In Situ Alcohol Oxidation-Wittig Reactions Using Non-stabilised Phosphoranes

Leonie Blackburn, Chengxin Pei, Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK
Fax +44(1904)434523; E-mail: rjkt1@york.ac.uk

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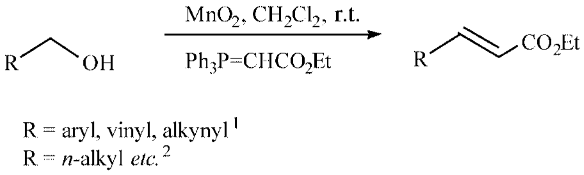
Abstract: New procedures have been developed which allow the in situ alcohol oxidation-Wittig reaction using manganese dioxide to be employed with non-stabilised phosphoranes and stabilised phosphonate anions. A number of examples are described utilising benzylic, allylic and propargylic alcohols.

Key words: alkenes, Horner–Wadsworth–Emmons, oxidation, tandem, Wittig

We have recently reported the in situ alcohol oxidation-Wittig reaction using manganese dioxide in the presence of stabilised phosphoranes (Scheme).[1] The initial studies concentrated on activated alcohols but we subsequently established that this procedure is also applicable to unactivated primary alcohols.[2] Other groups have reported similar procedures utilising the Dess–Martin periodinane,[3] barium manganate[4] and IBX[5] as the oxidants. This one-pot, tandem methodology obviates the need to isolate the intermediate aldehydes, a particularly useful feature in the case of aldehydes, which are volatile, toxic or highly reactive.

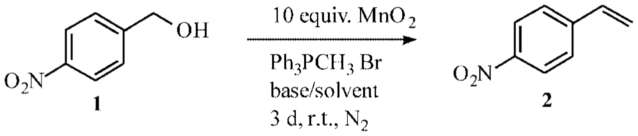


Scheme

Herein we report the extension of the manganese dioxide procedure to encompass the use of non-stabilised phosphoranes and stabilised phosphonate anions.

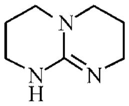
The Wittig reaction using non-stabilised phosphonium salts typically requires the use of anhydrous conditions and relatively strong bases such as *n*-butyllithium. Recently, however, Simoni et al. have shown that a number of guanidines can promote in situ Wittig reactions between non-stabilised phosphonium salts and aldehydes.[6] We have now demonstrated that Simoni's conditions are compatible with manganese dioxide oxidations (Table 1).

Table 1 In situ Oxidation-Wittig reactions using a Range of Bases



Base/solvent	Yield **2** (%)	Base/solvent	Yield **2** (%)
K_2CO_3, MeOH	0	DBU, THF	20
Triton B, THF	0	**3**, THF	0
LiOH, THF	3	PS-3,[a] THF	0
t-BuOK, THF	11	**4**, THF	34 (91)

[a]PS-**3** = polymer supported-**3**



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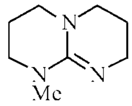

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Initial studies were carried out using *p*-nitrobenzyl alcohol **1**, methyl(triphenyl)phosphonium bromide and a range of inorganic bases. Even after 3 days at room temperature (r.t.), the best yield of *p*-nitrostyrene **2** was only 11% (*t*-BuOK, THF). We therefore turned to the use of strong organic bases. DBU in THF gave an encouraging yield (20%) and in view of Simoni's results[6] we were optimistic about the use of 1,5,7-triazabicyclo[4.4.0]dec-5-ene **3**. However, this reagent was totally ineffective as was its polymer supported variant. We were thus delighted to find that 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) **4** gave a 34% yield of alkene **2** under these standard conditions. Moreover, optimisation studies revealed that the yield of **2** could be increased to 91% by the use of pre-dried manganese dioxide in refluxing THF. The reactions between a number of alcohols and phosphonium salts were then investigated under these optimised conditions (Table 2).[7]

