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Bismuth (III) Bromide in Organic Synthesis. A Catalytic Method for the Allylation of Tetrahydrofuranyl and Tetrahydropyranyl Ethers.

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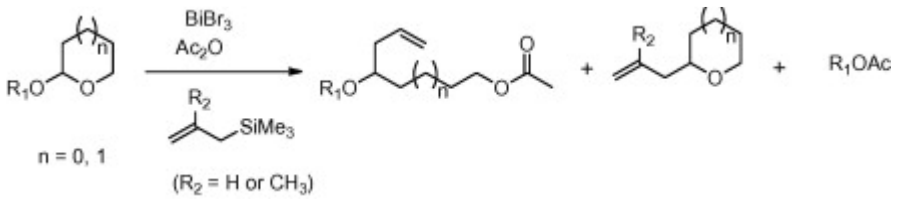
Abstract

A bismuth bromide-catalyzed (10.0 mol %) multicomponent reaction involving the allylation of THF- and THP-ethers, followed by in situ derivatization with acetic anhydride to generate highly functionalized esters has been developed under solvent-free conditions. To the best of our knowledge, this is the first report of a catalytic procedure for the allylation of THF- and THP-ethers to yield ring-opened products.

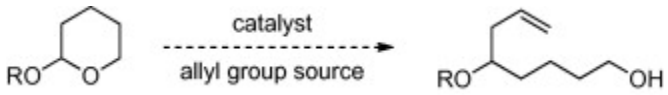
Keywords: Allylation, THP ethers, Bismuth bromide, Acetates

Graphical Abstract



Tetrahydropyranyl (THP)-ethers are useful protecting groups for alcohols and phenols but they can also be converted to other useful functional groups.[1] For example, the direct conversion of THP-ethers to acetates has been reported.[1b] Despite numerous literature examples of allylations of acetals to yield homoallyl ethers,[2] very little attention has been given to the potentially useful allylation of THP ethers (Scheme 1).

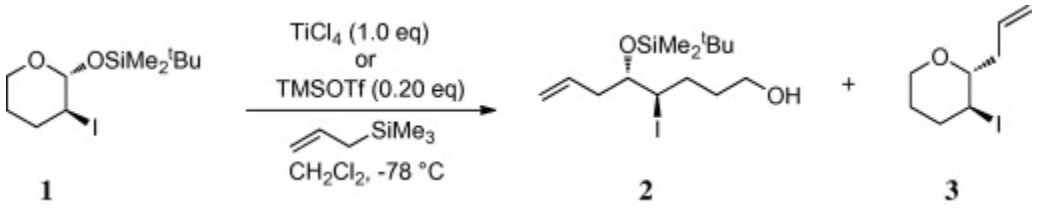
Scheme 1



Despite the obvious synthetic utility of such a transformation, to the best of our knowledge, there are only two reports of the allylation of THP-ethers. Maeda et al.[3] have reported the Lewis acid-

induced allylation of α-iodo mixed acetals with allylsilanes. They found that the allylation of *trans*-2-(*tert*-butyldimethylsilyloxy)-3-iodo-1-oxacyclopentane **1** promoted by $TiCl_4$ (1.0 equiv) in CH_2Cl_2 afforded a 58% yield of the open chain product, anti-4-(*tert*-butyldimethylsilyloxy)-3-iodo-6-hepten-1-ol **2** (the ratio of anti/syn product was >99/1) (Scheme 2). When the reaction was carried out in the presence of TMSOTf (20.0 mol %) instead of $TiCl_4$ (1.0 equiv), the siloxy group was replaced with the allyl group to yield allylated-tetrahydropyran **3** in 90% yield (*trans*/*cis* ratio was >99/1).

Scheme 2



Hunter et al. have reported the TMSOTf (1.2 equiv)-promoted allylation of 2-methoxytetrahydropyran, using lithium *n*-butyltriallylborate as the allyl source.[4] They reported a 40% yield of the open chain product and 24% yield of 2-allyltetrahydro-2*H*-pyran. As can be seen from these two examples, both these methods require the use of highly corrosive catalysts such as TMSOTf or $TiCl_4$, and are carried out at low temperatures in CH_2Cl_2, an environmentally unfriendly solvent. In addition, allyl sources, such as lithium *n*-butyltriallylborate are not commercially available and must be synthesized when needed. Although not examples of THP ether allylation, a few other bismuth-catalyzed reactions that are relevant and deserve mention include a novel stereoselective construction of cyclic ethers using a tandem two-component etherification developed by Evans et al.[5] They utilized a $BiBr_3$-catalyzed allylation of a ketone in CH_3CN followed by cyclization to generate substituted tetrahydropyrans. They also carried out elegant mechanistic studies that suggest that the active catalysts are HBr and bismuth oxybromide, BiOBr. Daich and co-workers have reported a bismuth triflate-catalyzed intermolecular α-amidoalkylation of a variety of α-acetoxylactams with silanes and enoxysilanes.[6] Floreancig and co-workers report a very efficient $BiBr_3$ mediated allylation of a lactol to yield a tetrahydropyranyl alcohol.[7] This reaction was a key step in their studies directed toward the construction of Leucascandrolide A, an antifungal macrolide. In studies devoted to the synthesis of galactofuranoside mimics, Martin and co-workers report a highly efficient bismuth triflate mediated allylation of a glucofuranosylamine.[8] In contrast to $Bi(OTf)_3$, $Sc(OTf)_3$ did not catalyze the reaction.

