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Tetrahedron Letters 45 (2004) 3925–3928
Tetrahedron Letters

(*E*)-Selective Wittig reactions of Garner's aldehyde with nonstabilized ylides

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Received 4 March 2004; revised 16 March 2004; accepted 18 March 2004

Abstract—In the Wittig olefination reactions of Garner's aldehyde with certain nonstabilized ylides, the (*E*)-alkenes could be produced as a major product by simply quenching the reactions with a large excess of MeOH at −78 °C. Even under the salt-free conditions, more than a 10:1 ratio of the (*E*)- to (*Z*)-alkene was resulted consistently from the ylides of a linear alkyl chain. Without addition of MeOH, usual selectivity for the (*Z*)-alkene was obtained in a ratio of 94:6.

Since the first report on Garner's aldehyde **1** (Fig. 1),[1] it has been extensively used as a chiral building block in asymmetric synthesis.[2] The Wittig olefination reactions of **1** among others have provided the intermediates for various biologically active compounds such as sphingosine, phytosphingosine, curacin A, and their stereoisomers.[3,4] β,γ-Unsaturated-α-amino acids **2** also have been prepared from **1**.[5] Recently there has been considerable interest in **2** because of their biological activity as irreversible enzyme inhibitors or mechanistic probes for some enzymes.[6,7] They can also serve as conformationally restricted analogues of naturally occurring amino acids and offer insight into the biologically active conformation of such molecules when incorporated into peptides.

The Wittig reaction of **1** with nonstabilized ylides has been well known to give the (*Z*)-olefins as a major product.[2,8] The (*E*)-olefins can become a major product by following the Schlosser modification of the Wittig reaction although a strong base is required and the original recipe should be strictly followed in order to obtain a reliable and excellent (*E*)-stereoselectivity.[9] We learned, however, that quite a good selectivity for the (*E*)-alkenes could be obtained just by adding an excess of methanol at low temperature at the end of the usual Wittig reactions with nonstabilized ylides while we were working on the diastereoselective dihydroxylation reactions of olefins.[10] Anderson and Henrick reported an increased selectivity for an (*E*)-alkene ((*E*):(*Z*) = 3:1) with BuLi and MeOH and 80–90% (*E*)-selectivity was considered to be maximal with the reagents.[11a] There have been several scattered reports on the increased ratio for (*E*)-alkenes using the similar procedure but the selectivity was not high enough to be useful.[11] In addition, the (*E*)-alkenes in the present study were obtained as a major under the salt-free conditions that normally favor the formation of the (*Z*)-alkenes. We herein wish to report a simple procedure to obtain the (*E*)-alkenes in a high selectivity from the Wittig olefination reactions of **1**, a versatile chiral synthon, with nonstabilized ylides, and its scope and limitations.

In the beginning, butyltriphenylphosphonium bromide was used for screening of the reaction conditions (R = propyl in Scheme 1, see Representative procedure

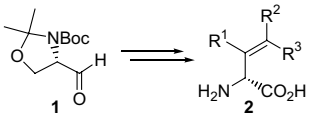
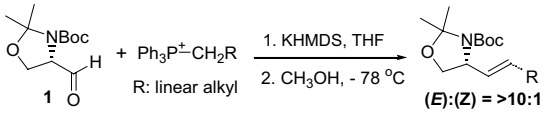


Figure 1.



Scheme 1. The (*E*)-selective Wittig reactions of **1**.

Keywords: (*E*)-Olefination; Wittig reaction; Garner's aldehyde.
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doi:10.1016/j.tetlet.2004.03.101

for details). A solution of **1** in THF was added to the ylide at −78 °C that was generated using KHMDS. After the reaction was completed, an excess of methanol was added to the reaction mixture at −78 °C and then the resulting mixture was warmed to room temperature. The crude product after the usual work-up procedure was characterized with gas chromatography (G/C) and the ^{1}H NMR spectrum. The (*E*)-alkene showed a typical larger olefinic coupling constant ($J = 15$ Hz) than that of the (*Z*)-alkene ($J = 11$ Hz). For comparison, the alkene sample containing a 97:3 ratio of the (*E*):(*Z*) mixture was prepared independently by the Schlosser modification.[9]

First, the effect of amount of methanol on the (*E*)- to (*Z*)-selectivity of the olefin is shown in Table 1. It seems critical for the selectivity how much methanol is used. A large excess of methanol should be used in order to secure the high selectivity for the (*E*)-alkene. Addition of just 1 equiv of MeOH did not nearly change the selectivity and the usual high (*Z*)-selectivity was obtained without addition of methanol. Addition of more than 20 mL of MeOH did not look practical in terms of a reaction scale. The same high selectivity (93:7) was observed when a reduced amount of the reaction solvent and MeOH was used (5 mL of THF and 5 mL of MeOH; not shown).

