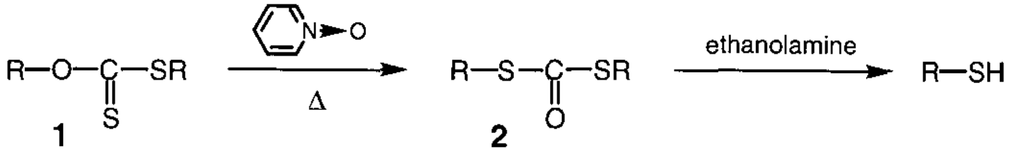
CATALYTIC THIONE-THIOL REARRANGEMENT OF XANTHATES BY 4-DIALKYLAMINOPYRIDINE

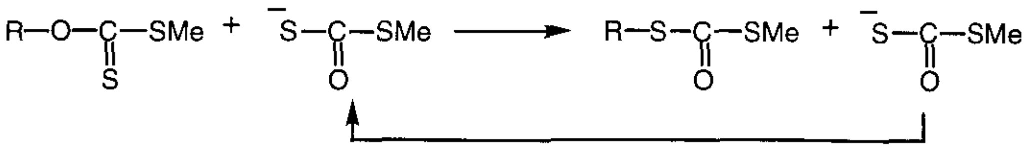
Hidetoshi Nakagawa, Masashi Eto, and Kazunobu Harano*†

Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-hon-machi,
Kumamoto 862-0973, Japan

Abstract- Pyridines bearing electron-donating substituents are useful catalysts for the rearrangement of *O,S*-dialkyl xanthates (**1**) to *S,S*-dialkyl dithiocarbonates (**2**). The rearrangement was analyzed by semiempirical and *ab initio* molecular orbital methods. The transition-structure analyses indicate that the pyridine-ring nitrogen of dialkylaminopyridine rather than the dialkylamino nitrogen attacks the *O*-alkyl carbon of xanthates. The reaction proceeds through an S_N2 mechanism to give the dithiolcarbonate anion ($RSCOS^-$) which acts as an actual catalyst.

A brief synthesis of thiols from alcohols under neutral non-aqueous conditions would be very attractive to synthetic chemists.[1] Combination of the catalytic thione-thiol rearrangement of *O,S*-dialkyl dithiocarbonates (xanthates **1**) and aminolysis of the rearranged products (**2**) with ethanolamine serves as an efficient method for the generation of thiols,[2] in which all of the reactions and work-up can be carried out in only a distilling flask. In this connection, we have reported that pyridine *N*-oxides are efficient catalysts for the thione-thiol rearrangement, in which the dithiolcarbonate anion ($RSCOS^-$) is the actual catalyst which attacks *O,S*-dialkyl xanthates to give the dithiol ester with regeneration of $RSCOS^-$.[3]



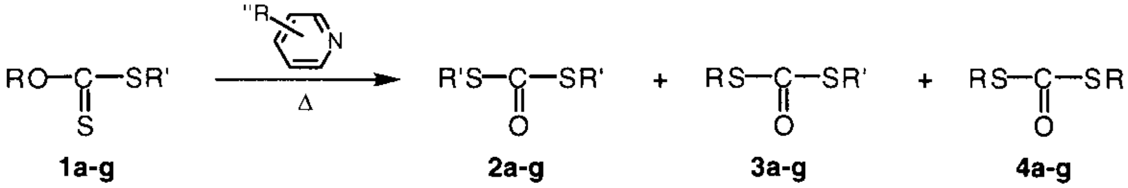


In the rearrangement, pyridine *N*-oxides are assumed to act as triggers to generate $RSCOS^-$.[3d]

In the course of our study, we found that 4-dialkylaminopyridines have similar catalytic activity and communicated the synthetic application of 4-piperidinopyridine.[4] These results are discussed here in detail in comparison with previous works and with further additional data that we have obtained.

