Transition metal-free activation of allylic acetates toward regioselective S-allylation of thiols

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ABSTRACT

Allylic acetates have been used as allylating agents under transition metal-free condition toward an economical and sustainable regioselective S-allylation of aromatic and aliphatic thiols in the presence of potassium carbonate in DMF.

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The nucleophilic substitution of allylic compounds is a useful process in organic synthesis and is frequently used as an important tool in the synthesis of complex organic molecules.[1] Usually these reactions are performed using allyl alcohol derivatives[2a–j] or allyl halides[2k–o] catalyzed by a variety of transition metal (Pd, Ni, and Ru) complexes.[2] Allyl acetates are preferred as allylating agents because of their easy availability and configurational stability and on the other hand, the limitation of more highly activated allyl halides and tosylates.[2j] However, use of less reactive allyl acetates requires the involvement of a transition metal catalyst to activate the allylic system toward nucleophilic addition. Although metal-catalyzed allylation reaction with carbon, oxygen, and nitrogen nucleophiles is well studied,[3] allylation of sulfur nucleophiles is more challenging probably because of deactivation of metal catalyst by sulfur compounds due to their strong co-ordinating properties.[4a,b,d] Moreover, metal-catalyzed allylations often led to a mixture of regioisomers.[4] Although a few transition metal-free Lewis/protic acid-catalyzed procedures have been developed using allyl alcohols, these reactions also ended up with the formation of regioisomers.[5] Thus, a transition metal-free regioselective allylation of thiols is appreciated. We report here a simple and efficient protocol for highly regioselective allylation of thiols with allyl acetates in the presence of a mild base K$_2$CO$_3$ in DMF (Scheme 1). In our attempts for allylic alkylation of thiols by allyl acetates we discovered that the reaction does not require any transition metal
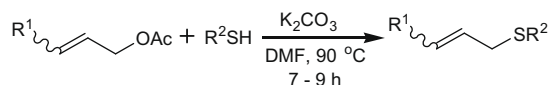
Scheme 1. Allylation of thiols with allylic acetates.

Table 1
Standardization of the reaction condition for S-allylation
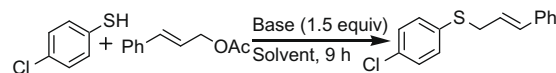
Entry	Base	Solvent	Temp. (°C)	Yield (%)
1	Na$_2$CO$_3$	DMF	90	70
2	K$_3$PO$_4$	DMF	90	53
3	NaOH	DMF	90	15
4	**K$_2$CO$_3$**	**DMF**	**90**	**88 (E:Z = 100:0)**
5	K$_2$CO$_3$	DMF	70	69
6	K$_2$CO$_3$	DMF	rt	0
7	K$_2$CO$_3$	DMF	90	76[a]
8	K$_2$CO$_3$	DMF	90	82[b]
9	No base	DMF	90	0
10	K$_2$CO$_3$	THF	Reflux	Trace
11	K$_2$CO$_3$	H$_2$O	90	74
12	K$_2$CO$_3$	CH$_3$CN	Reflux	66
13	K$_2$CO$_3$	Toluene	90	0

[a] 1 equiv of base was used.
[b] Reaction was carried out for 5 h.

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catalyst. We rationalized that thiols being stronger nucleophiles compared to amines and alcohols[6] are capable of adding directly to the allylic system without any pre-activation by metal.

To standardize the reaction conditions a representative reaction of 4-chloro thiophenol and cinnamyl acetate was carried out with a variety of bases in different solvents at varied temperature and time. The best result was obtained using 1.5 equiv of K_2CO_3 in DMF at 90 °C for 9 h (Table 1). As illustrated in Table 1, the reaction did not proceed at all in the absence of base. Probably, the base K_2CO_3 accelerates the thiol toward nucleophilic attack generating the more nucleophilic thiolate anion and also participates in the neutralization of acetic acid formed during the reaction.

