TIN-HYDRIDE-MEDIATED RADICAL ADDITION OF ALKYL HALIDES TO 2-METHYLENE-1,3-DITHIANE MONOXIDE AS A KETENE EQUIVALENT

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Abstract – Reductive radical addition of alkyl halides to ketene dithioacetal monoxide in the presence of tributyltin hydride and a radical initiator provides the corresponding adducts, 2-alkyl-1,3-dithiane monoxides, in good yields.

INTRODUCTION

Intermolecular addition of alkyl radicals to activated alkenes mediated by tin hydride is one of the most important methodologies for carbon–carbon bond formation via radical processes.1 α,β-Unsaturated carbonyl compounds, unsaturated nitriles, and styrenes are usually employed as radical acceptors. We have been interested in ketene dithioacetal and its derivatives as useful ketene equivalents in organic synthesis.2 Recently, we disclosed that ketene dithioacetal monoxides 1 serve as activated alkenes in rhodium-catalyzed addition of arylboronic acids.3 We anticipated that ketene dithioacetal monoxides 1 could behave as activated alkenes also in intermolecular radical addition. The captodative effect4 from the sulfanyl and sulfinyl groups should stabilize radical intermediate 2, facilitating the radical addition (Scheme 1). The stability of intermediate 2 could prevent undesired side reactions such as polymerization. Here, we report the full details5 of tin-hydride-mediated radical addition of alkyl halides to ketene dithioacetal monoxide 1 as a ketene equivalent.6

\[ R^+ + S\text{R}^+ \rightarrow R\text{S}^- + S\text{R} \]

Scheme 1. Radical Addition to Ketene Dithioacetal Monoxide

Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.
RESULTS AND DISCUSSION

Tributyltin hydride (2.0 equiv) was added dropwise over 1 h to a benzene solution of tert-butyl bromide (3.0 equiv), 2-methylene-1,3-dithiane 1-oxide (1a, 1.0 equiv), and 2,2'-azobis(isobutyronitrile) (AIBN, 0.10 equiv) at reflux (Table 1, entry 1). The resulting mixture was stirred for an additional 1 h to afford 3a in 84% isolated yield. Thanks to the highly polar nature of 3a, sulfoxide 3a could be separated by silica-gel column purification without contamination by tin residues.

Table 1. Radical Addition of Alkyl Halides to Ketene Dithioacetal Monoxide 1a

<table>
<thead>
<tr>
<th>entry</th>
<th>R–X</th>
<th>3</th>
<th>yield /%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>3a</td>
<td>84 (&gt;99:1)</td>
</tr>
<tr>
<td>2</td>
<td>n-C8H17Br</td>
<td>3b</td>
<td>84 (&gt;99:1)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3c</td>
<td>91 (17:1)</td>
</tr>
<tr>
<td>4</td>
<td>PhSBr</td>
<td>3d</td>
<td>67 (&gt;99:1)</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td>3e</td>
<td>75 (8:1)</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td>3f</td>
<td>80 (6:1)</td>
</tr>
<tr>
<td>7b</td>
<td>n-C6H13I</td>
<td>3g</td>
<td>58 (3:1)</td>
</tr>
</tbody>
</table>

a Diastereomer ratios are in parentheses. The major isomer is a trans isomer.

b AIBN (0.20 equiv) was used.

It is worth noting that the reaction with acyclic ketene dithioacetal monoxide 1b yielded a complex mixture including polymeric materials (Figure 1). Phenyl-substituted 1c failed to participate in the radical addition, probably because of the steric reason. Treatment of tert-butyl bromide with 2-methylene-1,3-dithiane (4) provided the corresponding adduct in only 43% yield.

Figure 1. Other Radical Acceptors
The use of triphenyltin hydride instead of tributyltin hydride allowed us to decrease the amount of alkyl halide employed. Addition of triphenyltin hydride (2.0 equiv) dropwise over 1 h to a solution of tert-butyl bromide (1.0 equiv), 1a (1.2 equiv), and AIBN (0.20 equiv) furnished 3a in 70% yield (Equation 1). Smoother hydrogen abstraction of the stabilized radical intermediate 2 from triphenyltin hydride would increase the efficiency of the reaction, because of the weaker Sn–H bond of triphenyltin hydride.\(^7\)

We next investigated the scope of alkyl halides (Table 1). The addition of tertiary alkyl bromides proceeded smoothly to yield the desired products in high yields (entries 1–4). The phenylthio group was compatible under the reaction conditions (entry 4). Secondary alkyl iodides also underwent the radical reaction smoothly with 1a, although the products were mixtures of two diastereomers (entries 5 and 6). Primary alkyl iodide reacted with 1a to provide 3g in moderate yield with lower diastereoselectivity. In all cases, trans isomers were predominantly formed.\(^8\) The reason for the high trans selectivity is not clear.

