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A simple microwave-assisted preparation of 2-bromo-1-alkenes from 1-alkynes using the LiBr–TMSCl–TEAB reagent system

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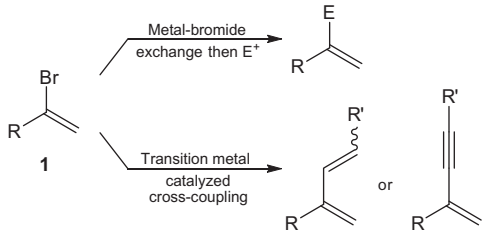
ABSTRACT

2-Bromo-1-alkenes are cleanly and conveniently generated in good yields and selectivities via microwave-assisted hydrobromination of 1-alkynes using a combination of lithium bromide (LiBr), chlorotrimethylsilane (TMSCl), and tetraethylammonium bromide (TEAB) in acetonitrile (MeCN).

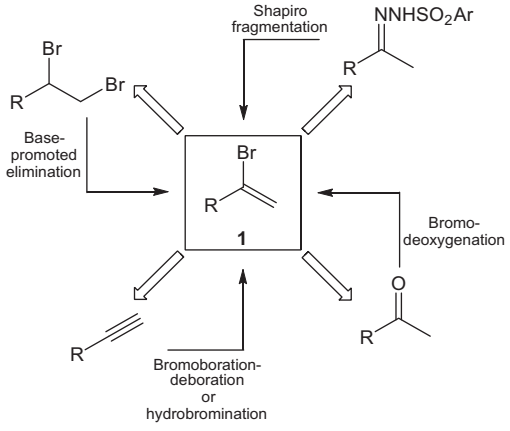
2-Bromo-1-alkenes **1** are widely used in organic synthesis as valuable building blocks in various reactions (e.g. Scheme 1) which result in products containing the methylene (1,1-disubstituted alkene) moiety; a versatile synthetic handle for transformations into other functionalities. Vinyl bromides are also generally more stable than their iodide counterparts, making them frequently preferred due to their ease of handling.

As shown in Scheme 2, a number of methods are available to prepare compounds of type **1**. These methods include the Shapiro fragmentation[1] of methyl hydrazone derivatives, bromo-deoxygenation of methyl ketones,[2] base-promoted regioselective hydrogen bromide (HBr) elimination of 1,2-dibromoalkanes,[3] regioselective bromoboration-deboration of terminal alkynes,[4,5] and regioselective hydrobromination of terminal alkynes using HBr.[6] In the latter method, the reaction is typically conducted by treating a saturated solution of (stoichiometric) tetraethylammonium bromide (TEAB) or tetrabutylammonium bromide (TBAB) in dichloromethane with gaseous HBr; the absorption of HBr on the ammonium salt causes these materials to become soluble. The corresponding 1-alkyne is then introduced into this solution and the reaction mixture is heated at reflux. Although more straightforward than many protocols, the procedure is marred by the use of toxic and corrosive HBr gas, in addition to a rather cumbersome laboratory set-up and protocol.

In this communication, we present our study on the hydrobromination reaction of terminal alkynes which resulted in an alternative protocol which is simple, effective, and more practical. During a cyclization study of an enynyl alcohol, we required 2-bromo-1-buten-4-ol (**6a**), an intermediate which could be generated by hydrobrominating homopropargyl alcohol (**5a**). Based on similar chemistry for the synthesis of 2-iodo-1-alkenes from 1-alkynes using a combination of sodium iodide (NaI), chlorotrimethylsilane (TMSCl) and water,[7] we found that lithium bromide (LiBr), when combined with TMSCl in commercial grade acetonitrile (MeCN)



Scheme 1. Use of 2-bromo-1-alkenes in synthesis.



Scheme 2. Synthesis methods to prepare **1**.

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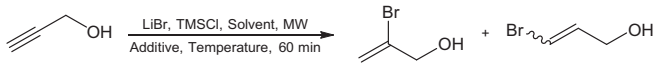
Table 1
Optimization of the hydrobromination reaction of propargyl alcohol

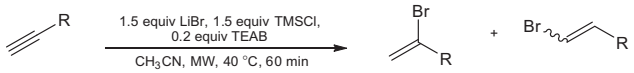


2 **3** **4**

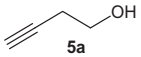
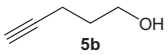
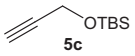
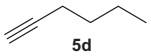
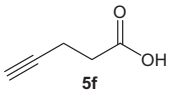
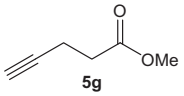
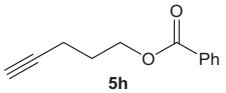
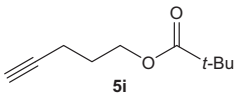
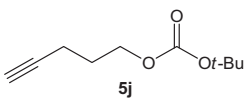
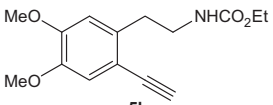
Entry	Conc. of **2** (M)[a]	Solvent	LiBr (equiv)	TMSCl (equiv)	TEAB (equiv)	Temp (°C)	Conversion (%)	Ratio of **3**:**4**	^{1}H NMR yield (%)[b]
1	0.57	MeCN	1.2	1.2	—	80	74	85:15	50
2	0.57	MeCN	2.0	2.0	—	80	96	90:10	57
3	0.86	MeCN	1.2	1.2	—	80	87	87:13	56
4	0.86	MeCN	2.0	2.0	—	80	100	90:10	80
5	1.72	MeCN	1.2	1.2	—	80	82	88:12	82
6	1.72	MeCN	1.5	1.5	—	80	100	86:14	95
7	**1.72**	**MeCN**	**1.5**	**1.5**	**0.2**	**40**	**100**	**>90:10**	**100**
8	1.72	CH_2Cl_2	1.2	1.2	—	80	50	92:8	42

