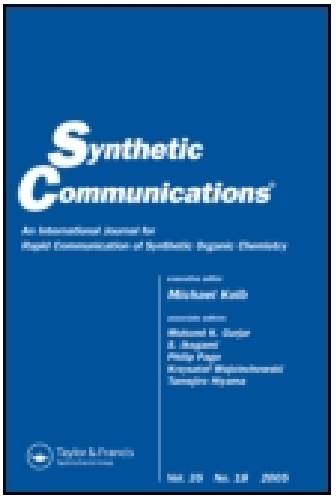

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PDC-MEDIATED TANDEM OXIDATIVE–WITTIG OLEFINATION

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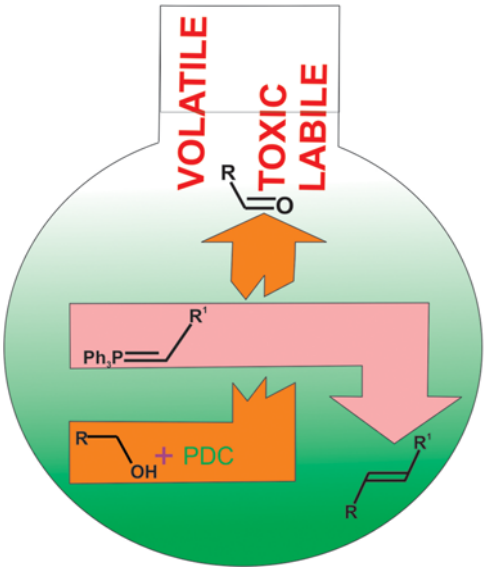
GRAPHICAL ABSTRACT



Abstract *A convenient tandem oxidative–Wittig olefination of a primary alcohols to α,β-unsaturated compounds using pyridinium dichromate (PDC) is described.*

Keywords Olefination; oxidation; PDC; tandem; Wittig reaction

INTRODUCTION

One of the routine organic transformations in organic synthesis for the homologation sequence is the oxidation of primary alcohol to aldehyde and further condensation with an appropriate Wittig reagent to get an α,β-unsaturated compound. The

