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# One-pot conversion of activated alcohols into terminal alkynes using manganese dioxide in combination with the Bestmann–Ohira reagent

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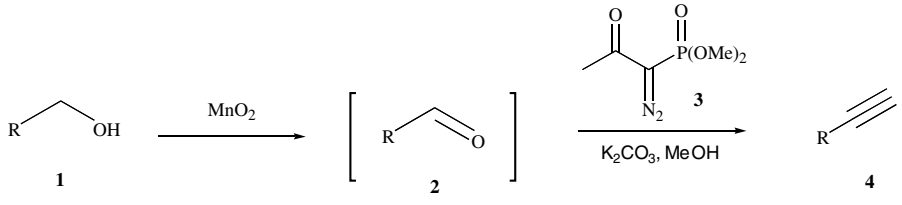
**Abstract**—The direct conversion of activated primary alcohols into terminal alkynes through a sequential one-pot, two-step process involving oxidation with manganese dioxide and then treatment with the Bestmann–Ohira reagent is described. This transformation proceeds efficiently (59–99% yield) under mild reaction conditions with a range of benzylic, heterocyclic and propargylic alcohols. A tandem variant is also described, which is successful only with highly activated substrates.


Terminal alkynes are extremely valuable synthetic intermediates and their formation from aldehydes is a widely used preparative procedure. The Corey–Fuchs sequence has often been employed for the conversion of aldehydes into alkynes[1] but the need for strong bases to dehydrohalogenate the intermediate 1,1-dibromoalkenes, can limit its generality. Diazoalkylphosphonate reagents are of rapidly increasing importance for the same transformation due to their ready availability and the milder reaction conditions needed for the transformations. Seyferth and Gilbert[2] and Colvin and Hamill[3] first showed that dialkyl diazomethylphosphonates undergo Horner–Wadsworth–Emmons reactions with aldehydes generating diazoalkenes, which lose nitrogen in situ to produce alkylidene carbenes, which undergo 1,2-rearrangement to give the alkyne products. More recently, the groups of Ohira[4] and Bestmann and co-workers[5] reported a valuable modification to the original Seyferth–Gilbert procedure, which utilises dimethyl 1-diazo-2-oxopropylphosphonate **3**. The Bestmann–Ohira reagent is stable, readily prepared from commercially available precursors,[6] and reacts with aldehydes at room temperature on treatment with $MeOH/K_2CO_3$. The use of these diazoalkylphosphonate reagents in complex natural product synthesis is now well established.[7]

We recently initiated a programme to develop novel one-pot manganese dioxide-mediated tandem oxidation processes (TOP), leading directly from primary alcohols to a range of synthetically useful functionalities (alkenes, imines, etc.) via in situ trapping of the intermediate aldehydes.[8] In this letter we report the development of procedures for the one-pot conversion of activated alcohols **1** into terminal alkynes **4** using the Bestmann–Ohira reagent **3** as shown in Eq. 1.[9]




1 2 4 (1)

