Computer-Aided Reaction Design. Development of a New Facile Procedure to Synthesize 2-Mercapto-3-alkoxycarboxylate on the Basis of ab Initio Molecular Orbital Calculations

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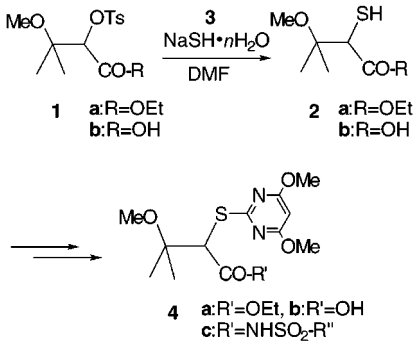
This paper describes a new facial procedure to substitute a tosyloxy group in 2-(tosyloxy)alkanoate with SH^- to yield 2-mercaptoalkanoate on the basis of ab initio MO calculations. Combination of substrate and solvent effects can control both reactivity and selectivity of reaction for 2-(tosyloxy)-3-alkoxycarboxylic acid which gave 2-mercapto-3-alkoxycarboxylic acid in good yield while its ethyl ester gave α,β-unsaturated carboxylate ester as a main product. The difference of carboxylate moiety in the substrate causes remarkable change in reactivity and selectivity. To clarify origin of the difference, ab initio MO calculations in the gas phase and in DMF have been carried out. The solvent effect was considered at RHF/6-31+G* with the IPCM-SCRF model. It was confirmed that the substrate with an ester fragment prefers the E1cB to the S_N2 mechanism. In the transition state of the S_N2 mechanism with a carboxylate ion fragment, the nucleophile SH^- locates far from the reaction center due to the electrostatic repulsion between the COO^- fragment and SH^-. This repulsion causes high activation barrier in the gas phase while polar solvent can reduce the barrier height. Therefore, reaction conditions can control reactivity of carboxylic acid. On the basis of analysis of the MO calculations, subsequent experiments were designed for a new dianion system to synthesize 2-pyrimidinylthio carboxylic acid from 2-tosyloxy carboxylate. We succeeded in developing a new facile method that the two reactions for thioether carried out in a one-pot procedure in excellent yield.

Introduction

2-Mercapto carboxylate derivatives are frequently used as intermediates for synthesizing many pesticides, medicines and heterocyclic compounds.[2] For example, Akiyoshi et al. reported synthesis of 2-(4,6-dimethoxypyrimidin-2-ylthio)-3-methoxy-3-methylbutanoic acid derivatives **4a**−**c**[3] via ester intermediate shown in Scheme 1. These derivatives inhibit acetolactate synthase (ALS)[4] in branched chain amino acids biosynthesis as herbicides and also have high herbicidal activities to various weeds.

In synthesizing the 2-mercapto carboxylate derivatives, 2-tosyloxy carboxylate ester **1** has been frequently used as a precursor of 2-mercapto carboxylate **2**.[5] Although several reagents such as sodium hydrosulfide hydrate, thiourea, and dithiocarboxylate have been applied to substitute the tosyloxy group of **1a** with the SH one, no corresponding ethyl 3-alkoxy-2-mercapto carboxylate **2a** was obtained. In many cases, α,β-unsaturated carboxylate ester **5** was obtained as one of the major products shown in Scheme 2. That is, β-elimination mainly proceeds to form **5** when **1a** was used as the substrate. Fortunately, we found an alternative new and more general route that used 2-tosyloxy carboxylic acid **1b** for substitution reaction with SH^-.[6] This reaction produced 2-mercapto carboxylic acid **2b** in excellent yield more than 85%. As the reaction of **1b** with SH^- yielded the

Scheme 1



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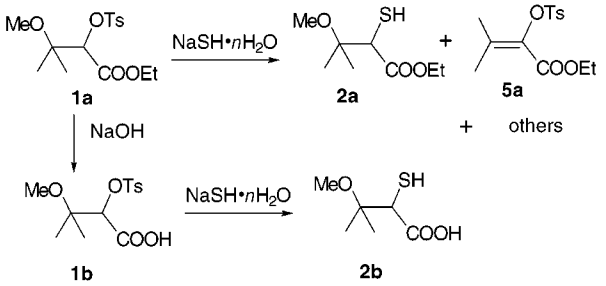
Scheme 2

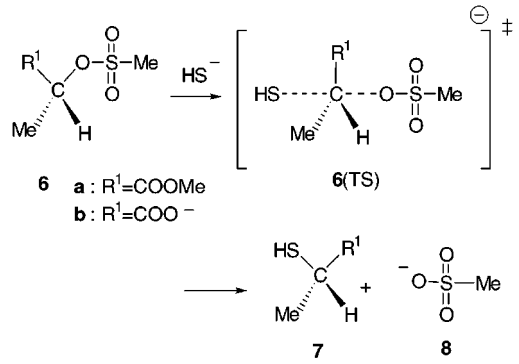


required products, the key of the present method is to use the carboxylic acid instead of the ester as a reactant.

