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In situ alcohol oxidation–Wittig reactions using *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide: application to the synthesis of a novel analogue of 5-oxo-eicosatetraenoic acid

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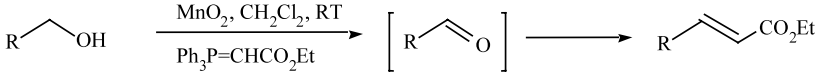
Abstract—Benzylic, allylic, propargylic and unactivated alcohols can be oxidised with activated manganese dioxide in the presence of *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide to generate directly the corresponding α,β-unsaturated Weinreb amides. Elaboration of the resulting Weinreb amides is also described, in particular as part of a new route to analogues of the arachidonic acid metabolite 5-oxo-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid.

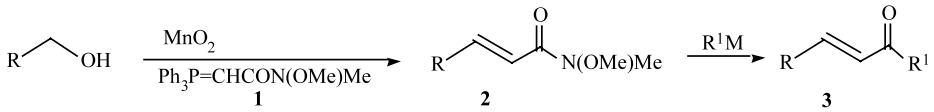
We have recently described an in situ manganese dioxide-mediated alcohol oxidation-stabilised Wittig sequence which can be applied to both activated[1] and non-activated[2] primary alcohols (Eq. (1)), as well as to 1,2-glycols.[3] We subsequently extended the oxidation–Wittig methodology to allow the use of phosphonates and non-stabilised phosphonium salts.[4] This one-pot methodology removes the need to isolate the intermediate aldehydes, and so is beneficial in terms of time and particularly advantageous if the intermediate aldehydes are unstable, toxic or difficult to handle. In order to further extend the scope of this process, and to increase its utility in analogue synthesis, we decided to investigate the use of the commercially available stabilised Wittig reagent, *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide (**1**).[5] If successful, we felt that the product Weinreb amides **2** would be valuable for the preparation of a diverse range of unsaturated aldehydes and ketones **3** (R′ = H, alkyl, aryl, Eq. (2)). This letter describes the success of this methodology for a range of alcohols and also outlines the elaboration of one amide adduct **2** into different carbonyl derivatives **3**. In addition, we report the application of this new methodology to the preparation of a novel analogue of the bioactive arachidonic acid metabolite 5-oxo-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid.

We first set out to establish that phosphorane **1** was compatible with manganese dioxide (Eq. (3)). Using benzyl alcohol as substrate, we were delighted to observe that the in situ manganese dioxide-mediated alcohol oxidation-stabilised Wittig sequence proceeded in dichloromethane at room temperature (RT) to give product **2a** in almost quantitative yield. The room temperature reaction was rather slow but by carrying out the reaction in dichloromethane at reflux, the transformation was complete overnight.



(1)

R = aryl, vinyl, alkynyl[1]
R = *n*-alkyl *etc.*[2]



(2)

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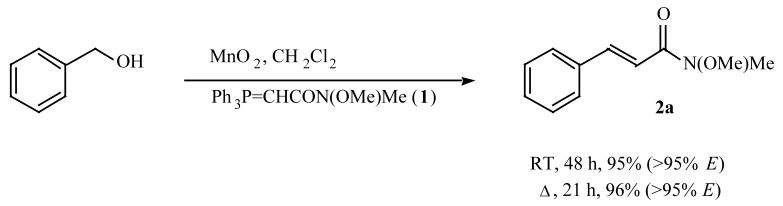
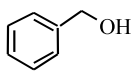
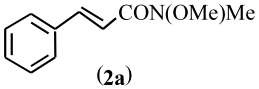
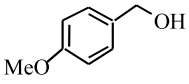
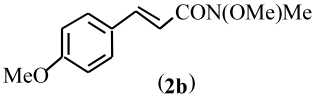
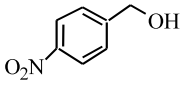
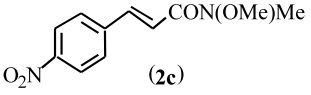
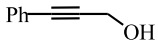
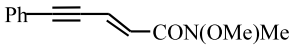
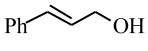
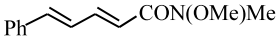
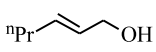
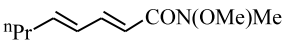
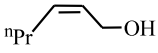
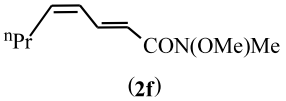
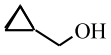
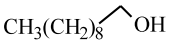
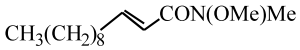


(3)

