Synthesis of Benzofurans via CuI-Catalyzed Ring-Closure

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Supporting Information

Table of Content

Page S1-7 Experimental procedures for compounds **6**, **6a-d**, **11**, **15**, **17**, **19**, **21**

Page S8-28 ¹H and ¹³C NMR spectra for compounds **6**, **6a-d**, **11**, **15**, **17**, **19**, **21**

Page S28-45 ¹H and ¹³C NMR spectra for benzo[*b*]furans

All reactions were carried out under nitrogen. Flash chromatography was carried out with EM science Silica gel 60 (neutral, 230-400 mesh). ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance 400 NMR Spectrometer with chemical shifts reported in ppm relative to the residual CHCl₃ for ¹H NMR and CDCl₃ for ¹³C NMR.

General Procedure for Friedel-Crafts Acylation of 2-Halophenyl Acetyl Chloride:

Preparation of Bromoketone **6**

To a solution of 2-bromophenyl acetyl chloride (2.34 g, 10 mmol) and anisole (2.16 g, 20 mmol) in 30 ml of CH₂Cl₂ at 0 °C was added AlCl₃ (1.60 g, 12 mmol) portionwise, keeping the reaction temperature below 10 °C. The mixture was warmed to room temperature and stirred at this temperature for 2 h. The mixture was quenched into 40 mL of 3 N HCl and the CH₂Cl₂ layer was separated. The aqueous layer was extracted with 30 ml of CH₂Cl₂. The CH₂Cl₂ extracts were combined, dried (MgSO₄) and concentrated in vacuum to give crude product as a solid. The solid was recrystallized from 1:1 MTBE/heptane to afford bromoketone **6** (2.50 g, 81% yield) as tan solid: mp: 91-92 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.74 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.02-7.28 (m, 7H), 4.42 (t, *J* = 7.0 Hz, 1H), 3.42 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.00 (dd, *J* = 14.1, 7.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 198.8, 136.9, 135.4, 133.5, 132.2, 132.0, 130.6, 130.1, 129.4, 128.4, 128.2, 128.0, 125.6, 59.2, 34.7. Anal. Calcd. for C₁₅H₁₃BrO₂: C, 59.04; H, 4.29. Found: C, 58.93; H, 4.06.

6a: yellow oil; ¹H NMR (400 MHz, CDCl₃): δ 8.02 (m, 2H), 7.60 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.27 (m, 4H), 7.15 (m, 1H), 4.44 (s, 2H), 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 196.0, 144.2, 135.2, 134.2, 132.8, 130.3, 129.4, 128.7, 128.5, 127.5, 125.1, 45.7, 21.7. exact mass *m/z* calcd for C₁₅H₁₃BrO, [M+H] 289.02225, found 289.02316

6b: pale tan powder solid; mp 85-87°C; ^1H NMR (400 MHz, CDCl_3): δ 7.97 (m, 2H), 7.60 (dd, J = 8.0, 1.2 Hz, 1H), 7.27 (m, 4H), 7.15 (m, 1H), 4.42 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.5, 146.3, 135.2, 132.9, 132.8, 131.7, 128.9, 128.8, 127.6, 125.1, 45.6, 14.8. exact mass m/z calcd for $\text{C}_{15}\text{H}_{13}\text{BrOS}$, $[\text{M}+\text{Na}]$ 342.97627, found 342.97664.

6c: pale yellow solid; mp 91-93°C; ^1H NMR (400 MHz, CDCl_3): δ 8.07 (m, 2H), 7.89 (m, 1H), 7.28 (m, 2H), 6.95 (m, 3H), 4.42 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.0, 163.8, 139.5, 139.0, 130.9, 130.8, 129.9, 128.7, 128.5, 114.0, 101.6, 55.6, 50.2. Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{IO}_2$: C, 51.16; H, 3.72. Found: C, 51.14; H, 3.41.

