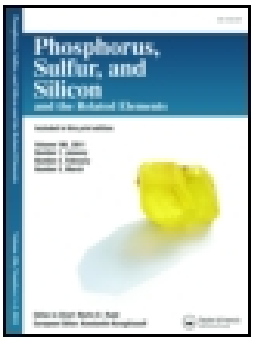

Phosphorus, Sulfur, and Silicon and the Related Elements

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PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
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An efficient hydrocyanation of α, β-unsaturated diesters with TMSCN catalyzed by MgI_2 etherate

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ABSTRACT

A mild, efficient and highly regioselective addition of trimethylsilyl cyanide (TMSCN) to α,β-unsaturated diesters has been achieved by using MgI_2 etherate as catalyst under solvent-free conditions. This protocol provides the corresponding β-cyano esters in high yields.

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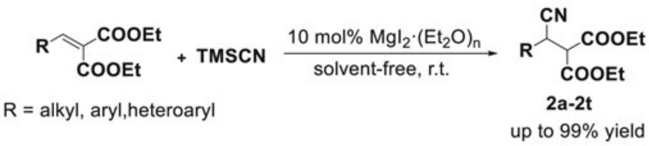
α,β-Unsaturated diester; TMSCN; hydrocyanation; MgI_2 etherate

GRAPHICAL ABSTRACT



Introduction

As one of the most general and versatile methods for C–C bond formation, the conjugate addition to α,β-unsaturated carbonyl compounds has received much attention.[1] Hydrocyanation of α,β-unsaturated carbonyl compounds usually provides a practical method for the synthesis of β-cyano carbonyl derivatives. The conjugate addition of cyanide ion to α,β-unsaturated ketones has been studied using different types of cyanide sources such as acetone cyanohydrin,[2] potassium hexacyanoferrate(II),[3] tributylsilyl cyanide[4] and trimethylsilyl cyanide (TMSCN).[5] Several catalytic systems have been used to promote this process, including quinidinium salts,[2a,2b] metal complexes,[2c,4,5a,5b,5d,5h,6] CsF,[5c,5g] and potassium carbonate,[7] as well as KOH.[8] Recently, Bronsted basic ionic liquid as catalytic and reusable media for conjugate cyanation of CF_3-substituted alkylidenemalonates using acetone cyanohydrin.[9] Moreover, organic nitriles (R-CN) are common and important intermediates that can be transformed into different classes of molecules such as amines,[10] carboxylic acids,[11] esters,[12] and heterocycles.[13] Many drugs containing a nitrile functionality show important pharmacological activities.[14] To the best of our knowledge, there is only a few reports on the 1,4-hydrocyanation of α,β-unsaturated esters.[15] Therefore, the development of less expensive, environmentally friendly, and easily handled promoters for the addition of TMSCN to α,β-unsaturated esters is still highly desirable.

In our previous paper, we have demonstrated that MgI_2 etherate could efficiently promote one-pot three-component condensation of aldehydes or ketones, amines and TMSCN catalyzed by MgI_2 etherate under solvent-free conditions.[16] In continuation of our research field, we will report a highly regioselective hydrocyanation of TMSCN with diethyl alkylidenemalonates in the presence of 10 mol% MgI_2 etherate under solvent-free conditions.

Results and discussion

We optimized the reaction conditions by the hydrocyanation of diethyl n-butylidenemalonate **1a** with TMSCN as a model reaction and the results are summarized in Table 1. We firstly explored the effect of solvents on this addition. It is evident that 1,4-hydrocyanation was carried out smoothly in various solvents in the presence of 10 mol% $MgI_2{\bullet}(Et_2O)_n$ at room temperature. Among them, an excellent yield was formed using MeCN as a solvent (Table 1, entry 3). Interestingly, a nearly quantitative yield was afforded under solvent-free conditions (Table 1, entry 7). The reaction stoichiometry was checked by varying the amounts of $MgI_2{\bullet}(Et_2O)_n$ under solvent-free conditions. The yields of ethyl 2-carbethoxy-3-cyano-3-butylpropionate **2a** are improved by increasing the amount of $MgI_2{\bullet}(Et_2O)_n$ (Table 1, entries 7–10). 10 mol% of $MgI_2{\bullet}(Et_2O)_n$ was sufficient. To examine the effect of other catalysts, a variety of Lewis acids, such as $MgCl_2$, $Mg(ClO_4)_2$, $MgBr_2$, $TiCl_4$, $SnCl_4$, ZnI_2 and $ZnCl_2$ were compared under parallel reaction conditions (Table 1, entries 11–17). $TiCl_4$, $Mg(ClO_4)_2$, $MgCl_2$ and $MgBr_2$ could give the desired product in moderate to good

