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Iodine as a novel and efficient reagent for the synthesis of α-aminonitriles by a three-component condensation of carbonyl compounds, amines, and trimethylsilyl cyanide

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Abstract—A straightforward and general method has been developed for the synthesis of α-aminonitriles by simply combining aldehydes or ketones, amines, and trimethylsilyl cyanides in the presence of a catalytic amount of molecular iodine at room temperature.

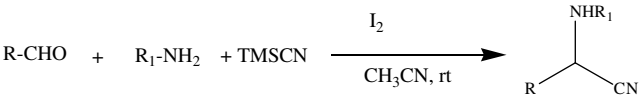
1. Introduction

α-Aminonitriles are important intermediates in the preparation of many amino acids[1] and various nitrogen containing heterocycles such as imidazoles and thiadiazoles.[2,3] They are usually synthesized by the nucleophilic addition of a cyanide anion to imines. Numerous methods describing the preparation of α-aminonitriles have been reported[4–12] in the literature. However, most of these methods involve the use of expensive reagents, lengthy reaction times, and tedious work-up procedure. Furthermore, many of these protocols are limited to aldehydes only and are not applicable to acyclic ketones. Most recently, we reported $BiCl_3$ as a catalyst[13] for the Strecker amino acid synthesis reaction, but this procedure did not work with ketones. Therefore, there is a need of an efficient and inexpensive catalyst for the synthesis of α-aminonitriles.

In continuation of our work to develop new organic transformations,[14] we report herein that iodine, which acts as a mild Lewis acid, might be a useful and inexpensive catalyst for the synthesis of α-aminonitriles. Although, iodine has been extensively used as a mild catalyst for a plethora of organic transformations,[15] there are no examples of the use of molecular iodine as catalyst for the synthesis of α-aminonitriles.

2. Results and discussion

The treatment of benzaldehyde and benzyl amine with TMSCN in the presence of a catalytic amount of iodine afforded 2-(*N*-benzylamino)-1-phenylacetonitrile in 94% yield. In the same manner, a variety of aldehydes were coupled with a wide range of amines and trimethylsilyl cyanide in a one-pot operation in the presence of a catalytic amount of iodine at room temperature to give the corresponding α-aminonitriles in good to excellent yields (Scheme 1). Both aromatic and aliphatic aldehydes afforded excellent yields, whereas ketones gave moderate yields. On the other hand, all types of primary and secondary amines are readily coupled to give the desired product in good yields. Due to steric hindrance (or a combination of steric hindrance and electronic factors), benzophenone did not give the desired product in good yield. However, acid sensitive aldehydes such as furfuraldehyde gave the aminocyano compound in high yield. This method does not require any other additives to promote the reaction. No undesired side product



Scheme 1.

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Table 1. Iodine-catalyzed synthesis of α-amino nitriles with trimethylsilyl cyanide

Entry	Aldehyde/ketone	Amine	Time (h)	Yield[a] (%)
1	Benzaldehyde	Aniline	1	94
2	4-Chlorobenzaldehyde	Aniline	1	90
3	Isobutyraldehyde	Benzyl amine	2	88
4	Decylaldehyde	Aniline	2	79
5	3-Methoxybenzaldehyde	Benzyl amine	1	91
6	Furfural	Benzyl amine	1	84
7	Thiophene 2-carboxaldehyde	Benzyl amine	1	86
8	Benzaldehyde	Morpholine	2	78
9	Butyraldehyde	Pyrrolidine	2	81
10	Benzaldehyde	Furfurylamine	2	86
11	Benzaldehyde	3-Methoxybenzyl amine	2	88
12	Benzaldehyde	Butylamine	3	87
13	2,4-Dimethoxybenzaldehyde	3,4,5-Trimethoxyaniline	3	84
14	4-Methylbenzaldehyde	Aniline	2	89
15	Acetophenone	3,4,5-Trimethoxyaniline	8	68
16	Cyclohexanone	Benzyl amine	6	76
17	Cyclohexanone	Butylamine	8	72

[a] Yields refer to pure isolated products and were characterized by spectral data.

