An Effective Synthesis of α-Cyanoenamines by Peterson Olefination

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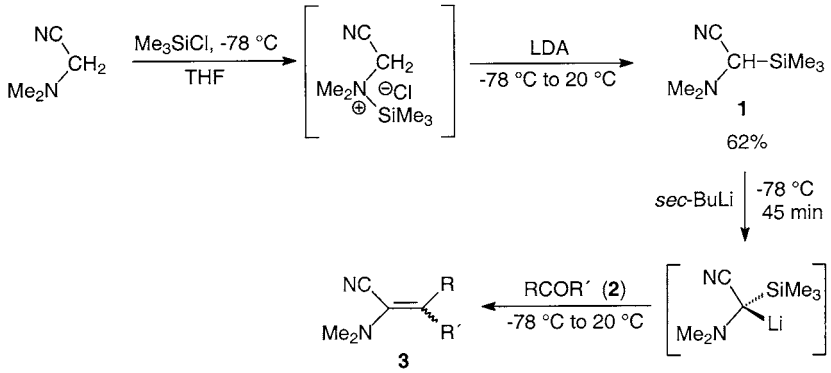
Abstract: A convenient and gentle method for the synthesis of α-cyanoenamines based on the Peterson olefination has been developed. For these sensitive, highly functionalized olefins, the present method is superior to the Horner–Emmons condensation, as manifested by the higher yields and broader scope.

Key words: α-Cyanoenamines, Peterson olefination, Horner–Emmons condensation

During our research work we required an efficient and gentle method for the synthesis of diverse terminally substituted acceptor-donor olefins, in particular α-cyanoenamines. Such doubly functionalized olefins have been shown to be of great utility in organic synthesis, as demonstrated by their conversion into 1,4-diones,[1a] 1,2-diones,[1b] ketenimines,[1c] carboxylic acids [1b,2a,d] and lactones.[1d] Moreover, the allylic anions derived from α-cyanoenamines have been used for α or γ alkylation,[1b,d] 1,2 or 1,4 addition to enones,[1d,e] and as β-carboxylvinyl anion equivalents.[1o–r] The noteworthy methods to prepare the desired α-cyanoenamine in a one-pot reaction include the Horner–Emmons, Peterson, and Knoevenagel condensations.[2]

Despite these popular methods which have been developed during the last decades,[1,2] the synthesis of α-cyanoenamines under mild conditions still remains to be a challenge in synthetic organic chemistry, as the following brief exposition manifests. For example, the preparation of α-cyanoenamines by the Horner–Emmons reaction was reported by Gross and Costisella[2a] under a variety reaction conditions, but this reaction is not generally applicable because the employed conditions are too drastic for labile carbonyl partners. The Knoevenagel reaction was utilized by the Ahlbrecht's group[2b] with LDA and by Jończyk[2c] under phase-transfer conditions, but both are limited to *N*-methylanilinoacetonitrile as active methylene unit. This α-cyanoenamine method was also employed by Takahashi et al,[2d] who prepared a series of homologated carboxylic acids through the hydrolysis of the corresponding α-cyanoenamines. Their attempt to extend this methodology to other aminoacetonitriles failed and only traces of the expected condensation products were detected. Subsequently, Padwa and coworkers[3] showed through trapping experiments with trimethylsilyl chloride that the carbanion essential for condensation could only be confirmed in the case of *N*-methylanilinoacetonitrile. The α-silylated product was obtained in a mere 10% yield, other aminoacetonitriles gave the respective selfcondensation products.

A convenient synthesis of the pertinent Peterson precursor, namely the silylated aminoacetonitriles **1**, was provided also by Padwa's group, who inverted the addition order of the reagents, that is, first the trimethylsilyl chloride and subsequently LDA as base (Scheme 1). Deprotonation of the silammonium salt generated in situ a nitrogen ylide intermediate, which undergoes 1,2-silyl transposition to the desired α-silylated aminoacetonitrile **1**. This reaction procedure was later optimized by Sato



Scheme 1 Synthesis of the α-Cyanoenamines **3** from α-Dimethylamino-α(trimethylsilyl)acetonitrile (**1**) and Carbonyl partner **2** by the Peterson Olefination

