

Tandem Chlorination - Oxidation - Wittig Reactions: An Efficient Approach to (*Z*)- α -chloro- α,β -unsaturated esters

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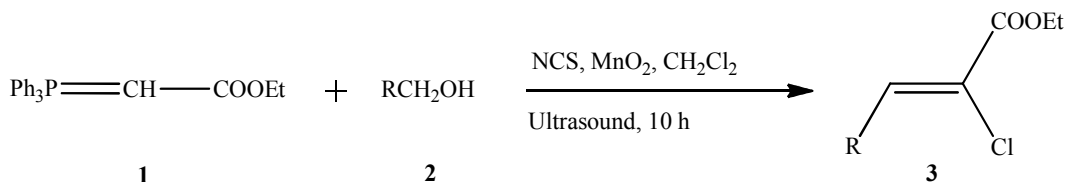
Summary: In this study, a series of the (*Z*)- α -chloro- α,β -unsaturated esters **3** were efficiently prepared in a one-pot sequence. In the presence of *N*-chlorosuccinimide (NCS) and manganese dioxide, under ultrasonication conditions, (carboethoxymethylene)triphenylphosphorane **1** underwent tandem chlorination/oxidation/Wittig olefination sequence with the activated alcohol **2**, to afford (*Z*)- α -chloro- α,β -unsaturated esters in moderate to good yields.

Keywords: Chlorination, Oxidation, Wittig olefination, One-pot Synthesis, Unsaturated esters, Ultrasonication.

Introduction

The Wittig olefination [1-5], for which Wittig was awarded the Nobel prize in chemistry in 1979, is a powerful method for the formation of carbon-carbon double bonds by the reaction of aldehydes, or ketones, with phosphoranes (Wittig reagents). The α -chloro- α,β -unsaturated esters have attracted considerable interest in organic synthesis [6-13] and have been synthesized on a commercial scale for their application in the polymer, food and cosmetic industries and in the medicinal applications such as antihypertensives and calcium channel blockers [14,15]. The α,β -unsaturated esters have been synthesized using several protocols [14-29], most of which are *E*-stereoselective [15]. Recently, we have reported the first general method for preparing (*Z*)- α -chloro- α,β -unsaturated esters by a one-pot chlorination/oxidation/Wittig olefination sequence from alcohols, using the DMSO/SO₃/pyridine complex as the oxidant [30]; this procedure can be applied to both activated and non-activated primary alcohols. We

further investigated this reaction using other selective oxidants, and evaluating *Z*-selectivity. In addition, we reported a one-pot halogenation/oxidation/Wittig olefination sequence (halogen = Br, I) using a selective, cost-effective, and environment-friendly oxidant manganese dioxide (MnO₂) for the synthesis of α -halo- α,β -unsaturated esters (halogen = Br, I) from activated primary alcohols [31, 32]. In this study, we report the applicability of the one pot halogenation/oxidation/Wittig olefination sequence for the preparation of (*Z*)- α -chloro- α,β -unsaturated esters **3** from activated alcohols **2**, using *N*-chlorosuccinimide (NCS) as chlorine source and MnO₂ as the oxidant, Scheme 1. This approach can prevent issues related to the handling of intermediate aldehydes, which are unsuitable substrates difficult to isolate, toxic, volatile, and show proclivity towards hydration, polymerization and oxidation.



Scheme-1: The one-pot preparation of the (*Z*)- α -chloro- α,β -unsaturated esters using NCS and MnO₂.

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Experimental

General Notes

Infrared (IR) were recorded as KBr disc on Perkin Elmer 883 spectrophotometer and data are expressed in wave number (ν cm^{-1}). Nuclear magnetic resonance (NMR) spectra for ^1H and ^{13}C were recorded on JEOL 400 MHz. Chemical shifts are expressed as δ ppm, and coupling constants (J) are given in Hertz. High resolution mass spectra (HRMS) were obtained on a QT of premier (waters) by direct injection of the sample (10 $\mu\text{g}/\text{mL}$) in methanol

General protocol for the one-pot preparation of (Z)- α -chloro- α,β -unsaturated esters.

