Supporting Information

The First Chemoselective Tandem Acylation of the Blaise Reaction Intermediate: A novel method for the synthesis of α-Acyl-β-Enamino Esters, Key Intermediates for Pyrazoles

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General. All reactions and manipulations were performed in a nitrogen atmosphere using standard Schelenk techniques. The reaction solvents were distilled prior to use (THF: distilled from sodium benzenophene ketyl). All purchased reagents were used without further purification. Anhydrous solvents were transferred by oven-dried syringe. Flasks were flames dried under a stream of nitrogen. The NMR spectra were recorded at 250 MHz (1H)/62.5 MHz (13C) or 400 MHz (1H)/100 MHz (13C). The chemical shifts were relative to TMS (as an internal reference) for 1H NMR.

Experimental

A typical procedure for the synthesis of 2. To a stirred suspension of commercial zinc dust (10 μm, 0.65 g, 10.0 mmol) was added 5.0 mol% of methansulfonic acid in THF (2.5 mL), and the mixture was refluxed for 10 min. While maintaining reflux, benzonitrile (0.52 mL, 5.0 mmol) was added all at once, followed by ethyl bromoacetate (0.83 mL, 7.5 mmol) over 1 h with syringe pump. After 1 h at reflux, the reaction temperature was cooled to 0°C. To the reaction mixture was added n-BuLi (2.0 M in cyclohexane, 2.5 mL, 5.0 mmol) and acetic anhydride (0.62 mL, 6.5 mmol) in sequence. After stirring 3 h at room temperature, the reaction was quenched with saturated aqueous NH4Cl, and the product was extracted with ethyl acetate (10 mL x 3). The combined organic layer was dried with anhydrous MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by silica chromatography to afford 2a (0.96 g, 82%).

2-(Amino-phenyl-methylene)-3-oxo-butyric acid ethylester (2a). Yield: 82%; 1H NMR (250 MHz, CDCl3) δ 11.00 (bs, 1H), 7.45 ~ 7.36 (m, 5H), 5.49 (bs, 1H), 3.76 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 0.71 (t, J = 7.2 Hz, 3H) ppm; 13C NMR (62.5 MHz, CDCl3) δ 13.3, 29.4, 60.0, 104.1, 126.6, 128.6, 130.0, 138.4, 166.9, 169.8, 197.1 ppm. HRMS (ESI) Cal. for (M+H):C13H16NO3:234.1130. Found:234.1121.

2-(Amino-o-tolyl-methylene)-3-oxo-butyric acid ethyl ester (2b). Yield: 72%; 1H NMR (400 MHz,CDCl3) δ 11.24 (bs, 1H), 7.29~7.11 (m, J= 6.8Hz, 4H), 5.52 (bs, 1H), 3.72 (m, 2H), 2.37 (s, 3H), 2.32 (s, 3H), 2.08 (s, 1H). 0.69 (t, J=6.8Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 13.30, 19.20, 30.0, 59.8, 103.3, 125.6, 128.9, 129.8, 130.1, 135.9, 137.7, 165.9, 168.3, 198.3 ppm. HRMS (ESI) Cal. for (M+H):C14H18NO3:248.1287. Found:248.1277.

2-(Amino-(4-fluoro-phenyl)-methylene]-3-oxo-butyric acid ethyl ester (2c). Yield: 53%; 1H NMR (400 MHz, CDCl3) δ 10.96 (bs, 1H), 7.37(dd, J = 8.0Hz, 2H), 7.11(dd, J=8.0Hz, 2H), 5.51 (bs, 1H), 3.80 (q, J = 8.0Hz, 2H), 2.36 (s, 3H), 0.81 (t, J=8.0Hz, 3H) ppm; 13C NMR (100 MHz, CDCl3) δ 14.1, 29.5, 53.5, 60.1, 104.3, 115.6, 116.2, 128.5, 116.0, 134.4, 165.7, 169.7, 197.0 ppm. HRMS (ESI) Cal. for (M+H):C13H13FNO3:252.1036. Found:252.1027.

2-(Amino-pyridin-3-yl-methylene]-3-oxo-butyric acid ethyl ester (2d).

2-Acetyl-3-aminobut-2-enoic acid ethyl ester (2g).

Yield: 83%; 1^H NMR (400 MHz, CDCl_3) δ 10.99 (bs, 1H), 8.74 (dd, J = 4.0Hz, 1H), 8.61 (d, 1H), 7.76 (m, J= 4.0Hz, 1H), 7.44 (m, J= 4.0Hz, 1H), 6.00 (bs, 1H), 3.78 (q, J= 7.2Hz, 2H), 2.38 (s, 3H), 0.79 (t, J= 7.2Hz, 3H) ppm; 13^C NMR (100 MHz, CDCl_3) δ 13.6, 30.0, 60.2, 104.5, 123.8, 134.9, 135.5, 147.1, 150.4, 163.0, 168.7, 197.8 ppm.