Next, a different type of alcohols was examined (Table 2). MeOH is the most effective for the (*E*)-alkene among alcohols used. Effect of water was studied as a mixture with MeOH because water alone was frozen when added at −78 °C. Water appears to erode the (*E*)-selectivity because the higher selectivity was observed with 5 mL of MeOH only (Table 2, entry 4 vs Table 1, entry 3).

We have also studied the nature of the proton in the additive added to the reaction mixture (Table 3). A couple of other additives could result in an increase of the (*E*)-selectivity as well. The presence of an acidic proton does not look the only factor to affect the selectivity but also the structure of the additive is important. It is interesting to note a little higher selectivity for the (*E*)-alkene with ethanethiol, compared to that with ethanol (Table 2, entry 2 vs Table 3, entry 2). However, it is still lower than that with MeOH (Table 1, entry 3 vs Table 3, entry 2) based on the amount of the additives used. It is anyhow more practical to use easily available and comfortable MeOH to work with.

The presence of a Li^+ salt is known to increase the formation of (*E*)-alkenes in the Wittig olefination reactions with nonstabilized ylides.[8] The Li^+ salt is also crucial in the Schlosser modification.[9] We therefore expected the better selectivity for the (*E*)-alkene by replacing the potassium base in the model Wittig reactions with a lithium base and/or by addition of a lithium salt in the reaction mixture. As shown in Table 4, however, the Li^+ salts have no effect on the (*E*)-selectivity at all.

With the above results in hand, we have tried to extend this method to other nonstabilized ylides using the same reaction conditions (Table 5). The (*E*)-selectivity with those of a linear alkyl chain is quite good but the olefination reaction with the ylide having a branch is poor (entry 5). Benzylphosphonium ylide, a semi-stabilized

Table 1. Effect of the amount of MeOH on the (*E*):(*Z*)-selectivity[a]

Entry	Amount of MeOH	Ratio ((*E*):(*Z*))	Yield (%)
1	20 mL	95:5	70
2	10 mL	93:7	70
3	5 mL	91:9	72
4	1 mL	73:27	74
5	1 equiv	7:93	82
6	none	6:94	80

[a] All the reactions in the present study were performed with the same reaction scale as shown in Representative procedure (ca. 0.1 M).

Table 2. Effect of the type of alcohols on the (*E*):(*Z*)-selectivity[a]

Entry	Alcohol (10 mL)	Ratio ((*E*):(*Z*))	Yield (%)
1	MeOH	93:7	70
2	Abs EtOH	82:18	68
3	*i*-PrOH	25:75	76
4	MeOH:H_2O (1:1)	86:14	68

[a] About 0.1 M of the reaction concentration.

Table 3. Effect of the type of protons in the additive

Entry	Additive (10 mL)	Ratio ((*E*):(*Z*))	pK_a (DMSO)[12]
1	MeOH	93:7	29
2	EtSH	88:12	ca. 18[b]
3	Phenol[a]	68:32	18.0
4	*i*-PrNH_2	6:94	ca. 44[b]
5	CH_3NO_2	7:93	17.2

[a] A solution of phenol (5 g) in THF (5 mL).
[b] Estimated value.

Table 4. The Wittig reactions with different base and LiBr

Entry	Base	Added salt	MeOH (mL)	Ratio ((*E*):(*Z*))
1	KHMDS	None	10	93:7
2	KHMDS	LiBr (1 equiv)	10	93:7
3	BuLi	None	10	93:7
4	BuLi	LiBr (1 equiv)	10	93:7
5	NaHMDS	None	10	93:7

Table 5. The Wittig reactions with several nonstabilized ylides

Entry	R ($Ph_3P^+CH_2R$)	Ratio ((*E*):(*Z*))	Yield (%)
1	CH_3	95:5[a]	48
2	C_3H_7	93:7[a]	70
3	C_8H_{17}	95:5[b]	81
4	$C_{11}H_{23}$	93:7[b]	70
5	$CH(CH_3)_2$	32:68[b]	65

[a] Determined by G/C.
[b] Determined by ^{1}H NMR.

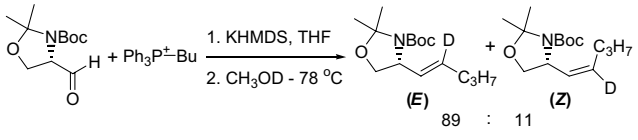
ylide, gave poor (*E*)-selectivity, too ((*E*):(*Z*) = 1:2.4, not shown).

Then, we have applied the method to other aldehydes. We could obtain the satisfactory (*E*)-selectivity (>9:1) with a couple of aldehydes such as *N*-Boc-L-prolinal and 2,3-di-*O*-isopropylidine-D-glyceraldehyde but the procedure was not so effective to yield useful (*E*)-selectivity for aliphatic aldehydes.

In an effort to elucidate the origin of the present results, addition of methanol-*d* (CH_3OD) instead of CH_3OH resulted in the product having most of the deuterium incorporated into the double bond (Scheme 2) albeit with somewhat lower selectivity ((*E*):(*Z*) = 89:11). Apparently, an isomerization process occurs through the deprotonation and protonation steps after addition of methanol at −78 °C before the reaction intermediate collapses to give the olefin product and phosphine oxide.

