

Improved *E*-Selectivity in the Wittig Reaction of Stabilized Ylides with α -Alkoxyaldehydes and Sugar Lactols

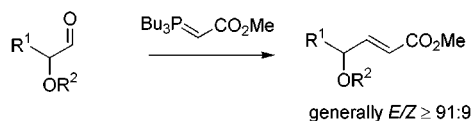
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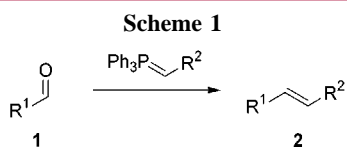
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ABSTRACT



The Wittig reactions of α -alkoxyaldehydes and sugar lactols with stabilized ylides such as (alkoxycarbonylmethylene)triphenylphosphoranes typically proceed with low *E*-selectivities. However, we have discovered that the reaction of such aldehydes with (methoxycarbonylmethylene)-tributylphosphorane in toluene in the presence of catalytic amounts of benzoic acid proceeds to give the *E*- α,β -unsaturated esters with high selectivities and in high yields.

The Wittig reaction of aldehyde **1** with a phosphorus ylide is one of the most commonly used constructions for forming substituted olefins **2** (Scheme 1). When stabilized ylides (R^2

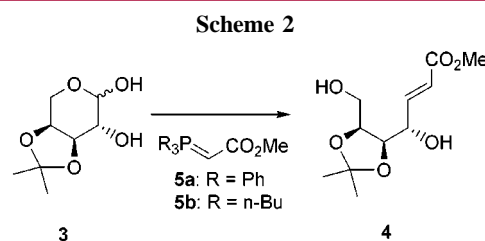


= EWG) are employed for the preparation of α,β -unsaturated carboxylic acid derivatives **2** ($R^2 = \text{EWG}$), the products are generally obtained with very good levels of *E*-selectivity.¹ However, such reactions with protected or unprotected α -alkoxyaldehydes, especially those derived from carbohydrates and sugar lactols, appear anomalous as they typically proceed with low selectivities. Indeed, the reactions are oftentimes *Z*-selective.

Despite the longstanding nature of this problem, no general solution has been described. The use of nonpolar solvents and elevated temperatures² or catalytic amounts of a car-

boxylic acid³ have been observed to increase the *E*-selectivity in certain cases. Protic solvents on the other hand appear to promote *Z*-selective olefinations in some cases. The *E*-selective Knoevenagel condensation and Horner–Wadsworth–Emmons reaction cannot be applied to sugar lactols, since the basic conditions often lead to racemization or cyclization of the initially formed hydroxyenoates.

In the course of our studies toward the synthesis of the solandelactone oxylipins,⁴ it was necessary to convert the arabinose derivative **3** to the α,β -unsaturated ester **4** (Scheme 2). However, when **3** was subjected to standard Wittig



conditions with the triphenylphosphorane **5a**, a 50:50 mixture of geometric isomers of **4** was isolated in moderate yield.

(1) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, 89, 863–927.

Changes in solvent or temperature had little effect upon the product ratio (Table 1, entries 1–3), but adding benzoic acid

Table 1. Wittig Reactions of Lactol **3**

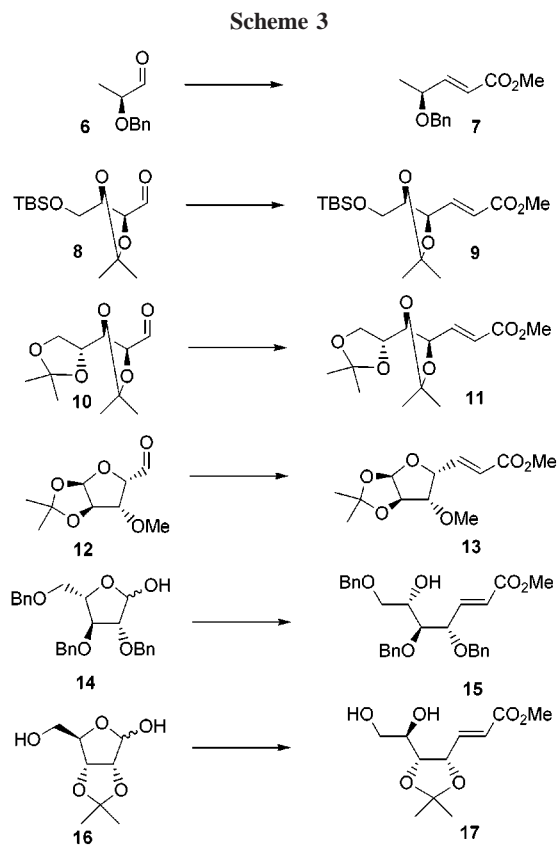
entry	ylide	solvent	equiv of acid	temp (°C)	% yield (<i>E/Z</i>) ⁶
1	5a	CH ₂ Cl ₂		rt	59 (40:60)
2	5a	toluene		90	55 (50:50)
3	5a	DME		90	50 (40:60)
4	5a	toluene	0.05	90	70 (78:22)
5	5a	toluene	0.20	90	48 (82:18)
6	5a	toluene	0.50	90	49 (75:25)
7	5b	toluene	0.20	90	78 (91:9)

