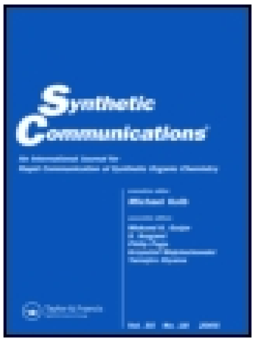

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Unique chemoselective Strecker-type reaction of acetals with TMSCN catalyzed by MgI_2 etherate

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ABSTRACT

An efficient and convenient Strecker-type addition of various substituted aromatic acetals, heteroaromatic acetals and α, *β*-unsaturated acetals with trimethylsilyl cyanide (TMSCN) is achieved catalyzed by 10 mol% of MgI_2 etherate (MgI_2•$(Et_2O)_n$) in a mild, and high chemoselective manner with good to excellent yields. A non-coordinating reaction media (i.e., CH_2Cl_2) played a vital role in this catalytic process.

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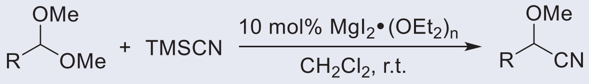
KEYWORDS
Acetal; MgI_2 etherate; Strecker-type reaction; trimethylsilyl cyanide

GRAPHICAL ABSTRACT



R = aromatic, heteroaromatic, vinyl

Introduction

The carbon–carbon bond formation is a fundamental process in organic synthesis and numerous methods have been developed for achieving it. One of the most powerful methods is the reaction of the carbonyl groups with a variety of carbon nucleophiles.[1–6] Acetals are a typical carbonyl protecting group as well as a synthetic equivalent of the carbonyl group. In general, acetals are stable under strongly basic to neutral conditions and do not react with nucleophilic reagents, for example, organolithium reagents and Grignard reagents, under these conditions. However, acetals act as strong electrophiles toward various nucleophiles under acidic conditions owing to the generation of an oxonium ion intermediate. Many Lewis acids, such as trimethylsilyl triflate (TMSOTf),[7] $TiCl_4$,[8,9] $BiBr_3$,[10] ZnI_2,[11] $CoCl_2$,[12] $[Rh(COD)Cl]_2$,[13] $SnBr_2$,[14] BF_3•Et_2O[15,16] and $SnCl_2$[17,18] could promote the cyanation of acetals with trimethylsilyl cyanide (TMSCN). In addition, tetracyanoethylene (TCNE) also catalyzed the reaction of acetals with TMSCN.[19] Furthermore, the cyanation of acetals with α-cyanoamine as a cyanating reagent in the presence of trichlorosilyl triflate was developed by Kotani.[20] Mild cyanation of acetals with TMSCN in the presence of TESOTf and 2,4,6-collidine or 2,2′-bipyridyl via the pyridinium-type salts has been developed by Fujioka.[21,22] Recently,

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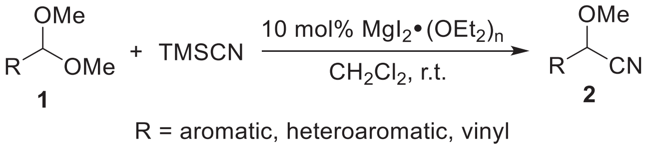


Scheme 1. MgI_2 etherate-catalyzed Strecker-type reaction of acetals with TMSCN.

Kumamoto's group has reported high-pressure-promoted uncatalyzed cyanation of acetals using TMSCN in nitromethane.[23]

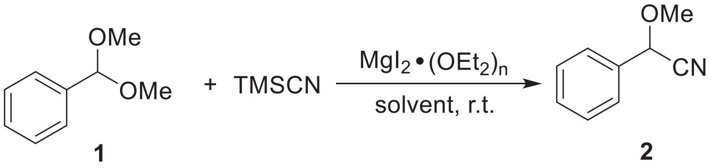
However, conventional methods using Lewis acids must be carried out under strictly anhydrous conditions, which are difficult to handle on a particularly large scale. Therefore, the development of less expensive, environmentally benign, and easily handled promoters for the synthesis of C–C bond under 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.[24] In our previous work,[25–27] we have demonstrated that MgI_2 etherate could efficiently catalyze Strecker of aldehydes, nitrones, and imines with TMSCN. Herein, we wish to report a mild and efficient Strecker-type addition of TMSCN to various acetals catalyzed by MgI_2 etherate (Scheme 1).

