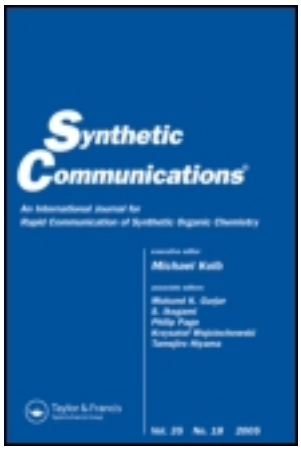

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

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Published online: 17 Aug 2006.

To cite this article: Zhizhen Huang , Lei Wang & Xian Huang (2003) Stereoselective Synthesis of α-Bromo-α,β-unsaturated Ketones via Wittig Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:5, 757-762, DOI: 10.1081/SCC-120016319

To link to this article: http://dx.doi.org/10.1081/SCC-120016319

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SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 5, pp. 757–762, 2003

Stereoselective Synthesis of α-Bromo-α,β-unsaturated Ketones via Wittig Reaction

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ABSTRACT

The synthesis of α-bromo benzoylmethylene triphenylphosphorane **2** is firstly reported and α-bromo ylide **2** has sufficient activity to undergo Wittig reaction, affording a novel method for the stereoselective synthesis of α-bromo-α,β-unsaturated ketones **5**.

Recently it was reported that chalcones had many physiological activities.[1–3] Gasha et al. revealed that α-bromochalcones had even higher physiological activities.[3,4] However, the methods for their synthesis were rarely reported and almost were focused on the dibromonation and dehydrobromination of chalcones.[5,6] It is well-known that Wittig reaction

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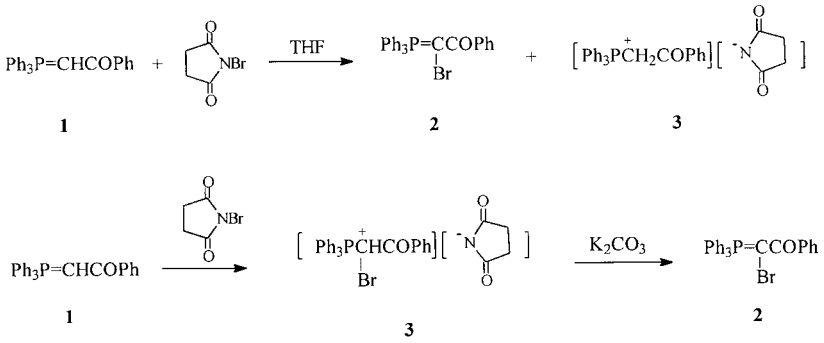
DOI: 10.1081/SCC-120016319 0039-7911 (Print); 1532-2432 (Online)

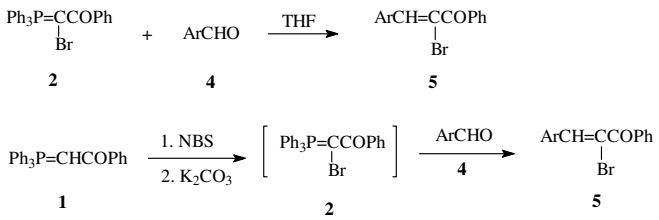
offers an important method for the formation of carbon–carbon double bonds. Therefore we tried to synthesize α-bromo acylmethylene triphenylphosphorane and develop its Wittig reaction for the synthesis of α-bromo-α,β-unsaturated ketones.

Considering benzoylmethylene triphenylphosphorane **1** is a strong nucleophile and bromosuccinimide (NBS) is a good electrophile, we treated them and found the transylidation reaction took place smoothly to give α-bromo benzoylmethylene triphenylphosphorane **2** in the yield of 85% (Method A) (see Sch. 1). However, the transylidation reaction also results in an equimolar side product **3**. We considered that α-hydrogen with an electron-withdrawn group in phosphonium salt **3** had some acidity, the presence of a suitable base in reaction mixture might convert phosphonium salt **3** to phosphorus ylide **2**. Our experimental result shows that phosphorus ylide **1** can react with equimolar NBS to give phosponium salt **3**, which then reacts in situ with potassium carbonate to give α-bromo ylide **2** in the yield of 88% (Method B). As white crystalline, **2** is the first example of α-bromo acylmethylene triphenylphosphorane and can be stored below 0°C for several days.

