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A highly selective synthesis of (Z)-α,β-unsaturated ketones

Wensheng Yu, Mei Su and Zhendong Jin *

Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA

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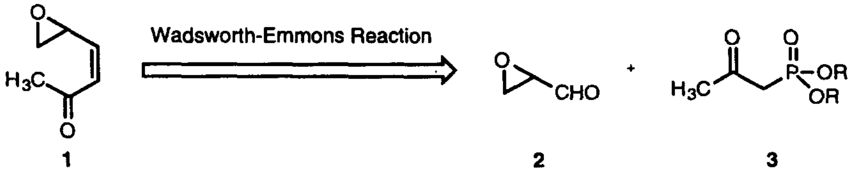
Abstract

New Wadsworth–Emmons reagents, bis(2,2,2-trifluoroethyl)-(2-oxopropyl)phosphonate **6** and bis(2,2,2-trifluoroethyl)-(1-methyl-2-oxopropyl)-phosphonate **7** were prepared and their reactions with aldehydes yielded disubstituted and trisubstituted (Z)-α,β-unsaturated ketones.

Keywords: Wadsworth–Emmons reaction; (Z)-α,β-unsaturated ketone.

In connection with a project in our laboratory, we needed a selective method for the preparation of the disubstituted (Z)-α,β-unsaturated ketone **1**. Although there are a few known methods to construct (Z)-α,β-unsaturated ketones,[1] they are either lengthy, low yielding, or poorly selective. The ideal choice in our case is to form the double-bond via a Wadsworth–Emmons reaction between glycidal **2** and β-keto phosphonate **3**. However, it is well known that β-keto phosphonates generate the stabilized ylide and give predominately the *E*-isomer.



Still's electrophilic bis(2,2,2-trifluoroethyl) phosphonoesters react with aldehydes in the strongly dissociated base systems like potassium bis(trimethylsilyl)amide (KHMDS)/18-crown-6 to afford highly *Z*-selective α,β-unsaturated esters.[2] This method has also been extended to α-cyano phosphonates.[3] Surprisingly, this method has not been applied to the synthesis of (Z)-α,β-unsaturated ketones and a reagent like bis(2,2,2-trifluoroethyl)-(2-oxopropyl)-phosphonate **6** has not been reported. Therefore, we decided to prepare compounds **6** and **7** and study their Wadsworth–Emmons reaction.

Savignac's method[4] for the preparation of bis(2,2,2-trifluoroethyl) phosphonoacetates was adopted for the synthesis of compound **6**. We found that the common method involving simultaneous addition

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* Corresponding author. E-mail: zhendong-jin@uiowa.edu

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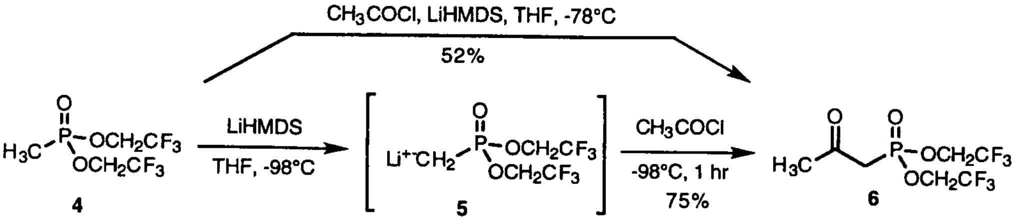
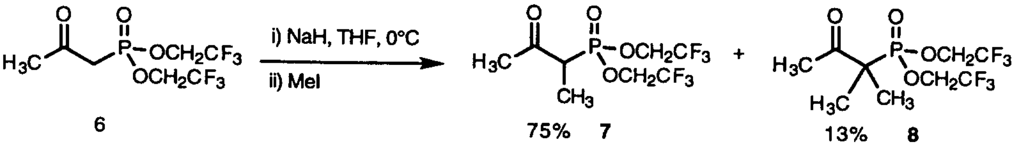
of **4** and acetyl chloride to LiHMDS (2 equiv.) at −78°C gave only 52% yield of the desired product **6** (Eq. 1).[5] The optimized conditions were to generate the lithiated phosphonoenolate by LiHMDS at −98°C followed by addition of acetyl chloride to give 75% yield of compound **6** (Eq. 1). The low temperature of −98°C is important since the lithiated carbanion **5** derived from **4** is not stable, even at −78°C. Treatment of compound **6** with NaH and MeI in THF provided compound **7** in 75% yield and 13% of the dialkylation product **8** (Eq. 2).[6]



(1)



(2)