Table 1. MnO_2 oxidation-stabilised Wittig reactions

	 (**2a**)	CH_2Cl_2, Δ, 21 h 96% (> 95% *E*)
	 (**2b**)	CH_2Cl_2, Δ, 23 h 81% (*E*:*Z* = 12:1)
	 (**2c**)	CH_2Cl_2, Δ, 21 h 90% (*E*:*Z* = 12:1)
	 (**2d**)	CH_2Cl_2, Δ, 24 h 86% (*E*:*Z* = 4.5:1)
	 (**2e**)	CH_2Cl_2, Δ, 24 h 92% (2*E*,4*E*:2*Z*,4*E*= 8.1:1)
	 (**2f**)	CH_2Cl_2, RT, 50 h 81% (2*E*,4*E*:2*Z*,4*E*= 6.4:1)[b]
	 (**2f**)	CH_2Cl_2, RT, 50 h 69% (2*E*,4*Z*:2*Z*,4*Z* = 5.3:1)[c,d]
	 (**2g**)	PhMe, Δ, 6 h 63% (*E*:*Z* = 15:1)
	 (**2h**)	PhMe, Δ, 6 h 57% (*E*:*Z* = 11.5:1)

[a] Activated MnO_2 (Aldrich, ca. 10 equiv.) was added to the alcohol and stabilised Wittig reagent (1.2 equiv.) in dichloromethane or toluene and heated if required.

[b] At reflux (21 h), a 53% yield was obtained (*E*,*E*:*Z*,*E* = 12.5:1).

[c] Trace amounts of the other two isomers were also observed.

[d] At reflux (23 h), a 62% yield was obtained (2*E*,4*Z*:2*Z*,4*Z*:2*E*,4*E*:2*Z*,4*E* = 7.7:1:1:trace).

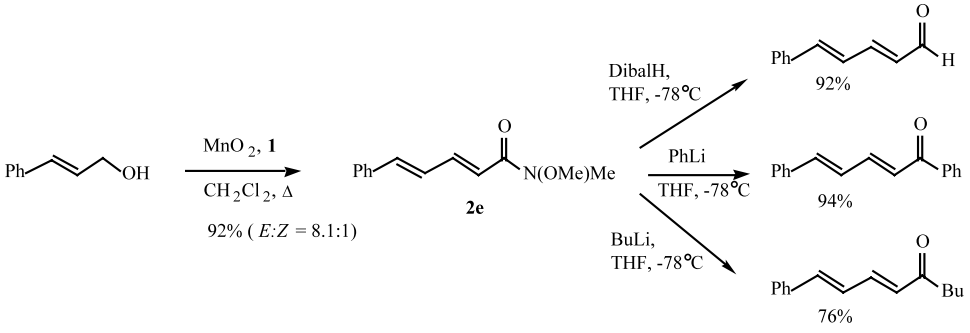
We next went on to explore the scope of the process (Table 1).[6,7] In addition to benzyl alcohol, substituted analogues with electron-donating and electron-withdrawing substituents could be employed, giving adducts **2b** and **2c**, respectively. 3-Phenylpropargyl alcohol and cinnamyl alcohol also underwent the expected transformation in good yields giving **2d** and **2e**, respectively. In all of these examples, the newly-formed alkene was predominantly *E*- as expected.

We next examined reactions of *E*- and *Z*-hex-2-en-1-ol. In both cases, when the reactions were carried out at RT, the pre-existing alkene geometries were essentially retained in adducts **2f**. In refluxing dichloromethane, *Z*-hex-2-en-1-ol underwent ca. 10% isomerisation, however.

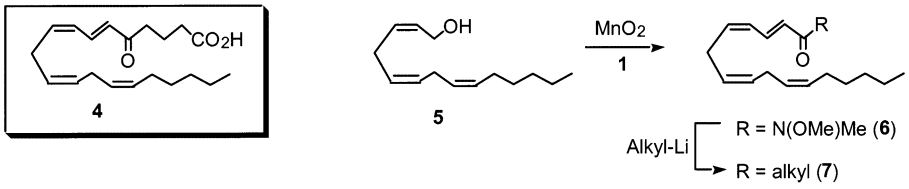
Finally, examples of semi-activated and unactivated systems were examined. Both cyclopropylmethanol and decanol required refluxing toluene for the conversions to proceed at an acceptable rate, but the expected products **2g** and **2h** were then obtained in reasonable yields.

We next explored applications of the resulting Weinreb amides (Schemes 1–3). Initially, we looked at the cinnamyl derivative **2e** and demonstrated that efficient conversion to the corresponding aldehyde, phenyl ketone and butyl ketone[8] took place under standard conditions, as shown in Scheme 1. Dienamide **2e** was used as the chromatographically pure *E*,*E*-isomer, and the three adducts all retained this *E*,*E*-configuration.

