Asymmetric synthesis of α-chloro-α-haloketones by decarboxylative chlorination of α-halo-β-keto carboxylic acids

Kazumasa Kitahara*, Haruna Mizutani*, Seiji Iwasa*, Kazutaka Shibatomi*

* Department of Applied Chemistry and Life Science, Toyohashi University of Technology, 1-1 Hibarigaoka, Tempaku-cho, Toyohashi 441-8580, Japan

E-mail: shiba@chem.tut.ac.jp

Supporting Information

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1. Synthesis of $\alpha$-alkyl-$\beta$-keto esters 7

$\beta$-keto esters 7 were prepared by following procedure below. 7b\(^1\) and 7f\(^2\) was prepared by following literature method and \(^1\)H NMR spectra were in good agreement with those reported in the literatures.

**Synthesis of 7a\(^3\), 7c\(^4\), 7d\(^5\)**

\[
\begin{align*}
\text{RN} & \quad \text{NaH (2.0 equiv.)} \\
\text{N-Boc pyrrole (2.0 equiv.)} & \quad \text{THF, reflux} \\
\text{R} & \quad \text{CO}_2\text{Bu} \\
\end{align*}
\]

To a stirred suspension of NaH (60% in oil, washed with hexane, 2.0 equiv.) in THF (20 mL) was added a solution of ketone (1 equiv.) in THF at room temperature and the mixture was stirred for 1 h under reflux condition. Then, N-Boc pyrrole (2.0 equiv.) was added to the mixture at room temperature and the reaction mixture was monitored by Thin-Layer chromatography and after full consumption of starting material, the reaction mixture was quenched by adding 1.2N HCl at 0 °C, and then extracted with diethylether, dried over anhydrous Na$_2$SO$_4$, concentrated, and then purified by flash column chromatography on silica gel to give alkylated $\alpha$-alkyl-$\beta$-ketoester 7.

**Synthesis of 7e, 7g**

\[
\begin{align*}
\text{Ph—CHO (1 equiv.)} & \quad \text{MnO}_2 (10 \text{ equiv.)} \\
\text{n-BuLi (1.2 equiv.)} & \quad \text{CH}_2\text{Cl}_2, \text{ reflux, 17 h} \\
\text{Pb} & \quad \text{CO}_2\text{Bu} \\
\end{align*}
\]

To a stirred solution of diisopropyl amine (1.2 equiv., 24 mmol) in THF (25 mL) was added a solution of $n$-butyl lithium in 1.6 M hexane (1.2 equiv., 24 mmol) at 0 °C. The solution was stirred at 0 °C for 15 min. Then, $n$-butyl acetate (1 equiv., 20 mmol) was added dropwise at $-78$ °C. After stirring for 30 min, benzaldehyde (1 equiv., 20 mmol) was added, and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was quenched by adding saturated NH$_4$Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous Na$_2$SO$_4$, concentrated. The resulting crude mixture was directly subjected to oxidation without further purification. The crude mixture was dissolved with dichloromethane (24 mL) and manganese (IV) oxide (10 equiv., 200 mmol) was added. The reaction mixture was stirred under reflux condition for 17 h, then cooled to 0 °C, filtered by Celite. The filtrate was concentrated, and then purified by flash column chromatography on silica gel to give $\beta$-ketoester 8.

7e\(^6\): $\beta$-ketoester 8 (1 equiv., 6.81 mmol) was dissolved with acetone (16 mL). The solution was added K$_2$CO$_3$ (1.1 equiv., 7.49 mmol), MeI (1.45 equiv., 9.87 mmol) and stirred at 40 °C for 23 h. The reaction mixture was filtered by Celite and diluted by dichloromethane, washed by 1.2N HCl, dried over Na$_2$SO$_4$, concentrated. The crude mixture was purified by flash column chromatography on silica
gel (hexane/diethyl ether 19:1 to 87:13) to give 7e (1110 mg, 70% yield).

7g: To a stirred suspension of NaH (60% in oil, washed with hexane, 1.2 equiv., 8.17 mmol) in THF (29 mL) was added a solution of β-ketoester 8 (1 equiv., 6.81 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then, benzyl bromide (1.5 equiv., 10.2 mmol) was added, and the reaction mixture was stirred at room temperature for 19 h. The reaction mixture was quenched by adding saturated NH₄Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous Na₂SO₄, concentrated, and then purified by flash column chromatography on silica gel (hexane/diethyl ether 10:1) to give 7g (967 mg, 46% yield).

