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Microwave-Assisted Allylation of Acetals with Allyltrimethylsilane in the Presence of CuBr

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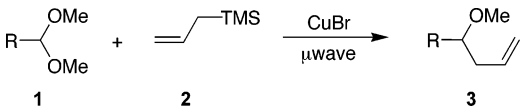
Abstract: We describe the first synthesis of homoallyl ethers from acetals and allyltrimethylsilane using microwave heating and CuBr as a promoter. This method works best for aromatic acetals, giving the corresponding homoallyl ethers in good to quantitative yield.

The allylation of carbonyl compounds and their derivatives with allyltrimethylsilane is an important method for the synthesis of homoallyl alcohols and ethers.[1] For aldehydes, this reaction can be catalyzed by fluoride ions or Lewis acids, whereas for acetals and ketals, only Lewis acids, such as $TiCl_4$,[2] TMSOTf,[3] and others,[4] are known to catalyze or promote this reaction. We recently described a mixed Lewis acid system comprised of $AlBr_3$ and CuBr, which acts as a potent catalyst for the allylation of aromatic and aliphatic acetals and ketals with allyltrimethylsilane.[5] To scavenge unwanted HBr that is formed or present in the reaction, a small amount of $AlMe_3$ was added to the reaction mixtures. Despite the efficiency of this and other previously described Lewis acids for this process, a method not requiring the use of highly reactive and acidic reagents would be desirable since it might help to preserve sensitive functional groups present in the starting materials. In this paper, we describe the first allylation of acetals **1** with allyltrimethylsilane **2** in the absence of strong Lewis acids, a reaction promoted by microwave heating in the presence of CuBr, to generate the desired homoallyl ethers **3** (Scheme 1).

SCHEME 1



1 **2** **3**

We first studied the allylation of benzaldehyde dimethyl acetal with allyltrimethylsilane as a model reaction. Among the various metal salts screened, we found that stoichiometric amounts of CuBr promoted the allylation when the starting materials were heated in a conventional microwave reactor in anhydrous 1,2-dichloroethane for 60 min at 100 °C (see Experimental Section for a detailed procedure). Different solvents were examined for this reaction, but only dichloromethane and 1,2-dichloroethane could be successfully used, with the latter being preferred due to its higher boiling point. In diethyl ether or THF, the allylations did not take place, presumably due to competitive binding of the solvent to the CuBr during the reaction. With catalytic amounts of CuBr, the product yields were low, and microwave heating of the starting materials in the absence of CuBr was unsuccessful. Interestingly, benzaldehyde itself did not give the allylation under these conditions, and only starting materials could be recovered. We also tested allyltributylstannane, which is known to be an excellent allylation agent for various carbonyl compounds.[1b] However, in the allylation of both benzaldehyde and its dimethyl acetal with allyltributylstannane, no product formation was detected.[6] Table 1 summarizes the results of the allylation of various acetals with allyltrimethylsilane.[7] Aromatic acetals **1a**−**c** and **1e** gave the best product formation, with isolated yields of the corresponding homoallyl ethers ranging from 82 to 100%. From a comparison of the yields of **3a**−**e**, it is apparent that the electron-withdrawing nitro substituent on the aromatic ring disfavors the reaction. With the chloro and bromo substituents in **1b** and **1c**, the corresponding homoallyl ethers **3b** and **3c** are formed in slightly decreased yields compared to the unsubstituted **1a**. Nitro derivative **3d** is formed in only moderate yield, reflecting the strong electron-withdrawing effect of the nitro substituent present in **1d**. In contrast, acetal **1e**, having a propyl substituent in the para position on the aromatic ring, gave **3e** in quantitative yield, which can be attributed to the electron-donating character of the alkyl substituent.

Next, we examined aliphatic acetals **1f** and **1g** and obtained the expected products **3f** and **3g** in yields of 58 and 65%, respectively. Longer reaction times or larger amounts of CuBr did not improve the product yields. The lowest yield was with cyclic ketal **1h**, which provided **3h** in only 21% yield. Interestingly, the only other product detected in the crude reaction mixture was cyclohexanone (79% by GC), resulting from cleavage of the ketal function in **1h**.

(1) For reviews, see: (a) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043−1054. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(2) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941−942.

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(4) (a) For $AlCl_3$ and $BF_3{-}Et_2O$: Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1978**, 499. (b) For trityl perchlorate and Ph_2BOTf: Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Ohshima, M. *Chem. Lett.* **1985**, 977−980. (c) For montmorillonite: Kawai, M.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1986**, 381−384. (d) For TMSI: Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745−748. (e) For $TiCp_2(OTf)_2$: Hollis, T. H.; Robinson, N. P.; Whelan, J.; Bosnich, B. *Tetrahedron Lett.* **1993**, *34*, 4309−4312. (f) For $BiBr_3$: Komatsu, N.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215−7218. (g) For $Bi(OTf)_3$: Wieland, L. C.; Zerth, H. M.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597−4600. (h) For $TMSNTf_2$: Ishii, A.; Kotera, O.; Saeki, T.; Mikami, K. *Synlett* **1997**, 1145−1146. (i) For $Sc(OTf)_3$: Yadav, J. S.; Subba Reddy, B. V.; Srihari, P. *Synlett* **2001**, 673−675.

