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Iron(III) Chloride-Catalyzed Convenient One-Pot Synthesis of Homoallyl Benzyl Ethers Starting from Aldehydes

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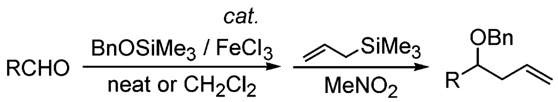
ABSTRACT



Iron(III) chloride-catalyzed effective allylation reactions of acetals with allyltrimethylsilane proceeded smoothly in high to excellent yields. In addition, this method could be applied to the one-pot synthesis of homoallyl benzyl ethers by a combination of dibenzyl acetalization of aldehydes and consecutive allylation of dibenzyl acetals.

Lewis acid-catalyzed allylations of carbonyl compounds with allyltrimethylsilane (Hosomi−Sakurai reaction) are important carbon−carbon bond-forming reactions, since they afford synthetically useful homoallyl alcohol derivatives.[1] Allylation of acetals is also well documented, and the corresponding products are homoallyl alkyl ethers. Several Lewis acids have been used to perform this reaction efficiently. In particular, traditional Lewis acids such as $TiCl_4$, $BF_3{\cdot}OEt_2$, and $AlCl_3$ have been generally utilized,[2] though stoichiometric or near-stoichiometric amounts of Lewis acid were required to accomplish the reaction completely. Other Lewis acids, such as trityl perchlorate,[3] TMSI,[4] TMSOTf,[5] $TMSNTf_2$,[6] $Sc(OTf)_3$,[7] and $Bi(OTf)_3$[8] were reported to be utilized as Lewis acid catalysts to promote the allylation reaction of acetals. However, these methods involve some annoying problems. (1) Homoallyl methyl ethers obtained by the reaction of dimethyl acetals with allylsilane cannot readily lead to further manipulation due to the inactivity of the aliphatic ether linkage. (2) The preparation of homoallyl methyl ethers from aldehyde requires a two-step conversion comprising acetalization of aldehydes and subsequent allylation of acetals. On the other hand, we have recently developed a highly efficient method for the allylation of aldehydes with allyltrimethylsilane catalyzed by $FeCl_3$.[9] This reaction took place smoothly using only 5 mol % $FeCl_3$ and could be applied to a broad range of aldehydes, and in particular, hindered aliphatic aldehydes could be allylated efficiently at room temperature. Therefore, we planned to elaborate the one-pot synthesis of homoallyl benzyl ethers from aldehydes in order to overcome the above problems. I. E. Markó et al. reported one-pot synthesis of homoallylic ethers from aldehydes catalyzed by TMSOTf; however, the scope and limitations were not described at all.[10] In this communication, we wish to report a convenient procedure

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(1) For leading reviews, see: (a) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (d) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (e) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(2) (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1978**, 499. (c) Hosomi, A.; Ando, M.; Sakurai, H. *Chem. Lett.* **1986**, 365.

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(4) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745.

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(9) Watahiki, T.; Oriyama, T. *Tetrahedron Lett.* **2002**, *43*, 8959. We have also investigated the effect of Lewis acid catalysts for allylation of benzaldehyde under the optimal conditions: $FeCl_3$ (92%), $FeCl_3{\cdot}6H_2O$ (14%), $FeCl_2$ (0%), $TiCl_4$ (13%), $BF_3{\cdot}OEt_2$ (10%), $AlCl_3$ (5%), $SnCl_4$ (73%), $Cu(OTf)_2$ (4%), $ZnCl_2$ (0%).

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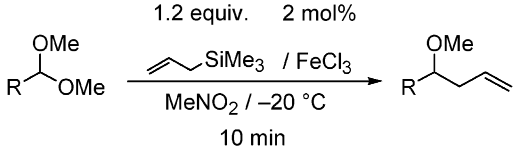
for the allylation of various acetals and dibenzyl acetalization of various aldehydes catalyzed by $FeCl_3$ and, additionally, an efficient procedure for the one-pot synthesis of homoallyl benzyl ethers directly from the parent aldehydes.

