A Convenient One-Pot PCC Oxidation–Wittig Reaction of Alcohols

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Abstract: A simple one-pot process for the PCC oxidation of alcohols followed by in situ trapping of the aldehyde with a Wittig reagent is described.

Key words: oxidations, aldehydes, Wittig reactions, tandem reactions, esterification

Alcohols hold a central position in synthesis as they are easily converted to a multitude of functional groups through many rapid, facile transformations. One such transformation frequently employed is the oxidation of primary and secondary alcohols followed by coupling of the carbonyl[1] with a Wittig reagent. While this reaction sequence is viewed as classic, recently, while attempting to synthesize several glutaconic acid derivatives, we observed great difficulty isolating aldehydes generated from low molecular weight alcohols.

It has been noted that aldehydes may be difficult to isolate due to their volatility, toxicity, and their penchant to polymerize or hydrolyze.[2] Ireland was able to circumvent these problems through a one-pot scheme in which an aldehyde was generated using Swern oxidation conditions and trapped in situ by the Wittig reagent.[3] This procedure alleviated the necessity of isolating the intermediate aldehyde and vastly improved the yield.

More recently, two other variations have emerged to trap the intermediate aldehyde without isolation. Barrett effected the one-pot transformation utilizing the Dess–Martin periodinane,[4] while Wei and Taylor demonstrated an effective one-pot procedure treating various allylic alcohols[2,5] and unactivated alcohols[6] with MnO_2.

Pyridinium chlorochromate (PCC) is readily available, stable, and easy to use. A one-pot oxidation–olefination utilizing PCC would expand the tools available to chemists needing to perform Wittig reactions on sensitive or volatile aldehydes. In this communication, we report the development of methodology utilizing PCC in the one-pot oxidation–olefination of alcohols.

To investigate the utility of PCC in a one-pot reaction, benzyl alcohol **1** was treated with PCC and Celite followed immediately by addition of a Wittig reagent in a manner similar to that used by Ireland. Regardless of reaction times, no reaction occurred and the starting alcohol was recovered.

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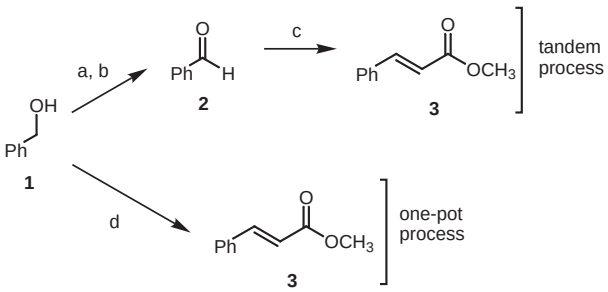
Next, a tandem process was investigated. Alcohol **1** was treated with PCC/Celite and allowed to react at room temperature (Scheme 1). Once the oxidation was complete, as determined by TLC, the reaction mixture was simply filtered through a small plug of silica gel removing the reduced chromium salts. The eluent, containing the crude aldehyde **2**, was then treated with the Wittig reagent and heated to reflux for 3 hours. This set of conditions led to a dramatic doubling of the yield of the α,β-unsaturated ester **3** as compared to the overall yield obtained in the traditional two-step process where the aldehyde is isolated and purified before the subsequent olefination (Table 1).



Scheme 1 *Reagents*: (a) PCC, celite, CH_2Cl_2, 3 h; (b) filter through SiO_2; (c) $(Ph)_3P{=}CHCO_2CH_3$, reflux, 3 h; (d) PCC, celite, CH_2Cl_2, 3 h, then $(Ph)_3P{=}CHCO_2CH_3$.

Heartened by these results, several additional alcohols were subjected to this tandem procedure. As Table 1 demonstrates, the yields from the new tandem process demonstrated marked improvement over the traditional procedure.