The reactions between phosphonates **6** and **7** with aldehydes are summarized in Table 1.[7] The isomer ratios were measured by integration of well-resolved signals in the 500 MHz ^{1}H NMR. We found that excess amount of KHMDS greatly prolonged the reaction time and decreased the *Z*-selectivity. Therefore, it is highly recommended that the base should be freshly titrated and only 0.95 equiv. should be used.[8] It should also be noted that only 1.2 equiv. of 18-crown-6 was used to achieve high *Z*-selectivity.[9] Aryl aldehydes gave exclusively (*Z*)-α,β-unsaturated ketones with nearly quantitative yields (entries 1–4). The *Z*-selectivity is relatively lower with alkyl aldehydes, giving only 3:1 ratio of *Z* to *E* in the case of octyl aldehyde (entry 6). However, the *Z*-selectivity increases to 7:1 in the case of α-epoxy aldehyde (entry 5). In addition, conjugated aldehyde also gave higher ratio of *Z* to *E* (entry 7). The reaction between compound **7** and aldehydes gave exclusive *Z*-selectivity in both aryl- and conjugated aldehydes (entries 8 and 9).[10]

A typical procedure used in the above Wadsworth–Emmons reactions follows: To a solution of **6** (1.0 mmol) and 18-crown-6 (1.2 mmol) in 5 mL anhydrous THF at −78°C was added KHMDS (0.95 mmol) under nitrogen. The resulting mixture was stirred for 20 min at −78°C, and then the aldehyde (0.93 mmol) was added at −78°C and the resulting mixture was stirred for about 1 h at −78°C. The reaction was monitored by TLC. In some cases prolonged reaction time and higher temperature were necessary for complete reaction. After the reaction was complete, a saturated NH_4Cl solution was added and the reaction mixture was extracted with ether three times. The ether extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The product was purified by flash column chromatography.

Acknowledgements

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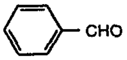
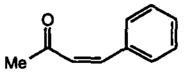
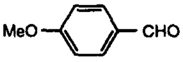
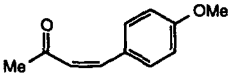
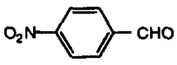
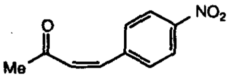
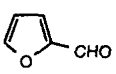
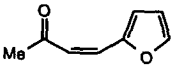
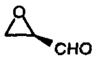
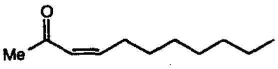
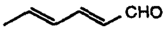
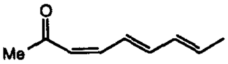
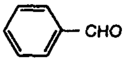
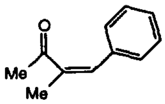
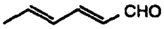
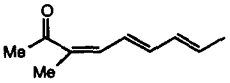
Table 1
Selective synthesis of (Z)-α,β-unsaturated ketones

Entry	Aldehydes	Phosphonates	Conditions[a]	α, β-Unsaturated Ketones[b]
1		**6**	-78°C, 1 h	 95%, Z:E=100:0
2		**6**	-30°C, 7 h	 98%, Z:E=100:0
3		**6**	-78°C, 1 h	 98%, Z:E=100:0
4		**6**	-78°C, 1 h	 94%, Z:E=100:0
5		**6**	-78°C, 1 h	 92%,[c] Z:E=7:1
6		**6**	-30°C, 1 h	 81%, Z:E=3:1
7		**6**	-78°C, 1 h	 82%, Z:E=10:1
8		**7**	-78°C, 1 h	 95%, Z:E=100:0 [d]
9		**7**	-78°C, 1 h	 97%, Z:E=100:0 [d]

[a] 0.95 Equiv of KHMDS and 1.2 equiv of 18-C-6 were used, and the reactions were run in THF; [b] Isolated yields unless noted; [c] The yield was determined by ^{1}HNMR of the crude reaction mixture. [d] The geometry of the double bond was determined by NOE experiments.

References

1. Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908 and references cited therein.
2. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
3. Hensel, M. J.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1285.
4. Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1991**, *21*, 2391.

5. ^{1}H NMR of the crude reaction mixture showed there are many unidentified side-products along with the desired product **6**.
6. Several other procedures have been examined to minimize the dialkylation product **8**. It appeared the present conditions gave the highest yield of compound **7** and the best ratio as well. It is quite difficult to separate both compounds. Therefore, we simply used the mixture of compounds **7** and **8** and calculated the amount of aldehyde, base, and crown ether needed for the reaction according to the amount of **7** present in the mixture. The separation of the Wadsworth–Emmons reaction product and compound **8** is very easy.
7. All compounds were fully characterized.
8. Ireland, R. E.; Meissner, R. S. *J. Org. Chem.* **1991**, *56*, 4566.
9. 5 equiv. of 18-crown-6 was used by Still and Gennari, see Ref. 2.
10. (*Z*)-α,β-Unsaturated ketones, to the extent that they can be purified, are prone to isomerization.