Supplementary Material (ESI) for Chemical Communications

Supplementary Information

for

Copper-Catalyzed Oxidative Desulfurization-Oxygenation of Thiocarbonyl Compounds Using Molecular Oxygen: An Efficient Method for the Preparation of Oxygen Isotopically Labeled Carbonyl Compounds

Fumitoshi Shibahara,* Aiko Suenami, Atsunori Yoshida and Toshiaki Murai*

Department of Chemistry, Faculty of Engineering, Gifu University
Yanagido, Gifu 501-1193 (Japan)

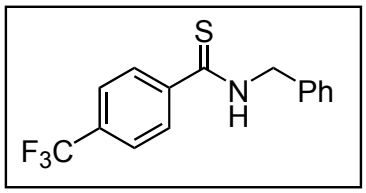
Experimental

General remarks. IR spectra were obtained on a JASCO FT-IR spectrophotometer. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a JEOL α-400 (400, 100, 376 MHz) in $CDCl_3$. Chemical shifts of ^{1}H and ^{13}C are reported in δ values referred respectively to tetramethylsilane and $CDCl_3$ as internal standards. ^{19}F chemical shifts are expressed in δ value deshielded with respect to CF_3COOH as an external standard. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a JEOL JMS 700 mass spectrometer. Elemental analyses were carried out by Elemental Analysis Center of Kyoto University. Melting points were determined using a Yanagimoto melting point apparatus and are reported uncorrected.

Materials. Unless otherwise noted, reagents were commercially available and used without purification. CuCl was purified by reprecipitation from a saturated conc. HCl aqueous solution with water.[S1] DMF and DMSO were distilled over calcium hydride under reduced pressure. Silica gel used for column chromatography was Silica gel 60 N (Spherical, Neutral, 100–210 mm) from Kanto Chemical Co., Inc. Isotopic oxygen gas ($^{18}O_2$, containing minimum 99 atom % of ^{18}O, Cat. No. 602892, Lot No. IS1146) was purchased from ISOTEC, and the gas was introduced into reactor via gas-tight syringe. *N*-Benzyl aromatic thioamides **4** and **6a-c** were prepared by conventional Willgerodt–Kindlar reactions.[S2] *N*-Benzyl aliphatic thioamides **6d-f** and **8f**,[S3] thioester **10**,[S3] dithioimide **11**[S3], and thionated protected sialic acid **16** were obtained by treatment of the corresponding carbonyl compounds with Lawesson's reagent. Thiourea **13**[S5] and selenoamide **14**[S6] were prepared by the methods according to literatures.

General procedure for the desulfurization–oxygenation of thioamides. (Table 1, Figure 1)
A mixture of thioamide (1.00 mmol), copper(I) chloride (20 mg, 0.20 mmol) and DMSO (1 ml) was stirred at 80 °C under O_2 atmosphere. The reaction progress was monitored by thin-layer chromatography. The reaction was quenched by addition of aqueous saturated ammonium chloride solution or aqueous ammonia solution and extracted with ether. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The conversion was determined by ^{1}H NMR. The residue was purified by column chromatography on silica gel to give the corresponding amide quantitatively.

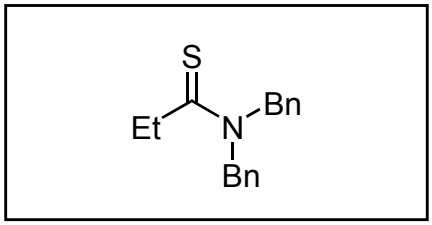
Synthesis of *N*-benzyl-4-trifluoromethylbenzenecarbothioamide (6c)



A solution of elemental sulfur (72 mg, 2.2 mmol), 4-trifluoromethylbenzaldehyde (0.27 mL, 2.0 mmol), and benzylamine (0.24 mL, 2.2 mmol) in DMF (2 mL) was stirred at 80 °C for 3 h. The resulting solution was poured onto ice. To the mixture was added conc HCl (ca. 5 mL). The aqueous layer was extracted with ether. The combined organic layer was washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by

