Alumina-Catalyzed Addition of Thiols to Methyl Propiolate

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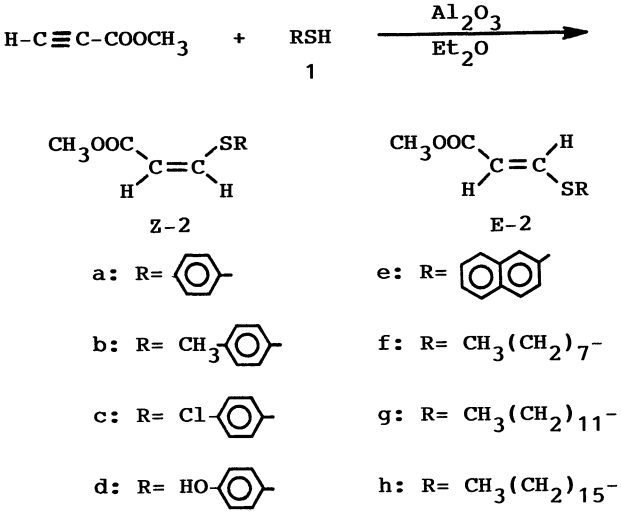
(Received June 10, 1991)

Synopsis. The addition of thiols to methyl propiolate was remarkably accelerated in the presence of alumina to give the *Z*-isomer of the 1:1 adducts stereoselectively, in which alumina acts as a bifunctional catalyst of acid and base.

Recently, a significant improvement of the reagent activity or selectivity has been achieved for a variety of organic reactions by the use of reagents supported on an inorganic solid or by the adsorption of substrates onto the surface of an inorganic solid.[1] The application of an inorganic solid (e.g., silica gel,[2] alumina,[3], zeolite[4]) as a solid base and an acid catalyst for organic reactions in the liquid phase has also attracted the attention of organic chemists. We previously reported that addition of phenols to dimethyl acetylenedicarboxylate adsorbed on alumina in the absence of a base gives *cis*-addition products selectively.[5] Although the addition of phenol to methyl propiolate under similar conditions did not occur, thiols reacted with methyl propiolate in the presence of alumina to give the *Z*-isomer of the 1:1 adducts in high yield. Herein, we report on these results.

Results and Discussion

The reaction of thiols, especially aliphatic thiols, with esters of propiolic acid is very slow in the absence of catalysts, but is remarkably accelerated by a base, giving 1:1 adducts which are a mixture of both the *E*- and *Z*-isomer. The ratio of the *E*- and *Z*-isomer is dependent on the nature of the solvents. The reaction in a protic polar solvent gives predominantly the *Z*-isomer and in an aprotic solvent mainly the *E*-isomer.[6]



Scheme 1.

A reaction of 2-naphthalenethiol (**1e**) with methyl propiolate was carried out in diethyl ether in the absence of a base at 10 °C for 1 h to give a 19% yield of methyl 3-(2-naphthylthio)acrylate (**2e**), which was a mixture of the iosmers (*Z*/*E* 50/50). By adding triethylamine as a catalyst the reaction was accelerated to give a 85% yield of **2e**. The *Z*/*E* ratio of the product isomers, however, was about the same as in the absence of a catalyst. In contrast, the reaction in the presence of neutral alumina under similar conditions gave a 96% yield of **2e**; the *Z*/*E* ratio of the product isomers was 90/10. Neutral alumina was most effective in promoting the reaction. Silica gel and a molecular sieve (5A) were entirely ineffective. The yield of **2e** and the ratio of the product isomers obtained in a variety of solvents are about the same as in diethyl ether (see Table 1). These results suggest that the reaction occurs on the sulface of alumina rather than in the solution. Substituted aromatic thiols also reacted with methyl propiolate in the presence of alumina under similar conditions to give the corresponding *Z*-isomer of **2** in high yields. The reaction with aliphatic thiols, which are less reactive than aromatic thiols, required a long reaction time; the stereoselectivity is slightly lower than in a reaction with aromatic thiols. Neutral alumina showed a higher catalytic activity than that of basic alumina; acidic alumina was ineffective (see Table 2). Although thiol is readily oxidized to disulfide in the presence of alumina under mild conditions,[7] disulfides were not detected under these reaction conditions. It is well-known that *cis*-(2-substituted vinyl) sulfides are isomerized by thiyl radical to an equilibrium mixture consisting mainly of the *E*-isomer.[8] A mixture of *Z*-**2b** and catalytic amounts of *p*-toluenethiol in diethyl ether was stirred at 10 °C for 10 h. However, no isomerization of the *Z*-

Table 1. Addition of 2-Naphthalenethiol (**1e**) to Methyl Propiolate[a]

Catalyst	Solvent	Yield of **2e**/%[b]	Ratio of *Z*-**2e**/*E*-**2e**[c]
None	Et_2O	19	50/50
Al_2O_3[d]	Et_2O	96	90/10
	$CHCl_3$	97	90/10
	CH_3CN	99	94/6
	EtOH	98	91/9
SiO_2[e]	Et_2O	20	55/45
MS-5A[f]	Et_2O	20	58/42
NEt_3[g]	Et_2O	85	42/58

a) A mixture of **1e** (1 mmol), methyl propiolate (1 mmol) and a catalyst (0.5 g) in diethyl ether was stirred at 10 °C for 1 h. b) By GLC. c) Determined by ^1H NMR. d) Neutral alumina for column chromatography. e) For column chromatography. f) Powder. g) 0.1 mmol.