improved the *E/Z* ratio to 82:18 (entries 4–6). After some experimentation, we discovered that using the tributylphosphorane **5b**⁵ instead of **5a** and catalytic amounts of benzoic acid significantly increased the selectivity (*E/Z* = 91:9) and the yield of the reaction (78%) (entry 7). Pure **4** was readily obtained by recrystallization.

The increased *E*-selectivity in reactions of nonstabilized and semistabilized tributylphosphoranes with aldehydes has been reported.⁷ It is also known that replacing the aryl rings on the phosphorus atom of stabilized ylides with alkyl groups can lead to increased *E*-selectivity in reactions with benzaldehyde.⁸ However, the utility of stabilized tributylphosphoranes as reagents for *E*-selective olefinations has not been generally established. Tributylphosphoranes are known to be

more nucleophilic than the corresponding triarylphosphoranes, thus possibly explaining the increased yields.⁹

To define the scope and limitations of this improved methodology, we examined the reactions of a variety of α -alkoxyaldehydes and sugar lactols with **5b** (1.3 equiv) in the presence of benzoic acid (20 mol %) under standard conditions (Scheme 3).¹⁰ We specifically selected those



substrates whose reactions with **5a** under standard conditions were known from the literature to proceed with low *E*-selectivity.

(2) Valverde, S.; Martin-Lomas, M.; Herradon, B.; Garcia-Ochoa, S. *Tetrahedron* **1987**, *43*, 1895–1901.

(3) The basis for the effect, which has been known for some time, of carboxylic acids upon Wittig reactions of stabilized ylides is not well understood. See: (a) Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Theaker, P. D. *Carbohydr. Res.* **1974**, *38*, C22–C24. (b) Corey, E. J.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3463–3466. (c) Marriott, D. P.; Bantick, J. R. *Tetrahedron Lett.* **1981**, *22*, 3657–3658. (d) Mulzer, J.; Kappert, M. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 63–64.

(4) Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Kwon, B.-M.; Bok, S.-H.; Song, J.-I. *Tetrahedron* **1996**, *52*, 10583–10596.

(5) Bu₃P=CHCO₂Me was freshly prepared from the corresponding phosphonium bromide as a toluene solution according to Aspinall, I. A.; Cowley, P. M.; Mitchell, G.; Raynor, C. M.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2591–2599.

(6) *E/Z* ratios were determined of the crude product by ¹H NMR. All yields are of the pure *E/Z* mixture after chromatography.

(7) (a) Meyers, A. I.; Lawson, J. P.; Carver, D. R. *J. Org. Chem.* **1981**, *46*, 3119–3132. (b) Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821–5823. (c) Linderman, R. J.; Meyers, A. I. *Heterocycles* **1983**, *20*, 1737–1740. (d) Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948–3958. (e) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723–2728.

(8) Bissing, D. E. *J. Org. Chem.* **1965**, *30*, 1296–1298.

(9) Johnson, A. W.; LaCount, R. B. *Tetrahedron* **1960**, *9*, 130–138.

(10) **Typical procedure:** A solution of tributyl(methoxycarbonylmethylene)phosphonium bromide (17.8 g, 50.0 mmol) in CH₂Cl₂ (60 mL) was washed with aqueous NaOH (1 M, 2 × 50 mL), dried (MgSO₄), and diluted with toluene (50 mL). The CH₂Cl₂ was successively evaporated. This solution was then added to a stirred solution of **3** (7.60 g, 40.0 mmol) and benzoic acid (976 mg, 8.00 mmol) in toluene (200 mL) at 90 °C. After 10 min the solvent was evaporated, and the residue was purified by flash chromatography with hexanes/EtOAc (1:1 → 1:2) to give 7.71 g (78%) of **4** (*E/Z* = 91:9) as a pale yellow solid.