A lack of catalytic methods for the allylation of THP-ethers coupled with our continued interest in bismuth compounds prompted us to develop a bismuth(III) salt-based methodology for the allylation of THF- and THP-ethers. Bismuth compounds have attracted considerable attention in the last decade due to their remarkably low toxicity, low cost, and ease of handling.[9] Herein, we report that bismuth(III) bromide is a suitable catalyst for the allylation of THF- and THP-ethers followed by in situ derivatization of the putative alkoxide intermediate with acetic anhydride (Scheme 3) to yield highly functionalized acetates in moderate yields (Table 1).

Scheme 3

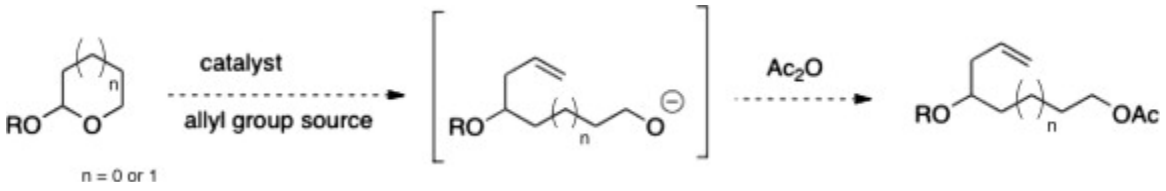
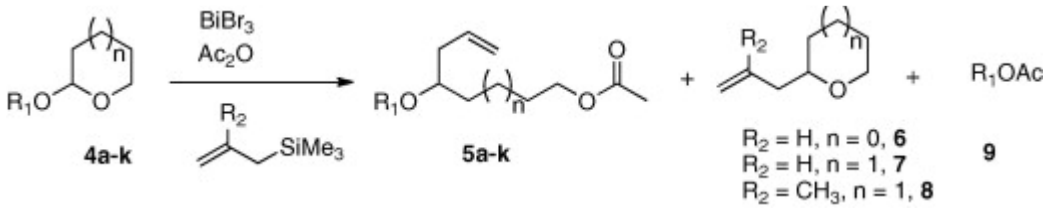


Table 1. BiBr3 catalyzed allylation of THF- and THP-ethers followed by in situ derivatization with Ac2O12



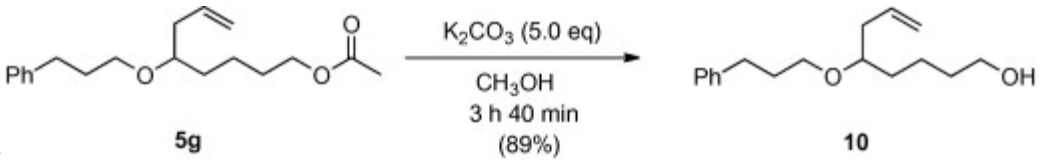
Entry	R_1	R_2	*n*	*t*[a]	Yield[b] (%) 5a–k
a	CH_3	H	1	1 h	58[c]
b	$CH_3(CH_2)_4$	H	1	1 h 45 min	53
c	$CH_3(CH_2)_6$	H	1	2 h 35 min	62
d	Cyclohexyl	H	1	1 h 30 min	44
e	$HC{\equiv}CCH_2CH_2$	H	1	1 h 15 min	43[d]
f	$BrCH_2(CH_2)_2$	H	1	1 h 30 min	45
g	$PhCH_2(CH_2)_2$	H	1	2 h 15 min	49[e]
h	$CH_3(CH_2)_4$	CH_3	1	1 h 35 min	35
i	CH_3	CH_3	1	1 h 30 min	30[f]
j	$CH_3(CH_2)_6$	H	0	2 h 10 min	21
k	$PhCH_2(CH_2)_2$	H	0	1 h 30 min	25

a Reaction progress was followed by GC or TLC.
b Refers to yield of isolated, purified ester; reported yield is calculated assuming that the ester is the only product. In all cases the reaction mixture contained a significant amount (20–50%, by GC) of 2-allyltetrahydro-2H-furan or 2-allyltetrahydro-2H-pyran and much smaller amounts (ca. 10%) of the corresponding acetate (9a–k). Pure samples of the 2-allyltetrahydro-2H-furan or 2-allyltetrahydro-2H-pyran could not be isolated due to the fact that they had Rf values very similar to the corresponding acetates.
c 2-Allyltetrahydro-2H-pyran was isolated in 24% yield (96% pure by GC).
d 2-Allyltetrahydro-2H-pyran was isolated in 28% yield (99% pure by GC, 1H and 13C NMR analysis).
e 3-Phenylpropyl acetate (96% pure by GC and 1H NMR) was isolated in 31% yield.
f 2-Methallyltetrahydro-2H-pyran was isolated in 55% yield (99% pure by GC, 1H and 13C NMR analysis).

