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One Pot Synthesis of Mono- and Spirocyclic α-Phosphonato-α,β-Unsaturated Cycloenones

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Abstract: A one pot ozonolysis/intramolecular aldol condensation(with the aid of TsOH and Et_3N as catalysts) of β-keto-ω-alkenylphosphonates provided the α-phosphonato-α,β-unsaturated cycloenone with good yields.

Phosphonates, vinyl- and β-ketophosphonates, are valuable reagents in organic synthesis.[1,2] Especially, vinylphosphonates bearing electron-withdrawing substituents, such as ethoxycarbonyl and cyano groups at the α-position, have been widely used in the carbon homologations by a two carbon unit and in the synthesis of carbocyclic or heterocyclic compounds *via* the tandem Michael addition/Hornor-Emmons reaction. Therefore, α-phosphonato-α,β-unsaturated enone will be useful intermediates in the synthesis of α,β-unsaturated cyclic keto-compounds. However, about synthetic methods of cyclic α-phosphonato-α,β-unsaturated cycloenone, to the best of our knowledge, there is no example of *monocyclic form*, but just only one example of *bicyclic form* which was obtained as a side product in the synthesis of bicycloalkenone.[3]

Herein we report the intramolecular aldol synthesis of mono- and spirocyclic α-phosphonato-α,β-unsaturated cycloenone (**5**),[5] which will be the solution(*via* the Michael addition to **5**) to the regiochemical problem[4] in the previous synthetic route to cyclic β-ketophosphonates.

For the synthesis of the α-phosphonato-α,β-unsaturated cycloenone, we envisaged the β,ω-dicarbonylphosphonates could be converted to α-phosphonato-α,β-unsaturated cycloenone *via* intramolecular aldol condensation and the β,ω-dicarbonylphosphonates could be prepared from β-keto-ω-alkenylphosphonates since ω-olefin could be converted to carbonyl group by ozonolysis.

First, we prepared the β-ketophosphonates by the method of Savignac and Mathey[6] and the β-keto-ω-alkenylphosphonates by γ-alkylation of the corresponding β-ketophosphonates with allyl or homoallyl bromide by the reported synthetic methods[7] in good yields. And then, ozonolysis of β-keto-ω-alkenylphosphonates (**3**) afforded acyclic dicarbonyl compound with a little of the corresponding cyclization product, while complete cyclization could be accomplished in good yields with the aid of TsOH and Et_3N as

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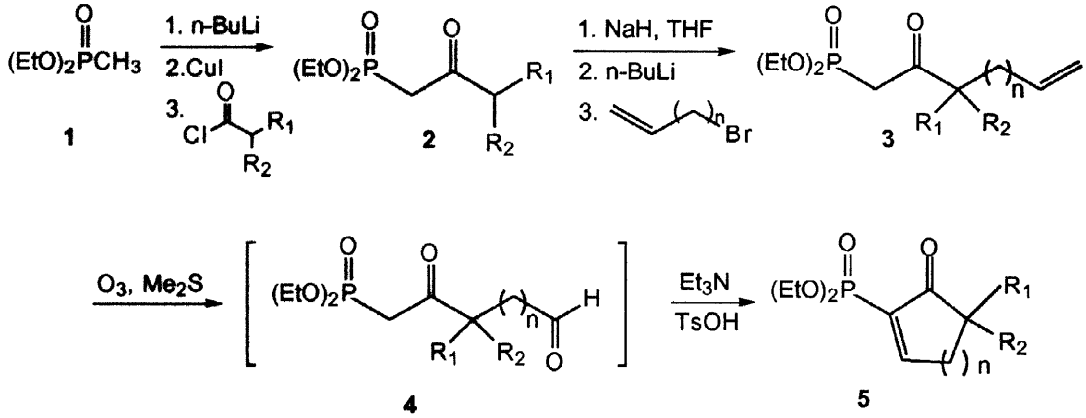
catalysts (**Scheme 1, Table**).



