Heterocycl. Commun., Vol. 16(4-6), pp. 249–252, 2010 • Copyright © by Walter de Gruyter • Berlin • New York. DOI 10.1515/HC.2010.009

Synthesis of piperazino-substituted benzo[*b*]furans as potential CNS agents

Jeff Klenc and Lucjan Strekowski*

Department of Chemistry, Georgia State University, Atlanta, GA 30302-4098, USA

*Corresponding author
e-mail: Lucjan@gsu.edu

Abstract

The synthesis of a series of substituted benzofurans is reported. Selected compounds have been shown to bind strongly and with high selectivity to the serotonin receptor 5-HT_{2A} in the presence of the receptor 5-HT_7 *in vitro*.

Keywords: benzo[*b*]furans; central nervous system (CNS); 5-HT_{2A}; 5-HT_7; serotonin receptors; synthesis.

Introduction

The serotonin (5-HT) receptors are part of the central nervous system (CNS). These receptors are of immense interest in the drug development process. They belong to the superfamily of G-protein coupled transmembrane structures. Homology studies have indicated that the receptors consist of seven helical segments that span the lipid bilayer of cell membrane (Hartig, 1989). The detailed structures of these proteins remain unknown, which is largely attributed to crystallization problems. As these receptors are important from a therapeutic standpoint, attempts have been made to build pharmacophore or receptor models based on the structure of 5-HT ligands. Arylpiperazines and heteroarylpiperazines have been shown to be particularly effective in this regard as they offer high binding affinity (Leopoldo, 2004) and variability in design (Harden et al., 1988). Recently, we have shown that furyl-substituted compounds containing the piperazine moiety bind strongly to various subtypes of 5-HT receptors. In continuation of our work we now present the synthesis of a series of piperazino-substituted benzo[*b*]furans. Some of the synthesized new drug candidates show high affinity to the 5-HT_{2A} receptor *in vitro*. This serotonin receptor is of special interest because of its role in normal brain function (Saczewski et al., 2009).

Results and discussion

The synthetic route for the series of substituted benzofurans **4a-4e** is detailed in Scheme 1. Synthesis of **3d** has been reported previously (Baldwin et al., 2006) and the published procedure has been modified and applied to the preparation of the desired compounds **3a-e**. This chemistry begins with nucleophilic substitution of 2-bromo-1,1-diethoxyethane with bromophenols **1a-e**. A subsequent ring closure of the resultant intermediate products **2a-e** in chlorobenzene under acidic conditions provided benzo[*b*]furans **3a-e**. Compounds **3a-e** were then coupled with *N*-methylpiperazine using the catalysts as shown (Wolfe and Buchwald, 2002). Compounds **4a-e** were obtained in moderate yields and purified by silica gel chromatography. Analytically pure products **4a-e** gave satisfactory results of elemental analysis and their ^{1}H-NMR spectra were fully compatible with the given structures. Derivatives **4b** and **4e** were additionally characterized by ^{13}C-NMR spectroscopy.

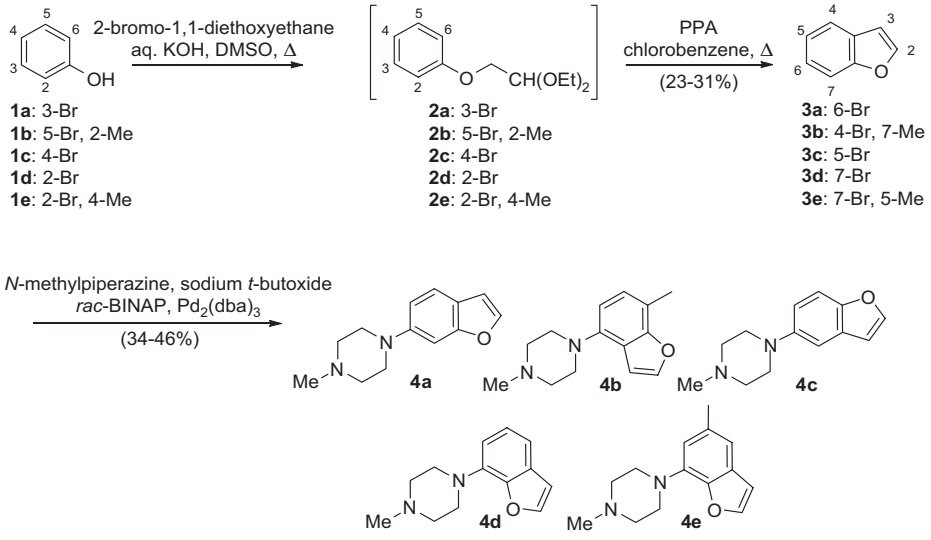
Compounds **6a** and **6b** (Scheme 2) are analogs of a simple *N*-methylpiperazine derivative **4e**. By modifying the piperazino group, additional binding interactions with the 5-HT receptors may be available, as suggested by experimental (Raubo et al., 2006; Leopoldo et al., 2008) and computational results (Kolaczkowski et al., 2006). Specifically, the substituents at the piperazine of **6a** and **6b** have been studied previously by using different compounds that showed an increased biological activity in comparison to simple *N*-methyl derivatives.

