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Pummerer-Type Reaction of α-Acylsulfides Using Phenyl Iodosyl Bis(trifluoroacetate)

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Treatment of α-acylsulfides with phenyl iodosyl bis(trifluoroacetate) (PIFA) resulted in a Pummerer-type reaction to give the same products as obtained by the Pummerer reaction of the α-acylsulfoxides. The Pummerer-type reaction of α-acylsulfides using PIFA was applied to Friedel–Crafts type cyclization of *N*-phenyl-α-(methylthio)acetanilide (**1**) and ethyl α-(1-phenethylthio)-acetate (**9**) to give *N*-phenyl-3-(methylthio)oxindole (**3**) and ethyl isothiochroman-1-carboxylate (**10**), respectively, olefin cyclization of α-(methylthio)acetamides (**11**, **13** and **15**) to give the lactams (**12**, **14** and **16**), and also intermolecular condensation and α-methoxylation of methyl α-(methylthio)acetate (**7**).

Keywords——phenyl iodosyl bis(trifluoroacetate); Pummerer-type reaction; α-acylsulfide; oxindole; Friedel–Crafts type cyclization; olefin cyclization; intermolecular condensation; α-methoxylation

In recent years, it has been shown that α-acylsulfoxides exposed to the Pummerer reaction conditions undergo carbon–carbon bond forming reactions such as Friedel–Crafts type reaction[1] and olefin cyclization,[2] and this reaction provides a useful synthetic procedure. Synthesis of an oxindole, for example,[1g] can be achieved starting from *N*-phenyl-α-(methylthio)acetanilide (**1**) by a three-step reaction, which involves oxidation of **1** to the sulfoxide (**2**), cyclization of **2** to *N*-phenyl-3-(methylthio)oxindole (**3**) under the Pummerer reaction conditions and desulfurization of **3** to the oxindole (**4**) as shown in Chart 1. In this synthesis, we found that treatment of **1** with phenyl iodosyl bis(trifluoroacetate) (PIFA)[3] caused cyclization to give **3**, and the reaction afforded a more practical route to oxindoles (Chart 1). The cyclization from **1** to **3** is assumed to proceed through the Pummerer reaction intermediate (**6**) which would be formed by attack of PIFA on the sulfur atom of **1**, followed by simultaneous elimination of the α-proton and iodobenzene from the resultant sulfonium

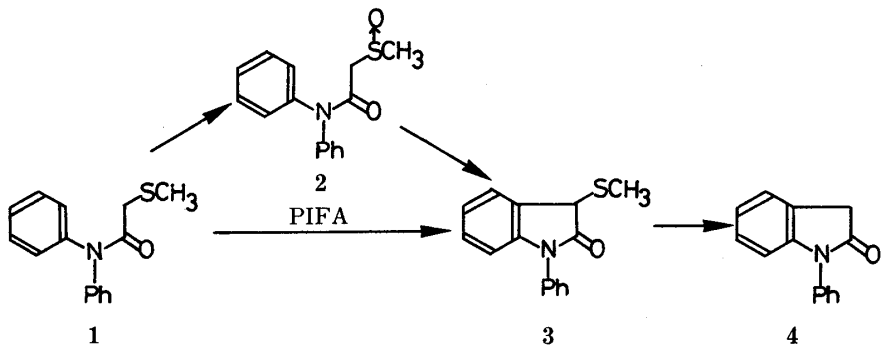
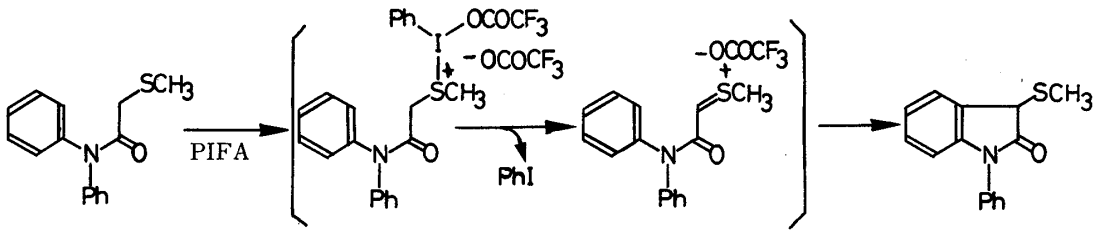