Results and discussion

Initially, the benzaldehyde dimethyl acetal **1a** was chosen as a 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 acetal **1a** with TMSCN was carried out smoothly in the presence of MgI_2 etherate. The targeted product 2-phenyl-2-methoxyacetonitrile **2a** was provided by silica gel flash chromatography. The best result was observed with 10 mol% of MgI_2 etherate using CH_2Cl_2 as solvent in 3 h time. (Table 1, entry 1–4). Next, the effect of solvent was examined in the presence of 10 mol% of MgI_2 etherate. Among the solvents screened, non-coordinating reaction media CH_2Cl_2 and $CHCl_3$ have proven to be the best solvents. Toluene and 1,2-dichloroethane show good yields as well (Table 1, entries 6–7), while lower yields were afforded in less polar solvents such as MeCN and tetrahydrofuran (THF). (Table 1, entries 8–9). No reaction occurred in the polar solvent, MeOH (Table 1, entry 10).

Encouraged by these results, the Strecker-type reactions of various acetals **1** with TMSCN were investigated using 10 mol% of MgI_2 etherate in CH_2Cl_2 at room temperature. The results are summarized in Table 2. Aryl aldehyde acetals bearing electron-donating groups on the benzene ring (i.e., Me, OMe) afforded excellent yields of the desired products **2b–2d**, (Table 2, entries 2–4). Furthermore, good yields were obtained for aryl aldehyde acetals possessing halo groups (i.e., Cl, Br, F) at the *para* position on the benzene ring (Table 2, entries 5–7), while lower yields were observed with 4-nitrobenzaldehyde acetal and 4-cyanobenzaldehyde acetal (Table 2, entries 9–10). Meanwhile, heteroaromatic acetals such as 2-thiophenecarboxaldehyde acetal, 2-furanaldehyde acetal also gave high yields (Table 2, entries 11–12). 1-Naphalenealdehyde acetal, which

Table 1. Optimization of reaction conditions for MgI_2 etherate-catalyzed Strecker-type reaction[a].



Entry	MgI_2 (mol%)	Solvent	Time (h)	Yield (%)[b]
1	15	CH_2Cl_2	3	95
2	10	CH_2Cl_2	3	95
3	5	CH_2Cl_2	24	75
4	1	CH_2Cl_2	36	53
5	10	$CHCl_3$	4	94
6	10	1,2-dichloroethane	4	87
7	10	PhMe	4	92
8	10	MeCN	4	69
9	10	THF	4	50
10	10	MeOH	4	N.A.

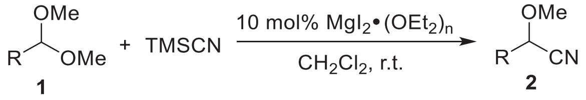
[a] The reaction was carried out by the addition of benzaldehyde dimethyl acetal **1a** (1.5 mmol) and TMSCN (1.8 mmol) in the presence of 10 mol % of MgI_2 etherate under the above reaction conditions.
[b] Isolated yield by silica gel flash chromatography.

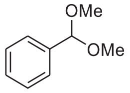
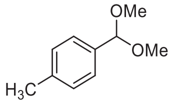
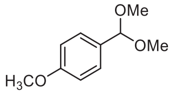
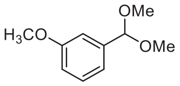
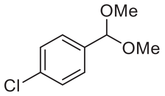
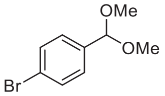
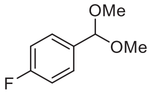
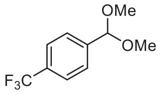
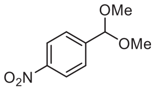
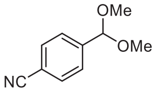
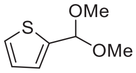
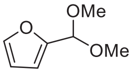
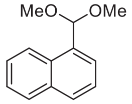
contains a highly conjugated plane, seems to be effective and gave the corresponding adduct in 68% yield (Table 2, entry 13). Moreover, α, *β*-unsaturated acetal such as cinnamaldehyde acetal gave the desired product in good yield (Table 2, entry 14). Unfortunately, very poor yields were observed with *ortho*-substituted aromatic aldehyde acetals due to its steric hinderance (Table 2, entries 15–16). However, aliphatic aldehyde acetals were inert to this silylcyanation under the similar conditions (Table 2, entries 17–18).