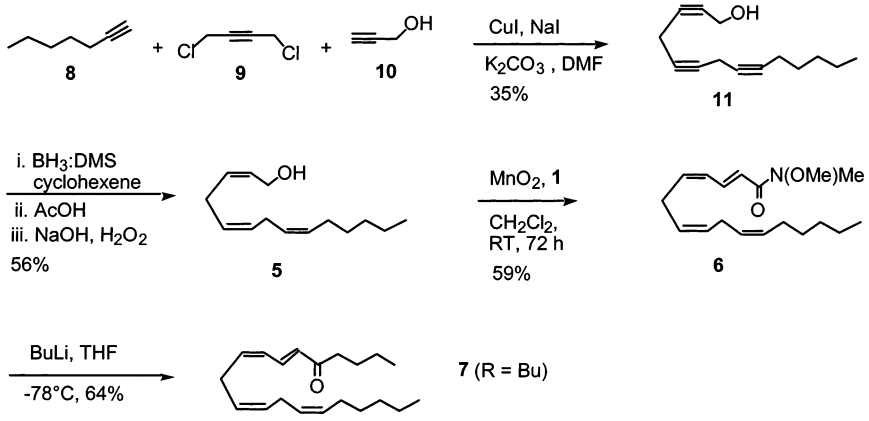
We then went on to utilise this methodology as the cornerstone of a new approach (Scheme 2) to novel analogues **7** of the bioactive arachidonic acid lipoxygenase metabolite 5-oxo-6*E*,8*Z*,11*Z*,14*Z*-eicosatetraenoic acid (5-oxo-ETE, **4**).[9,10] 5-Oxo-ETE **4** is an important mediator of inflammatory and allergic reactions,[9,10] and has attracted considerable recent synthetic attention.[10]



Scheme 1.



Scheme 2.



Scheme 3.

In order to investigate the synthetic approach to 5-oxo-ETE **4** shown in Scheme 2, we required trienol **5** for use in the in situ manganese dioxide-mediated alcohol oxidation-stabilised Wittig sequence. The complete approach is illustrated in Scheme 3.

Triynol **11** has been described in the literature (as its THP derivative),[11] but we were attracted by a one-pot preparation as shown in Scheme 3. Thus, a mixture of hept-1-yne (**8**) and propargyl alcohol (**10**) were added to a suspension of CuI, NaI and K_2CO_3 in DMF after which 1,4-dichlorobut-2-yne (**9**) was added slowly. After chromatography, the required product **11** was obtained in 35–40% yield. Stereocontrolled reduction of triyne **11** to give triene **5** was carried by treatment with dicyclohexylborane followed by protonolysis. Triene **5**[12] was obtained in 56% yield (as a single stereoisomer according to ^{13}C NMR spectroscopy).

We next investigated the crucial in situ manganese dioxide-mediated alcohol oxidation-stabilised Wittig sequence using *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide (**1**) with trienol **5**. We were delighted to find that the process took place in reasonable yield (59%) giving Weinreb amide **6** with the original alkenes in the all-*Z*-configuration and the newly formed alkene predominantly in the *E*-configuration (*E*,*Z*,*Z*,*Z*:*Z*,*Z*,*Z*,*Z* = 6.4:1), as established by high field ^1H NMR spectroscopy. In order to establish the viability of Weinreb amide **6** as a versatile intermediate for the preparation of 5-oxo-ETE analogues, we examined its reaction with *n*-butyllithium (Scheme 3). When treated with *n*-butyllithium in THF at −78°C, amide **6** was cleanly transformed into the terminally reduced 5-oxo-ETE analogue **7**, which was fully characterised. It should be noted that the tetraene stereochemistry was unaffected by the organometallic addition (and that no 1,4-addition was observed).

We are currently optimising the methodology described in this paper, and also utilising the chemistry described in Scheme 3 for the preparation of 5-oxo-ETE and novel analogues.

Acknowledgements

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5. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clady, J.; Stout, T. J. *J. Am. Chem. Soc*. **1990**, *112*, 7001–7031.
6. Novel products were fully characterised; known products gave consistent spectroscopic data.
7. General procedure for the manganese dioxide process: To a stirred solution of the alcohol (1 mmol) in CH_2Cl_2 or toluene (20 ml) was added *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide (**1**, 1.2 mmol) followed by activated MnO_2 (Aldrich, 21764-6; 10 mmol) and the reaction was stirred at the specified temperature. After the specified time, the mixture was filtered through Celite® washing with dichloromethane, and the volatiles removed in vacuo. The products were then purified by column chromatography.
8. As well as the 1,2-addition product (76%), the 1,4-adduct was also obtained (14%).
9. Powell, W. S.; Gravel, S.; Halwani, F.; Hii, C. S.; Huang, Z. H.; Tan, A. M.; Ferrante, A. *J. Immunol*. **1997**, *159*, 2952–2959 and references cited therein.
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