We next examined the utility of the products. Treatment of sulfoxide 3b with a catalytic amount of sulfuric acid in boiling toluene afforded aldehyde 5 almost quantitatively (Equation 2). Sulfoxide 3b could be easily reduced into 1,3-dithiane.\(^9\) Thus, treatment of sulfoxide 3b with trifluoroacetic anhydride and sodium iodide gave 1,3-dithiane 6 in excellent yield (Equation 3).

The reaction of tertiary alkyl bromide 7 bearing an amide moiety\(^10\) with 1a and tributyltin hydride proceeded efficiently to give desired adduct 8 in high yield (Scheme 2). Treatment of adduct 8 with hydrochloric acid followed by an addition of benzoyl chloride provided dihydropyrrole 9 having a
quaternary carbon atom in good yield. The present protocol would be useful for the synthesis of heterocycles bearing such a quaternary carbon moiety.

In conclusion, we have developed radical addition of alkyl halides to a ketene equivalent, 2-methylene-1,3-dithiane 1-oxide (1a), in the presence of tributyltin hydride and AIBN. The reaction afforded alkanal equivalents protected as dithioacetal monoxide, which could be subjected to a variety of organic transformations.

**EXPERIMENTAL**

**Instrumentation and Chemicals**

$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra were taken on Varian UNITY INOVA 500 spectrometers and were recorded in CDCl$_3$. Chemical shifts ($\delta$) are in parts per million relative to tetramethylsilane at 0.00 ppm for $^1$H and relative to CDCl$_3$ at 77.23 ppm for $^{13}$C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra (FAB unless otherwise noted) were determined on a JEOL MStation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F$_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Tributyltin hydride and triphenyltin hydride were purchased from Aldrich. Benzene was purchased from Wako Pure Chemical and dried over slices of sodium. Ketene dithioacetal monoxides 1$^{11}$ and dithiane 4$^2$ were prepared according to the literature. Most of alkyl halides and AIBN were purchased from Wako Pure Chemical. 2-Bromo-2-methyldecane$^{12}$ (Table 1, entry 2) and 6-bromo-6-methyl-1-phenylthioheptane$^{13}$ (entry 4) were prepared by bromination of the corresponding alcohol with hydrobromic acid. Alkyl halide 7 was prepared according to the literature.$^{10}$ All reactions were carried out under argon atmosphere.

**Typical Procedure for Radical Addition Reaction (Table 1, entry 1):** A benzene (1.0 mL) solution of 2-methylene-1,3-dithiane 1-oxide (1a, 49.4 mg, 0.33 mmol), 2-bromo-2-methylpropane (0.11 mL, 0.99 mmol), and 2,2'-azobis(isobutynitrile) (5.0 mg, 0.030 mmol) was placed in a flask under an atmosphere
of argon. Then, a benzene (1.0 mL) solution of tributyltin hydride (0.18 mL, 0.66 mmol) was added over 1 h with a syringe pump at reflux. After the addition was completed, the mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was poured into saturated aqueous NaHCO₃ (5 mL) and extracted with AcOEt (3 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by chromatography on silica gel (hexane/AcOEt = 1/2) provided 2-(2,2-dimethylpropyl)-1,3-dithiane 1-oxide (3a, 58.0 mg, 0.28 mmol, 84%).

**Transformation of 3b to 5:** A toluene (2.0 mL) solution of 2-(2,2-dimethyldecyl)-1,3-dithiane 1-oxide (3b, 61.6 mg, 0.20 mmol) was placed in a flask under an atmosphere of argon. Then, sulfuric acid (7.1 mg, 0.072 mmol) was added, and the resulting mixture was stirred at reflux for 2 h. The reaction mixture was poured into sat. aq NaHCO₃ (5 mL) and extracted with AcOEt (3 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. Purification by chromatography on silica gel (hexane/AcOEt = 40/1) provided 3,3-dimethylundecanal (5, 39.6 mg, 0.20 mmol, 99%).