Scheme 1

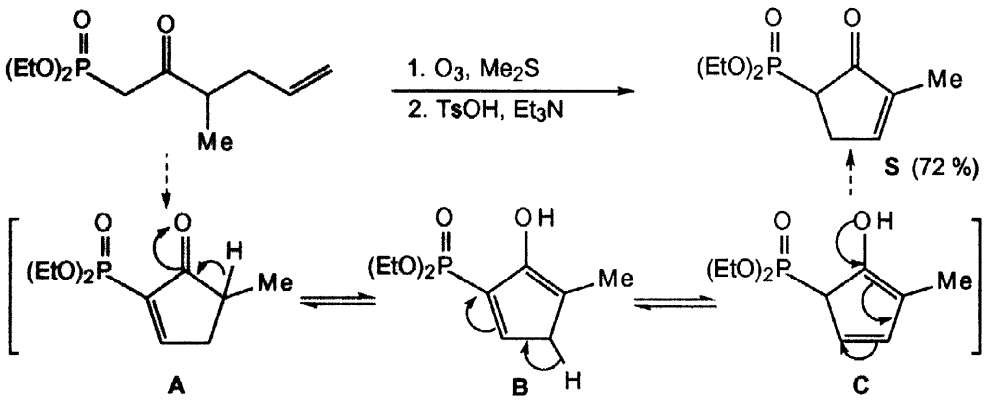
Table Preparation of β-ketophosphonates, β-keto-ω-alkenylphosphonates and α-phosphonato-α, β-unsaturated cycloenones

entry	R_1	R_2	yield % of 2[a]	n	yield % of 3[b]	yield % of 5[c]
a	Me	Me	87	1	80	83
b	-(CH_2)$_3$-		90	1	75	80
c	-(CH_2)$_4$-		91	1	71	88
d	H	H	89	2	74	57
e	H	Et	91	2	65	65
f	-(CH_2)$_4$-		90	2	69	79
g	-(CH_2)$_5$-		93	2	66	76

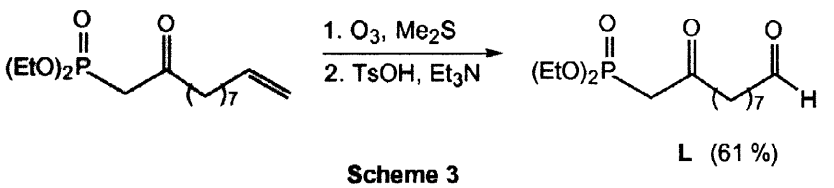
a isolated yields (from 1 to 2)
b isolated yields (from 2 to 3)
c isolated yields (from 3 to 5)

In this ozonolysis-aldol sequence, the following points should be noted. First, there is no enol form in β-keto-ω-alkenylphosphonates (3) (it is evident from NMR spectra) although α-proton is much acidic, otherwise a lot of the compounds might be lost in the ozonolysis step[8]. Second, it was necessary to control the conditions employed in the synthesis of cyclopentenone system. When γ-carbon of 3 was quaternary, cyclization proceeded without any problem(entry a~c). But, when γ-substituent was methyl group, initially formed aldol product isomerized to S[9] (**Scheme 2**). We could verify the mechanism by the crude NMR spectra[10] (A+S were detected concurrently, but B,C were not) of initial step (20 min) and that of totally

isomerized product S by longer reaction time (3 h). And in case of no γ-substituent in **3** (n=1), a undistinguishable solid product was obtained after evaporation of the solvent. Third, in cases of n=3,4, the complicated mixtures, instead of the cyclized products, were obtained by the mixed intermolecular aldol reactions. But, n=6, unexpected linear β,ω-dicarbonylphosphonate (**L**)[11] was obtained in good yield (**Scheme 3**).



Scheme 2



Scheme 3

The following provides a typical experimental procedure. β-Ketophosphonates (**2**) and β-keto-ω-alkenylphosphonates (**3**) could be prepared as in the literature[6,7]. For the conversion of **3** to α-phosphonato-α,β-unsaturated cycloenone (**5**), a stream of ozone was passed through a cold (-78 °C), dichloromethane (8 ml) solution dissolving **3** (2 mmol) until the distinctive blue color of ozone was observed. Ozone bubbling was then terminated, and the excess ozone was displaced by passing a stream of oxygen through the dichloromethane solution for 10 min. The solution was allowed to warm to room temperature, neat dimethyl sulfide (4 mmol) was added, and the solution was allowed to be stirred at reflux for 1 hour and additional 3 hours with TsOH (0.2 eq) and Et_3N (0.2 eq) in one-pot. Rotary evaporation of the crude product, followed by silica gel chromatography (using ethyl acetate as eluent) and evaporation of solvent (ethyl acetate) under high vacuum provided the cyclic α-phosphonato-α,β-unsaturated cycloenone (**5**) in good yields.