One further variation was then explored to determine if a true one-pot reaction similar to the procedure of Ireland was possible. Benzyl alcohol **1** was treated with PCC/Celite and allowed to react at room temperature (Scheme 1). Once the oxidation was complete, as determined by TLC, the Wittig reagent was added to the reaction mixture and allowed to stir at room temperature.

To our delight, this modified procedure resulted in a 99% yield of ester **3**. Treatment of the alcohols in Table 1 with this new one-pot procedure resulted in excellent yields of the desired esters (Table 1) that were higher than those obtained in either the traditional or tandem methods. Additionally, a benefit to this methodology was the product purification. Simply filtering the reaction through a small plug of silica gel was the only purification required! As expected, the *E*:*Z* ratio of the products obtained by this

Table 1 Yields of Esters Obtained by Traditional, Tandem, and One-pot Oxidation Reactions

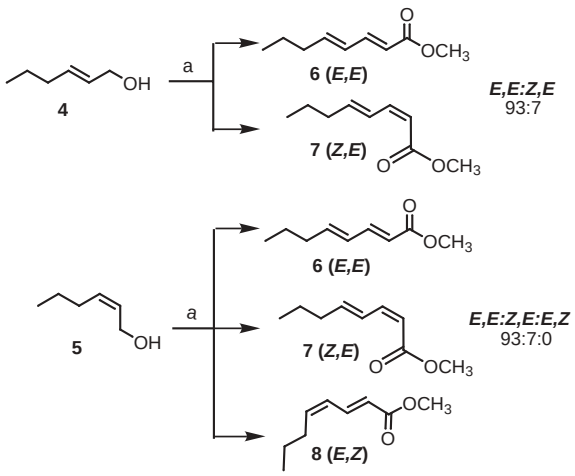
Entry	Alcohol	Yield of ester (%) traditional method[a]	Yield of ester (%) tandem method[b]	Yield of ester (%) one-pot method[b]	*E*:*Z* Ratio[c]
1	Benzyl alcohol	45	92	99	97:3
2	1-Cyclohexylmethanol	5	78	84	95:5
3	1-Butanol	–[d]	51	73	97:3
4	1-Hexanol	–[d]	80	82	97:3
5	3-Methyl-1-butanol	–[d]	67	74	93:7
6	2-Methyl-1-butanol	–[d]	70	78	99:1
7	3-*t*-Butyldimethylsiloxy-1-propanol	45	73	80	95:5
8	(*E*)-2-Hexen-1-ol	15	55	79	93:7
9	(*Z*)-2-Hexen-1-ol	10	50	71	93:7[e]

[a] Normal two-step sequence involving PCC oxidation, aldehyde isolation–purification, then Wittig Olefination.
[b] See notes for detailed experimental procedure.
[c] Determined by GC analysis.
[d] No recovery of starting material or product.
[e] Geometry of the starting alkene was isomerized during the reaction.

one-pot procedure favor the formation of the *E*-isomer. In all cases, the *E*:*Z* ratio obtained using this new method meets, or slightly exceeds the selectivity contained in the literature.[2,7]

Of particular interest are the isomeric allylic 2-hexen-1-ols (Scheme 2). When the *E*-isomer **4** was subjected to the one-pot oxidation–olefination reaction, the *E*,*E*-diene **6** was favored over the *Z*,*E*-diene (93:7), as expected.

When the *Z*-isomer **5** was subjected to the same conditions, a 93:7 mixture of the *E*,*E*-diene **6** and the *E*,*Z*-diene **7** was also recovered. This result suggests isomerization of the alkene contained in alcohol **5** occurred during the reaction.



Scheme 2 One-Pot Oxidation–Olefination of (*E*)- and (*Z*)-2-hexene-1-ol. *Reagents*: (a) PCC, celite, CH_2Cl_2, 3 h then $(Ph)_3P{=}CHCO_2CH_3$.