**Transformation of 3b to 6:** A solution of 2-(2,2-dimethyldecyl)-1,3-dithiane 1-oxide (3b, 30.2 mg, 0.10 mmol) and sodium iodide (38.3 mg, 0.25 mmol) in acetone (2.0 mL) was placed in a flask under argon. Trifluoroacetic anhydride (0.042 mL, 0.30 mmol) was then added dropwise at 0 °C, and the resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into sat. aq NaHCO₃ (5 mL) and extracted with AcOEt (3 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. Chromatographic purification on silica gel (hexane/AcOEt = 40/1) yielded 2-(2,2-dimethyldecyl)-1,3-dithiane (6, 26.3 mg, 0.091 mmol, 92%).

**Synthesis of 8:** A benzene (1.0 mL) solution of 2-methylene-1,3-dithiane 1-oxide (1a, 44.6 mg, 0.30 mmol), tert-butyl N-(2-bromo-2-ethylbutyl)carbamate (7, 250 mg, 0.90 mmol), and 2,2'-azobis(isobutyronitrile) (5.0 mg, 0.030 mmol) was placed in a flask under an atmosphere of argon. Tributyltin hydride (0.18 mL, 0.60 mmol) in benzene (1.0 mL) was then added over 1 h with a syringe pump at reflux. After the addition was completed, the mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was poured into sat. aq NaHCO₃ (5 mL) and extracted with AcOEt (3 × 10 mL). The combined organic layer was dried and concentrated. Silica gel column purification by using hexane/AcOEt = 1/2 as eluent afforded 2-[2-(tert-butoxycarbonylaminomethyl)-2-ethylbutyl]-1,3-dithiane 1-oxide (8, 95.4 mg, 0.27 mmol, 90%).

**Synthesis of 9:** An acetonitrile (5.0 mL) solution of 2-[2-(tert-butoxycarbonylaminomethyl)-2-ethylbutyl]-1,3-dithiane 1-oxide (8, 59.0 mg, 0.17 mmol) was placed in a flask under argon atmosphere. Hydrochloric acid (0.31 mL, 11 M, 3.4 mmol) was added at 25 °C, and the resulting mixture was stirred at the same temperature for 48 h. Benzoyl chloride (0.096 mL, 0.82 mmol) was then added at 25 °C,
and the resulting mixture was stirred at the same temperature for 12 h. The reaction mixture was poured into sat. aq NaHCO₃ (5 mL). Extractive workup followed by silica gel column purification (hexane/AcOEt = 10/1) provided N-benzyol-3,3-diethyl-2,3-dihydropyrrole (9, 23.8 mg, 0.10 mmol, 62%).

**Characterization Data of Compounds**

**2-(2,2-dimethylpropyl)-1,3-dithiane 1-oxide (3a)**

IR (neat) 2955, 2868, 1474, 1425, 1367, 1241 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (s, 9H), 1.41 (dd, J = 14.5, 4.5 Hz, 1H), 2.25–2.34 (m, 1H), 2.37 (d, J = 14.5 Hz, 1H), 2.45–2.50 (m, 1H), 2.53–2.58 (m, 1H), 2.67 (dd, J = 10.0, 10.0, 2.0 Hz, 1H), 2.75 (dd, J = 12.0, 12.0 Hz, 1H), 3.40–3.45 (m, 1H), 3.56 (d, J = 9.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 29.4, 30.2, 30.6, 31.4, 42.1, 53.9, 63.0. Anal. Calcd for C₉H₁₈O₂S₂: C, 52.38; H, 8.79%. Found: C, 52.55; H, 8.75%.

**2-(2,2-dimethyldecyl)-1,3-dithiane 1-oxide (3b)**

IR (neat) 2925, 2853, 1468, 1425, 1389, 1367, 1171, 1038, 870, 830, 404 cm⁻¹; ¹H NMR (CDCl₃) 0.87 (t, J = 7.0 Hz, 3H), 0.97 (s, 3H), 0.98 (s, 3H), 1.21–1.36 (br, 14 H), 1.41 (dd, J = 15.0, 5.0 Hz, 1 H), 2.20–2.34 (m, 2H), 2.40–2.58 (m, 2H), 2.64 (dd, J = 13.0, 13.0, 3.0 Hz, 1H), 2.72 (dd, J = 12.0, 12.0 Hz, 1H), 3.53 (d, J = 9.0 Hz, 1H); ¹³C NMR (CDCl₃) 14.2, 22.8, 24.1, 27.6, 27.9, 29.2, 29.5, 29.8, 30.4, 30.6, 32.0, 33.7, 40.2, 42.8, 53.9, 62.9. HRMS (FAB⁺) (m/z) Observed: 305.1979 (Δ = +1.9 ppm). Calcd for C₁₆H₃₃O₂S₂: [MH⁺]: 305.1973.