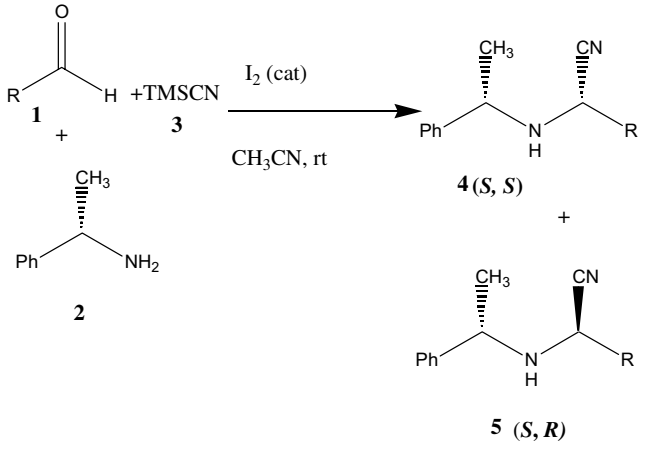
(such as cyanohydrin trimethyl silyl ether, an adduct between the aldehyde and trimethylsilyl cyanide) was observed because of the rapid formation of the imine intermediate. The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to various carbonyl compounds and amines.

In comparison with other catalysts such as $Sc(OTf)_3$, $InCl_3$, $BiCl_3$, $Pr(OTf)_3$, $Lu(OTf)_3$, and $RuCl_3$ employed for the aminocyanation of acetophenone, molecular iodine shows more catalytic reactivity than the others in terms of the amount of catalyst required, reaction times, and yields of the product (Table 2).

To evaluate the possibility of 1,3-asymmetric induction, we extended this procedure to the preparation of optically active α-aminonitriles derived from (*S*)-(−)α-methylbenzylamine and aldehydes. The reaction with both aryl and alkyl aldehydes in every case produced mixtures of diastereoisomers, with one diastereoisomer predominating. The relative stereochemistry of the products was determined by ^{1}H NMR spectroscopy using the literature methods.[16] For instance, the ^{1}H NMR of the crude α-(1-methylbenzyl)amino valeronitrile (R = *iso*-propyl, Scheme 2) showed two doublets, one at 2.92 ppm (J = 6.5 Hz) and the other at 3.32 ppm (J = 6.5 Hz) in a ratio of 71:29. Each doublet is derived from the proton attached to the carbon bearing the nitrile. According to the literature[16] hypothesis, nucleophilic attack on the imine should take place antiperpendicular to the α-phenyl group. In all cases, in this

Table 2. Comparison of the effect of catalysts in the aminocyanation of acetophenone with 3,4,5-trimethylaniline and trimethylsilyl cyanide

Catalyst	Catalyst load (mol%)	Time (h)	Yield (%)
$Sc(OTf)_3$	20	12	15
$InCl_3$	20	10	12
$Pr(OTf)_3$	20	12	5
$RuCl_3$	20	12	5
$BiCl_3$	20	12	8
$Lu(OTf)_3$	20	12	6
I_2	10	8	68



R	4:5	Yield (%)
i-propyl	71:29	91
tert-butyl	68:32	87
Phenyl	81:19	92
4-MeO-phenyl	84:16	84

Scheme 2.

reaction *S*-α-methylbenzylamine and *R*-α-methylbenzylamine gave similar enantiomeric excesses but opposite chiralities.

3. Conclusion

We have demonstrated a very simple, efficient, and practical method for the synthesis of α-aminonitriles through a one-pot three component coupling of carbonyl compounds, amines, and trimethylsilyl cyanide using a catalytic amount of molecular iodine. High diastereoselection can be obtained in the synthesis of α-aminonitriles using *R* or *S*α-methylbenzylamine. The major advantage of this method is that it is truly a one-pot procedure that does not require a separate step to prepare an imine for subsequent use. The important

features of this method include (a) operational simplicity, (b) no need for any other additive to promote the reaction, (c) short reaction times, (d) the use of cheap, commercially available, relatively non toxic reagents, and (e) high yields of the desired products.

4. Experimental

4.1. A typical procedure

A mixture of benzaldehyde (212 mg, 2 mmol), aniline (186 mg, 2 mmol), and trimethylsilyl cyanide (300 mg, 3 mmol) in dry acetonitrile (2 mL) was stirred at room temperature in the presence of iodine (51 mg, 0.2 mmol). After completion of reaction (TLC), the reaction mixture was extracted with ethyl acetate (2×20 mL). The organic layer was washed with water (20 mL), and brine (20 mL) dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel, eluted 20% ethyl acetate in hexane to afford the pure product 2-(*N*-Anilino)-2-phenylacetonitrile in excellent yield (391 mg, 94%). Although we could isolate TMS-protected α-aminonitrile without aqueous work-up of the reaction mixture, the isolated yield was low due to partial cleavage of silyl group to aminonitrile during column chromatography. In fact, partial cleavage was even observed during TLC run. All yields refer to isolated products. All products are known and were characterized by NMR and mass spectra.

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Supplementary data

Representative experimental procedures in details and spectral data of all compounds. The supplementary data are available online with the paper at doi:10.1016/j.tetlet.2005.05.005.

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