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Facile Nucleophilic Substitution of 3-*tert*-Butyldimethylsilyloxyalk-2-enylphosphonium Salts

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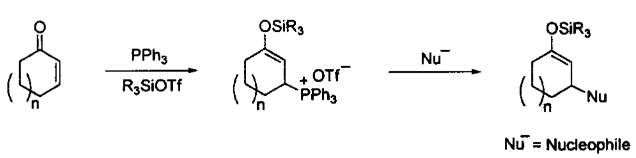
Abstract: Phosphoniosilylation of α,β-enones with TBSOTf and triphenylphosphine at 0 ℃ affords 3-*tert*-butyldimethylsilyloxyalk-2-enylphosphonium salts, which undergo facile nucleophilic substitution with various nucleophiles to give 3-substituted silyl enol ethers in good yields.

Keyword; *phosphoniosilylation, nucleophilic substitution, 3-substituted silyl enol ether*

The conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is one of the most useful and reliable methods for carbon-carbon bond formation. It has been normally achieved using organocopper reagents.[1-4] Although β-substituted silyl enol ethers are generally accessible from α,β-enones by copper conjugate addition followed by enolate trapping, such procedures are sometimes inadequate and the requisite organocuprates are difficult to obtain.[5-8] Furthermore, as far as we are aware, there have been very few reports on preparation of silyl enol ethers in which substituents such as diethylamino or thioacetate are present at β-position.[9] Recently, we reported the phosphoniosilylation[10-13] of α,β-unsaturated carbonyl compounds to generate highly reactive 3-trialkylsilyloxyalk-2-enylphosphonium salts which could subsequently be used to introduce a wide variety of electrophiles at the β-position,[14-16] as well as α-functionalization.[17] As part of our continuing effort to expand the synthetic utility of 3-trialkylsilyloxyalk-2-enylphosphonium salts, we now report the convenient direct displacement of the triphenylphosphine moiety with several nucleophiles to yield the β-substituted silyl enol ethers (Scheme 1).



Scheme 1

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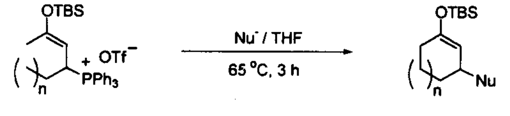
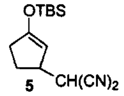
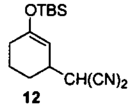
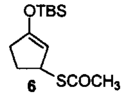
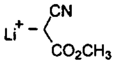
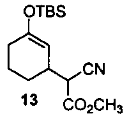
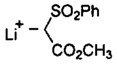
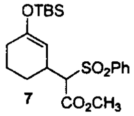
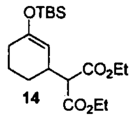
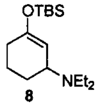
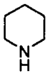
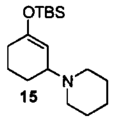
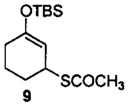
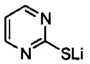
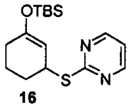
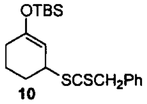
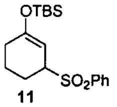
The phosphoniosilylation of α,β-enones was carried out with *tert*-butyldimethylsilyl triflate (1.0 equiv) and triphenylphosphine (1.05 equiv) in tetrahydrofuran at 0 ℃ to give the phosphonium salts. Nucleophilic substitutions of 3-*tert*-butyldimethylsilyloxyalk-2-enylphosphonium salts with various nucleophiles were studied using **1** and **2** as shown in Table 1. Typically, the reaction was carried out with 1.2 equiv of nucleophile in THF at 65 ℃ for 3 h, resulting in conjugate addition to give trapping product **3** and **4** in good yields.[18] Treatment of **1** with the lithium salt of malononitrile under the same conditions gave **5** (entry 1, Table 1) in 62% yield. Similarly, the triphenylphosphine moiety in **2** was easily displaced by the lithium salts of methyl phenylsulfonylacetate, thioacetic acid and 2-mercaptopyrimidine and diethylamine and piperidine to afford **7** (entry 3), **9** (entry 5), **16** (entry 12), **8** (entry 4) and **15** (entry 11) in good yields. As compared with the sulfonium salts derived from the sulfoniosilylation reaction,[9] the phosphonium salt was turned out to be more stable than the sulfonium salts. Because triphenylphosphonium group has the lower leaving ability than dimethylsulfonium group, the phosphonium salts would undergo the substitution reactions at high temperature as we expected. The present method reaches a limit with sodium salt of benzenesulfinic acid (entry 7) and lithium salt of methyl cyanoacetate (entry 9) in which the desired product was obtained in 25% and 38% yield, respectively, together with the ketone compound which silyl enol ether was hydrolyzed. In addition, we have examined whether Michael reaction of α,β-enones with several nucleophiles without triphenylphosphine would occur or not. When the solution of lithium salt of methyl phenylsulfonylacetate or lithium thioacetate in THF was added to the solution of 2-cyclohexen-1-one and TBSOTf at -78 ℃, the desired products **7** and **9** were isolated only in 5% and 7% yield, respectively. When the order of adding the reagents was changed, the reaction gave the totally different results. To the solution of lithium salt of methyl phenylsulfonylacetate in THF was added 2-cyclohexen-1-one at room temperature. After being stirred for 1 h at room temperature, the reaction mixture was cooled to -78 ℃ and treated with TBSOTf to produce methyl 2-(3-oxocyclohexyl)phenylsulfonylacetate (**17**) and ester silyl enolate of **17** in 40% and 14% yields, respectively. Therefore, it seems to be reasonable that 3-*tert*-butyldimethylsilyloxyalk-2-enylphosphonium salts are intermediates in which triphenylphosphine moiety is displaced easily by a variety of nucleophiles. Futhermore, the present method is mechanistically different from normal Michael reactions,[6] allowing the synthetically useful β-functionalized silyl enol ethers.