**2-(1-adamantylmethyl)-1,3-dithiane 1-oxide (3c, the major diastereomer)**

Mp 130–131 °C; IR (nujol) 2922, 2853, 1654, 1559, 1507, 1378, 1279, 1024 cm⁻¹; ¹H NMR (CDCl₃) 1.27 (dd, J = 15.0, 4.5 Hz, 1H), 1.58–1.75 (m, 12 H), 1.99 (br s, 3H), 2.20 (d, J = 15.0 Hz, 1H), 2.23–2.33 (m, 1H), 2.42–2.56 (m, 2H), 2.65 (dd, J = 13.0, 13.0, 2.0 Hz, 1H), 2.75 (dd, J = 13.0, 13.0 Hz, 1H), 3.38–3.44 (m, 1H), 3.59 (d, J = 10.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 28.7, 29.3, 30.5, 33.1, 37.0, 42.8, 42.9, 53.8, 61.2. HRMS (FAB⁺) (m/z) Observed: 284.1268 (Δ = –0.2 ppm). Calcd for C₁₅H₂₄O₂S₂: 284.1269.

**2-(7-phenylthio-2,2-dimethylheptyl)-1,3-dithiane 1-oxide (3d)**

IR (neat) 2921, 2853, 1584, 1480, 1471, 1438, 1425, 1367, 1092, 1038, 740, 691 cm⁻¹; ¹H NMR (CDCl₃) δ 0.99 (s, 6H), 1.26–1.36 (m, 4H), 1.37–1.44 (m, 3H), 1.62–1.70 (m, 2H), 2.22–2.36 (m, 2H), 2.42–2.48 (m, 1H), 2.50–2.55 (m, 1H), 2.65 (dd, J = 10.0, 10.0, 2.0 Hz, 1H), 2.73 (dd, J = 12.0, 12.0 Hz, 1H), 2.93 (t, J = 7.0 Hz, 2H), 3.38–3.43 (m, 1H), 3.53 (d, J = 8.0 Hz, 1H), 7.15–7.19 (m, 1H), 7.26–7.30 (m, 2H), 7.31–7.35 (m, 2H); ¹³C NMR (CDCl₃) δ 23.6, 27.7, 27.8, 29.3, 29.7, 30.5, 33.7, 33.8, 40.1, 42.5, 53.9, 62.7, 125.9, 129.1, 129.2, 137.3. HRMS (FAB⁺) (m/z) Observed: 370.1462 (Δ = +0.9 ppm). Calcd for C₁₅H₂₉O₃S₃: 370.1459.
2-(cyclohexylmethyl)-1,3-dithiane 1-oxide (3e, the major diastereomer)
Mp 93–94 °C;  IR (nujol) 2920, 2853, 1685, 1559, 1507, 1375, 1023 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85–1.45 (m, 6H), 1.46–1.76 (m, 5H), 1.80–1.86 (m, 1H), 2.20–2.32 (m, 2H), 2.42–2.48 (m, 1H), 2.52–2.70 (m, 3H), 3.38–3.44 (m, 1H), 3.65 (dd, J = 11.0, 3.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 26.1, 26.3, 26.5, 29.5, 30.1, 32.1, 34.1, 34.2, 36.3, 54.0, 64.1. Anal. Calcd for C₁₁H₂₀OS₂: C, 56.85; H, 8.67%. Found: C, 56.62; H, 8.39%.

2-(2-methylpropyl)-1,3-dithiane 1-oxide (3f, the major diastereomer)
IR (neat) 2957, 2911, 2869, 2826, 1469, 1426, 1368, 1034, 682, 657 cm⁻¹; ¹H NMR (CDCl₃) δ 0.97 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 1.51–1.60 (m, 1H), 1.92–2.02 (m, 1H), 2.16–2.34 (m, 2H), 2.43–2.49 (m, 1H), 2.54–2.72 (m, 3H), 3.38–3.46 (m, 1H), 3.63 (dd, J = 11.0, 3.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.4, 23.6, 25.0, 29.5, 30.1, 37.8, 54.0, 64.6. Anal. Calcd for C₈H₁₆OS₂: C, 49.96; H, 8.38%. Found: C, 50.06; H, 8.35%.

