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Convenient Synthesis of Stable Sulfur Ylides by Reaction of Active Methylene Compounds with Corey–Kim Reagent

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A new preparation method for a variety of stable sulfur ylides is described. Reactions of the Corey–Kim reagent with active methylene compounds having two electron withdrawing groups in the presence of triethylamine afforded stable sulfur ylides in satisfactory yields.

Keywords stable sulfur ylide; active methylene compound; Corey–Kim reagent; electron withdrawing group; acid-labile functional group; ylidation; ylide-carbon signal; ^{13}C-NMR; long-range ^{13}C–^{13}C coupling; coupling constant

In recent years, the so-called stable sulfur ylides, such as sulfonium dicarbonylmethylides, have been attracting much attention as useful precursors of siloxydienes, which can undergo cycloaddition with dienophiles, or cyclocondensation with aromatic aldehydes.[1] These ylides have heretofore been prepared chiefly from active methylene compounds such as 1,3-dicarbonyl derivatives by the following methods; (a) heating with dimethylsulfoxide in acetic anhydride[2,3]; (b) treatment with dimethylsulfoxide and phosphorus pentoxide in triethylamine[3]; (c) condensation in the presence of sodium hydride with the ethoxysulfonium salt[3]; (d) treatment with dimethylsulfoxide and dicyclohexylcarbodiimide in the presence of phosphorus pentoxide,[4] or phosphoric acid[2b]; (e) treatment with dimethylsulfoxide and sulfopropanoic anhydride[5]; (f) diazotization followed by photolysis,[6,7] or thermal decomposition catalyzed by copper salts,[6] or rhodium(II) acetate[8] in the presence of dimethylsulfide. However these methods are not necessarily satisfactory as regards the yield,[9] generality,[10] or reaction conditions.[11]

Recently, we have found that the reactions of the 3-hydroxycarbonyl compounds (**2**) with a large excess of the Corey–Kim reagent (*S,S*-dimethylsuccinimidosulfonium chloride) (**1**)[12] did not give the expected 1,3-dicarbonyl compounds (**3**), but led to the formation of the dimethylsulfonium dicarbonylmethylides (**4**) as sole products in excellent yields (Fig. 1).[13] These results imply that the diones, initially generated by reaction of the hydroxycarbonyl compounds with the Corey–Kim reagent, were more reactive with the reagent than the substrates, and immediately reacted with the reagent to give the stable sulfur ylides. This suggests that use of the 1,3-diones as alternative substrates for reaction with the Corey–Kim reagent will provide a new synthetic route for the preparation of stable sulfur ylides. On the basis of the above described background, we examined the reaction of the Corey–Kim reagent with various active methylene compounds having two electron-withdrawing groups, such as the 1,3-diketones. In this paper we describe a convenient method for the preparation of the stable sulfur ylides (**6**) from various active methylene compounds (**5**) by use of the Corey–Kim reagent (**1**) in the presence of triethylamine (Fig. 2).[14]

Results and Discussion

In all cases, the reaction of the active methylene compounds (**5**) with a small excess (*ca.* 1.3 eq) of reagent (**1**) was carried out in dry methylene chloride at −78 °C under an atmosphere of argon in the presence of triethylamine. The mixture was treated with cold brine, and extracted with ether, followed by purification by column chromatography to give the sulfur ylides (**6**). The results are summarized in Table I. The structure of the sulfur ylides (**6**) was confirmed by comparing the spectral and physical data with those of authentic samples.

The reactions of the reagent (**1**) with active methylene compounds (**5a**—**e**) having two acyl groups as the electron-withdrawing groups, X and Y, were investigated. The sulfur ylides (**6a**—**e**) were obtained in excellent yields (runs 1—5). These reactions proceeded smoothly even in the presence of acid-labile functional groups such as ethylene ketal or benzylether on the substrate (run 4).

