Exploration of Ionic Liquids as Soluble Supports for Organic Synthesis. Demonstration with a Suzuki Coupling Reaction

Weishi Miao and Tak Hang Chan*

Department of Chemistry, McGill University, Montreal, Quebec
Canada H3A 2K6

Email: Tak-Hang.Chan@mcgill.ca

Supporting information

Experimental and Characterization of Compounds:

General. All reagents were obtained commercially and were used without further purification unless otherwise noted. Microwave assisted reaction was performed in a domestic microwave oven (Panasonic Model NN-S562WF, 1200 W, 2450 MHz). ^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz) or Mercury-400 (400 MHz) at 20 °C. Chemical shifts for protons are reported in parts per million and referenced to residual protium in deuterated chloroform (δ 7.26), deuterium oxide (δ 4.60) or acetone (δ 2.06). Carbon chemical shifts are reported in parts per million relative to the carbon resonance of the methyl group of chloroform- d_1 (δ 77.0) or acetone- d_6 (δ 29.8, 206). Mass spectroscopic data were obtained at the McGill University Mass Spectrometry Facility.

Preparation of 1-(2-hydroxyethyl)-3-methylimidazolium bromide¹: A mixture of 1-methylimidazole (3.28g, 0.04 mol) and 1-bromoethanol (5.0g, 0.04 mol) in a 25 ml round bottom flask equipped with a drying tube was placed in a 100 ml beaker containing 30 ml of water. The reaction mixture was heated intermittently (360W 60s + 50s + 30s) in the microwave oven and mixed occasionally by swirling between intervals.² The temperature of the water bath was below 70 °C during the course of the reaction. The pale brown oil solidified on cooling and was washed by ether (10ml×3) and dried at 70 °C under vacuum. The product was obtained as a pale yellow

¹ Dzyuba, S. V.; Bartsch, R. A. *Tetrahedron Lett.* **2002**, 43, 4657.

² Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem.* **2002**, 4, 328.

solid (8.2g, 99%); Mp 81- 85 °C; ¹H NMR (400 MHz, D₂O) δ 8.55 (s, 1H), 7.31 (s, 1H), 7.25 (s, 1H), 4.12 (t, *J* = 4.8 Hz, 2H), 3.73 (t, *J* = 4.8 Hz, 2H), 3.71 (s, 3H).

Preparation of 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate 6:³ A mixture of 1-(2-hydroxyethyl)-3-methylimidazolium bromide (8.2g, 0.04 mol), NaBF₄ (8.8g, 0.08 mol) and dry acetonitrile (25 ml) was heated to reflux with stirring for 25 h under nitrogen. Upon cooling, the white precipitate was filtered off and washed with acetonitrile (10 ml×2). The organic filtrate was concentrated in vacuum to give liquid product **6** (8.0g, 95%); ¹H NMR (400 MHz, Acetone-*d*₆) δ 8.99 (s, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 4.43 (t, *J* = 4.4 Hz, 2H), 4.05 (s, 3H), 3.92 (t, *J* = 4.4 Hz, 2H).

