

NEW METHODS FOR β -CONJUGATE ADDITION AND β -HYDROXYALKYLATION OF ENONES[†]

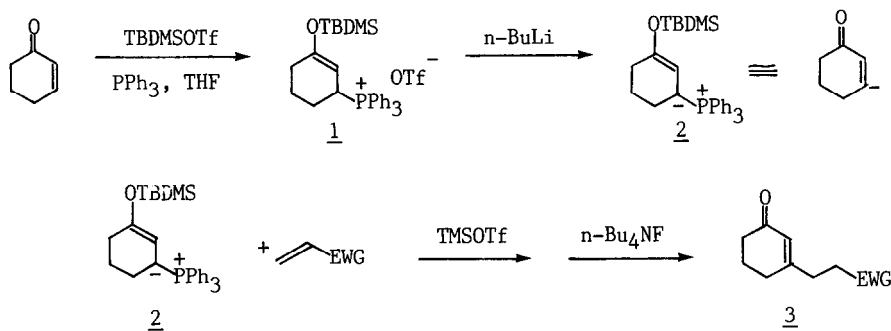
Sunggak Kim* and Phil Ho Lee

Department of Chemistry

Korea Advanced Institute of Science and Technology, Seoul 130-012, Korea

Summary: β -Conjugate addition and β -hydroxyalkylation of enones have been accomplished by the reaction of ylides, derived from enones via phosphoniosilylation, with activated olefins and aldehydes in the presence of trimethylsilyl triflate in tetrahydrofuran at -78°C and subsequent elimination of phosphonium salts by one-pot procedure.

The functionalization of enones can be normally accomplished by dipole reversal process, namely, the conversion of enones into adducts which serve as β -acylvinyl anion equivalents.¹ These approaches consist of the introduction of suitable functional groups at β -position, which is capable of generating stable anions at β -position as well as being easily eliminated to regenerate double bonds. Although examination of the literature indicates that a number of different synthetic methods have been developed,² one of the promising methods involves phosphoniosilylation of enones using triphenylphosphine and silylating agents, previously developed by Evans³ and Kozikowski.⁴

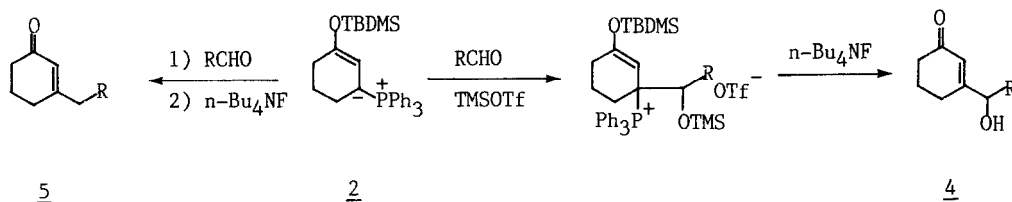


β -Conjugate Addition of Enones to Activated Olefins. Although the conjugate addition of Wittig reagents to activated olefins proceeds by several pathways,⁵ the formation of cyclopropane derivatives is of synthetic importance.⁶ However, we have found that the ylide (**2**) derived from phosphonium salt of silyl enol ether (**1**) cleanly react with activated olefins in the presence of trimethylsilyl triflate (TMSOTf)⁷ in tetrahydrofuran at -78°C to give β -alkylated enones (**3**) in good yields by one-pot procedure.

[†]Dedicated to Professor E.J. Corey on the occasion of his 60th birthday.

Reaction of the ylide (2) derived from cyclohexenone via phosphoniosilylation with ethyl vinyl ketone in tetrahydrofuran at -78°C for 1 h followed by the addition of tetra-*n*-butylammonium fluoride gives 3-(3-oxopentyl)-2-cyclohexen-1-one in 21% yield along with several byproducts. It is expected that the low yield might be resulted from tautomerism of an initial Michael adduct to another enolate due to the presence of the unreacted ethyl vinyl ketone and further conjugate addition of enolates to ethyl vinyl ketone to produce the dialkylated products.^{8,9} The addition of hexamethylphosphoric triamide (HMPA) improves the present reaction to some extent, yielding the desired product in 47% yield together with the dialkylated products in 20% yield.