Chart 1



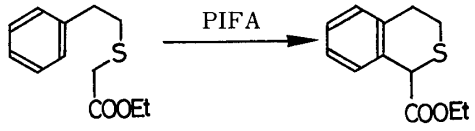
1 5 6 3

Chart 2

salt (**5**) as shown in Chart 2. If this mechanism is correct, the Pummerer reaction could be carried out by using α-acylsulfides and PIFA instead of α-acylsulfoxides. Treatment of methyl α-(methylthio)acetate (**7**) with PIFA in chloroform–methanol was found to give the Pummerer reaction product, methyl α-methoxy-α-(methylthio)acetate (**8**) as expected. Further investigation revealed that PIFA effected Friedel–Crafts type cyclization of ethyl α-(1-phenethylthio)acetate (**9**) to give ethyl isothiochroman-1-carboxylate (**10**), olefin cyclization of α-(methylthio)acetamides (**11**, **13** and **15**) to give the lactams (**12**, **14** and **16**), and also the intermolecular condensation of **7** and arenes to give methyl α-(methylthio)arylacetates (**17** and **18**). We describe here details of these reactions.

Freidel–Crafts Type Cyclization and Olefin Cyclization of α-Acylsulfide Using PIFA

Treatment of *N*-phenyl-α-(methylthio)acetanilide (**1**) with PIFA in 1,2-dichloroethane at room temperature caused Friedel–Crafts type cyclization to give *N*-phenyl-3-(methylthio)oxindole (**3**) in 63% yield, and **3** was easily desulfurized with Raney-nickel to give the oxindole (**4**)[1g] (Chart 1). Similar treatment of ethyl α-(1-phenethylthio)acetate (**9**) with PIFA gave ethyl isothiochroman-1-carboxylate (**10**) in 79% yield (Chart 3).