The reactant **1** has a bulky substituents near the reaction center. It is expected that steric hindrance caused by the bulky group largely retarded substitution reactions such as those of neopentyl bromide with sodium alkoxides in protic solvents. In this case, the alkyl neopentyl ethers are not major products because side reactions such as neopentyl rearrangement, elimination, and its decomposition proceed.[7] However, there were several successful examples of S_N2 reaction of neopentyl tosylate with the large steric hindrance. Stephenson reported[8] that the reaction of (*S*)-neopentyl-1-*d* tosylate and nucleophiles proceeded through S_N2 mechanism. They proved that the inversion of the asymmetric environment occurs in the experiment. Masada also obtained results supporting the S_N2 mechanism in the reaction of neopentyl methanesulfonate and potassium 2,4,6-tri-*tert*-butylphenoxide in 1,3-dimethyl-2-imidazolinone.[9] Therefore, the S_N2 mechanism is applicable to substrates with a bulky group in aprotic solvent, for example, DMSO, DMF, DMI, and HMPA, when they have a leaving group such as iodine, tosylate, mesylate, etc. Combination of the good leaving group and aprotic solvent make the reaction possible under the S_N2 mechanism even though the reactant has bulky substituents.

In the present experiment, we used 2-(tosyloxy)-3-methoxy-3-methylbutyric acid and DMF. This is the condition that the S_N2 mechanism is applicable although we used a different nucleophile, SH^-. The kinetics data of our preliminary experiments showed that the rate is proportional to the product of **1b** and SH^-.[10] Therefore, we regarded the substitution in Scheme 1 as a reaction in which SH^- ion acts as nucleophile and replaces the tosyloxy group of **1** through the S_N2 mechanism.

In the present study, we performed ab initio molecular orbital (MO) calculations at the MP2/6-31+G*//RHF/6-31+G* level of theory in order to answer why the carboxylic acid is suitable for controlling the reaction. **1** is too large to perform ab initio MO calculations with large basis sets such as 6-31+G*.[11] Therefore, we used model molecules **6** as shown below for simplicity of calculations. In the model molecules, a tosyl group in **1** was replaced with a mesyl group and the $C(CH_3)_2(OCH_3)$ fragment with a methyl group. Methyl ester in **6a** was adopted instead of ethyl ester used in the experiments. As experiments used large excess of sodium hydrosulfide hydrate, the carboxyl group in **1b** should release a proton in the reaction conditions so that the reactant exists in a carboxylate ion form.



The reaction for **6b** contains two negative charges, one on carboxylate anion of **6b** and the other on sulfide anion. Hereafter, the S_N2 reactions for the ester and the carboxylate ion are called path A and B, respectively. According to the results of MO calculations, we examined a new type of the reaction which directly produces **4** with R^1 = OH from **1**. The reaction worked well in excellent yield more than 90%.

Method of Calculation

Ab initio MO calculations were performed by using the Gaussian94 program.[12] All the geometries were fully optimized at the RHF/6-31+G* levels of theory, and the energy relation among reactants, transition states (TSs), and products were refined at the MP2/6-31+G*//RHF/6-31+G* levels of theory. The vibration frequency calculation showed the obtained TS structures to have only one imaginary frequency. Solvent effects were taken into account for the optimized geometries by means of the isodensity surface polarized continuum model (IPCM) SCRF calculation[13] with a dielectric constant of 36.7, whose value corresponds to that of dimethylformamide (DMF). The intrinsic reaction coordinates (IRCs)[14] were also calculated to analyze the mechanism in detail at the RHF/6-31+G* level of theory. Table 1 summarizes total and relative energies of the structures obtained.

Results and Discussion

Experimental Results. The thiolation used sodium hydrosulfide hydrate **3** by 5-hold equiv mol of reactants

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(10) We have carried out kinetic experiments and found that the present reaction proceeds in the second-order reaction which depends on the first order with respect to the concentration of **1b** and sodium hydrosulfide hydrate.

