Rhodium-Catalyzed Reaction of Thiols with Polychloroalkanes in the Presence of Triethylamine

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I. General

Anhydrous CH_2Cl_2 (No. 27,099-7) and $(\text{CH}_2\text{Cl})_2$ (No. 28,450-5) were obtained from Aldrich and used as received. TOYOZYME LIP was obtained from TOYOBO ENZYMES. All other reagents were obtained from commercial sources and used as received (without degassing and dehydrating). All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring.

II. Reaction of Thiols with Polychloroalkanes (Table 2 and Scheme 4)

General Procedure 1 (Table 2, entry 1): Under an Ar atmosphere, CH_2Cl_2 (0.5 mL) solution of $\text{RhCl}(\text{PPh}_3)_3$ (23.1 mg, 0.0250 mmol) was added to CH_2Cl_2 (0.5 mL) solution of octanethiol (73.1 mg, 0.500 mmol) and Et_3N (0.5 mL) by using CH_2Cl_2 (1.0 mL). The mixture was stirred at rt for 24 h. The resulting solution was concentrated and purified by preparative TLC (hexane), which furnished 1-octylsulfanylmethylsulfanyloctane (61.7 mg, 0.203 mmol, 81%) as a colorless oil.

1-Octylsulfanylmethylsulfanyloctane (Table 2, entry 1).¹

Colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 3.65 (s, 2H), 2.62 (t, J = 7.2 Hz, 4H), 1.59 (quint, J = 7.2 Hz, 4H), 1.16-1.45 (m, 20H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 35.5, 31.8, 30.9, 29.2, 29.1, 28.9, 22.6, 14.0.

1-Dodecylsulfanylmethylsulfanyldodecane (Table 2, entry 2).²

Colorless solid; Mp 34-35 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 3.65 (s, 2H), 2.62 (t, J = 7.2 Hz, 4H), 1.59 (quint, J = 7.2 Hz, 4H), 1.20-1.45 (m, 36H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 35.5, 31.9, 30.9, 29.64, 29.62, 29.59, 29.53, 29.3, 29.2, 29.1, 28.9, 22.7, 14.1.

1,1'-[Methylenebis(thiomethylene)]bisbenzene (Table 2, entry 3).³

Colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 7.19-7.34 (m, 10H), 3.82 (s, 4H), 3.37 (s, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 137.7, 129.1, 128.5, 127.0, 34.4, 33.4.

11-(11-Hydroxyundecylsulfanylmethylsulfanyl)undecan-1-ol (Table 2, entry 4).

Colorless solid; Mp 87-88 °C; IR (neat) 3200, 1600 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz,) δ 3.59-3.68 (m, 6H), 2.62 (t, J = 7.4 Hz, 4H), 1.51-1.64 (m, 8H), 1.20-1.44 (m, 28H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 63.1, 35.4, 32.8, 30.9, 29.54, 29.47, 29.38, 29.2, 29.1, 28.9, 25.7. HRMS (EI, ditrifluoroacetate): calcd for $\text{C}_{27}\text{H}_{46}\text{S}_2\text{O}_4\text{F}_6$ $[\text{M}]^+$, 612.2743; found, 612.2692.

2-*t*-Butoxycarbonylamino-3-(2-*t*-butoxycarbonylamino-2-methoxycarbonyl-ethylsulfanylmethylsulfanyl)propionic acid methylester (Table 2, entry 5).

Colorless oil; IR (neat) 3320, 2930, 1690, 1495, 1350, 1150, 1030 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 5.33-5.44 (m, 2H), 4.49-4.61 (m, 2H), 3.77 (s, 6H), 3.68 (s, 2H), 3.14 (dd, J = 14.1, 4.8

Hz, 2H), 3.00 (dd, $J = 14.1, 5.9$ Hz, 2H), 1.45 (s, 18H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.4, 155.0, 80.2, 53.0, 52.5, 36.4, 33.0, 28.2. Anal. Calcd for $\text{C}_{19}\text{H}_{34}\text{N}_2\text{O}_8\text{S}_2$: C, 47.28; H, 7.10; N, 5.80. Found: C, 47.48; H, 7.45; N, 5.46.

1-*p*-Tolylsulfanylmethylsulfanyl-*p*-toluene (Table 2, entry 6).⁴

Colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 7.29-7.36 (m, 4H), 7.12 (d, $J = 7.8$ Hz, 4H), 4.26 (s, 2H), 2.33 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 137.4, 131.5, 131.3, 129.7, 42.0, 21.1.

