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Synthesis of 2-Substituted-4-chloromethylfurans Using 2-(Chloromethyl)-3-(trimethylsilyl)propene

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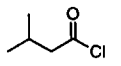
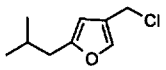
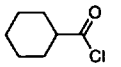
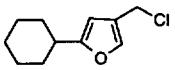
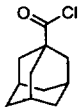
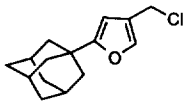
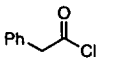
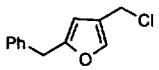
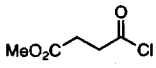
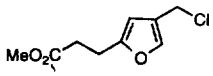
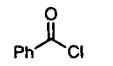
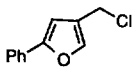
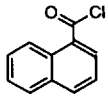
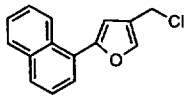
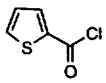
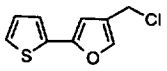
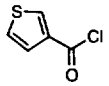
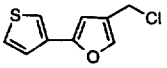
The 3-furylmethyl moiety is present in various natural products such as perillene,[1] dendrolasin,[1] amilol-A and B,[2] anonene,[3] pallescensin-1,2,3, and A,[4] pleraplysillin-1,[5] nakafuran-8 and 9.[6] Most of them were synthesized from 3-chloromethylfuran. 3-Chloromethylfuran itself has been synthesized.[1a,7] However, the reports on alkyl or aryl substituted 3-chloromethylfurans are rare.[8] Though numerous synthetic routes to furans have been developed,[9] a regioselective preparation of highly substituted furans is still demanding. We describe here a general, convenient preparation of 2-substituted-4-chloromethylfurans **5**, which are useful for the synthesis of the substituted furanosesquiterpenes.

The epoxycarbonyl compounds, good precursors of furans, have been prepared from homoallylic alcohols by epoxidation followed by oxidation.[10,11] And the homoallylic alcohols have been synthesized from the reaction of allylic chlorides with aldehydes in the presence of magnesium or zinc.[12] However, these synthetic routes have some limitations for the preparation of variously substituted epoxycarbonyl compounds. Recently, we found that allylic ketones, which were obtained from the Lewis acid-mediated reactions of allysilanes with acid chlorides,[13] could be transformed to epoxycarbonyl compounds by epoxidation with m-chloroperoxybenzoic acid (MCPBA). Following this procedure, 2-substituted-4-chloromethylfurans **5** were prepared from the allysilane, 2-(chloromethyl)-3-(trimethylsilyl)propene (**1**)[14] as shown in the Scheme.

Table 1. Synthesis of 2-Substituted-4-chloromethylfurans **5**[a]

Entry	Acid Chloride **2**	Furan **5**	Overall Yield,[b] %
a			57
b			49
c			44
d			47
e			35
f			43
g			42
h			46
i			53

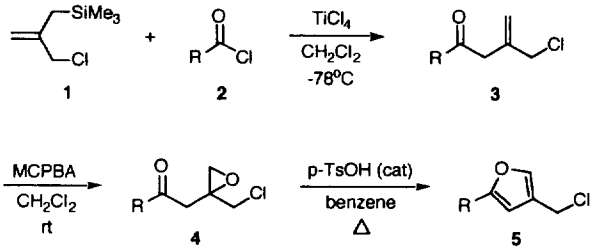
[a] The three step reactions were carried out consecutively without isolation of the intermediate products (See text). [b] Isolated yields (not optimized).

Reaction of allysilane **1** with isovaleryl chloride (**2a**) in the presence of one equiv of $TiCl_4$ at -78 ℃ in CH_2Cl_2 led to the allylic ketone **3a** in 92% yield after chromatography (SiO_2, hexane : ether = 8 : 1). The possible formation of conjugated enones coming from an acidic isomerization of **3** was not observed under our experimental conditions. Epoxidation of **3a** with MCPBA (2 equiv) in CH_2Cl_2 at 0 ℃ ~ room temperature gave the epoxide **4a** in 85% yield after purification (SiO_2, CH_2Cl_2). When a benzene solution of **4a** with a catalytic amount of p-toluenesulfonic acid was refluxed for 1 h, 2-isobutyl-4-chloromethylfuran **5a** was produced in 66% yield after purification by molecular distillation. The furan products **5**, especially aryl substituted ones, were lost significantly during chromatography on silica gel and alumina.