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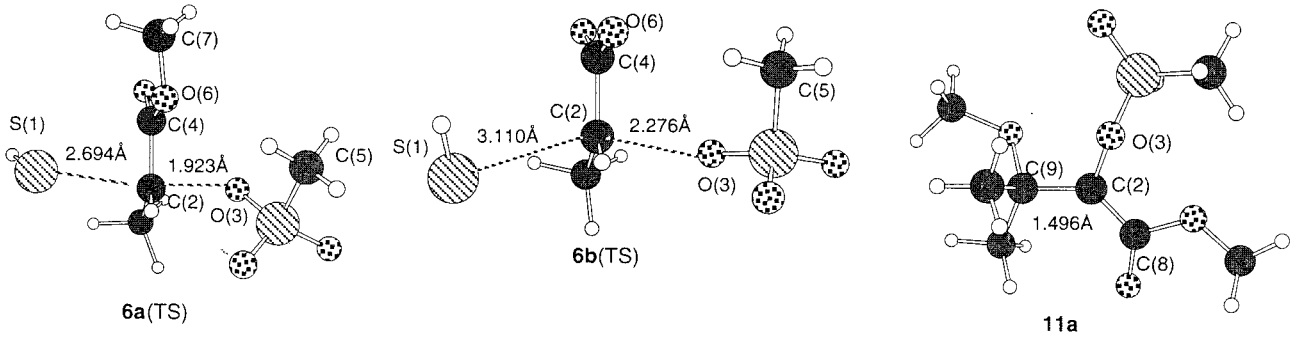

Figure 1. Optimized structures of transition states for paths A and B, and the intermediate **11a** of the ElcB mechanism for **10**.

Table 1. Total Energies (hartree) and Relative Energies (ΔE, kcal mol^{-1}) of Reactants, TSs, and Products of the S_N2 Reaction

compound	MP2/6-31+G*// RHF/6-31-G* [c]	ΔE (kcal mol^{-1})	MP2/6-31+G*// RHF/6-31+G* (DMF)[d]	ΔE (kcal mol^{-1})
6a + SH$^-$ [a]	−1366.90011	0	−1366.99506	0
6a(TS)	−1366.87610	15.1	−1366.96279	20.2
7a + **8**[a]	−1366.94865	−30.5	−1367.04208	−29.5
6b + SH$^-$ [b]	−1327.18870	0	−1327.38263	0
6b(TS)	−1327.06955	74.8	−1327.33362	30.8
7b + **8**[b]	−1327.23529	−29.2	−1327.43238	−31.2

[a] Total energies for the geometries of the combined system which were optimized by using the last geometry of IRC calculations. [b] Relative energies (ΔE) are estimated on the base of total energies of reactants, **6a** or **6b**, and SH$^-$. [c] Total energies of SH$^-$, **6b**, **7b**, and **8** and SH$^-$ at MP2/6-31+G*//RHF/6-31+G* level of theory are −398.22952, −928.95917, −664.69333, and −662.5419629 hartree, respectively. [d] The MP2/6-31+G*//RHF/6-31+G* energies of IPCM-SCRF calculations with $\epsilon = 36.7$ in DMF for SH$^-$, **6b**, **7b**, and **8** are −398.33268, −929.04995, −664.78855, and −662.64382 hartree, respectively.

Table 2. Geomerical Parameters of Reactants and TSs for the S_N2 Reaction

		6a	**6b**	**6a**(TS)	**6b**(TS)
bond lengths (Å)	S(1)−C(2)	−	−	2.694	3.110
	C(2)−O(3)	1.428	1.464	1.923	2.276
	S(1)−C(4)	−	−	2.905	3.839
	S(1)−O(6)	−	−	3.306	4.255
	O(3)−O(6)	2.638	2.710	2.902	3.334
	C(4)−C(5)	4.218	3.713	4.054	3.778
bond angles (deg)	∠S(1)−C(2)−O(3)	−	−	172.7	203.6

and was performed in DMF, the polar aprotic solvent. In path A, carboxylate ester **3** was added to **1a** in DMF and stirred for 30 min at 5−10 °C. TLC check indicated that **1a** disappeared and many spots appeared in the reactant mixture. The reaction gave **5** in yield ca. 20% as the main product, and no target compound **2a** was obtained. The amount of other compounds was too small to isolate. For carboxylic acid in path B, **3** was added to **1b** in DMF at room temperature and stirred for 3 h at 50−55 °C. The reaction gave **2b** in excellent yield more than 85% as the main product and no α,β-unsaturated carboxylate ester was obtained.

Difference of the S_N2 Mechanism between 6a and 6b. There are large difference between the carboxylate ester and the carboxylic acid in the calculated TS structures shown in Figure 1. Their geometrical parameters are summarized in Table 2. S(1)−C(2) and C(2)−O(3) distances in **6a**(TS) were calculated to be 2.694 and 1.923 Å. As the S(1)−C(2)−O(3) angle was calculated to be 172.7°, S(1), C(2), and O(3) atoms align almost linear in the TS, i.e., a typical TS geometry for S_N2 reactions.

