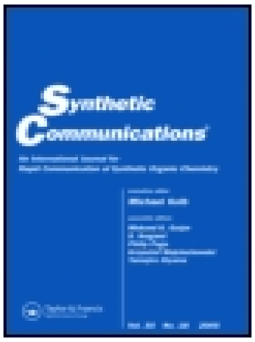

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An Efficient and Mild Strecker-Type Reaction of Nitrones Catalyzed by MgI_2 Etherate

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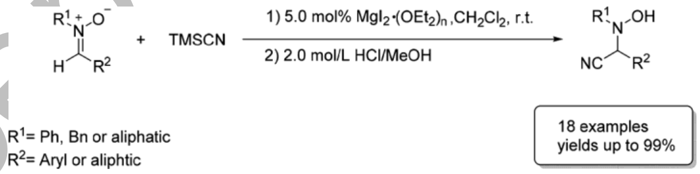
Abstract

An efficient Strecker-type reaction of nitrones with TMSCN catalyzed by MgI_2 etherate has been achieved in a short time under mild condition. The condensations of aromatic nitrones, heterocylic nitrones and aliphatic nitrones with TMSCN are carried out in good to excellent yields. Further dehydration of □-cyanohydroxylamine smoothly produced the □-imine nitrile in good yields by hydrolysis with treatment of 2.0 mol/L HCl in methanol.

Graphical Abstract



KEYWORDS: Strecker-type reaction; nitrones; TMSCN; α-cyanohydroxylamines; MgI_2 etherate

INTRODUCTION

The Strecker reaction is a process for the preparation of α-amino nitriles, which are versatile intermediates for the synthesis of amino acids via hydrolysis of the nitrile. [1] In recent years, there are many studies on Strecker reaction of aldehydes, ketones and imines, while little attention has been drawn to nitrones. Among organic nitrogen compounds bearing a carbon-nitrogen double bond, nitrones are a particularly interesting class of compounds by virtue of their utility in organic synthesis. They possess electronegative oxygen, which can coordinate strongly to metals[2] and polarizes a carbon-nitrogen double bond to effectively enhance the electrophilic reactivety[3]. They are readily available to form aldehydes and ketones, and they are excellent electrophilic substrates capable of reacting with a variety of nucleophiles showing a higher reactivity and stability than imines. The nitrones are reactive starting materials in a large amount of 1,3-dipolar cycloadditions[4] and act as electrophiles with a variety of both carbon and heteronucleophiles[5].

It occurred to us that the reaction of trimethylsilyl cyanide (TMSCN) with nitrones would give rise to □-cyanohydroxylamine derivatives, which is also a useful way to give natural or unnatural amino acids sequentially undergoing hydrolysis and catalytic hydrogenation. Accordingly, this work was undertaken to synthesize and investigate the chemistry of □-cyanohydroxylamine.

To date there are few catalysts to be extended to the Strecker-type reaction of nitrones, such as TMSOTf[6], Et_2AlCl[6], thiourea[7]. Recently, Ukaji's group has reported Strecker-type reaction of nitrones with acetone cyanohydrins in the presence of *n*-BuMgCl-catalysis.[8] Therefore, the development of less expensive, environmentally benign, and easily handled promoters for the synthesis of □-cyanohydroxylamine by Strecker condensation under neutral, mild, and convenient condition is still highly desirable. Magnesium (II) species are widely applied as Lewis acid catalysts in various functional transformations and C-C bond-forming reactions due to the high eletrophilicity of the Mg^{2+} ion and its tendency to form a *multi*-coordinate (up to 5 or 6) complex.[9] In our previous work,[10] we have demonstrated that MgI_2 etherate could efficiently catalyze Strecker addition of aldehydes and imines with TMSCN. Herein, we wish to report a mild and efficient Strecker-type addition of TMSCN to various nitrones catalyzed by MgI_2 etherate.

