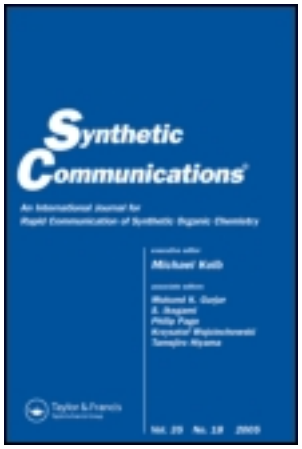


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# One-Pot Combination of the Wittig Olefination with Bromination and Oxidation Reactions

Usama Karama [a], Refat Mahfouz [a], Zeid Al-Othman [a], Ismail Warad [a] & Abdulrahman Almansour [a]

[a] Chemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia

Accepted author version posted online: 10 May 2012.Version of record first published: 21 Dec 2012.

To cite this article: Usama Karama , Refat Mahfouz , Zeid Al-Othman , Ismail Warad & Abdulrahman Almansour (2013): One-Pot Combination of the Wittig Olefination with Bromination and Oxidation Reactions, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:6, 893-898

To link to this article: http://dx.doi.org/10.1080/00397911.2011.614712

*Synthetic Communications*®, 43: 893–898, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.614712

Taylor & Francis
Taylor & Francis Group

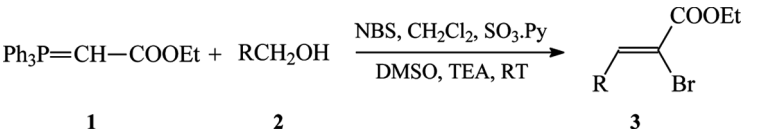


# ONE-POT COMBINATION OF THE WITTIG OLEFINATION WITH BROMINATION AND OXIDATION REACTIONS

**Usama Karama, Refat Mahfouz, Zeid Al-Othman, Ismail Warad, and Abdulrahman Almansour**

*Chemistry Department, College of Science, King Saud University, Riyadh, Kingdom of Saudi Arabia*

## GRAPHICAL ABSTRACT




**Abstract** *A simple one-pot process for in situ bromination of (ethoxycarbonylmethylene)-triphenylphosphorane* ***1*** *was carried out. This was followed by oxidation of alcohol using $SO_3$. Pyridine complex as a mild oxidant and in situ trapping of the aldehyde. This process constitutes a stereoselective one-pot procedure for the preparation of Z-configured -bromo-, -unsaturated esters in good yield.*

**Keywords** Halogenation; olefination; one-pot synthesis; oxidation

## INTRODUCTION

Wittig olefination, which has evolved to include the Horner–Wittig and Horner–Wadsworth–Emmons reaction, is the most powerful and attractive method for the formation of carbon–carbon double bonds[1] and has been widely used in the synthesis of natural products.[2] Recently it was found that alcohols can undergo in situ oxidation–Wittig reaction with phosphonium ylides to give the corresponding olefination products, which have great potential utilities in organic synthesis.[3–7] This one-pot methodology removes the need to isolate the intermediate aldehydes and so is beneficial in terms of time and particularly advantageous if the intermediate aldehydes are unstable, toxic, or difficult to handle. Therefore, one-pot oxidation–Wittig reactions of alcohols to α-bromo-α,β-unsaturated esters is attractive. α-bromo-α,β-unsaturated esters are useful intermediate in organic synthesis[8] and are widely used as precursors for C-C bond formation with conservation of olefin geometry.[9] For example, the synthesis of α-trifluoromethyl-α,β-unsaturated esters,

Received February 28, 2011.

Address correspondence to Usama Karama, Chemistry Department, College of Science, King Saud University, P. O. Box 2455, Riyadh 11451, Kingdom of Saudi Arabia. E-mail: Karama@ksu.edu.sa

building blocks for the preparation of trifluoromethylated biologically active compounds,[10,11] is based on trifluoro-methylation of α-iodo-α, β-unsaturated esters[12] as well α-bromo-α,β-unsaturated esters.[8] They are usually prepared by the Wittig reaction of aldehydes with haloylides[13,14] and condensation of aldehydes with halo-phosphonates in the presence of a base.[15] Recently, we described a one-pot sequential halogenation–oxidation–Wittig reaction using manganese dioxide as the oxidant for reactive alcohol such as aromatic, allylic, and propargylic alcohols to obtain the corresponding α-halo-α,β-unsaturated esters in good yield,[16,17] although this process is limited to activated alcohols. In this article we describe a one-pot procedure to synthesize (Z)-α-bromo-α,β-unsaturated esters from reactive as well as unreactive alcohols.