2-(Amino-phenyl-methylene)-4-methyl-3-oxo-pentanoic acid ethyl ester (2i).
Yield: 45%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 11.22 (bs, 1H), 7.45 $\sim$ 7.37 (m, 5H), 5.47 (bs, 1H), 3.75 (q, $J$ = 7.2 Hz, 2H), 3.35 $\sim$ 3.24 (m, 1H), 1.16 (d, $J$ = 6.8 Hz, 6H), 0.72 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 13.3, 19.6, 36.6, 60.2, 103.7, 126.6, 128.7, 130.0, 138.4, 166.4, 170.0, 203.5 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{15}$H$_{20}$NO$_3$:262.1443. Found: 262.1438.

2-(Amino-phenyl-methylene)-5-methyl-3-oxo-hexanoic acid ethyl ester (2m).
Yield: 94%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 11.39 (bs, 1H), 7.47 $\sim$ 7.35 (m, 5H), 5.58 (bs, 1H), 3.73 (q, $J$ = 7.2 Hz, 2H), 2.58 (d, $J$ = 7.0 Hz, 2H), 2.22 $\sim$ 2.11 (m, 1H), 0.95 (d, $J$ = 6.6 Hz, 6H), 0.70 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 13.3, 22.8, 25.5, 49.4, 60.1, 104.6, 126.6, 128.6, 130.0, 138.4, 166.4, 169.9, 199.1. HRMS (ESI) Cal. for (M$^+$+H):C$_{16}$H$_{22}$NO$_3$:276.1600. Found: 276.1586.

2-(Amino-phenyl-methylene)-4,4,4-trifluoro-3-oxo-butyric acid ethyl ester (2n).
Yield: 81%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 10.68 (bs, 1H), 7.51 $\sim$ 7.35 (m, 5H), 6.15 (bs, 1H), 3.88 (q, $J$ = 7.2 Hz, 2H), 0.93 (t, $J$ = 7.2 Hz, 3H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 13.4, 61.2, 100.7, 126.1, 126.6, 128.9, 129.2, 131.0, 135.9, 166.9, 170.7 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{16}$H$_{22}$F$_3$NO$_3$:288.0848. Found: 288.0854.

A typical experiment for the synthesis of pyrazoles 3 and 4: To a solution of 2a (0.11g, 0.47 mmol) in absolute ethanol (1.0 mL) was added hydrazine monohydrate (0.13 mL, 2.5 mmol). After 2 h at reflux, solvent was evaporated, and the resulting residue was dissolved in ethyl acetate and organic layer was washed with 1.0 N aqueous HCl solution and brine, dried with MgSO$_4$, and concentrated under reduced pressure. Silica chromatographic purification afforded the pyrazole 3a (92 mg, 85%)

5-Methyl-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester (3a).
Yield: 85%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 12.2 (bs, 1H), 7.56 $\sim$ 7.50 (m, 2H), 7.37 $\sim$ 7.31 (m, 3H), 4.17 (q, $J$ = 7.1 Hz, 2H), 2.12 (s, 3H), 1.18 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 11.9, 14.1, 59.8, 108.8, 127.9, 128.6, 129.5, 132.1, 147.5, 152.3, 164.1 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{13}$H$_{14}$N$_2$O$_2$:231.1134. Found: 231.1143.

3-Benzyl-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (3b).
Yield: 76%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 11.15 (bs, 1H), 7.26 $\sim$ 7.16 (m, 5H), 4.24 (q, $J$ = 7.1 Hz, 2H), 4.21 (s, 2H), 2.40 (s, 3H), 1.28 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 12.98, 14.32, 33.17, 59.75, 108.79, 126.4, 128.5, 138.7, 148.4, 150.9, 164.3 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{14}$H$_{17}$N$_2$O$_2$:245.1290. Found: 245.1285.

3,5-Diphenyl-1H-pyrazole-4-carboxylic acid ethyl ester (3c).
Yield: 91%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 9.95 (bs, 1H), 7.60 $\sim$ 7.31 (m, 10H), 4.10 (q, $J$ = 7.1 Hz, 2H), 1.02 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 13.7, 60.3, 109.0, 128.1, 128.4, 128.9, 129.1, 130.0, 130.2, 130.7, 133.2, 150.5, 164.0, 170.5 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{18}$H$_{17}$N$_2$O$_2$:293.1290. Found: 293.1295.

5-(4-Methoxy-phenyl)-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester (3d).
Yield: 95%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 12.74(bs, 1H), 7.39 $\sim$ 7.23 (m, 7H), 6.77 (d, $J$ = 7.1 Hz, 2H), 4.09(q, $J$ = 7.1 Hz, 2H), 3.79 (s, 3H), 1.03 (t, $J$ = 7.1 Hz, 3H) ppm; $^{13}$C NMR (CDCl$_3$, ppm) $\delta$ 13.8, 55.2, 60.2, 108.5, 113.4, 122.7, 127.9, 128.6, 129.1, 130.4, 131.2, 160.0, 164.1 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{18}$H$_{19}$N$_2$O$_2$:323.1396. Found: 323.1390.

