Efficient Alkenation of Aldehydes and Ketones to α,β-Unsaturated Esters Using α,α-Bis(dimethylsilyl)-substituted Esters

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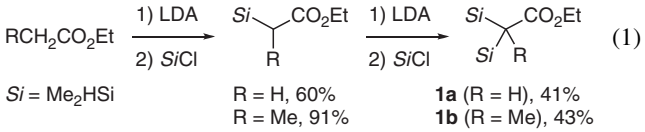
α,α-Bis(dimethylsilyl)-substituted esters **1** were found to be quite valuable for alkenation of various aldehydes and ketones to α,β-unsaturated esters. The reaction of aldehydes with **1** proceeded spontaneously in DMSO at 30 °C to give α,β-unsaturated esters with good to high E selectivity. Under the same conditions, ketones were insensitive to **1**; however, Li_2SO_4 and $CaCl_2$ effectively accelerated their alkenation.

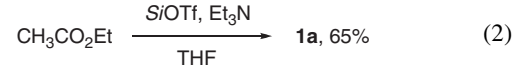
Alkenation of aldehydes and ketones provides a convenient route to α,β-unsaturated esters, which serve as versatile synthetic intermediates convertible to highly functionalized organic molecules. Wittig, Horner–Wadsworth–Emmons (HWE), and Peterson reactions have frequently been utilized for this transformation.[1] However, these reactions require deprotonative preformation of reactive alkenating agents from α-phosphorus- and α-silicon-substituted esters under basic conditions. The HWE and Peterson reactions are carried out usually at low temperatures such as −78 °C for fine control of the deprotonation and subsequent alkenation. The conventional methods, therefore, have much room for improvement toward a simple reaction operation and mild reaction conditions.

In this context, Palomo and co-workers have reported that *t*-butyl bis(trimethylsilyl)acetate is valuable for alkenation of carbonyl compounds to α,β-unsaturated esters under catalysis by TASF, a fluoride ion source.[2] This alkenation involves a fluoride-catalyzed aldol reaction[3] and the subsequent Peterson elimination. It can be conducted at ambient temperature by a simple operation; however, the applicability is rather limited. The alkenation of enolizable carbonyl compounds competes with the formation of their silyl enolates because the intermediary metal-free enolate generated from the alkenating agent is basic enough for deprotonation of the carbonyl compounds.[4] We have previously reported that α-(dimethylsilyl)-substituted esters smoothly add to aldehydes and ketones at 30 °C in the presence of metal chlorides.[5,6] Since this aldol reaction is applicable to a wide range of carbonyls, we expected that α,α-bis(dimethylsilyl)-substituted esters **1** would act as versatile alkenating agents in the tandem aldol-Peterson reaction. Expectedly, **1** affected carbonyl compounds to afford α,β-unsaturated esters. We herein report the scope of this carbonyl alkenation using the newly designed organosilicon reagents.

Bis(dimethylsilyl)-substituted esters **1** were prepared by stepwise double silylation of esters using LDA and Me_2SiHCl (eq 1).[7] Later, we developed direct synthesis of **1a** by treatment with $Me_2SiHOTf$ and Et_3N (eq 2). The organosilicon reagents **1** are storable without any degradation under anhydrous conditions. The reaction of benzaldehyde (**2a**) with **1a** was selected to optimize the reaction conditions. When DMSO was used as solvent, the desired alkenation proceeded spontaneously at 30 °C to give ethyl cinnamate (**3a**) in high yield with high E selectivity (eq 3).[8] HMPA was as effective as DMSO, but no alkenation was observed in other polar solvents (DMF, MeCN, THF, etc.). Use of an equimolar amount of DMSO largely reduced the reaction rate.