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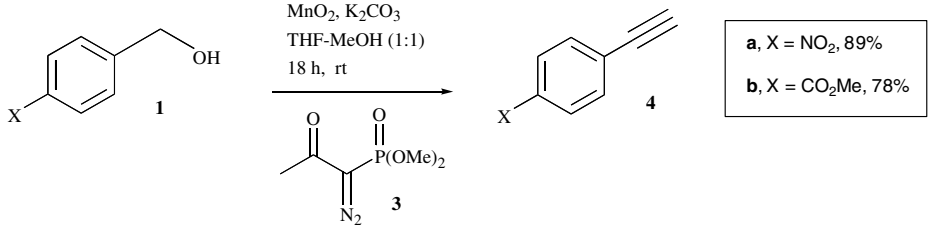
The Bestmann–Ohira reagent **3** was easily prepared from commercially available dimethyl (2-oxopropyl)-phosphonate in high yield (>97% on a 5–10 g scale) using Koskinen's diazo-transfer procedure.[10] We initially explored the TOP sequence illustrated in Eq. 2, in which the alcohol, $MnO_2$ and the Bestmann–Ohira reagent **3** were mixed together so that the aldehyde **2** would be trapped as soon as it was generated. Using *p*-nitrobenzyl alcohol **1a** (1 equiv), $MnO_2$ (5 equiv), Bestmann–Ohira reagent **3** (1.2 equiv) and $K_2CO_3$ (2 equiv) in a mixture of THF–MeOH (1:1) at room temperature for 18 h we were delighted to find that the desired terminal alkyne **4a** was obtained in 89% isolated yield. We also established that the presence of methanol, which deacetylates the Bestmann–Ohira reagent, is crucial for success—reactions in THF alone failed to generate any alkyne. In addition, attempts to replace MeOH by other alcohols failed; when *iso*-propanol was employed as co-solvent the *p*-nitrobenzyl alcohol was acetylated by the Bestmann–Ohira reagent. Unfortunately, the presence of methanol reduces the activity of the manganese dioxide and the only other satisfactory substrate for this TOP sequence was found to be 4-carbomethoxybenzyl alcohol **1b**, which gave alkyne **4b** in 78% yield. Other benzyl alcohol derivatives with electron-withdrawing substituents (e.g., *p*-bromobenzyl alcohol) reacted only partially, while benzyl alcohol itself, and derivatives containing electron-donating substituents, did not give any observable alkyne product, even under forcing conditions. Thus, only electron-deficient benzylic alcohols such as **1a** and **1b**, which undergo rapid oxidation, are suitable substrates for this tandem process.

The results in Table 1 clearly show that the two-step sequence proceeds efficiently (59–99% isolated yields after chromatography) and that it has general applicability. Thus, excellent yields were achieved using benzylic alcohols with electron-withdrawing groups (entries i–iii), electron-donating groups (entry v) and with benzyl alcohol itself (entry iv). In certain cases (entries i and ii) the reactions were so efficient that the products were pure (by NMR spectroscopy) after extractive work-up and further chromatographic purification was not required. Chromatography was also difficult when benzyl alcohol was employed (entry iv), due to the volatile nature of phenyl acetylene: in this example direct distillation from the crude reaction mixture gave the product alkyne in 87% yield, although this procedure needed to be carried out on a 10 mmol scale. Success was also achieved using naphthalene–1-methanol (entry vi), a heteroaromatic alcohol (entry vii) and a propargylic alcohol (entry viii). It should be noted that allylic alcohols cannot be employed in this methodology because, as originally reported by Bestmann and co-workers,[5] methanol adds to the intermediate α,β-unsaturated aldehydes.

The times needed for the oxidation step varied from 3 to 24 h, with 2,4-dimethoxybenzyl alcohol, pyridine 2-methanol and 3-phenylpropargyl alcohol taking the longest (8, 10 and 24 h, respectively). This method does not appear to be over-sensitive to steric factors as the *ortho*-substituted examples, dimethoxybenzyl alcohol and naphthalene–1-methanol, underwent oxidation–alkynylation in good to excellent yields (entries v and vi).



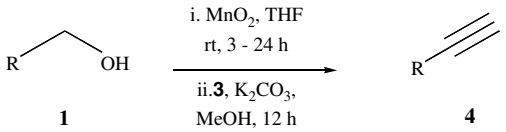

(2)

Given the above observations, we decided to develop a sequential one-pot procedure in which the oxidation was carried out using $MnO_2$/THF before the addition of the Bestmann–Ohira reagent in methanol. Thus, the oxidations were accomplished using 5 equiv of $MnO_2$ in THF at room temperature. Once all of the alcohol had been converted into the intermediate aldehyde **2** (TLC monitoring, 3–24 h), methanol was added followed by $K_2CO_3$ (2 equiv) and the Bestmann–Ohira reagent **3** (1.2 equiv). After, stirring for a further 12 h, the terminal alkynes were obtained in good to excellent yield. It is worth noting that the Bestmann–Ohira alkynylation proceeds smoothly in the presence of the unreacted $MnO_2$. This procedure was successful with a range of activated alcohols as can be seen from Table 1.