While the S(1)−C(2) and C(2)−O(3) lengths in **6b**(TS) turned out to be 3.110 and 2.276 Å, respectively. They are much longer by 0.416 and 0.353 Å than the corresponding lengths for **6a**(TS). The two distances in **6b**(TS) are rather long in comparison with those of TSs for S_N2 mechanisms concerning SH$^-$ ion as a nucleophile.[15] The S(1)−C(2)−O(3) angle of **6b**(TS) was calculated to be 203.6°, which is larger by 30.9° than that of **6a**(TS). Therefore, the geometry of **6b**(TS) largely deviates from ordinal S_N2 TS structures. The S(1)−O(6) distance was calculated to be 4.255 Å which is longer by 0.949 Å than the corresponding length of **6a**(TS). The long S(1)−C(2) distance and the wide S(1)−C(2)−O(3) angle are convenient to avoid large electrostatic repulsion between the two anion centers.

It may not be true that **6b**(TS) is a real TS for the S_N2 reaction since its geometry largely deviates from the ordinal TS structures for S_N2 reactions. To confirm whether **6**(TS) connects **6** and **7**, IRC calculations were performed for both **6a**(TS) and **6b**(TS). Figure 2 displays the geometry transformation together with potential energy profiles along the IRCs. The C(2)−O(3) distance at $s = -2.75$ amu$^{1/2}$ Bohr in path A is 1.500 Å, which is similar to that in **6a** (1.428 Å). The reaction almost completes at $s = 5.15$ amu$^{1/2}$ Bohr because the S(1)−C(2) distance is 1.883 Å, which is longer a little than that of **6a** (1.834 Å). The potential energy goes up and down sharply in both sides of the TS.

In the geometry at $s = -7.90$ amu$^{1/2}$ Bohr in path B, **6b** weakly interacts with SH$^-$ ion. Although the S(1)−C(2) distance at $s = 7.90$ amu$^{1/2}$ Bohr is 1.993 Å, longer slightly by 0.154 Å than that in **7b** (1.839 Å), the product thiol forms at this point. The potential energy goes up and down gradually in both sides of the TS. Therefore, **6b**(TS) is the real TS for the S_N2 mechanism of **6b** and SH$^-$. It should be noted that the IRC length for path B is much longer than that for path A. This propensity well correlates with the height of activation energies for each path and the Hammond postulate,[16] which expects that

(15) Several optimizations have been reported for TS geometries of S_N2 reactions using SH$^-$ ion. The distances between S atom of nucleophile and C atom of reaction center (d_{S-C}) are shown below. (a) d_{S-C}; 2.537 Å in HS- - -CH_2(CH=CH_2)- - -Cl at the mp2/6-31++G** level. Lee I.; Kim C. K.; Lee B−S. *J. Comput. Chem.* **1995**, *16*, 1045. (b) d_{S-C}; 2.515 Å in HS- - -CH_2(CH_2CN)- - -Cl at the mp2/6-31+G* level. Chung D. S.; Kim C. K.; Lee B-S.; Lee I. *J. Phys. Chem. A* **1997**, *101*, 9097. (c) d_{S-C}; 2.378 Å in HS- - -CH_2(CH_3)- - -SCH_3 at the mp2/6-31+G* level. Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 6731.

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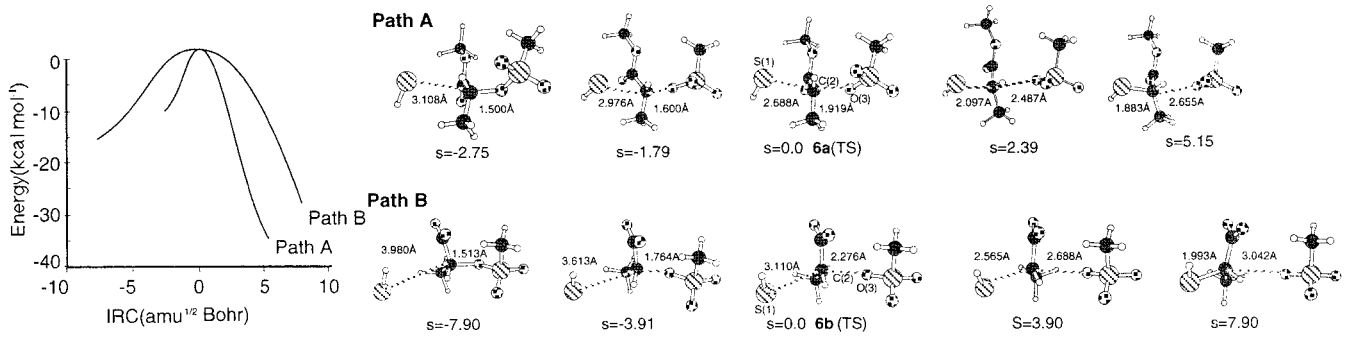

Figure 2. Potential energy profiles and the geometry transformation along the IRC for **6a** and **6b**.