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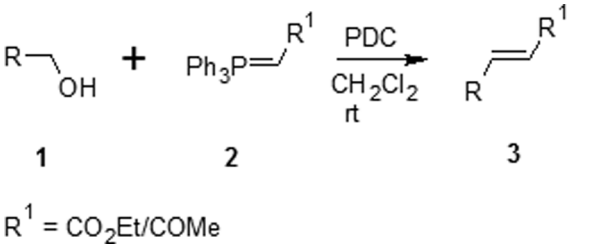
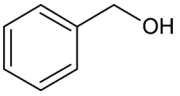
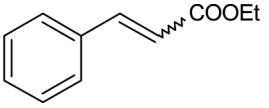
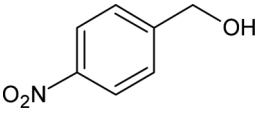
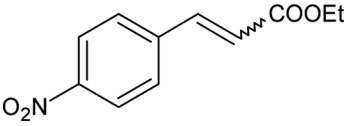
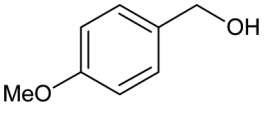
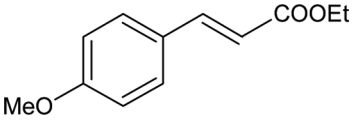
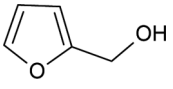
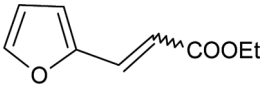
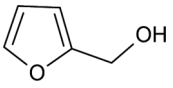
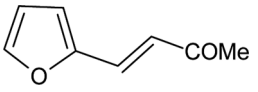
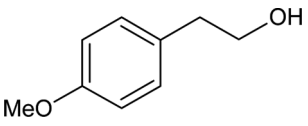
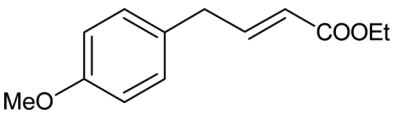
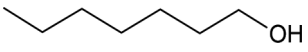
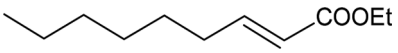
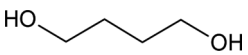
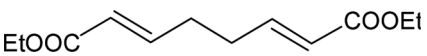
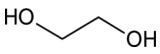
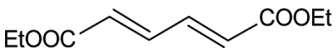
problem associated with this sequence is the handling of the intermediate aldehyde, particularly in the case of aldehydes, which are unstable, volatile, and toxic. This problem has been overcome to a great extent by the development of what is called as tandem oxidative procedure[1] (TOP) or domino reactions. These reactions slightly differ from the ''one-pot'' procedures wherein first aldehyde is obtained and then immediately reacted with a stabilized Wittig reagent.[2] In TOP, oxidation is carried out in the presence of a Wittig reagent so that as soon as aldehyde is formed it can further condense with the Wittig reagent. In this procedure the crucial part is the choice of the oxidizing agent, as it should not react with the Wittig reagent to oxidize it or overoxidize the initial alcohol further to an acid or ester. There are several reagents available for the selective oxidation of a primary alcohol to aldehyde but all cannot be used for TOP. For example, the most popular Swern oxidation[2] has to be used in a sequential manner and not in TOP as intermediate oxalyl chloride readily reacts with phosphorane. The first such TOP was reported by Barrett et al. in 1997 wherein primary alcohol was condensed with stable phosphorane in the presence of Dess–Martin periodinane[3] as an oxidizing agent. Benzoic acid was added to the reaction mixture to expedite the reaction in dimethylsulfoxide (DMSO)–CH_2Cl_2 (1:6) solvent mixture. In 1998 Wie and Taylor reported TOP for activated alcohols such as allylic, benzylic, and propargylic alcohols using excess of MnO_2.[1] The procedure is suitable for sensitive aldehydes that are normally difficult to isolate. In the same year Shuto and coworkers used $BaMnO_4$[4] again for activated alcohol in TOP. In 1999 Davies and McKervey extended the MnO_2 TOP for *N*-protected β-amino alcohols[5] under refluxing acetonitrile conditions. In the same year Crich and Mo reported use of iodoxybenzoicacid (IBX)[6] in dimethylsulfoxide (DMSO) for homologation of nucleosides. Catalytic aerobic oxidation using Ru[7] catalyst for TOP was reported by Kim et al. in 2001. The popular Corey reagent pyridinium chlorochromate (PCC)[8] in combination with NaOAc was reported from our laboratory in 2004. Recently Karama et al. in 2010 reported synthesis of α-bromo-α,β-unsaturated esters using a combination *N*-bromosuccinimide (NBS),[9] stable Wittig reagent, and primary alcohol under ultrasonic conditions. Because PCC is not a choice of reagent for the oxidations of allylic and propargylic alcohols, we were interested in using pyridinium dichromate (PDC) for such TOP. It was reported by Shuto[4] and coworkers that PDC is not suitable for such TOP. Hence we thought of investigating this reaction as it would be complementary to our PCC methodology for synthesizing homologated compounds of activated alcohols. In this article, we describe PDC-mediated tandem oxidative Wittig reaction procedure for the synthesis of α,β-unsaturated esters.



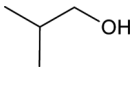
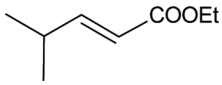
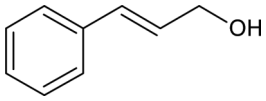
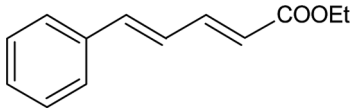
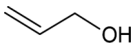
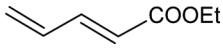
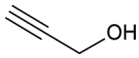
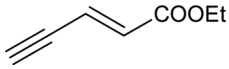
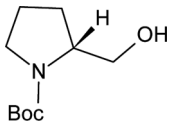
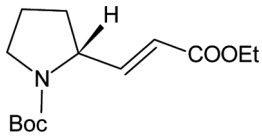
Scheme 1. Tandem oxidative Wittig reaction.