## RESULTS AND DISCUSSION

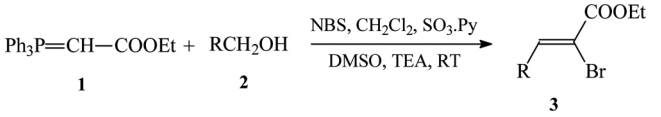
In the framework of our studies on the conversion of multistep reactions into economically and environmentally favored one-pot processes, we attempted to find an alternative system for one-pot halogenation/oxidation/Wittig sequences for activated alcohols as well for alkanols. The in situ halogenations of (ethoxycarbonylmethylene)triphenylphosphorane **1** was reported by Kayser *et al.*[18] We carried out the one-pot halogenation–oxidation–Wittig sequences including Dess–Martin, pyridinium chlorochromate (PCC), PCC-NaOAc, and pyridinium dichromate (PDC) oxidants. Unfortunately, all attempts were unsuccessful. We decided to explore the $SO_3 \cdot$ pyridine complex, a mild, selective, cheap, safe, and easily handled oxidant, as chemoselective oxidant for primary alcohol in the presence of a free secondary or tertiary alcohol.[7] After some experimental work, we were pleased to find that treatment of (ethoxycarbonylmethylene)triphenylphosphorane **1** (1.5 equiv) with N-bromosuccinimide (NBS) (1.5 equiv) in dichloromethane followed by addition of alcohol (1 equiv), $SO_3$ pyridine complex (3 equiv), dimethylsulfoxide (DMSO), and triethylamine afforded the (Z)-α-bromo-α,β-unsaturated esters **3** in good yield and very high stereoselectivity as shown in Table 1. In this procedure the stereoselectivity was almost greater than our recent procedure using $MnO_2$ as oxidant.[16,17] In all reactions, the *E* and *Z* isomers were not separated, but the *Z*/*E* ratios were readily determined by $^1$H NMR spectroscopy. The vinylic protons of *Z* isomer were downfield of the *E* isomer. This assignment was confirmed by nuclear Overhauser effect spectroscopy (NOESY) experiments of the allylic alcohol derived from the corresponding esters by diisobutyialuminumhydride (DIBAL) reduction. NOE effects were observed between the olefinic proton and the methylic hydrogens of the alcohol.

In conclusion we have developed an efficient one-pot procedure for in situ halogenation–oxidation–Wittig reaction for the highly stereoselective synthesis of (Z)-α-bromo-α,β-unsaturated esters from alcohols. This methodology is a safe, economical, and bench-friendly procedure.

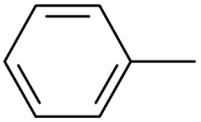
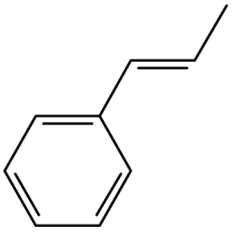
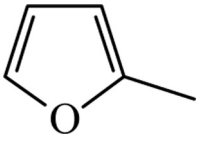
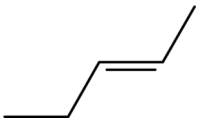
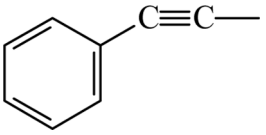
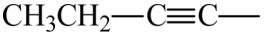
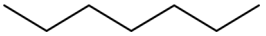
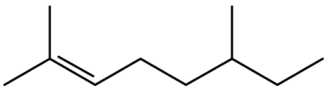
## EXPERIMENTAL

Infrared (IR) spectra were recorded on a Perkin-Elmer 883 spectrophotometer and expressed in $cm^{-1}$ NMR spectra were recorded on a Jeol ECP 400 (400 MHz) instrument in $CDCl_3$. Chemical shifts are expressed as δ in parts per million (ppm),