Synthesis of 7f

To a stirred solution of diisopropyl amine (1.05 equiv., 5.23 mmol) in THF (20 mL) was added a solution of n-butyl lithium in 1.6 M hexane (1.05 equiv., 5.23 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h. Then, a solution of t-butyl 2-phenylacetate (1 equiv., 4.98 mmol) in THF (5 mL) was added dropwise. After stirring for 30 min, benzoyl chloride (1.2 equiv., 5.98 mmol) was added, and the reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched by adding saturated NH₄Cl aqueous solution at 0 °C, and then extracted with dichloromethane, dried over anhydrous Na₂SO₄, concentrated, and then purified by column chromatography on silica gel (hexane/EtOAc = 30:1 to 4:1) and the resulting solid was washed by cold hexane to give 7f.

Yield: 815 mg (55% yield); white solid; Rₚ = 0.33 (hexane/EtOAc 4:1), mp: 81.2 °C.

IR (NaCl): 3063, 3030, 2978, 1741, 1682, 1449, 1393, 1369, 1264, 1144, 747, 698, 402 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 7.97–7.96 (m, 2 H, H₆), 7.51 (t, J = 7.3 Hz, 1 H, H₇), 7.43–7.39 (m, 4 H, H₇), 7.35 (t, J = 7.3 Hz, 2 H, H₈), 7.29 (t, J = 7.3 Hz, 1 H, H₈), 5.51 (s, 1 H, CH), 1.42 (s, 9 H, C₃H₉).

¹³C NMR (CDCl₃, 126 MHz): δ = 193.6 (CO), 167.8 (COO), 135.9 (C₆), 133.3 (C₆), 133.2 (C₆), 129.5 (C₆), 128.7 (C₆), 128.6 (C₆), 127.9 (C₆), 82.2 (CH), 61.4 (C₃H₉), 27.8 (C₃H₉).


Synthesis of 7h

To a stirred solution of diisopropyl amine (1.05 equiv., 5.94 mmol) in THF (14 mL) was added a
solution of n-butyl lithium in 1.6 M hexane (1.05 equiv., 5.80 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h. Then, a solution of t-butyl 2-phenylacetate (1 equiv., 5.66 mmol) in THF (5 mL) was added dropwise. After stirring for 1 h, acetaldehyde (1.05 equiv., 5.94 mmol) was added, and the reaction mixture was stirred at −78 °C for 14 h. The reaction mixture was quenched by adding 1.2N HCl at 0 °C, extracted with dichloromethane, dried over anhydrous Na₂SO₄, concentrated, and then purified by column chromatography on silica gel (hexane/EtOAc = 7 : 1 to 4 : 1) to give 9 as diastereomixture.

**t-butyl 3-hydroxy-2-phenylbutanoate 9**

Yield: 1075 mg (80%); colorless oil; R₇ = 0.3 (major), 0.23 (minor), (hexane/EtOAc 7:1).

IR (NaCl): 3438, 3030, 2976, 2934, 1705, 1600, 1492, 1455, 1393, 1369, 1248, 1142, 948, 754, 700, 595, 515 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): (major) δ = 7.36–7.32 (m, 5 H, H₉), 4.32–4.27 (m, 1 H, CHO), 3.40 (d, J = 7.3 Hz, 1 H, PhCH), 1.40 (s, 9 H, C₆H₃), 1.19 (d, J = 6.1 Hz, 3 H, CH₃). (minor) δ = 7.32–7.23 (m, 5 H, H₉), 4.27–4.22 (m, 1 H, CHO), 3.39 (d, J = 9.2 Hz, 1 H, PhCH), 1.39 (s, 9 H, C₆H₃), 1.02 (d, J = 6.5 Hz, 3 H, CH₃).

¹³C NMR (CDCl₃, 126 MHz): (major) δ = 172.3 (COO), 135.6 (C₉), 128.9 (C₈), 128.4 (C₆), 127.4 (C₅), 81.2 (PhC), 68.5 (CC₆H₃), 59.7 (CHO), 27.8 (C₅H₃), 20.4 (CH₃). (minor) δ = 172.9 (COO), 136.8 (C₉), 128.5 (C₈), 128.1 (C₆), 127.2 (C₅), 81.3 (PhC), 69.6 (CC₆H₃), 60.8 (CHO), 27.8 (C₅H₃), 20.3 (CH₃).


Resulting 9 was subjected to oxidation reaction with pyridinium chlorochromate. MS 4A (9.05 g) was added to a flask and the flask was flame dried in vacuo. The flask was added dichloromethane (73 mL) and a solution of 9 (1 equiv., 4.13 mmol) in dichloromethane (10 mL). The suspension was added pyridinium chlorochromate (3 equiv, 12.4 mmol) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was diluted diethylether (80 mL) and filtered by Celite, and then purified by column chromatography on silica gel (hexane : EtOAc = 6 : 1) to give 7h.