(5) Jung, M. E.; Maderna, A. *Tetrahedron Lett.* **2004**, *45*, 5301−04.

(6) We have no good explanation for why the allylstannane does not undergo the same allyl transfer as does the allylsilane, although we observed similar results in our earlier Lewis acid-catalyzed allylations.[5]

(7) Compounds **3d** and **3e** are new compounds; the other products are known in the literature. For **3a**, see ref 3c. For **3b**, see ref 4g. For **3c**, see ref 4i. For **3f**, see ref 4f. For **3g**, see: Barentsen, H. M.; Sieval, A. B.; Cornelisse, J. *Tetrahedron* **1995**, *51*, 7495. For **3h**, see ref 2.

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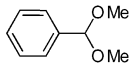
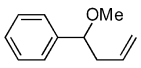
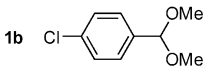
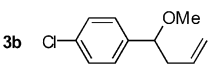
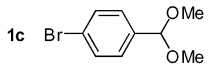
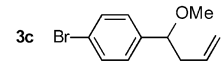
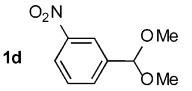
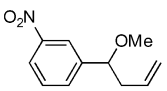
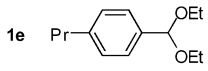
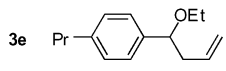
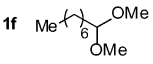
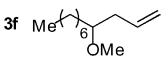
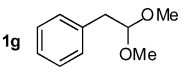
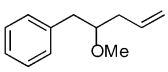
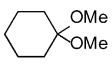
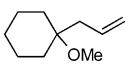
TABLE 1. Allylation of Acetals 1a−h with Allyltrimethylsilane 2 Using Microwave Heating in the Presence of CuBr

Entry	Substrate	Product	Isolated Yield (%)
1			92
2			82
3			86
4			54
5			100
6			58
7			65
8			21

Under normal conditions, CuBr is not generally recognized as a Lewis acid. For example, in most Lewis acidity scales,[8] it is not included. Indeed, in one of the few reports determining the Lewis acidity of Cu(I) salts,[9] it is listed as the weakest of all salts examined. Thus, it is fair to say that under usual conditions, it behaves as, at best, a very weak Lewis acid. However, under our microwave conditions, it appears to act as a very mild, but efficient, Lewis acid, promoting the formation of the carbocation (oxocarbenium ion) by complexation with the oxygen atom of the acetal. The lack of reaction in strongly coordinating solvents, where it would be completely complexed, and the fact that stoichiometric amounts of CuBr are required are also in agreement with this hypothesis. Also, normal thermal heating of the reaction mixture does not afford the products observed under microwave irradiation.[10]The precise mechanism for its activation under microwave irradiation remains to be determined.

In summary, we have described the allylation of acetals **1** with allyltrimethylsilane **2** in the absence of normal strong Lewis acids using microwave heating and CuBr as a promoter to produce the homoallyl ether **3**. The reaction works best for aromatic acetals in the absence of strong electron-withdrawing substituents on the aromatic ring.

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(9) Zhang, Y. *Inorg. Chem.* **1982**, *21*, 3889.

(10) Although we have not investigated this thoroughly, simply heating the mixture gives back mostly the starting materials with the very slow formation of allylated products.

Experimental Section

General Information. All reactions were carried out using a CEM Corporation Focused Microwave System, Model Discover. 1,2-Dichloroethane was dried over phosphorus pentoxide and distilled. All commercial reagents were used directly. NMR data were obtained on a 500 MHz spectrometer and IR data on an FT-IR spectrometer.

Representative Procedure. In a typical experiment, 1.5 mmol of CuBr was placed in a 10 mL glass pressure vial equipped with a stir bar. The pressure vial was closed using a PTFE silicon septum. Anhydrous 1,2-dichloroethane was added into the vial followed by 1.5 mmol of acetal **1** and 2.25 mmol of allyltrimethylsilane **2**. The suspension was heated to 100 °C while being stirred for 60 min in the CEM microwave reactor described above. For acetals **1f**−**h**, 1.5 mmol of the acetal, 2.2 mmol of CuBr, and 3 mmol of silane **2** were used. After the completion of the reaction, the suspension was filtered, the volatiles were removed in vacuo, and the crude oils were purified by flash chromatography. The isolated yields of homoallyl ethers **3** are given in Table 1. We have not carried out the experiment on any scale larger than the 1.5 mmol scale described above due to the size limitations of the commercial microwave equipment we are using, although we would expect that with a larger instrument, one could carry out the experiment on a much larger scale.