Results and Discussion

Catalytic Activity of Pyridines Based on the results of pyridine *N*-oxides,[3] we considered that the parent pyridines bearing electron-donating groups might also show a similar catalytic reactivity because they have a high-lying highest occupied molecular orbital (HOMO) with the large HOMO coefficient and a negative net charge on the pyridine nitrogen atom. We compared the relative reactivity of several pyridines by using *O*-ethyl *S*-methyl xanthate (**1a**, R=Et) as a substrate. The reaction was carried out by warming a mixture of the xanthate and various amounts of pyridines at 80-100°C. The product mixtures were analyzed by 400 MHz ^{1}H-NMR spectrometer.



a: R=Et, R'=Me; **b**: R=*n*-Pr; R'=Me; **c**: R=*n*-Bu, R'=Me; **d**: R=*i*-Pr, R'=Me;
e: R=$PhCH_2CH_2$, R'=Et; **f**:$C_5H_4NCH_2CH_2$, R'=Et; **g**: R=Cyclohexyl, R'=Me

Table 1. Effect of Reactant/Catalyst Ratio on the Yield of **2a**, **3a** and **4a** in the Reaction of *O*-Ethyl *S*-Methyl Xanthate (**1a**)

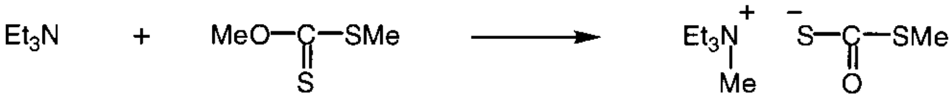
Exp. No.	Pyridines **1a**:Cat.	Temp. (°C)	Time (hrs)	Total Yield of the Products (%)
	4-Dimethylamino (DMAP)[a)]			
1	1:0.1	80	4.0	56
	4-Piperidino (PP)[b)]			
2	1:0.5	80	1.5	64
3	1:0.2	80	2.0	61
4	1:0.1	80	3.0	65[c)]
5	1:0.05	80	6.0	72
6	1:0.02	80	10.0	72
	3,5-Dimethyl[b)]			
7	1:0.5	100	3.0	74
	4-Methyl[b)]			
8	1:0.5	100	4.0	67
	Pyridine[b)]			
9	1:0.5	100	24.0	40

a) In DMSO-d_6. Use of the *N*-oxide of DMAP gave the dithiol esters in 87% yield. b) No solvent was used. c) Use of 4-piperidinopyridine *N*-oxide (PPNO) gave the dithiol esters in 75% yield.

Table 1 shows that a small amount of 4-dimethylaminopyridine (DMAP) exhibited sufficient activity to induce the rearrangement, whereas, a large amount of 3,5-dimethylpyridine (3,5-lutidine) was required for the same catalytic activity.

The activity of DMAP is assumed to be comparable to that of the corresponding *N*-oxide (DMAPNO).[3c] In the cases of DMAP and DMAPNO, dimethyl sulfoxide (DMSO) was used as solvent because of the low solubility in xanthates. In contrast, 4-piperidinopyridine (PP) which is freely miscible with xanthates, showed high catalytic activity. The yield is not sensitive to reactant/catalyst ratio and the best yield was obtained at a reactant to catalyst molar ratio of 20-50 (Exp. Nos. 5, 6). When a large amount of catalyst was used (Exp. No. 2), the yield of the rearranged products decreased, presumably a consequence of formation of the pyridinium salt and its decomposition product. The application of PP as catalyst to several xanthates is shown in Table 6 (EXPERIMENTAL). Xanthates of primary alcohols easily underwent the thione-thiol rearrangement to give the mixtures of the dithiol esters in moderate yields. On the other hand, xanthates of secondary alcohols required more forcing reaction conditions.

Catalytic Activity of Aliphatic Amines Previously, it has been reported that *O*,*S*-dimethyl xanthate reacted with triethylamine to give the quaternary salt, during which the thione-thiol rearrangement occurred.[5] However, the reaction with triethylamine is limited only to *O*-methyl and *O*-ethyl S-alkyl xanthates.



$$\mathrm{Et_3N} + \mathrm{MeO{-}\underset{\underset{S}{\|}}{C}{-}SMe} \longrightarrow \mathrm{Et_3\overset{+}{\underset{\underset{Me}{|}}{N}}}\ \ \mathrm{\overset{-}{S}{-}\underset{\underset{O}{\|}}{C}{-}SMe}$$