The experimental procedure is very simple.[7] A mixture of allyl acetate and thiol was heated in DMF at 90 °C in the presence of K_2CO_3 for a period of time as required for the completion of the reaction (TLC). A wide range of diversely substituted thiols underwent allylations by a variety of allyl acetates to provide the corresponding allyl sulfides. The results are summarized in Table 2. The

aromatic, heteroaromatic, and aliphatic thiols participated in this reaction uniformly. In addition to allyl acetate, substituted alkyl, aryl, and heteroaryl allylic acetates such as crotyl, cinnamyl, and thienyl also underwent reactions without any difficulty. The reactions proceed with high regioselectivity giving only linear allylic sulfides without any exception. Several substituents such as Cl, Br, OH, NH_2, and OMe on the aromatic rings of thiols and allyl acetates are compatible with this procedure. The trans-allyl acetates (Table 2, entries 5, 6, 10, 12–14) retain their stereochemistry to produce the (E)-products; however, the cis allyl acetates (Table 2, entries 7, 8, and 15) lead to the mixture of (Z)- and (E)-isomers with (Z)-allyl sulfides predominating. It was observed that when this mixture of (E)- and (Z)-isomers was subjected to heating at 100 °C in DMF for 36 h in the presence of K_2CO_3, the (Z)-isomer was totally converted to (E)-isomer (Eq. (1)). Thus, it is likely that cis allyl acetate initially produces (Z)-isomer which is partially transformed into thermodynamically more stable (E)-isomer under the reaction conditions.

Table 2
Allylation of thiols with various allylic acetates

Entry	Thiol	Allylic acetate	Product	Time (h)	Yield[a] (%)	Ref.
1	PhSH	∕∖∕OAc	PhS∖∕∕∕	8	86	4d
2	4-OH–C_6H_4SH	∕∖∕OAc	HO–C$_6$H$_4$–S∕∕	8	78	4a
3	2-NH_2–C_6H_4SH	∕∖∕OAc	(2-NH$_2$-C$_6$H$_4$)S∕∕	8	75	8
4	4-Cl–C_6H_4SH	∕∖∕OAc	(4-Cl-C$_6$H$_4$)S∕∕	8	90	9
5	4-Cl–C_6H_4SH	∕∖∕∕OAc	(4-Cl-C$_6$H$_4$)S∕∕∕	7	77	10
6	4-Cl–C_6H_4SH	Ph∕∕∕OAc	(4-Cl-C$_6$H$_4$)S∕∕∕Ph	9	88	
7	4-Cl–C_6H_4SH	Ph∕∕OAc (cis)	(4-Cl-C$_6$H$_4$)S∕∕∕Ph E : Z = 32 : 68	9	85	
8	4-Cl–C_6H_4SH	(CH$_2$)$_5$∕OAc (cis)	(4-Cl-C$_6$H$_4$)S∕∕∕(CH$_2$)$_5$ E : Z = 17 : 83	9	82	
9	4-Cl–C_6H_4SH	PhCH$_2$∕OAc	(4-Cl-C$_6$H$_4$)S∕CH$_2$Ph	9	85	11
10	4-Br–C_6H_4SH	thienyl∕∕∕OAc	(4-Br-C$_6$H$_4$)S∕∕∕thienyl	8	78	
11	2-pyridyl SH	∕∖∕OAc	2-pyridyl–S∕∕	8	89	4a
12	PhCH$_2$SH	MeO-C$_6$H$_4$∕∕∕OAc	PhH$_2$CS∕∕∕C$_6$H$_4$-OMe	9	73	
13	n-BuSH	MeO-C$_6$H$_4$∕∕∕OAc	n-BuS∕∕∕C$_6$H$_4$-OMe	7	75	
14	CH$_3$(CH$_2$)$_{10}$SH	Ph∕∕∕OAc	CH$_3$(CH$_2$)$_{10}$S∕∕∕Ph	9	83	
15	CH$_3$(CH$_2$)$_{10}$SH	Ph∕∕OAc (cis)	CH$_3$(CH$_2$)$_{10}$S∕∕∕Ph E : Z = 27 : 73	9	84	

[a] Isolated yields of pure products.