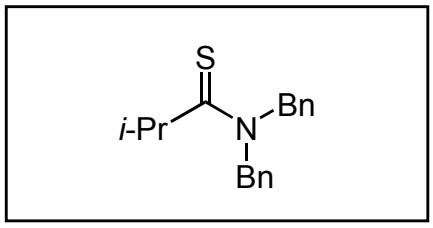
column chromatography on silica gel (Hex : EtOAc = 5 : 1) to give *N*-benzyl-4-trifluoromethylbenzenecarbothioamide (**6c**) in 93% yield as a pale yellow powder. mp 96–97 °C; Rf = 0.30; IR (KBr) 3293, 1528, 1523, 1485, 1404, 1091, 833, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.98 (d, *J* = 4.9 Hz, 2H, CH_2), 7.25-7.82 (m, 10H, NH, Ar); ^{13}C NMR ($CDCl_3$) δ 51.3 (CH_2), 123.7 (q, *J* = 272.5 Hz, $\underline{C}F_3$), 125.6 (q, *J* = 3.9 Hz, $\underline{C}CCF_3$), 127.1, 128.47, 128.49, 129.2 (Ar), 132.7 (q, *J* = 32.7 Hz, $\underline{C}CF_3$), 135.8 (Ar), 144.7 (q, *J* = 1.1 Hz, $\underline{C}CCCF_3$), 199.9 (C=S); MS (EI) *m/z* 295 (M^++1); Anal. Calcd for $C_{15}H_{12}F_3NS$: C, 61.00; H, 4.10, N, 4.74. Found: C, 61.05; H, 4.17; N, 4.73.

Synthesis of *N*,*N*-bis(phenylmethyl)propanethioamide (8d)



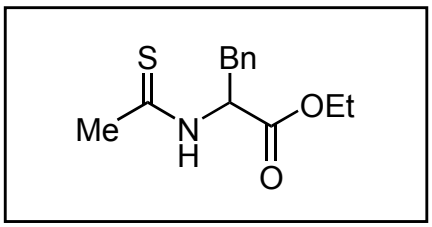
A solution of 2.2 g (8 mmol) of *N*,*N*-bis(phenylmethyl)-propionamide in dry toluene (8 mL) was treated with 1.8 g (4.4 mmol) of Lawesson's reagent. The mixture was stirred and heated to reflux for 1 h. The reaction mixture was concentrated in *vacuo*. The resulting oil was purified by column chromatography on silica gel (AcOEt : hexane = 1 : 5) to give *N*,*N*-bis(phenylmethyl)propanethioamide (**8d**) (1.2 g, 55% yield, Rf = 0.50) as a pale yellow oil.; IR (KBr) 3086, 3061, 3029, 2977, 2930, 1604, 1496, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.38 (t, *J* = 7.6 Hz, 3H, $CH_2C\underline{H}_3$), 2.92 (q, *J* = 7.6 Hz, 2H, $C\underline{H}_2CH_3$), 4.74 (s, 2H, $C\underline{H}_2Ph$), 5.35 (s, 2H, $C\underline{H}_2Ph$), 7.13 (d, *J* = 6.8, Hz, 2H, Ar), 7.23-7.41 (m, 8H, Ar) ; ^{13}C NMR ($CDCl_3$) δ14.3, 36.7, 53.1, 55.5, 126.2, 127.8, 127.9, 128.0, 128.8, 129.2, 134.9, 135.7, 208.3 (C=S); MS (EI) m/z 269 (M^+); HRMS Calcd for $C_{17}H_{19}NS$: 269.1238. Found: 269.1238

Synthesis of 2-methyl-*N*,*N*-bis(phenylmethyl)propanethioamide (8e)



A solution of 3.2 g (12 mmol) of 2-methyl-*N*,*N*-bis(phenylmethyl)-propionamide in dry toluene (12 mL) was treated with 2.7 g (6.6 mmol) of Lawesson's reagent. The mixture was stirred and heated to reflux for 1 h. The reaction mixture was concentrated in *vacuo*. The resulting oil was purified by column chromatography on silica gel (AcOEt : hexane = 1 : 5) to give 2-methyl-*N*,*N*-bis(phenylmethyl)propanethioamide(**8e**) (3.2 g, 94% yield, Rf = 0.53) as a pale yellow solid.; mp 54.9-56.6 °C; IR (KBr) 2955, 2919, 1964, 1821, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.92 (d, *J* = 6.3 Hz, 6H, $CH(C\underline{H}_3)_2$), 3.18 (sep, *J* = 6.3 Hz, 1H, $C\underline{H}(CH_3)_2$), 4.77 (s, 2H, $C\underline{H}_2Ph$), 5.83 (s, 2H, $C\underline{H}_2Ph$), 7.10 (d, *J* = 7.3, Hz, 2H, Ar), 7.24-7.40 (m, 8H, Ar) ; ^{13}C NMR ($CDCl_3$) δ 23.6, 37.0, 52.7, 55.6, 125.9, 127.6, 127.7, 127.9, 128.7, 129.1, 135.2, 135.8, 213.8 (CS); MS (EI) m/z 283 (M^+); HRMS Calcd for $C_{18}H_{21}NS$: 283.1395. Found: 283.1367