5-Isopropyl-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester (3e).
Yield: 96%; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 12.14 (bs, 1H), 7.43 $\sim$ 7.26 (m, 5H), 4.17 (q, $J$ = 7.1 Hz, 2H), 3.60 $\sim$ 3.54 (m, 1H), 1.26 $\sim$ 1.12 (m, 9H) ppm; $^{13}$C NMR (62.5 MHz, CDCl$_3$) $\delta$ 13.9, 21.5, 26.4, 59.8, 107.5, 127.7, 128.4, 129.4, 132.0, 151.6, 157.0, 164.1 ppm. HRMS (ESI) Cal. for (M$^+$+H):C$_{16}$H$_{19}$N$_2$O$_2$:259.1447. Found: 259.1434.

5-Isobutyl-3-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester (3f)
Synthesis of pyrazole 5: To a solution of 4a (70 mg, 0.23 mmol) in ethanol (2.0 mL) was added 1.0 M aqueous NaOH solution (1 mL), and the mixture was heated at reflux for 2 h. After removal of ethanol in vacuo, the residue was diluted in water (3.0 mL) and acidified with 1.0 N HCl (1.5 mL). The mixture was extracted with ethyl acetate (3 mL x 3), and the combined organic layer was dried with MgSO₄ and concentrated in vacuo. The resulting crude acid was heated at 150 °C for 2 h and cooled to room temperature. The residue was purified by silica gel chromatography (EtOAc/n-Hexane = 9/1) to afford product (50 mg, 0.21 mmol, 96 %). ¹H NMR (250 MHz, CDCl₃) δ 7.69 ~ 7.65 (m, 2H), 7.49 ~ 7.36 (m, 8H), 4.23 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.0 Hz, 3H), 13C NMR (CDCl₃) δ 13.9, 22.2, 28.9, 33.8, 59.9, 110.2, 126.7, 127.6, 128.1, 128.8, 129.2, 129.4, 133.1, 139.1, 148.5, 153.5, 164.2 ppm. HRMS (ESI) Cal. for (M⁺+H):C₂₂H₂₅N₂O₂:349.1916. Found:349.1909.
$^1$H NMR and $^{13}$NMR spectra of 2a
$^1$H NMR and $^{13}$NMR spectra of 2b
$^1$H NMR and $^{13}$NMR spectra of 2c
$^1$H NMR and $^{13}$NMR spectra of 2d
$^1$H NMR and $^{13}$NMR spectra of $2e$
$^1$H NMR and $^{13}$NMR spectra of 2f
$^1$H NMR and $^{13}$C NMR spectra of 2g
$^{1}H$ NMR and $^{13}N$MR spectra of $2h$
$^1$H NMR and $^{13}$NMR spectra of 2i
$^1$H NMR and $^{13}$NMR spectra of 2j
$^{1}H$ NMR and $^{13}N$MR spectra of 2k
$^1$H NMR and $^{13}$NMR spectra of 21
$^1$H NMR and $^{13}$NMR spectra of 2m

[Image of NMR spectra]
$^1$H NMR and $^{13}$NMR spectra of 2n
$^1$H NMR and $^{13}$NMR spectra of 3a
$^1$H NMR and $^{13}$NMR spectra of 3b
$^1$H NMR and $^{13}$NMR spectra of 3c
$^1$H NMR and $^{13}$NMR spectra of 3d
\(^1\)H NMR and \(^{13}\)NMR spectra of 3e
$^1$H NMR and $^{13}$NMR spectra of 3f
$^1\text{H}$ NMR and $^{13}\text{NMR}$ spectra of $3g$
$^1$H NMR and $^{13}$NMR spectra of 4a
$^1$H NMR and $^{13}$NMR spectra of 4b
$^1$H NMR and $^{13}$NMR spectra of 4c
$^1$H NMR and $^{13}$NMR spectra of 4d
$^1$H NMR and $^{13}$NMR spectra of 4e
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$^1$H NMR and $^{13}$C NMR spectra of 5

Current Data Parameters

**1H NMR**
- **Sample**: Compound 5
- **Solvent**: DMSO-$_d_6$

**13C NMR**
- **Sample**: Compound 5
- **Solvent**: DMSO-$_d_6$

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**1H NMR Parameters**
- **Frequency**: 500 MHz
- **Sweep Width**: 2000 Hz
- **Sweep Time**: 32.00 sec
- **Power**: 100 W

**13C NMR Parameters**
- **Frequency**: 125 MHz
- **Sweep Width**: 20000 Hz
- **Sweep Time**: 1000 sec
- **Power**: 10 W

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**1H NMR Plot Parameters**
- **Field**: 21.06 ppm
- **Pip**: 12.00 ppm
- **Phase**: 0.00 ppm
- **Temperature**: 1.00 ppm

**13C NMR Plot Parameters**
- **Field**: 215.3 ppm
- **Pip**: 210.0 ppm
- **Phase**: 0.00 ppm
- **Temperature**: 1.00 ppm

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