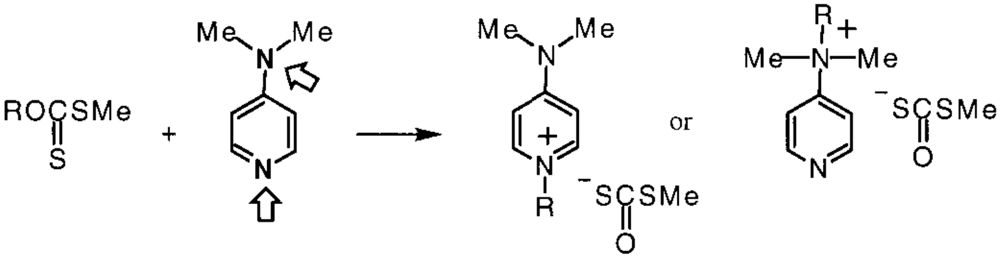
Based on our results, we considered that the steric hindrance of alkyl group of amines is a main contributor for rate retardation. Therefore, we tried to use cyclic *tert*-amines as catalysts. The results are summarized in Table 2. Consequently, the activity of triethylenediamine is comparable to that of 4-piperidinopyridine.

Table 2. Effect of Reactant/Catalyst Ratio on the Yield of **2a**, **3a** and **4a** in the Reaction of *O*-Ethyl *S*-Methyl Xanthate (**1a**)

Exp. No.	Amines **1a**:Cat.	Temp. (°C)	Time (hrs)	Total Yield of the Products (%)
	Triethylamine			
1	1:0.1	80	11.0	56
	Triethylenediamine			
2	1:0.1	80	2.5	52
3	1:0.05	80	4.5	67
4	1:0.02	80	9.0	68
	Quinuclidine			
5	1:0.1	80	2.0	55
	Hexamethylenetetramine			
6	1:0.5	100	2.0	10

The yields of the rearranged products for *O*-Alkyl *S*-methyl xanthates using triethylenediamine catalyst are as follows; *n*-propyl 62%, *n*-butyl 56%, isopropyl 54%, cyclohexyl 21%. The product ratios are listed in Table 7.

Molecular Orbital Study In the catalysis of 4-dialkylaminopyridine, both pyridine-ring nitrogen and dialkylamino one would react with xanthates to form the 1-alkylpyridinium and 4-pyridyltrialkylammonium dithiocarbonates, respectively.



In order to determine the reaction site of the first-step reaction, the molecular orbital (MO) studies were carried out.

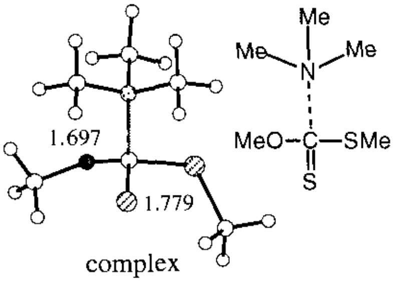
First of all, we undertook MO calculations on the reactions of trimethylamine with *O,S*-dimethyl xanthate using PM3 approximation.[6a,b] Before the formation of TS, a molecular complex might be formed from the Coulombic interaction between the lone pair of trimethylamine and the thiocarbonyl carbon. However, the heat of reaction was calculated to be endothermic, ruling out the intervention of such a complex.

The S_Ni and S_N2 transition structures are depicted in Figure 1 and the heats of formation are listed in Table 3. The S_N2 transition state is found to be 24.7 kcal/mol more stable than the S_Ni transition state, in accordance with the result for the reaction of pyridine *N*-oxide with *O,S*-dimethyl xanthate.[3d]

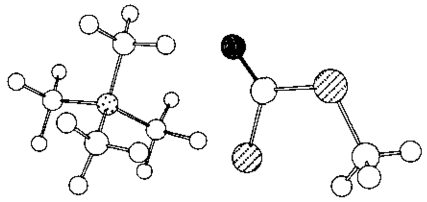
Table 3. Heats of Formation of the GS's and TS's involved in the Reaction of *O,S*-Dimethyl Xanthate with Trimethylamine[a)]

Compound	ΔHf	ΔΔHf
MeO(C=S)SMe	-0.8	
Me_3N	-10.9	
MeO(C=S)SMe + Me_3N	-11.7	0.0
TS S_N2-type	36.0	47.7[b)]
TS S_Ni-type	60.7	72.4
Tetramethylammonium dithiocarbonate[c)]	-14.5	-2.8
Complex[d)]	13.5	25.2

a) kcal/mol. b) B3LYP/6-31G* calculation gave 24.7 kcal/mol. c) Derived from IRC calculation. d) Optimized structure.

