AN INTRAMOLECULAR NUCLEOPHILE-CATALYZED ALDOL-LACTONIZATION (NCAL)
REACTION OF S-ARYL-(E)-6-OXOHEX-2-ENETHIOATE WITH N,N-4-DIMETHYLAMINOPYRIDINE N-OXIDE

Hiroki Mandai,* Keita Shimowaki, Kohei Hongo, Koichi Mitsudo, and Seiji Suga*

Division of Applied Chemistry, Graduate School of Natural Science and Technology, Okayama University,
3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530
E-mail: mandai@cc.okayama-u.ac.jp, suga@cc.okayama-u.ac.jp

Supporting Information

Table of Contents

<table>
<thead>
<tr>
<th>Table of Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis of substrates 1c, 1f–j</td>
<td>S1</td>
</tr>
<tr>
<td>$^1$H NMR and $^{13}$C NMR data for substrates 1c, 1f–j and NCAL products 3c, 3f–i</td>
<td>S5</td>
</tr>
<tr>
<td>References</td>
<td>S16</td>
</tr>
</tbody>
</table>
Synthesis of substrates 1c, 1f–j

\[ \text{Ph} \cdot \text{Br} \rightarrow \text{Ph} \cdot \text{S} \cdot \text{Br} \]

\( S \)-Phenyl \( \alpha \)-bromothioacetate.\(^1\) To a solution of benzenethiol (22.5 g, 0.204 mol) in CH\(_2\)Cl\(_2\) (100 mL) was added sequentially 2-bromoacetylbromide (46.4 g, 0.230 mol) and DMAP (2.45 g, 20.1 mmol), then pyridine (17.0 mL, 0.205 mol) was added dropwise to the stirred resulting mixture at 0 °C. After allowing to stir for 1.5 h at room temperature, the reaction mixture was quenched with saturated aqueous NH\(_4\)Cl (200 mL) and extracted with EtOAc (3 × 200 mL). The organic layer was washed with brine (200 mL) and dried over MgSO\(_4\), and concentrated in vacuo to give crude \( S \)-phenyl \( \alpha \)-bromothioacetate (5.04 g) as a yellow oil. This crude product was directly used for the following reaction without further purification.

\[(2\text{-Oxo-2-(phenylthio)ethyl})\text{triphenylphosphonium bromide.}\] To a solution of crude product 8c (5.04 g) in benzene (40 mL) was added a solution of triphenylphosphine (54.0 g, 0.206 mol) in benzene (80 mL). After the reaction mixture was stirred at room temperature for 11 h, the precipitate was collected by filtration and washed with Et\(_2\)O to give phosphonium salt (92.5 g, 0.188 mol) as a colorless solid. This crude product was directly used for the following reaction without further purification.

\[2\text{-Phenylthio(triphenylphosphonylidene)ethan-2-one.}\] To a solution of phosphonium bromide (9.84 g, 20.0 mmol) in CH\(_2\)Cl\(_2\) (50 mL) was added 2 M aqueous NaOH (50 mL). After the reaction mixture was stirred at room temperature for 30 min, organic layer was separated, washed with brine (100 mL), dried over MgSO\(_4\), and concentrated in vacuo to give the ylide (7.87 g, 19.1 mmol) as a pale yellow solid. This crude product was directly used for the following reaction without further purification.

\[(E\text{-6-Phenylthio-6-oxo-4-hexenal (1c).}\] To a solution (suspension) of ylide (4.68 g, 11.4 mmol) in CH\(_2\)Cl\(_2\) (87 mL) was added succinaldehyde (9.77 g, 113.5 mmol). After stirring at room temperature for 8 h, the reaction mixture was elaborately dried under reduced pressure to remove the solvent and excess succinalde-
hyde. The purification of crude product by flash column chromatography on silica gel (eluent: hexane/Et₂O = 1/1, v/v and eluent: toluene/EtOAc = 10/1, v/v) gave unsaturated aldehyde 1c (0.879 g, 3.99 mmol, 35% yield) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.82 (s, 1H), 7.46–7.39 (m, 5H), 6.95 (dt, J = 15.6, 6.6 Hz, 1H), 6.21 (dt, J = 15.6, 1.4 Hz, 1H), 2.71–2.65 (m, 2H), 2.61–2.52 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 200.2, 187.7, 143.9, 134.6, 129.4, 129.2, 128.6, 127.4, 41.6, 24.5; IR (KBr) 3061, 2725, 2359, 1138, 746 cm⁻¹; TLC Rᶠ 0.25 (hexane/Et₂O = 1/1), 0.5 (toluene/EtOAc = 10/1); HRMS (FAB) m/z: [M+H]+ calcd for C₁₂H₁₃O₂S: 221.0630, found: 221.0600

