Michael-type Additions of 2-(Diethoxyphosphinyl) Cyclohexanone to Activated Alkenes and Alkynes†

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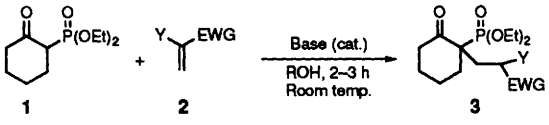
Michael reaction of phosphonate stabilized anions with activated alkenes and alkynes results in 1,4-addition, diastereoselective Robinson annulation, or (n + 2) ring enlargement reactions.

Reactions of phosphonate stabilized anions with aldehydes and ketones have been studied extensively, especially in connection with the Horner–Wadsworth–Emmons (HWE) olefination procedure.[1] However, few reports exist involving the Michael reaction of phosphonate stabilized anions,[2–5] specifically those derived from cyclic β-keto phosphonates such as **1**, which have been relatively inaccessible until recently.[6] We were originally interested in synthesizing cyclic β-keto phosphonates bearing functionalized side chains, for use as templates in subsequent ring enlargement reactions. Our initial attempts focused on synthesizing **3** by reacting anions of **1** with alkylating agents,[7] however, use of β-substituted alkylating agents to afford **3** met with little success. We thus decided to further explore the reactivity of the carbanion derived from **1** by reacting it with Michael acceptors.

The Michael reaction of **1**, synthesized using the Wiemer methodology,[6] with activated alkenes and alkynes was investigated under a variety of conditions. The method of choice for the reaction of **1** with electron deficient alkenes involves use of a catalytic amount of base in a protic solvent. With this method good yields of Michael adducts **3** were obtained (Table 1). On the other hand, use of a molar amount of base in an aprotic solvent resulted only in recovery of unreacted starting material. The reaction of **1** is, further, prone to steric factors since no Michael addition occurred when the β-substituted Michael acceptors methyl crotonate or ethylidene malonate were used. These results are not surprising since Dauben and Bunce[8] have reported that elevated pressures are required for the Michael addition of activated cycloalkanones with β-substituted enones.

The reaction of phosphonate stabilized carbanions with α,β-unsaturated ketones could result in either 1,2-addition to afford the HWE product, or 1,4-addition to give the Michael adduct.[2,4] The potassium enolate of **1** did not undergo any reaction with methyl vinyl ketone (MVK) in THF, however, exclusive 1,4-addition occurred upon reaction of **1** with MVK under protic conditions, in the presence of a catalytic amount of base. The reaction of **1** with MVK involves initial Michael addition followed by aldol condensation to afford Robinson annulation product **4** in 73% yield (Scheme 1). This reaction is highly stereoselective, leading to formation of only the *cis* isomer (predominately existing in the conformation where the phosphonate group is equatorial with respect to the cyclohexane ring). The stereochemical assignment was made on applying the Karplus correlation between the dihedral angle φ(PCCC) and the $^3J_{PC}$ values[9] obtained from the ^{13}C NMR data. Drieding models of *cis*-**4** show the dihedral angles φ(PCCC) to be 60° for C-1, P and C-3, P and 180° for C-6, P and C-8, P. A larger $^3J_{PC}$ coupling value for carbons 6 and 8 is thus expected. This correlates well with the $^3J_{PC}$ values of 0 Hz, 1.7 Hz, 9.6 Hz, and 9.5 Hz obtained for carbons 1, 3, 6 and 8 of compound **4**. These experimental values thus eliminate the possibility of the *trans* isomer, as *trans*-**4** would give small and equivalent coupling values for carbons 1, 3, 6 and 8 (since the dihedral angles φ(PCCC) are all 60°). Similarly, on reacting **1** with but-3-yne-2-one a mixture of the Robinson annulation product, *cis*-**5**, and the *trans* Michael adduct, **6**, was obtained in a 1 : 2 ratio. The *cis* stereoselectivity observed in the reactions leading to the bicyclic ketols **4** and **5** is consistent with earlier reports which suggest that formation of ketols in the Robinson annulation may be kinetically controlled.[10]

The reaction of cyclic β-keto phosphonate **1** with alkynyl esters was also investigated. For example, in the presence of cat. KOH in Bu^{t}OH, **1** underwent Michael addition with methyl propynoate to give the Michael adduct in 72% yield, as a 1.3 : 1 mixture of *cis* and *trans* geometrical isomers. Methyl propynoate exhibits reactivity similar to that of the activated alkenes, such that upon reaction with the potassium enolate of **1**, only unreacted keto phosphonate was obtained, due to the unfavourable equilibrium for formation of the Michael adduct. However, when the potassium enolate of **1** was reacted with dimethyl acetylenedicarboxylate (DMAD) no retro-Michael reaction resulted, and instead only ring enlarged product **8** was formed. Formation of **8** occurs *via* a tandem Michael–Aldol reaction sequence to give cyclobutene intermediate **7**. Fragmentation of **7** affords the ring enlarged product **8** (Scheme 2). A similar mechanism is given to explain the formation of (n + 2) ring enlarged products obtained on reacting sodium salts of cyclic β-keto esters[11] and cyclic β-keto sulfonium ylides[12] with DMAD.