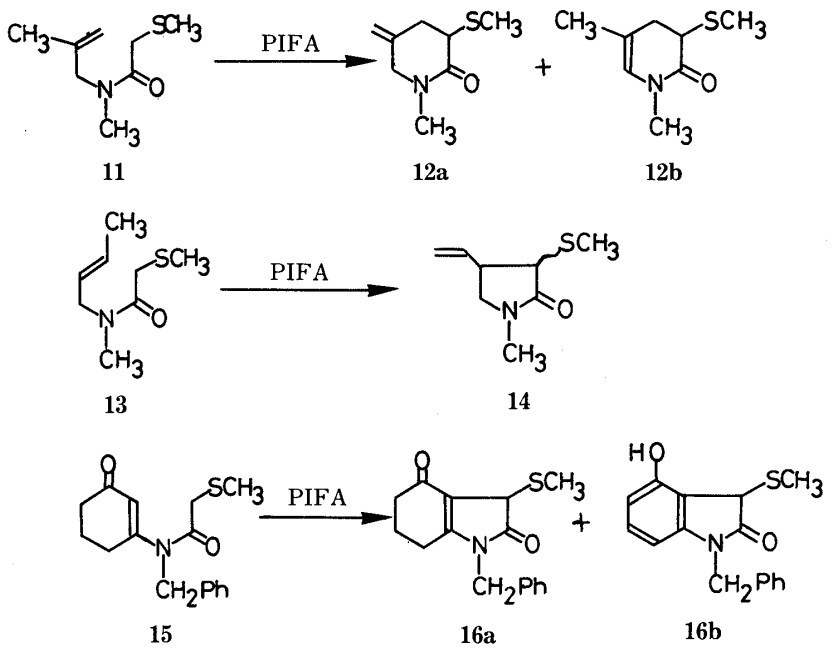
9 10

Chart 3

Next, olefin cyclization of *N*-methyl-*N*-(2-methyl-2-propenyl)-α-(methylthio)acetamide (**11**) using PIFA was examined. The cyclization was carried out in 1,2-dichloroethane at 50 °C to afford the 5-methylene-2-piperidinone (**12a**) and the 3,4-dihydro-2(1*H*)-pyridone (**12b**) in 40% and 40% yields, respectively. Olefin cyclization of *N*-(2-butenyl)-*N*-methyl-α-(methylthio)acetamide (**13**) using PIFA gave the 4-vinyl-2-pyrrolidinone (**14**) as a mixture of stereoisomers (*ca.* 1/1).[4] Similarly, *N*-benzyl-*N*-(3-oxo-1-cyclohexen-1-yl)-α-(methylthio)acetamide (**15**) gave 2,3,4,5,6,7-hexahydro-1-benzyl-3-(methylthio)indole-2,4-dione (**16a**) and 1-benzyl-4-hydroxy-3-(methylthio)oxindole (**16b**) in 28% and 24% yields, respectively (Chart 4). The formation of **16b** is assumed to be caused by further oxidation of **16a** with PIFA, because the isolated **16a** was easily converted to **16b** with PIFA.[5]

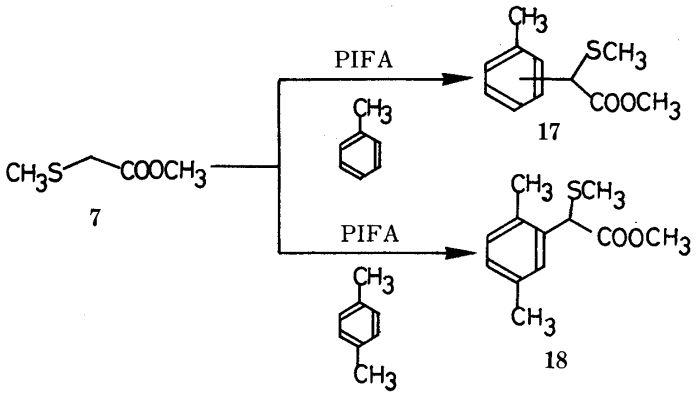
Intermolecular Condensation and α-Methoxylation of Methyl α-(Methylthio)acetate (7) Using PIFA

Intermolecular condensation of **7** with arenes was effected by treatment with PIFA. Thus, when a 1,2-dichloroethane solution of **7**, toluene and PIFA was refluxed, methyl α-(methylthio)tolylacetate (**17**) ($o/p = 1/3.8$)[6] was produced in 78% yield. Similarly, condensation of **7** with *p*-xylene gave an 80% yield of methyl α-(methylthio)*p*-xylylacetate (**18**) (Chart 5).



11 12a 12b 13 14 15 16a 16b

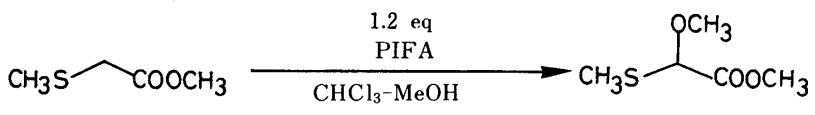
Chart 4



7 17 18

Chart 5

α-Methoxylation of **7** was carried out as a typical example of the Pummerer-type reaction using PIFA. Treatment of **7** with 1.2 eq of PIFA at room temperature in chloroform–methanol afforded methyl α-methoxy-α-(methylthio)acetate (**8**) in 48% yield (Chart 6). Recently, Nagao *et al.* have reported an analogous reaction of α-acylsulfides using an excess of thallium (III) nitrate (TTN), leading to α-oxoacetals.[7] The reaction is supposed to be initiated by Pummerer-type conversion of an α-acylsulfide to an α-methoxy-α-acylsulfide with TTN effects similarly to PIFA, followed by further oxidation to an α-oxoacetal with an excess of TTN.



