommended procedure).

Scheme V




**8** **3** **5** **2**

**Stereochemistry of α-Cyanoenamines 2**

The stereochemistry of α-cyanoenamines **2** was determined by NMR spectrometry. The coupling constant between the nitrile carbon atom ($^{13}$C NMR) and the olefinic β-hydrogen (if $R^2$ = H) is markedly different for the (*E*)- and (*Z*)-isomers. The coupling constant $J_{HC=C-C\equiv N}$ of the (*E*)-isomers is about 12 Hz, while the value for the (*Z*)-isomers is about 5 – 6 Hz[19]. A more simple method for α-cyanoenamines bearing only one β-alkyl group ($R^2$ = H) consists of measuring the chemical shift of the olefinic β-hydrogen ($^1$H NMR). The δ-value of the olefinic hydrogen of (*E*)-α-cyanoenamines ranges from 5 – 5.4 ppm while the value for the (*Z*)-isomer is much higher, namely 5.7 – 5.9 ppm[19]. Concerning the infrared spectra of α-cyanoenamines **2**, it was found that the nitrile absorption of the *E*-isomer was situated at higher wave number (2225 – 2230 $cm^{-1}$) as compared to the *Z*-isomer (2205 – 2215 $cm^{-1}$) (Table 3). It should be pointed out that considerable changes in the *E*/*Z* ratio of α-cyanoenamines **2a – h** occur under gas chromatographic circumstances (see Table 1).

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## Experimental Part

Infrared spectra: Perkin Elmer model 1310 spectrophotometer. – $^1$H NMR: Varian T-60 NMR spectrometer. – $^{13}$C NMR spectra ($CDCl_3$): Varian FT-80 NMR-spectrometer (TMS as internal standard). – Mass spectra: Varian-Mat 112 mass spectrometer (70 eV).

*Synthesis of Enamines* **3**

Enamines **3** were prepared by standard literature procedures. Enamines **3a,c,d,e,f,g,h** were synthesized by reaction of aldehydes **8** ($R^2$ = H) with two molar equivalents of the secondary amine in the presence of dry potassium carbonate (60 g/mol aldehyde)[35,36] at room temperature (1 h); filtration and distillation afforded the desired enamines. Enamine **3j** (NRR = pyrrolidino) was prepared from butanal and pyrrolidine in benzene using a Dean-Stark apparatus, while enamine **3i** originated from the reaction of morpholine with excess isobutyraldehyde without solvent[37].

B.p.'s: **3a** 44–47°C/11 Torr, **3b** 71–75°C/11 Torr, **3c** 80–84°C/12 Torr, **3d** 48–49°C/11 Torr, **3e** 83–84°C/11 Torr, **3f** 70–71°C/12 Torr, **3h** 75–81°C/12 Torr, **3i** 56–58°C/11 Torr.

*Conversion of Enamines* **3** *into β-Bromo-α-(dialkylamino)nitriles* **5** *or α-Cyanoenamines via α-Bromoimmonium Bromides* **4**

A solution of 0.05 mol of freshly prepared enamine **3** in 150 ml of dry pentane, cooled to −50°C, was treated dropwise under stirring with 0.0525 mol of bromine, dissolved in 20 ml of pentane. A yellow precipitate of α-bromoimmonium bromide **4** is immediately formed. The suspension was stirred for another ten minutes and subsequently treated with 0.15 mol of potassium cyanide and 20–25 ml of dimethylformamide. Pentane was evaporated under vacuo at ambient temperature and the remaining reaction mixture was treated as described in Table 1 (Procedure A). If the reaction of potassium cyanide with α-bromoimmonium bromides **4** is performed in another solvent, e.g. methanol, water or acetonitrile, then a 10%-solution of **4** in this solvent was used.

Work-up of the reaction mixture was performed by pouring into 200 ml of water and extraction with pentane/ether (1 : 1). The reaction mixture was analyzed by spectrometry (NMR, IR) and gas chromatography, followed by distillation in vacuo. The results are described in Table 1.

*General Procedure for the Conversion of Enamines* **3** *into α-Cyanoenamines* **2** *(Recommended procedure)*

A solution of 0.10 mol of enamine **3** in 130 ml of acetonitrile was treated portionwise, under stirring, with 0.10 mol of cyanogen bromide (cooling with a waterbath). Stirring was continued for five minutes after which the solvent was evaporated in vacuo (Procedure B). The remaining crude β-bromo-α-(dialkylamino)nitrile **5** was treated with 60 ml of 2 N sodium methoxide in methanol (0.12 mol) upon which sodium bromide started to precipitate. The reaction mixture was additionally refluxed under stirring during twenty minutes. After cooling to ambient temperature, the reaction mixture was poured into 250 ml of water and extraction was performed with dichloromethane or diethyl ether. The combined extracts (three extractions with 100 ml, 80 ml and 50 ml, respectively) were dried ($MgSO_4$) and after evaporation of the solvent the remaining clear oil was distilled in vacuo to afford the α-cyanoenamine **2**. Physical and spectrometric data (NMR, IR) are given in Table 3. As an example, the mass spectrum (70 eV) of 2-morpholino-2-pentenenitrile (**2b**) is given here: *m/e* (relative intensity), 166 ($M^+$, 19); 151 (61); 138 (14); 125 (24); 108 (61); 93 (100); 81 (26); 80 (42); 68 (35); 66 (96); 57 (32); 56 (32); 55 (29); 54 (58); 53 (58); 52 (38); 51 (16); 42 (96); 41 (89); 39 (67).

The $^{13}C$ NMR spectrum of compound **2j** serves also as an example: δ ($CDCl_3$): 24.62 (N–C–$CH_2$); 52.08 (N–$CH_2$); 19.03 and 21.74 (β-methyls); 114.71 ($C{\equiv}N$); 145.77 (N–C=$C$); 119.17 (N–$C$=C).

*Preparation of β-Bromo-α-(dialkylamino)nitriles* **5**

The addition of cyanogen bromide to enamines **3** was performed as described in the General Procedure. After evaporation of acetonitrile in vacuo, the remaining β-bromo-α-(dialkylamino)-

nitrile **5** was found to be sufficiently pure (NMR). The product may be recrystallized from ether/hexane (freezer at −20°C). As an example, 3-bromo-2-(diethylamino)-4-methylpentanenitrile (**5d**) was obtained from enamine **3d** and had m.p. 41°C. Mass spectrum of **5d**: *m/e* (relative abundance), 246/8 ($M^+$, 1%); 204/6 (1.5); 167 (1.5); 140(2); 126(3); 111(100; $Et_2\overset{+}{N}=CH-CN$); 83(9); 67(5); 56(46); 42(27); 41(21).

$^{13}C$ NMR data of compounds **5** are compiled in Table 2.


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