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Trimethylsilyl Triflate Promoted 1,4-Addition of Silyl Phosphites to Cyclic Enones

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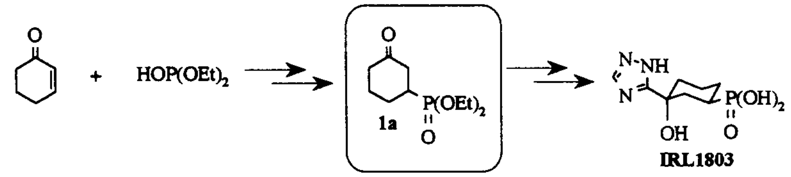
Abstract: A catalytic amount of trimethylsilyl triflate (TMSOTf) remarkably facilitates the selective conjugate addition of a variety of silyl phosphites, prepared in situ from dialkyl phosphites and *N,O*-bis(trimethylsilyl)acetamide, to cyclic enones giving 1,4-adducts in high yields.

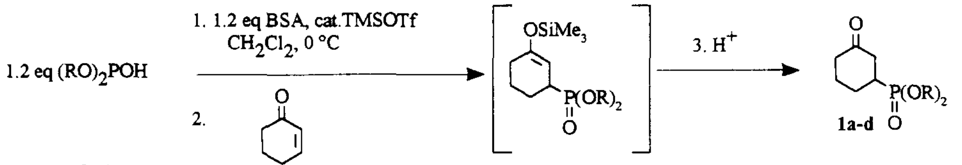
Functionalized phosphonates are important intermediates for the synthesis of many biologically active compounds.[1] During our ongoing program for the rational design of herbicides, we became interested in preparing derivatives of cyclic β-ketophosphonate **1a** which was used as a synthetic intermediate for the potent IGPD inhibitor **IRL1803** (Ki = 10 nM).[2]



IRL1803

Although the conjugate addition of silyl phosphites to acyclic α,β-unsaturated ketones and esters proceeds smoothly at room temperature, forcing conditions are required for cyclic enones.[3] For example, the addition of diethyl trimethylsilyl phosphite to 2-cyclohexen-1-one occurs only at high temperature with prolonged reaction time (180 °C /12 h in sealed tube), affording 1,4-adduct **1a** with the concomitant formation of a 1,2-adduct.[4] In addition, dimethyl trimethylsilyl phosphite does not react with the enone under the same conditions.

Herein we wish to report a facile method for the preparation of cyclic β-ketophosphonates via silyl phosphites under very mild conditions. The addition of diethyl trimethylsilyl phosphite, prepared in situ from diethyl phosphite and *N,O*-bis(trimethylsilyl)acetamide,[5] to 2-cyclohexen-1-one was very sluggish at room temperature, giving only 10% yield of **1a** even after 30 h. However, it was found that an addition of 5 mol% of trimethylsilyl triflate remarkably facilitated the reaction to afford 95% yield of **1a** in 1 h at 0 °C. Moreover, the reaction proceeded in a highly regioselective manner to give almost exclusively 1,4-adduct **1a**, and only a trace amount of a 1,2-adduct was detected by ^{1}H-NMR. With this procedure, other dialkyl phosphonates (R = Me, Bn, Ph) were obtained in 75-83% yields, as shown in Table 1. Other Lewis acids, (i.e. CF_3SO_3H, $TiCl_4$, $BF_3{\bullet}OEt_2$), were less effective and the adduct **1a** was obtained in much lower yields (52%,19%, and 1%, respectively).



BSA: *N,O*-bis(trimethylsilyl)acetamide

Table 1. Addition of Silylated Dialkyl Phosphites to 2-Cyclohexen-1-one Promoted by TMSOTf[a]

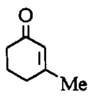
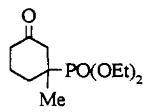
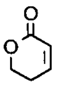
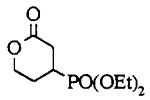
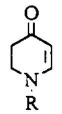
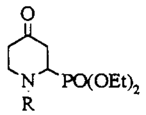
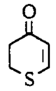
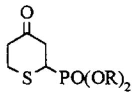
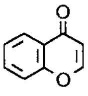
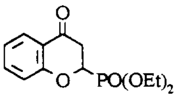
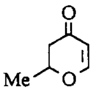
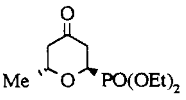
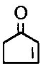
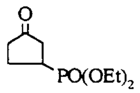
Entry	$(RO)_2POH$	Eq. of TMSOTf	Time (h)	Product	% Yield[c]
1	R = Et	none	30[b]	**1a**	10
2	R = Et	0.01	1	**1a**	70
3	R = Et	0.05	1	**1a**	95
4	R = Me	0.05	1	**1b**	83
5	R = $PhCH_2$	0.05	1	**1c**	86
6	R = Ph	0.05	7.5[b]	**1d**	75

[a] All reactions were carried out in dichloromethane at 0 °C unless otherwise stated. [b] At room temperature. [c] Isolated yield. Only 1,4-adducts were obtained.