RESULTS AND DISCUSSION

Initially, the (*Z*)-benzylideneaniline N-oxide (**1a**) was chosen as the model substrate treated with TMSCN for investigating the reaction parameters in the Strecker-type reaction, and the results are summarized in Table 1. The Strecker-type reaction of (*Z*)-benzylideneaniline N-oxide **1a** with TMSCN was carried out using Mg(II) catalysts. The targeted product α-cyanohydroxylamine **2a** was provided by treatment with 2.0 mol/L HCl in methanol. As shown in Table 1, the reaction proceeded very sluggishly and gave the desired adduct in a low yield in CH_2Cl_2 without any catalysts. $MgCl_2$ and $MgBr_2$ etherate were less effective to this reaction and gave the product in 53% and 67% yield, respectively. The best result was observed with 5.0 mol% of MgI_2 etherate using CH_2Cl_2 as solvent in a very short time, while $Mg(ClO_4)_2$ also showed good yield. (Table 1, entries 1-4). Next the effect of solvent was examined in the presence of 5.0 mol% of MgI_2 etherate. Among the solvents screened, non-coordinating reaction media CH_2Cl_2 and $CHCl_3$ are proven to be the best solvents (Table 1, entries 5-6). Less polar solvents, MeCN, THF and Et_2O, showed good yields as well (Table 1, entries 7-9), while moderate yield was given in toluene (Table 1, entry 10). Lower yields were afforded in polar solvents, MeOH, acetone and DMF (Table 1, entries 11-13).

Encouraged by these results, the Strecker-type reaction of various nitrones **1** with TMSCN was investigated using 5.0 mol% of MgI_2 etherate in CH_2Cl_2 at room temperature. The results are summarized in Table 2. The reaction of 4-methyl and 4-methoxy substituted nitrones on aromatic ring **1b** and **1c** gave the α-cyanohydroxylamine **2b** and **2c** in excellent yields in very short time (Table 2, entries 2 and 3). As well, the nitrone bearing electron-withdrawing groups on aromatic ring also provided the corresponding products in good yields (Table 2, entries 4 and 5). In the case of heteroaromatic nitrone **1f** the Strecker-type reaction proceeded well to produce **2f** in 95% yield (Table 2, entry 6). However, in the case of nitrones **1g** derived from

3-methyl-2-thiophene aldehyde, α-cyano-*O*-trimethylsilyl hydroxylamine as a stable product was obtained in near quantitatively yield without affording α-cyanohydroxyl amine due to its instability (Table 2, entry 7). Furthermore, the Strecker-type reaction of nitrones **1h**, prepared from cinnamaldehyde and nitrobenzene, with TMSCN exclusively occurred 1,2-addition and gave the stable *O*-trimethylsilyl derivative in moderate yield (Table 2, entry 8). Next, the influence of the substituents on the nitrogen atom of the nitrones was examined. As shown in Table 2, the Strecker-type reactions of *N*-benzyl nitrone **1i-1o** were carried out in good to excellent yields in terms of various nitrones bearing electron-withdrawing groups and electron-donating groups on aromatic ring (Table 2, entries 10-14). It was worthy to be noted that the more sterically hindered nitrone **1l** also gave an excellent yield (Table 2, entry 12). In addition, the Strecker reaction of the aliphatic nitrones **1p** and **1q**, which are derived from the oxidation of its corresponding secondary amine,[11] also proceeded smoothly and afforded the desired product in 96% and 94%, respectively (Table 2, entries 16 and 17). Furthermore, MgI_2 etherate could effectively catalyze Strecker-type reaction of chiral nitrone **1r** (Table 1, entry 18). The cyanation afforded the unseparable diastereomer in the excellent yield with moderate stereoselectivity. Apparently, the substituents on the nitrogen atom of nitrone did not affect the reaction.

Interestingly, cyanation of *N*-phenyl nitrones with 4-chloro, 4-bromo, 4-trifluromethyl substituents on aromatic ring proceeded well and gave a dehydrated cyanoimine **3a-3c** in good to excellent yield, respectively (Table 3, entries 1-3). In terms of nitrone derived from furfuryl aldehyde, the reaction gave a dehydrated cyanoimine **3d** exclusively (Table 3, entry 4). Especially, the cyanation of a cyclic nitrone, 3,4-dihydroisoquinoline *N*-oxide, also carried out smoothly and gave a dehydrated imine **3e** in good yield (Table 3, entry 5), which is much better than that of the cyanation catalyzed by *n*-BuMgCl reported by Ukaji [8].