Initially, we investigated the reaction conditions of allylation of acetals in detail. The reaction of benzaldehyde dimethyl acetal with 1.2 equiv of allyltrimethylsilane in the presence of 2 mol % anhydrous $FeCl_3$ ($MeNO_2$, −20 °C) afforded the corresponding homoallyl methyl ether in 97% yield (Table 1, run 1). It was found that the reaction proceeded smoothly under similar conditions for allylation of aldehydes as reported in our previous paper.[9] Additional experimental results of this allylation are summarized in Table 1. Electron-deficient aromatic dimethyl acetals having halogen or acyloxy substituents were allylated in excellent yields (runs 2 and 3). Likewise, reaction of electron-rich aromatic dimethyl acetals having methyl or methoxy substituents on the benzene ring with allylsilane proceeded efficiently (runs 4−8), and over-allylation products, obtained in the case of allylation of *p*-tolualdehyde or *p*-anisaldehyde were not observed. Also, α,*β*-unsaturated dimethyl acetal was transformed into the corresponding homoallyl methyl ether in 93% yield (run 10), while over-allylation occurred mainly in $TiCl_4$-induced allylation of acetal.[2b] In general, it is anticipated that the allylation of an aliphatic dimethyl acetal is more difficult than that of an aromatic dimethyl acetal because of the higher electron density of the acetal carbon center. Fortunately, aliphatic dimethyl acetals could be also allylated in high yields in shorter reaction time at room temperature (runs 11 and 12). Furthermore, when benzaldehyde diethyl acetal and dibenzyl acetal were used as a substrate instead of dimethyl acetal, the corresponding homoallyl ethyl ether and homoallyl benzyl ether could be similarly obtained in 95 and 87% yields, respectively (runs 13 and 14).

Table 1. Allylation of Various Dimethyl Acetals



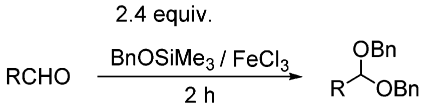
run	R	yield[a] (%)
1	Ph−	97
2	4-BrC_6H_4−	97
3	4-$AcOC_6H_4$−	91
4	4-MeC_6H_4−	92
5	3-MeC_6H_4−	93
6	2-MeC_6H_4−	86
7	2,4,6-$Me_3C_6H_2$−	100
8	4-$MeOC_6H_4$−	100
9	1-Naphtho−	77
10	(*E*)-PhCH═CH−	93
11[b]	$Ph(CH_2)_2$−	95
12[b]	PhCH(Me)−	96
13[c]	Ph−	95
14[d]	Ph−	87

[a] Isolated yields of purified product. [b] Reaction was performed for 15 min at room temperature. [c] Diethyl acetal was used as a starting substrate. [d] Dibenzyl acetal was used as a starting substrate.

Next, we attempted $FeCl_3$-catalyzed one-pot synthesis of homoallyl benzyl ether directly from aldehyde. Homoallyl methyl ethers obtained by the reaction of dimethyl acetals with allylsilane do not readily lead to further manipulation as mentioned above. From the synthetic viewpoint, it is very significant to prepare homoallyl benzyl ethers starting from dibenzyl acetals, which are more suitable for further manipulation. However, dibenzyl acetals are not so widely used in comparison with dimethyl acetals because of their lability to acidic conditions.[11] Therefore, we attempted at first the synthesis of dibenzyl acetals from aldehydes catalyzed by $FeCl_3$.