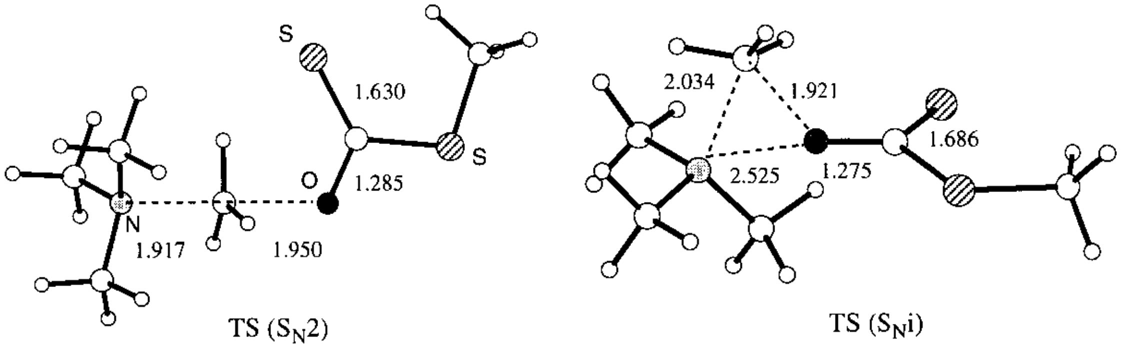


complex



Tetramethylammonium dithiocarbonate

In the S_N2 transition structure, the interacting N--C and C--O distances are 1.917 and 1.950 Å, respectively. The methyl carbon has a typical sp^2 character (summation of angles around the carbon is 358.6°) and the O--CSSMe and S--COSMe distances are 1.285 and 1.630 Å, respectively. The IRC calculation starting from the S_N2 transition structure gave tetramethylammonium dithiocarbonate.

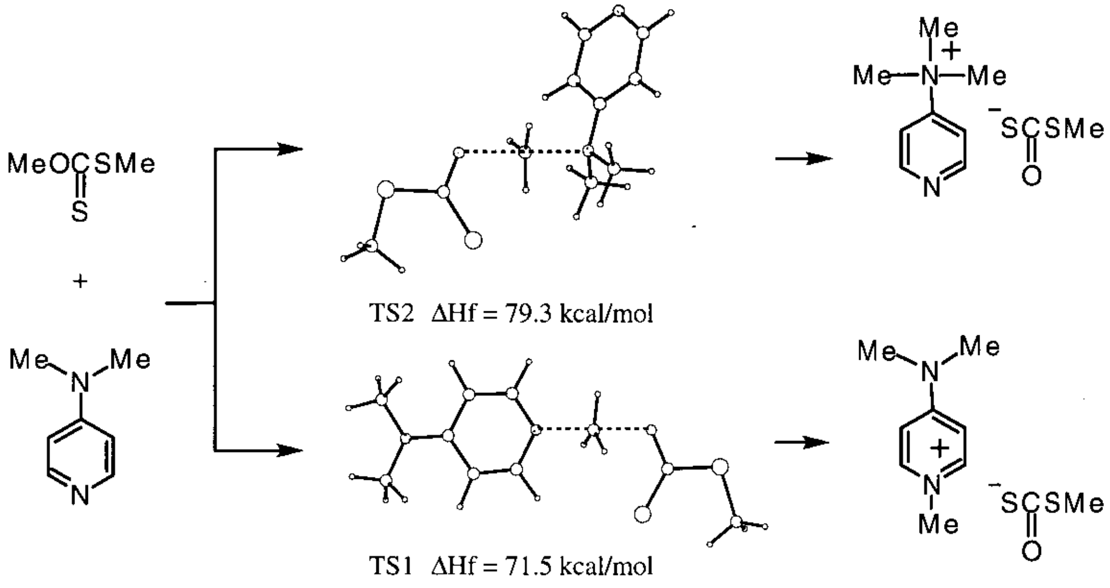


TS (S_N2)