Earlier studies on the geometric isomerization of allylic alcohols upon oxidation by Prestwich and Xiao gave similar results.[8] They reported that treating *Z*-allylic alcohols with PDC or CrO_3·pyridine gave greater than 50% isomerization. Indeed, upon treatment of alcohol **5** with PCC, we confirmed that isomerization occurred during oxidation, and, proceeded with complete isomerization to yield only the isomerized *E*-α,β-unsaturated aldehyde.[9]

Interestingly, both Prestwich and Taylor demonstrated that using MnO_2 as the oxidant gave products with retention of the *Z*-stereochemistry. Table 2 compares the one-pot results obtained in our labs using PCC and those reported by Taylor using MnO_2.[2] This comparison is noteworthy because it suggests that, for allylic alcohols, the stereochemical outcome of the reaction can be controlled by choice of oxidizing agent. Where retention of the *Z*-stereochemistry is desired, MnO_2 is the preferred oxidizing agent. Conversely, when inversion of the *Z*-stereochemistry is desired, PCC should be used.

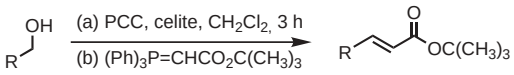
Finally, several alcohols were subjected to the one-pot oxidation–olefination procedure using *t*-butyl (triphenylphosphoranylidene)-acetate as the Wittig reagent

Table 2 Comparison of PCC and MnO_2 with *Z*-2-Hexen-1-ol

Alcohol	Conditions	Yield (%)	*E*,*E*:*E*,*Z*:*Z*,*E*:*Z*,*Z*
5	MnO_2/Wittig (r.t., 2 d)[2]	81	0:90:0:10
5	PCC/Celite (3 h) then Wittig (r.t., 24 h)[a]	71	93:0:7:0

[a] A detailed experimental is given below.

(Scheme 3). Remarkably, the use of this sterically hindered Wittig reagent gave excellent results, with only modest reductions in the yield and *Z*:*E* ratio. This suggests that other stabilized Wittig reagents should be compatible with this new one-pot methodology.



R	Yield (%)	*E*,*E*:*E*,*Z*
Ph	89	91:9
$CH_3CH_2CH_2$	70	90:10
$CH_3CH_2(CH_3)CH$	73	90:10

Scheme 3

In conclusion, we have developed an efficient one-pot process for the oxidation–olefination of alcohols combining PCC and stabilized Wittig reagents.

General Procedure for Tandem Reaction: PCC (1.5 g, 3.5 mmol) and Celite® (1.5g) were added to a dry 100 mL round bottomed flask under N_2. To this mixture CH_2Cl_2 (50 mL) was added and stirred. Benzyl alcohol (0.25 g, 2.3 mmol) was then added dropwise and the mixture was allowed to stir at r.t. until the reaction was complete, as verified by TLC, (usually 2–3 h). An amount of 15 mL Et_2O was added and the solution was vacuum filtered through a fritted funnel charged with ca. 2 inches of silica gel and then washed with 100 mL of a hexane/EtOAc solution (9:1). The solution was transferred to a 250 mL round bottomed flask. To the stirring solution was added methyl (triphenylphosphoranylidene)-acetate (2.15 g, 6.4 mmol). The solution was heated to reflux for 3 h. The reaction was cooled and the solvent was removed by rotary evaporation. The resulting solid was purified by column chromatography.

General Procedure for One-pot Reactions: PCC (29.78 g, 138 mmol) and Celite® (30 g) were added to a dry 500 mL round bottomed flask under N_2. To this mixture CH_2Cl_2 (250 mL) was added and stirred. Benzyl alcohol (10.0 g, 92 mmol) was dissolved in 5 mL CH_2Cl_2 and added dropwise to the reaction mixture, which was then allowed to stir at r.t. until the reaction was complete, as verified by TLC, (usually 2–3 h). Methyl(triphenylphosphoranylidene)acetate (52 g, 156 mmol) was then added and the reaction was allowed to stir at r.t. for 24 h. An amount of 75 mL Et_2O was added to the reaction mixture which was vacuum filtered through a 140 mL fritted funnel charged with ca. 2 inches of silica gel (2/3 full) and rinsed with hexane–EtOAc solution (9:1, 100 mL). The solvent was then removed by rotary evaporation to afford the pure product.