**Table 1.** One-pot synthesis of (*Z*)-α-bromo-α,β-unsaturated esters




1 2 3

| Entry | R | Product | Yield (%)[a] | Z/E[b] |
|---|---|---|---|---|
| 1 |  | **3a** | 87 | 95:5 |
| 2 |  | **3b** | 55 | 100:0 |
| 3 |  | **3c** | 77 | 100:0 |
| 4 |  | **3d** | 80 | 100:0 |
| 5 |  | **3e** | 85 | 100:0 |
| 6 |  | **3f** | 81 | 82:18 |
| 7 |  | **3g** | 86 | 89:11 |
| 8 |  | **3h** | 76 | 86:14 |

[a]Yields were based on alcohols. [b]This ratio was determined by $^1$H NMR spectroscopy.

and coupling constants (*J*) were given in hertz. Mass (MS) spectra were obtained using electron impact (EI) at 70 eV.

### General Procedure for the Synthesis of (Z)-α-Bromo-α,β-unsaturated Esters

N-Bromosuccinimide (1.5 mmol) was added to a solution of (ethoxycarbonylmethylene)-triphenylphosphorane (1.5 mmol) in 6 mL of $CH_2Cl_2$. After 5 min,

alcohol (1 mmol) in 1 mL of $CH_2Cl_2$ was added followed by $SO_3$ pyridine (3 mmol), 0.8 mL of DMSO, and 1.4 mL of $Et_3N$, and the mixture was stirred for 12 h at room temperature. The reaction mixture was poured on 5% HCl and extracted with $CH_2Cl_2$. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuum to ca. 1–2 ml. The residue was purified by column chromatography on silica gel (petroleum ether–ethyl acetate 15:1).

### (Z)-Ethyl 2-Bromo-3-phenylpropenoate 3a

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$ (t, $J = 7.3$ Hz, 3H); 4.33 (q, $J = 7.3$ Hz, 2H), 7.41–7.45 (m, 3H, arom-H), 7.83–7.85 (m, 2H, arom-H), 8.21 (s, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 14.3$, 62.8, 113.2, 128.2, 128.4, 130.2, 130.3, 140.8, 163.4; IR ($\nu_{max}$, thin film) 2980, 1724, 1610, 1259, 1037, 765; MS (EI), $m/z$ (%) = 256 (54), 254 [$M^+$] (54), 175 (91), 174 (100), 102 (97).

### (2Z,4E)-Ethyl 2-Bromo-5-phenylpenta-2,4-dienoate 3b

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR: $\delta = 1.37$ (t, $J = 7.3$ Hz, 3H), 4.29 (q, $J = 7.3$ Hz, 2H), 7.04 (d, $J = 16.1$ Hz, Hz, $^1$H), 7.16 (dd, $J = 10.3$ Hz, $J = 16.1$ Hz, $^1$H), 7.32–7.39 (m, 3H, arom-H), 7.51–7.53 (m, 2H, arom-H), 7.81 (d, $J = 10.3$ Hz); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 14.3$, 62.5, 114.4, 125.3, 127.5, 127.6, 128.9, 129.7, 141.2, 142.80, 163.1; IR ($\nu_{max}$, thin film) 2980, 1714, 1614, 1583, 1261, 1041, 744; MS (EI), $m/z$ (%) = 282 (26), 282 [$M^+$] (27), 155 (47), 129 (100), 102 (25).

### (Z)-Ethyl 3-(Furan-2-yl)-2-Bromo-3-propenoate 3c

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR: $\delta = 1.33$ (t, $J = 7.3$ Hz, 3H), 4.30 (q, $J = 7.3$ Hz, 2H), 6.54 (m, 1H), 7.42 (d, $J = 3$ Hz, 1H), 7.57 (d, $J = 2$ Hz, 1H), 8.13 (s, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 14.3$, 62.7, 112. 3, 112.5, 116.8, 129.1, 145.1, 150.1, 163.1; IR ($\nu_{max}$, thin film) 2981, 1716, 1249, 1039, 748; MS (EI), $m/z$ (%) = 246 (39), 244 [$M^+$] (38), 165 (58), 137 (100), 92 (30).