**t-butyl 3-oxo-2-phenylbutanoate 7h**

Yield: 364 mg (38% yield); white solid; R₇ = 0.70–0.36 (hexane/EtOAc 4:1), mp: 48.5 °C.

IR (NaCl): 3003, 2979, 2933, 1713, 1496, 1455, 1369, 1355, 1249, 1137, 856, 751, 699 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ = 7.36–7.28 (m, 5 H, H₉), 4.62 (s, 1 H, CH), 2.14 (s, 3 H, CH₃), 1.46 (s, 9 H, C₆H₃).

¹³C NMR (CDCl₃, 126 MHz): δ = 201.6 (CO), 167.4 (COO), 132.8 (C₉), 129.1 (C₈), 128.5 (C₆), 127.8 (C₅), 81.8 (CH), 66.3 (CC₆H₃), 28.5 (CH₃), 27.6 (C₅H₃).

2. References


$^1$H NMR spectrum (1b)

$^{13}$C NMR spectrum (1b)

$^{19}$F NMR spectrum (1b)
$^1$H NMR spectrum (1f)

$^{13}$C NMR spectrum (1f)

$^{19}$F NMR spectrum (1f)
$^1$H NMR spectrum (1h)

$^{13}$C NMR spectrum (1h)

$^{19}$F NMR spectrum (1h)
$^1$H NMR spectrum (2b)

$^{13}$C NMR spectrum (2b)

$^{19}$F NMR spectrum (2b)
$^1$H NMR spectrum (2c)

$^{13}$C NMR spectrum (2c)

$^{19}$F NMR spectrum (2c)
$^1$H NMR spectrum (2d)

$^{13}$C NMR spectrum (2d)

$^{19}$F NMR spectrum (2d)
$^1$H NMR spectrum (2e)

$^{13}$C NMR spectrum (2e)

$^{19}$F NMR spectrum (2e)
$^1$H NMR spectrum (2f)

$^{13}$C NMR spectrum (2f)

$^{19}$F NMR spectrum (2f)
$^1$H NMR spectrum (2h)

$^{13}$C NMR spectrum (2h)

$^{19}$F NMR spectrum (2h)
$^1$H NMR spectrum (3a)

$^{13}$C NMR spectrum (3a)

$^{19}$F NMR spectrum (3a)
HPLC optically active (3a)

HPLC racemic (3a)

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$^{13}$C NMR spectrum (3b)
$^{19}$F NMR spectrum (3b)

HPLC optically active (3b)  HPLC racemic (3b)

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$^1$H NMR spectrum (3c)
$^{13}$C NMR spectrum (3c)

$^{19}$F NMR spectrum (3c)

HPLC optically active (3c)  

HPLC racemic (3c)
$^1$H NMR spectrum (3d)

$^{13}$C NMR spectrum (3d)

$^{19}$F NMR spectrum (3d)
HPLC optically active (3d)  

HPLC racemic (3d)

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$^1$H NMR spectrum (3e)

$^{13}$C NMR spectrum (3e)
$^{19}$F NMR spectrum (3e)

HPLC optically active (3e)  HPLC racemic (3e)

$^1$H NMR spectrum (3f)
$^{13}$C NMR spectrum (3f)

$^{19}$F NMR spectrum (3f)

HPLC optically active (3f)    HPLC racemic (3f)

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$^1$H NMR spectrum (3g)

$^{13}$C NMR spectrum (3g)

$^{19}$F NMR spectrum (3g)
HPLC optically active (3g)  

HPLC racemic (3g)  

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$^1$H NMR spectrum (3h)  

$^{13}$C NMR spectrum (3h)
$^{19}$F NMR spectrum (3h)

HPLC optically active (3h)  
HPLC racemic (3h)

$^1$H NMR spectrum (3i)
\( ^{13} \text{C} \) NMR spectrum (3i)

\( ^{19} \text{F} \) NMR spectrum (3i)

HPLC optically active (3i)

HPLC racemic (3i)
$^1$H NMR spectrum (4)

$^{13}$C NMR spectrum (4)

$^1$H NMR spectrum (5)
$^{13}$C NMR spectrum (5)

$^1$H NMR spectrum (6)

$^{13}$C NMR spectrum (6)
HPLC optically active (6)  
HPLC racemic (6)

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2 & 10.9 & 50.167
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$^1$H NMR spectrum (7f)

$^{13}$C NMR spectrum (7f)
$^1$H NMR spectrum (7h)

$^{13}$C NMR spectrum (7h)

$^1$H NMR spectrum (9)
$^{13}$C NMR spectrum (9)