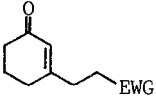

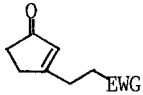
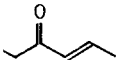
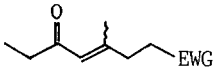
In order to avoid the side reactions, we considered the possibility of trapping an initial Michael adduct with silylating agents. Among several silylating agents tested in this study, TMSOTf gives best results and is generally recommended, while trimethylsilyl chloride is ineffective for this purpose. Thus, the addition of the premixed solution of ethyl vinyl ketone and TMSOTf in tetrahydrofuran at -78°C to the ylide (2) at -78°C followed by the addition of tetra-*n*-butylammonium fluoride gives 3-(3-oxopentyl)-2-cyclohexene-1-one in 79% yield without the contamination of dialkylated products. Using a modified procedure, the reaction of ylides derived from several enones with α,β -unsaturated carbonyl compounds proceeds cleanly and rapidly, yielding 2,3-unsaturated-1,6-dicarbonyl compounds in high yields.¹⁰ The present method works well with other activated olefins such as acrylonitrile and vinyl sulfone. Some experimental results are given in Table 1 and illustrate the efficiency and the applicability of the present method.



β -Hydroxyalkylation of Enones. Encouraged by the results obtained in conjugate addition reaction of enones to activated olefins, we have studied the possibility of β -hydroxyalkylation of enones. As far as we are aware, no successful reports have appeared for quenching betaine intermediates prior to the formation of oxaphosphetane with silylating agents, although it has been reported that the similar intermediate in the boron-Wittig reaction has been quenched with trimethylsilyl chloride.¹¹

The present method is based on the Wittig reaction of ylides with aldehydes,⁴ quenching betaine intermediates with TMSOTf, and facile elimination of phosphonium salts via desilylation. Reaction of the ylide (2) with an equimolar amount of benzaldehyde in tetrahydrofuran at -78°C for 10 min followed by the addition of tetra-*n*-butylammonium fluoride at -78°C gives β -hydroxybenzylated cyclohexenone (4) in 29% yield together with the Wittig product (5) in 21% yield. TMSOTf is found to be much more effective than *t*-butyldimethylsilyl triflate (TBDMSTf) in quenching the betaine intermediate, yielding the desired product in 72% yield without the contamination of the Wittig product.¹² In the case of using aliphatic aldehydes, it is

Table 1. β -Conjugate Addition of Enones to Activated Olefins

enone	activated olefin	product	isolated yield, % ^a
			
	CH ₂ =CHCOCH ₂ CH ₃	EWG=COCH ₂ CH ₃	79 (21) ^b
	CH ₂ =CHCOC ₆ H ₅	=COC ₆ H ₅	(68) ^b
	CH ₂ =CHCOOCH ₂ CH ₃	=COOCH ₂ CH ₃	58 (0) ^b
	CH ₂ =CH-SO ₂ C ₆ H ₅	=SO ₂ C ₆ H ₅	68 (0) ^b
	CH ₂ =CH-CN	=CN	58
			
	CH ₂ =CHCOCH ₂ CH ₃	EWG=COCH ₂ CH ₃	68
	CH ₂ =CHCOOCH ₂ CH ₃	=COOCH ₂ CH ₃	64
			
	CH ₂ =CHCOCH ₂ CH ₃	EWG=COCH ₂ CH ₃	73 (70:30) ^c
	CH ₂ =CH-CN	=CN	77 (85:15) ^c

^a the yields are based on enones. ^b the reactions are performed in the absence of TMSOTf.
^c the ratio of trans/cis isomer.

