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Tandem reaction of α-hypervalent iodo functionalized phosphonium and arsonium ylides as umpolung reagents

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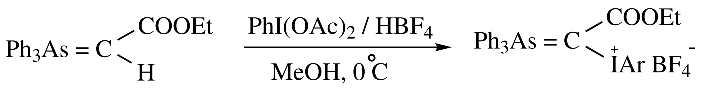
Abstract—α-Hypervalent iodo functionalized phosphonium and arsonium ylides **2** can be used as umpolung ylides to react with nucleophiles to give α-heteroatom substituted ylides **4** in good yields. A tandem sequence of nucleophilic substitution then Wittig reaction occurs smoothly to form (*Z*)-α-halo-α,β-unsaturated esters **6**, stereoselectively, in moderate to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

Since its discovery, the Wittig reaction has remained one of the primary methods for the formation of carbon–carbon double bonds and is widely used in the synthesis of natural products.[1–3] Research on α-heteroatom substituted ylides is a very important aspect in ylide chemistry. Through the Wittig reaction of α-heteroatom substituted ylides, carbon–carbon double bonds can be formed and heteroatoms can be readily introduced to α-position at the same time.[3–7] In general, electrophiles react with ylides and this is the basis for the synthesis of α-heteroatom substituted ylides. However, many electrophiles reacted with ylides are often unstable or difficult to prepare or handle. We considered whether it would be possible to reverse the polarity of the α-carbon in ylides and enable the umpolung ylide to react with a nucleophile, explore and simplify the methods for the synthesis of α-heteroatom substituted ylides and develop ylide chemistry as well.

Recently, hypervalent iodides have been increasingly used in organic synthesis.[8] When a hypervalent iodo group is linked to an unsaturated carbon–carbon bond, the carbon can be attacked by nucleophiles. In view of this we tried to utilize a hypervalent iodo group to reverse the polarity of the α-carbon in an ylide. Although the synthesis of α- hypervalent iodo functionalized phosphonium ylides has been previously reported,[9] their application has not been demonstrated until now. Using a similar protocol, we synthesized the new α-hypervalent iodo functionalized arsonium ylide **2** in a yield of 82% (Scheme 1).

As expected, the polarity of the α-carbon in phosphonium and arsonium ylides **2** has been reversed and they can be reacted with nucleophiles **3**, such as, the bromide, thiophenyl and phenylselenenyl anions (see Table 1). This nucleophilic substitution reaction has the advantages of simpler manipulation and mild reaction conditions over the previous electrophilic protocols, and gives the corresponding α-heteroatom substituted ylides **4** in good yields (Scheme 2).

Compared with their precursors, the nucleophilicity of the phosphonium or arsonium ylides **2** has been decreased dramatically. Experiments showed that phosphonium or arsonium ylides **2** do not undergo the Wittig reaction with benzaldehyde. Therefore, we added



$$Ph_3As=C\begin{smallmatrix}COOEt\\H\end{smallmatrix}\ \xrightarrow[\text{MeOH, }0^{\circ}C]{PhI(OAc)_2\,/\,HBF_4}\ Ph_3As=C\begin{smallmatrix}COOEt\\\overset{+}{I}Ar\ BF_4^-\end{smallmatrix}$$

1 **2**

Scheme 1.

Keywords: umpolung reagent; nucleophilic substitution; Wittig reaction; tandem reaction; synthesis.

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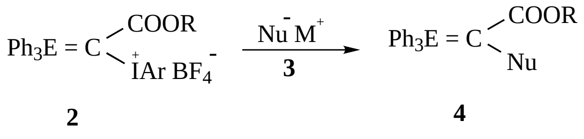
Table 1. Nucleophilic substitution reactions of ylides **2**

E	R	NuM	Yield of **4** (%)[a]
P	C_2H_5	C_6H_5SH	84
P	C_2H_5	C_6H_5SeNa	85
P	C_2H_5	n-Bu_4NBr	81
As	CH_3	C_6H_5SH	86
As	C_2H_5	4-$CH_3C_6H_4SH$	80
As	CH_3	C_6H_5SeNa	70

[a] The structures of the products were confirmed by ^1H NMR, IR and MS spectroscopy.



E = P, As NuM = n-Bu_4NBr, PhSNa, PhSeNa

Scheme 2.

the aldehydes **5** to the reaction mixture of phosphonium or arsonium ylides **2** with the nucleophiles. Fortunately, the tandem nucleophilic substitution–Wittig reaction can be carried out smoothly to form the desired (*Z*)-α-halo-α,β-unsaturated esters **6** stereoselectively.[10] The yields of the tandem reaction are higher than that of two-step reactions of substitution and Wittig reaction (Scheme 3, Table 2).