(11) All reactions were run according to the conditions given for the typical procedure.¹¹ *E/Z* ratios were determined from the crude reaction product by ¹H NMR. All yields are of the pure *E/Z* mixture after chromatography.

(12) Prepared in one step (90% yield) from L-arabinose: Perigaud, C.; Gosselin, G.; Imbach, J.-L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1943–1952.

(13) Prepared in two steps (67% yield) from (*S*)-ethyl lactate: Enders, D.; Jandeleit, B.; von Berg, S. *J. Organomet. Chem.* **1997**, *553*, 219–236.

(14) Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 491–502. The reaction of **6** with **5a** in MeOH provides **7** in 81% yield (*E/Z* = 20:80), see ref 2.

(15) Prepared in two steps (78%) from 2,3-*O*-isopropylidene-D-threitol: Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337–3342.

(16) Prepared in one step (44%) from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol: Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 3586–3588.

(17) Horton, D.; Machinami, T.; Takagi, Y. *Carbohydr. Res.* **1983**, *121*, 135–161. The reaction of **10** with **5a** in MeOH provides **11** in 70% yield (*E/Z* = 12:88), see ref 2.

(18) Prepared in two steps (68%) from 1,2:5,6-di-*O*-isopropylidene- α -D-glucufuranose: Kovár, J.; Baer, H. H. *Can. J. Chem.* **1973**, *51*, 1801–1811.

(19) Tronchet, J. M. J.; Gentile, B. *Helv. Chim. Acta* **1979**, *62*, 2091–2098. The reaction of **12** with **5a** in MeOH provides **13** in unknown yield (*E/Z* = 8:92).

(20) Prepared in three steps (33%) from L-arabinose: Tejima, S.; Fletcher, H. G., Jr. *J. Org. Chem.* **1963**, *28*, 2999–3004.

(21) For the *tert*-butyl ester: Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102–3104.

Table 2. Wittig Reaction of α -Alkoxyaldehydes and Sugar Lactols with (Methoxycarbonylmethylene)tributylphosphorane (**5b**)^{10,11}

aldehyde or lactol	olefin	% yield (<i>E/Z</i>)	% yield (<i>E/Z</i>) with 5a
3 ¹²	4	78 (91:9)	55 (50:50)
6 ¹³	7	94 (95:5)	70–75 (63:37) ¹⁴
8 ¹⁵	9	83 (92:8)	87 (68:32) ¹⁵
10 ¹⁶	11	73 (95:5)	47 (75:25) ¹⁷
12 ¹⁸	13	80 (91:9)	NA (80:20) ¹⁹
14 ²⁰	15	95 (91:9)	92 (40:60) ²¹
16 ²²	17	64 (67:33)	65 (38:62) ²³

The results of these experiments together with the literature data for the reactions of these aldehydes with **5a** are summarized in Table 2. The *E*-selectivities in the olefinations of all substrates except **16** with **5b** were dramatically higher

(22) Prepared in one step (68%) from D-ribose: Kaskar, B.; Heise, G. L.; Michalak, R. S.; Vishnuvajjala, B. R. *Synthesis* **1990**, 1031–1032.

(23) Herrera, F. J. L.; Gonzalez, M. S. P. *Carbohydr. Res.* **1986**, *152*, 283–291.

than those reported in the literature; the yields were also generally higher. Simple substrates such as the lactate **6** underwent olefination with excellent *E*-selectivities (*E/Z* = 95:5). The ketal and silyl protecting groups in aldehydes **8**, **10**, and **12** were stable to the reaction conditions, although the ketal protecting group in the ribose derivative **16** proved somewhat labile. Prior protection of the primary hydroxyl group in **16** with *tert*-butyldiphenylsilyl chloride had no effect on the *E/Z* ratio.

In conclusion, we have developed a useful method for transforming α -alkoxyaldehydes and sugar lactols to α,β -unsaturated esters in good yields and *E*-selectivities. Thus, this protocol nicely complements the known *Z*-selective conditions for the Wittig reactions of these aldehydes with stabilized phosphoranes.¹

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