Methyl 3-Phenyl-2-propenoate. ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 7.65 (d, 1 H), 7.35 (m, 5 H), 6.40 (d, 1 H), 3.74 (s, 3 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 167.72, 144.74, 134.43, 130.22, 128.85, 128.10, 117.88, 51.46.

Methyl 3-Cyclohexyl-2-propenoate ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 6.93 (dd, 1 H), 5.74 (dd, 1 H), 3.71 (s, 3 H), 1.49 (m, 11 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 167.20, 154.36, 118.73, 51.21, 40.54, 31.87, 26.09, 25.84.

Methyl 2-Hexenoate ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 6.95 (dt, 1 H), 5.80 (dt, 1 H), 3.70 (s, 3 H), 2.18 (q, 2 H), 1.50 (h, 2 H), 0.93 (ds, 6 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 147.90, 121.35, 96.08, 50.63, 34.07, 21.32, 13.64.

Methyl 2-Octenoate ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 6.98 (dt, 1 H), 5.73 (dt, 5 H), 3.65 (s, 3 H), 2.15 (m, 2 H), 1.31 (m, 2 H), 0.90 (m, 7 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 165.64, 148.52, 121.35, 50.75, 32.26, 31.56, 28.03, 22.64, 14.06.

Methyl 5-Methyl-2-hexenoate ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 6.95 (dt, 1 H), 5.80 (ds, 1 H), 3.70 (s, 3 H), 2.11 (m, 3 H), 0.92 (ds, 6 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 166.87, 148.32, 122.17, 51.19, 35.31, 22.28, 13.87.

Methyl 4-Methyl-2-hexenoate ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 6.85 (dd, 1 H), 5.76 (ds, 1 H), 3.70 (s, 3 H), 2.22 (m, 1 H), 0.92 (ds, 6 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 167.23, 154.61, 119.58, 51.26, 38.30, 28.93, 19.01, 11.58.

Methyl 2-(*E*)-,4-(*E*)-Octadienoate

Starting with 0.25 g of *cis*-2-hexene-1-ol**,** the diene was obtained in a 71% yield. ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 7.23 (dd, 1 H), 6.17 (s, 1 H), 5.91 (s, 1 H), 5.65 (s, 1 H), 3.73 (s, 3 H), 2.09 (m, 2 H), 1.39 (m, 2 H), 0.92 (m, 3 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 167.60, 145.42, 144.48, 128.95, 119.30, 51.39, 35.24, 22.17, 13.75.

Starting with 0.25 g of *trans*-2-hexene-1-ol, the diene was obtained in a 79% yield. ^{1}H NMR (60 MHz, 5% TMS/$CDCl_3$): δ = 7.23 (dd, 1 H), 6.17 (s, 1 H), 5.91 (s, 1 H), 5.65 (s, 1 H), 3.73 (s, 3 H), 2.09 (m, 2 H), 1.39 (m, 2 H), 0.92 (m, 3 H). ^{13}C NMR (14 MHz, 5% TMS/$CDCl_3$): δ = 167.60, 145.42, 144.48, 128.95, 119.30, 51.39, 35.24, 22.17, 13.75.

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References

(1) (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.
(2) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815.
(3) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.
(4) Barrett, A. G.; Hamprecht, D. *J. Org. Chem.* **1997**, *62*, 9376.
(5) Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616.
(6) Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, *14*, 1337.
(7) Patil, V. J.; Mavers, U. *Tetrahedron Lett.* **1996**, *37*, 1281.
(8) Prestwich, G. D.; Xiao, X. *Synth. Commun.* **1990**, *20*, 3125.
(9) Determined by GC.