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STEREOSPECIFIC NUCLEOPHILIC ADDITION REACTION OF THIOPHENOL TO α,β-UNSATURATED ESTERS

Okiko MIYATA, Tetsuro SHINADA, Takeaki NAITO,* and Ichiya NINOMIYA
Kobe Women's College of Pharmacy, Motoyamakita, Higashinada, Kobe 658, Japan

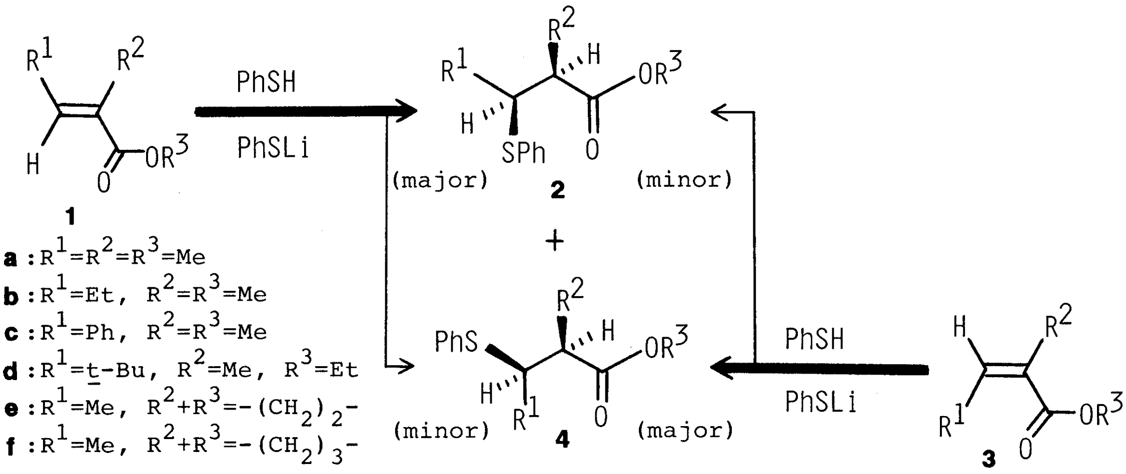
A concerted method for the stereospecific addition of thiophenol to α,β-unsaturated esters **1** and **3** has been developed. This provides a convenient route for the stereoselective preparation of less available Z-α,β-unsaturated esters and lactones **3**.

KEYWORDS nucleophilic addition; stereospecificity; thiophenol; α,β-unsaturated ester; diastereoselectivity; β-(phenylthio)ester

Generally, nucleophilic addition reactions such as Michael addition proceed in two-step processes with an initial attack of a nucleophile on olefin followed by an electrophile on the intermediary enolate in its most stable conformation.[1] Recent studies[2-4] have revealed that some conjugate addition reactions to the Michael-type substrate, irrespective of E- or Z-configuration in aprotic solvent, yielded the same diastereomers, as a result of the attack of an electrophile from the preferred face of the enolate in its lowest energy conformation.[5,6] This shows that these reactions are stereoselective but not stereospecific. On the other hand, the stereochemistry of nucleophilic addition reactions in protic solvent has not been fully understood in spite of the great number of the reactions known.[1]

We investigated the reaction of α,β-unsaturated esters with lithium thiophenoxide in the presence of thiophenol as a proton source and found that the addition reaction of thiophenol to the E- and Z-substrates proceeds stereospecifically to give the respective trans-adducts. Although the sulfur atom-centered nucleophile is well known as an effective Michael-donor to α,β-unsaturated carboxylic acid derivatives,[7,8] surprisingly few systematic studies concerning stereochemical control of the reaction have been reported.[9,10] We first examined the addition reaction of thiophenol to the open-chained trisubstituted E-olefinic esters in the presence of thiophenol as a proton source. The results are summarized in Table I.

The addition of thiophenol to methyl tiglate (**1a**) proceeded smoothly in the presence of lithium thiophenoxide in THF even at room temperature to afford the trans-adduct **2a** with high diastereoselectivity in an excellent yield (entries 1-3), while the same reaction using triethylamine as a base gave the adduct **2a**, also with high diastereoselectivity but in a moderate yield (entry 6). On the other hand, the reaction in the absence of lithium thiophenoxide or in the presence of a proton source such as methanol failed to give the adduct **2a**. Instead the starting ester **1a** was recovered (entries 5 and 7). Similarly, methyl β-ethyl- and β-phenylmethacrylates (**1b,c**) underwent smooth diastereoselective addition of thiophenol to give the trans-adducts **2b,c** (entries 8 and 9), while the addition reaction to the t-butyl congener **1d** proceeded slowly to give a 1:1 mixture of the two diastereomers **2d** and **4d** in poor yield (entry 10). To establish the generality of this highly diastereoselective addition of thiophenol, the reaction was extended to the E-ethylidene lactones **1e,f** which gave the trans-adducts **2e,f** with 84% of diastereomeric excess at temperatures from 0°C to -20°C (entries 12 and 15). On the other hand, when the addition reaction was ap-