7 8

Chart 6

The present results demonstrate that PIFA is a useful reagent for the Pummerer-type reaction of α-acylsulfides.

Experimental

Infrared (IR) spectra were recorded on a JASCO IRA-1 spectrometer and nuclear magnetic resonance (NMR) spectra on a Hitachi R-20A (60 MHz) or a Hitachi R-22 (90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution mass spectra (MS) were obtained with a JEOL JMS D-300 instrument, with a direct inlet system. Extracts were dried over $MgSO_4$. Column chromatography was carried out on Merck Silica gel 60. PIFA was prepared by the reported method.[8]

The starting *N*-phenyl-α-(methylthio)acetanilide (**1**) was easily prepared by the reported method.[1g]

***N*-Phenyl-3-(methylthio)oxindole (3)**——A solution of **1** (128 mg, 0.5 mmol) in 1 ml of anhydrous 1,2-dichloroethane was added slowly to a stirred solution of PIFA (258 mg, 0.6 mmol) in 4 ml of anhydrous 1,2-dichloroethane at room temperature. The reaction mixture was stirred for 3 h at room temperature, quenched with water (10 ml) and extracted with dichloromethane (3 × 25 ml). The organic layer was washed with water (3 × 20 ml) and dried. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel using benzene–ethyl acetate (5 : 1) as an eluent to give pure **3** (80 mg, 63%). mp 63—64 °C (hexane) (lit.[1g] mp 64—65 °C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s), 4.42 (1H, s), 7.0—7.6 (9H, m). The spectral data for **3** are in accord with those reported.[1g]

The starting ethyl α-(1-phenethylthio)acetate (**9**) was prepared by phenethylation of ethyl thioglycolate with phenethyl bromide according to the literature procedure.[9] Colorless oil. bp 156—157 °C/7 mmHg (lit.[10] bp 135—136 °C/0.2 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J = 7 Hz), 2.84 (4H, s), 3.14 (2H, s), 4.14 (2H, q, J = 7 Hz); 7.0—7.35 (5H, m).

Ethyl Isothiochroman-1-carboxylate (10)——A mixture of PIFA (516 mg, 1.2 mmol) and **9** (224 mg, 1 mmol) in 18 ml of anhydrous 1,2-dichloroethane was stirred at room temperature for 14 h, quenched with water (15 ml) and extracted with ether (3 × 20 ml). The organic layer was washed with water (3 × 20 ml) and dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel using benzene as an eluent to give pure **10** as a colorless oil (175 mg, 79%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J = 7 Hz), 2.6—3.3 (4H, m), 4.18 (2H, q, J = 7 Hz), 4.48 (1H, s), 7.1—7.3 (4H, m). *Anal.* Calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35; S, 14.42. Found: C, 64.81; H, 6.38; S, 14.38.

The starting *N*-methyl-*N*-(2-methyl-2-propenyl)-α-(methylthio)acetamide (**11**) was prepared by *N*-acylation of *N*-(2-methyl-2-propenyl)methylamine with α-(methylthio)acetyl chloride.[1g,2a] Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.69 (3H, br s), 2.21 (3H, s), 2.93, 2.99 (3H, 2s), 3.22, 3.29 (2H, 2s), 3.8—4.0 (2H, m), 4.65—5.0 (2H, m).

The Reaction of *N*-Methyl-*N*-(2-methyl-2-propenyl)-α-(methylthio)acetamide (11) with PIFA——A solution of **11** (95 mg, 0.55 mmol) in 0.5 ml of anhydrous 1,2-dichloroethane was added dropwise to a stirred solution of PIFA (283 mg, 0.66 mmol) in 1 ml of anhydrous 1,2-dichloroethane at room temperature. The reaction mixture was stirred for 5 min at room temperature, and then heated at 50 °C for 2 h. After cooling, the resultant mixture was quenched with water (5 ml) and extracted with ether (3 × 20 ml). The organic layer was washed with water (3 × 10 ml), then dried. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography using benzene–ethyl acetate (3 : 1) as an eluent to give pure **12a** (38 mg, 40%) and **12b** (38 mg, 40%).