With *p*-nitrobenzyl alcohol, we next examined its reaction with benzyl(triphenyl)phosphonium chloride (entry ii). This reaction proceeded efficiently and gave a slight predominance of the *E*-adduct, as would be expected from a semi-stabilised phosphorane under these conditions. We then moved on to the use of *n*-butyl(triphenyl)-phosphonium bromide with *p*-nitrobenzyl alcohol (entry iii). In

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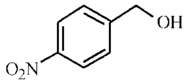
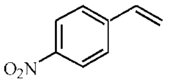
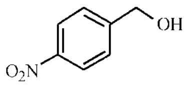
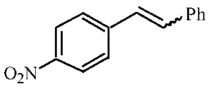
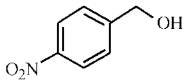
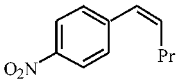
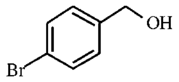
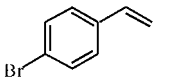
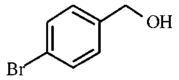
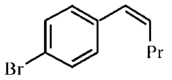
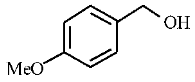
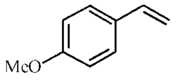
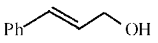
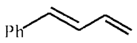
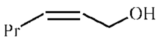
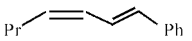
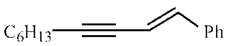
this case we found that the yield of the in situ oxidation-Wittig reaction could be improved (54% to 64%) by the addition of an equimolar amount of titanium isopropoxide. The addition of titanium isopropoxide was utilised in all of the other examples shown in Table 2 and in some cases gave dramatic improvements (see entry vi). It should be noted that the reaction of 4-nitro- and 4-bromobenzyl alcohols with *n*-butyl(triphenyl)phosphonium bromide proceeded with *Z*-stereoselectivity (entries iii and v), as expected.

Table 2 In situ Oxidation-Wittig Reactions using Guanidine **4**

Entry	Alcohol	Conditions[a]	Product (yield)
(i)		Ph_3PCH_3Br 4 h	 (91%)
(ii)		Ph_3PCH_2PhCl 12 h	 (92%; *Z*:*E* = 4:5)
(iii)		Ph_3PCH_2PrBr $Ti(i\text{-}PrO)_4$, 24 h	 (64%; *Z*:*E* = 4:1)[b]
(iv)		Ph_3PCH_3Br $Ti(i\text{-}PrO)_4$, 48 h	 (88%)
(v)		Ph_3PCH_2PrBr $Ti(i\text{-}PrO)_4$, 72 h	 (64%; *Z*:*E* = 5:1)
(vi)		Ph_3PCH_3Br $Ti(i\text{-}PrO)_4$, 48 h	 (61%)[c]
(vii)		Ph_3PCH_3Br $Ti(i\text{-}PrO)_4$, 48 h	 (54%; *E*-only)
(viii)		Ph_3PCH_2PhCl $Ti(i\text{-}PrO)_4$, 24 h	 (55%; *Z*,*E*:*Z*,*Z*:*E*,*E* = 1.0:0.4:0.15)
(ix)		Ph_3PCH_2PhCl $Ti(i\text{-}PrO)_4$, 24 h	 (62%; *Z*:*E* = 1:2)

[a] Using pre-dried manganese dioxide (10 equiv) under nitrogen in refluxing THF containing phosphonium salt (1.1 equiv), guanidine **4** (2.2 equiv) and in some cases $Ti(i\text{-}PrO)_4$ (1 equiv).

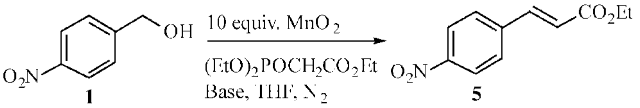
[b] 54% without $Ti(i\text{-}PrO)_4$.

[c] 25% after 3 d without $Ti(i\text{-}PrO)_4$.