In summary, 3-*tert*-butyldimethylsilyloxyalk-2-enylenephosphonium salts underwent facile nucleophilic substitution with various nucleophiles to give 3-substituted silyl enol ethers. Because the β-substituted silyl enol ethers are generally accessible to α,β-enones by copper conjugate addition followed by enolate trapping, the present method contrasts with and complements the existing synthetic methods. Also, since the phosphonium salts have been utilized mainly in the generation of phosphorus ylides[19-21] and use as leaving group is few, the present method enhances the synthetic utility of 3-*tert*-butyldimethylsilyloxyalk-2-enylphosphonium salts.

Table 1. Facile Nucleophilic Substitution of 3-Trialkylsilylalk-2-enylphosphonium Salts



n = 0, **1** n = 1, **2** n = 0, **3** n = 1, **4**

entry	Nu$^-$	product	isolated yield/%^{a}	entry	Nu$^-$	product	isolated yield/%^{a}
1	(CN)$_2$CHLi	 **5**	62	8	(CN)$_2$CHLi	 **12**	70
2	CH$_3$COSLi	 **6**	51	9		 **13**	38(10)
3		 **7**	67(17)	10	(EtCO$_2$)CHLi	 **14**	53(24)
4	Et$_2$NH	 **8**	54	11		 **15**	66
5	CH$_3$COSLi	 **9**	56	12		 **16**	72
6	PhCH$_2$CSSLi	 **10**	78				
7	PhSO$_2$Na	 **11**	25(25)				

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[a] The numbers in parentheses indicated isolated yields of the ketones which silyl enol ethers were hydrolyzed.

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[18] Typical procedure: *tert*-Butyldimethylsilyl triflate (264.3 mg, 1.0 mmol) was added to a solution of 2-cyclohexen-1-one (96.1 mg, 1.0 mmol) and triphenylphosphine (275.3 mg, 1.05 mmol) in THF (2.5 mL) at 0 °C. The reaction mixture was warmed to room temperature over 10 min and stirred for 30 min. Lithium salt derived from the reaction of malononitrile (79.3 mg, 1.2 mmol) and *n*-butyllithium (0.76 mL, 1.2 mmol) in THF (2.5 mL) at 0 °C followed by stirring at room temperature for 30 min was transferred to phosphonium salt at 0 °C and reflux at 65 °C. After 3 h, the reaction mixture was quenched with $NaHCO_3$ (sat. aq.). The aqueous layer was extracted with ether (3 x 25 mL), and the combined organics washed with water (20 mL), brine (20 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by silica gel chromatography to give 193.0 mg (70%) of 2-(3-*tert*-butyldimethylsilyloxy-2-cyclohexenyl)malononitrile.

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