The possible mechanism for the formation of α-cyanohydroxylamine catalyzed by MgI_2 etherate is shown in Scheme 1. The uniqueness of MgI_2 etherate is attributed to the dissociative character of iodide counterion, which is cooperation with coordination of Lewis basic oxygen atom of nitrone **1** with Mg (Ⅱ) leading to a more Lewis acidic cationic Mg-coordinate **4**. It is feasible to promote a nucleophilic addition of TMSCN to form an intermediate **5**. The *irreversible* silylation of intermediate **5** by transient TMSI to regenerate MgI_2 etherate catalyst and produce the desired product **6** as shown in the proposed catalytic cycle. Then α-cyanohydroxylamine was obtained by acidification.

CONCLUSION

In conclusion, we have developed a highly efficient Strecker-type reaction of nitrones with TMSCN catalyzed by MgI_2 etherate. This magnesium-catalyzed Strecker-type addition is rapid, mild, environmentally friendly and operationally simple. We have demonstrated that iodide counterion, weakly coordinating peripheral ethereal ligands for

Mg(II), and a non-coordinating reaction media are critical factors for the unique reactivity of this catalytic system. Further studies on magnesium-catalyzed asymmetric Strecker-type reaction of nitrones with TMSCN are in progress in our laboratory.

EXPERIMENTAL

General

For product purification by flash column chromatography, silica gel (200~300 mesh) and light petroleum ether (PE, b.p. 60~90 ^{o}C) were used. The reactions monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. Melting points were performed on X-4B microscopic melting point meter. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ using TMS as internal standard. ^{13}C NMR spectral measurements were performed at 125 MHz using TMS as an internal standard. All compounds were identified by ^{1}H NMR and are in good agreement with those reported. EI-MS were determined on a PerkinElmer spectrometer. HRMS (ESI) were determined on a Therm LCQ TM Deca XP plus spectromer. HRMS (TOF-EI) were determined on GCT premier spectrometer. IR spectroscopy was performed on a Nicolet 6700 infrared spectrometer.

General Procedure For Strecker-Type Reaction Of Nitrones.

To a solution of the corresponding nitrones **1** (1.0 mmol) in CH_2Cl_2 (5 mL) was added trimethylsilyl cyanide (1.5 mmol) and a freshly prepared MgI_2 etherate [12] (0.05 mmol, 1.0 mol/L in Et_2O/toluene 1:1, 5.0 mol %). The reaction mixture was stirred at room temperature for 10 to 15 minutes. The solvent was evaporated after completion of reaction, and the resulting mixture was treated with 2.0 mol/L HCl/MeOH (2 mL). Saturated $NaHCO_3$ aqueous was added and the resulting mixture was extracted with dichloromethane (3×20 mL). The combined organic phase was washed with brine and concentrated. The residue was purified by flash column chromatography on a silica gel to give the cyanated product.

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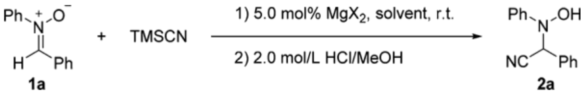
Table 1. Optimization of reaction conditions for MgX_2-catalyzed Strecker-type reaction[a]

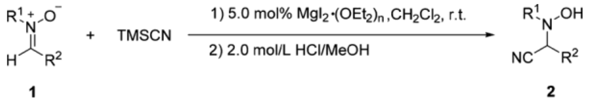


Entry	Catalyst	Solvent	Time (min)	Yields (%)[b]
1	None	CH_2Cl_2	180	38
2	$MgCl_2$	CH_2Cl_2	30	53
3	$MgBr_2$	CH_2Cl_2	30	67
4	$Mg(ClO_4)_2$	CH_2Cl_2	15	81
5	MgI_2	CH_2Cl_2	10	92
6	MgI_2	$CHCl_3$	15	90
7	MgI_2	MeCN	10	85
8	MgI_2	THF	15	80
9	MgI_2	Et_2O	15	76
10	MgI_2	Toluene	15	66
11	MgI_2	Acetone	30	31
12	MgI_2	MeOH	30	18
13	MgI_2	DMF	30	29

