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Synthesis of Homoallyl Ethers via Allylation of Acetals in Ionic Liquids Catalyzed by Trimethylsilyl Trifluoromethanesulfonate

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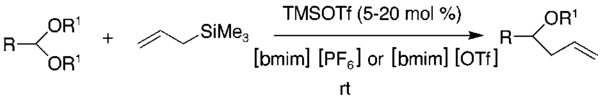
ABSTRACT



The chemoselective allylation of acetals using allyltrimethylsilane in ionic liquids is catalyzed by TMS triflate (5.0–20.0 mol %). The reaction proceeds smoothly at room temperature to afford the corresponding homoallyl ether in good yield. Since the ionic liquids are easily recovered and recycled, they are a useful alternative to dichloromethane, which is the commonly used solvent for allylations.

Of all the organic reactions, carbon−carbon bond-forming reactions rank among the most important. Of particular interest are Lewis acid-catalyzed carbon−carbon bond-forming reactions since there is a wide range of selectivity and catalytic behavior among various Lewis acids. The allylation of acetals using organosilicon reagents has attracted much attention as a useful method to generate homoallyl ethers. Several catalysts have been used to effect this transformation. These include $TiCl_4$,[1] $AlCl_3$,[2] $BF_3{\cdot}Et_2O$,[2] trityl perchlorate,[3] diphenylboryl triflate,[3] montmorillonite,[4] Pb/Al,[5] trimethylsilyl bis(fluorosulfonyl)imide,[6] $(CH_3)_4SiI$,[7] TMSOTf,[8] $TiCp_2(CF_3SO_3)_2$,[9] CF_3COOH,[10] $BiBr_3$,[11] trimethylsilyl bis(trifluoromethanesulfonyl)amide [$TMSNTf_2$],[12] $Sc(OTf)_3$,[13] indium metal,[14] and $Bi(OTf)_3$.[15] While most of these allylations require an activated alkene such as allyltrimethylsilane, other allyl group sources such as allyl bromide,[2] and lithium *n*-butyltriallylborate[16] have also been used. Most of these methods require the use of chlorinated organic solvents such as CH_2Cl_2 and often inconveniently low temperatures. With increasing environmental concerns, it is imperative that new "environment friendly" solvents be developed and used.[17] Room temperature ionic liquids are becoming increasingly popular as solvents in organic synthesis for several reasons.[18] They are practically nonvolatile and hence do not the pose the risks associated with volatile organic compounds. In addition, they are nonflammable and

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(1) Hosomi, A.; Masahiko, E.; Sakurai, H. *Chem. Lett.* **1976**, 941.

(2) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1978**, 499.

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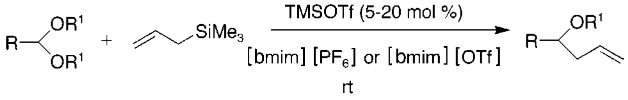
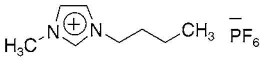
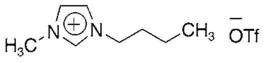
Scheme 1



can be recycled easily without any significant loss in activity. Often, unexpected or improved reactivity is seen in ionic liquids. The allylation of carbonyl compounds in ionic liquids to yield homoallyl alcohols has been reported.[19] We now report that the TMS triflate catalyzed chemoselective allylation of acetals in ionic liquids, butylmethylimidazolium hexafluorophosphate, [bmim][PF_6], **1** and butylmethylimidazolium triflate, [bmim][OTf], **2** affords the corresponding homoallyl ethers in good yields (Scheme 1).[20]



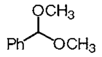
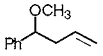
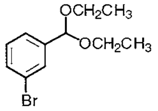
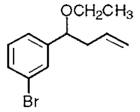
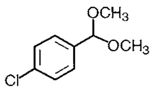
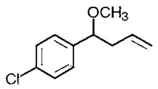
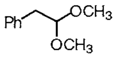
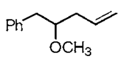
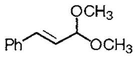
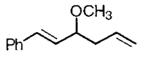
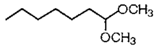
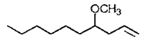
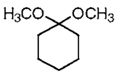
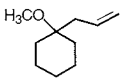
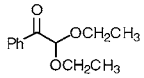
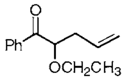
1



