Synthesis of Mexiletine Stereoisomers and Related Compounds via S_NAr Nucleophilic Substitution of a $Cr(CO)_3$-Complexed Aromatic Fluoride

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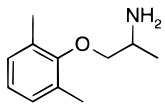
As part of a program aimed at discovering new sodium channel blockers, we required authentic samples of the enantiomers of the class I-B antiarrhythmic agent mexiletine (**1**).[1] Both enantiomers of mexiletine have previously been prepared via classical resolution[2,3] and via enzymatic hydrolysis of an *N*-acyl derivative.[4] Recently, the (*R*)-isomer of mexiletine was prepared in 7.2% overall yield using a stereospecific, four-step procedure which established that this isomer is levorotatory.[3] We report here a short, unambiguous synthesis of both isomers of mexiletine. We also report that the procedures used to prepare the stereoisomers of mexiletine can serve as a general and efficient route to related aryl aminoalkyl ethers.



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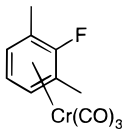

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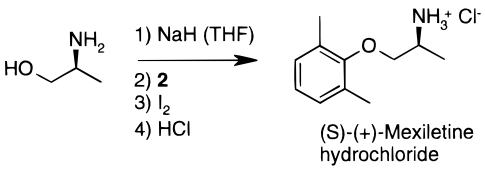
Chromium tricarbonyl complexes of aryl halides have long been known to undergo facile nucleophilic aromatic substitution with simple, monofunctional alkoxides.[5] More recently Davies and Hume reported that sodium salts of (1*R*,2*S*)-ephedrine and (1*S*,2*S*)-pseudoephedrine displace fluoride from the chromium tricarbonyl complexes of fluorobenzene or *p*-fluoroanisole to give aryl ether chromium tricarbonyl complexes; these intermediates were employed without isolation in a novel variation of the Smiles rearrangement to afford complexed aniline derivatives.[6] We have found that a variety of primary and secondary alkoxides bearing unprotected primary, secondary, or tertiary amino functionality smoothly displace fluoride from the sterically congested 1,3-dimethyl-2-fluorobenzenetricarbonylchromium complex, **2**,[7] to afford a corresponding 2,6-dimethylphenyl ether complex as the sole detectable product. Oxidative decomposition of the chromium−arene complexes followed by treatment of the free base products with HCl gave crystalline hydrochloride salt derivatives of novel mexiletine analogues in 28−66% overall yield. Thus a simple, one-pot synthesis of each isomer of **1** was planned which would make use of the aryl chromium tricarbonyl complex **2** and the commercially available enantiomers of 2-amino-1-propanol. As shown in eq 1, the sodium alkoxide derived from (*S*)-(+)-2-amino-1-propanol was treated with aryl chromium tricarbonyl complex **2**. Iodine-induced decomposition of the product chromium complex,[8] followed by chromatography, provided (*S*)-mexiletine, isolated as its hydrochloride salt. A similar sequence, using (*R*)-(−)-2-amino-1-propanol provided (*R*)-mexiletine hydrochloride. The enantiomeric purities of these materials were determined by chiral HPLC analysis to be 99% ee or greater. Specific rotations observed for the hydrochloride salts were consistent with previously reported stereochemical assignments.



(1)

The S_NAr coupling procedure used to prepare the mexiletine stereoisomers was used as a general route to several related aryl aminoalkyl ethers;[9] the structures and yields of these products are presented in Figure 1.

In summary, a novel and practical stereospecific synthesis of both enantiomers of mexiletine has been achieved. It has also been demonstrated that the coupling procedure described herein may serve as an attractive route to a variety of aryl aminoalkyl ethers.

Experimental Section

General Procedures. Melting points are uncorrected. Amino alcohols were obtained from Aldrich and were used without purification. Yields reported are relative to chromium complex **2**. NMR spectra were obtained in DMSO-d_6 (unless otherwise specified) at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Chiral HPLC analysis of mexiletine stereoisomers was performed using a Chiralcel OD-H column eluted at a flow rate of 0.8 mL/min with 97:3:0.1 hexane/2-propanol/diethylamine.

(*S*)-(+)-Mexiletine Hydrochloride. To a solution of 226 mg (3.01 mmol) of (*S*)-(+)-2-amino-1-propanol in 7 mL of THF at

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(2) Turgeon, J.; Uprichard, A. C. G.; Belanger, P. M.; Harron, D. W. G.; Grech-Belanger, O. *J. Pharm. Pharmacol.* **1991**, *43*, 630−635.