Table 3. Charges Distribution for Molecules Related to the S_N2 Reactions. Values in Parentheses Are Changes Relative to Those of 6a or 6b

	Nu	RC	LG		Nu	RC	LG
6a	-1.000	0.193	-0.193	**6b**	-1.000	-0.720	-0.280
6a (DMF)	-1.000	0.206	-0.206	**6b (DMF)**	-1.000	-0.745	-0.255
6a(TS)	-0.645(-0.355)	0.208(0.015)	-0.564(0.371)	**6b (TS)**	-0.908(-0.092)	-0.298(-0.422)	-0.794(0.514)
6a (TS, DMF)	-0.528(-0.472)	0.078(-0.128)	-0.550(0.344)	**6b (TS, DMF)**	-0.773(-0.227)	-0.394(-0.351)	-0.833(0.578)

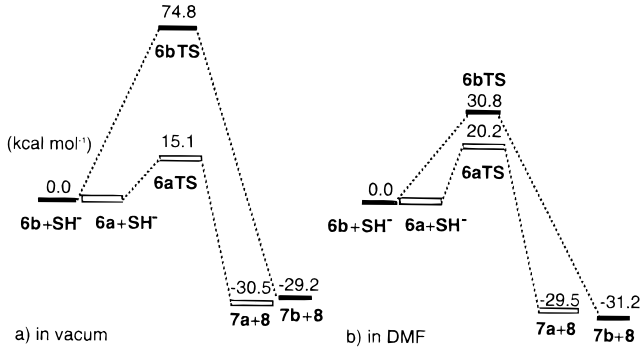

Figure 3. Energy-level diagrams (in kcal mol^{-1}) of the thiolation for **6a** and **6b**. At (a) the MP2/6-31+G*//RHF/6-31+G* level of theory and (b) the MP2/6-31G*//RHF/6-31G* level of theory including solvent effects of the IPCM−SCRF method with DMF dielectric constant.

a TS with a low activation energy locates an early point on reaction coordinate.

Figure 3 displays the energy diagram for **6a** and **6b** at the MP2/6-31+G*//RHF/6-31+G* level of theory. The activation energies (E_a) in a vacuum were estimated to be 15.1 and 74.8 kcal mol^{-1}, respectively. **6b** is higher by 59.7 kcal mol^{-1} than **6a** in term of the activation energy. The electrostatic repulsion between the two anion centers causes such a high activation barrier for **6b**(TS).

Solvent Effects. The activation barrier in a vacuum for path B is too high to expect that the S_N2 reaction proceeds under our experimental conditions. It is common knowledge[17] that polarity of solvents largely affects rates of S_N2 reactions. The IPCM−SCRF calculations were adopted to estimate the solvent effect in the present study. The E_a of **6a** in DMF was calculated to be 20.2 kcal mol^{-1} which is larger by 5.1 kcal mol^{-1} than that in a vacuum shown in Figure 3. On the other hand, that of **6b** in DMF was calculated to be 30.8 kcal mol^{-1}. The solvent effect as dielectric field decreases the barrier by as large as 44.0 kcal mol^{-1}. Therefore, the polarity of DMF reduces the electrostatic repulsion between the COO^- fragment and the SH^-. Although this value is still higher by 10.6 kcal mol^{-1} than that of **6a**, the S_N2 reaction with the two anions system is expected to proceed in our experimental conditions.

The existence of two negative charges is the key for understanding the reaction so that the solvent effects for the charge distribution is analyzed. Table 3 summarizes charge distribution of three fragments, i.e., SH^-, the reaction center, and the leaving group, of **6** and **6**(TS) in a vacuum and DMF. They are designated as Nu, RC, and LG, respectively.

The charges of the MsO fragment (LG) of **6a** in a vacuum and in DMF were estimated to be −0.193 and −0.206, respectively. As those for **6a**(TS) are −0.564 and −0.550, the difference of charges of between **6a** and **6a**(TS) are 0.371 and 0.344. The SH^- fragment (Nu) loses its charge by 0.355 in **6a**(TS) and the MsO moiety gets almost of this density. Although the Nu in **6a**(TS, DMF) loses its electron density by 0.472 which is larger than that of **6a**(TS), the MsO fragment in DMF accepts electron density by 0.344 less than that of **6a**(TS), and

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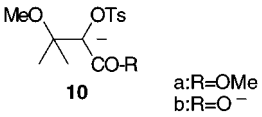
the residual charge stays in the RC. The electron density smoothly flows from the nucleophile to the MsO fragment in a vacuum while DMF disturbs its smooth redistribution. This is partially responsible for the increase in the height of the activation barrier of path A in DMF.