(E)-6-(4-Fluorophenylthio)-6-oxo-4-hexenal (1f). According to similar procedure for synthesis of 1c, the product 1f was obtained as a yellow oil (0.235 g, 0.985 mmol, 7% overall yield from 4-fluorobenzenethiol). ¹H NMR (400 MHz, CDCl₃) δ 9.80 (s, 1H), 7.43–7.35 (m, 2H), 7.15–7.07 (m, 2H), 6.94 (dt, J = 15.2, 6.9 Hz, 1H), 6.20 (dt, J = 15.2, 1.4 Hz, 1H), 2.67 (t, J = 6.9 Hz, 2H), 2.60–2.51 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ 200.1, 187.8, 163.6 (d, J = 249.2 Hz), 144.2, 136.8 (d, J = 8.6 Hz), 128.6, 122.8 (d, J = 8.6 Hz), 116.6 (d, J = 22.0 Hz), 41.8, 24.6; IR (neat) 3069, 2826, 2725, 1225, 793 cm⁻¹; HRMS (FAB) m/z: [M+H]+ calcd for C₁₂H₁₂FO₂S: 239.0536, found: 239.0539

(E)-6-(4-Methoxyphenylthio)-6-oxo-4-hexenal (1g). Because substrate 1g cannot be synthesized efficiently by a similar procedure for the synthesis of 1c, an alternative route was selected (Scheme S1).

Scheme S1. An overview of synthesis of 1g

To a solution of the 4-(tert-Butyldimethylsilyl)oxy-1-butanol² (0.57 g, 2.79 mmol) in CH₂Cl₂ (1.0 mL) was
added 2,2,6,6-tetramethylpiperidin-1-oxyl (5.10 mg, 32.6 μmol) and potassium bromide (33.8 mg, 0.28 mmol). The reaction mixture was stirred and cooled to –10 °C with a salt-ice bath, then 1 M aqueous sodium hypochlorite (3.1 mL, 3.10 mmol) was added dropwise over 20 min with maintaining pH 8. The reaction mixture was kept between 10 and 15 °C and stirred for a further 10 min. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), washed with 3 M HCl aq (30 mL) containing potassium iodide (30.0 mg), 10% aqueous sodium thiosulfate (30 mL), and brine (30 mL). The organic layer was dried over MgSO₄ and concentrated \textit{in vacuo}.

The crude aldehyde was dissolved in CH₂Cl₂ (4.0 mL) and a solution of 5g in CH₂Cl₂ (6.0 mL) was added at room temperature. After stirring for 24 h, the reaction mixture was dried under reduced pressure to remove the solvent. The filtration of the residue through a short pad of silica gel (eluent: hexane/Et₂O = 1/1, v/v) gave crude product 6g (0.730 g) as an colorless oil.

To a solution of crude product 6g in CH₃CN (6.0 mL) was added HF aq (0.14 mL) at room temperature. After allowing to stir for 2 h, the reaction was quenched by NaHCO₃ aq, and the organic layer was extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine (20 mL), dried over MgSO₄, and concentrated \textit{in vacuo} to give crude product 7g (0.536 g) as a colorless oil.