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(5) (a) Nicholls, B.; Whiting, M. C. *J. Chem. Soc.* **1959**, 551−556. (b) Brown, D. A.; Raju, J. R. *J. Chem. Soc. A* **1966**, 40−43. (c) Knipe, A. C.; McGuinness, S. J.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1979**, 842−843. (d) Mahaffy, C. A. L.; Paulson, P. L. *J. Chem. Res., Synop.* **1979**, 128. (e) For a recent example, see: Semmelhack, M. F.; Hilt, G.; Colley, J. H. *Tetrahedron Lett.* **1998**, *39*, 7683−7686.

(6) Davies, S. G.; Hume, W. E. *Tetrahedron Lett.* **1995**, *36*, 2673−2674.

(7) Mahaffy, C. A. L.; Hamilton, J. *Synth. React. Inorg. Met.-Org. Chem.* **1986**, *16*, 137−143.

(8) Semmelhack, M. F.; Hall, H. T. *J. Am. Chem. Soc.* **1974**, *96*, 7091−7092.

(9) Compounds **3** and **5** have been previously reported in the abstracts from the 1st Italian−Swiss Meeting on Medicinal Chemistry; however, we were unable to discover any reference to the physical characterization or method of synthesis of these substances. Franchini, C.; Catalano, A.; Corbo, F.; Duranti, A.; Lentini, G.; Tortorella, V. Poster A16 (compound **3**) and Duranti, A.; Catalano, A.; Franchini, C.; Lentini, G.; DeLuca, A.; Natuzzi, F. Poster A14 (compound **5**), 1st Italian−Swiss Meeting on Medicinal Chemistry, Turin, Italy, September 23−26, 1997.

(10) Aberg, G. A. K.; Af Ekenstam, B. T. U.S. Patent 4822778 A, 1989.

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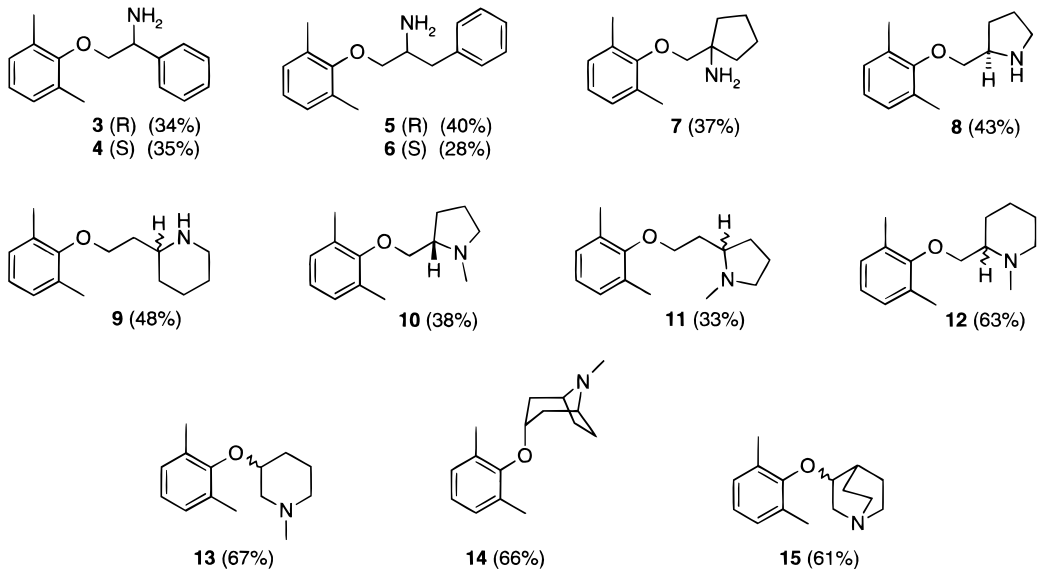

Figure 1. Yields of isolated hydrochloride salts are presented in parentheses.