### (2Z,4E)-Ethyl 2-Bromohepta-2,4-dienoate 3d

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR: $\delta = 1.04$ (t, $J = 7.3$ Hz, 3H), 1.31 (t, $J = 6.6$ Hz, 3H), 2.22 (quint. $J = 7.3$ Hz, 2H), 4.25 (q, $J = 7.3$ Hz, 2H), 6.32–6.44 (m, 2H), 7.63 (d, $J = 10$ Hz); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 12.8$, 14.3, 29.7, 62.4, 112.17, 126.8, 141.6, 149.2, 163.2; IR ($\nu_{max}$, thin film) 3055, 1726, 1265, 705; MS (EI), $m/z$ (%) = [$M^+$ cannot be detected], 208 (41), 206 (36), 106 (39), 104 (39).

### (2Z)-Ethyl 2-Bromo-5-phenylpent-2-en-4-ynoate 3e

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR: $\delta = 1.34$ (t, $J = 7.3$ Hz, 3H), 4.33 (q, $J = 7.3$ Hz, 2H), 7.29–7.58 (m, 4H,

arom-H), 7.50 (s, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 14.2$, 62.9, 86.4, 104.8, 124.2, 128.6, 129.8, 129.0, 131.9, 132.1, 162.16; IR ($\nu_{max}$, thin film) 2980, 1718, 1265, 738; MS (EI), $m/z$ (%) = 280 (42), 278 [$M^+$] (42), 199 (73), 171 (100), 106 (39), 126 (97).

### (Z)-Ethyl 2-Bromohept-2-en-4-ynoate 3f

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR: $\delta = 1.21$ (t, $J = 8$ Hz, 3H), 1.30 (t, $J = 7.3$ Hz, 3H), 2.44 (dq, $J = 7.3$ Hz, $J = 2.2$ Hz, 2H), 4.27 (q, $J = 7.3$ Hz, 2H, 7.26 (t, $J = 2.2$ Hz, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 13.4$, 14.0, 14.2, 62.8, 109.1, 122.6, 124.44, 125.1, 162.3; IR ($\nu_{max}$, thin film) 2998, 1718, 1265, 740; MS (EI), $m/z$ (%) = 232 (49), 230 [$M^+$] (51), 186 (40), 151 (96), 77 (100).

### (Z)-Ethyl 2-Bromonon-2-enoate 3g

Yellow oil. The spectroscopic data matched that reported in the literature,[17] $^1$H NMR: $\delta = 1.24$ (t, $J = 7.3$ Hz, 3H), 1.27–1.32 (m, 11H), 2.33 (q, $J = 7.3$ Hz, 2H), 4.27 (q, $J = 7.3$ Hz, 2H), 7.27 (t, $J = 7.30$ Hz, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 14.1$, 14.2, 22.5, 27.6, 29.0, 31.6, 32.2, 62.3, 116.3, 146.3, 162.6; IR ($\nu_{max}$, thin film) 2926, 1732, 1259, 1041, 802.

### (Z)-Ethyl 2-Bromonon-5,9-dimethyldeca-2,8-dienoate (3h)

Yellow oil, $^1$H NMR: $\delta = 0.94$ (d, $J = 6.6$ Hz, 3H), 1.21–1.26 (2H, m), 1.32 (t, $J = 7.3$ Hz, 3H), 1.59 (3H, s), 1.69 (3H, s), 1.69–1.74 (1H, m), 2.30–2.35 (1H, m), 4.26 (q, $J = 7.3$ Hz, 2H), 5.08 (t, $J = 7.30$ Hz, 1H), 7.29 (t, $J = 7.30$ Hz, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta = 14.2$, 17.8, 19.8, 25.6, 25.8, 32.1, 36.8, 39.3, 62.4, 117.0, 124.3, 131.7, 145.3, 162.6; HRMS (EI) calcd. for $C_{14}H_{23}O_2Br$ (M+) 302.0881, obsd. 302.0876; IR ($\nu_{max}$, thin film) 3003, 2925, 2871, 1715, 1622, 1259, 1217, 1043, 669.

## ACKNOWLEDGMENT

The authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through Research Group Project No. RGP-VPP-128.

