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A sequential tetra-*n*-propylammonium perruthenate (TPAP)–Wittig oxidation olefination protocol

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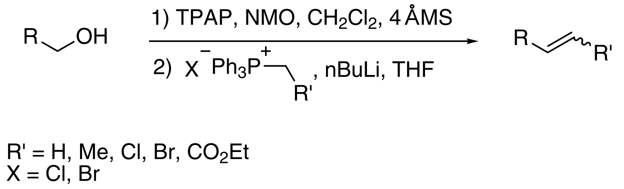
Abstract—A convenient sequential oxidation–olefination protocol is reported using tetra-*n*-propylammonium perruthenate (TPAP) as oxidant and phosphonium salts as olefin source. The oxidation reaction mixture is added directly to the phosphorane facilitating an efficient method for this transformation that avoids work-up of potentially sensitive aldehyde intermediates.

The oxidation of alcohols to aldehydes and ketones and their subsequent transformation to alkenes using a Wittig olefination is an important functional group manipulation, which is frequently used in natural product synthesis.[1,2] However, the utility of this sequence can be limited when applied to aldehydes that are problematic to isolate due to their instability or volatility. This research investigates a tetrapropylammonium perruthenate (TPAP) oxidation, followed by immediate Wittig olefination without work-up, to prepare alkenes from alcohols with improved efficiency and scope over previously reported one-pot methods (Scheme 1).

Recently, several oxidation–Wittig procedures have been developed that circumvent the need to isolate unstable products. Various oxidising reagents, including MnO_2,[3] $BaMnO_4$,[4] and Dess–Martin periodinane,[5] have been utilised but are restricted with respect to their scope and applicability to complex substrates. Requiring harsh conditions and large excess of reagents, these methods are often not compatible with sensitive natural product intermediates. Primarily, they are restricted to stabilised ylides in the oxidation–Wittig processes. Only the most thorough study by Taylor and co-workers[6] has investigated nonstabilised ylides with MnO_2 as oxidant, but the success of the reaction was mainly confined to benzylic alcohols and other activated systems.



Scheme 1. Sequential TPAP oxidation–Wittig olefination reactions.

TPAP is an air stable and nonvolatile reagent that has been widely applied to the oxidation of alcohols to aldehydes and ketones.[7] It is commercially available, readily soluble in organic solvents, catalytic in the presence of NMO or O_2, active at room temperature, and devoid of noxious or explosive side products. In our procedure,[8] the oxidations are complete in less than 30 min and then the reaction mixtures are added, without work-up, directly into a flask of the phosphorane. The work-up of these sequential reactions is a simple extraction followed by a filtration through a pad of silica or commercially available Bond Elut™ cartridge with hexanes to obtain clean alkene product. The general utility of this method is demonstrated by the oxidation and nonstabilised Wittig olefination of the series of alcohols depicted in Table 1.

Naphthalene methanol **1** and biphenyl methanol **3** afforded the desired ethylene products **2** and **4** in good yields. Thiazole alcohol **5** was investigated in order to illustrate the applicability of this method to heterocycles. The ethylene product **6** was obtained in lower yield, presumably due to competing oxidation of the heteroatoms during the TPAP oxidation. All aldehyde formed reacted further to give alkene product **6**. Although the reaction of dodecanol **7** seemed to proceed by TLC, some of the product alkene **8** may have

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Table 1. Sequential TPAP oxidation–nonstabilised Wittig olefination of alcohols to ethylenes

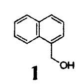
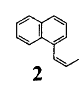
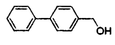
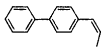
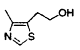
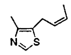
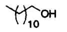
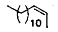
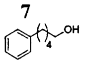
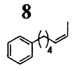
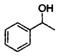
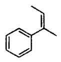
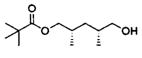
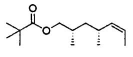
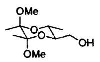
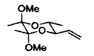
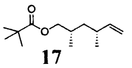
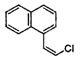
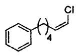
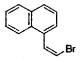
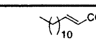
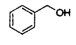
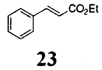
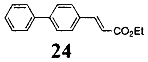
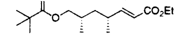
Entry	Alcohol	Alkene	Yield %	*E*:*Z*
1	 **1**	 **2**	88	1:4
2	 **3**	 **4**	94	1:2
3	 **5**	 **6**	44	1:>11
4	 **7**	 **8**	62	1:4
5	 **9**	 **10**	79	all *Z*
6	 **11**	 **12**	13	1:>9
7	 **13**	 **14**	71	1:3
8	 **15**	 **16**	67	N/A
9	**13**	 **17**	59	N/A
10	**1**	 **18**	94	1:2
11	**9**	 **19**	92	1:3
12	**1**	 **20**	62	1:2