1-(2-Octylsulfanylethylsulfanyl)octane (Table2, entry 7).⁵

Reaction temperature: 80 °C.

Colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 2.71 (s, 4H), 2.54 (t, $J = 7.5$ Hz, 4H), 1.59 (quint, $J = 7.2$ Hz, 4H), 1.22-1.43 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 32.2, 32.1, 31.8, 29.7, 29.2, 28.9, 22.6, 14.1.

1-*p*-Tolylsulfanylethylsulfanyl-*p*-toluene (Table2, entry 8).⁶

Reaction temperature: 80 °C.

Colorless solid; Mp 74-76 °C; ^1H NMR (CDCl_3 , 300 MHz) δ 7.19-7.24 (m, 4H), 7.05-7.12 (m, 4H), 3.01 (s, 4H), 2.32 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 136.7, 131.3, 130.7, 129.8, 34.0, 21.0.

Thioformic acid S-dodecylester (Table2, entry 9).

Procedure 1 was followed using $\text{RhCl}(\text{PPh}_3)_3$ (92.5 mg, 0.100 mmol), dodecanethiol (101.2 mg, 0.500 mmol), Et_3N (0.55 mL), and CHCl_3 (10 mL), which furnished thioformic acid *S*-dodecylester (26.5 mg, 0.115 mmol, 69%).

Colorless oil; IR (neat) 2900, 1670, 1450 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz,) δ 10.13 (s, 1H), 2.98 (t, $J = 7.2$ Hz, 2H), 1.61 (quint, $J = 7.5$ Hz, 2H), 1.17-1.42 (m, 18H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 187.8, 31.9, 29.59, 29.52, 29.45, 29.42, 29.3, 29.0, 28.7, 26.7, 22.7, 14.1. HRMS (EI): calcd for $\text{C}_{12}\text{H}_{25}\text{S}$ $[\text{M}-\text{CHO}]^+$, 201.1677; found, 201.1659.

1-Deuteriumthioformic acid *S*-dodecylester (Scheme 4).

Procedure 1 was followed using $\text{RhCl}(\text{PPh}_3)_3$ (92.5 mg, 0.100 mmol), dodecanethiol (101.2 mg, 0.500 mmol), Et_3N (0.55 mL), and CDCl_3 (10 mL), which furnished 1-deuteriumthioformic acid *S*-dodecylester (23.4 mg, 0.102 mmol, 61%).

Colorless oil; IR (neat) 2900, 1670, 1450 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz,) δ 2.98 (t, $J = 7.2$ Hz, 2H), 1.61 (quint, $J = 7.2$ Hz, 2H), 1.17-1.42 (m, 18H), 0.88 (t, $J = 6.8$ Hz, 3H); ^2H NMR (CDCl_3 , 61 MHz) δ 10.17 (s, 1D).

Ditiocarbonic acid *S,S*-dihexylester (Table2, entry 10).

Procedure 1 was followed using $\text{RhCl}(\text{PPh}_3)_3$ (92.5 mg, 0.100 mmol), hexanethiol (59.1 mg, 0.500 mmol), Et_3N (0.55 mL), and CCl_4 (10 mL), which furnished ditiocarbonic acid *S,S*-dioctylester (20.1 mg, 0.0766 mmol, 61%).

Colorless oil; IR (neat) 2940, 1640, 1450, 870 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz,) δ 2.98 (t, $J = 7.2$ Hz, 4H), 1.61 (quint, $J = 7.2$ Hz, 4H), 1.20-1.44 (m, 12H), 0.88 (t, $J = 6.8$ Hz, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 189.8, 31.2, 30.6, 29.7, 28.4, 22.5, 14.0. HRMS (EI): calcd for $\text{C}_{13}\text{H}_{26}\text{OS}_2$

[M]⁺, 262.1425; found, 262.1397.

III. Reaction of Thiols with Alkyl Halides (Schemes 2, 3, and 5)

General Procedure 2 (Scheme 2): Under Ar atmosphere, Et₃N (0.25 mL) solution of RhCl(PPh₃)₃ (11.6 mg, 0.0125 mmol) was added to Et₃N (0.25 mL) solution of benzylchloride (31.6 mg, 0.250 mmol) and octanethiol (36.6 mg, 0.250 mmol) by using Et₃N (0.50 mL). The mixture was stirred for at 80 °C for 24 h. The resulting solution was concentrated and purified by preparative TLC (hexane), which furnished 1-octylsulfanylmethylbenzene (43.7 mg, 0.185 mmol, 74%) as a colorless oil.