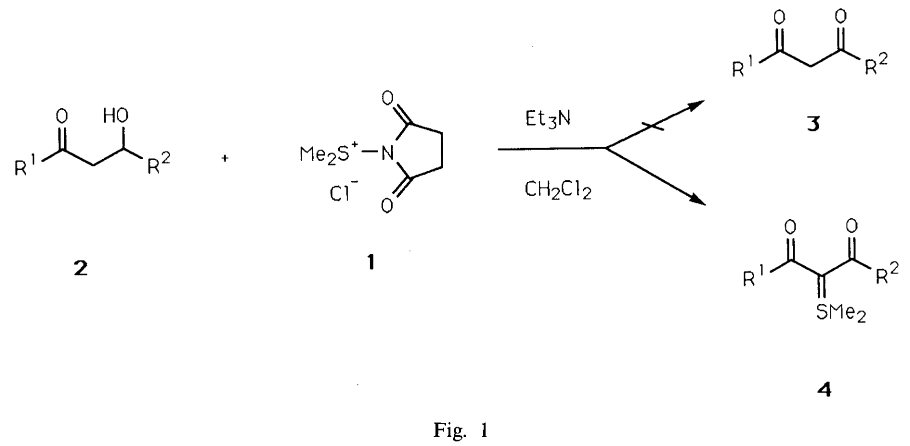
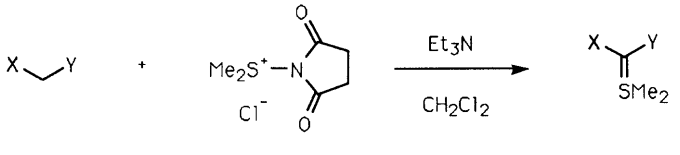


Fig. 1

The reactions of the reagent (**1**) with the active methylene compounds (**5f**—**i**) having acyl and alkoxycarbonyl groups, or acyl and aminocarbonyl groups as X and Y, were examined. The sulfur ylides (**6f**—**i**) were obtained in satisfactory yields (runs 6—9). In the case of the substrate (**5h**) having two reaction sites (run 8), only mono-ylidation proceeded to give **6h**. This fact is thought to be due to lowering of the acidity of the remaining active methylene position as a result of the first ylidation.

The reactions of the reagent (**1**) with active methylene compounds (**5j**—**l**) having two alkoxycarbonyl groups, or alkoxycarbonyl and cyano groups, or two cyano groups as X and Y, were examined next. The sulfur ylides (**6j, k**) were obtained in satisfactory yields in the case of the substrates (**5j, k**) (runs 10 and 11) although the reaction in the case of **5l** was sluggish and resulted in a low yield (46%) of the desired sulfur ylide (**6l**) (run 12).

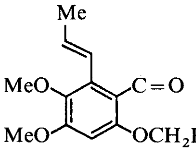
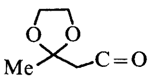
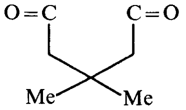


5 1 6

X, Y = electron-withdrawing groups

Fig. 2

Table I. Reaction of Active Methylene Compounds (**5**) with the Corey–Kim Reagent (**1**)

Run		Active methylene compounds (5) X-CH$_2$-Y X	Y	Stable ylide (6) Yield (%)	δ C=S (^{13}C-NMR)
1	**a**	PhC=O	PhC=O	99	88.1
2	**b**	PhC=O	MeC=O	96	88.9
3	**c**	MeC=O	MeC=O	78	87.9
4	**d**			80	91.5
5	**e**			95	86.2
6	**f**	PhC=O	CO$_2$Et	98	74.2
7	**g**	MeC=O	CO$_2$Me	94	73.7
8	**h**	EtOCOCH$_2$C=O	CO$_2$Et	88	74.4
9	**i**	MeC=O	CONHPh	97	76.8
10	**j**	CO$_2$Me	CO$_2$Me	78	58.6
11	**k**	CO$_2$Me	CN	82	36.4
12	**l**	CN	CN	46	15.8
13	**m**	PhC=O	Ph	0	—

The reaction of the reagent (**1**) with a compound (**5m**) having weaker acidity than **5a**—**l** described above did not afford the desired sulfur ylide and resulted in recovery of the substrate.