The reaction of benzaldehyde with 2.4 equiv of benzyloxytrimethylsilane (BnOTMS) in the presence of 2 mol % $FeCl_3$ without a solvent at 0 °C afforded the desired dibenzyl acetal in 92% yield (Table 2, run 1). We examined the reaction of various aldehydes with BnOTMS. Dibenzyl acetalization of *p*-bromobenzaldehyde took place smoothly in excellent yield (run 2). In contrast, *m*-tolualdehyde and *p*-anisaldehyde, such as electron-rich aromatic aldehydes, showed lower reactivity and the corresponding dibenzyl acetals were obtained in only 44 and 20% yields, respectively (runs 3 and 4). In the case of aliphatic aldehydes, CH_2Cl_2 was necessary as a reaction solvent because the $FeCl_3$ catalyst was insoluble under neat condition. Various aliphatic aldehydes were transformed into the corresponding dibenzyl acetals at room temperature in high yields (runs 5−8). Thus, it was demonstrated that $FeCl_3$ was also a very effective catalyst for dibenzyl acetalization of aldehydes as well as allylation of dialkyl acetals.

Table 2. Dibenzyl Acetalization of Various Aldehydes



run	RCHO	method[a]	yield[b] (%)
1	PhCHO	A	92
2	*p*-BrC_6H_4CHO	A	97
3	*m*-MeC_6H_4CHO	A	44
4	*p*-$MeOC_6H_4CHO$	A	20
5	$Ph(CH_2)_2CHO$	B	87
6	*c*-$C_6H_{11}CHO$	B	60
7	PhCH(Me)CHO	B	92
8	*t*-BuCHO	B	60

[a] Method A: $FeCl_3$ (2 mol %), 0 °C. Method B: $FeCl_3$ (5 mol%), CH_2Cl_2, rt. [b] Isolated yields of purified product.

Considering the above-mentioned successful results, we speculated that one-pot synthesis of homoallyl benzyl ether

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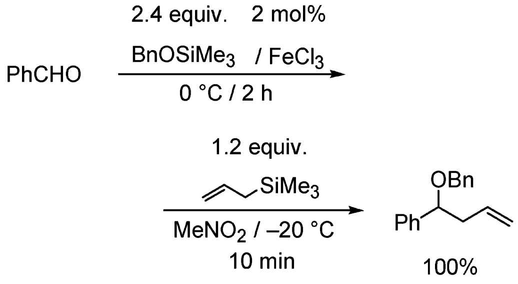
(11) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett*. **1980**, *21*, 1357.

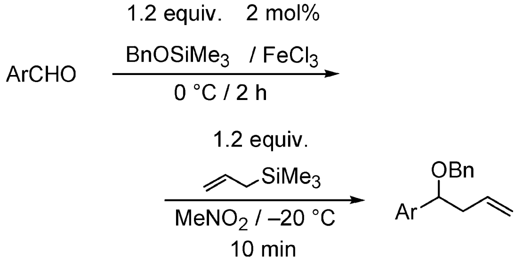
from aldehyde could be accomplished by a combination of dibenzyl acetalization and subsequent allylation. Actually, after dibenzyl acetalization of benzaldehyde with 2.4 equiv of BnOTMS, allylation of in situ-formed dibenzyl acetal with allylsilane catalyzed by $FeCl_3$ was performed very smoothly, and the desired homoallyl benzyl ether could be isolated quantitatively (Scheme 1).

Scheme 1. One-Pot Synthesis of Homoallyl Benzyl Ether Using 2.4 Equiv of $BnOSiMe_3$