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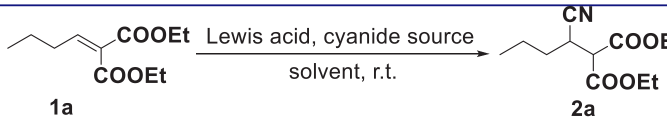
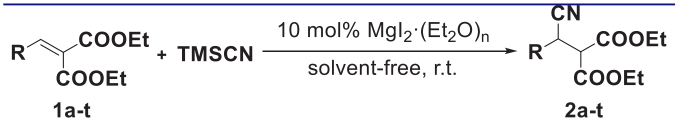
Table 1. Optimization of reaction conditions.[a]



Entry	Lewis acid (mol%)	Solvent	Cyanide source	t (h)	Yield (%)
1	$MgI_2\bullet(Et_2O)_n$ (10)	CH_2Cl_2	TMSCN	4.5	83
2	$MgI_2\bullet(Et_2O)_n$ (10)	$CHCl_3$	TMSCN	4.5	85
3	$MgI_2\bullet(Et_2O)_n$ (10)	MeCN	TMSCN	4.5	95
4	$MgI_2\bullet(Et_2O)_n$ (10)	THF	TMSCN	5.0	88
5	$MgI_2\bullet(Et_2O)_n$ (10)	toluene	TMSCN	7.5	85
6	$MgI_2\bullet(Et_2O)_n$ (10)	MeOH	TMSCN	4.5	70
7	$MgI_2\bullet(Et_2O)_n$ (10)	none	TMSCN	5.0	97
8	$MgI_2\bullet(Et_2O)_n$ (20)	none	TMSCN	4.5	97
9	$MgI_2\bullet(Et_2O)_n$ (5)	none	TMSCN	12.0	69
10	$MgI_2\bullet(Et_2O)_n$ (3)	none	TMSCN	12.0	35
11	$MgCl_2$(10)	none	TMSCN	5.0	82
12	$Mg(ClO_4)_2$(10)	none	TMSCN	5.0	76
13	$MgBr_2$(10)	none	TMSCN	5.0	75
14	$TiCl_4$(10)	none	TMSCN	5.0	80
15	ZnI_2(10)	none	TMSCN	5.0	55
16	$SnCl_4$(10)	none	TMSCN	5.0	25
17	$ZnCl_2$(10)	none	TMSCN	5.0	12
18	$MgI_2\bullet(Et_2O)_n$(10)	none	CNCOOMe	5.0	35
19	$MgI_2\bullet(Et_2O)_n$(10)	none	CNCOOEt	5.0	37
20	$MgI_2\bullet(Et_2O)_n$(10)	none	$K_4Fe(CN)_6$	5.0	N.R.
21	$MgI_2\bullet(Et_2O)_n$(10)	none	CuCN	5.0	N.R.

[a] To a solution of diethyl 2-butylidenepropanedioate (2.0 mmol) and cyanide source (2.4 mmol) in solvents (10 mL) was added (0.2 mmol) Lewis acid at room temperature.

Table 2. $MgI_2\bullet(Et_2O)_n$-catalyzed 1,4-hydrocyanation of TMSCN to diesters.[a]



Entry	R	Time (h)	Product	Yield(%)[b]
1	n-Pr	5.0	**2a**	97
2	Et	5.0	**2b**	95
3	c-hexyl	6.0	**2c**	94
4	Ph	5.0	**2d**	96
5	2-FPh	7.0	**2e**	92
6	2-ClPh	7.0	**2f**	93
7	2-BrPh	7.0	**2g**	94
8	4-ClPh	5.0	**2h**	94
9	4-BrPh	5.0	**2i**	95
10	4-MePh	7.0	**2j**	89
11	2-MeOPh	7.0	**2k**	85
12	3-MeOPh	6.0	**2l**	87
13	4-MeOPh	6.0	**2m**	84
14	$2-NO_2Ph$	3.0	**2n**	99
15	$3-NO_2Ph$	3.0	**2o**	99
16	$4-NO_2Ph$	2.0	**2p**	99
17	1-naphthyl	8.0	**2q**	95
18	2-furanyl	3.0	**2r**	93
19	3-pyridyl	4.0	**2s**	96
20	3-indolyl	3.0	**2t**	94