Preparation of 3 -iodobenzoyloxyethyl-(1-methylimidazolium tetrafluoroborate 5 and 9: To a mixture of ionic liquid **6** (3.21g, 0.015 mol), *para* or *meta*-iodobenzoic acid (4.96g, 0.020 mol) and dimethylaminopyridine (0.25g, 0.002 mol) in dry acetonitrile (80 ml) was added dicyclohexylcarbodiimide (1M in CH₂Cl₂, 20 ml, 0.020 mol). The reaction was stirred vigorously for 36 h at room temperature under nitrogen. After filtration, the organic phase was concentrated in vacuum. The crude residue was washed firstly with benzene (20ml×3), then water (10ml) and dried at 70 °C under vacuum to give the product. **3-*p*-Iodobenzoyloxyethyl-(1-methylimidazolium tetrafluoroborate 5:** Slightly yellow solids (5.92g, 89%), Mp 113-115 °C; ¹H NMR (400 MHz, Acetone-*d*₆) δ 9.18 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.90 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 1H), 4.86-4.76 (m, 4H), 4.06 (s, 3H); ¹³C NMR (100 MHz, Acetone-*d*₆) δ 165.6, 138.6 (2C), 137.9, 131.7 (2C), 129.7, 124.6, 123.7, 101.4, 64.1, 49.4, 36.6; HRMS (FAB) *m/z* calcd. for M⁺ C₁₆H₃₀O₂ 357.0100, found 357.0100. **3-*m*-Iodobenzoyloxyethyl-(1-methylimidazolium tetrafluoroborate 9:** Slightly yellow solids (5.66g, 85%), Mp 76-79 °C; ¹H NMR (300 MHz, Acetone-*d*₆) δ 9.17 (s, 1H), 8.28 (s, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.89 (s, 1H), 7.72 (s, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 4.87-4.77 (m, 4H), 4.06 (s, 3H); ¹³C NMR (75 MHz, Acetone-*d*₆) δ 164.3, 142.4, 138.2, 137.5, 131.7, 131.0, 129.2, 124.2, 123.3, 93.8, 64.0, 49.0, 36.3; HRMS (FAB) *m/z* calcd. for [2M⁺ + A]⁺ C₂₆H₂₈O₄I₂BF₄ 801.0229, found 801.0224.

General procedure for the coupling reactions of ionic liquid supported iodobenzoate 5 or 9 with arylboronic acids 2a-e in aqueous media: To a solution of ionic liquid supported iodobenzoate **5** or **9** (0.125 mmol) in 2 ml of degassed water at 80 °C under nitrogen was added arylboronic acid (0.187 mmol or 0.250 mmol, see table 1) and CsF (0.625 mmol) in one portion. The resulting mixture was stirred at this temperature for 15 min before Pd(OAc)₂ (0.018 mmol) was added. The reaction system was then stirred vigorously for 22 h at 80 °C under nitrogen atmosphere. The solvent was removed at 55 °C under reduced pressure. The residue was washed with ether (15 ml×3) and small amount of water (1 ml). After decanting the liquid phase, the crude product **8a-e** or **10a-e** was dried on vacuum pump, examined by NMR and subjected to the next step of cleavage reaction.

(8a): ¹H NMR (400 MHz, Acetone-*d*₆) δ 9.58 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.99-7.98 (m, 1H), 7.79-7.78 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.95-4.78 (m, 4H), 4.12 (s, 3H), 3.87 (s, 3H); ¹³C NMR (75 MHz, Acetone-*d*₆) δ 165.8, 160.7, 145.9, 138.0, 132.2, 130.8 (2C), 128.8 (2C), 128.0, 127.0 (2C), 124.5, 123.7, 115.1 (2C), 63.8, 55.6, 49.5, 36.7.

³ Branco, L. C.; Rosa, J. N.; Moura Ramos, J. J.; Afonso, C. A. M. *Chem. Eur. J.* **2002**, 8, 3671.

(8b): ^1H NMR (400 MHz, Acetone- d_6) δ 9.59 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.99-7.98 (m, 1H), 7.80-7.79 (m, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 4.96-4.79 (m, 4H), 4.11 (s, 3H), 1.37 (s, 9H).

(8c): ^1H NMR (400 MHz, Acetone- d_6) δ 9.82 (s, 1H), 8.06 (d, J = 8.8 Hz, 2H), 8.04-8.03 (m, 1H), 7.81-7.80 (m, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.61 (dd, J = 3.6, 0.8 Hz, 1H), 7.57 (dd, J = 5.2, 0.8 Hz, 1H), 7.10 (dd, J = 5.2, 3.6 Hz, 1H), 4.98-4.78 (m, 4H), 4.10 (s, 3H).

(8d): ^1H NMR (400 MHz, Acetone- d_6) δ 9.47 (s, 1H), 8.11 (d, J = 8.8 Hz, 2H), 7.95-7.94 (m, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.74-7.73 (m, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.51-7.47 (m, 2H), 7.44-7.40 (m, 1H), 4.89-4.75 (m, 4H), 4.03 (s, 3H).

(8e): ^1H NMR (400 MHz, Acetone- d_6) δ 9.58 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 8.8 Hz, 2H), 7.99-7.98 (m, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 7.79-7.78 (m, 1H), 4.94-4.81 (m, 4H), 4.11 (s, 3H), 2.64 (s, 3H).

