

Uncatalysed trimethylsilyl cyanide addition to aldehydes

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Trimethylsilyl cyanide adds to aldehydes in acetonitrile without the use of a catalyst whereas reaction with ketones under similar conditions is extremely slow. By this procedure aldehydes can react chemoselectively with trimethylsilyl cyanide in the presence of ketones.

Cyanohydrin trimethylsilyl ethers are versatile intermediates in organic synthesis.¹ Such ethers are usually prepared by the addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds in the presence of a catalyst, e.g. Lewis acids² and KCN/18-Crown-6.³ Other catalysts like Lewis bases⁴ and trimethylsilyl triflate⁵ are also known to be used in this type of reaction. Although these catalysts work well one can expect problems when used with complex molecules as they may interfere with other functionalities present in the molecules.

Here, we report that TMSCN adds to aldehydes in acetonitrile without the use of a catalyst.† Benzaldehyde, for example, reacts with 1.05 equivalents of TMSCN in acetonitrile at room temperature for 10 h to give the desired product in >95% yield.‡ This procedure does not require an aqueous work-up. After completion of the reaction, the solvent and excess of TMSCN are removed under reduced pressure to give the desired product. The method works well with different types of aldehydes to give the desired products in high yields (see Table 1).

The reaction of ketones with TMSCN under the same conditions is extremely slow. For example, cyclohexanone and propyl methyl ketone do not give any product when refluxed with TMSCN in acetonitrile for 10 h, whereas acetophenone gave the desired product in only 2–3% yield. One can take advantage of this fact and allow aldehydes to react with TMSCN in the presence of ketones with high chemoselectivity.⁶ In the event, benzaldehyde and acetophenone when treated with TMSCN in 1:1:1 ratio in refluxing acetonitrile for 2 h gave product derived from benzaldehyde only, in quantitative yield, and unchanged acetophenone. Similarly, reaction of butyraldehyde, propyl methyl ketone and TMSCN in refluxing acetonitrile for 10 h gave product derived from butyraldehyde only.

Trimethylsilyl enol ethers were also reported to undergo uncatalysed Michael addition with enones.⁷ Later it was shown to be catalysed by some phosphorus compound present in acetonitrile when it had been dried over P₂O₅.⁸ In experiments conducted in our laboratory the acetonitrile used was dried over CaH₂.

In conclusion, it has been shown that TMSCN undergoes uncatalysed addition reaction with aldehydes in acetonitrile chemoselectively. Due to the simplicity of the conditions, the above methodology should find utility in organic synthesis.

† Evans has reported that the reaction of aldehydes as well as ketones take place with TMSCN when they are heated together without solvent.²

‡ The reaction also occurs at a comparable rate in nitromethane, but no reaction was observed in dichloromethane and benzene.

Table 1 Uncatalysed addition of TMSCN to aldehydes^a

$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{H} \end{array} \xrightarrow[\text{MeCN}]{\text{TMSCN}} \begin{array}{c} \text{TMSO} \quad \text{CN} \\ \diagdown \quad / \\ \text{C} \\ / \quad \backslash \\ \text{R} \quad \text{H} \end{array}$				
Entry	R	Temp./°C	Time/h	Yield (%)
1	Ph	20	12	95
2	<i>p</i> -ClC ₆ H ₄	85	10	94
3	<i>o</i> -NO ₂ C ₆ H ₄	20	12	95
4	<i>p</i> -MeOC ₆ H ₄	85	18	33 ^b
5	PhCH ₂ CH ₂	85	8	90
6	PhCH=CH	85	3	92
7	Cyclohexyl	20	12	89
8	C ₆ H ₁₃	85	10	90
9	2-Furyl	85	10	90

^a In each of the experiments a 0.5 mol dm⁻³ solution of aldehyde in acetonitrile was treated with 1.05 equiv. of TMSCN. ^b Rest was starting material.

Experimental

General procedure

A mixture of the aldehyde (1.00 mmol) and trimethylsilyl cyanide (1.05 mmol) in acetonitrile (2 cm³) in a flame-dried flask under a nitrogen atmosphere was refluxed or stirred at 20 °C (see Table 1). The reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure to give the product, which was analytically pure, in high yield as indicated in Table 1.

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