TS (S_Ni)

Figure 1. PM3-Calculated TS Structures for the S_N2- and S_Ni-type Reaction of *O,S*-Dimethyl Xanthate with Trimethylamine

Next, based on these results, the MO calculations on the reactions of *O,S*-dimethyl xanthate with DMAP were carried out. In the reaction, two reaction sites, the pyridine-ring nitrogen (TS1) and dimethylamino nitrogen (TS2) are possible. Inspection of the FMO[7] energies and coefficients indicates that the HOMO (-8.86 eV) has a large coefficient (-0.651) on the dimethylamino nitrogen, whereas the ring nitrogen lone pair coefficient (-0.727) appeared in 3rd HOMO (-10.07 eV).



TS2 ΔHf = 79.3 kcal/mol

TS1 ΔHf = 71.5 kcal/mol

Figure 2. PM3-Calculated TS Structures for the S_N2-type Reactions of *O,S*-Dimethyl Xanthate with DMAP

The FMO analyses could not afford a definitive clue for clarification of the reaction site. Therefore, the TS structure calculations were carried out. The PM3-calculated S_N2 transition structures for both transition states are shown in Figure 2. As shown in Figure 2, the TS1 is 7.8 kcal/mol more stable than the TS2, indicating that the attack at the pyridine-ring nitrogen is more favorable than the attack at the dimethylanimo nitrogen. The solvent effect on the reaction barrier was estimated by COSMO approach (Table 4).[6c] The calculated reaction barriers in the solvents are hardly influenced by the change of solvent polarity and *ca.* 13 kcal/mol more stable than that in gas phase.

Table 4. Energetics for the Reaction of *O,S*-Dimethyl Xanthate with Trimethylamine

Solvent (ε)	ΔHf[a)]			ΔΔHf[a)]
	MeO(C=S)SMe	Me_3N	TS	
gas (1.0)	-0.8	-10.9	36.0	47.7
ethyl acetate (6.0)	-7.9	-13.7	15.9	37.5
MeCN (35.9)	-10.5	-14.5	9.9	34.9
water (78.5)	-10.9	-14.6	9.1	34.6

a) kcal/mol.

In order to confirm the result of the semiempirical SCF MO calculations in which *3d* AOs have not as yet been included in the treatment, the B3LYP density functional theory (DFT) calculations with 6-31G* basis set were carried out.[8] The results are summarized in Table 5 and the B3LYP/6-31G* transition structures are depicted in Figure 3. The *ab initio* calculations gave similar trend to those of the semiempirical calculations. The B3LYP/6-31G* reaction barriers (ΔE) for TS1 and TS2 deduced are 23.8 and 35.3 kcal/mol, respectively. As can be seen in Figure 3, the TS2 is energetically unfavorable for steric crowding. Inspection of the nuclear repulsion energies supports this assumption.

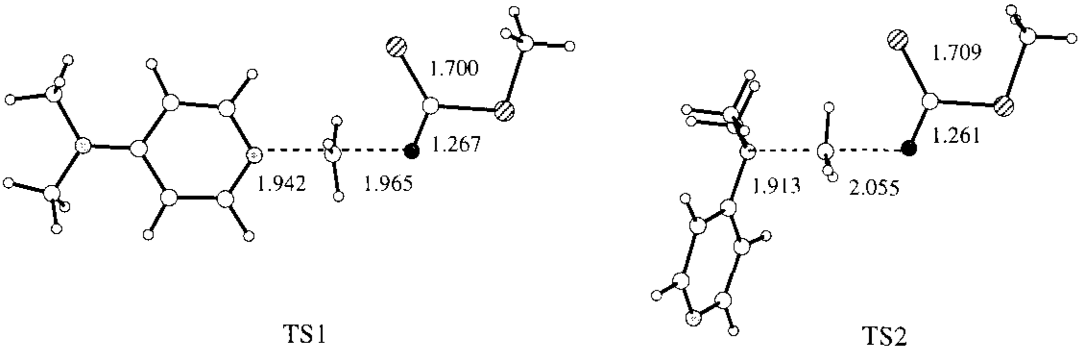


Figure 3. B3LYP/6-31G* Calculated TS Structures for the S_N2-type Reactions of *O,S*-Dimethyl Xanthate with DMAP

