

FACILE SYNTHESIS OF α -AMINONITRILES

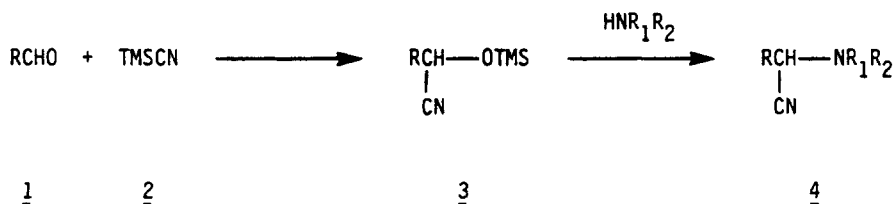
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Summary: α -Aminonitriles were prepared by reacting α -trimethylsilyloxynitriles with various amines in methanol. The silyloxynitriles were obtained by condensing a wide range of aldehydes (aliphatic, aromatic and heteroaromatic) with trimethylsilyl cyanide (TMSCN) in the presence of a catalytic amount of zinc iodide.

α -Aminonitriles are important intermediates in the preparation of aminoacids,¹ thiadiazoles² and imidazole derivatives.³ Numerous methods describing the preparation of α -aminonitriles are reported in the literature;^{3,4} as yet, none provide a general satisfactory procedure. Most of these reactions involved lengthy reaction conditions and tedious work-ups. Recently, Ojima and co-workers have shown that TMSCN reacts with ketimines to give the corresponding α -aminonitriles in excellent yield.⁵

We wish to report our preliminary results on the preparation of α -aminonitriles from α -silyloxynitriles.



The α -silyloxynitrile 3 was prepared by the addition of TMSCN to aldehyde in the presence of catalytic amount of zinc iodide as described by Evans^{6a}, Gassman^{6b} and their co-workers. This reaction can be carried out neat or by using ether, tetrahydrofuran, methylene chloride or chloroform as solvent. Solvent was used only when the reaction was exceedingly exothermic or when the aldehyde was a solid. The subsequent amination giving α -aminonitriles 4, however required an alcohol as solvent. We have found that the amination did not proceed in an aprotic medium. In contrast to the aqueous conditions of the classical Strecker synthesis, this reaction was carried out under non-aqueous conditions. It is noteworthy that the method worked particularly well with 2- or 2,6-disubstituted benzaldehydes as seen in table I where the yields were considerably higher as compared to the literature methods.

Table I. α -Aminonitriles

#	R	$\begin{array}{c} \text{RCH—NR}_1\text{R}_2 \\ \\ \text{CN} \end{array} \cdot \text{HCl}$		Yield, % ^a () ^b	Mp, °C
		R ₁	R ₂		
1	C ₂ H ₅	H	H	91 (38) ⁷	144-6
2	n-C ₆ H ₁₃	H	H	83	147-9
3	i-C ₄ H ₉	H	H	95	>225
4	n-C ₄ H ₉ C(Et)H	H	H	87 (13) ⁷	131-2
5	C ₆ H ₅ CH ₂	H	H	99 (36) ⁷	173-5
6	2-ClC ₆ H ₄	H	H	96 (24) ³	148-9
7	3-ClC ₆ H ₄	H	H	97 (9) ³	175-6
8	4-ClC ₆ H ₄	H	H	98 (16) ³	174-5
9	2,6-diClC ₆ H ₃	H	H	90 (27) ³	201-2
10	3-MeOC ₆ H ₄	H	H	99	173-5
11	4-MeC ₆ H ₄	H	H	96	175-6
12	4-MeSC ₆ H ₄	H	H	97 ^c	106-7
13	4-NCC ₆ H ₄	H	H	15	159-63
14	4-MeO ₂ CC ₆ H ₄	H	H	77	177-9
15	2-Furyl	H	H	94	>200
16	2-Thienyl	H	H	92	172-3
17	2-ClC ₆ H ₄	C ₆ H ₅ CH ₂	H	94 (84) ³	155-6
18	2-ClC ₆ H ₄	CH ₃	CH ₃	96 ^d	135-6
19	2-ClC ₆ H ₄	(CH ₂) ₂ -O-(CH ₂) ₂		93	175-6
20	2-ClC ₆ H ₄	(CH ₂) ₄		91	147-9
21	3-O ₂ NC ₆ H ₄	(CH ₂) ₄		95	168-71
22	3-HOC ₆ H ₄	(CH ₂) ₄		87 ^e	

- (a) All compounds had correct elemental analyses and gave NMR and IR consistent with the structures listed.
- (b) Values in parentheses are from the literature.
- (c) Isolated as free amine.
- (d) Due to its volatility, 5 fold excess of dimethylamine was used.
- (e) This compound is very hygroscopic, and therefore the mp was not taken.

A typical procedure is as follows: To a mixture of 3-chlorobenzaldehyde (5.6 g, 40 mmol) and TMSCN (5 g, 50 mmol) was added a catalytic amount of zinc iodide. After stirring for 15 min, a saturated solution of methanolic ammonia (30 mL) was added in one lot. The reaction mixture was warmed to 40°C and stirred for 2 h. After evaporation, the residue was taken up with ether, dried over MgSO₄ and filtered. Gaseous HCl was bubbled through the filtrate and the precipitated crude product was collected as an off-white powder, 8.1 g (97.0%), mp 175°C, NMR (CD₃OD) δ 5.95 (s, 1H), 7.45-7.81 (m, 4H).

Similarly, compounds 17-22 were prepared, except that, after treating with methanol and an equivalent amount of amine, the mixture was refluxed for 2h.

The reaction is fairly general, although the substrates bearing an electron-withdrawing group tend to give lower yields than those with an electron-donating group.

We further extended this methodology to the preparation of α-aminonitriles from ketones. When the α-silyloxynitrile obtained from the ketone was treated with an amine, the resulting α-aminonitrile was isolated in poor yield. On using ammonia, ketimine was found to be the major product (Table II). Further investigation of these reactions is in progress.

The synthesis of optically active α-aminonitriles using this methodology and details of the mechanism will be reported elsewhere.

Table II. Products of Amination of α-Silyloxynitriles from Ketones

Starting Materials		Yield, %	
Ketone	Amine	Ketimine	Aminonitrile
Cyclohexanone	n-Propylamine	-	50 ^a
Cyclohexanone	NH ₃	11	40 ^b
Benzophenone	NH ₃	70 ^d	5 ^c

(a) Isolated as oxalate salt, mp 127-30°C.

(b) Isolated as HCl salt, mp 210-2°C.

(c) Isolated as HCl salt, mp >200°C.

(d) See note 8.

References and Notes

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8. A solution of α -trimethylsilyloxy- α,α -diphenylacetonitrile in methanolic ammonia was refluxed for 16 h and worked up as usual. The solid was identified as α -amino- α,α -diphenylacetonitrile. HCl, mp $>200^{\circ}\text{C}$. The filtrate was basified, dried over MgSO_4 and evaporated to an oil, which was distilled *in vacuo* to yield 70% of the ketimine.

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