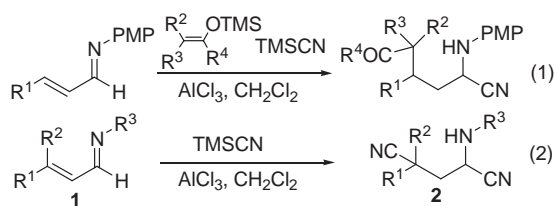# Double Nucleophilic Addition of Trimethylsilyl Cyanide to α,β-Unsaturated Aldimines Promoted by Aluminum Chloride: Preparation of 2-Aminopentanedinitrile

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In the presence of $AlCl_3$, trimethylsilyl cyanide underwent 1,4- and subsequent 1,2-additions with α,β-unsaturated imines to give 2-aminopentanedinitriles in good yields. An asymmetric version of this type of bis-cyanation was successfully conducted using a chiral α,β-unsaturated imine possessing a phenylglycinol derivative as a chiral auxiliary.

One of the most important reactions for the synthesis of α-amino acids involves the Strecker reaction.[1] Several methods have been reported involving their asymmetric versions.[2] We have introduced 1,4- and 1,2-double nucleophilic addition reactions to α,β-unsaturated aldimines, which avoids unnecessary isolation process of relatively unstable imino intermediates to give secondary amines in good yields.[3] Very recently, trimethylsilyl cyanide was successfully used as a second nucleophile to give the Strecker-type products in good yields (Scheme 1, Eq 1).[4] We have now found that trimethylsilyl cyanide is an excellent nucleophile for both the 1,4- and 1,2-additions to α,β-unsaturated aldimines to give 2-aminopentanedinitriles.[5] This paper reports a facile double nucleophilic addition of trimethylsilyl cyanide as well as its asymmetric version (Scheme 1, Eq 2).

Scheme 1.

First, the effect of Lewis acids for the double nucleophilic addition of TMSCN to imine **1** was investigated, and the results are summarized in Table 1.

Among the Lewis acids tested, $AlCl_3$ was found to be the most efficient promoter (Entries 1–6). In particular, the reaction in the presence of 0.5 equivalent of $AlCl_3$ promoted the double nucleophilic addition most effectively to give the pentanedinitrile in 83% yield, whereas the use of 1 equivalent of $AlCl_3$ induced the hydrolysis of the imine to some extent, resulting in the decrease in the product yield (Entries 2 and 3). Use of other Lewis acids such as $AlBr_3$, $TiCl_4$, TiI_4, TMSI only gave 1,2-addition products. Regarding the substituent at the nitrogen atom, diphenylmethyl, 2,4-dimethoxyphenyl, and benzyl groups could also be used, whereas the electron-withdrawing p-tosyl substituted imine did not give the desired addition product (Entries 7–10). It is noteworthy that use of the TMS derivative gave the desilylated dinitrile in good yield, indicating that this particular compound acted as an equivalent of the imine derived from acrolein, most of whose imino derivatives were readily polymer-

Table 1. Comparison of reaction conditions[a]

Entry	R^1	R^2	R^3	LA(equiv.)	$2/\%$[b]	dr[c]
1	Ph	H	PMP	$AlCl_3$(0.2)	34	88:12
2	Ph	H	PMP	$AlCl_3$(0.5)	83	51:49
3	Ph	H	PMP	$AlCl_3$(1.0)	65	79:21
4	Ph	H	PMP	$EtAlCl_2$(0.5)	57	56:44
5	Ph	H	PMP	Et_2AlCl(0.5)	28	65:35
6	Ph	H	PMP	Me_3Al(0.5)	50	51:49
7	Ph	H	Bn	$AlCl_3$(0.5)	58	65:35
8	Ph	H	$CHPh_2$	$AlCl_3$(0.5)	77	50:50
9	Ph	H	p-Ts	$AlCl_3$(0.5)	0	—
10	Ph	H	$2,4-(MeO)_2C_6H_3$	$AlCl_3$(0.5)	51	56:44
11	Me	H	PMP	$AlCl_3$(0.5)	79	52:48
12	Me	Me	PMP	$AlCl_3$(0.5)	69	—
13	Me	Me	$CHPh_2$	$AlCl_3$(0.5)	51	—
14	n-Pr	H	PMP	$AlCl_3$(0.5)	80	52:48
15	TMS	H	$CHPh_2$	$AlCl_3$(0.5)	70[d]	—

[a]Reaction was carried out according to the typical procedure.[6] [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR. [d]Desilylated product ($R^1 = H$) was obtained.

Table 2. Effects of chiral auxiliaries[a]

Entry	**3** or **4**	R^1	R^2	Yield/%[b]	$(R,S):(R,R)$[c]
1	**3**	Me	Me	76	93:7
2	**3**	$CH_2CH=CH_2$	Me	71	96:4
3	**3**	(E)-$CH_2CH=CHMe$	Me	68	86:14
4	**3**	(E)-$CH_2CH=CHPh$	Me	50	90:10
5	**3**	$CH_2(Me)C=CH_2$	Me	73	92:8
6	**4**	$CH_2CH=CH_2$	H	54	91:9
7	**4**	(E)-$CH_2CH=CHMe$	H	64	81:19
8	**4**	$CH_2C≡CH$	H	47	79:21

[a]Reaction was carried out according to the typical procedure.[6] [b]Isolated yield. [c]Isomer ratio determined by ^1H NMR and/or HPLC. Determination of the absolute configuration. See Ref. 7.

ized during preparation (Entry 15). We next investigated an asymmetric version of these processes using chiral imines possessing a chiral auxiliary at the nitrogen atom, and Table 2 summarizes the results.