2-heptyl-1,3-dithiane 1-oxide (3g, the major diastereomer)
IR (neat) 2955, 2926, 2855, 1469, 1426, 1231, 1036, 754, 725, 698, 663 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, J = 7.0 Hz, 3H), 1.25–1.50 (m, 9H), 1.62–1.77 (m, 2H), 2.22–2.35 (m, 2H), 2.42–2.49 (m, 1H), 2.57–2.73 (m, 3H), 3.40 (m, 1H), 3.60 (dd, J = 9.5 Hz, 3.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.3, 22.8, 26.0, 28.9, 29.2, 29.5, 29.7, 30.2, 31.9, 54.1, 66.5. HRMS (FAB⁺) (m/z) Observed: 234.1112 (Δ = 0.0 ppm). Calcd for C₁₁H₂₂OS₂: 234.1112.

3,3-dimethylundecanal (5)
IR (neat) 2958, 2928, 2854, 2729, 1723, 1468, 1368, 1267 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.0 Hz, 3H), 1.04 (s, 6H), 1.23–1.36 (br, 14H), 2.25 (d, J = 3.0 Hz, 2H), 9.84 (t, J = 3.0 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.3, 22.9, 24.2, 27.8, 29.5, 29.8, 30.5, 32.1, 33.7, 43.0, 55.0, 204.0. HRMS (m/z) Observed: 197.1909 (Δ = +1.8 ppm). Calcd for C₁₃H₂₅O [M–H]⁺: 197.1905.

2-(2,2-dimethyldecyl)-1,3-dithiane (6)
IR (neat) 2927, 2900, 2853, 1559, 1507, 1458, 1275 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, J = 7.0 Hz, 3H), 0.95 (s, 6H), 1.23–1.32 (m, 14H), 1.58 (d, J = 5.5 Hz, 2H), 1.76–1.86 (m, 1H), 2.05–2.12 (m, 1H), 2.77–2.82 (m, 2H), 2.92–2.99 (m, 2H), 4.04 (t, J = 5.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.4, 22.9, 24.3, 25.6, 27.6, 29.6, 29.9, 30.7, 31.6, 32.1, 34.0, 42.6, 43.5, 48.3. HRMS (m/z) Observed: 288.1941 (Δ = −1.5 ppm). Calcd for C₁₆H₃₂S₂: 288.1945.

2-[2-(tert-butoxycarbonylaminomethyl)-2-ethylbutyl]-1,3-dithiane 1-oxide (8)
IR (neat) 3307, 2880, 1683, 1505, 1366, 1250, 1161, 1022 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (t, J = 7.5 Hz, 6H), 1.15–1.40 (m, 5H), 1.41 (s, 9H), 2.18–2.31 (m, 2H), 2.42–2.56 (m, 2H), 2.59–2.66 (m, 1H), 2.72–2.84 (m, 2H), 3.35 (dd, J = 14.5, 9.0 Hz, 1H), 3.41–3.50 (m, 2H), 5.80 (br s, 1H); ¹³C NMR (CDCl₃) δ 7.4, 7.6, 25.5, 26.5, 28.6, 29.6, 31.1, 34.5, 40.5, 44.2, 54.3, 60.4, 78.8, 156.7. HRMS (m/z)
Observed: 349.1742 (Δ = –1.1 ppm).  Calcd for C_{16}H_{31}O_{3}NS_{2}: 349.1746.

**N-benzoyl-3,3-diethyl-2,3-dihydropyrrole (9)**

IR (neat) 2963, 2922, 1610, 1578, 1448, 1406, 1374, 831, 716, 700 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (t, J = 7.5 Hz, 6H), 1.48–1.56 (m, 4H), 3.74 (s, 2H), 4.99 (d, J = 4.0 Hz, 1H), 6.43 (d, J = 4.0 Hz, 1H), 7.40–7.46 (m, 3H), 7.48–7.52 (m, 2H); ¹³C NMR (CDCl₃) δ 8.8, 31.4, 49.8, 55.0, 119.2, 128.0, 128.6, 129.6, 130.5, 135.8, 167.1.  HRMS (m/z) Observed: 229.1466 (Δ = –0.2 ppm).  Calcd for C_{15}H_{19}NO: 229.1466.

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5. A part of this work was communicated: S. Yoshida, H. Yorimitsu, and K. Oshima, *Chem. Lett.*, 2009, **38**, in press.


8. The relative stereochemistry of 3 was determined by comparing the NMR spectra of 3 with those of closely related compounds.  See: P. C. B. Page, R. D. Wilkes, E. S. Namwindwa, and M. J. Witty, *Tetrahedron*, 1996, **52**, 2125.