The delicate chemoselectivity of Strecker reaction was evaluated by crossover experiments of various acetals and its parent aldehydes with TMSCN, respectively. MgI_2 etherate showed high levels of acetals discrimination in the competitive reactions (Table 3). MgI_2•$(Et_2O)_n$ can uniquely recognize the difference in aromatic acetals and aromatic aldehydes. Benzaldehyde is less reactive than benzaldehyde dimethyl acetal and the cyanosilylated product of benzaldehyde dimethyl acetal was predominately afforded (Table 3, entry 1). Similarly, the cyanosilylated product of 4-methoxy benzaldehyde acetal was exclusively obtained over 4-methoxy benzaldehyde (Table 3, entry 2). In the crossover experiment of 4-bromobenzaldehyde with 4-bromobenzaldehyde acetal, the reaction exclusively gave the cyanosilylated product of p-bromobenzaldehyde acetal (Table 3, entry 3). As well, the reactivity of 2- furanaldehyde acetal is better than that of its corresponding aldehyde in this MgI_2 etherate catalysis (Table 3, entry 4).

In view of the importance of acetal function as carbonyl equivalent for C–C bond cross-coupling, we revealed here that a mild Lewis acidic MgI_2 etherate could preferentially activate the acetal. The preferential activation of acetal over its parent aldehyde may be attributed to the fast and irreversible silylation of MgI_2 etherate by transient TMSI to regenerate MgI_2 etherate and expel TMSOMe as the thermodynamically favored by-product as shown in the proposed catalytic cycle (Scheme 2).

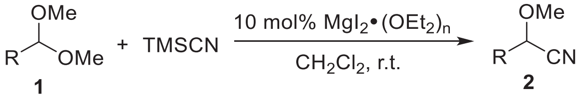
Table 2. Strecker-type reaction of various acetals catalyzed by MgI_2 etherate[a].

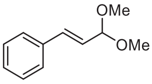
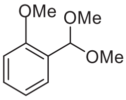
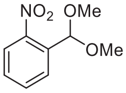
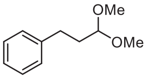
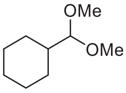


Enrty	Aldehyde	Time (h)	Product	Yield (%)[b]
1		3	**2a**	95
2		3	**2b**	94
3		2	**2c**	98
4		3	**1d**	92
5		3	**2e**	91
6		3	**2f**	92
7		3	**2g**	89
8		5	**2h**	91
9		12	**2i**	33
10		12	**2j**	trace
11		4	**2k**	90
12		3	**2l**	89
13		6	**2m**	68

(*continued*)

Table 2. Continued.



Enrty	Aldehyde	Time (h)	Product	Yield (%)[b]
14		4	**2n**	92
15		24	**2o**	N.R.
16		24	**2p**	trace
17		24	**2q**	N.R.
18		24	**2r**	N.R.