[a] The reaction was carried out by the addition of (Z)-benzylideneaniline N-oxide (1.0 mmol) and TMSCN (1.5 mmol) in the presence of 5.0 mol % of MgX_2 under the above reaction conditions, followed by hydrolysis with treatment of 2.0 mol/L HCl in methanol.

[b] Isolated yield by silica gel flash chromatography.

Table 2. Strecker-type reaction of various nitrones catalyzed by MgI_2 ethrerate[a]



Entry	R^1	R^2	Time (min)	Prod.	Yield (%)[b]
1	Ph	Ph	10	**2a**	92
2	Ph	4-MeC_6H_4	10	**2b**	95
3	Ph	4-$MeOC_6H_4$	10	**2c**	96
4	Ph	2-ClC_6H_4	10	**2d**	80
5	Ph	2-FC_6H_4	10	**2e**	81
6	Ph	2- Thienyl	10	**2f**	95
7	Ph	3-Me-2-thienyl	10	**2g**[c]	99
8	Ph	Cinnamyl	10	**2h**[c]	71
9	Bn	Ph	15	**2i**	80
10	Bn	4-$MeOC_6H_4$	15	**2j**	99
11	Bn	2-$MeOC_6H_4$	15	**2k**	95
12	Bn	2,6-$Me_2C_6H_3$	15	**2l**	94
13	Bn	4-ClC_6H_4	15	**2m**	91
14	Bn	2-ClC_6H_4	15	**2n**	94
15	Bn	2-Thienyl	15	**2o**	88

16	*tert*-Bu	Ph	10	**2p**	96
17	*n*-Bu	*n*-Pr	10	**2q**	94
18	(*R*)-$C_6H_5CH(CH_3)$	Ph	15	**2r**	87 (*dr* 37:63)[d]

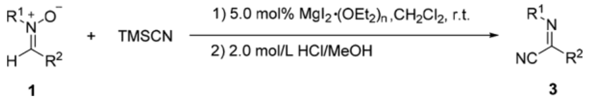
[a] The reaction was carried out by addition of nitrones (1.0 mmol) and trimethylsilyl cyanide (1.5 mmol) in the presence of 5.0 mol % of MgI_2 etherate in CH_2Cl_2 at room temperature, followed by hydrolysis with treatment of 2.0 mol/L HCl in methanol.

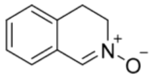
[b] Isolated yields by silica gel flash chromatography.

[c] The desired product is *O*-trimethylsilyl derivative.

[d] The ratio of *dr* value was determined by ^{1}H NMR analysis.

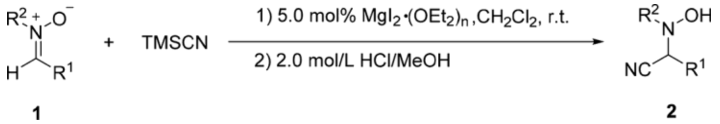
Table 3. The preparation of cyanoimines by dehydration from α-cyanohydroxylamines



Entry	R^1	R^2	Product	Yield (%)[a]
1	Ph	4-BrC_6H_4	**3a**	81
2	Ph	4-ClC_6H_4	**3b**	76
3	Ph	4-$CF_3C_6H_4$	**3c**	97
4	Ph	2-Furfuryl	**3d**	89
5			**3e**	82

[a]Isolated yields by silica gel flash chromatography.

Scheme 1. MgI_2 etherate-catalyzed Strecker-type reaction of nitrones with TMSCN.



Scheme2. The proposed mechanism of MgI_2 etherate-catalyzed Strecker-type reaction of nitrone.