2

The product is isolated by extraction with ether, and the ionic liquid can be reused after drying at 70 °C under vacuum. This procedure works well at room temperature and avoids the use of chlorinated compounds, such as CH_2Cl_2, that are typically used as solvents for allylation of acetals. The results are summarized in Table 1. The reaction progress was followed by TLC. Some of the acetals are not completely soluble in the ionic liquid, and hence, it is important to stir the reaction mixture well. In none of the cases was there any evidence of the formation of the diallylated product. In the case of cinnamaldehyde dimethyl acetal (entry 5), it was especially important to ensure that the ionic liquid was dry.[21] Otherwise, considerable amounts (20−50%) of cinnamaldehyde formed during the course of the reaction. It has been reported that with $TiCl_4$ as the activator, the reaction of cinnamaldehyde dimethyl acetal with allyltrimethylsilane gives only the diallylated product.[2] Even at low temperatures (−78 °C) the monoallylated product was not formed. Similar results were obtained when allylation of cinnamaldehyde dimethylacetal was carried out using allyl bromide in the presence of $AlBr_3$.[5] In contrast, we did not observe any diallylated product using TMSOTf as the catalyst in [bmim][PF_6] or [bmim][OTf] and the monoallylated product was obtained in good yield in both the ionic liquids. No diallylation product is observed when the allylation is carried out using TMSOTf in CH_2Cl_2 as the solvent.[8] When the allylation of cinnamaldehyde dimethyl acetal was attempted neat, the results were not reproducible and in most trials, an exothermic reaction occurred leading to the formation of black tar. The chemoselective allylation of 2,2′-diethoxyacetophenone **3** in [bmim][OTf] proceeded smoothly to afford the corresponding homoallyl ether **4** (Scheme 2).[23]

Table 1. TMS Triflate Catalyzed Allylation of Acetals in [bmim][PF_6][a] and [bmim][OTf][a]

entry[b]	substrate	product[c]	time & yield (%)[d] [bmim][PF_6]	time & yield (%)[d] [bmim][OTf]
1[1]			1 h 68	—
2[15]			1 h 15 min 80	1 h 15 min 84
3[5]			1 h 20 min 76	50 min 79
4[24]			1.5 h 76	—
5[8]			5.5 h 81	2 h 15 min 78
6[6]			25 min[e] 79	45 min[e] 79
7[1]			45 min 62	45 min 74
8			—	23 h 78

[a] Ionic liquids were purchased from Acros Chemical Co. [b] Literature reference for the product. [c] Reaction progress was followed by TLC. [d] Refers to yield of isolated, purified product. All products were at least 98% pure by ^1H and ^{13}C NMR and GC analysis. [e] 5 mol % TMSOTf used.

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(18) For reviews on ionic liquids, see: (a) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. (b) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2083. (c) Gordon, C. M. *Appl. Catal. A: General* **2001**, *222*, 101−117. (d) Butler, R. *Chem. Ind. (London)* **2001**, *17*, 532. (e) Wasserscheid, P. *Nachr. Chem.* **2001**, *49*, 12−16.

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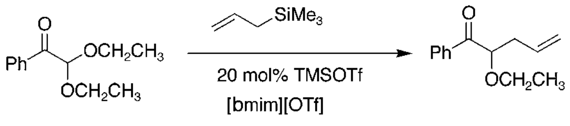
(20) **Typical procedure:** A flame-dried 25 mL round-bottomed flask was charged with the ionic liquid (1.5 mL, 2.05 g of [bmim][PF_6] or 1.94 g of [bmim][OTf] and heptanal dimethyl acetal (0.50 g, 3.12 mmol). Allyltrimethylsilane (0.463 g, 0.645 mL, 4.06 mmol, 1.3 equiv) was added with a syringe followed by TMS triflate (0.035 g, 0.030 mL, 0.156 mmol, 5.0 mol %), and the mixture was magnetically stirred vigorously for 45 min. The reaction mixture was extracted with ether (4 × 20 mL), and the combined ether extracts were washed with 10% aqueous Na_2CO_3 (25 mL) and saturated NaCl (15 mL) and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield 0.500 g of a pale yellow liquid that was further purified by flash chromatography to yield 0.42 g (79%) of a colorless liquid identified as the corresponding homoallyl ether (98% pure by GC, ^1H NMR and ^{13}C NMR). The recovered ionic liquid (typical recovery = 1.95 g) was dried at 70 °C (0.1 mmHg) for 4 h (as described in ref 22) prior to use in the next allylation. Based on ^1H NMR analysis, there was no evidence of either ionic liquid in the ether layer or any organic product in the ionic liquid.