References and Notes

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3. Piers, E.; Abeysekera, B.; Scheffer, J. R. *Tetrahedron Lett.* **1979**, 3279.
4. Gloer, K. B.; Calogeropoulou, T.; Jackson, J. A.; Wiemer, D. F. *J. Org. Chem.*, **1990**, *55*, 2842.
5. Selected NMR spectra for representative new compounds. **5b**: ^{1}H NMR(300 MHz, $CDCl_3$) δ 8.18(td, 1H, *J*=2.56, 10.64 Hz), 4.18-4.08(m, 4H), 2.89(dd, 2H, *J*=3.46, 2.62 Hz), 2.39-2.33(m, 2H), 2.03-1.70(m. 4H), 1.28(td, 6H, *J*=7.07, 0.29 Hz); ^{13}C NMR(75 MHz, $CDCl_3$) δ 207.48(d, *J*=10.05 Hz), 172.77(d, *J*=10.88 Hz), 135.42(d, *J*=189 Hz), 62.46(d, *J*=5.78 Hz), 49.60(d, *J*=10.05 Hz), 44.61(d, *J*=16.28 Hz), 31.32, 16.28(d, *J*=6.3 Hz), 15.95. **5d**: ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.80(td, 1H, *J*=3.96, 20.68 Hz), 4.12-4.00(m, 4H), 2.46-2.36(m, 4H), 2.00-1.93(m, 2H), 1.22(t, 6H, *J*=7.04 Hz); ^{13}C NMR(75 MHz, $CDCl_3$) δ 195.84(d, *J*=5.93 Hz), 163.26(d, *J*=10.8 Hz), 131.22(d, *J*=181 Hz), 62.30(t, *J*=3.83 Hz), 38.21(t, *J*=3.75 Hz), 26.58(d, *J*=14.55 Hz), 21.78, 16.14(q, *J*=6.83 Hz). **5e**: ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.75(td, 1H, *J*=3.25, 20.51 Hz), 4.13-4.04(m, 4H), 2.51-2.46(m, 2H), 2.27-2.13(m, 1H), 2.10-2.04(m, 1H), 1.80-1.72(m, 2H), 1.38-1.33(m, 1H), 1.27-1.22(m, 6H), 0.87(t, *J*=7.45 Hz); ^{13}C NMR(75 MHz, $CDCl_3$) δ 198.17(d, *J*=5.18 Hz), 161.97(d, *J*=5.48 Hz), 130.98(d, *J*=180 Hz), 62.28(d, *J*=5.93 Hz), 48.20(d, *J*=6.83 Hz), 26.50, 26.02(d, *J*=15.68 Hz), 21.61, 16.25(d, *J*=6.23 Hz), 11.19.
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7. Grieco, P.A.; Pogonowski, C.S. *J. Am. Chem. Soc.* **1973**, *95*, 3071.
8. An,Y-Z.; An, J. G.; Wiemer, D. F. *J. Org. Chem.*, **1994**, *59*, 8197.
9. For the previous report about the isomerization of cyclopentenone system, see : Brown, E.; Ragault, M. *Tetrahedron Lett.* **1973**, 1927. Spectral data for S: ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.28-7.27(m,1H), 4.13-4.03(m, 4H), 2.95-2.78(m, 3H), 1.71(d, 3H, *J*=1.48), 1.29-1.21(m, 6H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 202.22(d,*J*=4.28 Hz), 156.63(d, *J*=8.18 Hz), 141.77(d, *J*=3.3 Hz), 62.50(dd, *J*=53.85, 6.6 Hz), 43.76(d, *J*=137 Hz), 28.94(d, *J*=2.4 Hz), 16.20(t, *J*=3.83 Hz), 10.16.
10. The isolation of initially formed **A** was unsuccessful. However, we could verify the existence of **A** by the ^{1}H NMR peaks ((200 MHz, $CDCl_3$) δ 8.28(td, 1H, *J*=2.57, 10.55 Hz)) of the β-vinyl hydrogen.
11. Spectral data for **L**: ^{1}H NMR(300 MHz, $CDCl_3$) δ 9.60(d, 1H, *J*=1.77 Hz), 4.02-3.95(m, 4H), 2.94(d, 2H, *J*=22.83 Hz), 2.49-2.45(m, 2H), 2.30-2.13(m, 2H), 1.47-1.40(m, 4H), 1.21-1.16(m, 12H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 202.45, 201.74(d, *J*=6.38 Hz), 62.31(d, *J*=5.1 Hz), 43.57(d, *J*=10.95 Hz), 42.19(d, *J*=126.68 Hz), 33.71, 28.72(d, *J*=7.8 Hz), 28.49(d, *J*=16.8 Hz), 29.97, 22.95, 21.65, 15.99(d, *J*=6.15 Hz).