As **6b** has two negative charges, the electron density in the SH^- ion hardly moves to the reaction center in a vacuum. For example, the SH^- anion losses a small amount of the charge in **6b**(TS) (−0.092) while the LG gains much larger charge (0.514) than that for **6a**(TS). The difficulty in redistributing charge of the two charges system causes the activation barrier as high as 74.8 kcal mol^{-1} in a vacuum. It is important to note that DMF facilitates this charge redistribution very much. The SH^- anion in **6b**(TS, DMF) loses the electron density by 0.227 although this value is still smaller than that of **6a**(TS). The increase of charge in the LG of **6b**(TS, DMF) is the largest in all the TSs obtained (0.578), and then the electron density of the LG becomes −0.833. This easy redistribution of electron density in DMF is effective to reduce the activation energy of path B more than 40 kcal mol^{-1}.

In the two negative charges S_N2 reaction, the electrostatic repulsion prevents the SH^- anion from attacking the RC at the beginning of the reaction. However, the charge of the RC flows by more than half of its initial value to LG in the TS. This redistribution decreases the electrostatic repulsion between the SH^- and the COO^- fragment and makes MsO group leave easily from the RC. The SH^- anion can attack the RC after adequate redistribution of electron density is occurred in the RC.

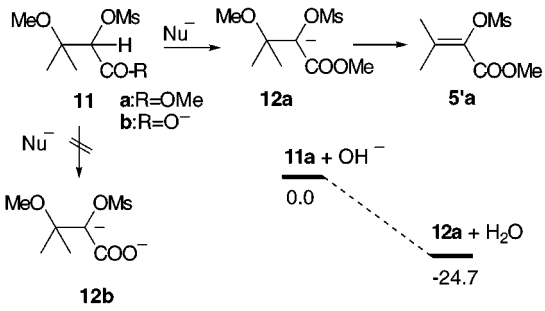
***β*-Elimination of 1a.** The main product for the reaction of **1a** and SH^- is not the thiolated one but the α,*β*-unsaturated carboxylate ester **5a** as discussed above. The first step for this product formation is extraction of the α-proton at the C(2) of **1a** to form an anionic intermediate **10a**. Therefore, the stability of **10a** is the key for formation of **5**.



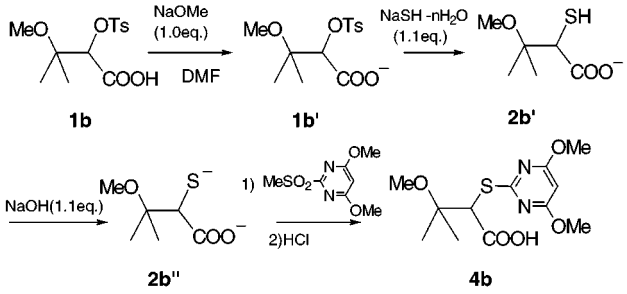
Two electron-withdrawing groups at the α-carbon, $COOCH_3$ and MsO, enhance acidity of the α-proton and stabilize the anion formed.[18] Furthermore, **1a** contains a leaving group (OMe) and two Me groups at the *β*-position. These groups also stabilize the anion intermediate very much.[19] Although we used **3** by 5-fold equiv mol of **1a** in our experiments, the SH^- ion mainly attacks not the α-proton but the α-carbon atom because of its high nucleophilic polarity.[16] The OH^- ion, which is generated from H_2O contained in sodium hydrosulfide hydrate, acts as base extracting a proton at the α-carbon.[20]

To confirm stability of this anionic intermediate, **12a** as a model for **10a**, shown in Scheme 3, was optimized, and its optimized structure was depicted in Figure 1.

Scheme 3



Scheme 4



The extraction of the α-proton is exothermic by 24.7 kcal mol^{-1}; that is, the anionic intermediate is more stable than **11a** as expected. These results suggest that E1cB mechanism[21] is applicable to formation of α,*β*-unsaturated carboxylate ester derivatives. Therefore, forming the anionic intermediate proceeds instead of replacing the TsO^- fragment with the SH^- ion. **12b** is expected to be very unstable because it possesses an anionic carbon adjacent to the carboxylate ion. We obtained no stable geometry for **12b**. The calculated results are consistent with the experimental one whereby **1b** gave no α,*β*-unsaturated product.

New Synthetic Procedure. The ab initio MO calculations indicate that 2-tosyloxy carboxylate ester in path A is too reactive to control its thiolation by using SH^- ion. In this path, it was observed that the reaction produces undesired α,*β*−unsaturated product because the ester reactant prefers E1cB to S_N2 mechanism as discussed above. On the other hand, the electrostatic repulsion between the SH^- ion and the carboxylic anion fragment in path B causes not only lowering reactivity of the reactant but also avoiding the undesired *β*-elimination. The SCRF calculations show that the appropriate polarity of solvent reduces the activation energy of the S_N2 reaction very much. Therefore, we can control the S_N2 reaction with a strong SH^- nucleophile by proper combination of a changed substrate and a polar solvent. According to this concept, we tried subsequent experiments and developed a new synthetic route shown in Scheme 4. This route makes it possible to synthesize 2-pyrimidinylthio carboxylic acid in a one-pot procedure.

