A Tandem Oxidation Procedure for the Conversion of Alcohols into 1,1-Dibromoalkenes

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Abstract: A practical and concise route to dibromoalkenes directly from activated alcohols in good to excellent yields using a new Tandem Oxidation Procedure (TOP) is reported. We also describe the use of these dibromoalkenes as intermediates in a one-pot route to 4,5-dihydro-1*H*-imidazoles and in the synthesis of bromoalkynes through MTBD-induced elimination.

Key words: dibromoalkenes, tandem oxidation procedure, one-pot, MTBD

1,1-Dibromoalkenes are valuable synthetic intermediates and are readily converted into amidines,[1] disubstituted bromoalkenes,[2] *Z*-bromoalkenes,[3] *E*-bromoalkenes,[4] disubstituted alkynes,[5] trisubstituted alkenes,[5] terminal alkynes (the Corey–Fuchs reaction),[6] bromoalkynes[7] and carboxylic acid derivatives[1] (Figure 1).

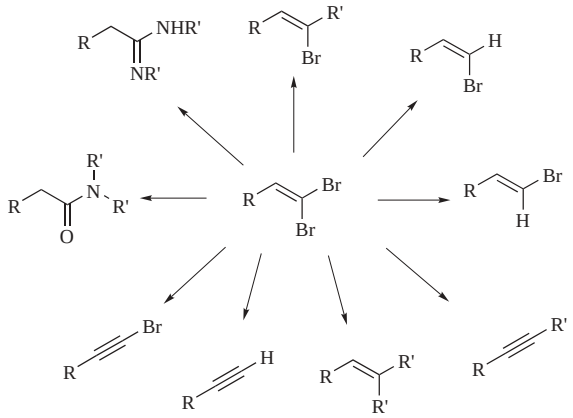
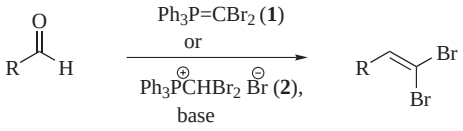


Figure 1

Dibromoalkenes are usually prepared using the procedure of Ramirez et al.[8] which involves treating aldehydes with phosphorane **1**, generated from the reaction of triphenylphosphine and carbon tetrabromide. Alternatively, dibromomethylphosphonium salt **2**[9] can be isolated and used to form ylide **1** (Equation 1).[10,11] More recently dibromoalkenes have also been formed through the intermediacy of hydrazones.[12]

Given the problematic nature of some aldehydes and the fact that there are many more commercially available alcohols than aldehydes,[13] we decided to explore the application of our Tandem Oxidation Procedure (TOP) to the preparation of 1,1-dibromoalkenes directly from alcohols (Equation 2). Previously we have demonstrated that TOP methodology can be employed for a range of MnO_2-mediated oxidation-Wittig processes,[14] including those involving non-activated phosphonium salts,[15] giving a variety of alkenes directly from alcohols, by-passing the need to isolate intermediate aldehydes and simplifying the original two step procedure. This methodology has since been employed by other groups.[16]



Equation 1

Equation 2

Initial studies were carried out with the electron deficient aromatic alcohol, *p*-nitrobenzyl alcohol (Scheme 1). Thus *p*-nitrobenzyl alcohol (1 equiv), MnO_2 (10 equiv), 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD)[17] (**3**, 2.3 equiv), phosphonium salt **2**[9] (3.0 equiv) and 4 Å molecular sieves in THF under reflux afforded the desired dibromoalkene **4** in a poor 24% yield after 15 hours (Table 1, entry i). Interestingly, however, bromoalkyne **5** was also isolated in 10% yield indicating that MTBD may be basic enough also to carry out the elimination of HBr and thus form bromoalkynes in a one-pot 3-step sequence from activated alcohols.

The reaction was then repeated, reducing the amounts of MTBD **3** and Wittig salt **2** to 1.5 and 2.2 equivalents, respectively (entry ii). Dichloromethane was then found to be the solvent of choice to circumvent solubility issues and increase ease of work-up. Gratifyingly, this resulted in an improved yield of 30% of dibromoalkene **4** with no bromoalkyne **5** detected. However, *p*-nitrobenzaldehyde **6** was also recovered and therefore optimization of the stoichiometries was investigated (Table 1). Increasing the amount of Wittig salt **2** used to 3.0 equivalents resulted in a marked increase in the yield of dibromoalkene **4** (80%) with only a trace of aldehyde **6** remaining (entry iii). Finally, increasing the amount of Wittig salt further to 3.5