(1)



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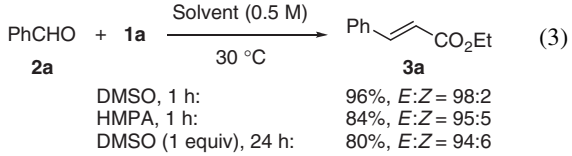
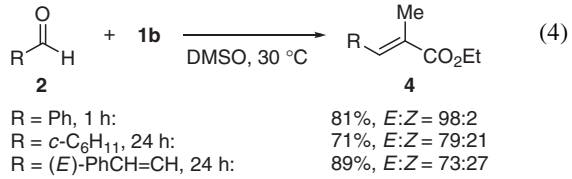


(3)

The uncatalyzed alkenation using **1a** in DMSO is applicable to a variety of aldehydes (Table 1). Substituted benzaldehydes were less reactive than **2a**. Elongation of the reaction time brought about good to high yields of **3** except for the case of **2d** (Entries 1–7). The reaction of 4-acetylbenzaldehyde (**2g**) took place chemoselectively at the formyl site, not at the acetyl site. Aldehydes **2i**–**2j**, bearing an acidic functionality, successfully underwent the alkenation with a two-fold amount of **1a** (Entries 8 and 9). The alkenation of aliphatic aldehydes also proceeded efficiently with E selectivity (Entries 10–12). Notably phenylacetaldehyde (**2m**), a readily enolizable aldehyde, could be converted into **3m** with high E selectivity.[9] Cinnamaldehyde (**2n**) reacted smoothly with **1a** to give ester-conjugated 1,3-diene **3n** in high yield.

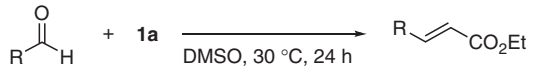
Bissilylated ester **1b** is similar in reactivity to **1a**. Alkenation of aldehydes with **1b** proceeded spontaneously in DMSO to afford trisubstituted alkenes **4** with E selectivity (eq 4).



(4)

Acetophenone (**5a**) hardly reacted with **1a** under the uncatalyzed conditions. We found that Li_2SO_4 efficiently promoted the alkenation of **5a** to β,β-disubstituted acrylate **6a** (Entry 1 in

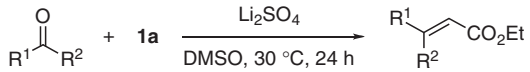
Table 1. Alkenation of aldehydes **2** with **1a**[a]



Entry	R in aldehyde **2**	Yield/%	E:Z[b]
1[c]	4-MeC_6H_4 (**2b**)	90	96:4
2	4-$MeOC_6H_4$ (**2c**)	99	90:10
3	4-$Me_2NC_6H_4$ (**2d**)	59	99:1
4	4-ClC_6H_4 (**2e**)	88	98:2
5	4-$MeO_2CC_6H_4$ (**2f**)	80	98:2
6	4-$Me(O)CC_6H_4$ (**2g**)	72	98:2
7	4-$O_2NC_6H_4$ (**2h**)	85	98:2
8[d]	4-HOC_6H_4 (**2i**)	89	96:4
9[d]	4-$HO_2CC_6H_4$ (**2j**)	75	98:2
10	$Ph(CH_2)_2$ (**2k**)	83	90:10
11	*c*-C_6H_{11} (**2l**)	79	91:9
12[e]	$PhCH_2$ (**2m**)	60	99:1
13	(*E*)-PhCH=CH (**2n**)	90	75:25

[a]Conditions: **2** (0.50 mmol), **1a** (0.60 mmol), DMSO (1.0 mL), 30 °C, 24 h. [b]Determined by GC or ^{1}H NMR analysis of the purified product. [c]For 4 h. [d]An increased amount of **1a** (1.20 mmol) was used. [e]For 1 h.