In a new procedure, **1b′** with a COO^- fragment was prepared with 1.0 mol equiv of sodium methoxide with **1b**, followed by adding 1.1 mol equiv of sodium hydrosulfide hydrate. Stirring for 3 h at 50 °C gave **2b′**. After cooling the reaction mixture to 10 °C, adding 1.1 mol equiv of 10% aqueous NaOH yielded **2b″** with two

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negatively charged fragments. Subsequently, methanesulfonylpyrimidine were added and stirred for 10 min, and finally, the reaction mixture was neutralized with 10% HCl. Thiolation and subsequent sulfidation proceeded in one pot and produced **4b** in excellent yield more than 92%.

Concluding Remarks

An S_N2 reaction cannot apply for thiolation of 2-tosyloxy carboxylate ester **1a** because of the stability of the anionic intermediate extracted its α-proton. On the other hand, thiolation of 2-tosyloxy carboxylic acid proceeds through the S_N2 reaction. Electrostatic repulsion between the COO^- fragment and the anionic nucleophile SH^- reduces the reactivity of the substrate for the *β*-elimination and gives selectivity for the S_N2 reaction. The combination of the two-charges technique and proper solvent makes it possible to control the simple S_N2 reaction. On the basis of above analysis of MO calculations, we succeeded in controlling the S_N2 reaction between sodium hydrosulfide hydrate with high nucleophilicity and 2-tosylate with high leaving ability. This procedure can be performed in one pot and gives **4b** in excellent yield. The development of a facile procedure for 2-pyrimidinylthio carboxylic acid from 3-alkoxy-2-hydroxy carboxylate made it possible to synthesize many 3-alkoxy-2-(pyrimidinylthio)alkanoate derivatives.

Experimental Section

General. Compounds **1a**, **1b**, **2b**, and **4b** were prepared according to the methods described perviously.[3a,6] All experimental works were performed under nitrogen atomosphere. ^{1}H NMR spectra were recorded at 300 MHz. All NMR spectra are reported in ppm. Mass spectra were recorded in *m*/*z*. Preparative chromatography was performed on Wako gel C-200.

Ethyl 3-Methoxy-3-methyl-2-(4-toluenesulfonyloxy)butanoate (1a). To a solution of ethyl 3-methoxy-3-methyl-2-hydroxybutanoate (17.6 g, 0.10 mol), *p*-toluenesulfonyl chloride (20.9 g, 0.11 mol), and triethylamine (11.1 g, 0.11 mol) in CH_2Cl_2 (150 mL) was added *N*,*N*-(dimethylamino)pyridine (0.2 g, 0.11 mol), and the mixture was allowed to stir at room temperature for 12 h. The reaction mixture was poured into water, and the organic phase was separated, washed with a brine solution twice, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and crude product was obtained as oil. Chromatography (silica gel/hexanes−ethyl acetate 3:1 v/v) gave **1a** as colorless oil in 89.4% yield (29.5 g). ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 1.26 (s, 3 H), 1.34 (s, 3 H), 2.43 (s, 3 H), 3.18 (s, 3 H), 4.07 (q, J = 7.2 Hz, 2 H), 4.71 (s, 1 H), 7.32−7.35 (d, 2 H), 7.80−7.83 (d, 2 H). MS *m*/*z*: 331 (MH^+). Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71. Found: C, 54.36; H, 6.76.

Ethyl 3-Methyl-2-(4-toluenesulfonyloxy)-2-butenoate (5a). To a solution of **1a** (3.3 g, 0.01 mol) in DMF (30 mL) was added sodium hydrosulfide hydrate (70% purity, 3.2 g, 0.03 mol) in DMF (10 mL), and the resulting mixture was allowed to stir for 1 h at room temperature. The reaction mixture was poured into 200 mL of acidic ice−water (5% HCl aqueous solution) and extracted with ethyl acetate (20 mL × 2). The organic phase was washed with brine twice and dried over anhydrous Na_2SO_4. Removal of solvent in vacuo afforded oil, which was subjected into column chromatography (hexanes−ethyl acetate 1:6 v/v) to give **5** as colorless oil (20.1%, 0.62 g). ^{1}H NMR ($CDCl_3$) δ 1.16−1.20 (t, J = 7.2 Hz, 3 H), 1.76 (s, 3 H), 2.15 (s, 3 H), 2.45 (s, 3 H), 4.07 (q, J = 7.2 Hz, 2 H), 7.33−7.36 (d, 2 H), 7.82−7.85 (d, 2 H). MS *m*/*z*: 299 (MH^+). Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 55.83; H, 6.15.