The carbon-13 nuclear megnetic resonance (^{13}C-NMR) spectra of the sulfur ylides **6k** and **6l** showed significant high field shifts of the ylide-carbon signals (δ 36.4, and δ 15.8) compared with those of the other sulfur ylides, **6a**—**j** (δ 91.5—δ 58.6). In addition, the long-range ^{13}C–^{13}C coupling of the ylide-carbon with the thiomethyl-carbon in the sulfur ylide (**6l**) was observed, and its coupling constant ($^{3}J_{C-C} = 4.0$ Hz) was consistent with reported values.15) It is thought that such a poor reactivity of the substrate (**5l**) and the observation of the ylide-carbon signal at abnormally high field in the ^{13}C-NMR spectrum of the product (**6l**) were probably attributable to the low electron withdrawing ability of the cyano group.

The formation of the sulfur ylides (**6**) from the 1,3-dicarbonyl compounds (**5**) can be explained by the reaction mechanism shown in Fig. 3.

In conclusion, we have demonstrated that the reactions of the Corey–Kim reagent with active methylene compounds having two electron withdrawing groups afforded stable sulfur ylides in excellent yields. These reactions proceeded at low temperature and were applicable to compounds containing acid-labile functional groups. Therefore, it is thought that this method provides a useful mean for the preparation of various stable sulfur ylides.

Experimental

Melting points were measured on a Yanaco micro-melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-810 spectrophotometer. NMR spectra were obtained in chloroform-*d* (CDCl$_3$) at 270 MHz on a JEOL JMN-GX270 instrument with chemical shifts being reported in δ units from tetramethylsilane as an internal standard and coupling constants in hertz. Mass spectra (MS) were taken on a JEOL JMS-DX300 mass spectrometer by direct insertion at 70 eV.

General Method for Preparation of Stable Ylides (6) from Active Methylene Compounds (5) Dimethylsulfide (2.7 ml, 36.9 mmol) was added dropwise to a suspension of *N*-chlorosuccinimide (3472 mg, 26.0 mmol) in anhydrous methylene chloride (110 ml) at −78 °C under argon, and stirring was continued for 1 h at the same temperature. Then, a solution of an active methylene compound (**5**) (20.0 mmol) was added at the same temperature. After 1 h, triethylamine (4.2 ml, 30.3 mmol) was added to the mixture, and stirring was continued for 1 h at the same temperature. Cold brine (60 ml) was added to the mixture, and the whole was extracted with ether (180 ml). The organic layer was washed with brine (3 × 60 ml), and

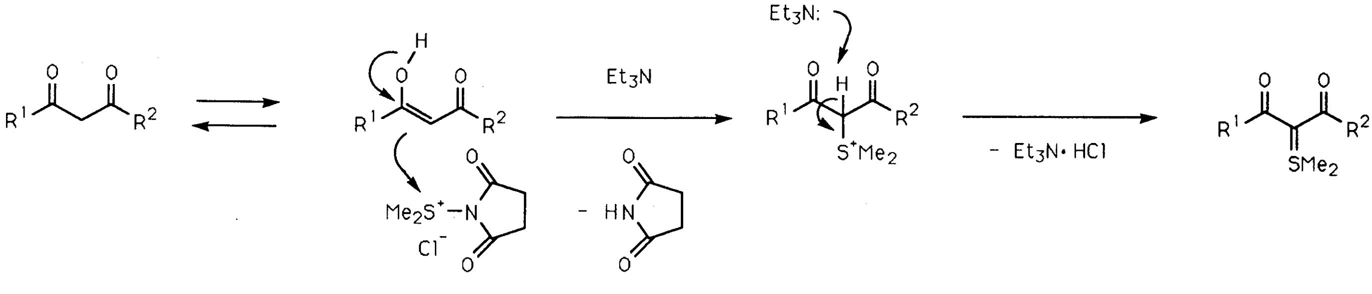


Fig. 3

dried over anhydrous magnesium sulfate. The solvent was evaporated off, and the resulting residue was purified by column chromatography on silica gel (100—200 mesh, Micro Bead 4B, Fuji-Davison Chemical Ltd., eluent, 5% acetone in $CHCl_3$) to afford the corresponding sulfur ylide (**6**).

