Microwave-Assisted Tandem Nucleophilic Substitution–Wittig Reaction of α-Hypervalent Iodine Functionalized Phosphonium Ylide

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Abstract: Under microwave irradiation conditions the tandem nucleophilic substitution-Wittig reaction of α-hypervalent iodine functionalized phosphonium ylide can occur readily to afford α-heteroatom substituted-α,β-unsaturated enoates in good yields stereoselectively.

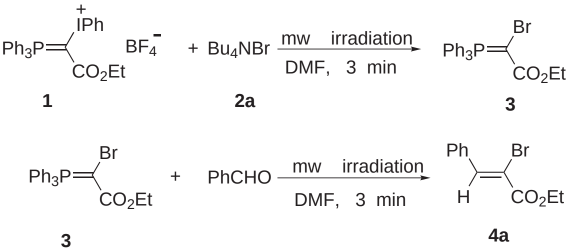
Keywords: microwave irradiation conditions, α-hypervalent iodine functionalized phosphonium ylide, umpolung ylides, tandem reaction

Since the appearance of the first paper[1] on the application of microwave irradiation in organic synthesis, the field has seen a steady growth to the point where a variety of transformations are now possible with microwave heating.[2] Carrying out reactions using microwave irradiation, as opposed to conventional heating, has the major advantage of shorter reaction time.

Our research group has been interested in the application of microwave to organic synthesis for years, and we firstly explored the Wittig reaction under microwave irradiation.[3] Wittig reaction plays an important role in synthetic organic chemistry for the construction of carbon-carbon double bond.[4] The research on α-heteroatom substituted ylide is an important aspect in ylide chemistry.[5] Recently, there are considerable current interest and research activity in hypervalent iodine compounds, which have been demonstrated that hypervalent iodine is a versatile reagent in organic synthesis.[6] When hypervalent iodine group is connected with an unsaturated carbon-carbon bond, the connected carbon can be attacked by nucleophiles.[7] In view of this, the polarity of α-carbon in ylide may be reversed through introducing hypervalent iodine group at α-carbon of an ylide, which enables the umpolung ylide to react with nucleophiles.

Although the synthesis of α-hypervalent iodine functionalized phosphonium ylides have been reported, few applications have appeared.[8] In order to increase the utility of these reagents, now we wish to report the reaction of α-hypervalent iodine functionalized phosphonium ylide under microwave irradiation.

At first we examined the substitution reaction of α-hypervalent iodine functionalized phosphonium ylide (**1**) and Bu_4NBr (**2a**). We optimized the reaction conditions, and the results are summarized in Table 1. Within 3 min the reaction in DMF afforded α-bromosubstituted phosphonium ylide **3** with high yield, so DMF was the optimal solvent.[9] We also observed the Wittig reaction of **3** with benzaldehyde under microwave irradiation conditions to give α-bromo α,β-unsaturated enoates **4a** in 83% yield (Scheme 1). While both of the above reactions were performed under conventional reaction conditions, the reaction times were much longer, i.e. 14 h and 12 h respectively.



Scheme 1

Table 1 The Reaction of α-Hypervalent Iodine Functionalized Phosphonium Ylide with Bu_4NBr under Microwave Irradiation Conditions (3 min)

Solvent	$CHCl_3$	CH_3CN	DMF	C_2H_5OH	C_6H_6
Yield (%)	84	79	94	47	19

We further investigated the reaction of **1** with aldehydes under the same reaction conditions but unfortunately no reaction was observed. Considering the above facts, we designed the following tandem nucleophilic substitution-Wittig reaction (Scheme 2).[10] Under microwave irradiation conditions in DMF the reaction completed in no more than 5 min to give α-halo- α,β-unsaturated enoates **4** stereoselectively with good yields.[11] Although the products can be similarly synthesized under conventional conditions, microwave irradiation conditions significantly reduced the reaction time from hours to several minutes with a slight improvement in the isolated yields. No changes were observed about the effects of microwave irradiation on stereoselectivity. The results of tandem reaction of α-hypervalent iodine functionalized ylide are listed in Table 2.

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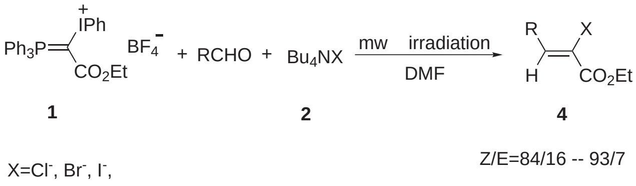
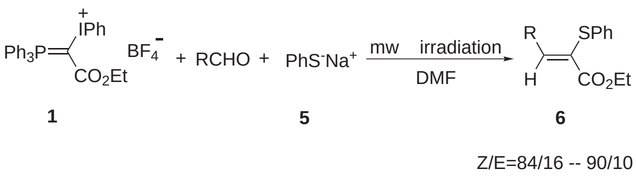


Scheme 2

Thioethers are useful heteroatom functional groups in organic synthesis, and thiophenyl anions are easy available.[12] Thus we used the thiophenyl anion as a nucleophile to the above tandem reaction to develop a methodology for the synthesis of α-thiophenyl-α,β-unsaturated enoates. By similar procedure of adding the solution of thiophenyl sodium in MeOH to a mixture of **1** and aldehydes in DMF under microwave irradiation conditions, we found this procedure occurred smoothly (Scheme 3) and obtained satisfying results (Table 2). These results show that α-hypervalent iodine functionalized phosphonium ylide as umpolung ylide has versatility.