The three step procedures, the $TiCl_4$-promoted reaction of allylsilane **1** with an acid chloride, epoxidation with MCPBA, and cyclization process could be performed successively

Table 2. Spectral Data of 2-Substituted-4-chloromethylfurans **5**

Furans	^{1}H NMR ($CDCl_3$) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$) δ	MS m/z (rel. intensity, %)
5a	0.93 (6H, d, *J*=6.6), 1.89-2.03 (1H, m), 2.45 (2H, d, *J*=7.0), 4.43 (2H, s), 6.05 (1H, s), 7.30 (1H, s)	22.3, 27.8, 37.1, 37.6, 106.4, 122.8, 138.9, 157.1	174 (M+2, 11), 172 (M^+, 32), 137(25), 129 (100)
5b	1.2-1.4 (5H, m), 1.6-1.8 (3H, m), 1.95-2.05 (2H, m), 2.45-2.6 (1H, m), 4.40 (2H, s), 5.97 (1H, s), 7.26 (1H, s)	26.0, 26.2, 31.4, 37.3, 37.5, 103.7, 122.6, 138.5, 162.2	200 (M+2, 18), 198 (M^+, 55), 163 (43), 155 (100)
5c	1.2-2.0 (15H, m), 4.45 (2H, s), 5.98 (1H, s), 7.31 (1H, s)	28.2, 34.6, 36.7, 37.8, 41.0, 102.3, 122.3, 138.5, 165.9	252 (M+2, 11), 250 (M^+, 39), 215 (10), 193 (26), 84 (100)
5d	3.93 (2H, s), 4.41 (2H, s), 6.05 (1H, s), 7.21-7.34 (6H, m)	34.5, 37.4, 107.0, 123.0, 126.6, 128.5, 128.7, 137.5, 139.6, 156.1	208 (M+2, 2), 206 (M^+, 8), 171 (9), 128 (13), 84 (100)
5e	2.65 (2H, t, *J*=15.0), 2.94 (2H, t, *J*=15.0), 3.69 (3H, s), 4.43 (2H, 1s), 6.10 (1H, s), 7.32 (1H, s)	23.5, 32.2, 37.4, 51.8, 106.2, 123.0 139.4, 155.6, 172.8	204 (M+2, 3), 202 (M^+, 10), 167 (11), 149 (29), 129 (28), 84 (100)
5f	4.49 (2H, s), 6.69 (1H, s), 7.2-7.7 (6H, m)	37.2, 105.4, 123.5, 123.8, 127.8, 128.7, 130.3, 140.0, 155.1	194 (M+2, 5), 192 (M^+, 15), 157 (16), 128 (22), 84 (100)
5g	4.55 (2H, s), 6.74 (1H, s), 7.45-7.54 (3H, m), 7.61 (1H, s), 7.67-7.70 (1H, m), 7.80-7.86 (2H, m), 8.31-8.35 (1H, m)	37.1, 124.2, 125.3, 125.6, 126.0, 126.4, 126.7, 128.2, 128.6, 129.1, 130.5, 134.1, 140.3, 154.9	244 (M+2, 17), 242 (M^+, 53), 179 (44), 119 (100), 84 (92)
5h	4.45 (2H, s), 6.53 (1H, s), 7.0-7.4 (4H, m)	37.0, 105.4, 123.1, 124.3, 124.6, 127.6, 133.1, 139.4, 150.5	200 (M+2, 10), 198 (M^+, 27), 163 (15), 135 (36), 84 (100)
5i	4.48 (2H, s), 6.52 (1H, s), 7.3-7.5 (4H, m)	37.2, 105.2, 119.6, 124.0, 124.6, 126.3, 132.1, 139.3, 152.1	200 (M+2, 6), 198 (M^+, 15), 163 (14), 135 (24), 84 (100)



without isolation of the intermediate products. The consecutive procedure afforded the furan **5a** in a little improved yield (57%, Table 1, entry a) compared to the intermediate isolation procedure (52%). The furans **5** which were prepared by the consecutive procedure are presented in Table 1. The method is general in scope since it has been applied to the synthesis of 2-aliphatic-(**5a-d**), 2-carbomethoxyethyl-(**5e**), 2-aryl-(**5f-g**), and 2-heteroaromatic-4-chloromethylfurans (**5h-i**). The structure of products was established by spectral characterization (Table 2).

In summary, the present reaction sequence offers a facile route to various substituted furans by using properly designed allylsilanes.