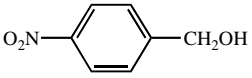
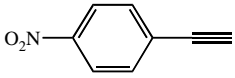
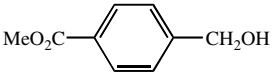
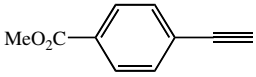
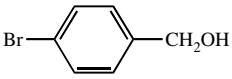
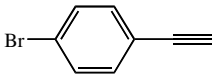
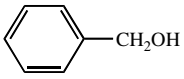
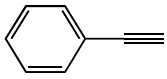
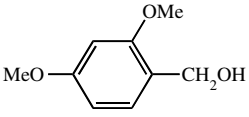
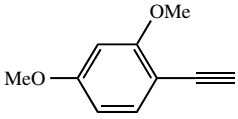
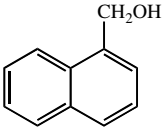
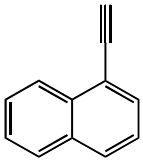
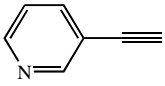
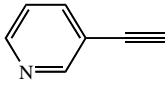
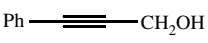
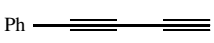
Finally, the efficient preparation of 4-bromophenylacetylene (entry iii) is noteworthy: transition metal-mediated cross-coupling methods have been used to prepare this and related compounds, but these processes require anhydrous conditions and expensive catalysts, require alkyne protection, and lead to product mixtures.[13]

In conclusion, we have developed a very mild and straightforward sequential one-pot method for the conversion of a variety of benzylic, heterocyclic and propargylic alcohols into their corresponding homologated terminal alkynes in good to excellent yield. In addition, a tandem process has been developed for use with benzyl alcohols containing highly electron-withdrawing substituents (nitro, ester) on the aromatic ring. We are currently applying this methodology in target molecule synthesis.

**Table 1.** Sequential one-pot $MnO_2$ oxidation/Bestmann–Ohira alkynylation to give terminal alkynes **4**




**1** **4**

| Entry | Alcohol | Alkyne | Yield (%)[a] |
|---|---|---|---|
| i[11,12] |  |  | 99[b] |
| ii |  |  | 97[b] |
| iii |  |  | 85 |
| iv |  |  | 87[c] |
| v |  |  | 59[d] |
| vi |  |  | 89 |
| vii |  |  | 68[d] |
| viii |  |  | 59[d] |

[a] Carried out on a 0.15–0.5 mmol scale, as above, unless stated otherwise. Yields refer to isolated products. Spectroscopic/analytical data of alkynes are in agreement with those reported.
[b] Chromatographic purification not required: product essentially pure after extractive work-up.
[c] Carried out on a 10 mmol scale and the alkyne purified by distillation.
[d] Longer oxidation times required: 8 h for v, 10 h for vii and 24 h for viii.

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11. *Representative procedure: 1-ethynyl-4-nitrobenzene* **4a** *p*-Nitrobenzyl alcohol (50 mg, 0.33 mmol) was dissolved in dry THF (6 mL) and activated $MnO_2$ (Aldrich 21,764-6, 5 equiv) was added. The heterogeneous mixture was efficiently stirred at room temperature for 4 h. Anhydrous MeOH (6 mL) was added followed by $K_2CO_3$ (84 mg,

0.6 mmol) and Bestmann reagent **3** (70 mg, 0.36 mmol). The reaction was stirred overnight at room temperature under argon and the crude mixture filtered through a short Celite pad (dichloromethane eluent). The organic solvent was removed in vacuo, the residue redissolved in dichloromethane (10 mL) and then washed with 5% $NaHCO_3$ aqueous solution (10 mL) and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure, to give 1-ethynyl-4-nitrobenzene **4a** (38.4 mg, 0.29 mmol, 99%) as a white solid, mp 150–151 °C (lit.[12] mp 150–150.5 °C), which displayed consistent spectroscopic data.

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