a : $R^1=R^2=R^3=Me$
b : $R^1=Et$, $R^2=R^3=Me$
c : $R^1=Ph$, $R^2=R^3=Me$
d : $R^1=\underline{t}\text{-}Bu$, $R^2=Me$, $R^3=Et$
e : $R^1=Me$, $R^2+R^3=-(CH_2)_2-$
f : $R^1=Me$, $R^2+R^3=-(CH_2)_3-$

Table I. Addition Reaction of Thiophenol

Entry	Substrate	PhSLi (eq)	PhSH (eq)	Temp. (°C)	Isolated yield (%)	Ratio[a)] **2** : **4**
1	**1a**	3	3	20	90	91 : 9
2	**1a**	0.1	10	20	99	96 : 4
3	**1a**	0.1	1.2	20	95	94 : 6
4	**1a**	0.1	10	0	59	96 : 4
5	**1a**	—	10	20	—	—
6	**1a**	Et_3N	3	20	53	93 : 7
7	**1a**	1.2	MeOH	20	—	—
8	**1b**	0.1	10	20	85	87 : 13
9	**1c**	0.1	10	20	99	81 : 19
10	**1d**	0.1	10	20	25	57 : 43[b)]
11	**1e**	0.1	10	20	87	84 : 16
12	**1e**	0.1	10	0	94	92 : 8
13	**1e**	0.1	10	-78	60	90 : 10
14	**1f**	0.1	10	0	90	80 : 20
15	**1f**	0.1	10	-20	63	92 : 8
16	**3a**	0.1	10	20	85	14 : 86
17	**3e**	0.1	10	0	99	14 : 86
18	**3f**	0.1	10	-20	87	14 : 86

a) Determined by 200 MHz ^1H NMR.

b) Stereochemical assignment of **2d** and **4d** have not been established.

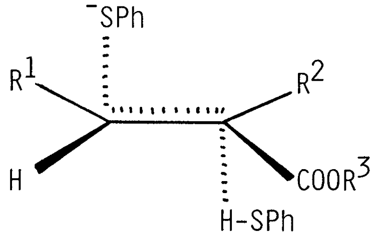


Fig. 1. Concerted Mechanism for the Addition Reaction of Thiophenol

plied to the ester **3a** and lactones **3e,f** having Z-geometry, mostly **4a** and **4e,f** were obtained (entries 16, 17, and 18).

The fact that the addition reaction of thiophenol to the unsaturated E- and Z-esters **1** and **3** respectively gave the erythro- and threo-isomers **2** and **4** with high diastereoselectivity clearly suggests that the addition reaction is stereospecific. This stereospecificity can be explained as follows. This reaction is not a two-step process via the enol or enolate, as in the well known Michael addition reaction in which the E- and Z-substrates give rise to the same product, but proceeds via the concerted process shown in Figure 1. The nucleophilic attack of lithium thiophenoxide and the electrophilic attack of a proton from thiophenol on the double bond occur concomitantly, without forming the intermediary lithium enolate from the opposite faces of an olefin, due to the stereoelectronic effect of the transiently formed carbon-sulfur bond.

The structures of the adducts **2a-f** and **4a, e,** and **f** were deduced from the result of the syn-elimination reaction of the corresponding sulfoxide which gave the corresponding Z- and E-olefinic esters **3a-f** and **1a, e**, and **f** as follows. Heating the corresponding sulfoxide of the adducts **2a-f**, except **2d**, under neat condition or in boiling toluene gave mostly the Z-olefins **3a-f** in good yields. Similarly, the diastereomers **4a**, and **4e,f** prepared from the Z-olefinic ester **3a** and lactones **3e,f** were converted regioselectively into the E-isomers **1a**, and **1e,f** respectively. The structures of the other adducts **4b-f** were deduced by comparing their n.m.r. spectra with those of the diastereomers **2b-f**.

We have now established the stereospecific nucleophilic addition reaction of thiophenol to olefins which provides a potential route for synthesizing the less available Z-olefins by pyrolytic combination of the corresponding sulfoxide of the adducts obtained from E-olefins.

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