To a solution of crude product 7g in CH₂Cl₂ (26.0 mL) was added Dess-Martin Periodinane (0.662 g, 1.56 mmol) at room temperature. After allowing to stir for 2 h, the reaction mixture was diluted by Et₂O and NaHCO₃/Na₂SO₃ aq. The organic layer was extracted with CH₂Cl₂ (3 × 50 mL), dried over MgSO₄, and concentrated \textit{in vacuo}. The purification of crude product by flash column chromatography on silica gel (eluent: toluene/Et₂O = 50/1, v/v) gave 1g (72.2 mg, 0.24 mmol, 9% overall yield from 4-((tert-Butyldimethylsilyl)oxy-1-butanol) as an colorless solid. \(^1\)H NMR (400 MHz, CDCl₃) δ 9.82 (d, J = 0.9 Hz, 1H), 7.55 (dt, J = 8.9, 2.0 Hz, 2H), 7.30 (dt, J = 8.9, 2.0 Hz, 2H), 6.96 (dt, J = 15.6, 6.7 Hz, 1H), 6.20 (dt, J = 15.6, 1.2 Hz, 1H), 2.69 (t, J = 6.7 Hz, 2H), 2.61–2.54 (m, 2H); \(^1\)C NMR (100 MHz, CDCl₃) δ 200.1, 187.2, 144.4, 136.2, 128.5, 117.9, 114.8, 55.3, 41.6, 24.4; IR (KBr) 2965, 2839, 2743, 1717, 1246, 1051 cm⁻¹; HRMS (ESI) m/z: [M+Na]⁺ calcd for C₁₂H₁₀BrO₂S: 320.9555, found: 320.9555; m.p. = 76.5–77.0 °C.
(E)-6-(2,6-Dimethylphenylthio)-6-oxo-4-hexenal (1i). According to similar procedure for synthesis of 1c, the product 1i was obtained as a pale yellow oil (0.56 g, 2.26 mmol, 15% overall yield from 2,6-dimethylbenzenethiol).  \( ^1 \)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.82 (t, \( J = 1.1 \) Hz, 1H), 7.23 (dd, \( J = 8.0, 7.0 \) Hz, 1H), 7.16 (d, \( J = 7.0 \) Hz, 2H), 6.94 (dt, \( J = 15.6, 6.6 \) Hz, 1H), 6.25 (dt, \( J = 15.6, 1.6 \) Hz, 1H), 2.73–2.65 (m, 2H), 2.62–2.52 (m, 2H), 2.35 (s, 6H); \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 200.3, 187.0, 143.5, 143.0, 130.0, 128.9, 128.4, 126.8, 41.8, 24.5, 21.8; IR (neat) 2723, 2386, 1726, 1632, 773 cm\(^{-1}\); HRMS (FAB) \( m/z \): [M+H]\(^+\) calcd for C\(_{14}\)H\(_{17}\)O\(_2\)S: 249.0943, found: 249.0941.

(E)-7-Phenylthio-7-oxo-5-heptenal (1j)

To a solution (suspension) of ylide (8.35 g, 20.2 mmol) in EtOH (78 mL) was added 50% aqueous glutaraldehyde solution (86 mL, 404 mmol). After stirring at room temperature for 18 h, water (100 mL) was added to the solution and the combined layer was extracted with CH\(_2\)Cl\(_2\) (3 × 80 mL). The organic layer was washed with HCl aq (0.2 M, 3 × 100 mL), brine (80 mL), and dried over MgSO\(_4\). After evaporation, the crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/Et\(_2\)O = 1/1, v/v and eluent: toluene/EtOAc = 10/1, v/v) gave 1j (1.48 g, 6.32 mmol, 11% overall yield from benzenethiol) as a pale yellow oil. \( ^1 \)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 9.79 (t, \( J = 1.2 \) Hz, 1H), 7.45–7.41 (m, 5H), 6.94 (dt, \( J = 15.6, 6.9 \) Hz, 1H), 6.21 (dt, \( J = 15.6, 1.4 \) Hz, 1H), 2.51 (dt, \( J = 7.2, 1.2 \) Hz, 2H), 2.29 (dq, \( J = 7.2, 1.4 \) Hz, 2H), 1.84 (quin, \( J = 7.2 \) Hz, 2H); \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 201.6, 187.9, 145.1, 134.7, 129.5, 129.2, 128.6, 127.5, 43.0, 31.4, 20.3; IR (neat) 2938, 2723, 1722, 1686, 1477, 1441, 976 cm\(^{-1}\), HRMS (FAB) \( m/z \): [M+H]\(^+\) calcld for C\(_{13}\)H\(_{15}\)O\(_2\)S: 235.0781, found: 235.0790.
$^1$H NMR and $^{13}$C NMR data for substrates 1c, 1f–j and NCAL products 3c, 3f–i
References