1-Methyl-5-methylene-3-methylthio-2-piperidinone (**12a**): Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.56 (1H, dd, J = 14, 4 Hz), 2.8—3.1 (1H, m), 2.94 (3H, s), 3.37 (1H, t, J = 4 Hz), 3.96 (2H, br s), 4.98 (2H, br s).

3,4-Dihydro-1,5-dimethyl-3-methylthio-2(1*H*)-pyridone (**12b**): Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, s), 2.18 (1H, dd, J = 17, 3 Hz), 2.20 (3H, s), 2.6—2.8 (1H, m), 3.05 (3H, s), 3.30 (1H, dd, J = 6, 3 Hz), 5.65—5.8 (1H, m). The spectral data for **12a** and **12b** are in accord with those reported.[2a]

The starting *N*-(2-butenyl)-*N*-methyl-α-(methylthio)acetamide (**13**) was prepared by *N*-acylation of *N*-(2-butenyl)methylamine with α-(methylthio)acetyl chloride.[1g,2a] Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.8 (3H, m), 2.20 (3H, s), 2.90, 2.99 (3H, 2s), 3.24 (2H, s), 3.7—4.0 (2H, m), 5.1—5.8 (2H, m).

1-Methyl-3-methylthio-4-vinyl-2(1*H*)-pyrrolidinone (14)——A solution of **13** (255 mg, 1.47 mmol) in 5 ml of anhydrous 1,2-dichloroethane was added slowly to a stirred solution of PIFA (761 mg, 1.77 mmol) in 10 ml of anhydrous 1,2-dichloroethane at room temperature. The reaction mixture was stirred for 5 min at room temperature, and then heated at 50 °C for 4.5 h. After cooling, the resultant mixture was quenched with water (30 ml) and extracted with ether (3 × 25 ml). The organic layer was washed with water (3 × 10 ml) and dried. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using benzene–ethyl acetate (4 : 1) as an eluent to give pure **14** as a colorless oil (159 mg, 63%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.5—3.6 (4H, m), 2.89 (3H, s), 4.9—6.1 (3H, m). The spectral data for **14** are in accord with those reported.[2a]

***N*-Benzyl-*N*-(3-oxo-1-cyclohexen-1-yl)-α-(methylthio)acetamide (15)**——A solution of 3-benzylamino-2-cyclohexen-1-one (2 g, 10 mmol) in α-(methylthio)acetic anhydride (12.6 g, 65 mmol) and pyridine (0.4 ml, 5 mmol) was heated at 160 °C for 1 h. After removal of the solvent under reduced pressure, chloroform was added to the residue. The organic layer was washed with 5% NaOH solution and water, then dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel using benzene–ethyl acetate (2 : 1) as an

eluent to give **15** as a yellow oil (0.66 g, 23%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.73 (6H, m), 2.20 (3H, s), 3.31 (2H, s), 4.80 (2H, s), 5.75 (1H, br s), 7.23 (5H, s). High-resolution MS Calcd for $C_{16}H_{19}NO_2S$: 289.1123. Found: 289.1133.

Reaction of *N*-Benzyl-*N*-(3-oxo-1-cyclohexen-1-yl)-α-(methylthio)acetamide (15) with PIFA——A solution of **15** (79 mg, 0.273 mmol) in 1 ml of anhydrous 1,2-dichloroethane was added dropwise to a stirred solution of PIFA (141 mg, 0.328 mmol) in 2 ml of anhydrous 1,2-dichloroethane at 0 °C. The reaction mixture was stirred at 0 °C, and then overnight at room temperature. The resultant mixture was quenched with water (10 ml) and extracted with dichloromethane (3 × 20 ml). The organic layer was washed with water (3 × 10 ml) and dried. The solvent was evaporated off *in vacuo* and the residue was purified by column chromatography on silica gel using benzene–ethyl acetate (10 : 1) as an eluent to give **16a** (21 mg, 28%) and **16b** (19 mg, 24%).