(10a): ^1H NMR (300 MHz, Acetone- d_6) δ 9.80 (s, 1H), 8.17-8.16 (m, 1H), 8.01-8.00 (m, 1H), 7.98-7.95 (m, 1H), 7.87-7.83 (m, 1H), 7.79-7.78 (m, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.57-7.52 (m, 1H), 7.05 (d, J = 8.7 Hz, 2H), 4.96-4.78 (m, 4H), 4.04 (s, 3H), 3.83 (s, 3H).

(10b): ^1H NMR (300 MHz, Acetone- d_6) δ 9.80 (s, 1H), 8.23-8.22 (m, 1H), 8.03-8.00 (m, 1H), 8.00-7.99 (m, 1H), 7.92-7.89 (m, 1H), 7.78-7.77 (m, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.55-7.52 (m, 2H), 4.98-4.85 (m, 4H), 4.05 (s, 3H), 1.36 (s, 3H).

(10c): ^1H NMR (400 MHz, Acetone- d_6) δ 9.66 (s, 1H), 8.22-8.21 (m, 1H), 8.00-7.99 (m, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H), 7.80-7.79 (m, 1H), 7.58-7.54 (m, 3H), 7.17 (dd, J = 5.2, 3.6 Hz, 1H), 4.97-4.84 (m, 4H), 4.13 (s, 3H).

(10d): ^1H NMR (400 MHz, Acetone- d_6) δ 9.55 (s, 1H), 8.23-8.22 (m, 1H), 8.04-8.02 (m, 1H), 7.98-7.97 (m, 1H), 7.94-7.92 (m, 1H), 7.76-7.75 (m, 1H), 7.71-7.69 (m, 2H), 7.62-7.58 (m, 1H), 7.52-7.48 (m, 2H), 7.44-7.40 (m, 1H), 4.92-4.78 (m, 4H), 4.04 (s, 3H).

(10e): ^1H NMR (400 MHz, Acetone- d_6) δ 9.70 (s, 1H), 8.28-8.27 (m, 1H), 8.10-8.07 (m, 2H), 8.09 (d, J = 8.8 Hz, 2H), 8.03-8.02 (m, 1H), 8.00-7.97 (m, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.80-7.79 (m, 1H), 7.65-7.61 (m, 1H), 4.95-4.78 (m, 4H), 4.12 (s, 3H), 3.87 (s, 3H).

General procedure for the cleavage reaction of ionic liquid supported coupling product 8a-e or 10a-e: The crude coupling product **8a-e** or **10a-e** from the previous step was dissolved in ammonia-saturated methanol (2 ml). The resulting solution was then stirred at room temperature overnight. After removing the solvent under reduced pressure, the residue was extracted with ether (20 ml $\times$ 3). Concentration of the combined ether extracts under reduced pressure afforded biaryl products **3a-e** or **11a-e** and the yields (2 steps from **5** or **9**) were shown in Table 1.

(3a)⁴: ^1H NMR (300 MHz, CDCl_3) δ 8.07 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 3.87 (s, 3H).

(3b)⁵: ^1H NMR (400 MHz, Acetone- d_6) δ 8.07 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 1.37 (s, 9H).

⁴ Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, 68, 3729.

(3c)⁶: ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.42 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.36 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.11 (dd, *J* = 5.2, 3.6 Hz, 1H), 3.90 (s, 3H).

(3d)⁵: ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.53-7.50 (m, 2H), 7.44-7.40 (m, 1H), 3.91 (s, 3H).

(3e)⁴: ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 3.96 (s, 3H), 2.67 (s, 3H).

(11a)⁷: White solids, Mp. 71-73 °C (lit.⁷ 70-71.5 °C); ¹H NMR (300 MHz, CDCl₃) δ 8.25-8.24 (m, 1H), 7.99-7.96 (m, 1H), 7.76-7.73 (m, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.51-7.46 (m, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 3.96 (s, 3H), 3.87 (s, 3H).

(11b)⁵: ¹H NMR (400 MHz, CDCl₃) δ 8.29-8.28 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 3.96 (s, 3H), 1.39 (s, 9H).