The synthesis of the compounds **6a,b** involved the Buchwald-Hartwig coupling of compound **3e** with *tert*-butylcarbonyl (BOC) protected piperazine, followed by removal of the BOC protecting group in the resultant intermediate product **4f** to give compound **5**. Final alkylation of **5** furnished the desired products **6a,b**.

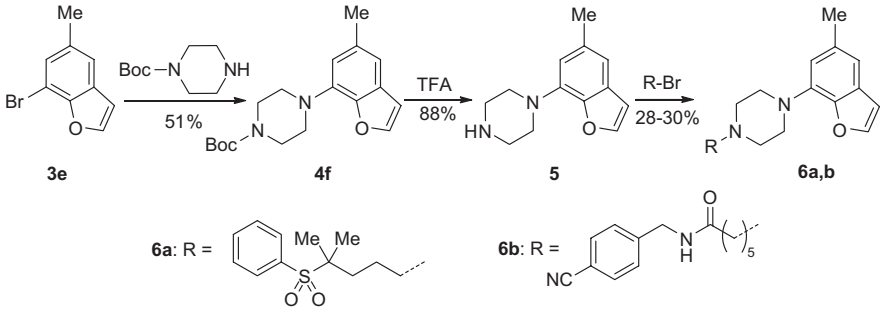
The affinities of selected compounds **4a-d** to 5-HT_{2A} and 5-HT_7 receptors were determined by using a radiolabeled ligand with known affinity (Thomas et al., 1998). As can be seen from Table 1, compounds **4b** and **4c** show a remarkable selectivity towards binding with the 5-HT_{2A} receptor. The selectivity and the absolute affinity are greatly affected by the structure of these simple derivatives. The biological studies with compounds **6a,b** are in progress. It should be noted that the activity of simple benzo[*b*]furans as CNS agents is reported here for the first time.

Experimental

All reagents were purchased from Aldrich Chemical Company or prepared according to the procedures outlined below. Reactions were monitored by TLC (EMD Chemicals, Silica Gel 60 F254) or GC-MS (Shimadzu GC-17A, QP-5000 MS). Preparative chromatographic separations were performed on a chromatotron (Harrison Research, Model 7924T). Solid samples were subjected to melting point analysis



Scheme 1 Synthesis of compounds **4a-e**.



Scheme 2 Synthesis of compounds **6a,b**.

Table 1 Biological activities (K_i, instability constants) *in vitro* of the selected agents **4a-d**.

Compound	K_i (nM) at 5-HT_{2A}	K_i (nM) at 5-HT_7
4a	Not tested	3631
4b	35	2291
4c	83	4677
4d	145	204

(Barnestead International, Mel-Temp 1201D). Elemental analyses were conducted on a Perkin Elmer 2400 Series II instrument. Unless stated otherwise, NMR spectra were recorded in $CDCl_3$ at room temperature using a Bruker Avance spectrometer at 400 MHz (^{1}H-NMR) and 100 MHz (^{13}C-NMR). Compounds were biologically evaluated *in vitro* as reported previously (Thomas et al., 1998) through collaboration with Dr. A. Bojarski of the Institute of Pharmacology, Polish Academy of Sciences.

General procedure for the synthesis of benzo[*b*]furans 3a-e

Benzofurans **3a-e** were synthesized by using the following modification of the published procedure (Baldwin et al., 2006). Briefly, the solution of potassium hydroxide (0.7 g, 10 mmol) in water (4 ml) was stirred during the sequential addition of DMSO (20 ml), the appropriate bromophenol **1a-e** (8.6 mmol), and 2-bromo-1,1-diethoxyethane (1.4 ml, 9.3 mmol). After complete addition, the mixture was heated under reflux for 1 day. After cooling, the mixture was extracted with diethyl ether (3×10 ml), and the extract was washed with water (20 ml) and 5% aqueous solution of sodium hydroxide (20 ml) and then dried over $MgSO_4$, filtered, and concentrated to yield **2a-e** as a colorless oil. A solution of polyphosphoric acid (20 g) in chlorobenzene (50 ml) was heated to reflux before the dropwise addition of **2a-e** (33 mmol). The solution was heated at reflux for 24 h resulting in a black mixture containing a large amount of tar. The solvent was decanted from the remaining solid, and the tar was washed with diethyl ether (2×20 ml). The combined organic solutions were washed with aqueous sodium hydroxide (5%, 100 ml), dried over magnesium sulfate and concentrated before purification by chromatography eluting with hexanes.

6-Bromobenzo[*b*]furan (3a) Crude compound was used in the subsequent step without characterization.

4-Bromo-7-methylbenzo[*b*]furan (3b) This compound was obtained in 23% yield as a white solid; mp 34°C; ^{1}H-NMR: δ 7.64 (d, *J*=2.0 Hz, 1H), 7.26–7.28 (d, *J*=7.8 Hz, 1H), 6.94–6.96 (d, *J*=7.8 Hz, 1H), 6.78 (d, *J*=2.0 Hz, 1H), 2.47 (s, 3H). ^{13}C-NMR: δ 153.8, 145.1, 128.2, 126.1, 125.7, 121.0, 111.1, 107.0, 14.8.

5-Bromobenzo[*b*]furan (3c) This compound was obtained in 28% yield as a colorless oil. Characterization agrees with that previously reported (van Otterlo et al., 2005).

7-Bromobenzo[*b*]furan (3d) This compound was obtained in 31% yield as a colorless oil. ^{1}H-NMR δ 7.69 (m, 1H), 7.55 (m, 1H), 7.48 (m, 1H), 7.13 (m, 1H), 6.85 (m, 1H).

7-Bromo-5-methylbenzo[*b*]furan (3e) This compound was obtained in 25% yield as a clear oil. ^{1}H-NMR: δ 7.64 (s, 1H), 7.31 (s, 1H), 7.29 (s, 1H), 6.75 (s, 1H), 2.42 (s, 3H). ^{13}C-NMR: δ 150.5, 145.7, 134.0, 128.7, 128.4, 120.3, 107.1, 103.5, 21.0.

General procedure for the synthesis of arylpiperazine hydrobromides 4a-f

Compounds **3a-e** were allowed to react with commercially available piperazines under Buchwald-Hartwig conditions (Wolfe and Buchwald, 2002). A mixture of the appropriate halide (**3a-e**, 1.0 mmol), 4-substituted piperazine (1.2 mmol), sodium *tert*-butoxide (2.0 mmol), tris(dibenzylideneacetone)dipalladium (0.01 mmol), and racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.01 mmol) in toluene (5 ml) was heated under reflux for 12 h before quenching with water. The products were then extracted into diethyl ether (3×20 ml), and the extract was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography using a mobile phase of dichloromethane/methanol (10:1). The purified compound was then dissolved in diethyl ether/methanol (3 ml, 10:1) before the addition of hydrobromic acid (0.2 ml, 48%). The treatment of the mixture with diethyl ether caused crystallization of the hydrobromide salt.

6-(*N*-Methylpiperazino)benzo[*b*]furan hydrobromide (4a) After workup as described above, an additional purification of **4a** required three-fold crystallization from methanol/ether in the presence of a small amount (one drop) of hydrobromic acid. A high-yield recovery of the product was achieved by treatment of the mixture with an additional amount of ether. Compound **4a** precipitated as a white solid and was obtained in an overall yield of 38%; mp 206–207ºC; ^{1}H-NMR (400 MHz, DMSO): δ 9.6 (broad s, 1H), 7.84 (d, *J*=2.0 Hz, 1H), 7.52 (d, *J*=8.5 Hz, 1H), 7.22 (s, 1H), 7.02 (dd, *J*=2.0 Hz, 8.5 Hz, 1H), 6.83 (d, *J*=1.4 Hz, 1H), 3.4–3.6 (m, 2H), 3.8–4.0 (m, 2H), 3.1–3.3 (m, 2H), 2.9–3.1 (m, 2H), 2.87 (s, 3H). *Anal.* Calculated (Calcd) $C_{13}H_{16}N_2O$•HBr: C, 52.54; H, 5.77; N, 9.43. Found: C, 53.07; H, 5.92; N, 9.71.

7-Methyl-4-(*N*-methylpiperazino)benzo[*b*]furan dihydrobromide (4b) The free base was obtained in 38% yield as a white crystalline solid; mp 62–64°C; ^{1}H NMR for the free base: δ 7.58 (d, *J*=2.0 Hz, 1H), 6.99–7.01 (d, *J*=7.8 Hz, 1H), 6.77 (d, *J*=2.0 Hz, 1H), 6.62–6.64 (d, *J*=7.8 Hz, 1H), 3.19–3.22 (m, 4H), 2.64–2.67 (m, 4H), 2.46 (s, 3H), 2.39 (s, 3H);^{13}C-NMR for the free base: δ 154.9, 144.3, 143.3, 125.3, 119.9, 115.7, 109.8, 105.5, 55.4, 51.4, 46.2, 14.6. *High resolution ms* (ESI, positive ion mode): calcd for $C_{14}H_{18}N_2O$, (M^++H), *m/z* 231.1497; found *m/z* 231.1490. A hydrobromide salt: mp 263–265°C. *Anal.* Calcd for $C_{14}H_{18}N_2O$•2 HBr: C, 42.88; H, 5.14; N, 7.14. Found: C, 42.76; H, 5.20; N, 7.14.

5-(*N*-Methylpiperazino)benzo[*b*]furan hydrobromide (4c) The free base was obtained as an oil in 34% yield. ^{1}H NMR for the free base: δ 7.56 (s, 1H), 7.39 (d, *J*=9.0 Hz, 1H), 7.11 (s, 1H), 7.00 (d, *J*=9.0 Hz, 1H), 6.68 (s, 1H), 3.19 (m, 4H), 2.64 (m, 4H), 2.38 (s, 3H). A hydrobromide salt. *Anal.* Calcd for $C_{13}H_{16}N_2O$•HBr•½ H_2O: C, 50.99; H, 5.93; N, 9.15. Found: C, 51.19; H, 5.93; N, 9.32.

7-(*N*-Methylpiperazino)benzo[*b*]furan dihydrobromide (4d) The free base was obtained in 39% yield and characterization matched that previously reported (van Steen et al., 1993). ^{1}H NMR for the free base: δ, 7.60 (s, 1H), 7.12–7.22 (m, 2H), 6.74–6.79 (m, 2H), 3.38 (m, 4H), 2.68 (m, 4H), 2.39 (s, 3H). *High resolution ms* (ESI, positive ion mode): calcd for $C_{13}H_{16}N_2O$, (M^++1), *m/z* 231.1497; found *m/z* 231.1490. A hydrobromide salt: mp 242–244°C. *Anal.* Calcd for $C_{13}H_{16}N_2O$•2 HBr•H_2O: C, 39.42; H, 5.09; N, 7.07. Found: C, 39.62; H, 5.21; N, 6.79.

5-Methyl-7-(*N*-methylpiperazino)benzo*[b]*furan hydrobromide (4e) The free base was obtained in 46% yield as a colorless oil. ^{1}H NMR: δ 7.58 (d, 1H, *J*=2.0 Hz), 6.99–7.01 (d, 1H, *J*=7.8 Hz), 6.62–6.64 (d, 1H, *J*=7.8 Hz), 6.77 (d, 1H, *J*=2.0 Hz), 3.19–3.22 (m, 4H), 2.64–2.67 (m, 4H), 2.46 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR; δ 154. 9, 144.3, 143.3, 125.3, 119.9, 115.7, 109.8, 105.5, 55.4, 514, 46.2, 14.6. *High resolution ms* (ESI, positive ion mode): calcd for $C_{13}H_{16}N_2O$, (M^++1), *m/z* 231.1497; found *m/z* 231.1490. A hydrobromide salt: mp 212–213°C (dec.). *Anal.* Calcd for $C_{14}H_{18}N_2O$•2 HBr: C, 42.88; H, 5.14; N, 7.14. Found: C, 42.76; H, 5.20; N, 7.14.

***tert*-Butyl 4-(5-methyl-7-benzo[*b*]furanyl)piperazino-1-carboxylate (4f)** The free base was obtained in 51% yield as an amorphous glass. ^{1}H-NMR: δ 7.56 (d, 1H, *J*=1.6 Hz), 7.01 (s, 1H), 6.67 (d,1H, *J*=1.6 Hz), 6.57 (s, 1H), 3.66 (m, 4H) 3.26 (m, 4H), 2.40 (s, 3H), 1.50 (s, 9H). ^{13}C NMR: δ 154.7, 145.3, 144.1, 136.7, 133.0, 128.7, 114.3, 112.8, 106.7, 79.8, 49.8, 43.5, 28.4, 21.6.

5-Methyl-(7-piperazino)benzo[*b*]furan (5) To a solution of **4f** (1.3 g, 4.1 mmol) in dichloromethane (5 ml) was added trifluoroacetic acid (2.0 ml). The mixture was stirred for several hours until the starting material was no longer detected by TLC. Purification by chromatography (dichloromethane:methanol, 10:1) gave **5** (0.78 g, 3.6 mmol, 88%) as an amorphous yellow glass. ^{1}H-NMR: δ 7.57 (d, 1H), 7.07 (s, 1H), 6.69 (d, 1H, *J*=2.0 Hz), 6.58 (s, 1H), 3.57 (m, 4H), 3.43 (m, 4H), 2.41 (s, 3H).

General procedure for the synthesis of compounds 6a,b

The bromides needed for the synthesis of **6a,b** were synthesized according to the literature (Raubo et al., 2006; Leopoldo et al., 2008). The appropriate bromide (0.25 mmol) in acetonitrile (5 ml) was treated with **5** (0.25 mmol) and K_2CO_3 (0.50 mmol). After heating at reflux for 12 h, purification by chromatography (dichloromethane:methanol, 10:1) yielded **6a,b**.

1-[4-(Benzenesulfonyl)-4-methylpentyl]-4-(5-methyl-7-benzo[*b*]furanyl)piperazine (6a) The free base was obtained in 30% yield as a light yellow oil; ^{1}H NMR: δ 7.89 (d, *J*=7.4 Hz, 2H), 7.66 (t, *J*=7.4 Hz, 1H), 7.56 (m, 3H), 6.99 (m, 1H), 6.66 (m, 1H), 6.56 (m, 1H), 3.33 (m, 4H), 2.68 (m, 4H), 2.41 (m, 5H), 1.76 (m, 2H), 1.64 (m, 2H), 1.32 (s, 6H); ^{13}C-NMR: δ 145.3, 144.0, 136.9, 135.6, 133.5, 133.0, 130.6, 128.7, 128.6, 113.9, 112.6, 106.6, 62.9, 58.7, 53.4, 49.8, 32.8, 21.7, 21.5, 20.9; $C_{25}H_{32}N_2O_3S$.

***N*-(4-Cyanobenzyl)-6-(4-(5-methyl-7-benzo[*b*]furanyl)piperazine-1)-hexanamide (6b)** The free base was obtained as an oil in 28% yield; ^{1}H NMR: δ 7.60 (d, *J*=7.8 Hz, 2H), 7.56 (s, 1H), 7.38 (d, *J*=7.8 Hz, 2H), 7.00 (s, 1H), 6.67 (m, 1H), 6.56 (m, 1H), 6.16 (broad s, 1H), 4.49 (d, *J*=5.8 Hz, 2H), 3.38 (m, 4H), 2.75 (m, 4H), 2.49 (t, *J*=7.6 Hz), 2.40 (s, 3H), 2.28 (t, *J*=7.4 Hz), 1.72 (m, 2H), 1.62 (m, 2H), 1.40 (m, 2H); ^{13}C NMR: δ 173.1, 145.2, 144.1 (2 signals), 136.6, 133.1, 132.4, 128.6, 128.2, 118.7, 114.1, 112.6, 111.2, 106.7, 58.3, 53.2, 49.4, 43.0, 36.3, 26.9, 26.1, 25.4, 21.7. *High resolution ms:* (ESI, positive ion mode): calcd for $C_{27}H_{32}N_4O_2$, (M^++1), *m/z* 445.2604; found *m/z* 445.2591.

Acknowledgments

The stipend for Jeff Klenc was provided by Molecular Basis of Disease Area of Focus at Georgia State University. We thank Dr. A. Bojarski for conducting the biological assays.

References

Baldwin, J. J.; Claremon, D. A.; Tice, C.; Cacatian, S.; Dillard, L. W.; Ishchenko, A. V.; Yuan, J.; Xu, Z.; McGeehan, G.; Zhao,W.; et al. Preparation of diaminoalkanes, particularly *N*-(1-aminopropan-2-yl)piperidine-1-carboxamides, as aspartic protease inhibitors. WO-2005US36230 application, **2006**.

Harden, D. B.; Mokrosz, M. J.; Strekowski, L. Addition and substitution reactions of chloropyrimidines with lithium reagents. *J. Org. Chem.* **1988**, *53*, 4137–4140.

Hartig, P. R. Molecular biology of 5-HT receptors. *Trends Pharmacol. Sci*. **1989**, *10*, 64–69.

Kolaczkowski, M.; Nowak, M.; Pawlowski, M.; Bojarski, A. J. Receptor-based pharmacophores for serotonin 5-HT_7 receptor antagonists – implications to selectivity. *J. Med. Chem.* **2006**, *49,* 6732–6741.

Leopoldo, M. Serotonin$_7$ receptors (5-HT_7Rs) and their ligands. *Curr. Med. Chem.* **2004**, *11,* 629–661.

Leopoldo, M.; Lacivita, E.; De Giorgio, P.; Fracasso, C.; Guzzetti, S.; Caccia, S.; Contino, M.; Colabufo, N. A.; Berardi, F.; Perrone, R. Structural modifications of *N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)-4-aryl-1-piperazinehexanamides: influence on lipophilicity and 5-HT_7 receptor activity. Part III. *J. Med. Chem*. **2008**, *51*, 5813–5822.

Raubo, P.; Beer, M. S.; Hunt, P.; Huscroft, I. T.; London, C.; Stanton, J. A.; Kulagowski, J. J. Aminoalkyl phenyl sulfones – a novel series of 5-HT7 receptor ligands. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 1255–1258.

Saczewski, J.; Paluchowska, A.; Klenc, J.; Raux, E.; Barnes, S.; Sullivan, S.; Duszynska, B.; Bojarski, A. J.; Strekowski, L. Synthesis of 4-substituted 2-(4-methylpiperazino)pyrimidines and quinazoline analogs as serotonin 5-HT_{2A} receptor ligands. *J. Heterocycl. Chem*. **2009**, *46*, 1259–1265.

Thomas, D. R.; Gittins, S. A.; Collin, L. L.; Middlemiss, D. N.; Riley, G.; Hagan, J.; Gloger, I.; Ellis, C. E.; Forbes, I. T.; Brown, A. M. Functional characterization of the human cloned 5-HT_7 receptor (long form); antagonist profile of SB-258719. *Br. J. Pharmacol.* **1998**, *124,* 1300–1306.

van Otterlo, W. A. L.; Morgans, G. L.; Madeley, L. G.; Kuzvidza, S.; Moleele, S. S.; Thornton, N.; de Koning, C. B. An isomerization-ring-closing metathesis strategy for the synthesis of substituted benzofurans. *Tetrahedron* **2005**, *61*, 7746–7755.

van Steen, B.; Wijngaarden, I.; Tulp, M.; Soudijn, W. Structure-affinity relationship studies on 5-HT_{1A} receptor ligands. 1. Heterobicyclic phenylpiperazines with N^4-alkyl substituents. *J. Med. Chem.* **1993**, *36*, 2751–2760.

Wolfe, J. P.; Buchwald, S. L. Palladium-catalyzed amination of aryl halides and aryl triflates: *N*-hexyl-2-methyl-4-methoxyaniline and *N*-methyl-*N*-(4-chlorophenyl)aniline. *Org. Synth.* **2002**, *78*, 23–30.