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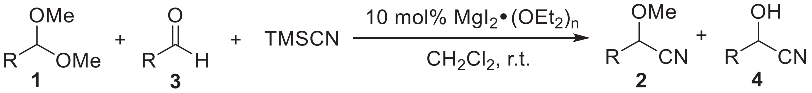
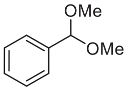
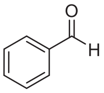
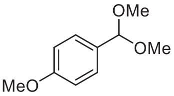
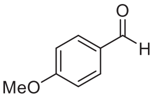
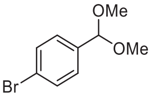
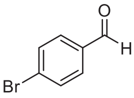
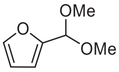
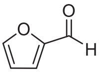
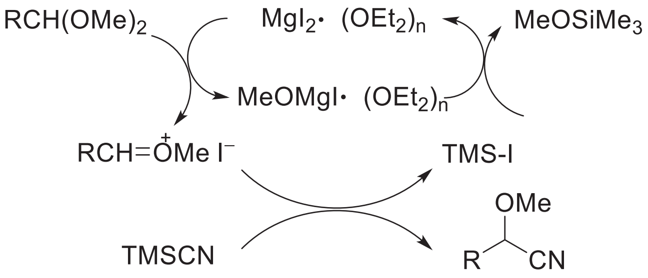
[a] The reaction was carried out by the addition of acetals (1.5 mmol) and TMSCN (1.8 mmol) in the presence of 10 mol % of MgI_2 etherate in CH_2Cl_2 at room temperature.
[b] Isolated yields by silica gel flash chromatography.

Table 3. Crossover cyanosilylation of aldehydes and acetals with TMSCN[a].



Entry	RCH $(OMe)_2$	RCHO	Ratio (2:4)[b]	Overall yield (%)[c]
1			>99/<1	95
2			>99/<1	95
3			>99/<1	92
4			>99/<1	89

$RCH(OMe)_2$: acetal; RCHO is aldehyde.
[a] Reactions were run with a mixture of 1.5 mmol of aldehyde, 1.5 mmol acetal, 1.5 mmol of TMSCN and 10 mol% of MgI_2•$(Et_2O)_n$ in CH_2Cl_2 at room temperature.
[b] The ratio was determined by isolated yields on silica gel.
[c] Isolated overall yields.



Scheme 2. Plausible mechanism for Strecker reaction of acetals with TMSCN catalyzed by MgI_2 etherate.

Conclusion

In conclusion, we have developed a highly efficient Strecker-type reaction of acetals with TMSCN catalyzed by MgI_2 etherate. This magnesium-catalyzed Strecker-type addition is rapid, mild, environmentally friendly and operationally simple. Further studies on magnesium-catalyzed asymmetric Strecker-type reaction of acetals 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 °C) were used. The reactions monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates. ^1H 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 ^1H NMR and are in good agreement with those reported. HRMS (EI) was determined on a PerkinElmer spectrometer.

General procedure for strecker-type reaction of acetals with TMSCN catalyzed by MgI_2 etherate

To a stirred benzaldehyde dimethyl acetal **1a** solution of (15 mmol) was added a freshly prepared MgI_2 etherate (1.5 mmol, 1.0 M in Et_2O/PhMe) at room temperature, followed by addition of trimethylsilyl cyanide (18 mmol). The resulting reaction mixture was stirred at room temperature for 3.0 h. chromatographic purification of the crude product on silica gel gave the 2-phenyl-2-methoxyacetonitrile **2a** in 95% yield.

Spectroscopic data for the unknown products

2-(3-methoxyphenyl)-2-methoxyacetonitrile (2d): Colorless transparent liquid; $R_f = 0.75$ (PE:EtOAc = 5:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, $J = 7.9$ Hz, 1H), 7.11–7.03 (m, 2H), 6.96 (dd, $J = 2.4$, 8.3 Hz, 1H), 5.16 (s, 1H), 3.81 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.88, 134.56, 129.89, 119.22, 116.84, 115.32, 112.42, 77.28, 77.03, 76.77, 71.87, 56.97, 55.13 ppm. HRMS (EI): calcd. for $C_{10}H_{11}NO_2$ $[M]^+$ 177.0790; found 177.0796.

2-(4-fluorophenyl)-2-methoxyacetonitrile (2g): Yellow liquid; $R_f = 0.89$ (PE:EtOAc = 5:1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.14–7.11 (m, 2H), 5.18 (s, 1H), 3.54 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.36, 162.38, 129.25 (t, $J = 8.3$ Hz), 116.76, 115.99 (d, $J = 22$ Hz), 71.49, 57.1 ppm. HRMS (EI): calcd. for C_9H_8FNO $[M]^+$ 165.0590; found 165.0594.

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