Into one-necked round-bottom flask containing (carboethoxymethylene)triphenylphosphorane **1** (1.3 mmol), *N*-chlorosuccinimide (1.4 mmol) in dichloromethane (12 mL), alcohol **2** (1 mmol) was added followed by activated manganese dioxide (from Aldrich, 10 mmol). The mixture was sonicated (BANDELIN SONOREX Ultrasonic 33KHz) for 10 h. After that the mixture was filtered through celite to remove the manganese dioxide and washed with dichloromethane. The organic solution concentrated in vacuo and purified via short column chromatography on silica gel to give the product **3**.

(*Z*)-Ethyl-2-chloro-3-phenylpropenoate ^[33] (**3a**). Yield: 77%. Yellow oil. IR (KBr) ν = 3028, 2983, 1725, 1638, 1617, 1493, 1447, 1367, 1263, 1199 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 7.90 (s, 1H), 7.35–7.85 (m, 5H aromatic), 4.36 (q, J = 7.32, 2H), 1.38 (t, J = 7.32, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 163.4, 136.9, 133, 130.7, 128.6, 122.2, 62.6, 14.4, 1.1 ppm. MS (m/z) (%): 235 [$\text{M} + \text{Na}^+ + 2$] (54), 233 [$\text{M} + \text{Na}^+$] (100), 207 (36), 199 (25), 183 (19), 165 (27).

(*Z,Z*,4*E*)-Ethyl-2-chloro-5-phenylpenta-2,4-dienoate ^[34] (**3b**). Yield: 52%. Yellow oil. IR (KBr) ν = 2958, 2924, 1707, 1616, 1261, 1047 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 7.30–7.53 (m, 5H aromatic), 6.88–7.02–7.20 (m, 2H), 4.32 (q, J = 7.32, 2H), 1.33 (t, J = 7.36, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 167.1, 163.0, 144.6, 142.0, 140.4, 137.2, 136.1, 129.1, 128.9, 127.6, 126.3, 123, 122.7, 121.4, 62.3, 60.4, 14.4, 1.1 ppm. MS (m/z) (%): 239 [$\text{M} + \text{H}^+ + 2$] (38), 237 [$\text{M} + \text{H}^+$] (100), 209 (98), 173 (53).

(*Z*)-Ethyl-3-(furan-2-yl)-2-chloro-2-propenoate [35] (**3c**). Yield: 59%. Yellow oil. IR (KBr) ν = 2926, 1726, 1620, 1471, 1259, 1045 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 7.82 (s, 1H), 7.47

(d, J = 4.40 Hz, 1H), 7.28 (d, J = 2.92 Hz, 1H), 6.57 (m, 1H), 4.31 (q, J = 6.60, 2H), 1.36 (t, J = 6.60, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 163.1, 149.3, 144.7, 125.4, 119, 116.8, 112.5, 62.5, 14.3 ppm. MS (m/z) (%): 225 [$\text{M} + \text{Na}^+ + 2$] (46), 223 [$\text{M} + \text{Na}^+$] (100), 203 (12), 201 [M^+] (30), 175. (28), 173 (56), 157 (30), 155 (81).

(*Z,Z*,4*E*)-Ethyl-2-chlorohepta-2,4-dienoate ^[30] (**3d**). Yield: 64%. Yellow oil. IR (KBr) ν = 2964, 1729, 1635, 1262.07, 1098, 1029 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 7.40 (d, J = 10.28, 1H), 6.28–6.50 (m, 2H), 4.29 (q, J = 7.32, 2H), 2.25 (q, J = 7.32, 2H), 1.35 (t, J = 6.6, 3H), 1.07 (t, J = 7.32, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 148.3, 138.1, 124.5, 62.1, 29.7, 26.6, 14.3, 12.8, 1.1, ppm. MS (m/z) (%): 213 [$\text{M} + \text{Na}^+ + 2$] (38), 211 [$\text{M} + \text{Na}^+$] (21), 189 [$\text{M} + \text{H}^+$] (100), 177 (56), 148 (51).

(*Z*)-Ethyl-2-chloro-5-phenylpent-2-ene-4-ynoate ^[33] (**3e**). Yield: 68%. Yellow oil. IR (KBr) ν = 2981, 2927, 2196, 1728, 1602, 1273, 1053 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 7.35–7.53 (m, 5H aromatic), 7.19 (s, 1H), 4.30 (q, J = 6.60, 2H), 1.37 (t, J = 7.32, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 162.1, 132.1, 129.7, 129.4, 128.5, 122.1, 120.1, 119.9, 105.1, 84.5, 77.1, 78.8, 62.7, 60.8, 14.2 ppm. MS (m/z) (%): 237 [$\text{M} + \text{H}^+ + 2$] (15), 235 [$\text{M} + \text{H}^+$] (40), 207 (100), 173 (22), 149 (62).