Scheme 3

In conclusion, we have demonstrated a simple and rapid procedure for the synthesis of (*Z*)-α-heteroatom-α,β-unsaturated enoates stereoselectively in moderate to high yields under microwave irradiation conditions through the tandem reaction of nucleophilic substitution-Wittig reaction of α-hypervalent iodine functionalized phosphonium ylide. The present work on umpolung ylides also enriches the contents of ylide chemistry. Further studies on the umpolung ylides and its application in organic synthesis are still in progress in our laboratory.

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Table 2 Results of Tandem Reaction of α-Hypervalent Iodine Functionalized Ylides under Microwave Irradiation

Entry	Nu$^-$	R	Product	Time[a]	Yield (%)[a,b]	Ratio(*Z*/*E*)[b,c]
1	Br$^-$	C_6H_5	**4a**	3 (20)	85 (71)	89:11(89:11)
2	Br$^-$	*p*-$NO_2C_6H_4$	**4b**	2 (8)	97 (97)	86:14 (85:15)
3	Br$^-$	*p*-$CH_3OC_6H_4$	**4d**	5 (24)	78 (70)	90:10 (90:10)
4	Br$^-$	$CH_3CH_2CH_2$	**4e**	5 (32)	76 (67)	89:11 (89:11)
5	Cl$^-$	*p*-ClC_6H_4	**4f**	2 (10)	92 (92)	92:8 (91:9)
6	Cl$^-$	*p*-$NO_2C_6H_4$	**4g**	2 (8)	94 (94)	85:15 (84:16)
7	Cl$^-$	C_6H_5	**4h**	5 (24)	84 (78)	89:11 (89:11)
8	I$^-$	*p*-$NO_2C_6H_4$	**4i**	2 (10)	92 (90)	84:16 (86:14)
9	I$^-$	*p*-ClC_6H_4	**4j**	2 (12)	91 (89)	91:9 (82:8)
10	I$^-$	$CH_3CH_2CH_2$	**4k**	5 (32)	68 (61)	88:12 (88:12)
11	PhS$^-$	*p*-$NO_2C_6H_4$	**6a**	2 (8)	89 (82)	90:10 (91:9)
12	PhS$^-$	C_6H_5	**6b**	3 (19)	81 (74)	84:16 (84:16)
13	PhS$^-$	*p*-ClC_6H_4	**6c**	2 (12)	84 (78)	88:12 (87:13)

[a] The number in brackets refers to conventional heating methods.

[b] Ylides of products based on the aldehyde and the products were identified by mp, ^{1}H NMR, MS, and IR spectra.

[c] Established using ^{1}H NMR.[11]

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(9) **Typical procedure for the synthesis of α-bromo-substituted phosphonium ylide 3 under microwave irradiation conditions:**
To a solution of α-hypervalent iodine functionalized phosphonium ylide in DMF was added Bu$_4$NBr, and the mixture was irradiated in a modified domestic microwave oven (National, power max. 750 W) for 3 min. The reaction mixture was poured into ice-cold water and extracted with benzene (4 × 20 mL), the organic layer was dried with Na$_2$SO$_4$. The solvent was evaporated to obtain a solid. Crystallization of this solid from acetone-hexane gave the pure α-bromosubstituted phosphonium ylide **3**. mp155–156 °C (lit.[13] Mp 157–158 °C)

(10) **General procedure for the synthesis of product under microwave irradiation conditions**:
To a solution of α-hypervalent iodine functionalized phosphonium ylide (2.0 mmol) and aldehyde (2.0 mmol) in anhydrous DMF was added the anions of nuleophiles (2.5 mmol), and the mixture was irradiated in a modified domestic microwave oven for a few minutes. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (3 × 20 mL), the organic layer was dried with Na$_2$SO$_4$. Removal of the solvent followed by column chromatography (ethyl acetate/hexane) of the crude product yielded (*Z*)-α-heteroatom-α,β-unsaturated enoates.
General procedure under conventional conditions:
Under N$_2$, to a solution of α-hypervalent iodine functionalized phosphonium ylide (2.0 mmol) (2.5 mmol) and aldehyde (2.0 mmol) in anhydrous DMF was added the anions of nuleophiles, the mixture was reacted under room temperature for 8–32 hours. After completion of the reaction, the following procedure was the same as above.[14]

(11) The ratio of *Z/E* was determined by the ^{1}H NMR spectra. It was reported that the signal of vinyl and the methyl proton in ester of *Z*-type α-heteroatom substituted-α,-unsaturated enoates were in lower field than that of the corresponding *E* compounds. For example, ^{1}H NMR spectrum shows that the chemical shifts of vinyl and the methyl in ester proton of *Z*-type ethyl 2-bromo-3-(4-methoxyphenyl)-2-propenoate are 7.80 ppm and 1.35 ppm, respectively. While the corresponding chemical shifts of the *E*-type ethyl 2-bromo-3-(4-methoxyphenyl)-2- propenoate compound are 7.07 ppm and 1.23 ppm, respectively.[12] The result is in accordance with our research.

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