In this reaction, 1 equiv of BnOTMS is supposed to be reproduced after completion of the reaction. From the viewpoint of atom economy, decreasing the number of equivalents of BnOTMS used in the one-pot synthesis would be favorable. So we tried the one-pot synthesis of homoallyl benzyl ether using 1.2 equiv of BnOTMS. This was also proven to be successful, and the corresponding homoallyl benzyl ether was given in 100% yield directly from benzaldehyde (Table 3, run 1). Other representative examples for the one-pot syntheses of various homoallyl benzyl ethers from aromatic and aliphatic aldehydes are listed in Tables 3 and 4. Aromatic aldehydes having an electron-withdrawing or an electron-donating group were transformed smoothly into the homoallyl benzyl ethers (Table 3). In the case of using methallyltrimethylsilane as an allyl nucleophile, the yield of the corresponding homoallyl benzyl ether was decreased to 66% (run 2). When the reaction was carried out with *p*-methoxybenzyloxytrimethylsilane, no reaction occurred (run 3). As depicted in Table 2, while dibenzyl acetalization of *m*-tolualdehyde and *p*-anisaldehyde proceeded in lower yield (44 and 20%, respectively), the corresponding homoallyl benzyl ethers could be obtained in 100 and 81% yields from the parent aldehydes, respectively (runs 5 and 6). These results can be explained by the mobile equilibrium of dibenzyl acetalization. That is, shifting the equilibrium of acetalization toward dibenzyl acetal by the allylation of acetal would improve the yield of homoallyl benzyl ether. In the presence of other functional groups such as ketone and ester, desired one-pot reaction of aldehydes also proceeded chemoselectively with these functional groups unaffected (runs 7 and 8). Moreover, aliphatic aldehydes had a slightly lower reactivity in comparison with aromatic ones, but these reactions were also successfully performed in high yields (Table 4). In particular, it should be noted that sterically hindered trimethylacetaldehyde transformed smoothly into the corresponding homoallyl benzyl ether in 87% yield (run 4).

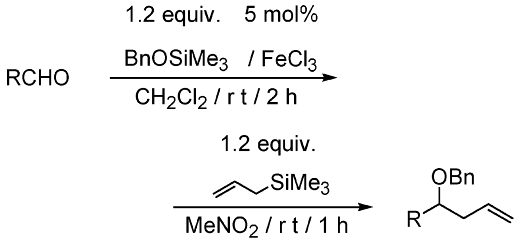
Table 3. One-Pot Synthesis of Homoallyl Benzyl Ethers from Various Aromatic Aldehydes



run	ArCHO	yield[a] (%)
1	PhCHO	100
2[b]	PhCHO	66
3[c]	PhCHO	0
4	*p*-BrC_6H_4CHO	99
5	*m*-MeC_6H_4CHO	100
6	*p*-$MeOC_6H_4CHO$	81
7[d]	*p*-$MeCOC_6H_4CHO$	85
8	*p*-$MeO_2CC_6H_4CHO$	95

[a] Isolated yields of purified product. [b] Methallyltrimethylsilane was used instead of allyltrimethylsilane. [c] *p*-Methoxybenzyloxytrimethylsilane was used instead of $BnOSiMe_3$. [d] Reaction was performed for 1 h at the second step.

Table 4. One-Pot Synthesis of Homoallyl Benzyl Ethers from Various Aliphatic Aldehydes



run	RCHO	yield[a] (%)
1	$Ph(CH_2)_2CHO$	80
2	*c*-$C_6H_{11}CHO$	83
3	PhCH(Me)CHO	81
4	*t*-BuCHO	87

[a] Isolated yields of purified product.

In conclusion, we have presented an efficient and convenient procedure for the one-pot synthesis of homoallyl benzyl ethers starting from a variety of parent aldehydes and demonstrated that $FeCl_3$ is a very effective catalyst for both acetalization and allylation. This convenient one-pot reaction took place smoothly using very low loading (2−5 mol %) of $FeCl_3$ at nearly ambient temperature and could be applied to a broad range of aldehydes. Furthermore, this procedure is quite promising in the case of synthesis of unstable homoallyl alcohol derivatives because no protection procedure is required. Additionally, $FeCl_3$ is a very cheap Lewis acid. These valuable features show that this new method is very practical and will be applicable to the synthesis of various complex natural products.

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Supporting Information Available: Experimental procedures and ^{1}H NMR, ^{13}C NMR, and IR spectra for homoallyl methyl ethers, dibenzyl acetals, and hoallyl benzyl ethers. This material is available free of charge via the Internet at http://pubs.acs.org.

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