In conclusion, this new type of tandem reaction can afford (*Z*)-α-halo-α,β-unsaturated esters **6**, stereoselectively, in moderate to excellent yields via the umpolung ylides **2**. Compared with the previous method, the synthesis is simpler and yields are higher. The discovery of umpolung ylides **2** should enrich ylide chemistry. Further research on the application of this type of umpolung ylides in organic synthesis is in progress now.

Acknowledgements

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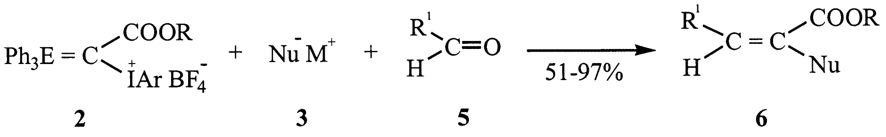
References

1. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
2. Cristau, H. *Chem. Rev.* **1994**, *94*, 1299–1314.
3. Johnson, A. W.; Kaska, W. C.; Starzewsky, K. A. O.; Dixon, D. *Ylides and Imines of Phosphorus*; Wiley: New York, 1993; pp. 587–621.
4. Speziale, A. J.; Ratts, W. *J. Am. Chem. Soc.* **1963**, *85*, 2790–2795.
5. Seyferth, D.; Worthorn, K. R.; Lin, J. F.; Sepalak, D. J. *J. Organomet. Chem.* **1979**, *181*, 293–304.
6. Mukaiyama, T.; Fukuyama, S.; Kimamoto, H. *Tetrahedron* **1988**, *44*, 633–656.
7. Huang, Z. Z.; Huang, X.; Huang, Y. Z. *Tetrahedron Lett.* **1995**, *36*, 425–426.
8. Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178.
9. Rorber, M. M.; Indra, P.; Wade, A. F. *J. Am. Chem. Soc.* **1984**, *106*, 6082–6084.



E = P, As

Z/E = 85/15-91/9

Scheme 3.

Table 2. Tandem reaction of umpolung ylides **2** to give alkenes **6**

E	NuM	R	R^1	Yield[a] (%)	Z/E[b]
P	n-Bu_4NCl	C_2H_5	4-ClC_6H_4	93	85/15
P	n-Bu_4NCl	C_2H_5	$CH_3CH_2CH_2$	55	89/11
P	n-Bu_4NBr	C_2H_5	4-$NO_2C_6H_4$	97	86/14
P	n-Bu_4NBr	C_2H_5	4-FC_6H_4	92	91/9
P	n-Bu_4NBr	C_2H_5	$CH_3CH_2CH_2$	60	89/11
P	n-Bu_4NI	C_2H_5	4-$CH_3OC_6H_4$	87	83/17
As	n-Bu_4NBr	CH_3	4-$Cl_2C_6H_4$	81	91/9
As	n-Bu_4NBr	CH_3	4-$NO_2C_6H_4$	74	85/15
As	n-Bu_4NI	CH_3	4-ClC_6H_4	75	90/10

[a] The structures of the products were confirmed by ^1H NMR, IR and MS spectroscopy.

[b] The Z/E ratios were determined by ^1H NMR or GC. The ^1H NMR spectra of the known α-halo-α,β-unsaturated esters and empirical formulae show that the chemical shift of the vinyl proton in (*Z*)-α-halo-α,β-unsaturated ester is larger than that of the *E*-isomer. For example, the chemical shifts of the vinyl protons in ethyl (*Z*)- and (*E*)-α-bromocinnamate are 8.13 and 7.37 ppm, respectively.[11] Thus, we assigned the configuration of the α-halo-α,β-unsaturated esters **6** by the comparison of the ^1H NMR data with known ^1H NMR data[12] or empirical formulae.

10. Tandem reaction of umpoled ylides **2** for the stereoselective synthesis of (*Z*)-α-halo-α,β-unsaturated esters **6**: The mixture of α-hypervalent iodo functionalized phosphonium or arsonium ylides **2** (2 mmol), tetrabutylammonium halide **3** (2 mmol) and aldehyde **5** (2 mmol) in CH_2Cl_2 (20 ml) was stirred at room temperature for 8–48 h. After the reaction was complete, the organic phase was washed with water (10 ml×2) and dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by preparative TLC (silica gel, hexane–ethyl acetate as eluent) to give α-halo-α,β-unsaturated esters **6**.
11. (a) Kopping, B.; Chatgillialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* **1992**, *57*, 3994–4000; (b) Bellina, F.; Carpita, A.; Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029–12046.
12. (a) Huang, Y. Z.; Shi, L. L.; Li, S. W.; Huang, R. *Synth. Commun.* **1989**, *19*, 2639–2646; (b) Zheng, Q. G.; Fu, W. Y.; Chen, B. C.; Huang, X. *Youji Huaxue* **1988**, *8*, 661–664; (c) Huang, Z. Z.; Wu, L. L.; Zhu, L. L.; Huang, X. *Synth. Commun.* **1996**, *26*, 677–682.