Table 5. B3LYP/6-31G* Energetics for the Reaction of *O,S*-Dimethyl Xanthate with DMAP[a)]

Compound	E	ΔE[b)]
MeO(C=S)SMe	-989.5242	
DMAP	-382.2573	
MeO(C=S)SMe + DMAP	-1371.7815	0.0
TS1 (S_N2 type, ring N)	-1371.7436	23.8
TS2 (S_N2 type, dimethylamino N)	-1371.7252	35.3

a) HF/3-21G* Energies for TS1 and TS2 are -1359.8393 and -1359.8181 Hartrees, respectively.
b) kcal/mol.

As previously reported, the steric effect of *O*-alkyl groups on the reaction rate has been found to be consistent with the S_N2 reaction behavior.[3] The steric interference between the atoms around the nitrogen lone pair and *O*-alkyl group of xanthates is a very important controlling factor for determination of the catalytic activity of amines. In this sense, the pyridine nitrogen lone pair is less hindered, being favorable for the manifestation of catalytic activity. Thus formed alkyldithiolcarbonate anions ($RSCOS^-$) act as actual catalysts.[3]

In conclusion, 4-dialkylaminopyridines are effective catalysts for thione-thiol rearrangement reaction of xanthates. *tert*-Amines having sterically unhindered nitrogen atom such as triethylenediamine also showed similar catalytic activity. The present method can be generally applied to the xanthates of primary alcohols. The MO modeling study gave a theoretical evidence for the reaction mechanism of *tert*-amine-catalyzed thione-thiol rearrangement of xanthates.

EXPERIMENTAL

IR spectra were determined on a Hitachi 270-30 infrared spectrophotometer equipped with a grating. ^1H-NMR spectra were obtained in $CDCl_3$ on a Hitachi R-600 (60MHz) or a JEOL GX-400 spectrometers for *ca.* 10% (w/v) solution using TMS as an internal standard and chemical shifts are expressed in δ values.

Materials Xanthates were synthesized by alkylation of the corresponding potassium xanthogenates with alkyl halides.[9] 4-Dimethylamino- and 4-piperidinopyridine were prepared according to the reported methods.[3c]

Catalytic Rearrangement of *O,S*-Dialkyl Xanthates to *S,S*-Dialkyl Dithiocarbonates (General Procedure) A mixture of *O,S*-dialkyl xanthate (**1**) and 0.1 molar eq of 4-piperidinopyridine was heated at 80°C until the spot for **1** was no longer visible by thin-layer chromatography (TLC) on silica gel. After cooling, the products were purified by choromatography on silica gel or by distillation under reduced pressure. The products derived from *O*-ethyl (**1a**), *O*-propyl (**1b**), *O*-isopropyl (**1d**), *O*-butyl (**1c**) and *O*-cyclohexyl *S*-methyl xanthates (**1g**) were identified by comparison of the spectral data with those of the authentic samples.[3,5,9] The physical data of *S*-(2-phenylethyl) *S*-methyl (**3e**), *S,S*-di(2-

phenylethyl) (**4e**), *S*-[2-(2-pyridyl)ethyl] *S*-ethyl (**3f**) and *S*,*S*-di[2-(2-pyridyl)ethyl] dithiocarbonates (**4f**) were recorded in the previous paper.[4]

Table 6. Catalytic Rearrangement of Xanthates [RO(C=S)SR', **1**] by Piperidinopyridine (PP)

Xanthate, **1**			Reaction Conditions[a)]		Yield(%)			
	R	R'	Temp.(°C)	Time (hrs)	**2**	**3**	**4**	Total
1a	Et	Me	80	3.0	17	31	17	65
1b	*n*-Pr	Me	90	3.0	25	45	18	88
1c	*n*-Bu	Me	90	4.0	20	38	17	75
1d	*i*-Pr	Me	110	4.0	18	30	8	56
1e	$C_6H_5CH_2CH_2$	Et	90	4.0	16	32	17	65[b)]
1f	$C_5H_4NCH_2CH_2$[c)]	Et	100	6.0	18	37	10	65[b)]
1g	Cyclohexyl	Me	130	35.0	1	12	0	13[d)]

a) PP/**1**=0.1. b) Isolated yield. c) 2-(2-Pyridyl)ethyl moiety. d) Cyclohexene was produced *via* Chugaev reaction.