Synthesis of *N*-thioacetyl-*L*-phenylalanine ethyl ester (9)



A solution of 470 mg (2 mmol) of Ac-Phe-OEt in 2 mL of dry CH_2Cl_2 was treated with 450 mg (1.1 mmol) of Lawesson's reagent. The mixture was stirred at room temperature for 15.5 h. The reaction mixture was filtered and the residue was washed with CH_2Cl_2. This solution was concentrated in *vacuo*. The resulting solid was purified by column chromatography on silica gel (AcOEt : hexane = 1 : 5) to give *N*-thioacetyl-*L*-phenylalanine ethyl ester (440 mg, 88 % yield, Rf = 0.18) as a pale yellow solid.; mp 76.8-80.0 °C ; IR (KBr) 3293, 3046, 1715, 1541, 1291, 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 2.55 (s, 3H, $C\underline{H}_3CS$), 3.22 (dd, *J* = 4.6, 13.9 Hz, 1H, $C\underline{H}_2Ph$), 3.40 (dd, *J* = 6.3, 14.1 Hz, 1H, $C\underline{H}_2Ph$), 4.20 (dq, *J* = 1.5, 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 5.37 (dt, *J* = 4.6, 6.6 Hz, 1H, C<u>H</u>Bn), 7.09 (d, *J* = 6.4 Hz, 2H, Ar), 7.11-7.31 (m, 3H, Ar), 7.66 (br, 1H, N<u>H</u>CS); ^{13}C NMR ($CDCl_3$) δ 14.1, 34.1, 36.1, 58.7, 61.9, 127.2, 128.6, 129.3, 135.5, 170.9 (COOEt), 200.8 (CS); MS (EI) m/z 251 (M^+); HRMS Calcd for $C_{13}H_{17}NO_2S$: 251.0980. Found: 251.0963.

Desulfurization–oxygenation of thioamides 4 under $^{18}O_2$ atmosphere (Tables 2 and 3)

A solution of thioamide **4** (0.50 mmol) and copper(I) chloride (10 mg, 0.10 mmol) in DMSO or DMF (0.5 ml) in 5 mL two-necked flask (total volume: ca. 15 mL) was degassed by three cycles of evacuation–introduction of Ar gas. Then, the mixture was evacuated again, and to this was added $^{18}O_2$ gas (ca. 20 mL, 0.9 mmol) via gas-tight syringe. The resulting mixture was vigorously stirred at 80 °C. During the reaction, aliquots of the solution (ca. 0.05 mL) were collected via syringe after 2 and 5 min and diluted with ether. The ether layers were analyzed by mass spectroscopy without further purification. After completion of the reaction, aliquots of the solution (ca. 0.05 mL) were collected and diluted with ether again to analyze mass spectroscopy, and then the reaction solution was quenched by addition of aqueous saturated ammonium chloride solution and extracted with ether. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (Hex : EtOAc = 1 : 1), and the obtained amide was analyzed by mass spectroscopy. The resulting introduction ratio of $^{16}O/^{18}O$ were summarized in Tables 2 and 3.

Treatment of partially labeled amide 4 with $^{16}O_2$ atmosphere in the presence of CuCl.

A solution of partially labeled amide **4** ($^{16}O/^{18}O$ = 15/85) (71.5 mg, ca. 0.33 mmol) and CuCl (6.7 mg, 0.067 mmol) in DMSO (0.35 mL) was stirred under oxygen atmosphere at 80 °C for 2 h. The resulting solution was diluted with ether and analyzed by mass spectroscopy. The resulting ratio of $^{16}O/^{18}O$ was 15/85 (unchanged).

Thionation of methyl(phenyl 4,7,8,9-tetra-*O*-acetyl-5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranoosid)onate (16) .