Dimethylsulfonium 1-Benzoyl-2-oxo-2-phenylethylide (**6a**): Yield 99%, colorless needles from *n*-hexane–$CHCl_3$, mp 210—211 °C (lit.,[7] 211—212 °C). IR (KBr): 1585, 1568, 1550 cm^{-1}. ^1H-NMR δ: 3.11 (6H, s, CH_3–S), 6.98—7.08 (6H, m, Ar-H), 7.27—7.32 (4H, m, Ar-H). ^{13}C-NMR δ: 27.0 (q, 2C, CH_3-S), 88.1 (s, C=S), 127.4 (d, 4C, Ar), 128.6 (d, 4C, Ar), 129.8 (d, 2C, Ar), 142.0 (s, 2C, Ar), 191.1 (s, 2C, C=O). MS *m*/*z* (%): 285 (M^++1, 4), 284 (M^+, 23), 222 (8), 105 (base). HRMS *m*/*z*: M^+ Calcd for $C_{17}H_{16}O_2S$: 284.0870. Found: 284.0890.

Dimethylsulfonium 1-Benzoyl-2-oxopropylide (**6b**): Yield 96%, colorless needles from ether–acetone, mp 105—107 °C (lit.,[3] 109—111 °C). IR (KBr): 1600, 1560 cm^{-1}. ^1H-NMR δ: 2.14 (3H, s, CH_3C=O), 2.97 (6H, s, CH_3–S), 7.39—7.42 (5H, m, Ar-H). ^{13}C-NMR δ: 26.7 (q, 2C, CH_3–S), 30.6 (q, CH_3–C=O), 88.9 (s, C=S), 127.3 (d, 2C, Ar), 128.3 (d, 2C, Ar), 129.9 (d, Ar), 143.1 (s, Ar), 190.2 (s, C=O), 192.7 (s, C=O). MS *m*/*z* (%): 223 (M^++1, 6), 222 (M^+, 32), 105 (base). HRMS *m*/*z*: M^+ Calcd for $C_{12}H_{14}O_2S$: 222.0713. Found: 222.0700.

Dimethylsulfonium 1-Acetyl-2-oxopropylide (**6c**): Yield 78%, colorless prisms from ether–acetone, mp 166—169 °C (lit.,[3] 168—169 °C). IR (KBr): 1600, 1560 cm^{-1}. ^1H-NMR δ: 2.36 (6H, s, CH_3), 2.99 (6H, s, CH_3–S). ^{13}C-NMR δ: 26.9 (q, 2C, CH_3–S), 30.2 (q, 2C, CH_3–C), 87.9 (s, C=S), 190.7 (s, 2C, C=O). MS *m*/*z* (%): 162 (M^++2, 6), 161 (M^++1, 10), 160 (M^+, base). HRMS *m*/*z*: M^+ Calcd for $C_7H_{12}O_2S$: 160.0558. Found: 160.0580.

