A Facile One-pot Benzylation of Sodium Enolates Using Trifluoromethansulfonic Anhydride and Diphenyl Sulfoxide

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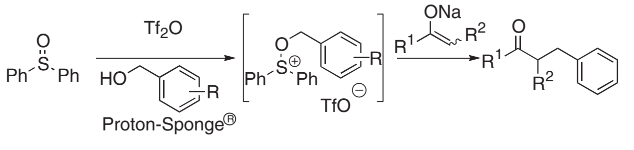
A facile one-pot *C*-benzylation reaction proceeded smoothly and in good yields by treating various sodium enolates and benzyl alcohol with in situ generated alkoxy diphenyl sulfonium salt derived from trifluoromethansulfonic anhydride and diphenyl sulfoxide.

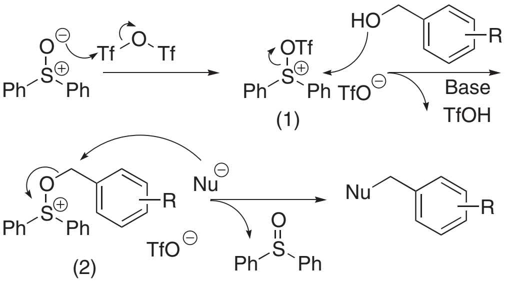
Alkylation of metal enolate is one of the most fundamental and frequently employed reactions in organic synthesis. Though alkylations of various metal enolates derived from ketones,[1] esters[2] and β-keto esters[3] with alkyl halides afforded the corresponding mono-alkylated products, mixture of di- and poly-alkylated products are often formed even when one equivalent of both base and alkylating reagent were used. Moreover, *C*-alkylation and *O*-alkylation is known to take place at the same time depending on the nature of alkylating reagent and reaction conditions. For example, *O*-monobenzylated, *C*-monobenzylated, and *C*-dibenzylated products (5:45:50) were obtained by benzylation of ethyl acetoacetate with benzyl bromide in dimethyl sulfoxide.[4] Thus, to develop an efficient method for the mono-*C*-alkylation of enolates still remains as an important topic in synthetic chemistry. It was reported from our laboratory that dialkyl sulfide bis(trifluoromethansulfonate) reacted with styrene[5] to afford the corresponding active sulfonium intermediate, which in turn reacted with amines to afford aziridines or β,γ-unsaturated amines. Thus, alkoxy dialkyl sulfonium species would similarly behave as an effective alkylating reagent in the reaction with carbon nucleophiles. A similar salt derived from dialkyl sulfoxide and trifluoromethansulfonic anhydride has been previously utilized in Swern-type oxidation,[6] sulfilimine synthesis,[7] and glycosylation reaction[8] as an useful reagent.

Here, we would like to report a new and efficient one-pot *C*-benzylation of sodium enolate with benzyl alcohol by using diphenyl alkoxy sulfonium salt derived from trifluoromethansulfonic anhydride and diphenyl sulfoxide.

A proposed reaction mechanism is shown in Scheme 2. Initially, diphenyl sulfoxide is activated with trifluoromethansulfonic anhydride to form an activated sulfonium complex (**1**). The successive reaction of benzyl alcohol in the presence of base affords in situ an active oxosulfonium trifluoromethanesulfonate (**2**), which in turn reacts with a nucleophile to give the corresponding *C*-benzylated product. Predominant formation of *C*-alkylated product can be explained by considering the soft carbon nucleophile attacking the benzyl carbon of the oxosulfonium trifluoromethane sulfonate, where diphenyl sulfoxide acts as a soft leaving group.



Scheme 1.



Scheme 2.

Initially, 4-methoxy benzyl alcohol and sodium methylmalonate was studied as a model reaction. After screening the effect of solvent, *C*-benzylated product was obtained in 35% and 57% yields when THF or toluene was used, respectively.