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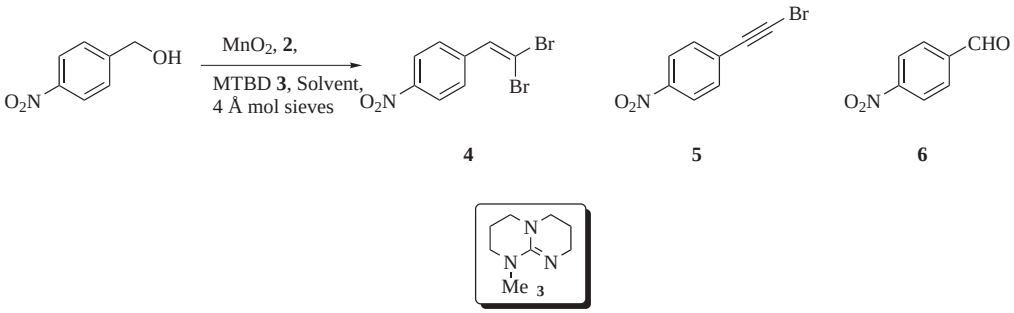


Scheme 1

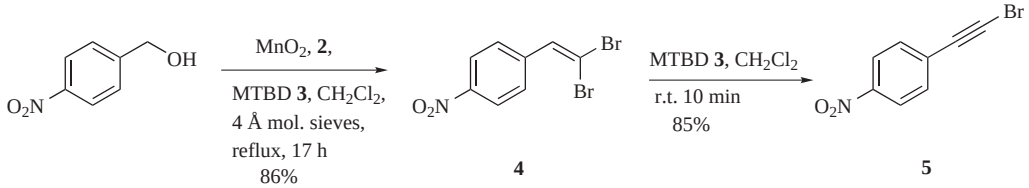
Table 1 Optimization of Study Towards the Synthesis of Dibromoalkene **4**

Entry	Conditions	**4** (%)	**5** (%)	**6** (%)
i	THF, 2.3 equiv MTBD, 3.0 equiv **2**, reflux, 15 h	24	10	0
ii	CH_2Cl_2, 1.5 equiv MTBD, 2.2 equiv **2**, reflux, 14 h	30	0	Ca. 50
iii	CH_2Cl_2, 1.5 equiv MTBD, 3.0 equiv **2**, reflux, 14.5 h	80	0	Trace
iv	CH_2Cl_2, 1.5 equiv MTBD, 3.5 equiv **2**, reflux, 16 h	86	0	0
v	$CHCl_3$, 1.5 equiv MTBD, 3.5 equiv **2**, reflux, 15 h	56	0	0

equivalents resulted in complete consumption of intermediate *p*-nitrobenzaldehyde and an isolated yield of 86% of the desired dibromoalkene **4** (entry iv). The use of chloroform as a reaction solvent was also investigated in an attempt to reduce the reaction time (entry v). Dibromoalkene **4** was isolated in a respectable yield but the dichloromethane procedure was preferred for *p*-nitrobenzyl alcohol (entry iv). However, in most other examples chloroform was the preferred solvent. The scope of the procedure was investigated using a range of alcohols (Table 2).

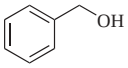
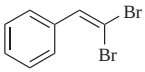
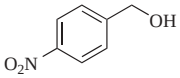
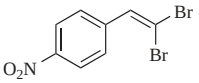
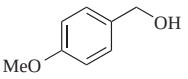
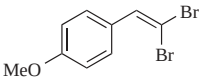
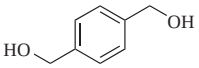
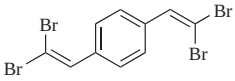
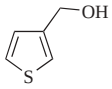
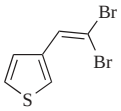
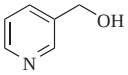
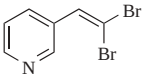
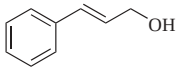
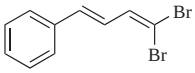
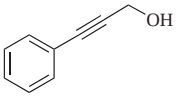
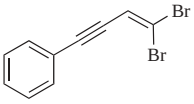
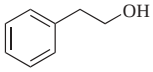
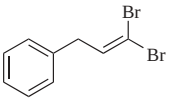
Table 2 shows that good to excellent yields of the dibromoalkenes were obtained directly from a range of activated alcohols including electron-neutral, electron-deficient and electron-rich aromatic examples (entries i–iii), an aromatic diol (entry iv), heterocyclic examples (entries v and vi) and allylic and propargylic examples (entries vii and viii). An aliphatic example was also studied but the reaction was slow and low yielding (entry ix). The synthetic utility of this one-pot method is further emphasized by the fact that comparable, or indeed better yields (entries iv[19] and vi[20]), can be obtained directly from the substrate alcohol compared to those previously reported in the literature for the conversion from the aldehyde. The low yield obtained from *p*-methoxybenzyl alcohol (entry iii) deserves comment, however. This is presumably due to the reduced electrophilicity of the intermediate *p*-methoxybenzaldehyde. Also, it should be pointed out that with electron-deficient examples (entries ii and viii), much higher yields can be achieved by carrying out the reaction in refluxing dichloromethane rather than chloroform; the lower temperature presumably minimizes side-reactions of the reactive electron deficient dibromoalkene products.

