Efficient Method for *β*-Conjugate Addition of *α,β*-Unsaturated Lactones and Esters

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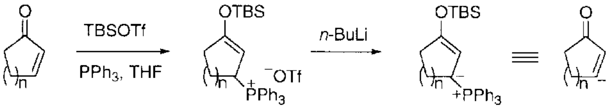
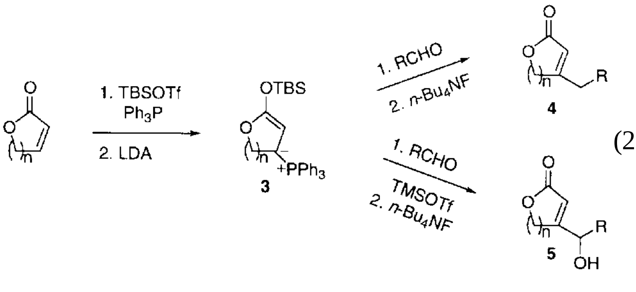
Received December 5, 2001

Keywords : Phosphoniosilylation, *β*-Conjugate addition, *α,β*-Unsaturated lactones and esters.

β-Functionalization of enones can be effected by a variety of methods, which generally involve either the organometallic conjugate addition process[1] or the dipole reversal (at the *β*-position of enones) process.[2] Recently, Kozikowski,[3] Kim[4] and Lee[5] have shown that many useful functional groups can efficiently be introduced at the *β*-position of enones by a dipole reversal process utilizing the phosphoniosilylation reaction of enones with triphenylphosphine and *tert*-butyldimethylsilyl triflate (TBSOTf). In this process, the ylides **2**, generated from phosphoniosilylation products **1** of enones by *n*-BuLi, serve as *β*-acylvinyl anion equivalents (equation 1). Very recently, we have shown that such process can also be employed to *α,β*-unsaturated lactones and esters by effecting *β*-alkylation and *β*-hydroxyalkylation of them.[6] The feasible ylide formation from phosphoniosilylation products of *α,β*-unsaturated lactones and esters by using lithium diisopropylamide (LDA) as a base was a key to the success in these cases (equation 2). These results prompted us to study other *β*-functionalizations of *α,β*-unsaturated lactones and esters. We now wish to report efficient *β*-conjugate addition of *α,β*-unsaturated lactones and esters.

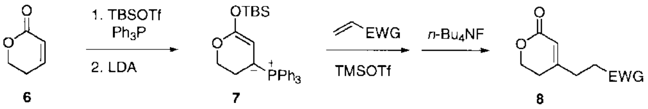


(1)



(2)

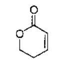
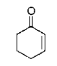
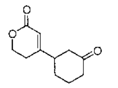
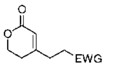
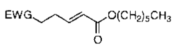
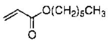
Kim has demonstrated that the ylides **2** derived from the phosphoniosilylation products **1** of enones can add to activated olefins in conjugate manner in the presence of trimethylsilyl triflate (TMSOTf) to give *β*-substituted enones in good yields. Since *β*-alkylation and *β*-hydroxyalkylation of *α,β*-unsaturated lactones and esters could be executed by the phosphoniosilylation process,[6] we envisaged that the *β*-conjugate addition of ylides **3** to activated olefins such as methyl acrylate can also be achieved. Thus, we examined *β*-conjugate addition of *α,β*-unsaturated lactones and esters by employing the phophoniosilylation reaction (Scheme 1).



Scheme 1

Upon examining various reaction conditions with 5,6-dihydro-2*H*-pyran-2-one **6** and methyl acrylate as model unsaturated lactone and activated olefin, respectively, it was found that the efficient *β*-conjugate addition of **6** could be accomplished by the reaction of the ylide **7** with premixed solution of methyl acrylate and TMSOTf in tetrahydrofuran at -78 °C and the subsequent treatment with tetra-*n*-butylammonium fluoride (TBAF) at -78 °C-rt in the same pot. In this way, the addition product **8** (EWG = CO_2Me) was obtained in 71% yield (Table 1, entry 2). As Kim reported in the *β*-conjugate addition of enones,[4a] the use of either TMSOTf or TBSOTf was necessary to avoid the side