Table 2. Alumina-Catalyzed Addition of Thiols to Methyl Propiolate[a]

Thiol/**1**	Time/h	Yield of **2**/%[b]	Ratio of *Z*-**2**/*E*-**2**[c]
1a	1	97 (7)	87/13 (63/37)
1b	1	97 (20)	88/12 (59/41)
1c	1	98 (21)	91/ 9 (59/41)
1d	1	90 (9)	84/16 (57/43)
1e	1	96 (19)	90/10 (50/50)
1f	48	86 (2)	83/17 (43/57)
1g	48	89 (3)	78/22 (39/61)
1g[d]	48	65	80/20
1g[e]	48	13	68/32
1h	48	81 (3)	70/30 (5/95)

a) All reactions were carried out at 10 °C in diethyl ether under nitrogen. b) By GLC. c) By ^{1}H NMR. b, c) Figures in parentheses show the yield and the *Z*/*E* ratio obtained in the reaction without alumina. d) Basic alumina. e) Acidic alumina.

isomer to the *E*-isomer occurred. *Z*-**2b** was isomerized to the *E*-isomer upon heating in the presence of *p*-toluenethiol at 80 °C in benzene. These results show that the *E*-isomer of the product isomers does not arise from the *Z*-isomer by post-isomerization under these reaction conditions. It has been reported that the nucleophilic ring opening of epoxides is catalyzed by zeolite, in which the cooperative function of both the acid and base sites on its surface is thougt to be essential for effective catalysis.[4] The effective catalysis of neutral alumina in the addition of thiols to methyl propiolate is also likely to be due to the cooperative function of acid and base sites on the alumina surface. Thus, the nucleophilicity of thiol is enhanced by a base site, and methyl propiolate can be activated by an acid site. The interaction between a acid site and a carbonyl group of methyl propiolate facilitates the formation of an enol during an attack by the nucleophile (RS^-) at the triple bond. The stereoselectivity in the reaction with aromatic thiols was higher than that in a reaction with aliphatic thiols, and the *Z*/*E* ratio of the product isomers in the reaction with aliphatic thiols decreased with incresing length of the alkyl group. These observations indicate that the *Z*-isomer is formed preferentially when the thiol molecule is strongly adsorbed on the surface of alumina. The resonance-stabilized anion intermediate, which is formed by the coordination of the thiolate ion at the β-carbon of methyl propiolate, is adsorbed on its surface. The intermediate therefore accepts a proton from thiol on its least hindered side to give the *Z*-isomer (see scheme 2).

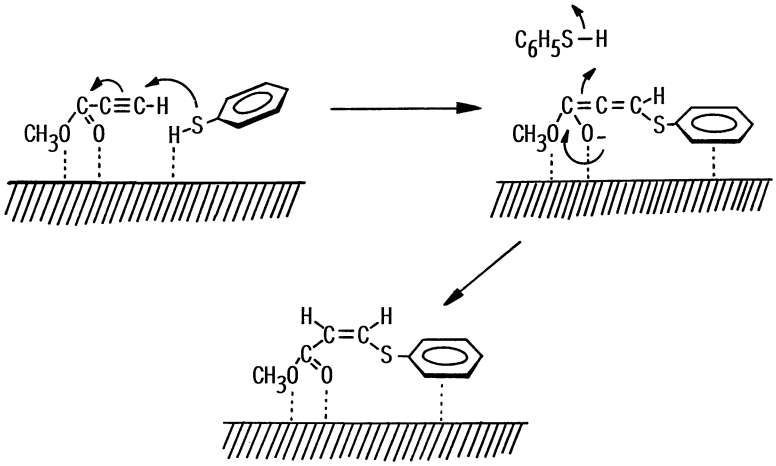
Experimental

Methyl (*Z*)-3-(2-Naphthylthio)acrylate (*Z*-2e). General Procedure. Neutral alumina (ICN Biomedicals, N-Super 1, 2.5 g) was added to a solution of methyl propiolate (5 mmol, 0.42 g) in diethyl ether (40 ml), and stirred at 10 °C for 20 min. To the mixture was added a solution of 2-naphthalenethiol (5 mmol, 0.80 g) in diethyl ether (20 ml); stirring continued at 10 °C for 1 h under nitrogen. The product mixture was filtered, and the solid was washed with diethyl ether. The combined filtrate was washed with 5% aqueous sodium hydroxide and water, and dried. Evaporation of the solvent under reduced pressure yielded 1.21 g of **2e** as a white solid. The *Z*/*E* ratio of the product isomers was determined by ^{1}H NMR. The *Z*/*E* ratio was 90/10. Pure *Z*-isomers of **2b**, **2c**, **2d**, **2e**, **2g**, and **2h** were readily obtained by recrystallization of the crude products from appropriate solvents. The melting point and spectrum data for these *Z*-isomers are shown below.