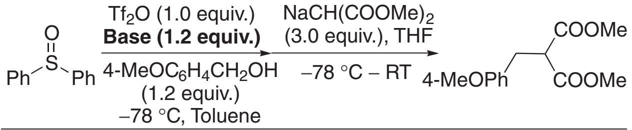
Next, the effect of base was examined (Table 1). The use of pyridine or potassium carbonate was found to afford *C*-benzylated compound in moderate yields (Table 1, Entries 2 and 6) while proton-sponge® gave the best result giving *C*-benzylated product in 97% yield (Table 1, Entry 7).

In order to obtain benzylated product in high yield, at least 3.0 equivalents of nucleophile was necessary. (Table 2, Entry 3). As expected, dibenzylated or *O*-benzylated product was not obtained under the above reaction condition.

The reaction was studied by using various substituted benzyl alcohols and all of the reactions proceeded smoothly to afford the corresponding *C*-benzylated products in moderate to high yields (Table 3). It was noted that the benzylated product was not obtained when the reaction was carried out in the absence of diphenyl sulfoxide (Table 3, Entry 2).

Reactions with other sodium enolates derived from β-keto

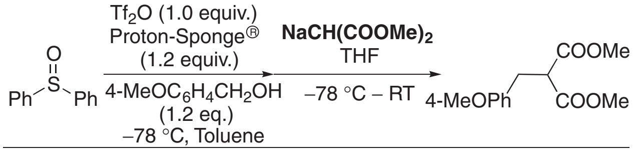
Table 1. The effects of base as a scavenger in benzylation reaction



Entry	Base	Yield /%	Entry	Base	Yield /%
1	Et_3N	ND[a]	5	$CsCO_3$	58
2	Pyridine	77	6	K_2CO_3	65
3	2,6-Lutidine	53	**7**	**Proton-Sponge®[b]**	**97**
4	CsF	54			

[a] Desired product was not detected. [b] 1,8-bis(dimethylamino)-naphthalene.

Table 2. The effect of yield on the amount of sodium enolate



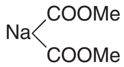
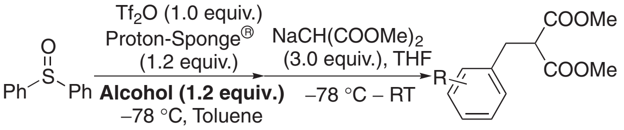
Entry	Nucleophile	Equivalent	Yield /%
1	 $\mathrm{NaCH(COOMe)_2}$	1.5	25
2		2.0	68
3		**3.0**	**97**

Table 3. Study of verious benzyl alcohols derivatives in benzylation reaction



Entry	Alcohol	Yield /%	Entry	Alcohol	Yield /%
1	BnOH	94	7	1-Naphthalenmethanol	83
2[a]	BnOH	ND[b]	8	4-NO$_2$-C$_6$H$_4$CH$_2$OH	74
3	4-MeO-C$_6$H$_4$CH$_2$OH	97	9	4-Cl-C$_6$H$_4$CH$_2$OH	88
4	3-MeO-C$_6$H$_4$CH$_2$OH	88	10	3-Cl-C$_6$H$_4$CH$_2$OH	74
5	4-Me-C$_6$H$_4$CH$_2$OH	85	11	2-Cl-C$_6$H$_4$CH$_2$OH	84
6	4-^{i}Pr-C$_6$H$_4$CH$_2$OH	85	12	2-F-C$_6$H$_4$CH$_2$OH	76

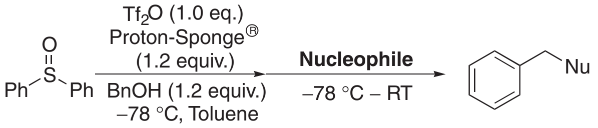
[a] The reaction was carried out without diphenyl sulfoxide. [b] Desired product was not detected.