Dimethylsulfonium 1-[3,4-Dimethoxy-6-(phenylmethoxy)-2-(1-propenyl)benzoyl]-3-(2-methyl-1,3-dioxolan-2-yl)-2-oxopropylide (**6d**)[16]: Yield 80%, yellow oil. IR (neat): 1570 cm^{-1}. ^1H-NMR δ: 1.55 (3H, s, CH_3), 1.83 (3H, d, *J*=5.0, CH_3–C=), 2.71 (3H, s, CH_3–S), 2.78 (3H, s, CH_3–S), 3.59 (2H, ABq, *J*=14.0, CH_2), 3.69 (3H, s, CH_3–O), 3.82 (3H, s, CH_3–O), 3.92—4.12 (4H, m, O–C_2H_4–O), 5.03 (2H, ABq, *J*=12.0, CH_2–O), 6.35—6.46 (2H, m, CH=), 6.44 (1H, s, Ar-H), 7.27—7.39 (5H, m, Ar-H). ^{13}C-NMR δ: 19.6 (q, CH_3–C=), 24.5 (q, $\underline{C}H_3$–C–O), 26.8 (q, CH_3–S), 26.9 (q, CH_3–S), 48.8 (t, CH_2–C=O), 55.9 (q, CH_3–O), 60.1 (q, CH_3–O), 64.5 (t, O–$\underline{C}H_2$–CH_2O), 64.6 (t, OCH_2–$\underline{C}H_2$–O), 72.0 (t, O–CH_2Ph), 91.5 (s, C=S), 98.3 (d, Ar), 109.0 (s, O–C–O), 123.7 (d, =C-Ar), 132.2 (d, =$\underline{C}$–CH_3), 185.3 (s, C=O), 191.7 (s, C=O). MS *m*/*z* (%): 514 (M^+, 1), 91 (98), 87 (base).

Dimethylsulfonium 4,4-Dimethyl-2,6-dioxocyclohexylide (**6e**): Yield 95%, colorless needles from ether–acetone, mp 172—175 °C (lit.,[3] 172—173 °C). IR (KBr): 1710, 1645, 1608, 1537 cm^{-1}. ^1H-NMR δ: 1.05 (6H, s CH_3), 2.30 (4H, s, CH_2), 2.98 (6H, s, CH_3–S). ^{13}C-NMR δ: 25.8 (q, 2C, CH_3–S), 28.4 (q, 2C, $\underline{C}H_3$–C), 31.2 (s, $\underline{C}$–CH_3), 51.6 (t, 2C, CH_2), 86.2 (s, C=S), 192.3 (s, 2C, C=O). MS *m*/*z* (%): 202 (M^++2, 7), 201 (M^++1, 14), 200 (M^+, base). HRMS *m*/*z*: M^+ Calcd for $C_{10}H_{16}O_2S$: 200.0871. Found: 200.0889.

Dimethylsulfonium 1-Benzoyl-2-ethoxy-2-oxoethylide (**6f**): Yield 98%, colorless needles from ether–benzene, mp 82—84 °C (lit.,[2d] 84—85 °C). IR (KBr): 1650, 1584, 1560 cm^{-1}. ^1H-NMR δ: 0.90 (3H, t, *J*=6.8, CH_3–C), 3.00 (6H, s, CH_3–S), 3.92 (2H, q, *J*=6.8, CH_2), 7.28—7.44 (5H, m, Ar-H). ^{13}C-NMR δ: 13.9 (q, $\underline{C}H_3$–C), 27.0 (q, 2C, CH_3–S), 59.3 (t, CH_2), 74.2 (s, C=S), 127.2 (d, 2C, Ar), 127.3 (d, 2C, Ar), 129.0 (d, Ar), 143.5 (s, Ar), 166.5 (s, COO), 190.9 (s, C=O). MS *m*/*z* (%): 254 (M^++2, 3), 253 (M^++1, 8), 252 (M^+, 44), 105 (base). HRMS *m*/*z*: M^+ Calcd for $C_{13}H_{16}O_3S$: 252.0820. Found: 252.0803.

Dimethylsulfonium 1-(Methoxycarbonyl)-2-oxopropylide (**6g**): Yield 94%, colorless plates from toluene, mp 112—114 °C (lit.,[2d] 115—117 °C). IR (KBr): 1680, 1565 cm^{-1}. ^1H-NMR δ: 2.40 (3H, s, CH_3–C=O), 2.93 (6H, s, CH_3–S), 3.69 (3H, s, CH_3–O). ^{13}C-NMR δ: 26.8 (q, 2C, CH_3–S), 30.0 (q, $\underline{C}H_3$–C=O), 50.5 (q, CH_3–O), 73.7 (s, C=S), 166.9 (s, COO), 192.3 (s, C=O). MS *m*/*z* (%): 178 (M^++2, 6), 177 (M^++1, 10), 176 (M^+), 161 (base). HRMS *m*/*z*: M^+ Calcd for $C_7H_{12}O_3S$: 176.0507. Found: 176.0497.