The isomerization process seems to occur very fast during the warm-up process because the reaction time up to 3 h at −78 °C after addition of methanol did not affect the selectivity. It did not take place either without addition of methanol (Table 2, entry 6) or with addition of methanol after warming the reaction mixture to room temperature. Therefore, the isomerization process of the reaction intermediate must occur after addition of methanol at −78 °C until decomposition of the intermediates. Addition of 5 equiv of NaOMe in MeOH did not improve the selectivity. Use of the less ylide than the stoichiometric amount (0.9 equiv to **1**) did not change the isomerization results at all, meaning that the deprotonation is not initiated by the excessive base in the reaction mixture but by the reaction intermediate, probably the oxaphosphetane.

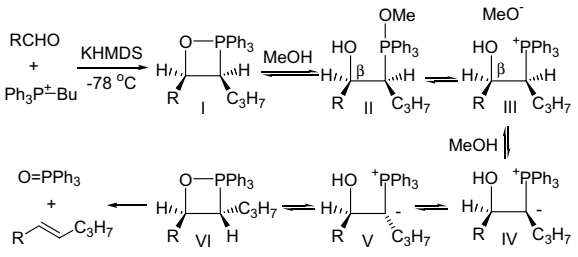
The supposed reaction mechanism is shown in Scheme 3. The well-established oxaphosphetane intermediate **I** under the salt-free conditions[8] opens up with addition of MeOH to give the acyclic intermediate **II** that is in equilibrium with the β-hydroxyphosphonium methoxide salt **III**. The betaine intermediate **V** formed after the deprotonation and protonation steps would decompose to give the (*E*)-alkene product. Equilibration to the starting ylide and aldehyde is excluded here because the methoxide is not basic enough to deprotonate the phosphonium salt, Ph_3P^+Bu.[11a] A large excess of alcohol or thiol seems necessary to shift the equilibrium toward **II** and **III**, and to stabilize the polar intermediates. Phosphorus atoms are known to be oxo- and thiophilic. Thus, the metal cations do not play a critical role here on the selectivity. The presence of neighboring oxygen or nitrogen atoms on the R group would also be helpful to shift the equilibrium to the right with hydrogen bonding to the β-hydroxyl group of **II** and **III**. The equilibrium and/or the deprotonation would not be favored with bulky alcohols or alkyl groups of the phosphonium salt that suffer steric hindrance from the phenyl groups on phosphorus.



Scheme 2. The results with addition of methanol-*d*.

In conclusion, the (*E*)-alkenes could be produced as a major product by simply quenching the reactions with a large excess of MeOH at −78 °C in the Wittig reactions of **1** with nonstabilized ylides of a linear alkyl chain. We have explored the scope and limitations of the method and found a few key factors for the desired selectivity such as no Li^+ salt effect on the selectivity, which is quite unexpected from the previous studies on the equilibration between (*E*)-and (*Z*)-alkenes in the Wittig reaction. It was well established that the presence of the Li^+ salt was necessary to yield an increased (*E*)-selectivity as manifested in the Schlosser modification procedure. Instead, a large amount of MeOH was required in the present work to give a high (*E*)-selectivity. The procedure should be useful as a simple alternative to generate the (*E*)-alkene derivatives of Garner's aldehyde **1** that has found diverse applications in the synthesis of chiral compounds and asymmetric synthesis. In addition, the (*E*)-alkene derivatives of prolinal and glyceraldehyde can be obtained in a good selectivity.

Representative procedure: To a suspension of butyltriphenylphosphonium bromide (784 mg, 1.94 mmol) in THF (9 mL) under nitrogen was added KHMDS (3.7 mL of 0.5 M in toluene, 1.84 mmol) at −78 °C and the mixture was warmed to room temperature with stirring for 0.5 h. After cooling the reddish orange solution to −78 °C, *tert*-butyl (4*S*)-2,2-dimethyl-4-formyloxazolidine-3-carboxylate (Garner's aldehyde **1**, 300 mg, 1.31 mmol) in THF (1 mL) was added dropwise under nitrogen. After the reaction was completed, methanol (10 mL) was added at −78 °C and then the resulting mixture was gradually warmed to room temperature for about 0.5 h by removing a dry ice–acetone bath. The resulting mixture was washed with a solution mixture of $CHCl_3$ (10 mL) and water (5 mL) twice. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on a silica gel column with hexane–ethyl acetate (8:1) as eluent. A G/C analysis was carried out on a Ds 6200 gas chromatography. The column used was HP-5 (cross-linked 5% PhMe Siloxane, 30 m × 0.25 mm × 0.25 μm).



Scheme 3. A probable reaction pathway.

Acknowledgements

We are grateful to the Ministry of Health and Welfare (HMP-98-D-5-0050), Pacific Corporation, and the Brain Korea 21 Project for financial support.

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