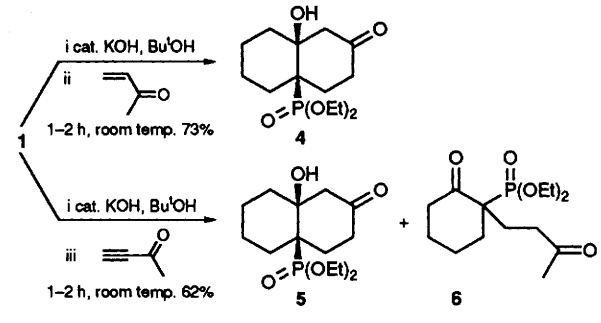


1 2 3

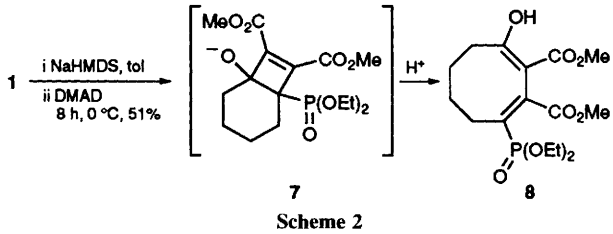
Table 1

Y	EWG	Base	ROH	Product	Yield (%)[a]
H	CO_2Et	NaOEt	EtOH	**3a**	69
H	CN	KOH	Bu^{t}OH	**3b**	75
H	SO_2Ph[b]	Bu^{t}OK	Bu^{t}OH	**3c**	58
Cl	CN	KOH	Bu^{t}OH	**3d**	79

[a] Isolated yields after chromatography on silica gel. [b] Reaction time of 48 h was required with phenyl vinyl sulfone to maximize the yield.



Scheme 1



Scheme 2

In summary, Michael reaction of cyclic β-keto phosphonate **1** results in 1,4-addition, diastereoselective Robinson annulation, or ring expansion depending on the nature of the Michael acceptor used.‡ The Michael adducts **3** and Robinson annulation products **4** and **5** could furnish ring enlarged products on being subjected to either an intramolecular aldol type condensation,[13] or fragmentation reaction, respectively. The (6 + 2) ring enlarged product **8** is obtained directly *via* the reaction of **1** with the highly activated alkyne DMAD. Such medium sized ring compounds bearing a phosphonate substituent could serve as precursors of annulated products formed as a result of an intramolecular HWE reaction, and hence could be used as templates for the synthesis of natural products containing medium sized rings with a bridgehead double bond.

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Footnotes

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‡ The ^{1}H and ^{13}C NMR data of selected compounds are as follows: **3b** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26–4.01 (m, 4H), 2.89 (m, 1H), 2.56–2.0 (m, 8H), 1.84–1.57 (m, 3H), 1.36 (t, 3H, *J* 7 Hz), 1.31 (t, 3H, *J* 7 Hz). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 207.8, 119.8, 63, 63.1, 55 (d), 41.2, 33, 29.6, 26.2, 21.4, 16.4, 16.3, 12.9. **4** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (br s, 1H), 4.2 (m, 4H), 3.1 (d, 1H, *J* 14.4 Hz), 2.85 (m, 1H), 2.43 (d, 1H, *J* 14.4 Hz), 2.38–2.04 (m, 4H), 1.84–1.4 (m, 7H), 1.37 (t, 3H, *J* 7 Hz), 1.36 (t, 3H, *J* 7 Hz). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 209.6 (s, C-2), 73.3 (d, *J* 3.9 Hz; C-9), 63.2 (d, *J* 7.3 Hz), 61.9 (d, *J* 7.8 Hz), 54.5 (s; C-1), 43.8 (d, *J* 133 Hz; C-10), 37.6 (d, *J* 1.7 Hz; C-3), 34.8 (d, *J* 9.5 Hz; C-8), 27.3 (d, *J* 1.8 Hz; C-4), 25.7 (d, *J* 3.4 Hz; C-5), 20.7 (s; C-7), 19.4 (d, *J* 9.6 Hz; C-6), 16.6 (d, *J* 5.8 Hz), 16.4 (d, *J* 6 Hz). **8** ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.1 (d, 1H, *J* 2.1 Hz), 4.16 (m, 4H), 3.78 (s, 3H), 3.74 (s, 3H), 2.67 (m, 1H), 2.48 (m, 1H), 2.2–1.84 (m, 5H), 1.7–1.55 (m, 1H), 1.36 (t, *J* 7 Hz, 3H), 1.34 (t, *J* 7 Hz, 3H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 179.8, 171.6, 168.4, 140.3, 134.3 (d, *J* 173 Hz), 99.2, 62.0, 62.5, 52.2, 32.9, 31, 24.7, 22.8, 16.41, 16.29.

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