[a] Reaction conditions: TMSCN (2.4 mmol), $MgI_2\bullet(Et_2O)_n$ (0.2 mmol), diethyl arylidene-, heteroarylidene- or alkylidene-malonates **1a–1t** (2.0 mmol) were stirred at room temperature under solvent-free conditions.

[b] Isolated yields after silica gel column chromatographic purification.

yield. ZnI_2 produced a low yield. $SnCl_4$ and $ZnCl_2$ were almost inactive in terms of substrate conversion and yield. Furthermore, various types of cyanide sources were screened, respectively (Table 1, entries 18 to 21). Low yields were given by using CNCOOEt or CNCOOMe as cyanide source. No reaction was observed by using $K_4Fe(CN)_6$ or CuCN as cyanide source in the presence of MgI_2 etherate, respectively.

Encouraged by these optimized reaction conditions, we chose a variety of structurally diversified diethyl alkylidene-malonates and arylidenemalonates possessing a wide range of functional groups to understand the scope and generality of this $MgI_2\bullet(Et_2O)_n$-catalyzed 1,4-hydrocyanation. The results are summarized in Table 2. A variety of substrates, including alkylidenemalonates, arylidenemalonates, and heteroarylidene malonates underwent addition with TMSCN to afford the corresponding *β*-cyano propionate derivatives. Diethyl alkylidene-malonates (**1a–1c**), especially with a bulkier substituent such as a cyclohexyl group, gave excellent yields (Table 2, entries 1–3). As well, excellent yields were afforded with diethyl arylidenemalonates possessing halogen groups (Table 2, entries 5–9). Moreover, diethyl arylidene-malonates with electron-donating groups afforded good yields of the desired products (Table 2, entries 10–13). Nearly quantitative yields were obtained with diethyl arylidenemalonate possessing electron-withdrawing groups (Table 2, entries 14–16). In addition, diethyl arylidenemalonate **1q** derived from 1-naphthaldehyde, which contains a highly conjugated plane, seems to be effective, and gave the desired adduct in 95% yield (Table 2, entry 17). Furthermore, diethyl heteroarylidenemalonates, derived from pyridine-3-carboxaldehyde, furane-2-carboxaldehyde and indol-3- carboxaldehyde, also provided high yields (Table 2, entries 18–20).

Experimental

General

All reagents were commercially available and directly used without further treatment. ^1H NMR and ^{13}C 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 as an internal standard. FTIR were recorded on a Bruker Tensor 27 spectrometer. EI-MS were determined on a Perkin Elmer spectrometer. HRMS(ESI) were determined on a Therm LCQ TM Deca XP plus spectrometer. 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 representative procedure for the synthesis of β-cyano diesters —To a stirred mixture solution of α,β-unsaturated diesters **1a–1t** (2.0 mmol) and TMSCN (198 mg, 2.4 mmol) was added a freshly prepared MgI_2 etherate (0.2 mL, 1.0 mol/L $PhMe/Et_2O$) at room temperature. The resulting reaction mixture was stirred at room temperature for several hours and quenched with saturated aqueous $NaHSO_3$. Extractive workup with ethyl acetate and chromatographic purification of the crude product on silica gel gave the desired adduct.

Spectroscopic data for the products (Table 2, entries 2a–2t) is provided in Supplemental Materials file.

Conclusions

We have disclosed a highly efficient 1,4-hydrocyanation of alkylidenemalonates and arylidenemalonates with TMSCN catalyzed by MgI_2 etherate at room temperature under solvent-free conditions. The broad substrate scope, simple operation, high regioselectivity, and mild condition make this a powerful method. Further investigation is in progress in our laboratories to study stereoselectivity, and to attempt the preparation of chiral units which might function as important synthetic targets in drugs and natural products.

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