Table 2. β -Hydroxyalkylation of Enones

enone	RCHO	isolated yield, % ^a
2-cyclopenten-1-one	C ₆ H ₅ CHO	57
	CH ₃ (CH ₂) ₇ CHO	54
	c-C ₆ H ₁₁ CHO	63
2-cyclohexen-1-one	C ₆ H ₅ CHO	72
	CH ₃ (CH ₂) ₇ CHO	63
carvone	C ₆ H ₅ CHO	48 (8) ^b
4-hexen-3-one	C ₆ H ₅ CHO	68
	c-C ₆ H ₁₁ CHO	60

^a the yields of β -hydroxyalkylated enones. ^b the yield of the recovered starting material

preferred to add an aldehyde and TMSOTf to the ylide separately and simultaneously because the use of an equimolar mixture of aliphatic aldehydes and TMSOTf results in the formation of the corresponding silyl enol ethers to some extent.¹³ Some experimental results are summarized in Table 2. The present method works well in both cyclic and acyclic enones with aliphatic and aromatic aldehydes. However, it is noteworthy that the ylide (2) does not react with ketones such as acetophenone and cyclohexanone due possibly to steric reasons.

Acknowledgment. We thank the Korea Advanced Institute of Science and Technology for financial support and we are grateful to Dr. Sung Soo Kim for experimental assistance.

References and Notes

1. For reviews, see: (a) J. C. Stowell, *Chem. Rev.*, **84**, 409 (1984). (b) D. Hoppe, *Angew. Chem. Int. Ed. Engl.*, **23**, 932 (1984).
2. (a) K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1007 (1975). (b) T. Cohen, D. A. Bennett, and A. J. Mura, Jr., *J. Org. Chem.*, **41**, 2506 (1976). (c) P. Bakuzis, M. L. F. Bakuzis, and T. F. Weingartner, *Tetrahedron Lett.*, 2506 (1976). (d) A. Debal, T. Cuvigny, and M. Larcheveque, *Ibid.*, 3187 (1977). (e) C. Shih and J. S. Swenton, *Ibid.*, 4217 (1981). (f) E. Piers and H. E. Morton, *J. Org. Chem.*, **44**, 3437 (1979). (g) D. Liotta, U. Sunay, and S. Ginsberg, *Ibid.*, **47**, 2229 (1982). (h) H. J. Cristau, B. Chabaud, and C. Niangoran, *Ibid.*, **48**, 1527 (1983).
3. D. A. Evans, K. M. Hurst, and J. M. Takacs, *J. Am. Chem. Soc.*, **100**, 3467 (1978).
4. (a) A. P. Kozikowski and S. H. Jung, *J. Org. Chem.*, **51**, 3402 (1986). (b) A. P. Kozikowski and S. H. Jung, *Tetrahedron Lett.*, 3227 (1986).
5. G. M. Kosolapoff and L. Maier, "Organic Phosphorous Compounds", Wiley Intersciences, Vol. 3, 1973 and references cited therein.
6. (a) H. J. Bestman and F. Seng, *Angew. Chem.*, **74**, 154 (1962). (b) P. A. Grieco and R. S. Finkelhor, *Tetrahedron Lett.*, 3781 (1972). (c) M. J. Devos, L. Hevesi, P. Bayet, and A. Krief, *Tetrahedron Lett.*, 3911 (1986).
7. For an excellent review, see: H. Emde et al., *Synthesis*, 1 (1982).
8. (a) M. E. Jung, *Tetrahedron*, **32**, 3 (1976). (b) R. E. Gawley, *Synthesis*, 777 (1976).
9. When phenyl vinyl ketone was used as an activated olefin, the desired product was obtained in 68% yield in the absence of TMSOTf, as shown in Table 1.
10. The ylide (2) did not react with ethyl acrylate in the absence of TMSOTf.
11. A. Pelter, D. Buss, and A. Pitchford, *Tetrahedron Lett.*, 5093 (1985).
12. The use of TBDMSOTf as a trapping agent was totally ineffective, yielding β -hydroxybenzylated cyclohexenone in 26% yield together with the Wittig product in 39% yield.
13. The formation of a small amount of aldol products was also observed.

(Received in Japan 22 August 1988)