(*Z*)-Ethyl-2-chlorohept-2-en-4-ynoate ^[30] (**3f**). Yield: 75%. Yellow oil. IR (KBr) ν = 2963, 2218, 1733, 1597, 1261, 1095 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 7.25 (s, 1H), 4.28 (q, J = 7.32, 2H), 2.45 (qd, J = 7.32; 2.2, 2H), 1.31 (t, J = 7.32, 3H), 1.21 (t, J = 7.32, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 162.2, 131.4, 129.3, 126.1, 120.9, 109.2, 75.4, 62.6, 60.6, 14.18, 13.9, 13.4, 1.1 ppm. MS (m/z) (%): 211 [$\text{M} + \text{Na}^+ + 2$] (26), 209 [$\text{M} + \text{Na}^+$] (61), 183 (100), 175 (32), 157 (30), 159 (30).

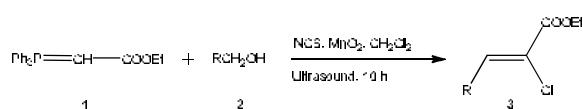
Results and discussion

As a part of our ongoing interest in one-pot procedures [31,32,36,37], which involve the design of the environmentally and economically favored one-pot reactions, our group has recently reported efficient one-pot preparation of (*Z*)- α -chloro- α,β -unsaturated esters through chlorination/oxidation/Wittig olefination cascade. NCS and the DMSO/ SO_3 -pyridine complex were used as the chlorinating agent and oxidant, respectively, and activated alcohols, such as allylic alcohol, propargylic alcohol, and aromatic alcohols, were used as starting compounds as well as alkanols [30]. For further evaluating the one-pot chlorination/oxidation/Wittig olefination sequence, we decided to conduct the one-pot sequential chlorination/

oxidation/Wittig olefination reaction under ultrasound conditions, using MnO_2 as a selective, cost-effective, and environment-friendly oxidant agent for activated alcohols **1**, such as allylic alcohol, propargylic alcohol, and benzylic alcohols, to give (*Z*)- α -chloro- α,β -unsaturated esters **3**, Scheme 1. The yields in these reactions were moderate to good, and the table 1 present the degree of geometrical selectivity of α -chloro- α,β -unsaturated esters thus obtained. It is noteworthy to mention that the presence of an aromatic ring in the substrate enhances the *Z*-stereoselectivity.

The main advantages of using MnO_2 as the selective oxidant are mild conditions and easy work-up. The product is isolated by simple filtration through Celite[®], followed by passing the solution through a short silica-gel column. The *Z* and *E* isomers were not separated in all reactions; however, the *Z/E* ratio was obtained from the integration of the vinylic proton signal: the vinylic proton signal of the isomer *Z* appeared downfield from that of the isomer *E*. The α,β -unsaturated esters were converted to the corresponding alcohols using diisobutylaluminium hydride (DIBAL) in order to determine the stereochemistry of the carbon-carbon double bonds (C=C) in α,β -unsaturated esters. The nuclear Overhauser Effect spectroscopy (NOESY) was performed with the allylic alcohol obtained by the reduction of the corresponding ester. Nuclear Overhauser Effects (NOEs) were observed between the methylic hydrogens and olefinic proton of the alcohol.

Table-1: The one-pot preparation of (*Z*)- α -chloro- α,β -unsaturated esters using NCS and MnO_2 .



Entry	R	Product	Yield (%) ^a	<i>Z/E</i> ^b
1		3a	77	100:0
2		3b	52	100:0
3		3c	59	89:11
4		3d	64	82:18
5		3e	68	90:10
6	$\text{CH}_3\text{CH}_2\text{-C}\equiv\text{C-}$	3f	75	77:22

^aYield was based on alcohols. ^bThe *Z/E* ratio was determined from ¹H-NMR.

Conclusion

In summary, starting from activated alcohols **2**, a series of (*Z*)- α -chloro- α,β -unsaturated esters **3** was successfully prepared by an efficient one-pot sequential chlorination/oxidation/Wittig olefination reaction under ultrasonication conditions.

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