Under the optimum conditions found for the present double

nucleophilic addition, chiral imines **3** and **4** possessing chiral auxiliaries derived from (*R*)-phenylglycinol[8] underwent diastereoselective addition. Regarding the derivatives, methyl, allyl, and methallyl ethers induced good diastereoselectivities (Entries 1, 2, 5, and 6). In particular, using the allylated chiral auxiliary, the TMS derivative **4** gave the dinitrile **5** in a good diastereoselective manner (Entry 6). In these instances where the TMS derivative **4** was used, the desilylated dinitrile **5** ($R^2 = H$) was obtained as in the case of the entry 15 in Table 1. The dinitrile obtained was converted into aminodiacid.[7]

In order to check the diastereoselectivity in the first conjugate addition reaction, the *tert*-butyldimethylsilylated derivative **6** was subjected to the present double addition conditions. In this case, however, three peaks of the adducts were detected by HPLC, indicating that the first conjugate addition was not diastereoselective. The use of the (*R*)-phenylethylimino derivative **8** resulted in decrease in the product yield as well as in the diastereoselectivity (Scheme 2).
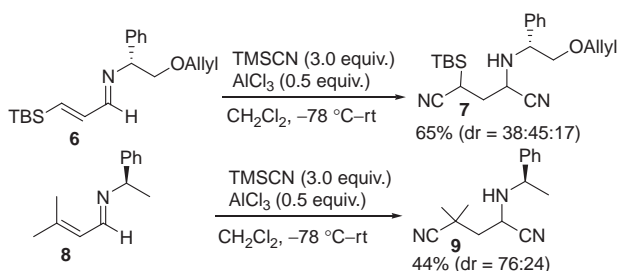
Scheme 2.

On the basis of these results and the reaction in the presence of an added proton source[9] as well as the deuterium incorporation ratio previously reported,[4] we propose a plausible reaction mechanism as shown in Scheme 3. The initial AlCl$_3$-promoted 1,4-addition reaction of cyanide produces the metalloenamine **11**, which after isomerization into the imine **12** and/or a hydrolyzed species with a certain proton source, is attacked by TMSCN to afford the 1,4–1,2-adduct (*R*,*S*)-**5**.
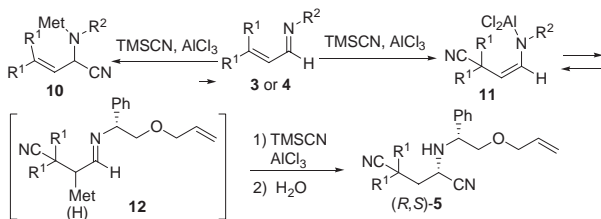
Scheme 3.

In conclusion, we have found an efficient method for 2-aminopentanedinitrile synthesis by double nucleophilic addition of trimethylsilyl cyanide to α,β-unsaturated aldimines. A chiral version realizes a diastereoselective synthesis of amino diacid precursors. The present reaction has an advantage that α-amino nitriles derived from relatively unstable imines can be obtained owing to in situ generation of imino species as intermediates.

References and Notes

1   a) A. Strecker, *Liebigs Ann.*, **75**, 27 (1850); A. Strecker, *Liebigs Ann.*, **91**, 349 (1854). b) For a review: G. C. Barrett, "Chemistry and Biochemistry of the Amino Acids," Chapman and Hall, New York (1985), p 251 and 261.

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5   For conjugate addition of cyanides, see for example; a) K. Higuchi, M. Onaka, and Y. Izumi, *Bull. Chem. Soc. Jpn.*, **66**, 2016 (1993). b) G. M. Zhdankina, G. V. Krystal, V. S. Bogdanov, V. I. Kadentsev, L. A. Yanovskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1982**, 346; *Chem. Abstr.*, **96**, 180736 (1982).

6   A typical experimental procedure for the addition reaction: To a suspension of AlCl$_3$ (13.3 mg, 0.10 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added a solution of the imine **4** (R^1 = allyl) (57.5 mg, 0.20 mmol) in CH$_2$Cl$_2$ (1.5 mL) at −78 °C and the mixture was stirred at −78 °C for 15 min. A solution of TMSCN (59.5 mg, 0.60 mmol) in CH$_2$Cl$_2$ (1.5 mL) was added to the resulting mixture. The mixture was gradually warmed to room temperature during 24 h. Saturated aqueous NaHCO$_3$ (10 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (15 mL × 3). The combined extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo to give the crude product. Purification on silica gel TLC (hexane:ethyl acetate = 5:1 as an eluent; developed three times) gave the 1,4–1,2-adduct **5** (29.3 mg, 54%) as a colorless oil. ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.06–2.16 (m, 2H), 2.33 (d, *J* = 13.2 Hz, 1H), 2.57 (t, *J* = 7.3 Hz, 2H), 3.27–3.57 (m, 3H), 4.02–4.06 (m, 2H), 4.23 (dd, *J* = 4.0, 9.9 Hz, 1H), 5.20–5.33 (m, 2H), 5.84–5.99 (m, 1H), 7.28–7.40 (m, 5H). IR (neat) 3317, 2859, 2248, 1494, 1454, 1421, 1361, 1134, 1092, 932, 804, 763 cm^{-1}.

7   The adduct was transformed into glutamic acid, and comparison of the optical rotation to that reported established the absolute stereochemistry.

8   For the use of phenylglycinol as a chiral auxiliary, see for example; a) Y. Ukaji, T. Watai, T. Sumi, and T. Fujisawa, *Chem. Lett.*, **1991**, 1555. b) A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.*, **43**, 892 (1978).

9   When the reaction (Entry 3, Table 1) was carried out in the presence of molecular sieves 4A containing 1 equiv. of H$_2$O,[3b] the dinitrile **2** was obtained in 37% yield.