4-Methoxy-4-phenyl-1-butene (3a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5H, Ar), 5.8 (m, 1H), 5.1 (m, 2H), 4.2 (t, 1H, J = 5.9 Hz), 3.3 (s, 3H), 2.6 (m, 1H), 2.5 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7, 134.8, 128.3, 127.6, 126.7, 116.9, 83.6, 56.6, 42.5; IR (neat) ν 3028, 2980, 2936, 2821, 1641, 1454, 1357, 1100, 915, 700 cm^{-1}.

4-(4-Chlorophenyl)-4-methoxy-1-butene (3b): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3 (d, 2H, J = 8.4 Hz), 7.2 (d, 2H, J = 8.3 Hz), 5.7 (m, 1H), 5.0 (m, 2H), 4.1 (t, 1H, J = 6.7 Hz), 3.2 (s, 3H), 2.5 (m, 1H), 2.3 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 134.2, 133.1, 128.4, 128.2, 117.1, 82.8, 56.6, 42.3; IR (neat) ν 2982, 2934, 2823, 1598, 1598, 1489, 1090, 1015 cm^{-1}.

4-(4-Bromophenyl)-4-methoxy-1-butene (3c): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (d, 2H, J = 8.3 Hz), 7.1 (d, 2H, J = 8.3 Hz), 5.7 (m, 1H), 5.0 (m, 2H), 4.1 (t, 1H, J = 6.5 Hz), 3.2 (s, 3H), 2.5 (m, 1H), 2.3 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 134.2, 131.4, 128.4, 121.3, 117.3, 83.0, 56.7, 42.3; IR (neat) ν 3077, 2980, 2931, 2821, 1641, 1591, 1485, 1404, 1344, 1104, 1010, 917 cm^{-1}.

4-(3-Nitrophenyl)-4-methoxy-1-butene (3d): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.2 (s, 1H), 8.1 (m, 1H), 7.6 (d, 1H, J = 7.6 Hz), 7.5 (m, 1H), 5.7 (m, 1H), 5.0 (m, 2H), 4.3 (t, 1H, J = 6.6 Hz), 3.2 (s, 3H), 2.5 (m, 1H), 2.4 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 140.3, 133.4, 132.9, 129.3, 123.4, 122.0, 117.9, 82.7, 57.0, 42.2; IR (neat) ν 2932, 2830, 1530, 1349, 1108, 1058 cm^{-1}; EI-LRES m/z = 207 [M$^+$] (100).

4-(4-Propylphenyl)-4-methoxy-1-butene (3e): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2 (d, 2H, J = 8.0 Hz), 7.1 (d, 2H, J = 8.0 Hz), 5.8 (m, 1H), 5.0 (m, 2H), 4.2 (t, 1H, J = 6.1 Hz), 3.4 (m, 2H), 2.6 (t, 3H, J = 4.4 Hz), 2.4 (m, 1H), 1.6 (m, 1H), 1.2 (t, 3H, J = 7.0 Hz), 1.0 (t, 3H, J = 7.4 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8, 139.5, 135.0, 128.4, 126.4, 116.4, 81.5, 63.9, 42.3, 37.6, 24.4, 15.2, 13.8; IR (neat) ν 2962, 2931, 2870, 1720, 1092, 917 cm^{-1}. EI-HRES calcd 204.1470. Found 204.1461.

4-Methoxy-1-undecene (3f): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.0 (m, 2H), 3.3 (s, 3H), 3.2 (m, 1H), 2.2 (m, 2H), 1.4−1.2 (m, 12H), 0.8 (m, 3H, J = 6.2 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0, 116.7, 80.5, 56.5, 37.8, 33.4, 31.8, 29.7, 29.3, 25.3, 22.7, 14.1; IR (neat) ν 2955, 2927, 2856, 1462, 1098, 911 cm^{-1}.

4-Methoxy-5-phenyl-1-pentene (3g): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.2−7.3 (m, 5H), 5.8 (m, 1H), 5.1 (m, 2H), 3.4 (m, 1H),

3.3 (s, 3H), 2.8 (m, 1H), 2.7 (m, 1H), 2.2 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 134.7, 129.4, 128.2, 126.1, 117.1, 81.7, 57.0, 39.8, 37.5; IR (neat) ν 3027, 2928, 2823, 1641, 1495, 1454, 1359, 1098, 914, 745, 700 cm^{-1}.

1-Methoxy-1-(2-propenyl)cyclohexane (3h): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.8 (m, 1H), 5.0 (m, 2H), 3.1 (s, 3H), 2.2 (d, 2H, J = 7.2 Hz), 1.2−1.6 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.0, 117.1, 74.8, 48.1, 40.9, 33.8, 25.8, 21.8; IR (neat) ν 2931, 2855, 2823, 1639, 1455, 1081, 910 cm^{-1}.

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Supporting Information Available: Experimental procedures and the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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