6d: pale yellow solid; mp 103-104°C; ^1H NMR (400 MHz, CDCl_3): δ 7.90 (m, 1H), 7.46 (m, 1H), 7.25 (m, 1H), 7.48 (m, 1H), 6.95 (m, 1H), 6.85 (m, 2H), 4.25 (s, 2H), 2.32 (s, 3H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 205.7, 139.6, 138.9, 138.6, 137.3, 132.9, 130.9, 128.9, 128.6, 128.4, 101.6, 55.9, 21.1, 19.5. Anal. Calcd. for $\text{C}_{17}\text{H}_{17}\text{IO}$: C, 56.06; H, 4.70. Found: C, 56.14; H, 4.48.

Preparation of Bromoketone 11

To a solution of 3-bromo-4-methylpyridine (0.86 g, 5 mmol) in 5 mL of THF at -20 °C was 1.0 M $\text{NaN}(\text{TMS})_2$ (6 mL in THF, 6 mmol), keeping the temperature below -5 °C. The mixture was aged at -20 °C for 30 min and ethyl 2-bromobenzoate (1.72 g, 7.5 mmol) in 5 mL of THF was added over 5 min. The mixture was stirred at -20 °C for 30 min, warmed to ambient temperature and stirred at this temperature for 1 h. The mixture was quenched with 10 mL of 1 M citric acid. The organic layer was separated and the aqueous layer was extracted with 30 mL of isopropyl acetate. Organic layers were combined, dried (MgSO_4), concentrated in vacuum and the residue was chromatographed over silica gel, eluted with EtOAc/Hexanes (1/1) to afford 0.60 g (67%) of the ketone as yellow solid: mp 97-98 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.76 (s, 1H), 8.50 (d, $J = 4.9$ Hz, 1H), 8.17 (m, 1H), 7.97 (m, 1H), 7.76 (m, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 7.24 (d, $J = 4.9$ Hz, 1H), 4.43 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 193.2, 151.9, 148.2, 143.4, 137.9, 136.6, 131.3, 130.5, 126.8, 126.6, 123.7, 123.2, 44.9. exact mass m/z calcd for $\text{C}_{13}\text{H}_{19}\text{Br}_2\text{NO}$, $[\text{M}+\text{H}]$ 353.91386, found 353.91237.

Preparation of Ketoester 15

To LiN(TMS)₂ (1.0 M in THF, 10 mL, 10 mmol) at -78 °C was added a solution of ethyl 2-bromophenylacetate (1.97 g, 10 mmol) and benzoyl chloride (1.05 g, 7.5 mmol) in 3 mL THF, keeping the reaction mixture below -65 °C. The mixture was warmed to 0 °C and quenched with 10 mL of sat. NaHCO₃ and extracted with 2x 20 mL of MTBE. The organic solution was separated, concentrated in vacuum and chromatographed over silica gel, eluted with EtOAc/Hexanes (1/6) to afford 1.39 g (80% yield) of a mixture of ketoester **15** and its enol as yellow oil: ¹H NMR (400 MHz, CDCl₃): δ 13.56 (s, 0.27H), 7.01-8.13 (m, 9H), 6.15 (s, 0.77H), 4.17-4.35 (m, 2H), 1.25 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 193.2, 172.5, 171.2, 168.2, 136.4, 135.4, 134.5, 133.7, 133.6, 133.1, 133.0, 132.4, 131.0, 130.5, 130.2, 129.8, 129.7, 128.9, 128.8, 128.5, 127.9, 127.7, 127.2, 124.8, 104.4, 61.9, 61.1, 59.8, 14.1, 14.0; exact mass *m/z* calcd for C₁₇H₁₅BrO₃, [M+H] 347.02773, found 347.02764.