Table 1 PDC-mediated tandem oxidation Wittig reaction

Entry	Reactant 1	Product **3**	Yield[a]
a			90 (*E*–*Z* = 17:1)
b			82 (*E*–*Z* = 17:1)
c			81 (*E*)
d			98 (*E*–*Z* = 20:1)
e			96 (*E*)
f			54 (*E*)
g			87 (*E*)
h			62 (*E*)
i			40 (*E*)

(*Continued*)

Table 1. Continued

Entry	Reactant 1	Product **3**	Yield[a]
j			66 (*E*)
k			73 (*E*)
l			70 (*E*)
m			56 (*E*)
n			84 (*E*)

[a]Isolated using column chromatographic technique with 2% EtOAc in petroleum ether. *E*–*Z* ratio derived from NMR data.

RESULTS AND DISCUSSION

In our efforts, initially we tried the reaction of benzyl alcohol **1a** with ethyl (triphenylphosphoranylidene)acetate in the presence of PDC in CH_2Cl_2. The reaction was found to be complete after prolonged stirring (24 h), comparatively longer than the PCC method. The yield of ethyl cinnamate **3a** (*E*–*Z*, 95:5) was found to be 90%. After this success we tested this protocol with various other alcohols (Table 1). Benzyl alcohol, having an electron-withdrawing group *p*-nitrobenzyl alcohol **1b**, gave the corresponding *E*-homologated product **3b** exclusively in 82% yield. Benzyl alcohol, having an electron-donating group *p*-methoxybenzyl alcohol **1c**, gave the corresponding *E*-homologated product **3c** exclusively in 81% yield. Acid-sensitive furfuryl alcohol **1d** with ethyl (triphenylphosphoranylidene)acetate and (triphenylphosphoran ylidene)acetone gave the products **3d** and **3e** in 98% and 96% yields respectively. Next the protocol was checked for aliphatic alcohols *n*-haptanol **1g** and isobutyl alcohol **1j**. In both the cases the homologated product **3g** and **3j** were obtained in good yield. 1,4-Butanediol **1h** with 2 equivalents of Wittig

reagent and oxidizing agent gave *bis*-homolgated product **3h** in 62% yield, while ethanediol **1i** gave the corresponding product **3i** in only 40% yield. We then subjected this protocol to allylic alcohols. Cinnamyl alcohol **1k** gave the corresponding product **3k** in 73% yield. The allyl alcohol **1l**, which is a poor substrate for PCC, gave the product **3l** in 70% yield. Propagyl alcohol **1m**, which is not amenable to PCC, gave the product **3m** in moderate yield of 56%. *p*-Methoxy homobenzyl alcohol **1f** gave homologated product **3f** in 54% yield. In this reaction formation of a trace amount of *p*-methoxy benzaldehyde was also observed on thin-layer chromatography (TLC). Boc-protected prolinol **1n** an, amino alcohol that is sensitive to the acidic PCC, gave the product **3n** successfully in 84% yield. However, Cbz-prolinol did not give the homologated product as the Cbz group was found to get knocked off, resulting in formation of ethyl cinnamate due to the formation of intermediate benzaldehye and decomposition of prolinol.

CONCLUSION

In conclusion, we have developed a PDC-mediated tandem oxidative Wittig olefination procedure for the homologation of primary alcohols. The present procedure is complementary to our PCC-mediated protocol wherein nonactivated alcohols can be more effectively homologated.

EXPERIMENTAL

Flash chromatography was performed on silica gel (230–400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FT-IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a Bruker instrument. Chemical shifts (ppm) are relative to the internal standard Me_4Si (0 ppm).

Wittig reagent (1.85 mmol) in anhydrous CH_2Cl_2 (10 mL) and alcohol (1.85 mmol) in anhydrous CH_2Cl_2(10 mL) were added in one portion to a magnetically stired suspension of pyridinium dichromate (1.85 mmol). The reaction mixture was stirred at rt for 24 h. Et_2O (30 mL) was added to the reaction mixture and filtered. The residue was washed with ether (2×5 mL) and dried over anhydrous Na_2SO_4. The combined filtrate was then evaporated to give the crude product. Further purification by column chromatography using petroleum ether as an eluent gave the product.

FUNDING

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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