(21) For allylation of cinnamaldehyde acetal, the ionic liquid was stirred with solid K_2CO_3 (0.5 g per 3 mL of ionic liquid) for 20 min, extracted with ethyl acetate, and dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. The ionic liquid was further dried by heating at 70 °C (0.1 mmHg) for 4 h. The potassium carbonate treatment removes any HF that might be formed by hydrolysis of the [bmim][PF_6]. Over the course of several weeks, we did not see any evidence of hydrolysis of the ionic liquid [bmim][PF_6], such as etching of the glassware.

(22) The ionic liquids were dried as follows after each run: The recovered ionic liquid was stirred over powdered activated 4 Å sieves for 12 h, dissolved in ethyl acetate, and filtered, and the solvent was removed on a rotary evaporator. The ionic liquid was further dried by heating at 70 °C (0.1 mmHg) for 4 h.

Scheme 2

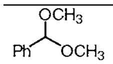
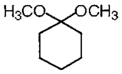
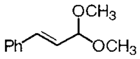
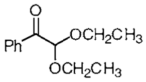


3 **4**

Thus, the acetal moiety can be selectively allylated over the carbonyl group.

When the same reaction was carried out in CH_2Cl_2, the allylation was very slow and less than 40% product resulting from allylation of the acetal formed after 24 h. With 5 mol % $Bi(OTf)_3$ as the catalyst in CH_2Cl_2, no reaction was observed.[15] This example illustrates that ionic liquids are not a mere substitute for volatile organics—rather, they can significantly influence the outcome of the reaction. In Table 2, yields of allylation of four acetals using four different methods are compared. It can be seen that allylations in CH_2Cl_2 using TMSOTf or $TiCl_4$ require inconveniently low temperatures while allylation in ionic liquids can be carried out at room temperature.

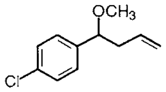
Table 2. Allylation of Acetals Using Allyltrimethylsilane in Various Solvents

acetal	% yield[a] using 1 eq $TiCl_4$, CH_2Cl_2, -78 °C	% yield[b] using 1-10 mol % TMSOTf, CH_2Cl_2, -78 °C	% yield using 20 mol % TMSOTf, [bmim][OTf], rt	% yield[c] using 1 mol % $Bi(OTf)_3$, CH_2Cl_2, rt
	74 (GC yield)	88 (GC)	68[d] (isolated)	84 (isolated)
	71 (GC yield)	81 (isolated)	74 (isolated)	82 (isolated)
	diallylation 100 (GC yield)	monoallylation 78 (isolated)	78 (isolated)	84 (isolated)
	–	40 % conversion	78 (isolated)	NR

[a] Data from refs 1 and 2. [b] Data from ref 8. [c] Date from ref 15. [d] Reaction carried out in [bmim][PF_6].

If the ionic liquid was used alone (no added TMSOTf), almost no allylation was observed. If the observed catalysis were due to any trace halides in the ionic liquids, one would expect allyaltion to proceed in the absence of TMSOTf. Similar results were obtained with the recycled ionic liquids (no added TMSOTf). The ionic liquid was easily recycled.[22] To determine the efficiency of recycling, the allylation of *p*-chlorobenzaldehyde dimethyl acetal was studied (Table 3). For each subsequent run, the recovered ionic liquid was used.

Table 3. Recycling of [bmim][PF_6]: Allylation of *p*-Chlorobenzaldehyde Dimethyl Acetal

trial no.	gc yield of 	% recovery (by mass) of ionic liquid
1	85	95
2	84	95
3	88	95
4	88	96

In summary, this work demonstrates a new environment friendly and mild method for the chemoselective allylation of acetals using catalytic amounts of TMS triflate in ionic liquids as solvents. The solvent can be easily recycled, thus allowing allylations to be carried out in non-chlorinated solvents.

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Supporting Information Available: Experimental details and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) IR (neat): 3084, 2985, 2873, 1692, 1593, 1439, 1111 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz): δ 1.18 (3 H, apparent triplet), 2.56 (2 H, apparent triplet), 3.50 (2 H, 16 line multiplet), 4.56 (1 H, apparent multiplet), 5.06 (2 H, multiplet), 5.83 (1 H, multiplet), 7.49 (3 H. multiplet), 8.05 (2 H, multiplet). ^{13}C NMR ($CDCl_3$, 67.5 MHz, 11 peaks): δ 15.2, 37.5, 65.6, 82.9, 117.6, 128.5, 128.7, 133.3, 133.5, 135.2, 200.3. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.48; H, 7.89. HRMS: *m*/*e* 205.122289 (M + 1), $C_{13}H_{16}O_2$ requires 205.12296 (M + 1).

(24) Barentsen, H. M.; Sieval, A. B.; Cornelisse, J. *Tetrahedron* **1995**, *51*, 7495.