Experimental

^{1}H NMR spectra were recorded on a JEOL JSX 270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a JEOL JSX 270 (58 MHz) spectrometer with $CDCl_3$ as solvent and internal standard. GC-MS analyses were performed with a Hewlett-Packard 5971 A spectrometer using a HP-1 column.

General procedure for the synthesis of 2-substituted-4-chloromethylfurans. The synthesis of 2-isobutyl-4-chloromethylfuran **5a** is typical: To a dichloromethane (5 m*l*) solution of $TiCl_4$ (1.25 g, 6.6 mmol) a mixture of isovaleryl chloride (**2a**) (0.78 g, 6.5 mmol) and 2-(chloromethyl)-3-(trimethylsilyl)propene (**1**) (1.02 g, 6.3 mmol) in CH_2Cl_2 (4 m*l*) was added slowly at −78 ℃. After 1 h, the mixture was quenched with 3 N HCl and extracted with ether. The ethereal extract was washed with sat. aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product **3a** (1.13 g) was treated with MCPBA (50%, 4.48 g, 13.0 mmol) in CH_2Cl_2 (10 m*l*) at 0 ℃ ~rt for 18 h. After removal of the solvent, benzene (10 m*l*) and p-toluenesulfonic acid (10 mg) was added, and refluxed for 1 h. The reaction mixture was partitioned between sat. aq NH_4Cl solution and ether, and the aqueous layer was separated and extracted with ether. The combined organic phases were washed with water and dried over Na_2SO_4, filtered, concentrated, and distilled (Kugelrohr, bp 70-72 ℃/0.04 mmHg) to afford 618 mg (57%) of **5a**.

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Conversion of Nitriles into Aldehydes by Diisobutylaluminum Hydride-Dimethyl Sulfide Complex

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The conversion of nitriles into aldehydes is one of the most desirable means in organic synthesis. Numerous useful methods have been proposed to achieve such purposes.[1] Especially noteworthy is that some reagents, such as potassium 9-*sec*-amyl-9-borarabicyclo[3.3.1]nonane (K-9-*sec*-Am-9-BBNH),[2] lithium tris(dihexylamino)aluminum hydride (LTDHA)[3] and sodium tris(dihexylamino)aluminum hydride (STDHA)[4], nicely achieved the chemoselective reduction of aromatic nitriles to the corresponding aldehydes in which aliphatic nitriles remain intact.

Very recently, we prepared diisobutylaluminum hydride-dimethyl sulfide (DIBAH-SMe_2) complex by a simple addition of dimethyl sulfide to the solution of diisobutylaluminum hydride (DIBAH)[5] (Eq. 1).

$$(i\text{-Bu})_2\text{AlH} + \text{SMe}_2 \xrightarrow{\text{toluene}} \underset{\text{DIBAH-SMe}_2}{(i\text{-Bu})_2\text{AlH-SMe}_2} \qquad (1)$$

The complex, DIBAH-SMe_2, is very stable and possesses unique reducing characteristics. Accordingly, we have examined the reducing characteristics of the complex systematically in order to enlarge the scope of applicability as a reducing agent.[5] In the course of this systematic study, we found that DIBAH-SMe_2 converted both benzonitrile and capronitrile into the corresponding aldehydes in higher yields than those obtained by DIBAH itselt. Consequently, we decided to investigate a full scope of such transformations. This paper reports the results for the reduction of nitriles by utilizing DIBAH-SMe_2 in a limiting amount at 0 ℃, along with the results obtained previously by DIBAH itself[6] for comparison.

In general, as shown in Table 1, the yields of aldehydes by DIBAH-SMe_2 are better than those by DIBAH itself which is well known as a superior reagent for synthesis of aldehydes from nitriles.

DIBAH-SMe_2 in toluene reduced unsubstituted aromatic nitriles, such as benzonitrile and naphthonitrile, to the corresponding aldehydes in yields of 90-91% in 3 h at 0 ℃. Dinitriles, such as phthalonitrile and terephthalonitrile, were reduced to dialdehydes in yields of 92-99%. Ring substituted derivatives are readily accommodated. Thus, chloro-and dichlorobenzonitriles were converted into the corresponding aldehydes in yields better than 90%. Tolunitriles, regardless of the position of the methyl substituent, were also readily reduced to give the aldehydes in better than 92% yields.

The reagent also reduced aliphatic nitriles to aldehydes in yields of 71-99% in 3h at 0 ℃. Alicyclic derivatives, such as cyclopropanecarbonitrile, worked equally well. α,β-Unsaturated nitriles, such as crotononitrile, provided the corresponding aldehydes in a yield of 97%. Finally, it is also possi-