Table 2. Alkenation of ketones **5** with **1a**[a]

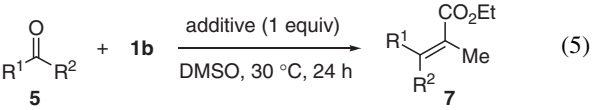


Entry	R^1 and R^2 in ketone **5**	Yield/%	E:Z[b]
1	Ph, Me (**5a**)	88	63:37
2	3,4,5-$(MeO)_3C_6H_2$, Me (**5b**)	78	63:37
3[c]	Ph, $CH(OEt)_2$ (**5c**)	97	25:75
4[c,d]	Ph, CH_2Cl (**5d**)	61	44:56
5[e]	Ph, CF_3 (**5e**)	67	97:3
6	$Ph(CH_2)_2$, Me (**5f**)	80	35:65
7	$-(CH_2)_4-$ (**5g**)	75	
8	$-(CH_2)_5-$ (**5h**)	76	
9[c]	$-(CH_2)_3CH=CH-$ (**5i**)	77	27:73
10[c]	(*E*)-PhCH=CH, (*E*)-PhCH=CH (**5j**)	90	
11[c]	(*E*)-PhCH=CH, Me (**5k**)	91	62:38
12[c]	(*E*)-PhCH=CH, Ph (**5l**)	86	59:41

[a]Conditions: **5** (0.50 mmol), **1a** (0.60 mmol), Li_2SO_4 (050 mmol), DMSO (1.0 mL), 30 °C, 24 h. [b]Determined by ^{1}H NMR analysis of the purified product. [c]$CaCl_2$ was used instead of Li_2SO_4. [d]An increased amount of **1a** (1.20 mmol) was used. [e]Without Li_2SO_4.

Table 2). In the presence of Li_2SO_4, aromatic ketone **5b** and aliphatic ketones **5f**–**5h** underwent the alkenation in good yield (Entries 2 and 6–8). $CaCl_2$ was more effective than Li_2SO_4 in the alkenation of α-functionalized acetophenones **5c**–**5d** (Entries 3 and 4). It is noteworthy that **5d** was converted into **6d** with retention of the C–Cl bond. The alkenation of 2,2,2-trifluoroacetophenone (**5e**) with **1a** occurred spontaneously with high E selectivity (Entry 5). The high reactivity of **5e** is probably due to the electron-withdrawing effect of the CF_3 group. The $CaCl_2$-promoted reaction enabled efficient alkenation of α,β-unsaturated ketones **5i**–**5l** (Entries 9–12). No conjugate adducts were formed in these cases. When Li_2SO_4 was used as promoter, the carbonyl alkenation competed with conjugate addition of **1a**.[10]

In the presence of $CaCl_2$ or Li_2SO_4, alkenation of ketones with **1b** also proceeded efficiently to give tetrasubstituted alkenes **7** (eq 5).



(5)

Unlike **1a** ethyl bis(trimethylsilyl)acetate was insensitive to **2a** even in DMSO. As described above, less polar solvents such as DMF, MeCN, and THF were not effective in the alkenation with **1a**. These results indicate that nucleophilic attack of a DMSO molecule to the sterically less hindered dimethylsilyl group activates the Si–C bond of **1** to initiate the tandem aldol-Peterson reaction. Li_2SO_4 and $CaCl_2$ also would serve for nucleophilic activation of the Si–C bond by attack of the counter anions.[5,6]

In conclusion, we have developed a new alkenation method for the synthesis of α,β-unsaturated esters from aldehydes and ketones. The present alkenation using **1** can be conducted under neutral conditions by a one-step procedure. This method can efficiently convert a variety of aldehydes and ketones into the corresponding α,β-unsaturated esters, in some cases, with high stereoselectivity. Mechanistic aspects of the E selective alkenation of aldehydes and modification of **1** towards highly stereoselective alkenation are now under investigation.[11]

References and Notes

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9 The $CaCl_2$-promoted reaction of **2m** with **1a** in DMF gave **3m** in 91% yield without stereoselectivity (E:Z = 49:51).

10 The Li_2SO_4-promoted reaction of **5l** with **1a** gave **6l** and ethyl 5-oxo-3,5-diphenylpentanoate (a conjugate adduct) in 48% and 30% yields, respectively.

11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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