In addition to the benzylic alcohols, allylic and propargylic alcohols also reacted well under the in situ oxidation Wittig conditions (entries vii–ix). It should be noted that *E*-cinnamyl alcohol underwent the in situ oxidation-Wittig reaction with complete retention of the pre-existing double bond configuration whereas *Z*-hex-2-en-1-ol underwent some isomerisation. Attempts to extend this methodology to unactivated alcohols[2] such as decanol were unsuccessful.

Having successfully developed conditions for the in situ alcohol oxidation-Wittig reaction with non-stabilised phosphonium salts, attention was turned to the use of phosphonates in these processes to effect in situ alcohol oxidation-Horner–Wadsworth–Emmons (HWE) transformations. Initial studies involved treatment of *p*-nitrobenzyl alcohol with manganese dioxide, triethyl phosphonoacetate and a range of bases as shown in Table 3.

Table 3 In situ Oxidation-HWE Reactions using a Range of Bases



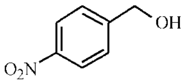
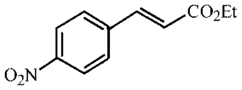
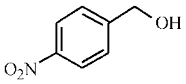
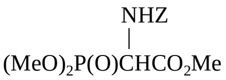
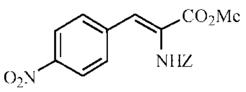
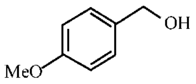
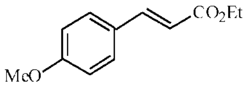
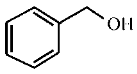
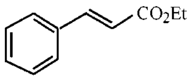
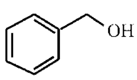
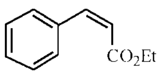
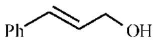
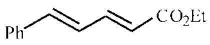
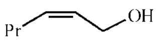
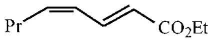
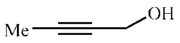
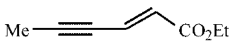
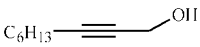
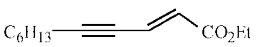
Base/conditions	Yield **5** (%)	Base/conditions	Yield **5** (%)
LiOH, r.t., 4 d	61	DBU, Δ, 18 h	57
LiOH, Δ, 18 h	75	DBU, LiCl, Δ, 18 h	35
Et_3N, Δ, 18 h	24	**4**, Δ, 18 h	71 (81)

Lithium hydroxide has recently been used as a base for phosphonate carbanion generation[8] and under the in situ manganese dioxide oxidation conditions with triethyl phosphonoacetate, anhydrous LiOH gave ester **5** in 75% yield when the reaction was carried out at reflux. Turning to amine bases, triethylamine gave a disappointing yield (24%) whereas DBU gave a 57% yield under the same conditions. Somewhat surprisingly,[9] the use of DBU/LiCl gave a reduced yield (35%). Once again, however, the best yield with an organic base was obtained using guanidine **4** (71%), and by using pre-dried manganese dioxide the yield was improved still further (81%).

In view of the results outlined in Table 3, the use of lithium hydroxide and guanidine **4** were explored with a number of activated alcohols and phosphonates (Table 4). With triethyl phosphonoacetate, successful results were obtained with both bases using a range of different benzyl alcohols (entries i, iii and iv), as well as allylic (entries vi and vii) and propargylic (entries viii and ix) systems. In general, lithium hydroxide is the preferred base, although in some cases guanidine **4** gives higher yields; both process are rather slow, however.[10] As seen from Table 4, it is possible to form didehydroamino acid derivatives via this in situ sequence (entry ii).

Pre-existing double bond geometry is retained (entries vi and vii). It should be noted that the *E*-alkene products predominated using the standard conditions. However, use of Ando's phenoxy phosphonate[11] (entry v) gave the *Z*-isomer as the major product.