A solution of α,β-mixture (ca. 1 : 2) of **16** (3.50g, 6.0 mmol) and Lawsson's reagent (1.21g, 3.0

mmol) in toluene was stirred at 80 °C for 1.5 h. The resulting solution was concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (Hex : EtOAc = 1 : 1 to 1 : 2) to give the corresponding thionated β-sialic acid **15** in 60% yield (2.16 g) as a colorless solid.; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H, C$\underline{H_3}$CO), 2.08 (s, 3H, C$\underline{H_3}$CO), 2.09 (s, 3H, C$\underline{H_3}$CO), 2.12 (s, 3H, C$\underline{H_3}$CO), 2.26-2.31 (m, 1H, CH), 2.45 (s, 3H, C$\underline{H_3}$CS), 2.69 (dd, J = 4.6, 13.7, 1H, CH), 3.58 (s, 3H, COOC$\underline{H_3}$), 4.03 (dd, J = 8.6, 12.1 Hz, 1H, CH), 4.54 (d, J = 10.3 Hz, 1H, CH), 4.86 (dd, J = 2.3, 10.2 Hz, 1H, CH), 4.97-5.01 (m, 2H, CH), 5.44 (bs, 1H, CH), 5.58 (td, J = 11.5, 4.6 Hz, 1H, CH), 7.31-7.44 (m, 5H, Ar), 7.90 (d, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 21.2, 21.5($\underline{C}H_3CO$), 34.5(CH_2), 37.4($\underline{C}H_3CS$), 52.7, 55.3, 62.7, 68.8, 69.4, 72.4, 73.8($\underline{C}$H-O or $\underline{C}$H-N), 89.3($\underline{C}$SPh), 128.8, 129.2, 129.9, 136.1(Ar), 168.1, 170.1, 170.3, 171.5, 171.8($\underline{C}$OOR), 203.8(C=S); HRMS Calcd for $C_{26}H_{34}NO_{11}S_2$ ($M + H^+$) : 600.1573. Found: 600.1549.

Desulfurization–oxygenation of methyl(phenyl 4,7,8,9-tetra-*O*-acetyl-5-thioacetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranoosid)on-ate (15) under $^{18}O_2$ atmosphere (eq. 4)

A solution of β-thionated sialic acid derivative **15** (300 mg, 0.50 mmol) and copper(I) chloride (10 mg, 0.10 mmol) in DMF (1 ml) in 5 mL two-necked flask (total volume: ca. 15 mL) was degassed by three cycles of evacuation–introduction of Ar gas. Then, the mixture was evacuated again and to this was added $^{18}O_2$ gas (ca. 20 mL, 0.9 mmol) via gas-tight syringe. The resulting mixture was vigorously stirred at 80 °C for 24 h. The reaction was quenched by addition aqueous saturated ammonium chloride solution and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was analyzed by mass spectroscopy, giving a $^{16}O/^{18}O$ ratio of 22/78, and purified by column chromatography on silica gel ($CHCl_3$: MeOH = 10 : 1) to give the corresponding desulfurized sialic acid derivative **16** in quantitative yield. The substance obtained after chromatography was analyzed by mass spectroscopy, giving a $^{16}O/^{18}O$ ratio of 23/77.

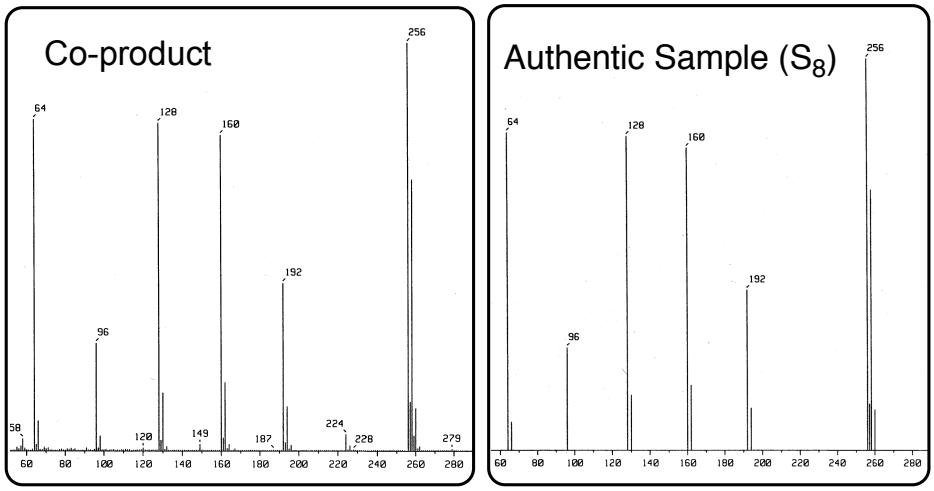


Figure S1 Mass spectrum of co-product and authentic elemental sulfur.

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