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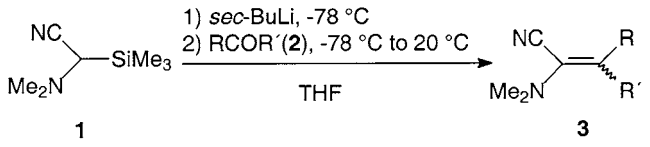
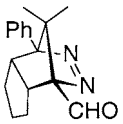
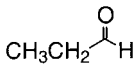
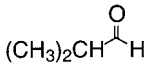
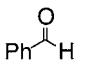
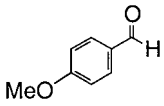
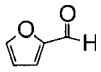
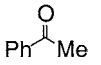
and coworkers,[4] who prepared a series of α-amino-α(trimethylsilyl)acetonitriles. These were converted to 1-(trimethylsilyl)alkylamines by replacing the cyano functionality of the α-silylated aminoacetonitriles by alkyl groups on treatment with the corresponding Grignard reagents.

The Peterson-olefination procedure (Scheme 1) was utilized in the present work to prepare the the α-cyanoenamines **3** in good yields from α-silylated aminoacetonitrile **1** and the carbonyl compounds **2** (Table 1).

Table 1 Synthesis of the α-Cyanoenamine **3** by the Peterson Olefination



1 3

RCOR′		Convn (%)[a]	yield of **3** (%)[b,c]	*E*:*Z*[d]
	(**2a**)	81	69	>95:05
	(**2b**)	>95	78 (50)	91:09
	(**2c**)	>95	76 (69)	90:10
	(**2d**)	>94	91 (64)	64:36
	(**2e**)	>95	93	54:46
	(**2f**)	>95	88	61:39
	(**2g**)	58	43 (24)	69:31

[a] Conversion determined from the re-isolated carbonyl compound **2**.
[b] Yield of the isolated α-cyanoenamine **3** after radial-chromatographic purification (Chromatotron).
[c] In parenthesis are given the yields for the Horner–Emmons method (ref.[2a]).
[d] *E*:*Z* ratio determined from the areas of the olefin signals in the ^{1}H NMR spectrum (± 5% of the stated value).

The critical carbonyl partner was the quite labile azoaldehyde **2a**, for which all previously reported olefination methods have failed; therewith the need was exposed to develop a more suitable method. Indeed, the present communication demonstrates that quite a good yield (69%) of the corresponding α-cyanoenamine **3a** may be obtained, as shown in the first entry of Table 1. Essential for success is the proper choice of the base for the deprotonation of the α-silylated *N*,*N*-dimethylacetonitrile **1**. Optimal results were obtained with *sec*-BuLi, which deprotonated selectively and efficiently the α-proton from the α-silylated *N*,*N*-dimethylacetonitrile **1** to generate the corresponding carbanion; therefore, this effective base was used for all subsequent reactions.[5]

The scope of the successful Peterson olefination method is displayed in Table 1, in which the set of diverse α-cyanoenamines **3** have been prepared. Some of them have been synthesized previously by the Horner–Emmons olefination. The high yields of the Peterson method confirm that this condensation procedure is superior to the Horner–Emmons one. The tested carbonyl compounds reveal that the best yields were obtained for the reactive aromatic and heteroaromatic aldehydes **2d**–**f**. Although the yields of the aliphatic α-cyanoenamines **3b**,**c** are lower, but still comparatively good, the diastereomeric differentiation is much better, since *E*:*Z* ratios of 90:10 were obtained for the derivatives **3b**,**c** compared to about 60:40 for the aromatic derivatives **3d**–**f**. In the case of acetophenone (**2g**) as carbonyl partner, the low conversion manifests the general reactivity trend of ketones versus aldehydes in such olefinations reactions.

All in all, we demonstrated herein that the presently developed olefination is the method of choice for the preparation of α-cyanoenamines **3**, as confirmed by the higher yields and a broader scope than the Horner–Emmons reaction. The efficacy of the Peterson methodology presumably derives from the higher oxygenphilicity of silicon versus phosphorus, which enables sufficiently gentle reaction conditions to employ labile carbonyl compounds and minimize as well the decomposition of the sensitive α-cyanoenamines **3**.