1-Octylsulfanylmethylbenzene (Scheme 2).⁷

Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.35 (m, 5H), 3.69 (s, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.54 (quint, *J* = 7.2 Hz, 2H), 1.15-1.40 (m, 10H), 0.88 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 138.6, 128.8, 128.4, 126.8, 36.2, 31.8, 31.3, 29.2, 29.14, 29.12, 28.8, 22.6, 14.1.

1-Dodecylsulfanylmethylbenzene (Scheme 3).⁸

RhCl(PPh₃)₃ (2.3 mg, 0.0025 mmol) was used. Reaction temperature: 50 °C. Reaction time: 30 h. Colorless oil; ¹H NMR (CDCl₃, 300 MHz) δ 7.18-7.36 (m, 5H), 3.70 (s, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 1.49-1.60 (m, 2H), 1.18-1.41 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 138.7, 128.8, 128.4, 126.8, 36.3, 31.9, 31.4, 29.63, 29.61, 29.57, 29.48, 29.3, 29.22, 29.20, 28.9, 22.7, 14.1.

(S)-(-)-1-Phenylethylbenzylsulfide (78% ee, Scheme 5).⁹

Reaction time: 48 h.

Colorless oil; $[\alpha]_D^{20} -196.9^\circ$ (c 0.344, EtOH, 78% ee) [lit.⁹ $[\alpha]_D^{20} -83.1^\circ$ (EtOH)]; ^1H NMR (CDCl_3 , 300 MHz) δ 7.18-7.37 (m, 10H), 3.80 (q, $J = 7.2$ Hz, 1H), 3.54 (d, $J = 13.5$ Hz, 1H), 3.43 (d, $J = 13.5$ Hz, 1H), 1.52 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 143.8, 138.4, 128.8, 128.5, 128.4, 127.4, 127.0, 126.8, 43.5, 35.7, 22.5. Chiraldex B-DM column, retention time = 37.5 min (*R* isomer) and 38.2 min (*S* isomer) (160 °C; isothermal).

IV. Synthesis of (*R*)-(1-Chloroethyl)benzene (78% ee, Scheme 5).

A mixture of methylbenzyl alcohol (1.0 g, 8.2 mmol), TOYOZYME LIP (75 mg), vinyl laurate (1.1 mL), and *i*-Pr₂O (10 mL) was stirred at rt for 2 days. The reaction mixture was filtered and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 20:1), which furnished (*S*)-methylbenzyl alcohol (0.43 g, 3.5 mmol, 43%, >99% ee) as colorless oil. ^1H NMR (CDCl_3 , 300 MHz) δ 7.23-7.41 (m, 5H), 4.91 (dq, $J = 6.6, 3.5$ Hz, 1H), 1.85-1.93 (m, 1H), 1.50 (d, $J = 6.6$, 3H). Chiraldex G-TA column, retention time = 11.8 min (*R* isomer) and 12.3 min (*S* isomer) (100 °C; isothermal).

To a solution of (*S*)-methylbenzyl alcohol (0.21 g, 1.7 mmol, >99% ee), pyridine (0.16 mL, 2.0 mmol), DMF (0.5 mL), and pentane (4.5 mL) was added methanesulfonyl chloride (0.18 mL 1.87 mmol), keeping the temperature below 0 °C, and the resulting mixture was stirred at rt for 5 h. The mixture was quenched by the addition of ice water, the organic layer was washed with 1M aqueous HCl, 5% aqueous NaHCO₃. The solvent was removed under reduced pressure to give (*R*)-methylbenzyl chloride⁹ (0.12 g, 0.85 mmol, 50%, 78% ee) as a colorless oil; ^1H NMR (CDCl_3 , 300 MHz) δ 7.26-7.46 (m, 5H), 5.10 (q, $J = 6.8$ Hz, 1H), 1.86 (d, $J = 6.6$ Hz, 3H). Chiraldex G-TA column, retention time = 7.53 min (*R* isomer) and 7.80 min (*S* isomer) (100 °C; isothermal).

V. References

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