3-Methoxy-3-methyl-2-(4-toluenesulfonyloxy)butanoic Acid (1b). To a solution of **1a** (16.5 g, 0.05 mol) in ethanol (60 mL) was added aqueous NaOH (5%, 30 mL), and the mixture was allowed to stir at room temperature for 1 h. Ethanol was removed under reduced pressure, and aqueous HCl (5%, 40 mL) was added to the residue. The resulting mixture was extracted with chloroform (50 mL). The organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford solid, which was washed with 30 mL of hexane to give **1b** as a white solid in 87.7% yield (13.2 g). ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.31 (s, 3 H), 2.45 (s, 3 H), 3.26 (s, 3 H), 4.77 (s, 2 H), 7.33−7.36 (m, 2 H), 7.82−7.85 (m, 2 H), 8.20−8.50 (br, 1 H). MS *m*/*z*: 303 (MH^+). Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.64; H, 6.00. Found: C, 51.68; H, 5.98.

2-Mercapto-3-methoxy-3-methylbutanoic Acid (2b). To a solution of **1b** (6.0 g, 0.02 mol) in DMF (30 mL) was added sodium hydrosulfide hydrate (70% purity, 6.4 g, 0.08 mol) in DMF (10 mL), and the mixture was allowed to stir at 60 °C for 3 h. The resulting mixture was cooled and poured into acidic ice−water (200 mL). The resulting mixture was extracted with ethyl acetate (20 mL × 2), and the organic phase was washed with brine twice and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified through chromatography (on silica gel eluting with hexane−ethylacetate−acetic acid 1:1:0.1 v/v) to give **2b** as colorless oil in 92.2% yield (3.54 g). ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 6 H), 2.32 (d, J = 9.2 Hz, 1 H), 3.30 (s, 3 H), 3.52 (d, J = 9.2 Hz, 1 H), 9.45 (br, 1 H). MS *m*/*z*: 165 (MH^+). Anal. Calcd for $C_6H_{12}O_3S$: C, 43.88; H, 7.37. Found: C, 43.43; H, 7.26.

2-(4,6-Dimethoxypyrimidin-2-ylthio)-3-methoxy-3-methylbutanoic Acid (4b). To a solution of **2b** (0.86 g, 5 mmol) in 4% aqueous NaOH (12 mL, 12 mmol) was added a solution of 4,6-dimethoxy-2-methylsulfonylpyrimidine (1.09 g, 5 mmol) in acetone (5 mL) at 5 °C, and the mixture was allowed to stir at room temperature for 1 h. The resulting solution was added to 10 mL of 5% aqueous HCl solution and extracted with ethyl acetate (20 mL × 2). The organic phase was washed with brine twice and dried over anhydrous Na_2SO_4. Ethyl acetate was removed under reduced pressure, and the obtained pale brown solid was purified through chromatography (hexanes−ethyl acetate−acetic acid 1:1:0.1 v/v) gave **4b** as white solid in 81.2% yield (1.34 g). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 1.46 (s, 3 H), 3.34 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.72 (s, 1 H), 5.75 (s, 1 H), 7.27 (s, 1 H). MS *m*/*z*: 331 (MH^+). Anal. Calcd for $C_{12}H_{18}N_2O_5S$: C, 47.67; H, 6.00. Found: C, 47.61; H, 5.92.

Synthesis of 4b by the One-Pot Method. To a solution of **1b** (3.0 g, 0.01 mol) in DMF (30 mL) was added sodium methoxide in methanol solution (28% solution, 1.93 g, 0.01 mol) at 5 °C, and the reaction mixture was allowed to stir for 0.5 h. Sodium hydrosulfide hydrate (70% purity, 0.8 g, 0.01 mol) was added to the mixture, which was allowed to heat at 50 °C for 2 h. After cooling to room temperature, and then aqueous NaOH (8% solution, 5.5 mL, 0.011 mol) was added to the solution. Ten minutes later, to a solution of the mixture was added 4,6-dimethoxy-2-(methylsulfonyl)pyrimidine (2.18 g, 0.01 mol) in DMF (5 mL), and the resulting mixture was allowed to stir for 0.5 h. The resulting solution was poured into aqueous HCl (5%, 30 mL) and extracted with ethyl acetate (30 mL x 2). The organic phase was washed with brine twice and dried over anhydrous Na_2SO_4. Ethyl acetate was removed under reduced pressure. The obtained pale brown solid was purified through chromatography (hexanes−ethyl acetate−acetic acid 1:1:0.1 v/v) to give **4b** as white solid in 92.4% yield (3.05 g).

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Supporting Information Available: Cartesian coordinates and calculated total energies of all the structures in the present study. This material is available free of charge via the Internet at http://pubs.acs.org.

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