[a] Propargyl alcohol (**2**) (0.10 mL, 1.72 mmol) was dissolved in 3 mL, 2 mL, and 1 mL of commercial grade, non-distilled MeCN to give ca. 0.57 M, 0.86 M, and 1.72 M solutions of alcohol **2**, respectively.
[b] Yield was determined by ^{1}H NMR spectroscopy using either toluene or 3,4,5-trimethoxybenzaldehyde as the internal standard.

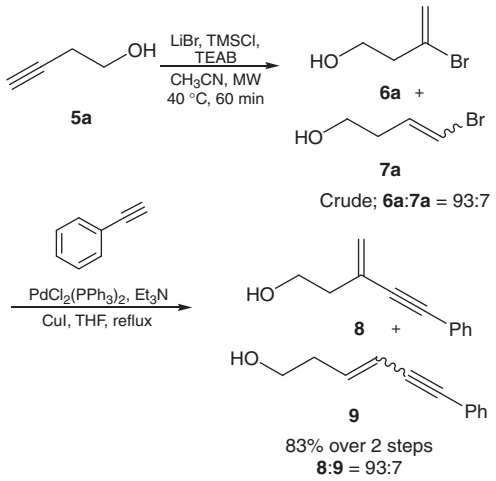
Table 2
Hydrobromination of terminal alkynes using the LiBr–TMSCl–TEAB reagent system[a]



5a-k **6a-k** **7a-k**

Entry	Substrate	Conversion (%)	Ratio of **6**:**7**	^{1}H NMR yield (%)[b]	Isolated yield (%)[c]
1	 **5a**	100	93:7	90	81
2	 **5b**	54	95:5	48	42
3	 **5c**	Partial desilylation and incomplete conversion.			
4	 **5d**	93	95:5	54	—[d]
5	 **5e**	91	92:8	87	—[d]
6	 **5f**	100	>99:1	89	70
7	 **5g**	Partial saponification and incomplete conversion.			
8	 **5h**	94	>99:1	82	73
9	 **5i**	100	>99:1	84	79
10	 **5j**	100	>99:1	77	69
11	 **5k**	100	>99:1	94	87

[a] All reactions were carried out using a CEM model Discover microwave reactor set at 40 °C in a 10 mL vial supplied by CEM Corporation.
[b] Yield was determined by ^{1}H NMR spectroscopy using either toluene or 3,4,5-trimethoxybenzaldehyde as the internal standard.
[c] Isolated yield of alkenes **6a**,**b**,**f**,**h–k**.
[d] The crude product could not be purified due to its volatility (compound **6d**) or as a result of its decomposition on silica gel (compound **6e**).



Scheme 3. Sonogashira cross-coupling performed on the crude products from hydrobromination of homopropargyl alcohol.

at reflux, resulted in the formation of HBr which added to the homopropargyl alcohol. Although the reaction proceeded in only 58% conversion after 3 h, we found that the desired **6a** was obtained as the major isomer (**6a**:**7a** = 87:13) in a combined yield of ca. 46% as determined by ^{1}H NMR spectroscopy using toluene as the internal standard. We then attempted this reaction again by adding water to the acetonitrile while keeping all the other conditions identical and found that the reaction still could not be driven to completion.

In an attempt to further optimize the reaction, propargyl alcohol (**2**) was chosen as the representative 1-alkyne substrate as it is less expensive than homopropargyl alcohol. In contrast to conventional heating, we found that microwave irradiation[8] could accelerate hydrobromination of **2** to completion within one hour using acetonitrile without the need of added water. Microwave irradiation was therefore used in our subsequent studies. Other reaction variables, including reagent equivalents, concentration effect, temperature and solvent, were investigated, the results of which are summarized in Table 1.