Further investigation shows that the α-bromo ylide **2** has sufficient activity to undergo Wittig reaction smoothly with aldehydes to form α-bromo-α,β-unsaturated ketones in moderate to good yields (Method A) (see Sch. 2 and Table 1). Since α-bromo ylide **2** is sensitive to air, it is not necessary to isolate the ylide **2** which can react in situ with aldehydes as one-pot reaction, giving bromo-α,β-unsaturated ketones in moderate yields (Method B). It is also noteworthy that this type of Wittig reaction has high stereoselectivity to form *Z*-type of α-bromo-α,β-unsaturated ketones **5** predominantly.



Scheme 1.



Scheme 2.

Table 1. Synthesis of α-bromo-α,β-unsaturated ketones **5**.

Product	Ar	Reaction time (h) Method A (Method B)	Isolated yield (%) Method A (Method B)	Z/E[a]
5a	4-$O_2NC_6H_4$	14 (16)	84 (82)	100/0
5b	4-FC_6H_4	13 (14)	76 (75)	85/15
5c	4-ClC_6H_4	15 (17)	82 (81)	92/8
5d	C_6H_5	15 (16)	73 (71)	91/9
5e	4-MeC_6H_5	19 (22)	81 (78)	100/0
5f	Furyl	16 (19)	63 (61)	100/0

[a]The ratio of Z/E was determined by ^{1}H NMR or GC in Method B.

The present methods have the advantages of mild reaction conditions, simple procedures, good yields and high stereoselectivities, constituting a new stereoselective synthesis of α-bromo-α,β-unsaturated ketones **5**.

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere. Reactions were monitored by TLC. Proton NMR spectra were determined in $CDCl_3$ on a Brucker Advance 400 (400 MHz) with TMS as internal standard. Mass spectra (EI) were obtained on a HP5989B mass spectrometer. Infrared spectra were taken with a Brucker Vector 22 spectrometer. Melting points were uncorrected. Benzoylmethylene triphenylphosphorane **1** was prepared according to the literature method.[7]

Procedure for the Synthesis of α-Bromo Benzoylmethylene Triphenyl Phosphorane 2

Method A

To the solution of benzoylmethylene triphenylphosphorane 1 (3.80 g, 5 mmol) in THF (25 mL), was added dropwise the solution of NBS (0.89 g, 5 mmol) in THF (25 mL) at −20°C. Then the mixture was stirred at room temperature for 10 h and a lot of precipitation was formed. After filtration, the precipitation was washed with ether and extracted with benzene. And the filtrate was evaporated and the residue was also extracted with benzene. Evaporation of combined benzene solution under reduced pressure gave α-bromo benzoylmethylene triphenylphosphorane **2** (1.94 g, 85%).

Method B

To the solution of NBS (0.89 g, 5 mmol) in THF (20 mL), was added dropwise the solution of benzoylmethylene triphenylphosphorane **1** (1.90 g, 5 mmol) in THF (20 mL) at −20°C. The mixture was stirred at this temperature for 30 min and a lot of precipitation was formed. Then potassium carbonate (1.38 g, 10 mmol) was added and the reaction mixture was stirred at room temperature for 5 h. After filtration the precipitation was washed with ether (30 mL × 3) and recrystallized from acetone–hexane to give α-bromo benzoylmethylene triphenylphosphorane **2** (2.01 g, 88%).

Compound 2. M.p. 168–169°C (Lit.[8] 168.5–169.5°C). ^{1}H NMR δ (ppm): 7.43–7.50 (m, 8H), 7.51–7.58 (m, 4H), 7.65–7.70 (m, 9H); IR (cm^{-1}): 1540, 1436, 1139, 692; MS (m/z): 458 (M^+,15), 77 (100).