2,3,4,5,6,7-Hexahydro-1-benzyl-3-(methylthio)indole-2,4-dione (**16a**): Colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1635, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.65 (6H, m), 2.28 (3H, s), 4.10 (1H, br s), 4.75 (2H, br s), 7.27 (5H, br s). High-resolution MS Calcd for $C_{16}H_{17}NO_2S$: 287.0977. Found: 287.0956.

1-Benzyl-4-hydroxy-3-(methylthio)oxindole (**16b**): Orange prisms, mp 176—178 °C (ethyl acetate–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1705. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s), 4.41 (1H, s), 4.87 (2H, d, J = 4 Hz), 6.2—7.1 (3H, m), 6.28 (1H, br s), 7.15—7.3 (5H, m). High-resolution MS Calcd for $C_{16}H_{15}NO_2S$: 285.0824. Found: 285.0825.

The starting methyl α-(methylthio)acetate (**7**) was prepared by the reported method.[11]

Methyl α-(Methylthio)tolylacetate (17)——A mixture of PIFA (516 mg, 1.2 mmol) and **7** (129 mg, 1 mmol) in 3 ml of anhydrous 1,2-dichloroethane was refluxed for 10 min, and then toluene (184 mg, 2 mmol) was added to the refluxing mixture. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the resultant mixture was quenched with water (10 ml) and extracted with ether (3 × 20 ml). The organic layer was washed with water (3 × 10 ml) and dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel using benzene as an eluent to give pure **17** as a colorless oil (164 mg, 78%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s), 2.33, 2.40 (3H, 2s), 3.71 (3H, s), 4.47 (1H, s), 6.9—7.4 (4H, m). High-resolution MS Calcd for $C_{11}H_{14}O_2S$: 210.0714. Found: 210.0724.

Methyl α-(Methylthio)*p*-xylylacetate (18)——A mixture of PIFA (1.828 g, 4.25 mmol) and **7** (425 mg, 3.54 mmol) in 8 ml of anhydrous 1,2-dichloroethane was refluxed for 15 min, and then *p*-xylene (750 mg, 7.08 mmol) was added to the refluxing mixture. The reaction mixture was refluxed for 4 h. Work-up of the resultant mixture as before gave pure **18** as a colorless oil (634 mg, 80%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.31 (3H, s), 2.35 (3H, s), 3.72 (3H, s), 4.68 (1H, s), 6.9—7.4 (3H, m). High-resolution MS Calcd for $C_{12}H_{16}O_2S$: 224.0871. Found: 224.0878.

Methyl α-Methoxy-α-(methylthio)acetate (8)——A solution of PIFA (516 mg, 1.2 mmol) in 2 ml of chloroform–methanol (1 : 1) was added dropwise to a stirred solution of **7** (120 mg, 1 mmol) in 3 ml of chloroform–methanol (1 : 1) at room temperature. The reaction mixture was stirred for 40 min at room temperature, quenched with water (10 ml) and extracted with ether (3 × 25 ml). The organic layer was washed with water (3 × 10 ml), then dried. The solvent was evaporated off under reduced pressure and the residue was purified by column chromatography on silica gel using benzene–ethyl acetate (10 : 1) as an eluent to give pure **8** as a colorless oil (72.2 mg, 48%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 3.47 (3H, s), 3.80 (3H, s), 4.82 (1H, s). High-resolution MS Calcd for $C_5H_{10}O_3S$: 150.0351. Found: 150.0357.

References and Notes

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4) The ratio was determined from the ^{1}H-NMR spectrum by using the shift reagent $Eu(fod)_3$.

5) The formation of **16b** from **16a** with PIFA was checked by thin layer chromatography and IR spectroscopy.

6) The ratio was determined from the ^{1}H-NMR spectrum.

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