Table 4 In situ Oxidation-HWE Reactions

Entry	Alcohol	Conditions[a]	Product[b] (yield)
(i)		$(EtO)_2P(O)CH_2CO_2Et$ THF, Δ A: 12 h B: 12 h	 (A: 75%) (B: 81%)
(ii)		 $(MeO)_2P(O)\overset{NHZ}{\overset{\vert}{C}}HCO_2Me$ A: 48 h, Δ B: 6 h, r.t.	 (A: 43%; > 95% *Z*) (B: 49%; > 95% *Z*)
(iii)		$(EtO)_2P(O)CHCO_2Et$ THF, Δ A: 48 h B: 72 h	 (A: 43%) (B: 70%)
(iv)		$(EtO)_2P(O)CH_2CO_2Et$ THF, Δ A: 48 h B: 48 h	 (A: 69%) (B: 53%)
(v)		$(PhO)_2P(O)CH_2CO_2Et$ THF, Δ A: 48 h B: 48 h	 (62%; *Z*:*E* = 2:1)
(vi)		$(EtO)_2P(O)CH_2CO_2Et$ THF, r.t. B: 72 h	 (A: 40%) (B: 70%)
(vii)[c]		$(EtO)_2P(O)CH_2CO_2Et$ THF, Δ A: 72 h	 (42%; > 95% *Z*,*E*)
(viii)		$(EtO)_2P(O)CH_2CO_2Et$ THF, Δ A: 24 h	 (72%)
(ix)		$(EtO)_2P(O)CH_2CO_2Et$ THF, Δ A: 24 h	 (66%)

[a] Using manganese dioxide (10 equiv) in refluxing THF containing phosphonate (1.2 equiv), guanidine **4** (2.2 equiv) or LiOH (2 equiv)/4Å molecular sieves. The manganese dioxide was pre-dried (75 °C, overnight) for the MTBD (**4**) procedures. A = using LiOH; B = using base **4**.

[b] > 95% *E*-isomer unless otherwise noted.

[c] Using pre-dried MnO_2.

In conclusion we have successfully extended the in situ alcohol oxidation-Wittig procedure using manganese dioxide to include non-stabilised phosphoranes and stabilised phosphonate anions. Benzylic, allylic and propargylic alcohols have all been successfully employed in these procedures. Work is currently underway to further optimise these procedures and to demonstrate their usefulness in natural product synthesis.

Acknowledgement

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References

(1) (a) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815. (b) Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 617.

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(4) Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 4489.

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(6) Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F. P. *Org. Lett.* **2000**, *2*, 3765.

(7) Manganese dioxide (activated, Aldrich 21, 764-6) was dried in an oven overnight (ca. 75 °C). Dried manganese dioxide (217 mg, 2.5 mmol) was then added to a solution of alcohol (0.5 mmol), phosphonium salt (0.55 mmol), guanidine **4** (1.1 mmol) and Ti(*i*-PrO)$_4$ (0.5 mmol, if specified in Table 2) in THF (12 mL) which was heated to reflux under nitrogen. A second portion of MnO_2 (217 mg, 2.5 mmol) was added after 1 h and the reaction mixture heated at reflux for the time stated. The reaction mixture was allowed to cool and then filtered through Celite washing well with Et_2O. The combined organic washings were neutralised with aq sat. NH_4Cl solution. The organic layer was separated and the aq layer extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by column chromatography. Known products gave data consistent with those published; novel compounds were fully characterised.

(8) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Orelli, L. R.; Scettri, A. *Tetrahedron Lett.* **1994**, *35*, 3383.

(9) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(10) Addition of Ti(*i*-PrO)$_4$ did appear to accelerate these reactions but some transesterification was observed and the procedure was not explored further. We were unable to utilise unactivated alcohols such as decanol in this sequence.

(11) (a) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105. (b) See also: Ando, K. *Synlett* **2001**, 1272; and references therein.