General Procedure for the Preparation of α-Cyanoenamine 3

A solution of 1.27 mmol of the α-dimethylamino-α(trimethylsilyl)acetonitrile **1** in 20 mL of abs. THF was cooled under an argon-gas atmosphere to –78 °C, 1.00 mL (1.3 M, hexane) of *s*-BuLi was added dropwise by means of a syringe, and the reaction mixture stirred magnetically for 45 min at –78 °C. To the solution was added 1.20 mmol of the corresponding carbonyl partner **2**, the reaction mixture was allowed to warm up slowly to r.t., and stirred an additional 2 h at ca. 20 °C. After addition of 20 mL of Et_2O, the organic phase was washed with H_2O (2 × 20 mL), brine (1 × 20 mL), and dried over $MgSO_4$. The solvent was removed by distillation (20 °C, 20 mbar) and the residue submitted to silica-gel radial chromatography (Chromatotron), to afford the pure α-cyanoenamines **3** (Table 1). The α-cyanoenamine **3b**–**d** and **3f**,**g** are known compounds and their spectral data matched those reported for the authentic substances.

(1*R,4*R**,4a*S**,7a*R**)-2*E*-Dimethylamino-3-[4′,4′*a*-5′,6′,7′,7′*a*-hexahydro-8′,8′-dimethyl-4′-phenyl-1′,4′-methano-1*H*-cyclopenta[*d*]pyridazin-1′-yl]acrylonitrile (3a).**

According to the general procedure, the α-cyanoenamine **3a** (555 mg, 1.65 mmol, 69%) was obtained as a colorless needles, mp 126–127 °C; R_f 0.36 [silica gel, dichloromethane–*n*-pentane (4:1)]. IR (KBr): ν (cm^{-1}) = 2921, 2905, 2201, 1606, 1598, 1114. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.31 (s, 3H, 9′-H), 0.78 (s, 3 H, 10′-H), 1.12–1.82 (m, 6 H, 4′-H, 5′-H and 6′-H), 2.31 (s, 6H, NMe_2), 2.85–3.00 (m, 1 H, 4′a-H), 3.30–3.50 (m, 1 H, 7′a-H), 6.14 (s, 1 H, 3′-H), 7.28–7.32 (m, 3 H, Ph), 7.62–7.75 (m, 2 H, Ph). ^{13}C NMR (50 MHz,

$CDCl_3$): δ = 18.3, 19.0, 26.6, 27.1, 29.8, 42.2, 50.2, 51.2, 68.6, 97.5, 98.3, 111.5, 115.2, 117.3, 128.4, 129.5, 129.6, 130.2, 138.3. Anal. Calcd for $C_{21}H_{26}N_4$ (334.4): C, 75.41; H, 7.84; N, 16.75. Found: C, 75.45; H, 7.69; N, 17.22.

2-Dimethylamino-3-(4-methoxyphenyl)acrylonitrile (3e). According to the general procedure, a *E*/*Z* (54:46) mixture of the α-cyanoenamine **3e** (226 mg, 1.12 mmol, 93%) was obtained as a colorless oil; R_f = 0.56 (silica gel, CH_2Cl_2). IR (KBr): ν (cm^{-1}) = 2915, 2910, 2205, 2195, 1590, 1500, 1030. ***E*-Isomer**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 6 H, NMe_2), 3.83 (s, 3 H, OMe), 6.36 (s, 1 H), 6.87 (d, ^3J = 8.8 Hz, 2 H, Ar), 7.67 (d, ^3J = 8.8 Hz, 2 H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 40.1, 54.7, 113.8, 116.2, 122.4, 126.4, 128.0, 131.9, 160.3. ***Z*-Isomer**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.84 (s, 6 H, NMe_2), 3.81 (s, 3 H, OMe), 5.97 (s, 1 H), 6.88 (d, ^3J = 8.8 Hz, 2 H Ar), 7.47 (d, ^3J = 8.8 Hz, 2 H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.4, 55.7, 113.9, 116.1, 121.4, 127.0, 128.9, 131.2, 159.0. Anal. Calcd for $C_{12}H_{14}N_2O$ (202.3): C, 71.26; H, 6.98; N, 13.85. Found: C, 71.02; H, 7.04; N, 13.81.

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(5) In our preliminary attempts on the Peterson olefination, we have employed *n*-BuLi and LDA for the reaction with the aldehyde **2a**, but obtained poor yields of the desired α cyanoenamine **3a**, e.g., none with *n*-BuLi and only a 7% yield in the case of LDA.