(11c)⁸: Pale yellow oil (lit.⁸ Mp. 40-42 °C); ¹H NMR (300 MHz, CDCl₃) δ 8.29-8.28 (m, 1H), 7.96-7.92 (m, 1H), 7.81-7.77 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.39 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.32 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.96 (s, 3H).

(11d)⁹: ¹H NMR (400 MHz, Acetone-*d*₆) δ 8.26-8.25 (m, 1H), 8.02-7.99 (m, 1H), 7.94-7.91 (m, 1H), 7.72-7.69 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.53-7.51 (m, 2H), 7.43-7.40 (m, 1H), 3.93 (s, 3H).

(11e): White crystals; Mp. 98-100 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.31-8.30 (m, 1H), 8.08-8.05 (m, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.83-7.80 (m, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 3.96 (s, 3H), 2.66 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 197.4, 166.6, 144.4, 140.0, 136.0, 131.4, 130.7, 129.1, 129.0, 128.9 (2C), 128.2, 127.1 (2C), 52.4, 26.8; HRMS (EI) *m/z* calcd. for C₁₆H₁₄O₃ M⁺ 254.0943, found 254.0940.

General procedure for the coupling reactions of methyl *p*-iodobenzoate 1 with arylboronic acids 2a-e in aqueous media: A mixture of methyl *p*-iodobenzoate **1** (0.125 mmol), arylboronic acid **2** (0.187 mmol) and CsF (0.625 mmol) in 2 ml of degassed water was stirred for 15 min at 80 °C under nitrogen before Pd(OAc)₂ (0.018 mmol) was added. The reaction mixture was stirred vigorously for 22 h at 80 °C under nitrogen atmosphere. After cooling, the resulting mixture was extracted with ether (15ml×3) and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was then examined by proton NMR. For the reaction of *p*-MeOPhB(OH)₂ **2a**, the crude was further purified by flash column chromatography (silica gel 230-400 mesh, hexane-ethyl acetate gradient) to give the biaryl product **3a** (See Table 2) and the homocoupling product **4a** as white crystals. **4, 4'-dimethoxybiphenyl (4a)**¹⁰: ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 8.8 Hz, 4H), 6.96 (d, *J* = 8.8 Hz, 4H), 3.85 (s, 6H).

⁵ Wang, X.; Parlow, J. J.; Porco, J. A. *Org. Lett.* **2000**, 2, 3509.

⁶ Li, X.; Abell, C.; Ladlow, M. *J. Org. Chem.* **2003**, 68, 4189.

⁷ Dauben, Wm. G.; Tanabe, M. *J. Am. Chem. Soc.* **1953**, 75, 4969.

⁸ Benati, Luisa; Tiecco, Marcello; *Bollettino Scientifico della Facolta di Chimica Industriale di Bologna, Supplemento.* **1966**, 24, 225.

⁹ Kang, S.-K.; Kim, J.-S.; Yoon, S.-K.; Lim, K.-H.; Yoon, S.-S. *Tetrahedron Lett.* **1998**, 39, 3011.

¹⁰ *The Aldrich Library of NMR Spectra*, Pouchert, C. J. Ed II, Vol 1, 854B.

pIIL-MeOPhB-Suz-Cleavage

Data Collected on: m300-mercury300
Archive directory: /export/home/miacos/vnmrsys/data
Sample directory:
File: pIIL-MeOPhB-SH2OCsF-etherheatNH3-Sep21

Pulse Sequence: szpul

Solvent: CDCl3

Temp: 25.8 C / 298.1 K

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.550 sec

Width 1693.1 Hz

5 repetitions

OBSERVE H1 300.0595485 MHz

DATA PROCESSING

FT size 32758

Total time 0 min

PIPhCO2Me-MeOPhB-SuzH2OCsF-crude

Data Collected on: m400-mercury400
Archive directory: /export/home/miacos/vnmrsys/data
Sample directory:
File: PIPhCO2Me-MeOPhB-SuzH2OCsF-crude-Sep12

Pulse Sequence: szpul

Solvent: CDCl3

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 1.550 sec

Width 6410.3 Hz

8 repetitions

OBSERVE H1 400.1310813 MHz

DATA PROCESSING

FT size 32758

Total time 0 min