## REFERENCES

1. Maryanoff, B. E.; Reitz, A. B. The Wittig olefination reaction and modifications involving phosphoryl-stabilized carbanions. *Chem. Rev.* **1989**, *89*, 863–927.
2. Nicolaou, K. C.; Haerter, M. W.; Gunzner, J. L.; Nadin, A. The Wittig and related reactions in natural product synthesis. *Liebigs Ann. Recueil* **1997**, 1283–1301.
3. Blackburn, L.; Wei, X.; Taylor, R. J. K. Manganese dioxide can oxidize unactivated alcohols under in situ oxidation–Wittig conditions. *Chem. Commun.* **1999**, 1337–1338.
4. Bressette, A. R.; Glover, L. C. A convenient one-pot PCC oxidation–Wittig reaction of alcohols. *Synlett* **2004**, *4*, 738–740.
5. Wei, X.; Taylor, R. J. K. In situ manganese dioxide alcohol oxidation–Wittig reactions: Preparation of bifunctional dienyl building blocks. *J. Org. Chem.* **2000**, *65*, 616–620.

6. Blackburn, L.; Kanno, H.; Taylor, J. In situ alcohol oxidation–Wittig reactions using *N*-methoxy-*N*-methyl-2-(triphenylphosphoranylidine)acetamide: Application to the synthesis of a novel analogue of 5-oxo-eicosatetraenoic acid. *Tetrahedron Lett*. **2003**, *44*, 115–118.
7. Crisostomo, F.; Carrillo, R.; Martin, T.; Tellado, F.; Martin, V. A convenient and chemoselective one-pot oxidation/Wittig reaction for the $C_2$-homologation of carbohydrate-derived glycols. *J. Org. Chem.* **2005**, *70*, 10099–10101.
8. Zhanh, X.; Qing, F. L.; Yu, Y. Synthesis of 2,3-dideoxy-2-trifluoromethylnucleosides from α-trifluoromethyl-α,β-unsaturated ester. *J. Org. Chem.* **2000**, *65*, 7075–7082.
9. Keiko, T.; Kogen, H. Bis(2,2,2-trifluoroethyl)bromophosphonoacetate, a novel HWE reagent for the preparation of (E)-bromoacrylates: A general and stereoselective method for the synthesis of trisubstituted alkenes. *Org. Lett.* **2000**, *13*, 1975–1978.
10. Wipf, P.; Henningen, T. C.; Geib, S. J. Methyl and trifluoromethyl alkene peptide isosters: Synthesis and evaluation of their potential as β-turn promoters and peptide mimetics. *J. Org. Chem.* **1998**, *63*, 6088–6089.
11. Johnson, T. R.; Silvenman, R. B. Synthesis of (Z)- and (E)-4-amino-2-(trifluoromethyl)-2-butenoic acid and their inactivation of gamma-aminobutyric acid aminotransferase. *Bioorg. Med. Chem.* **1999**, *7*, 1625–1636.
12. Zhang, X.; Zhong, P.; Chen, F. A facile one-pot synthesis of α–iodo-α,β-unsaturated esters. *Synth. Commun.* **2004**, *34*, 1729–1736.
13. Denney, D. B.; Ross, S. T. The preparation and reaction of some halophosphoranes. *J. Org. Chem.* **1962**, *27*, 998–1000.
14. Speziale, A. J.; Ratts, K. W. Reaction of phosphorus compounds v. resonance-stabilized α-halo-methylenephosphoranes. *J. Org. Chem.* **1963**, *28*, 465–469.
15. Zhang, X. G.; Qing, F. L.; Yang, Y.; Yu, J.; Fu, X. K. A new route to α-trifluoromethyl-α, β-unsaturated esters. *Tetrahedron Lett.* **2000**, *41*, 2935–2956.
16. Karama, U. One-pot approach to the conversion of alcohols into α-iodo-α, β-unsaturated esters. *Synth. Commun.* **2010**, *40*, 3447–3451.
17. Karama, U.; Al-Othman, Z.; Al-Majid, A.; Almansour, A. A facile one-pot synthesis of α-bromo-α,β-unsaturated esters from alcohols. *Molecules* **2010**, *15*, 3276–3280.
18. Kayser, M. M.; Zhu, J.; Hooper, D. L. Stabilized haloylides: Synthesis and reactivity. *Can. J. Chem.* **1997**, *75*, 1315–1321.