When using commercial grade MeCN, we found that with microwave irradiation at 80 °C for 60 min, higher reagent equivalents led to high conversion, a good **3**:**4** ratio and modest combined yield (entries 1 and 2). By increasing the concentration of alcohol **2** from 0.57 to 0.86 M using the same equivalents of LiBr and TMSCl, the yields could be improved significantly (compare entries 1 and 3, and 2 and 4). We also found that when the concentration of **2** was increased to 1.72 M, the number of equivalents of the reagents could be lowered to 1.5 to achieve 100% conversion with an acceptable **3**:**4** ratio and excellent combined yield (entry 6). Finally, addition of 0.2 equiv of tetraethylammonium bromide (TEAB) as an HBr-transferring agent[9] allowed the reaction to proceed at a much lower temperature (40 °C) yielding the products in an excellent 90:10 ratio and quantitative combined yield (entry 7). As a result, we used TEAB in our standard protocol for the hydrobromination reaction of terminal alkynes. TEAB can be easily removed by simple filtration of the crude reaction mixture after treatment with water and sodium sulfate (Na_2SO_4).[10,11] Interestingly, under the current conditions the reaction performed in CH_2Cl_2, a typical solvent used in the hydrobromination reaction, did not provide a satisfactory result compared to the reaction performed in MeCN (compare entries 5 and 8).

These optimized conditions were then applied to various terminal alkynes and the results are summarized in Table 2. The current protocol could be utilized to hydrobrominate 1-alkynes with high efficiency to provide bromoalkenes **6** in excellent ratios and high yields in most cases. In stark contrast to conventional heating (vide supra), homopropargyl alcohol (**5a**) was smoothly hydrobrominated under microwave irradiation to give **6a** and **7a** (93:7 ratio) in 90% combined yield as determined by ^{1}H NMR spectroscopy (entry 1). These results clearly confirmed the importance of microwave irradiation in this protocol. Functional groups such as aromatic rings, ester, carbonate, carbamate, and carboxylic acid were well-tolerated under the reaction conditions (entries 5–6, and 8–11). Limitations were observed with some substrates. Alkyne **5b** (entry 2), for example, was hydrobrominated in only 48% yield at 54% conversion, possibly due to the intramolecular participation from the hydroxy group which hindered the desired reaction or gave other side products.[12] Hydrobromination of 1-hexyne (**5d**; entry 4) proceeded in 93% conversion. However, the yield as determined by ^{1}H NMR spectroscopy was modest which may be due to the volatility of the products. Also, for alkynes **5c** and **5g** (entries 3 and 7) we observed partial desilylation and saponification, respectively, leading to incomplete reactions.

2-Bromo-1-alkenes obtained by the current procedure are free of the ammonium salt and are sufficiently clean to be used directly in subsequent transformations. For example, upon hydrobromination of **5a** under the optimized conditions, the resulting crude mixture of **6a** and **7a** was subjected to Sonogashira cross-coupling with phenyl acetylene to give enynes **8** and **9** in 83% overall yield as an inseparable mixture (Scheme 3).

In conclusion, the combination of LiBr, TMSCl, and TEAB in acetonitrile under microwave irradiation presents an efficient and selective reagent system for the hydrobromination of many 1-alkynes. The procedure is simple to conduct and the conditions are well-tolerated by many functional groups. The current protocol also allows for the convenient generation of HBr of known and exact stoichiometry from known amounts of reagents. Sufficiently clean 2-bromo-1-alkene products can be isolated conveniently by filtration to remove solid by-products and can be used directly in subsequent synthetic transformations. The current hydrobromination of terminal alkynes to give 2-bromo-1-alkenes should provide an efficient, safe, and convenient access to this important and useful synthetic building block.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.025.

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8. For a comprehensive review, see: *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002.
9. According to reference 6 above (and references 7–10 cited therein), the insoluble tetraalkylammonium bromide salt (R_4NBr) absorbs gaseous HBr to

form a new soluble complex, R_4NHBr_2, before it transfers HBr to add to the alkyne while regenerating the insoluble ammonium salt. The tetraalkylammonium bromide salt therefore effectively acts as an HBr-transferring agent in this reaction.

10. In a typical reaction procedure, a 10 mL microwave vessel (supplied by CEM) containing a magnetic stir bar was charged with 1 mL of commercial grade MeCN, LiBr (0.224 g, 2.58 mmol) and TEAB (0.072 g, 0.344 mmol). The resulting clear solution was treated with neat TMSCl (0.33 mL, 0.280 g, 2.58 mmol) via syringe to give a slightly cloudy mixture, followed by neat propargyl alcohol (**2**, 0.10 mL, 0.086 g, 1.72 mmol) which returned the mixture to a clear solution. The vessel was then sealed with the supplied cap and subjected to microwave irradiation in a microwave reactor (CEM model Discover) set to the following parameters: power, 300 W; pressure, 300 PSI; temperature, 40 °C; time, 60 min. Upon completion, the resulting clear brown solution and white precipitates was filtered. The clear filtrate was treated with 0.50 mL of H_2O and the resulting mixture was shaken with excess Na_2SO_4, filtered, and concentrated to give 0.270 g of an inseparable mixture of vinyl bromides **3** and **4** (>90:10 as determined by ^1H NMR spectroscopy) as a pale yellow oil.
11. The yields and ratios of crude products could be determined by ^1H NMR ($CDCl_3$) spectroscopy using toluene or 3,4,5-trimethoxybenzaldehyde as the internal standard. The crude products could either be purified by column chromatography or used directly in subsequent synthetic operations.
12. A side-product obtained in substantial amount was bromide **10** which was probably derived via the following pathway: