

Soluble Carbonate as Base in the Copper-Catalyzed Imidazole N-Arylations with Aryl Halides

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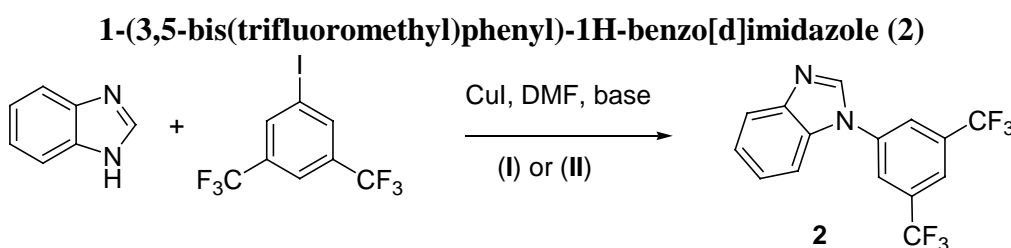
General

Cs₂CO₃ (powder), CuI, 8-Hydroxy quinoline (**IV**), N, N'-dimethylethane-1,2-diamine (**II**), 1,10-phenanthroline (**I**), TEAC, and anhydrous DMF were purchased from commercial sources.

Chromatography was performed on silica columns or cartridges.

Analytical HPLC was performed on C18 (5u) columns. The mobile phases are A: 0.1% TFA in H₂O, B: 0.1% TFA in CH₃CN. The HPLC method used is: 5-95%B over 14 min (total run time ~15 min). LCMS was performed on similar systems with varying run times.

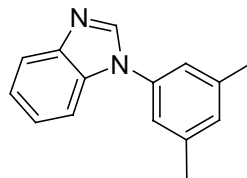
Table 1. Effect of Bases on Reaction Rate



(1) In a microwave reaction tube (10 mL), under a nitrogen stream, with a stirring bar was placed CuI (19 mg, 0.1 mmol), benzimidazole (136 mg, 1.15 mmol), 1-iodo-3,5-bis(trifluoromethyl)benzene (340 mg, 1.0 mmol, Maybridge), 1,10-phenanthroline (**I**, 36 mg, 0.2 mmol), and Cs₂CO₃ (650 mg, 2.0 mmol), and DMF (1.0 mL). The system was sealed with a pressure cap and was heated at 110°C in an oil bath for 10 h. The reaction tube was removed from the oil bath and an aliquot (1 uL) was taken (through a needle), dissolved in MeOH (0.2 mL) for HPLC analyses which indicated ~85% conversion based on the integration of the product (9.85 min) and unreacted iodide (13.9 min) at 215 nm. The reaction was continued for 22 h (total) and was cooled to room temperature. HPLC analyses indicated there was ~94% conversion. The reaction mixture was diluted with CH₂Cl₂-MeOH (2:1) (10 mL) and the mixture was filtered through a pad of Celite. The filter was further washed with CH₂Cl₂-MeOH (2:1) (3 x 5 mL). The combined filtrates were washed with H₂O x1, dried over Na₂SO₄, and concentrated. The residue was purified on silica gel with EtOAc as elutant (R_f 0.6) to afford the desired product (**2**) as a white solid (230 mg, 70 %).

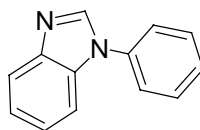
(2) A parallel reaction with TEAC (95%, 320 mg, 1.0 mmol) and N, N'-dimethylethane-1,2-diamine (**II**, 17 mg, 0.2 mmol) in place of Cs₂CO₃ and (**I**) was conducted for 10 h where HPLC analyses indicated the completion of the reaction. Same workup and purification afforded the product (**2**) in 76% yield (251 mg).

¹H NMR (400 MHz, CDCl₃) δ 8.17 (1H, s), 8.02 (2H, s), 7.99 (1H, s), 7.92 (1H, m), 7.51 (1H, m), 7.42 (2H, m). HRMS calcd for C₁₅H₉F₆N₂ (M + H): 331.0664, found: 331.0664. Anal. calcd for C₁₅H₈F₆N₂: C, 54.56; H, 2.44; N, 8.48; found: C, 54.58; H, 2.28; N, 8.43.



1-(3,5-Dimethylphenyl)-1H-benzo[d]imidazole (**3**)

This reaction was conducted at 120°C for 70 h. The cooled reaction mixture was filtered through a pad of Celite and was washed with 10% MeOH in CH₂Cl₂ (20 mL). The combined filtrates was concentrated and was diluted with toluene (2x 5 mL) to remove DMF under vacuum. The residue was purified on silica (0-1% MeOH in EtOAc) to afford a white solid (200 mg, 90%), as characterized earlier.

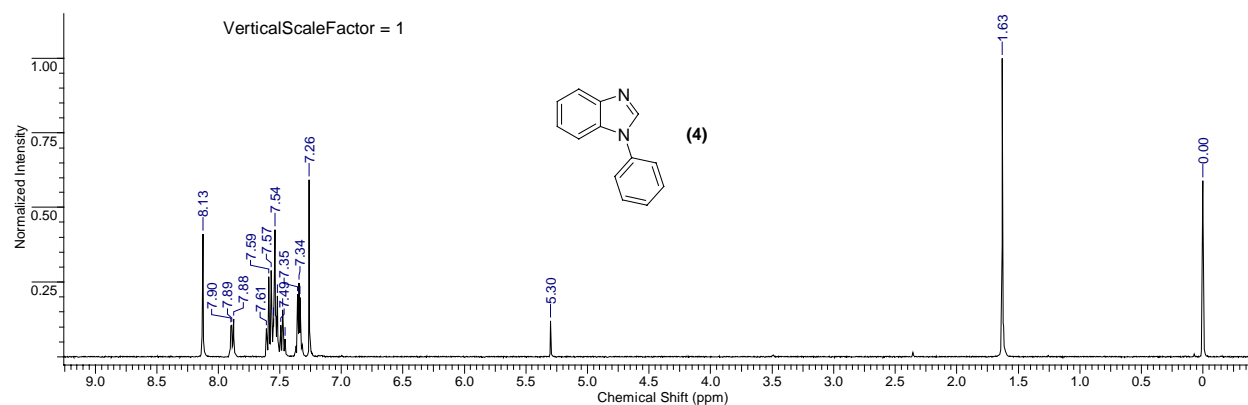


1-Phenyl-1H-benzo[d]imidazole (**4**)²

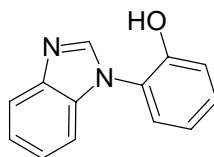
The reaction mixture was loaded directly onto a silica column and eluted 1:1 hexanes-EtOAc, then with 0-1% MeOH in EtOAc. A colorless solid (164 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ 8.13 (1H, s), 7.88 (1H, m), 7.58-7.48 (6H, m), 7.35 (2H, m). HRMS calcd for C₁₃H₁₁N₂ (M + H): 195.0917, found: 195.0916.

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				Solvent	CHLOROFORM-d



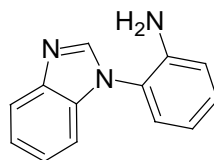
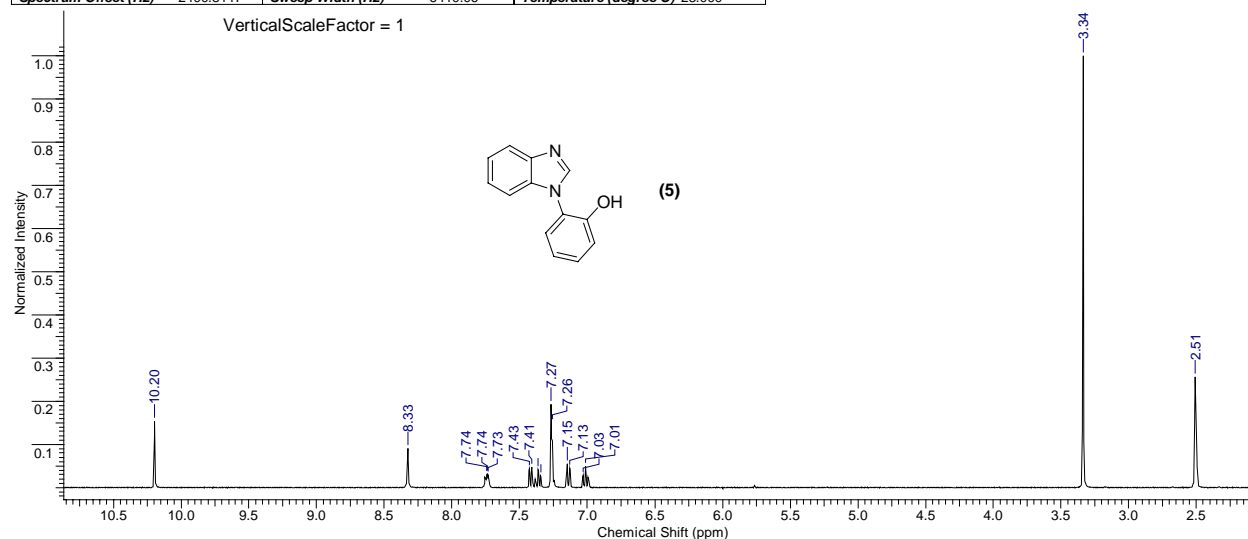
² (a) Yzhao, Z.; Peng, Y.; Dalley, N. K.; Cannon, J. F.; Peterson, M. A. *Tetrahedron Lett.* **2004**, *45*, 3621-3624. (b) Collman, J. P.; Zhong, M.; Zeng, Li.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528-1531 (molecular formulae was incorrectly indicated for compound 4h).

2-(1H-Benzo[d]imidazol-1-yl)phenol (**5**)³

The reaction mixture was loaded directly onto a silica column and eluted with 2% (2N NH₃-MeOH) in EtOAc; CH₂Cl₂; and CHCl₃ (3 columns, streaking). A white solid (140 mg, 62%).

¹H NMR (400 MHz, DMSO-d₆) δ 10.19 (1H, s), 8.33 (1H, s), 7.75 (1H, m), 7.41 (1H, d, J 7.8), 7.38 (1H, t, J 10), 7.26 (3H, m), 7.14 (1H, d, J 7.4), 7.01 (1H, t, J 7.6). HRMS calcd for C₁₃H₁₁N₂O (M + H): 211.0866, found: 211.0865.

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Spectrum Offset (Hz)	2400.8147	Sweep Width (Hz)	6410.06	Temperature (degree C)	23.000
				Solvent	DMSO-d6

2-(1H-Benzo[d]imidazol-1-yl)benzenamine (**1**)⁴

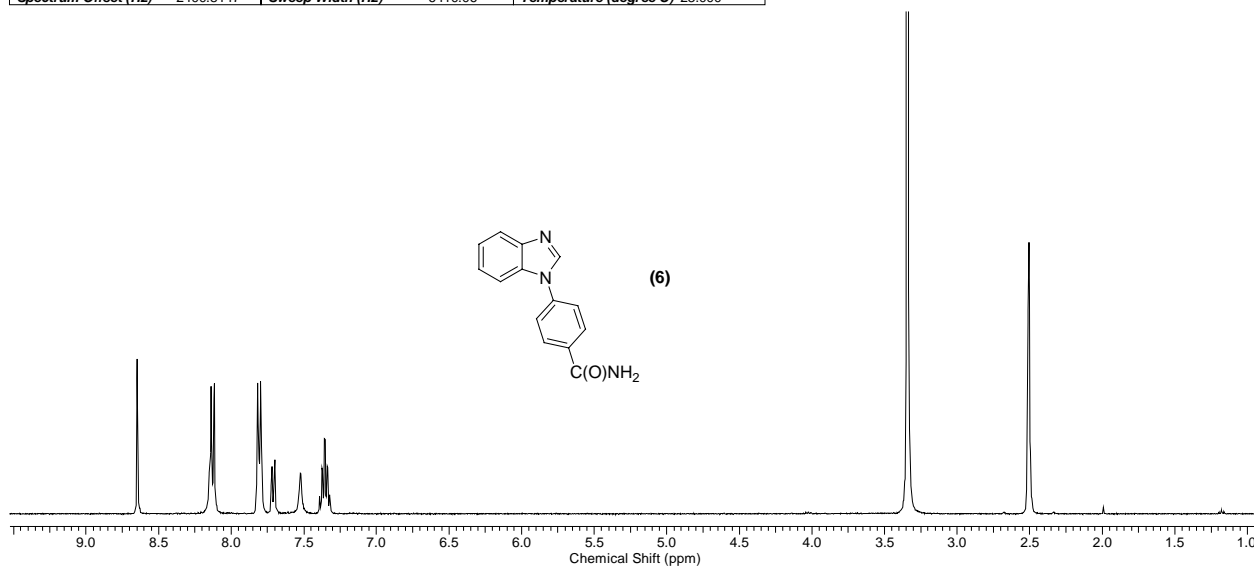
The reaction mixture was loaded directly onto a silica column and eluted with 2% (2N NH₃-MeOH) in EtOAc; CH₂Cl₂; and CHCl₃ (3 columns). A white solid (140 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 8.06 (1H, s), 7.90 (1H, d, J 7.2), 7.38-7.28 (4H, m), 7.19 (1H, dd, J 1.6, 7.6), 6.94-6.83 (2H, m), 3.62 (2H, bs). HRMS calcd for C₁₃H₁₂N₃ (M + H): 210.1026, found: 210.1026.

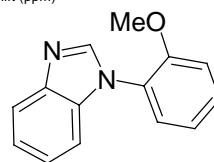
³ (a) Palmer, B. D.; Smaill, J.B.; Boyd, M.; Boschelli, D. H.; Doherty, A. M.; Hamby, J. M.; Khatana, S. S.; Kramer, J. B.; Kraker, A. J.; Panek, R. L.; Lu, G. H.; Dahring, T. K.; Winters, R. T.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 5457-5465. (b) Tashiro, M; Itoh, Takashi; Fukata, G. *Synthesis* **1982**, *3*, 217-19.

⁴ See, reference 3a.

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Spectrum Offset (Hz)	2400.8147	Sweep Width (Hz)	6410.06	Temperature (degree C)	23.000
		Solvent			DMSO-d6



(6)

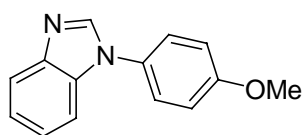
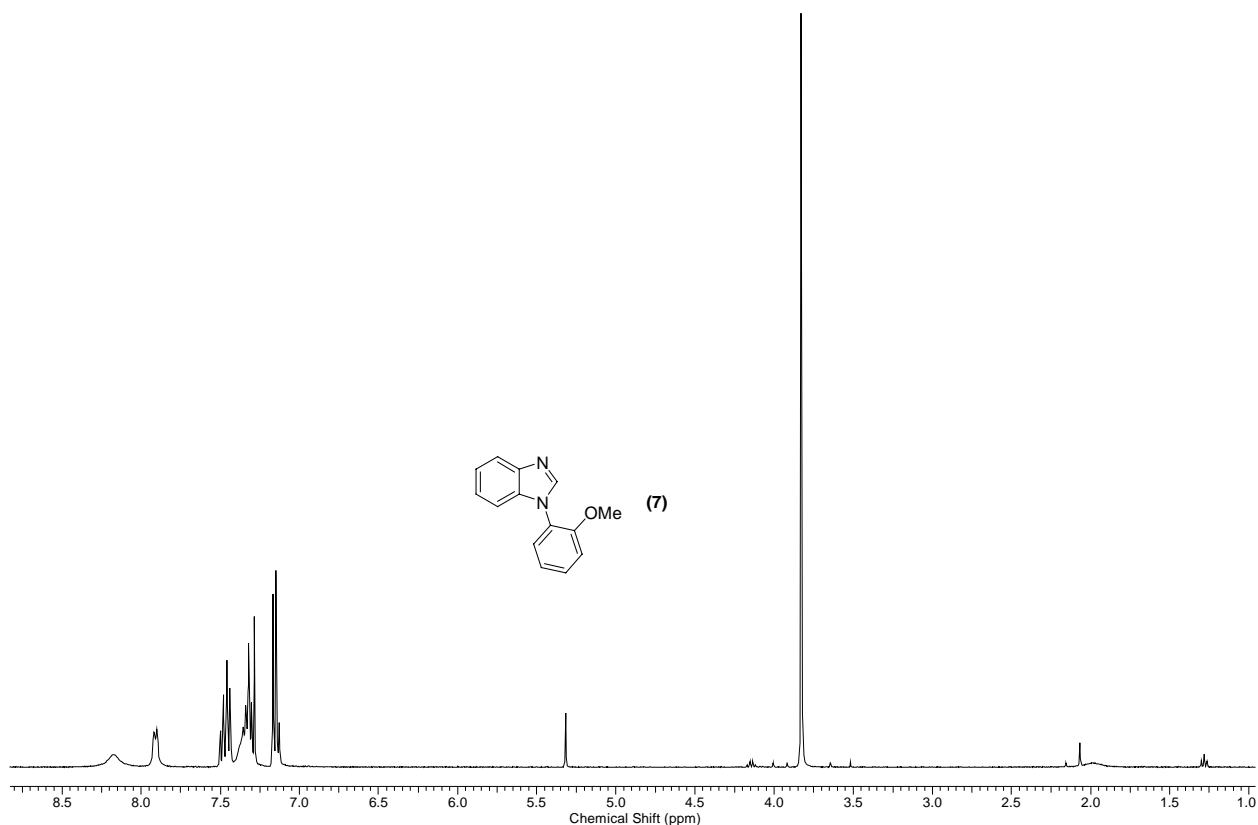
(7)⁶1-(2-Methoxyphenyl)-1H-benzo[d]imidazole (7)⁶

At the end of the reaction, HPLC analyses indicated there were 1:11 (5) : (7) formed. The reaction mixture was diluted with EtOAc (40 mL) and was washed with NaOH (0.5N, 3 x 10 mL), brine, dried over Na₂SO₄, and concentrated. Flash chromatography on silica gel (1-3% MeOH in EtOAc) afforded a yellow film (143 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 8.18 (1H, bs), 7.91 (1H, d, J 7.0), 7.50-7.743 (2H, m), 7.36-7.28 (2H, m), 7.15 (2H, t, J 8.0), 3.83 (3H, s). HRMS calcd for C₁₄H₁₃N₂O (M + H): 225.1022, found: 225.1023.

⁶ See, reference 3a.

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				Solvent	CHLOROFORM-d



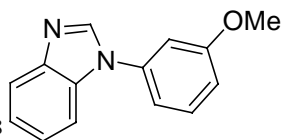
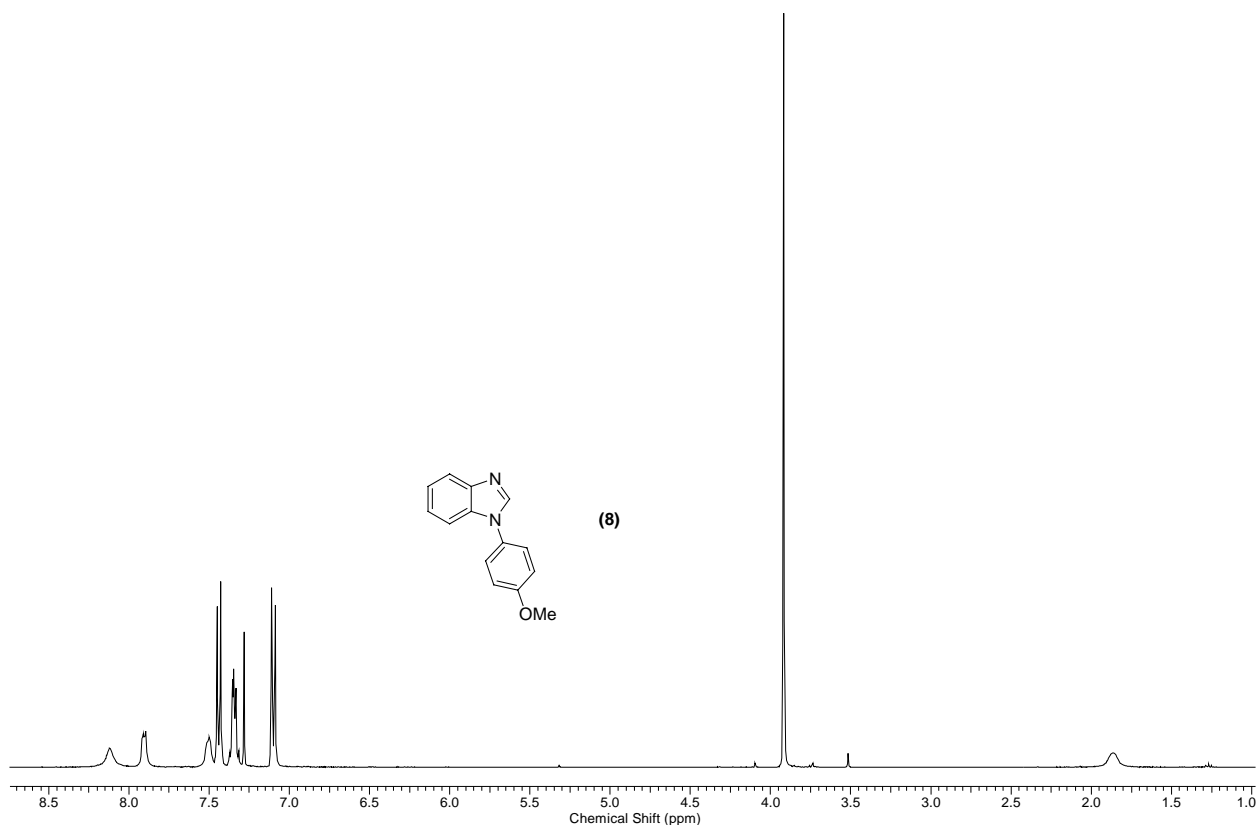
1-(4-Methoxyphenyl)-1H-benzimidazole (**8**)⁷

The cooled reaction mixture was diluted with EtOAc (30 mL) and was washed with H₂O, NaHCO₃ (aq), NH₄Cl (aq). The organic phase was dried over Na₂SO₄ and concentrated to an yellow oil. This was purified on preparative TLC (3% MeOH in EtOAc) to afford a white solid (197 mg, 88%).

¹H NMR (400 MHz, CDCl₃) δ 8.12 (1H, bs), 7.91 (1H, d, J 6.5), 7.50 (1H, bd), 7.44 (2H, d, J 8.8), 7.35 (2H, m), 7.10 (2H, d, J 8.8), 3.92 (3H, s). HRMS calcd for C₁₄H₁₃N₂O (M + H): 225.102245 found: 225.10242.

⁷ (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233-1236. (b) See, reference 2b. (c) See, reference 3a.

Acquisition Time (sec)	5.1120	Comment	liu	Date	03 Sep 2004 21:32:11
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Spectrum Offset (Hz)	2400.8147	Sweep Width (Hz)	6410.06	Temperature (degree C)	22.800
				Solvent	CHLOROFORM-d



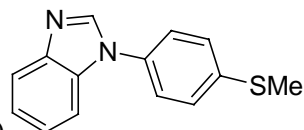
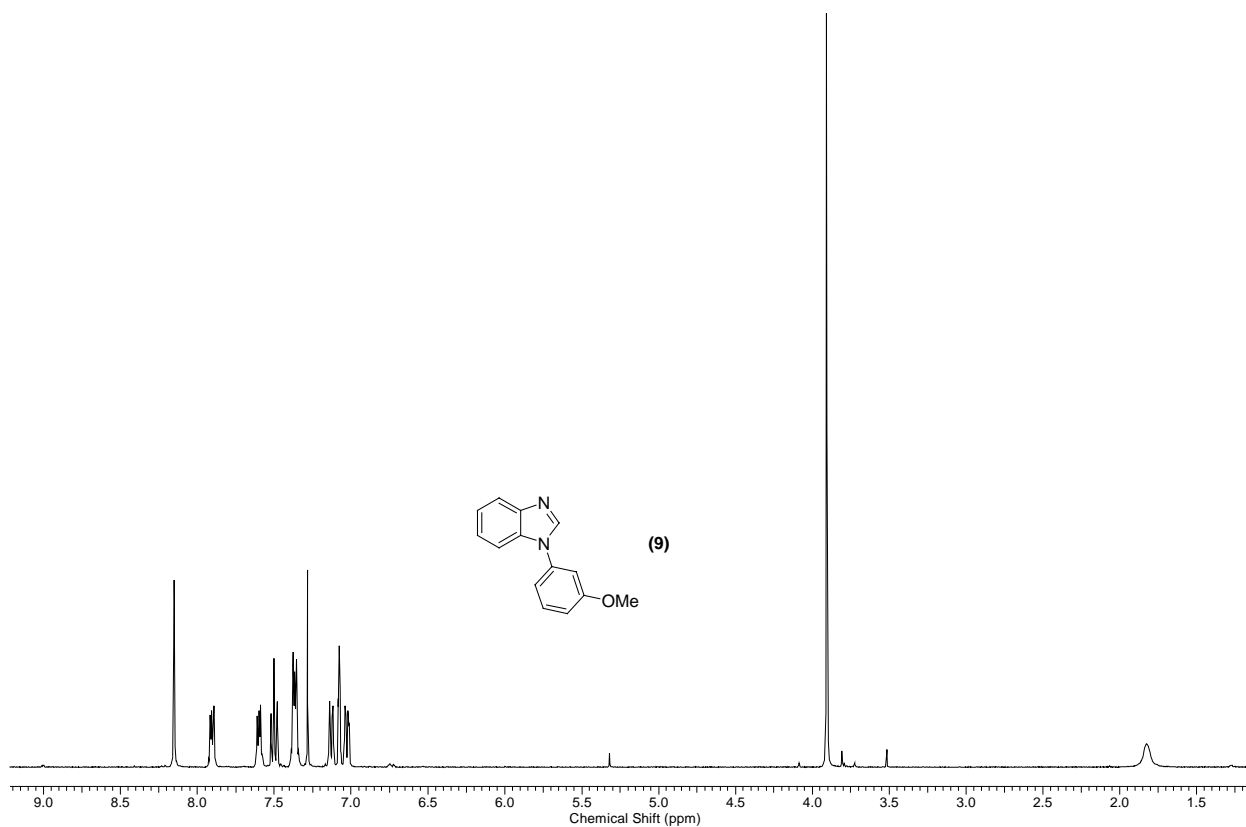
1-(3-Methoxyphenyl)-1H-benzodimidazole (**9**)⁸

The cooled reaction mixture was diluted with EtOAc (20 mL) and was washed with H₂O, NaHCO₃ (aq), NH₄Cl (aq). The organic phase was dried over Na₂SO₄ and concentrated to a yellow solid. This was purified on preparative TLC (3% (2N NH₃ in MeOH) in EtOAc) twice to afford a colorless oil (196 mg, 87%).

¹H NMR (400 MHz, CDCl₃) δ 8.15 (1H, s), 7.90 (1H, m), 7.60 (1H, m), 7.50 (1H, t, J 8.0), 7.37 (2H, m), 7.13 (1H, d, J 7.8), 7.08 (1H, t, J 2.2), 7.03 (1H, dd, J 2.4, 8.5), 3.91 (3H, s). HRMS calcd for C₁₄H₁₃N₂O (M + H): 225.10224 found: 225.10228.

⁸ (a) See, reference 3a. (b) Boschelli, D. H.; Denny, W. A.; Doherty, A. M.; Hamby, J. M.; Khatana, S. S.; Kramer, J. B.; Palmer, B. D.; Showalter, H. D. H. *US 5990146 A*, 1999.

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Spectrum Offset (Hz)	2400.8147	Sweep Width (Hz)	6410.06	Temperature (degree C)	22.800
				Solvent	CHLOROFORM-d



1-(4-(Methylthio)phenyl)-1H-benzimidazole (**10**)

The cooled reaction mixture was diluted with EtOAc (20 mL) and was washed with H₂O, NaHCO₃ (aq), NH₄Cl (aq). The organic phase was dried over Na₂SO₄ and concentrated to an yellow solid. This was purified on preparative TLC (3% (2N NH₃ in MeOH) in EtOAc) twice to afford a white solid (199 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 8.10 (1H, s), 7.91 (1H, m), 7.51 (1H, m), 7.45 (4H, s), 7.35 (2H, m), 2.58 (3H, s). HRMS calcd for C₁₄H₁₃N₂S (M + H): 241.07940, found: 241.07972. Anal. calcd for C₁₄H₁₂N₂S: C, 69.97; H, 5.03; N, 11.66; found: C, 69.91; H, 4.95; N, 11.64.

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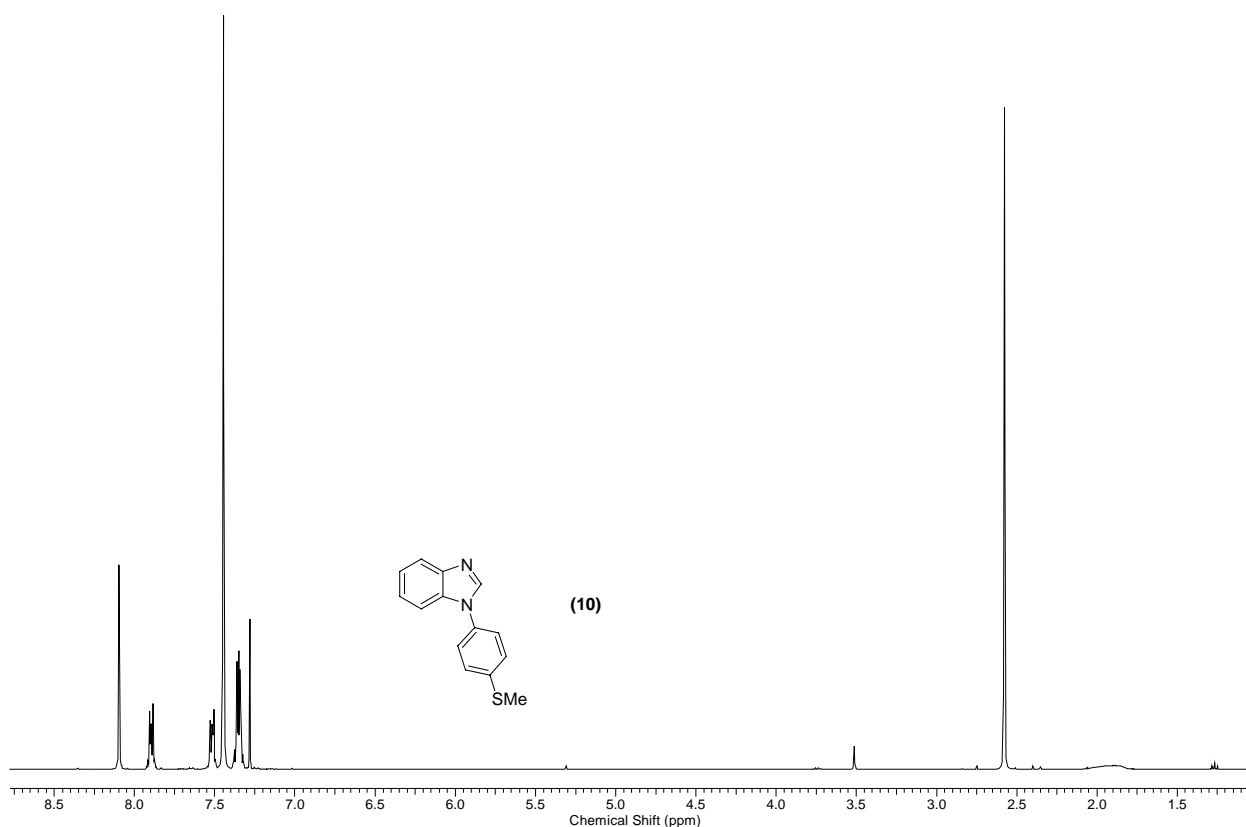
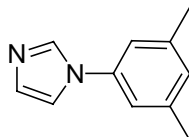


Table 3. N-Arylation of Imidazoles with Aryl Bromides

Typical experimental procedure for Table 3: Similar to the one used in Table 2 unless otherwise indicated. In a pressure reaction vessel (10 mL microwave tube) equipped with a magnetic stirring bar was added imidazole (1.43 mmol), CuI (0.019 g, 0.1 mmol), 8-hydroxyquinoline (**IV**, 0.015 g, 0.1 mmol), bis(tetraethyl ammonium carbonate) (TEAC, Fluka, 90-95 %, 0.37 g, 1.1 mmol), and aryl bromide (1.0 mmol). DMF (1.0 mL) and H₂O (0.1 mL) were added and the vessel was capped with a rubber septum. The system was stirred while degassed under vacuum and purged with nitrogen for three times. The septum was replaced with a pressure cap and the reaction mixture was heated to 130 °C in an oil bath for 16 h. Upon cooling to room temperature the mixture was subject to workup and purification.



1-(3,5-Dimethylphenyl)-1H-imidazole (**11**)⁹

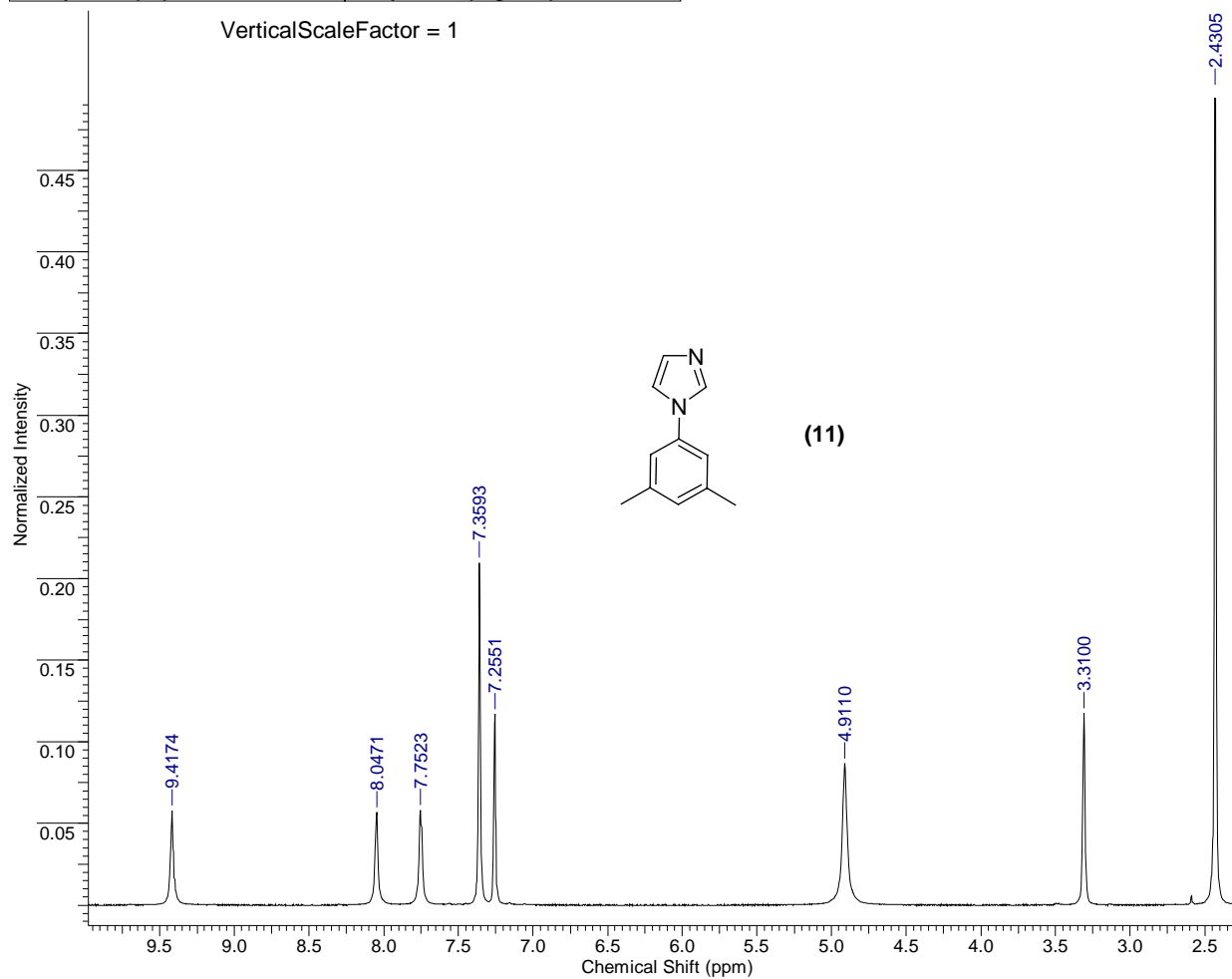
⁹ (a) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578-5587. (b) See, reference 1.

To a 25 mL two-necked round-bottom flask equipped with a magnetic stirring bar, an vacuum outlet and a N₂ inlet was added 5-bromo-m-xylene (0.37 g, 2.0 mmol), 1H-imidazole (0.19 g, 2.8 mmol), Cs₂CO₃ (0.72 g, 2.2 mmol), **IV** (0.029 g, 0.20 mmol) and CuI (0.038 g, 0.20 mmol). Under N₂ atmosphere, DMF (2 mL) and H₂O (0.2 mL) were added and the flask was vacuumed followed by refill of N₂. This process was repeated for three times. The reaction mixture was then heated to 130°C for 16 hours under N₂. The mixture was cooled to room temperature and was diluted with 50 mL of CHCl₃ and 30 mL of H₂O. The organic phase was separated, washed with 20 mL of brine, dried over Na₂SO₄ and concentrated in vacuo. The orange solid was dissolved in 5 mL of MeOH and was treated with 3 mL of 1N HCl in ether. The solvent was removed in vacuo and the residue was recrystallized with 8% MeOH in ether to give light yellow solid as the desired product (0.27 g, 78%) as its HCl salt. afford a white solid (199 mg, 83%).

¹H NMR (400 MHz, MeOH) δ 2.43 (s, 6 H), 7.26 (s, 1 H), 7.36 (s, 2 H), 7.75 (s, 1 H), 8.05 (s, 1 H), 9.42 (s, 1 H). ¹³C NMR (101 MHz, MeOH) δ 21.38, 121.11, 122.77, 132.76, 135.70, 136.53, 142.08.

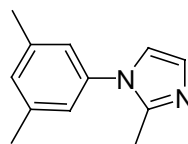
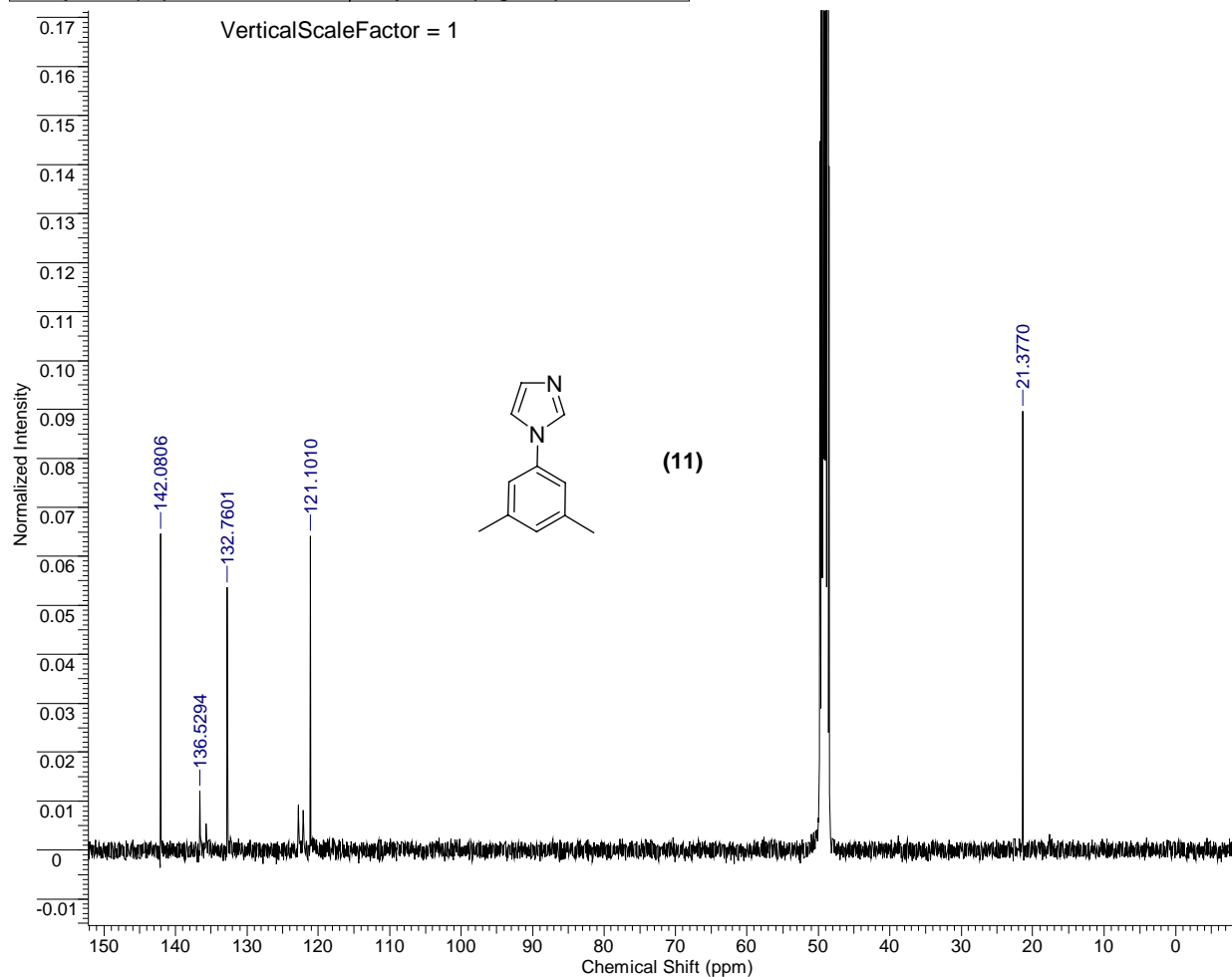
6/30/2005 11:31 AM

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Sweep Width (Hz)	6410.06	Temperature (degree C)	23.400		



6/30/2005 11:34 AM

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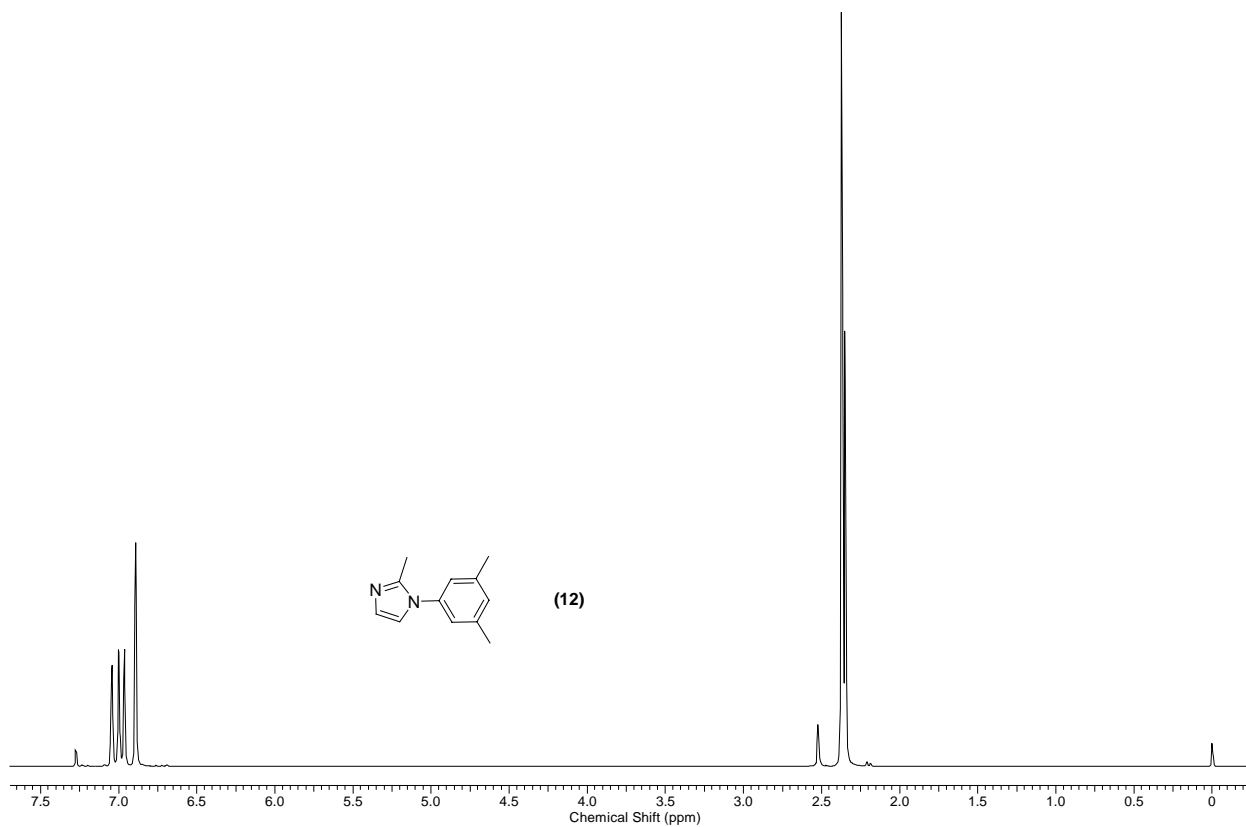
1-(3,5-Dimethylphenyl)-2-methyl-1H-imidazole (**12**)

In a microwave vials (10 mL) containing a stirring bar was added copper (i) iodide (19 mg, 100 μ mol), 1-bromo-3,5-dimethylbenzene (277 mg, 1498 μ mol), 2-methyl-1H-imidazole (82 mg, 999 μ mol), quinolin-8-ol (14 mg, 100 μ mol), and bis(tetraethylammonium) carbonate (360 mg, 1011 μ mol). DMF (1.0 mL) and H₂O (0.1 mL) were added and the mixture was capped with a rubber septum and was purged with nitrogen 3x under vacuum. The vials were sealed with a pressure cap and heated at 130 °C in an oil bath for 16 h. The cooled reaction mixture was loaded directly onto silica, washed with 1:1 hexane-DCM (30 mL), then eluted with 0-3% (2N NH₃-MeOH) in DCM containing 5% ether. A second column of the product fraction

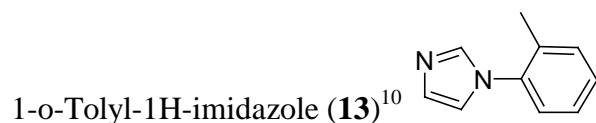
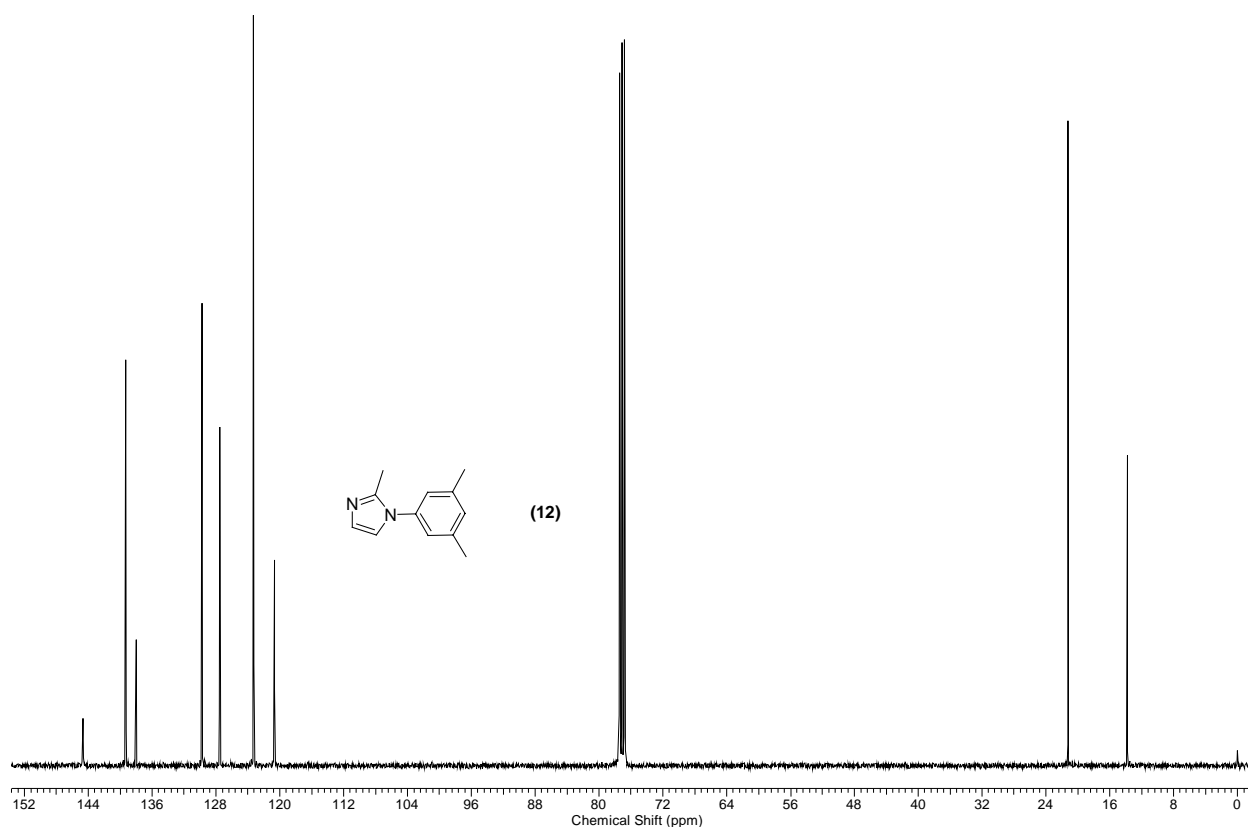
with 2.5% (2N NH₃-MeOH)-20% ether in EtOAc afforded the product as a clear oil (119 mg, 64%).

¹H NMR (400 MHz, CDCl₃) δ 7.04 (1H, s), 7.00 (1H, s), 6.96 (1H, s), 6.89 (2H, s), 2.37 (6H, s), 2.34 (3H, d, J 1.1). ¹³C NMR (101 MHz, CDCl₃) δ 144.67, 139.30, 137.98, 129.73, 127.50, 123.26, 120.68, 21.24, 13.83. HRMS calcd for C₁₂H₁₅N₂ (M + H): 187.1229, found: 187.1234. Anal. Calcd for C₁₂H₁₄N₂·(1/4)H₂O : C, 75.56; H, 7.66; N, 14.69; **found** C, 75.31; H, 7.66; N, 14.54.

Acquisition Time (sec)	5.1120	Comment	liu	Date	12 Jun 2005 19:54:44
File Name	\\Scone\jcamp\liu\65636-21-40_10.dx	Origin	Bruker BioSpin GmbH	Frequency (MHz)	400.13
Number of Transients	16	Points Count	32768	Original Points Count	32768
Owner	chemist	Sweep Width (Hz)	6410.06	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	2396.2573	Temperature (degree C)	25.000		



Acquisition Time (sec)	1.1600	Comment	liu	Date	12 Jun 2005 05:08:59
File Name	\\Scone\camp\liu\65636-21-4_10.dx	Origin	Bruker BioSpin GmbH	Frequency (MHz)	100.62
Number of Transients	4096	Points Count	32768	Nucleus	13C
Owner	chemist	Sweep Width (Hz)	28247.73	Original Points Count	32768
Spectrum Offset (Hz)	12078.1924	Temperature (degree C)	25.000	Solvent	CHLOROFORM-d

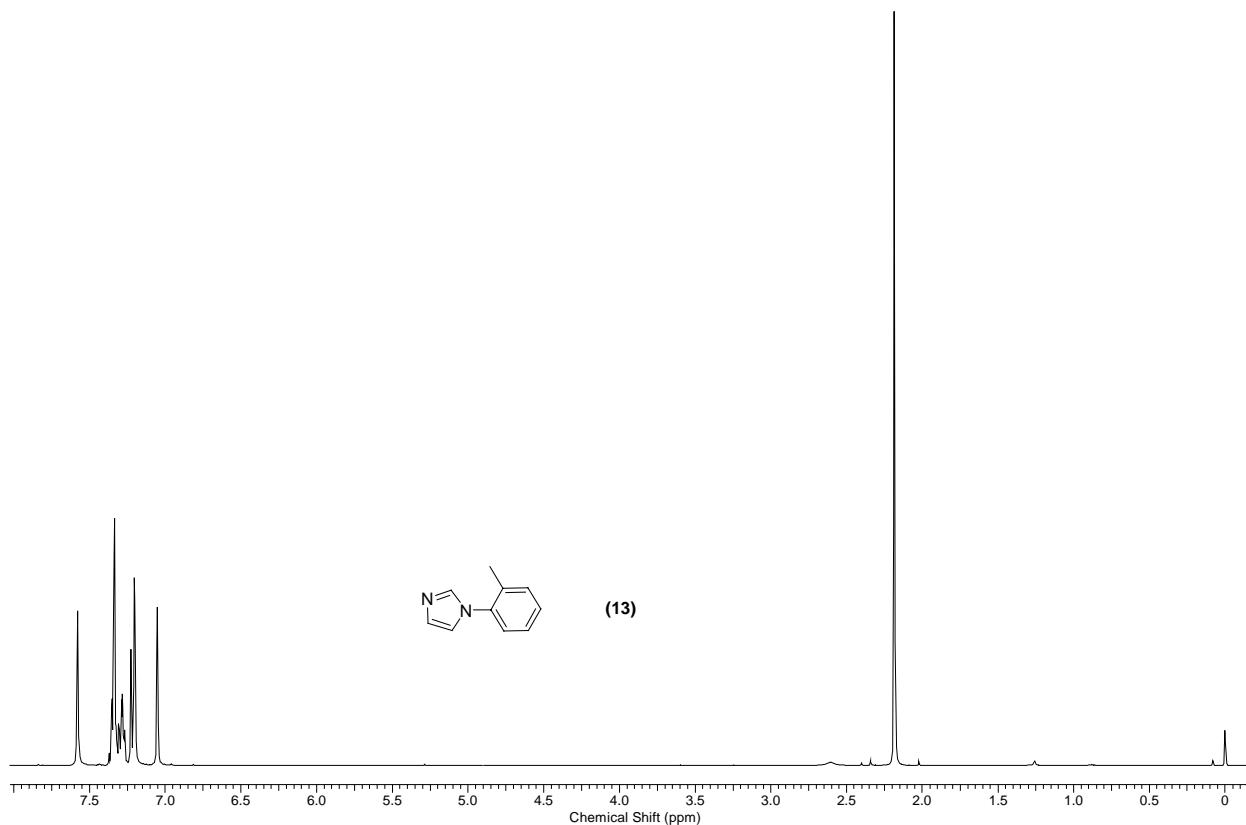


In a 10 mL high pressure-tube equipped with a stir bar and a rubber septum was added 1-bromo-2-methylbenzene (171 mg, 1.0 mmol), 1H-imidazole (204 mg, 3.0 mmol), TEAC (370 mg, 1.2 mmol), CuI (19 mg, 0.1 mmol), and **IV** (15 mg, 0.1 mmol). DMF (1.0 mL) and H₂O (0.1 mL). The atmosphere was evacuated and backfilled with argon three times, then the rubber septum was exchanged with a microwave cap and the cap was secured tightly. The resulting orange solution with small amount of precipitate was heated at 130°C (oil bath) for 16 h. The reaction mixture was cooled to room temperature and was diluted with 10% MeOH in EtOAc (15 mL) and washed with NaOH (0.5 N, 5 mL), NH₄OH (15%, 5 mL), H₂O (5 mL). The aqueous washes were extracted with CH₂Cl₂ 3x and the combined organic extracts were dried with Na₂SO₄ and concentrated to yellow oil which was purified by column chromatography (0 to 5% methanol/ dichloromethane gradient) to give 1-phenyl-2-methylbenzimidazole (103 mg, 49%).

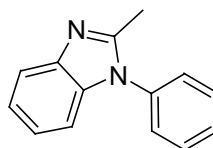
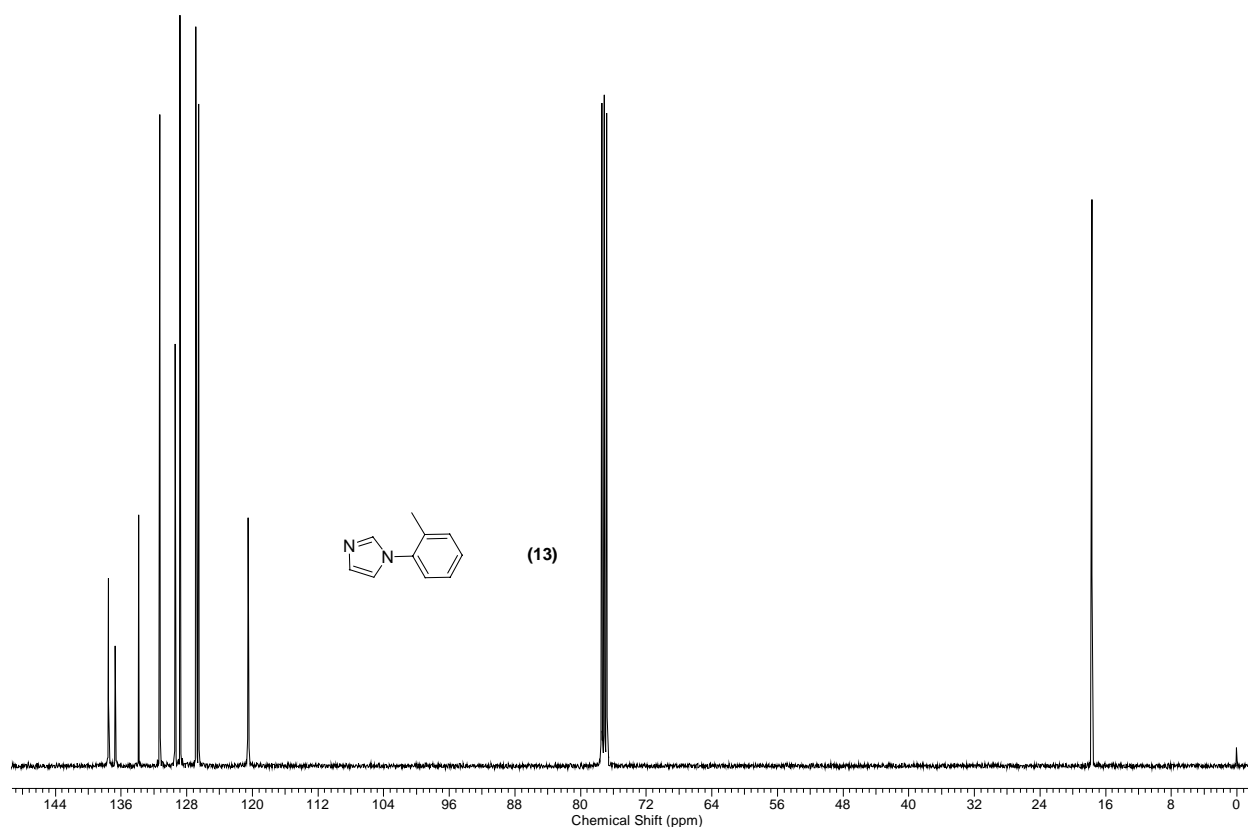
¹⁰ (a) See, reference 2b, 7a. (b) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607-5622.

^1H NMR (400 MHz, CDCl_3) δ 7.58 (1H, s), 7.35-7.33 (2H, m), 7.28 (1H, m), 7.20 (2H, m), 7.05 (1H, s), 2.18 (3H, s). ^{13}C NMR (100, CDCl_3) δ 137.53, 136.369, 133.88, 131.29, 129.41, 128.79, 126.87, 126.55, 120.49, 17.63. HRMS calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2$ (M + H): 159.0917, found: 159.0914.

Acquisition Time (sec)	5.1120	Comment	mfrohn	Date	18 Oct 2004 21:38:35
File Name	\\Scone\jcamp\mfrohn\2004\40841-92-1_10.dx	Frequency (MHz)	400.13	Nucleus	^1H
Number of Transients	16	Origin	Bruker BioSpin GmbH	Original Points Count	32768
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	6410.26
Spectrum Offset (Hz)	2400.6108	Sweep Width (Hz)	6410.06	Temperature (degree C)	25.300
				Solvent	CHLOROFORM-d



Acquisition Time (sec)	1.1600	Comment	mfrohn	Date	19 Oct 2004 05:12:56
File Name	\\Scone\camp\mfrohn\2004\40841-92-2_10.dx	Frequency (MHz)	100.62	Nucleus	13C
Number of Transients	4096	Origin	Bruker BioSpin GmbH	Original Points Count	32768
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	28248.59
Spectrum Offset (Hz)	12077.4785	Sweep Width (Hz)	28247.72	Temperature (degree C)	25.000
				Solvent	CHLOROFORM-d



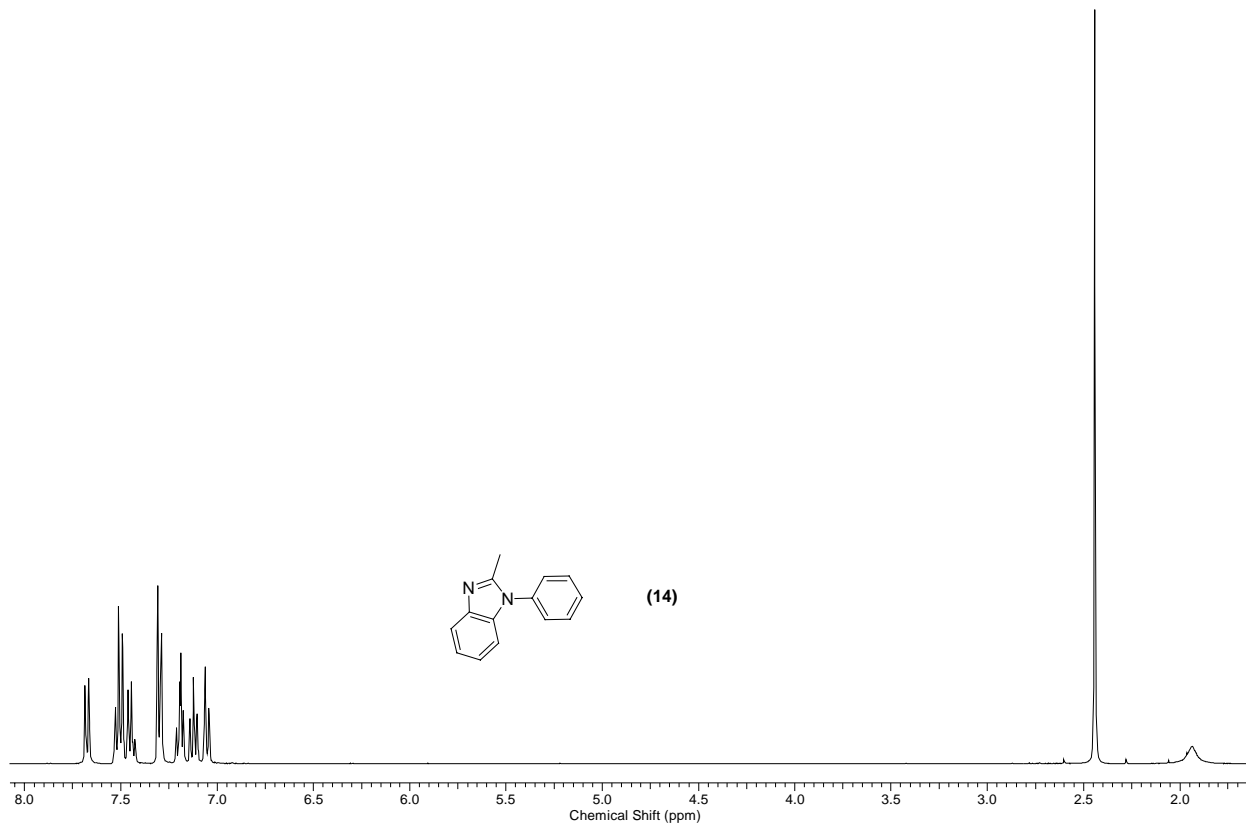
2-Methyl-1-phenyl-1H-benzimidazole (**14**)¹¹

2-Methyl-1H-benzimidazole (185 mg, 1.4 mmol), bromobenzene (157 mg, 1.0 mmol), copper (I) iodide (19 mg, 0.1 mmol), 8-hydroxyquinoline (15 mg, 0.1 mmol), tetraethylammonium carbonate (370 mg, 1.15 mmol), DMF (1 mL), and water (0.1 mL) were added to a microwave tube equipped with a stir bar and a rubber septum. The atmosphere was evacuated and backfilled with argon three times, then the rubber septum was exchanged with a microwave cap and the cap was secured tightly. The mixture was heated to 130 °C for 15 h, at which time an additional 19 mg CuI was added (*note added: additional catalyst is not necessary if the reaction system is not exposed to air*). The mixture was heated for an additional 21 h, cooled to room temperature, diluted with ethyl acetate (1 mL), and washed with water several times. The remaining organic layer was dried over MgSO₄, concentrated under vacuum, and purified by column chromatography (0 to 50% ethyl acetate/hexane gradient) to give 1-phenyl-2-methylbenzimidazole (103 mg, 49%).

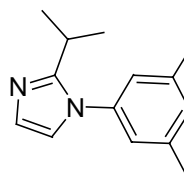
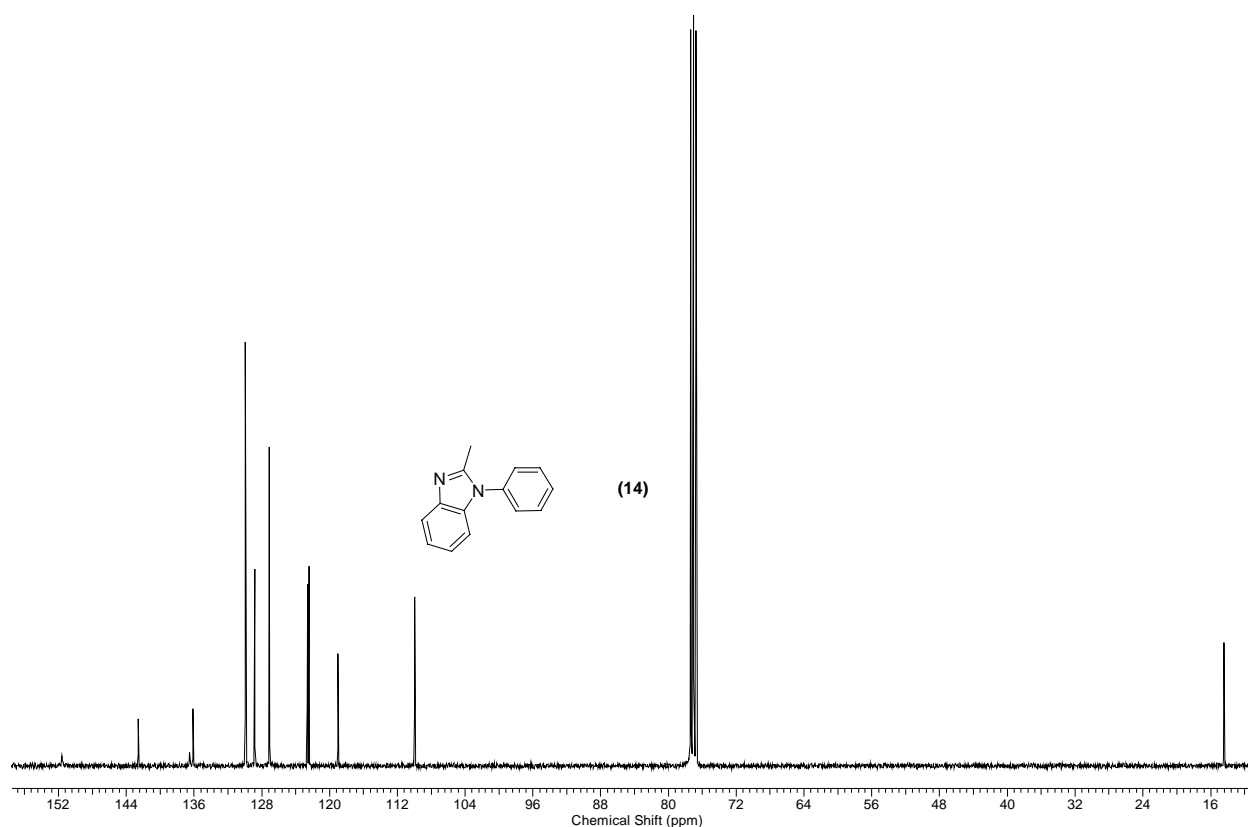
¹¹ (a) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814-6816.

^1H NMR, ^{13}C NMR match those reported in the literature. HRMS calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2$: 209.10732, found 209.10725.

Acquisition Time (sec)	5.1120	Comment	mfröhn	Date	07 Oct 2004 23:24:58		
File Name	\\Scone\camp\mfröhn\2004\40841-76-1_10.dx		Frequency (MHz)	400.13	Nucleus	^1H	
Number of Transients	16	Origin	Bruker BioSpin GmbH	Original Points Count	32768		
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	6410.26	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	2362.5583	Sweep Width (Hz)	6410.06	Temperature (degree C)	24.900		



Acquisition Time (sec)	1.1600	Comment	mfröhn	Date	09 Oct 2004 05:12:37
File Name	\\Scone\camp\mfröhn\2004\40841-76-3_10.dx	Frequency (MHz)	100.62	Nucleus	13C
Number of Transients	4096	Origin	Bruker BioSpin GmbH	Original Points Count	32768
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	28248.59
Spectrum Offset (Hz)	12076.6729	Sweep Width (Hz)	28247.73	Temperature (degree C)	25.000



1-(3,5-Dimethylphenyl)-2-isopropyl-1H-imidazole (**15**)

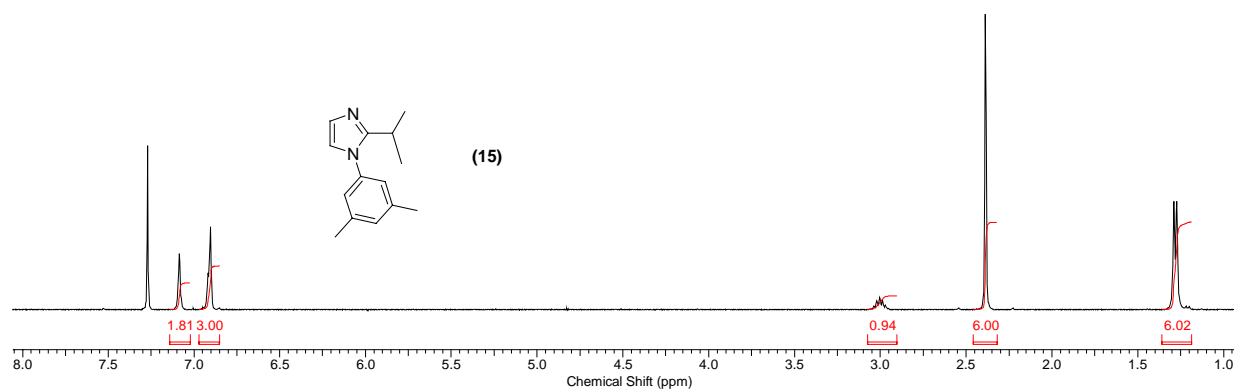
2-Isopropyl imidazole (1.4 mmol) and 5-bromo-*m*-xylene (1.0 mmol), 8-hydroxyquinoline (0.1 mmol), TEAC (2.1 mmol), and CuI (0.1 mmol) were added together in a microwave tube (copper was added last) with DMF (1.0 mL) and H₂O (0.1 mL), and the tube was evacuated and backfilled with nitrogen three times. The rubber septum was replaced with a microwave cap and the vessel was sealed and heated to 130 °C in an oil bath for 16 h. The mixture was cooled and poured into satd. NH₄Cl (3 mL) and then extracted with DCM three times. The extracts were dried over MgSO₄, concentrated under vacuum, and purified via column chromatography (50% ethyl ether/hexane as eluent) to give product as an oil that crystallized upon standing (off-white solid, 85 mg, 40% yield).

¹H NMR (400 MHz, CDCl₃): 7.01 (s, 2H), 6.84 (s, 1H), 6.83 (s, 2H), 2.93 (septet, J = 8.0 Hz, 1H), 2.31 (s, 6H), 1.20 (d, J = 8.0 Hz, 6H). ¹³C NMR (CDCl₃): 153.40, 139.23, 137.85, 129.98, 127.34, 123.92, 120.54, 25.85, 22.02, 21.21. HRMS: calcd for C₁₄H₁₉N₂ (M + H): 215.1543;

found: M+H = 215.1538. Anal. Calcd for [C₁₂H₁₄N₂ + (1/3) H₂O]: C, 76.32; H, 8.54; N, 12.72; found C, 76.11; H, 8.30; N, 12.67

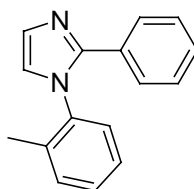
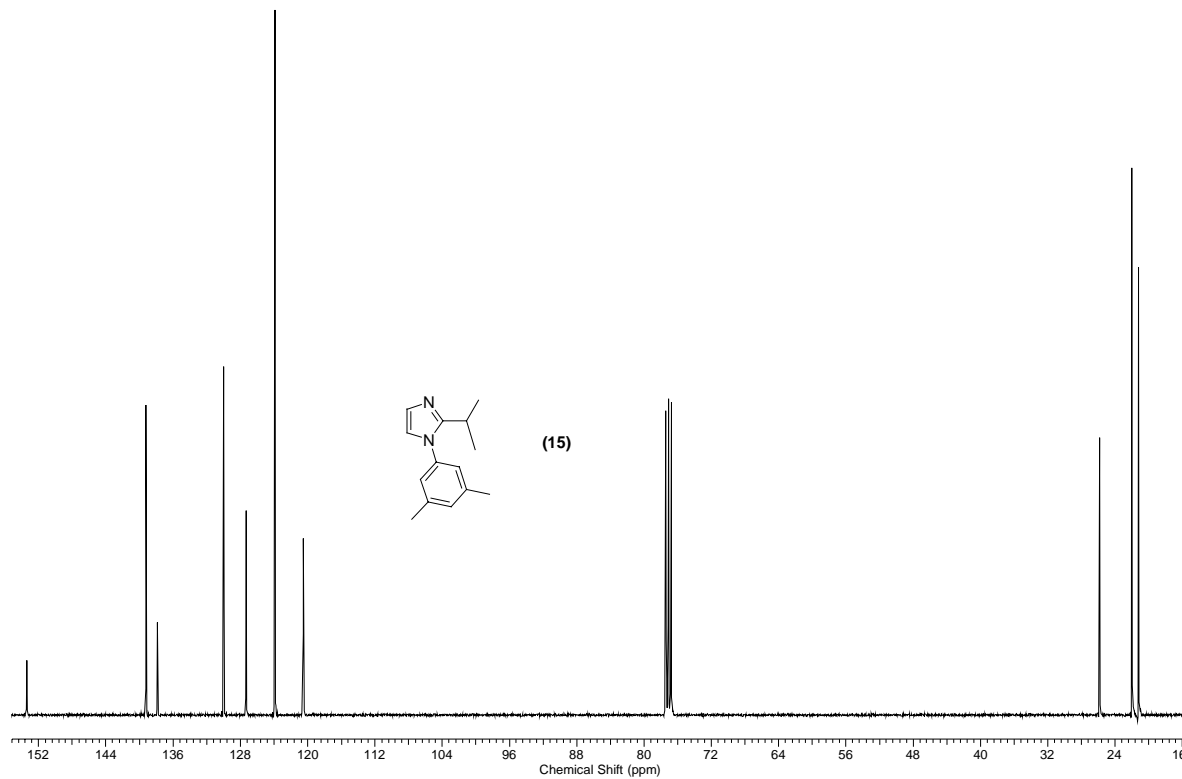
Acquisition Time (sec)	5.1120	Comment	mfrohn	Date	27 May 2005 00:35:02
File Name	\\scone\camp\mfrohn\65629-3-10_10.dx	Frequency (MHz)	400.13	Nucleus	1H
Number of Transients	32	Origin	Bruker BioSpin GmbH	Original Points Count	32768
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	6410.26
Spectrum Offset (Hz)	2395.3479	Sweep Width (Hz)	6410.06	Temperature (degree C)	25.000
		Solvent	CHLOROFORM-d		

¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.28 (d, *J*=6.85 Hz, 30 H) 2.39 (s, 30 H) 2.96 - 3.05 (m, 4 H) 6.89 - 6.94 (m, 15 H) 7.09 (s, 9 H) 7.27 (s, 12 H)



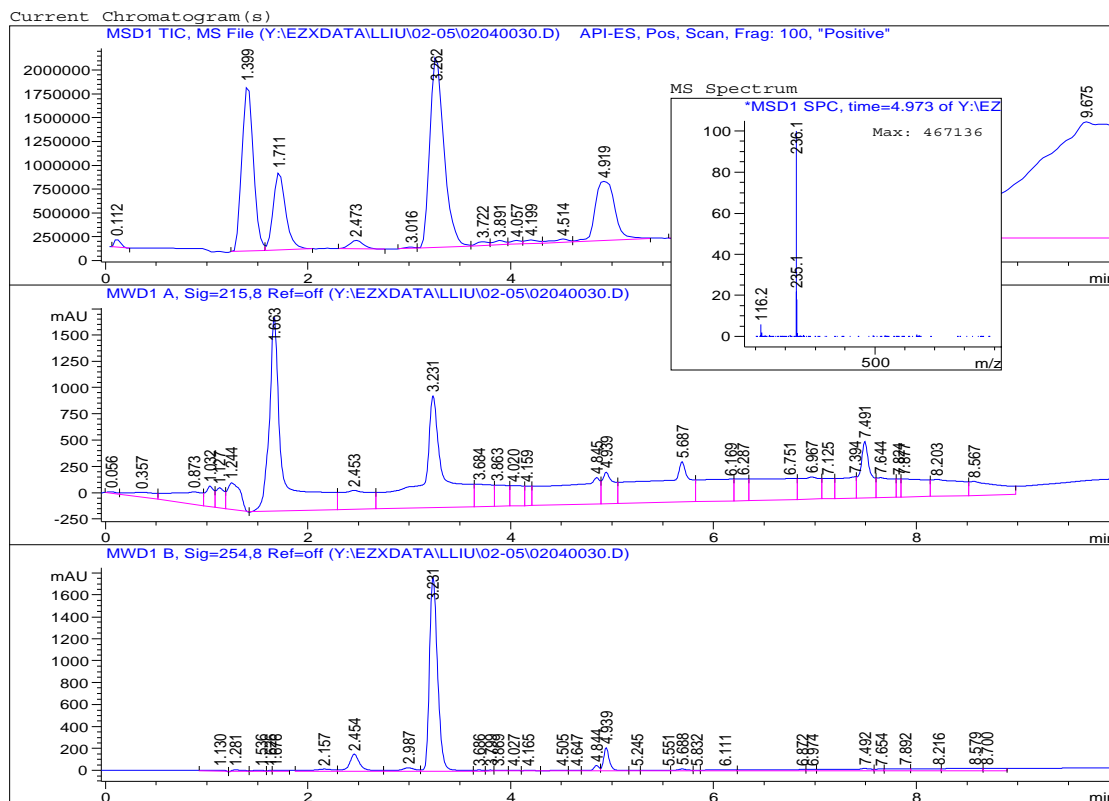
No.	(ppm)	Value	Absolute Value	Non-Negative Value	No.	Multiplet1	Shift1 (ppm)	(ppm)	J (Hz)	Type	H's
1	[1.19 .. 1.36]	6.024	1.08003e+10	6.024	1	M00	1.28	[1.21 .. 1.31]	6.85	d	30
2	[2.32 .. 2.46]	6.000	1.07571e+10	6.000	2	M01	2.39	[2.37 .. 2.41]	-	s	30
3	[2.90 .. 3.07]	0.937	1.68073e+9	0.937	3	M02	3.00	[2.96 .. 3.05]	-	m	4
4	[6.85 .. 6.97]	2.997	5.37376e+9	2.997	4	M03	6.91	[6.89 .. 6.94]	-	m	15
5	[7.02 .. 7.14]	1.809	3.24369e+9	1.809	5	M04	7.09	[7.07 .. 7.11]	-	s	9
6					6	M05	7.27	[7.26 .. 7.28]	-	s	12

Acquisition Time (sec)	1.1600	Comment	mfrohn	Date	28 May 2005 05:00:22
File Name	\\scone\camp\mfrohn\65629-3-11_10.dx	Origin	Brüker BioSpin GmbH	Frequency (MHz)	100.62
Number of Transients	4096	Points Count	32768	Original Points Count	32768
Owner	chemist	Sweep Width (Hz)	28247.73	SW(cyclical) (Hz)	28248.59
Spectrum Offset (Hz)	12076.6729	Temperature (degree C)	25.000	Solvent	CHLOROFORM-d

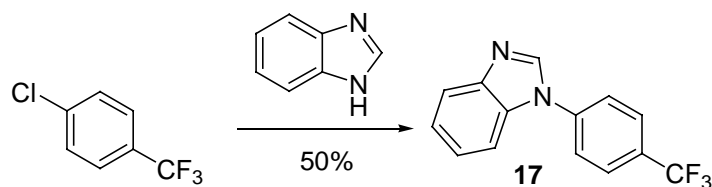


2-phenyl-1-o-tolyl-1H-imidazole (**16**)

After 60 h, LCMS of this reaction indicated the formation of the product at R_f 4.97 min with m/e 236 ($M+1$).



N-Arylimidazoles from Aryl Chlorides

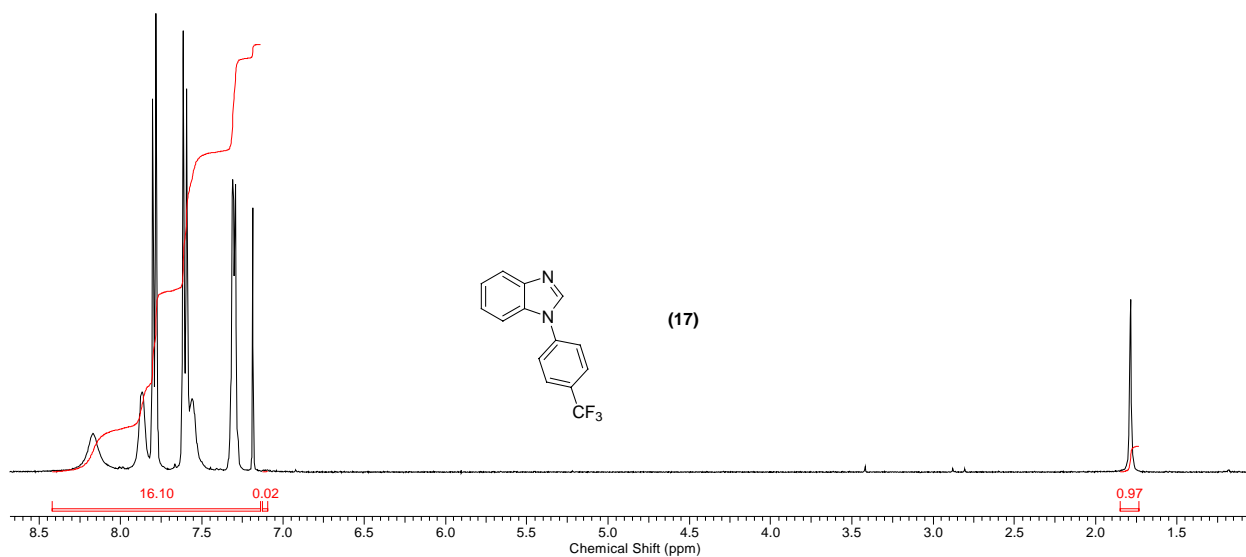


1-(4-(trifluoromethyl)phenyl)-1H-benzo[d]imidazole (**17**)

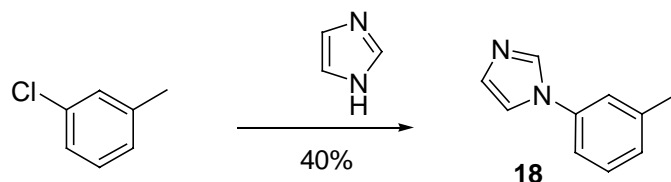
Prepared from benzimidazole (124 mg, 1.05 mmol) and 1-chloro-4-(trifluoromethyl)benzene (430 mg, 2.38 mmol) using the general procedure from Table 2. The reaction was run at 130°C for 64 h and the cooled mixture was loaded directly onto a silica column. Elution with hexane-CH₂Cl₂ (1:1), then 0-2% MeOH in CH₂Cl₂ afforded the product as a yellow solid (138 mg, 50%).

¹H NMR (400 MHz, CDCl₃) δ 8.25 (1H, s), 7.95 (1H, br), 7.87 (2H, d, J 8.5), 7.69 (2H, d, J 8.2), 7.64 (1H, br), 7.39 (2H, m). HRMS calcd for C₁₄H₁₀F₃N₂ (M + H): 263.07906, found 263.07935. Anal. Calcd for C₁₄H₉F₃N₂: C, 64.12; H, 3.46; N, 10.68; found C, 63.84; H, 3.40; N, 10.61

Acquisition Time (sec)	5.1120	Comment	liu	Date	04 Oct 2004 02:11:12
File Name	\\Scone\NMR-Archive\icamp\liu\2004\52536-9-1_10.dx	Frequency (MHz)	400.13	Nucleus	1H
Number of Transients	16	Origin	Bruker BioSpin GmbH	Original Points Count	32768
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	6410.26
Spectrum Offset (Hz)	2361.9421	Sweep Width (Hz)	6410.06	Temperature (degree C)	24.900



No.	(ppm)	Value	Absolute Value	Non-Negative Value
1	[1.73 .. 1.85]	0.966	4.24292e+9	0.966
2	[7.09 .. 7.13]	0.021	9.03507e+7	0.021
3	[7.14 .. 8.42]	16.099	7.07291e+10	16.099



2-m-Tolyl-1H-imidazole (**18**)¹²

Prepared from imidazole (102 mg, 1.49 mmol) and 1-chloro-3-methylbenzene (126 mg, 1.0 mol) using the general procedure from Table 2. The reaction was run at 130°C for 65 h (HPLC indicated ~ 59% conversion) and the cooled mixture was loaded directly onto a silica column, rinsed with 1:1 hexane-DCM to wash off DMF, then eluted with 0-3% (2N NH₃-MeOH)-8% ether in DCM. The product fraction was collected and concentrated to a yellow oil which was treated with HCl (1N, 1.5 mL, ether) and was stirred in ether (20 mL) for 20 min.

¹² (a) Lan, J.-B.; Chen, L.; Yu, X.-Q.; You, J.-S.; Xu, R.-G. *Chem. Commun.* **2004**, 188-189. (no data) (b) Shinoda, M. et al. *WO 2001025181 A1* **2001** (c) Johnson, Alexander Lawrence; Kauer, James C.; Sharma, Dinesh Chandra; Dorfman, R. I. *J. Med. Chem.* **1969**, *12*, 1024-8.

whereby a oily ppt formed. The ether layer was decanted and the residue was washed with ether 3x, and dried under high vacuum overnight. A green solid (hygroscopic!) formed. 78 mg (40% as HCl salt).

^1H NMR (400 MHz, DMSO- d_6): δ 9.74 (1H, bs), 8.31 (1H, bs), 7.95 (1H, bs), 7.68 (1H, s), 7.61 (1H, d, J 7.7), 7.52 (1H, t, J 7.6, 7.9), 7.39 (1H, d, J 7.5), 2.42 (3H, s). M/e: 159.2 (M + H). HRMS: calcd for $\text{C}_{10}\text{H}_{11}\text{N}_2$ (M+H): 159.0917; found 159.0913.

Acquisition Time (sec)	5.1120	Comment	liu	Date	01 Jun 2005 16:37:11		
File Name	\Scone\NMR-Archive\icamp\liu\65636-11-24_10.dx		Frequency (MHz)	400.13	Nucleus	^1H	
Number of Transients	16	Origin	Bruker BioSpin GmbH	Original Points Count	32768		
Owner	chemist	Points Count	32768	SW(cyclical) (Hz)	6410.26	Solvent	DMSO- d_6
Spectrum Offset (Hz)	2400.3945	Sweep Width (Hz)	6410.06	Temperature (degree C)	25.300		