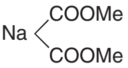
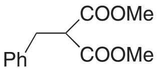
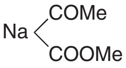
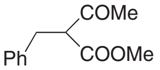
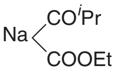
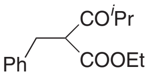
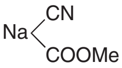
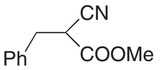
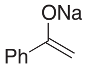
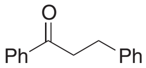
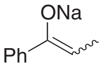
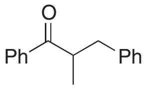
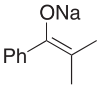
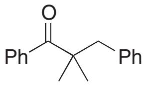
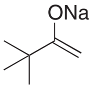
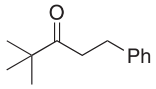
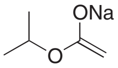
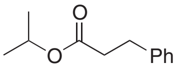
esters, α-cyano esters, esters and ketones were also investigated (Table 4). The desired products were obtained in good yields when β-keto esters were used (Table 4, Entries 2 and 3). Similarly, the reaction proceeded smoothly with α-aromatic or α-aliphatic enolates derived from ketones (Table 4, Entries 5–8). Furthermore, enolates derived from esters could also be used as a nucleophile in this reaction (Table 4, Entry 9). However, the desired product was not obtained when lithium enolates were used (Table 4, Entry 5).

A typical experimental procedure is as follows: to a solution of diphenyl sulfoxide (0.20 mmol) in toluene (1.0 mL) under an argon atmosphere was added a trifluoromethansulfonic anhydride (0.20 mmol) at −78 °C. After stirring for 30 min. A solution of benzyl alcohol (0.24 mmol) and proton-sponge® (0.24 mmol) in toluene (0.8 mL) was added, and the reaction was stirred for a further 30 min. Fleshly prepared sodium salt[9] of methyl malonate dissolved in THF (0.4 M, 1.5 mL) was added and the reaction mixture was slowly warmed to room temperature. After stirring for 2 h, the reaction mixture was quenched with water (5.0 mL) and the aqueous layer was extracted with ethyl acetate (30 mL). The organic layers were collected and dried (MgSO$_4$). After filtration and evaporation, the resulted residue was purified by preparative TLC to afford the corresponding benzylated product.

Thus, a new and efficient method for *C*-benzylation of various sodium enolates was established by using a new benzylating reagent generated in situ from diphenyl sulfoxide, trifuluoromethansulfonic anhydride and benzyl alcohols. Further study on this type of alkylation reaction is currently in progress.

Table 4. Investigation of other metal enolates



Entry	Nucleophile	Product	Yield /%
1			94
2			96
3			quant
4			70[a]
5[b]			78[c]
6			95[c,d]
7			95[a,d]
8			84[d,e]
9			98[a,d]

[a] 4 equiv. of nucleophile was used. [b] No reaction was observed when lithium enolate of acetophenone was used as a nucleophile. [c] 5 equiv. of nucleophile was used. [d] Yields were determined by ^{1}HNMR. [e] 6 equiv. of nucleophile was used.

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References and Notes

1 A. J. Waring, in "Comprehensive Organic Chemistry," ed. by J. F. Stoddart, University of Sheffield (1979), pp 1017–1104.
2 I. O. Sutherland, in "Comprehensive Organic Chemistry," ed. by I. O. Sutherland, University of Livarpool (1979), pp 869–956.
3 J. M. Brown, in "Comprehensive Organic Chemistry," ed. by I. O. Sutherland, University of Livarpool (1979), pp 779–814.
4 W. J. le. Noble and J. E. Puerta, *Tetrahedron Lett.*, **7**, 1087 (1966).
5 a) J. Matsuo, H. Yamanaka, A. Kawana, and T. Mukaiyam, *Chem. Lett.*, **32**, 392 (2003). b) H. Yamanaka, J. Matsuo, A. Kawana, and T. Mukaiyama, *Chem. Lett.*, **32**, 626 (2003).
6 J. B. Henderson and S. M. Schwartzman, *Tetrahedron Lett.*, **16**, 273 (1975).
7 M. D.Coburn and H. H. Hayden, *Synthesis*, **1986**, 490.
8 B. A. Garcia and J. L. Poole, *J. Am. Chem. Soc.*, **119**, 7597 (1997).
9 Sodium enolates were prepared by adding sodium hydride in THF (Table 4, Entries 1–4) or sodium hexamethyldisilazanide in THF (Table 4, Entries 5–8) to THF solution of the corresponding carbonyl compounds.

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