This method was applied to the reactions with a variety of cyclic enones, and in most cases selective 1,4-additions occurred (>98%) except for **2a** and **2j**, as shown in Table 2. Although the presence of a heteroatom at the γ-position of enones does not affect the regioselectivity, β,β-disubstituted enone **2a** predominantly afforded a 1,2-adduct (68% yield, with 20% yield of **3a**) presumably due to the hindrance around the β-carbon[6]. It is also worthwhile to note that enone **2i** gave only the trans 1,4-adduct **3i** in 81% yield.

In summary, we have developed a facile method for the preparation of cyclic β-ketophosphonates under very mild conditions. The formation of trimethylsilyl phosphites in situ is also advantageous for the rapid preparation of a variety of dialkyl β-ketophosphonates. Application of this method to inhibitor synthesis will be reported in due course.

Table 2. Addition of Dialkyl Phosphites to Cyclic Enones[a].

Entry	Enone	$(RO)_2POH$	Time (h)	Product	% yield[b]
1	 **2a**	R = Et	1	 **3a**	20 (68)[d]
2	 **2b**	R = Et	overnight[c]	 **3b**	70
3	 **2c**: R = H	R = Et	0.5	 **3c**: R = H	82
4	**2d**: R = Me	R = Et	2	**3d**: R = Me	40
5	**2e**: R = CO_2Et	R = Et	1.5	**3e**: R = CO_2Et	88
6	 **2f**	R = *i*-Pr	1	 **3f**: R = *i*-Pr	72
7	**2g**	R = $PhCH_2$	1	**3g**: R = $PhCH_2$	58
8	 **2h**	R = Et	0.5	 **3h**	98
9	 **2i**	R = Et	0.3	 **3i**	81
10	 **2j**	R = Et	1	 **3j**	82 (10)[d]

[a] All reactions were carried out in dichloromethane at 0 °C. [b] Isolated yield.
[c] At room temperature. [d] Yield of isolated 1,2-adducts in a parenthesis

Typical Procedure: Preparation of 3-(Diethylphosphono)-1-cyclohexanone (1a)

To a mixture of diethyl phosphite (1.46 mL, 11.4 mmol) and *N,O*-bis(trimethylsilyl)acetamide (3.06 mL, 12.4 mmol) in 5 mL of dichloromethane, was added trimethylsilyl triflate (0.1 mL, 0.52 mmol) at 0 °C. After 30 min, 2-cyclohexen-1-one (1.0 mL, 10.3 mmol) was added and the mixture was stirred for 1 h at 0 °C. The enolsilane intermediate was hydrolyzed by stirring the reaction mixture with 3 mL of 1N HCl for 3 h. The organic layer was separated, dried over $MgSO_4$, and concentrated. The crude product was purified by chromatography on silica gel to give 95% yield of **1a**.

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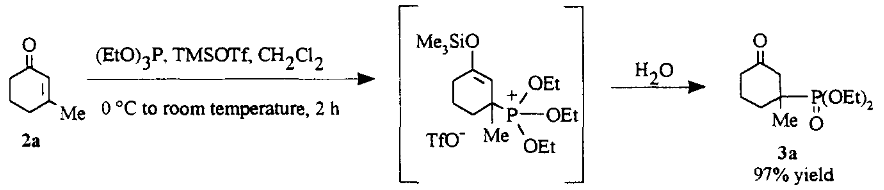
3. (a) Sekine, M.; Yamamoto, Y.; Hashizume, A.; Hata, T. *Chemistry Lett.* **1977**, 485-488. (b) Evans, D. A.; Hurst, K. M.; Truesdale, L. K.; Takacs. J. M. *Tetrahedron Lett.* **1977**, *18*, 2495-2498. (c) Hata, T.; Hashizume, A.; Nakajima, M.; Sekine, M. *Tetrahedron Lett.* **1978**, *19*, 363-366. (d) Evans, D. A.; Hurst, K. M.; Takacs. J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467-3477. (e) Thottathil, J. K. in *Handbook of Organophosphorous Chemistry*, Ed. Engel , R.; Maracel Dekker: New York, 1992; pp. 74-75.
4. Liotta, D.; Sunay, U.; Ginsberg, S. *J. Org. Chem.* **1982**, *47*, 2229-2231.
5. In situ silylation of phosphinic acids with *N,O*-bis(trimethylsilyl)acetamide: Thottathil, J. K.; Ryono, D. E.; Pyzybyla, C. A.; Moniot, J. L.; Neubeck, R. *Tetrahedron Lett.* **1984**, *25*, 4741-4744.
6. Interestingly, it was found that 1,4-adduct **3a** can be selectively formed by addition of triethyl phosphite to enone **2a** in the presence of a stoichiometric amount of TMSOTf.



2a

3a
97% yield

For the use of a stoichiometric amount of TMSOTf in the addition of triphenylphosphine to enones, see; (a) Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400-3402. (b) Kozikowski, A. P.; Jung, S. H. *Tetrahedron Lett.* **1986**, *27*, 3227-3230.

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