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

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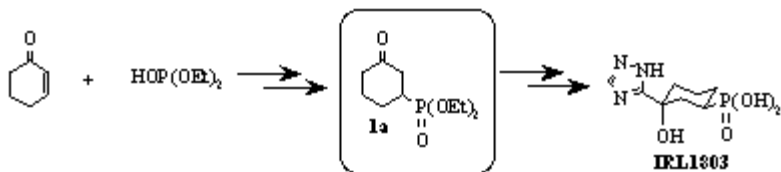
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Abstract: A catalytic amount of trimethylsilyl triflate (TMSOTf) remarkably facilitated the selective conjugate addition of a variety of silyl phosphites, prepared in situ from dialkyl phosphites and *N,O*-bis(trimethylsilyl)acetamide, to cyclic enones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

Introduction

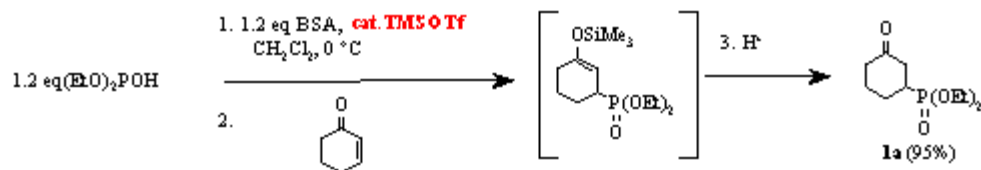
Functionalized phosphonates are important intermediates for the synthesis of many biologically active compounds. As one of such cases, **IRL-1803** was found to have potent inhibitory activity ($K_i = 10\text{nM}$) against IGPD enzyme which is involved in the histidine biosynthesis. For further optimization of the lead compound (**IRL-1803**), the development of the facile preparation method of synthetic intermediate **1a** was required.



Results and Discussion

It was found that an addition of trimethylsilyl triflate remarkably facilitates the conjugate addition of silyl phosphite to cyclic enones. The conjugate addition of diethyl trimethylsilyl phosphite, prepared in situ from diethyl phosphite and *N,O*-bis(trimethylsilyl)acetamide, to 2-cyclohexen-1-one proceeded smoothly in the presence of catalytic amount of trimethylsilyl triflate (5 mol%) at 0 deg.C to afford 95% yield of **1a**, while the reaction without trimethylsilyl triflate gave only 10% yield of **1a** even after 30 h at room temperature. Other Lewis acids, (i.e. $\text{CF}_3\text{SO}_3\text{H}$, TiCl_4 , BF_3

*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

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 1.

Table 1. Addition of Dialkyl Phosphites to Cyclic Enones ^a.

Entry	Enone	(RO) ₂ POH	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 ₂ Et	R = Et	1.5	3e : R = CO ₂ Et	88
6	 2f	R = <i>i</i> -Pr	1	 3f : R = <i>i</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

^b

All reactions were carried out in dichloromethane at 0 deg.C. Isolated yield.

^c At room temperature. ^d Yield of isolated 1,2-adducts in a parenthesis

Conclusion

We have developed a facile method for the preparation of cyclic [beta]-ketophosphonates under very mild conditions. The formation of trimethylsilyl phosphites in situ is also advantageous for the rapid preparation of a variety of dialkyl [beta]-ketophosphonates.

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 deg.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 deg.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 MgSO₄, and concentrated. The crude product was purified by chromatography on silica gel to give 95% yield of **1a**.

References and Notes

These results were published in Tetrahedron Letters and see references cited therein. *Tetrahedron Lett* **1997**, *38*, 3543-3546.

Comments

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