Dimethylsulfonium 2,4-Dioxo-4-ethoxy-1-(ethoxycarbonyl)butylide (**6h**): Yield 88%, colorless oil. IR (neat): 1725, 1660, 1585 cm^{-1}. ^1H-NMR δ: 1.26 (3H, t, *J*=7.2, CH_3), 1.27 (3H, t, *J*=7.2, CH_3), 2.96 (6H, s, CH_3–S), 3.83 (2H, s, CH_2), 4.14 (2H, q, *J*=7.2, CH_2–O), 4.17 (2H, q, *J*=7.2, CH_2–O). ^{13}C-NMR δ: 14.2 (q, $\underline{C}H_3$–C), 14.6 (q, $\underline{C}H_3$–C), 26.6 (q, 2C, CH_3–S), 48.4 (t, $\underline{C}H_2$–C=O), 59.5 (t, CH_2–O), 60.5 (t, CH_2–O), 74.4 (s, C=S), 166.1 (s, COO), 169.8 (s, COO), 186.3 (s, C=O). MS *m*/*z* (%): 264 (M^++2, 4), 263 (M^++1, 11), 262 (M^+, 62), 175 (base). HRMS *m*/*z*: M^+ Calcd for $C_{11}H_{18}O_5S$: 262.0785. Found: 262.0835.

Dimethylsulfonium 2-Oxo-1-[(phenylamino)carbonyl]propylide (**6i**): Yield 97%, colorless prisms from ethylacetate, mp 153—156 °C (lit.,[4] 156.5—158 °C). IR (KBr): 1620, 1585, 1510 cm^{-1}. ^1H-NMR δ: 2.26 (3H, s, CH_3–C), 3.05 (6H, s, CH_3–S), 6.97—7.58 (5H, m, Ar-H), 12.02 (1H, s, NH). ^{13}C-NMR δ: 27.0 (q, $\underline{C}H_3$–C), 28.8 (q, 2C, CH_3–S), 76.8 (s, C=S), 120.2 (d, 2C, Ar), 122.7 (d, Ar), 128.7 (d, 2C, Ar), 139.4 (s, Ar), 165.1 (s, N–C=O), 188.1 (s, C=O). MS *m*/*z* (%): 238 (M^++1, 3), 237 (M^+, 21), 175 (50), 145 (base), 103 (56). HRMS *m*/*z*: M^+ Calcd for $C_{12}H_{15}NO_2S$: 237.0824. Found: 237.0823.

Dimethylsulfonium 2-Methoxy-1-(methoxycarbonyl)-2-oxoethylide (**6j**): Yield 78%, colorless prisms from acetone, mp 168—170 °C (lit.,[6] 169—170 °C). IR (KBr): 1770, 1700, 1662, 1626 cm^{-1}. ^1H-NMR δ: 2.90 (6H, s, CH_3–O), 3.71 (6H, s, CH_3–S). ^{13}C-NMR δ: 27.8 (q, 2C, CH_3–S), 50.8 (q, 2C, CH_3–O), 58.6 (s, C=S), 166.8 (s, 2C, C=O). MS *m*/*z* (%): 194 (M^++2, 3), 193 (M^++1, 5), 192 (M^+, 56), 177 (base). HRMS: *m*/*z* M^+ Calcd for $C_7H_{12}O_4S$: 192.0456. Found: 192.0440.