Table 2. One-pot TPAP oxidation–stabilised Wittig olefination of various alcohols to ethyl esters

Entry	Alcohol	Alkene	Yield %	*E*:*Z*
1	**7**	 **21**	81	>9:1
2	 **22**	 **23**	68	>9:1
3	**3**	 **24**	87	>9:1
4	**13**	 **25**	64	>20:1

been lost due to its high volatility. With the intention of determining a yield for a non-volatile, aliphatic alcohol, phenylpentanol **9** was chosen as a substrate. Only the *Z* product **10** was obtained. Oxidation of secondary alcohol **11** went to completion; however, subsequent Wittig reaction of the ketone went poorly as is often the case with these types of reactions. Nevertheless, this result is an improvement on other sequential oxidation–Wittig techniques involving stabilised ylides[3] which report even lower yields for secondary alcohols. Notably, no epimerisation was observed when a chiral centre was present at the α-position of alcohol **13**, an intermediate available from our laboratory.

In order to investigate the scope of the Wittig reaction, this oxidation–olefination technique was also used in methylenation reactions with butane diacetal derivative **15** and chiral alcohol **13** (Table 1). In addition, vinyl halides **18**, **19**, and **20** were obtained in good yields using (chloromethyl)triphenyl phosphonium chloride and (bromomethyl)triphenyl phosphonium bromide.[9] Stabilised ylides[10] were also incorporated into the olefination step of this technique using a one-pot method that was applied successfully to several alcohols (Table 2).

Dodecanol **7**, benzyl alcohol **22**, and biphenyl methanol **3** all produced the corresponding esters **21**, **23**, and **24** in good to moderate yields and good selectivity for the *E* isomer. Once again, when this method was performed on the chiral alcohol **13** the ester product **25** was obtained without epimerisation.

In summary, this sequential TPAP oxidation–Wittig olefination technique is efficient and simple. It is widely applicable to a range of alcohols, including aromatic, aliphatic, heterocyclic, secondary, and chiral alcohols, with both stabilised and nonstabilised Wittig reagents to synthesise methylenes, ethylenes, vinyl halides, and esters. This method has potential for use in natural product synthesis.

Acknowledgements

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8. **Nonstabilised procedure (ethylene and methylene products)**: Alcohol (100 mg, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (2 ml/mmol) and stirred at rt under argon in the presence of NMO (1.05 equiv.) and 4 Å molecular sieves (200 mg/mmol). After 15 min, TPAP (0.05 equiv.) was added in small portions to give a black slurry. In a separate flask, triphenylphosphonium bromide (1.50 equiv.) was stirred at rt under argon in dry THF (3 ml), and *n*BuLi (2.5 M in hexanes, 1.43 equiv.) was added dropwise to give a bright orange slurry. After stirring the phosphorane for 1 h, it was cooled to −78°C and the TPAP reaction was added dropwise. The reaction mixture was warmed slowly to rt. Upon aldehyde consumption, the reaction mixture was diluted with saturated, aqueous NH_4Cl (15 ml) and stirred for 15 min. The mixture was extracted with Et_2O (45 ml) and the organic layer dried over $MgSO_4$, filtered, and concentrated in vacuo. The oil was then eluted through a Bond Elut cartridge (20 g, 60 ml) with hexanes (50 ml) and fractions collected and dried in vacuo to give the desired product.
9. **Nonstabilised procedure (vinyl halide products)**: Ethylene procedure[8] except that (chloromethyl) triphenylphosphonium chloride (1.50 equiv.) replaced the phosphorane. Use excess ^{n}BuLi (3.6 equiv.) to keep its bright yellow colour.
10. **Stabilised procedure (ester products)**: Ethylene procedure[8] except that (ethoxycarbonylmethylene)triphenylphosphorane (1.5 equiv.) was added directly to the oxidation reaction mixture, which was stirred for a further 16 h at rt. The crude reaction mixture was poured into 1:1 H_2O/CH_2Cl_2 and brine added until the two layers separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude product mixture. The alkene was purified by flash chromatography on silica gel (5% ethyl acetate/hexanes).