We recently reported a similar strategy for the allylation of dioxolanes catalyzed by bismuth triflate as a catalyst.[10] Encouraged by the success of this approach, we first attempted the allylation of THP-ethers using bismuth triflate as a catalyst. However, the results were not very promising and a significant amount of the corresponding acetate was obtained.[1b] Gratifyingly, bismuth(III) bromide, which is less expensive than bismuth(III) triflate, proved more efficient for the allylations.[11] These results are summarized in Table 1.

As can be seen from Table 1, the allylation of all THF- and THP-ethers gave nearly equal amounts of the open chain product and 2-allyltetrahydro-2*H*-furan or 2-allyltetrahydro-2*H*-pyran. Thus, in the case of THP-ethers, the open chain product could be typically isolated in ca. 50% yield after chromatographic purification (entries a–g). Less satisfactory yields of the desired open chain product were obtained when methallylsilane (entries h and i) was used as the allyl group source, or when the allylation was attempted on THF-ethers (entries j and k). Although, it was possible to isolate a pure sample of 2-allyltetrahydro-2*H*-pyran (entries a and e), in most cases, due to the small amount of silica used and close R_f values, the 2-allyltetrahydro-2*H*-pyran was isolated as a mixture with small amounts of the corresponding acetate. In the case of THP-ether derived from 3-phenylpropanol (entry g), the corresponding acetate was isolated in 31% yield. All reactions were carried out under solvent-free conditions and the product was isolated by direct filtration of the reaction mixture through a silica gel column, thus avoiding an aqueous waste stream. No reaction was observed in the absence of $BiBr_3$ or acetic anhydride. It was also shown that the acetate could be easily hydrolyzed to the corresponding alcohol in an

excellent yield (Scheme 4), thus providing an easy access to a variety of highly functionalized alcohols.



Scheme 4

In summary, this methodology allows the synthesis of highly functionalized acetates in a single step from the readily available THF- and THP-ethers. The use of an environmentally friendly catalyst, $BiBr_3$, and the solvent free procedure add to the synthetic utility of this procedure.

Representative procedure: A homogeneous mixture of 2-(heptyloxy)tetrahydro-2*H*-pyran[12] (entry c) (0.300 g, 1.498 mmol), allyltrimethylsilane (0.291 g, 0.40 mL, 2.547 mmol, 1.7 equiv), and acetic anhydride (0.260 g, 0.24 mL, 2.547 mmol, 1.7 equiv) was stirred at rt under N_2 as bismuth(III) bromide (67.2 mg, 0.150 mmol, 10 mol %) was added. The bismuth(III) bromide dissolved and the reaction mixture turned slightly yellow in color. After 2 h 35 min the reaction mixture was filtered through silica gel (25 g, EtOAc/heptane). A 240-mL prefraction was collected (EtOAc/heptane, 1:99) followed by elution with EtOAc/heptane (5:95). Seventy fractions (8 mL) were collected. Fractions 17–21 were combined to yield 80.3 mg of a clear liquid that was determined to be 2-allyltetrahydro-2*H*-pyran by ^{1}H NMR spectroscopy. Fractions 45–64 were combined to yield 0.263 g (62%) of a clear liquid that was determined to be >99% pure **5c** by GC analysis, ^{1}H and ^{13}C NMR spectroscopy. ^{1}H NMR δ 0.86 (t, 3H, J = 6.5 Hz), 1.22–1.36 (m, 8H), 1.40–1.66 (m, 8H), 2.02 (s, 3H), 2.14–2.32 (m, 2H), 3.20–3.29 (quintet, 1H), 3.29–3.51 (m, 2H), 4.01–4.06 (t, 2H, J = 6.5 Hz), 5.00–5.08 (m, 2H), 5.71–5.86 (m, 1H); ^{13}C NMR (17 peaks) δ 14.1, 21.0, 21.9, 22.6, 26.2, 28.6, 29.1, 30.1, 31.8, 33.5, 38.4, 64.5, 69.2, 78.7, 116.7, 135.0, 171.2. IR ν_{max} 2928, 1741, 1641 cm−1. HRMS-CI (*m*/*z*): M^+ calculated for $C_{17}H_{33}O_3$, 285.2430; found: 285.2431.

Acknowledgment

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