Methyl (*Z*)-3-(*p*-Tolylthio)acrylate (2b). Mp 53—54 °C (lit,[9] 54—55 °C) (from hexane); ^{1}H NMR ($CDCl_3$) δ=2.31 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 5.86 (1H, d, *J*=9.9 Hz, =CHO–), 7.12 (2H, d, *J*=10 Hz, PhH), 7.34 (1H, d, *J*=9.9 Hz, =CHS–), 7.35 (2H, d, *J*=10 Hz, PhH).

Methyl (*Z*)-3-(*p*-Chlorophenylthio)acrylate (2c). Mp 99—100 °C (from hexane); IR (KBr) 1696, 1222, 1170, 1094, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.76 (3H, s, OCH_3), 5.93 (1H, d, *J*=9.9 Hz, =CHCO–), 7.19 (1H, d, *J*=9.9 Hz, =CHS–), 6.98—7.65 (4H, m, PhH); MS *m*/*z* (%) 228 (M^+; 100), 197 (75), 169 (58), 143 (44), 134 (43), 125 (9), 117 (24), 108 (45). HRMS. Found: *m*/*z* 228.0006. Calcd for $C_{10}H_9O_2SCl$: M, 228.0012.

Methyl (*Z*)-3-(*p*-Hydroxyphenylthio)acrylate (2d). Mp 114—115 °C (from benzene–hexane); IR (KBr) 3287, 1671, 1228, 1168, 802 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.71 (3H, s, OCH_3), 5.87 (1H, d, *J*=10.8 Hz, =CHCO–), 6.91 (2H, d, *J*=9.5 Hz, PhH), 7.29 (1H, d, *J*=10.8 Hz, =CHS–), 7.37 (2H, d, *J*=9.5 Hz, PhH), 8.73 (1H, s, –OH); MS *m*/*z* (%) 210 (M^+, 100), 179 (52),



Scheme 2.

151 (46), 133 (10), 125 (42), 107 (12), 97 (14), 81 (15). HRMS. Found: m/z 210.0326. Calcd for $C_{10}H_{10}O_3S$: M, 210.0351.

Methyl (*Z*)-3-(2-Naphthylthio)acrylate (2e). Mp 73—74 °C (from hexane); IR (KBr) 1697, 1564, 1080, 865, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.74 (3H, s, OCH_3), 5.91 (1H, d, J=10.8 Hz, =CHCO–), 7.28 (1H, d, 10.8 Hz, =CHS–), 7.31—7.90 (7H, m, arom.); MS m/z (%) 244 (M^+; 57), 213 (15), 185 (100), 159 (8), 152 (10), 141 (8), 127 (12), 115 (53). HRMS. Found: m/z 244.0558. Calcd for $C_{14}H_{12}O_2S$: M, 244.0558.

Methyl (*Z*)-3-(Dodecylthio)acrylate (2g). Mp 47—48 °C (from methanol); IR (KBr) 2920, 2850, 1698, 1470, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (3H, t, $-CH_3$), 1.10—1.78 (20H, m, $-(CH_2)_{10}-$), 2.76 (2H, t, $-SCH_2-$), 3.72 (3H, s, $-OCH_3$), 5.84 (1H, d, J=10.8 Hz, =CHCO–), 7.11 (1H, d, J=10.8 Hz, =CHS–). MS m/z(%) 286 (M^+; 22), 225 (15), 213 (20), 199 (20), 117 (40), 100 (21), 87 (46), 69 (26), 55 (71), 43 (100). HRMS. Found: m/z 286.1996. Calcd for $C_{16}H_{30}O_2S$: M, 286.1967.

Methyl (*Z*)-3-(Hexadecylthio)acrylate (2h). Mp 63—64 °C (from methanol); IR (KBr) 2921, 2850, 1697, 1471, 804 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (3H, t, $-CH_3$), 1.14—1.78 (28H, m, $-(CH_2)_{14}-$), 2.75 (2H, t, $-SCH_2-$), 3.72 (3H, s, $-OCH_3$), 5.84 (1H, d, J=9.9 Hz, =CHCO–), 7.10 (1H, d, J=9.9 Hz, =CHS–); MS m/z (%) 342 (M^+; 11), 311 (10), 269 (14), 255 (26), 117 (26), 87 (36), 69 (19), 55 (67), 43 (100). HRMS. Found: m/z 342.2589. Calcd for $C_{20}H_{38}O_2S$: M, 342.2593.

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