Table 7. Rearrangement of *O*-Alkyl *S*-Methyl Xanthates [RO(C=S)SMe, **1**] in the Presence of Triethylenediamine

Xanthate, **1**		Reaction Conditions[a)]		Yield(%)			
	R	Temp. (°C)	Time (hrs)	**2**	**3**	**4**	Total
1b	*n*-Pr	80	3.5	17	33	12	62
		90	2.0	16	29	13	58
1c	*n*-Bu	80	3.5	15	28	13	56
		90	2.0	16	31	15	62
1d	*i*-Pr	110	4.0	19	33	2	54
		130	1.5	16	25	2	43
1g	cyclohexyl	150	4.0	7	7	7	21

a) Triethylenediamine/**1**=0.1.

MO Calculation Semi-empirical MO calculations were run through the ANCHOR II interface using MOPAC6.0[6b] on a Fujitsu S4/2 work station (WS) or through the CS Chem3D Pro interface using MOPAC93 on a Macintosh 8500/150 personal computer. The transition structures were fully optimized by using the XYZ keyword. The *ab initio* computations,[8] were carried out on a Scientists' Paradise Dragon AXP5A/433 computer. The stationary points calculated by PM3 method were used as starting geometries for the *ab initio* calculations. The TS structures were located by using the CALCALL option. We characterized the stationary point for the mechanism as a true transition state having a single negative Hessian eigenvalue. Graphic analysis of the MO calculation data was performed on a Macintosh 8500/150 or G3 personal computer.

The heats of formation for PM3 calculations and energies for *ab initio* calculation are summarized in Tables

3, 4 and 5. The reaction barriers of the parent reactions were estimated from the energy differences between the ground state and transition state, which are included in Tables 3, 4 and 5.

REFERENCES AND NOTES

† E-mail: harano@gpo.kumamoto-u.ac.jp

1. P. Molina, M. Alajarin, M. J. Vilaplana, and A. R. Katritzky, *Tetrahedron Lett.*, 1985, **26**, 479.
2. T. Taguchi, Y. Kiyoshima, O. Komori, and M. Mori, *Tetrahedron Lett.*, 1969, 3631.
3. a) K. Harano, H. Kiyonaga, S. Sugimoto, T. Matsuoka, and T. Hisano, *Heterocycles*, 1988, **27**, 2327; b) K. Harano, I. Shinohara, S. Sugimoto, T.Matsuoka, and T. Hisano, *Chem. Pharm. Bull.*, 1989, **37**, 576. c) K. Harano, H. Nakagawa, K. Kamei, H. Kiyonaga, and T. Hisano, *Chem Pharm. Bull.*, 1992, **40**, 1675 and references cited therein. d) H. Nakagawa, M. Eto, and K. Harano, *Tetrahedron*. 1998, **54**, 9333.
4. K. Harano, H. Nakagawa, H. Kiyonaga, and T. Hisano, *Org. Prep. Proced. Int.*, 1992, **24**, 200.
5. H Yoshida, *Bull. Chem. Soc. Jpn.,* 1969, **42,** 1948 and references cited therein.
6. a) J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 209; J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 221. b) The PM3 calculation is performed using MOPAC; J. J. P. Stewart, *QCPE Bull.*, 1989, **9**, 10. c) A. Klamt and G. Schuurmann, *J. Chem. Soc. Perkin Trans. 2*, 1993, 799.
7. a) K. Fukui, "Kagaku Hanno to Densi no Kido (Chemical Reactions and Electron Orbitals)," Maruzen, Tokyo, 1976; b) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," John Wiley & Sons, Ltd., London, 1976.
8. *Gaussian 94*, Revision D.4, M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1995.
9. T. Kawata, K. Harano, and T. Taguchi, *Chem. Pharm. Bull.*, 1973, **21**, 604 and references cited therein.

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