We also carried out a brief study to investigate further in situ elaborations of the 1,1-dibromoalkenes. Initially we looked at the in situ dibromoalkene formation–elimination reaction to afford the corresponding bromoalkynes following the promising results referred to earlier. Attempts to increase the yield of the bromoalkyne **5** by a one-pot method, however, proved fruitless (max. yield, 35%). Nevertheless, a two step process in which dibromoalkene **4** was first isolated and purified and then treated with MTBD (1.5 equiv at r.t.) was also investigated and furnished the desired bromoalkyne **5** in 85% yield from dibromoalkene **4** (Scheme 2).



Scheme 2

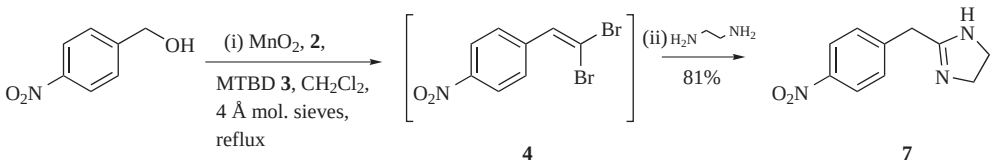
Table 2 Investigation of the Scope and Limitation of the Dibromoalkene Synthesis.[18]

Entry	Alcohol	Product	Reaction time (h)	Isolated yield (%)[a]
i			18	73
ii			17	86[b]
iii			18	46 (64)[c]
iv			20	86
v			18	85
vi			17	84[d]
vii			17	84
viii			3.5	65[e]
ix			36	14

[a] Reaction carried out in refluxing chloroform unless otherwise stated.
[b] In CH_2Cl_2 (56% in $CHCl_3$).
[c] Yield calculated with respect to recovered *p*-methoxybenzaldehyde.
[d] In CH_2Cl_2 (28% in $CHCl_3$).
[e] Eliminated dialkynyl bromide isolated in 5% yield.

Huh et al. have demonstrated that dibromoalkenes may be reacted with ethylenediamine to furnish 4,5-dihydro-1*H*-imidazoles.[1] Thus, we next went on to investigate a one-pot synthesis of such heterocycles directly from *p*-nitrobenzyl alcohol. After some optimization we have developed a simple procedure to give 4,5-dihydro-1*H*-imidazole (**7**) in 81% yield directly from *p*-nitrobenzyl alcohol (Scheme 3).[21]

In summary, we have reported a concise and high yielding synthesis of dibromoalkenes from activated alcohols. These dibromoalkenes are useful synthetic intermediates for a variety of functional group interconversions and we have further demonstrated their utility by carrying out an MTBD-induced elimination of **4** to afford bromoalkyne **5** as well as developing a practical and straightforward synthesis of 4,5-dihydro-1*H*-imidazole (**7**) directly from *p*-nitrobenzyl alcohol without the need to isolate either the aldehyde or dibromoalkene intermediates in the reaction pathway. Further in situ applications of the dibromoalkenes are under investigation.



Scheme 3

Acknowledgment

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(18) **Representative Procedure.** To a suspension of activated manganese dioxide (Aldrich, 21764-6; 867 mg, 9.97 mmol), phosphonium salt **2** (1.80 g, 3.50 mmol) and ground 4Å molecular sieves (100 mg) in solvent (CH_2Cl_2 or chloroform; 10 mL) was added MTBD **3** (0.22 mL, 1.50 mmol). The reaction mixture was heated at reflux for 30 min, cooled to r.t., then a solution of alcohol (1 mmol) in solvent (5 mL) added. The reaction mixture was then heated at reflux for the time specified, cooled to r.t. and filtered through Celite®. The resulting filtrate was then pre-loaded on to silica and the dibromoalkenes purified by silica chromatography, eluting with EtOAc/petroleum ether.
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(21) **Synthesis of 2-(4-Nitrobenzyl)-4,5-dihydro-1*H*-imidazole(7).** To a suspension of activated manganese dioxide (Aldrich, 21764-6; 867 mg, 9.97 mmol), phosphonium salt **2** (1.80 g, 3.50 mmol) and ground 4 Å molecular sieves (100 mg) in CH_2Cl_2 (10 mL) was added MTBD **3** (0.22 mL, 1.50 mmol). The reaction mixture was heated at reflux for 30 min, cooled to r.t., then a solution of *p*-nitrobenzyl alcohol (153 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was then heated at reflux for 17 h, cooled to r.t. and filtered through Celite®. Ethylenediamine (10 mL) was added and the reaction mixture concentrated in vacuo to afford a purple oil which was partitioned between conc. aq NH_3 solution (40 mL) and CH_2Cl_2 (40 mL). The NH_3 solution was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were then concentrated in vacuo then redissolved in CH_2Cl_2 (20 mL) and extracted with 10% aq HCl (20 mL). The aqueous extracts were then basified to pH 12 with 10 M NaOH solution and extracted with CH_2Cl_2 (4 × 10 mL) and the combined organics were dried over Na_2SO_4 and concentrated in vacuo to afford the title compound **7** (166 mg, 81%) as a purple solid (mp 124–126 °C, lit.[1] 135–137 °C). ^{1}H NMR data were consistent with those reported in the literature.[1]