Preparation of Ketonitrile **17**

A mixture of 2-bromophenyl acetonitrile (2.0 g, 10 mmol), ethyl benzoate (1.2 g, 12 mmol) and sodium hydride (65%, 1.2 g, 12 mmol) in 30 mL of THF was heated under reflux for 12h, cooled to ambient temperature followed by addition of 50 mL of MTBE and 50 mL of water. The organic layer was separated, concentrated in vacuum and chromatographed over silica gel, eluted with EtOAc/Hexanes (1/4) to afford ketonitrile **17** in 78% yield yellow oil: ¹H NMR (400 MHz, CDCl₃): δ 8.02 (m, 2H), 7.65 (m, 2H), 7.53 (m, 3H), 7.42 (m, 1H), 7.25

(m, 1H), 6.14 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 188.2, 134.7, 133.7, 133.5, 130.9, 130.7, 130.4, 129.2, 129.0, 128.6, 123.7, 115.5, 48.8; exact mass m/z calcd for $\text{C}_{15}\text{H}_{10}\text{BrNO}$, $[\text{M}+\text{H}]$ 300.00185, found 300.00185.

Preparation of Bromoketone 19

To sodium hydride (65%, 0.31g, 8.3 mmol) in 5 mL of NMP at 0 °C was added a mixture of 2-bromophenylacetone (1.4 g, 6.5 mmol) and 2-bromobenzyl bromide (2.0 g, 8 mmol) in 5 mL of NMP. The mixture was warmed to ambient temperature and quenched by addition of 20 mL of water and 50 mL of MTBE. The organic layer was separated, concentrated in vacuum and chromatographed over silica gel, eluted with EtOAc/Hexanes (1/5) to afford ketone 19 in 94% yield. pale yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 7.50 (m, 2H), 7.29 (m, 2H), 6.99-7.13 (m, 3H), 6.89 (m, 1H), 4.71 (dd, J = 8.3, 6.4 Hz, 1H), 3.60 (dd, J = 13.8, 6.4 Hz, 1H), 3.01 (dd, J = 13.6, 8.3 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.6, 138.1, 137.6, 133.2, 132.7, 131.5, 129.5, 128.9, 128.0, 127.6, 127.0, 125.6, 124.9, 57.0, 38.0, 29.6. exact mass m/z calcd for $\text{C}_{16}\text{H}_{14}\text{BrO}$, $[\text{M}+\text{H}]$ 380.94842, found 380.94861.

Preparation of Aldehyde 21

To LiN(TMS)₂ (1.0 M in THF, 12 mL, 12 mmol) at -10 °C was added a solution of 2-bromophenylacetonitrile (1.97 g, 10 mmol) and 4-chlorobenzyl chloride (1.93 g, 12 mmol) in 20 mL of THF, keeping the reaction mixture below 0 °C. The mixture was warmed to ambient temperature and stirred at this temperature for 1 h. 2 N HCl (20 mL) was added to the reaction mixture. The mixture was extracted with 40 mL of MTBE. The MTBE layer was separated, dried (MgSO₄) and concentrated in vacuum to give crude nitrile as oil (3.30 g). This material was directly subjected to Dibal-H reduction without further purification.

To crude nitrile (0.66 g, 2 mmol) in toluene (6 mL) at ambient temperature was added 20 W% of Dibal-H in toluene (2.84g, 4 mmol). The mixture was stirred at ambient temperature for 1 h and quenched into 20 mL of 2 N HCl. The toluene layer was separated, concentrated in vacuum to oil. The oil was chromatographed over silica gel, eluted with EtOAc/Hexanes (1/4) to afford aldehyde **21** (0.58 g, 90% yield) as colorless oil: ¹H NMR (400 MHz, CDCl₃): δ 8.04 (m, 2H), 7.59 (dd, *J* = 9.0, 1.1 Hz, 1H), 7.28 (m, 2H), 7.16 (m, 1H), 6.97 (m, 2H), 4.42 (s, 2H), 3.89 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 194.8, 163.6, 135.2, 132.7, 131.6, 130.6, 129.6, 128.5, 127.4, 125.0, 113.8, 55.4, 45.3. Mass [M-Cl] confirmed by GC.

6b

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