Dimethylsulfonium 1-Cyano-2-methoxy-2-oxoethylide (**6k**): Yield 82%, colorless prisms from ether–acetone, mp 157—160 °C (lit.,[4] 158—160 °C). IR (KBr): 2170, 1705, 1655 cm^{-1}. ^1H-NMR δ: 2.87 (6H, s, CH_3–S), 3.69 (3H, s, CH_3–O). ^{13}C-NMR δ: 29.4 (q, 2C, CH_3–S), 36.4 (s, C=S), 51.2 (q, CH_3–O), 118.9 (s, C–N), 167.7 (s, C=O). MS *m*/*z* (%): 161 (M^++2, 3), 160 (M^++1, 6), 159 (M^+, 67), 144 (base). HRMS *m*/*z*: M^+ Calcd for $C_6H_9NO_2S$: 159.0354. Found: 159.0386.

Dimethylsulfonium Dicyanomethylide (**6l**): Yield 46%, colorless needles from ether–acetone, mp 96—98 °C (lit.,[3] 99—100 °C). IR (KBr): 2190, 2150 cm^{-1}. ^1H-NMR δ: 2.83 (6H, s, CH_3). ^{13}C-NMR δ: 15.8 (s, $^3J_{C-C}=4$, C=S), 31.5 (q, $^3J_{C-C}=4$, CH_3–S), 116.9 (s, 2C, C–N). MS *m*/*z* (%): 128 (M^++2, 4), 127 (M^++1, 6), 126 (M^+, 68), 111 (base). HRMS *m*/*z*: M^+ Calcd for $C_5H_6N_2S$: 126.0252. Found: 126.0238.

References and Notes

1) S. Furukawa, J. Igarashi, K. Shima, M. Watanabe, and T. Kinoshita, *Chem. Pharm. Bull.*, **38**, 5 (1990); S. Furukawa, J. Igarashi, M. Watanabe, and T. Kinoshita, *ibid.*, **38**, 227 (1990); J. Igarashi, N. Watanabe, T. Kinoshita, K. Ogata, and S. Furukawa, *ibid.*, **38**, 329, (1990).

2) *a*) A. Hochrainer and F. Wessely, *Tetrahedron Lett.*, **1965**, 721; *b*) *Idem*, *Monatsch. Chem.*, **97**, 1 (1966); *c*) A. Hochrainer, *ibid.*, **97**, 823 (1966); *d*) R. Oda and Y. Hayashi, *Nippon Kagaku Zasshi*, **87**, 1110 (1966).

3) H. Nozaki, D. Tunemoto, Z. Morita, K. Nakamura, K. Watanabe, M. Takaku, and K. Kondo, *Tetrahedron*, **23**, 4279 (1967).

4) A. F. Cook and J. G. Moffatt, *J. Am. Chem. Soc.*, **90**, 740 (1968).

5) K. Schank and C. Schuhknecht, *Synthesis*, **1978**, 678.

6) W. Ando, T. Yagihara, S. Tozune, S. Nakaido, and T. Migita, *Tetrahedron Lett.*, **1969**, 1979.

7) W. Illger, A. Liedhegener, and M. Regitz, *Justus Liebigs Ann. Chem.*, **760**, 1 (1972).

8) C. J. Moody and R. J. Taylor, *Tetrahedron Lett.*, **29**, 6005 (1988).

9) The yields obtained using methods (a—e) were generally in the range from 10 to 50% and were higher (>60%) in only a few cases. Compared with these methods, method (f) leads to much better yields (45—88%) of the desired products.

10) In these methods, 3—5 examples of the reaction have been examined in most cases.

11) Methods (a—c) require rather drastic reaction conditions (>100 °C).

12) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).

13) S. Katayama, K. Fukuda, T. Watanabe, and M. Yamauchi, *Synthesis*, **1988**, 178.

14) Preliminary communication, S. Katayama, T. Watanabe, and M. Yamauchi, *Chem. Lett.*, **1989**, 973.

15) V. S. Vogdanov, V. V. Semenov, O. P. Shitov, S. A. Schevelev, and K. Ya. Burshtein, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1983**, 1528 [*Chem. Abstr.*, **99**, 211787*u* (1983)].

16) M. Yamauchi, S. Katayama, T. Todoroki, and T. Watanabe, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 389.