General Procedure for the Synthesis of α-Bromo-α,β-unsaturated Ketones 5a–f

Method **A**

To the solution of α-bromo benzoylmethylene triphenylphosphorane **2** (0.92 g, 2 mmol) in THF (10 mL), was added aldehyde **4** (2 mmol) at −20°C. The reaction mixture was stirred at this temperature for 30 min and at room temperature for 13–19 h (see Table 1). The solvent was evaporated under reduced pressure and the residue was extracted with hexane–ether (2:1). The extracted solution was concentrated and subjected to preparative TLC (silica gel, hexane–ether as eluent) to give α-bromo-α,β-unsaturated ketones **5a–f**.

Method B

To the solution of NBS (0.36 g, 2 mmol) in THF (20 mL), was added dropwise the solution of benzoylmethylene triphenylphosphorane **1** (0.76 g, 2 mmol) in THF (20 mL) at −20°C and the mixture was stirred at this temperature for 30 min. Then potassium carbonate (0.69 g, 5 mmol) and aldehyde **4** (2 mmol) were added and the reaction mixture was stirred at room temperature for 16–22 h (see Table 1). After filtration the solvent was evaporated under reduced pressure and the residue was extracted with hexane–ether (2:1). The extracted solution was concentrated and subjected to preparative TLC (silica gel, hexane–ether as eluent) to give α-bromo-α,β-unsaturated ketones **5a–f**.

Compound 5a: M.p. 77–78°C (Lit.[9] 76.5–77.5°C). ^{1}H NMR δ (ppm): 8.32–8.27 (m, 2H), 8.04 (d, 1H), 7.97 (d, 2H), 7.90–7.70 (m, 3H), 7.65–7.50 (m, 2H); IR (cm^{-1}): 1662, 1609, 1516, 845; MS (*m*/*z*): 331 (M$^+$, 5), 105 (100).

Compound 5b: Oil. ^{1}H NMR δ (ppm): 8.20–8.15 (m, 2H), 7.93 (*Z*), 6.88 (*E*) (d, $Z+E=1$H), 7.81–7.75 (m, 2H), 7.57–7.48 (m, 3H), 7.15–7.05 (m, 2H); IR (cm^{-1}): 1508, 1240, 734; MS (*m*/*z*): 304 (M$^+$, 4), 225 (26), 105 (100).

Compound 5c: M.p. 69–70°C. ^{1}H NMR δ (ppm): 8.35–8.25 (m, 2H), 7.97 (*Z*), 7.28 (*E*) (d, $Z+E=1$H), 7.88–7.60 (m, 5H), 7.55–7.50 (m, 2H); IR (cm^{-1}): 1659, 1605, 1490, 825; MS (*m*/*z*): 320 (M$^+$, 1), 77 (100).

Compound 5d: M.p. 65–66°C. ^{1}H NMR δ (ppm): 8.15–8.12 (m, 2H), 7.82 (*Z*), 7.18 (*E*) (s, $Z+E=1$H), 7.65–7.59 (m, 2H), 7.51–7.25 (m, 6H); IR (cm^{-1}): 1687, 1601, 1495, 709; MS (*m*/*z*): 286 (M$^+$, 14), 105 (100).

Compound 5e: M.p. 70–71°C. ^{1}H NMR δ (ppm): 8.02 (d, 2H), 7.82 (d, 1H), 7.60–7.45 (m, 5H), 7.30–7.15 (d, 2H), 2.40 (s, 3H); IR (cm^{-1}): 2919, 1599, 1221, 819; MS (*m*/*z*): 302 (M$^+$, 1), 207 (100).

Compound 5f: Oil. ^{1}H NMR δ (ppm): 8.18 (d, 2H), 7.63 (s, 1H), 7.52–7.40 (m, 3H), 6.79 (d, 1H), 6.72 (s, 1H), 6.43 (t, 1H). IR (cm^{-1}): 1679, 1650, 729; MS (*m*/*z*): 276 (M$^+$, 12), 105 (100).

ACKNOWLEDGMENT

We thank the National Natural Science Foundation of China for its financial support of the project 29972036.

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Received in Japan September 14, 2001