Table 1. *β*-Conjugated addition of *α,β*-unsaturated lactones (esters)

Entry	Unsaturated lactone (ester)	Activated olefin	Product	Yield (%)[a]
1				43
				
2	"	CH_2=$CHCO_2CH_3$	EWG= CO_2CH_3	71
3	"	CH_2=$CHCOCH_3$	EWG= $COCH_3$	64
4	"	CH_2=$CHCONMe_2$	EWG= $CONMe_2$	73
5	"	CH_2=$CHSO_2Ph$	EWG= SO_2Ph	49[b]
6	"	CH_2=$CHCN$	EWG= CN	39[b]
				
7		CH_2=$CHCOCH_3$	EWG= $COCH_3$	56[b]
8	"	CH_2=$CHCONMe_2$	EWG= $CONMe_2$	67
9	"	CH_2=$CHCN$	EWG= CN	34[b,c]

[a] Isolated yields based on *α,β*-unsaturated lactone when TMSOTf was used as an additive and TBAF was used as a protodesilylating agent, otherwise mentioned. [b] Saturated ammonium chloride solution was used instead of TBAF. [c] TBSOTf was used instead of TMSOTf.

reactions. In most cases the use of TMSOTf gave much better results than that of TBSOTf. However, in certain cases, TBSOTf was more effective (Table 1, entry 9). Trimethylsilyl chloride was not effective for this purpose.

As shown in Table 1, this chemistry also works well with activated olefins such as vinyl ketone and *N*,*N*-dimethyl acrylamide to give corresponding addition products in good yields (entries 3, 4, 7, 8). With cyclohexenone, acrylonitrile and vinyl sulfone, the yields which attend our process were relatively lower but acceptable (entries 1, 5, 6, 9). It should be noted that with 6,7-dihydro-5*H*-oxepin-2-one, 2(5*H*)-furanone and β-substituted α,β-unsaturated esters, β-conjugate addition to activated olefins was not successful, presumably due to side reactions during ylide generation from their corresponding phophoniosilylation products. Either yields were poor or no significant amount of addition products was obtained. It is also noteworthy that in most cases TBAF served best as a desilylating agent but in some cases the use of saturated ammonium chloride solution gave better results (entries 5, 6, 7, 9).

The typical experimental procedure is as follows. To a solution of triphenylphosphine (291.7 mg, 1.10 mmol) in tetrahydrofuran (3.0 mL) was added TBSOTf (253 μL, 1.10 mmol) and 5,6-dihydro-2*H*-pyran-2-one (86.1 μL, 1.10 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was cooled to -78 °C and LDA, prepared from diisopropylamine (252 μL, 1.80 mmol) and *n*-butyllithium (1.00 mL of 1.50 *M* solution in hexanes, 1.50 mmol) in THF, was added dropwise to give a dark brown-colored solution. The mixture was stirred at -78 °C for 1 h and premixed solution of methyl acrylate (135 μL, 1.50 mmol) and TMSOTf (272 μL, 1.50 mmol) in THF (4.5 mL) was added dropwise *via* cannula. After the reaction mixture being stirred for 30 min, TBAF (4.50 mL of 1 M solution in THF, 4.5 mmol) was added and the mixture was warmed to room temperature and stirred for 30 min. The extractive work-up and flash column chromatography gave the desired product (130 mg, 71%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.81 (s, 1H), 4.40 (t, J = 6.3 Hz, 2H), 3.72 (s, 3H), 2.60 (s, 4H), 2.43 (t, J = 6.3 Hz, 2H). IR (thin film) 2956, 1734 & 1721 (C=O), 1651 (C=C), 1458, 1376, 1182, 1082, 866 cm^{-1}.

In summary, we have shown that the one-pot β-conjugate addition of α,β-unsaturated lactones and esters to activated olefins can be accomplished by the phophoniosilylation process. However, it is noteworthy that this process does not work well with 6,7-dihydro-5*H*-oxepin-2-one, 2(5*H*)-furanone and β-substituted α,β-unsaturated esters such as methyl crotonate.

Acknowledgment. This work was supported by the Korea Ministry of Science and Technology.

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