room temperature was added 122 mg (3.05 mmol) of a 60% dispersion of NaH in mineral oil. After 0.5 h, 1,3-dimethyl-2-fluorobenzenetricarbonylchromium[7] (394 mg, 1.52 mmol) was added and the reaction mixture was allowed to stir at room temperature overnight. Iodine (1.50 g, 5.9 mmol) was then cautiously added. After an additional 2 h of stirring, the mixture was diluted with EtOAc and washed with 5% aqueous $NaHSO_3$. The aqueous phase was made alkaline with aqueous NaOH before the phases were separated. The aqueous phase was washed with Et_2O, and the combined organics were washed with brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed using a 150 mL sintered glass funnel filled with 230−400 mesh SiO_2 and eluting with 2:98, 5:95, and 10:90 $MeOH/CH_2Cl_2$ to provide 186 mg (68%) of an oil. A solution of this material in 15 mL of Et_2O was made acidic with 1 M HCl in Et_2O, and the precipitate was collected and recrystallized from $EtOH/Et_2O$ to give 136 mg (41%) of the title compound as a white solid, mp 202.1−202.7 °C. The enantiomeric purity of this material was determined to be 99% ee using chiral HPLC, t_R 18.2 min: ^{1}H NMR δ 1.36 (d, J = 6.6 Hz, 3H), 2.26 (s, 6H), 3.52−3.64 (m, 1H), 3.76−3.86 (m, 2H), 6.94 (dd, J = 8.6, 6.4 Hz, 1H), 7.03 (d, J = 7.4 Hz, 2H), 8.37 (br s, 3H); ^{13}C NMR δ 16.6, 17.6, 48.4, 73.3, 125.8, 130.4, 132.0, 155.9; MS m/z (%) 179 (M^+, 10), 58 (100); $[\alpha]_D$ = +2.6° (*c* 1.00, MeOH, lit.[3] +2.20°). Anal. Calcd for $C_{11}H_{18}ClNO$: C, 61.25; H, 8.41; N, 6.49. Found: C, 60.99; H, 8.38; N, 6.49.

(*R*)-(−)-Mexiletine Hydrochloride. The procedure described above, applied to (*R*)-(−)-2-amino-1-propanol, provided the title compound in 32% yield, mp 202.8−203.6 °C, >99% ee by chiral HPLC (t_R 17.1 min); $[\alpha]_D$ = − 2.9° (*c* 1.00, MeOH, lit.[3] −2.18°). Anal. Calcd for $C_{11}H_{18}ClNO$: C, 61.25; H, 8.41; N, 6.49. Found: C, 61.58; H, 8.49; N, 6.42.

General Procedure A. To a THF solution of the amino alcohol was added 1 equiv of sodium hydride dispersion followed, 20−30 min later, by the addition of 0.5 equiv of chromium complex **2**. After the reaction had stirred at room temperature for 1−16 h, it was cautiously treated with 2−3 equiv of I_2. Workup, as described above for mexiletine, was followed by chromatography, salt formation, and recrystallization to provide the desired product.

General Procedure B. A THF solution of the amino alcohol was treated with 1 equiv of sodium hydride dispersion and then, 15 min later, with 0.5−0.7 equiv of chromium complex **2**. After the reaction mixture had been refluxed for 1 h, it was cooled to room temperature and poured into water. The water was extracted multiple times with ether, and the combined ether fractions were treated with solid I_2 until a dark red-brown color persisted. After 20−60 min, water was added followed by solid $Na_2S_2O_3$ until the color was dissipated. After the aqueous layer had been made alkaline with 6 M NaOH, the phases were separated and the aqueous phase was washed multiple times with additional ether. The combined ether washes were dried ($MgSO_4$) and concentrated to give a residue which was dissolved in a small amount of ether and treated with HCl in ethanol. The precipitated salt of the desired product was isolated by filtration.

(*R*)-(−)-2-(2,6-Dimethylphenoxy)-1-phenylethylamine hydrochloride[9] (3): prepared in 34% yield via method A using (*R*)-(−)-2-phenylglycinol; mp 273.0−273.5 °C (EtOH); ^{1}H NMR δ 2.10 (s, 6H), 4.00−4.12 (m, 2H), 4.73 (br t, J = 5.4 Hz, 1H), 6.92 (dd, J = 8.6, 6.0 Hz, 1H), 7.00 (br d, J = 6.6 Hz, 2H), 7.39−7.51 (m, 3H), 7.61−7.67 (m, 2H), 8.87 (br s, 3H); ^{13}C NMR δ 17.4, 55.7, 73.5, 126.0, 129.5, 130.3, 130.5, 132.1, 136.8, 155.8; MS m/z (%) 241 (M^+, 2), 106 (100); $[\alpha]_D$ = −4.2° (*c* 0.55, MeOH). Anal. Calcd for $C_{16}H_{20}ClNO$: C, 69.18; H, 7.26; N, 5.04. Found: C, 68.93; H, 7.23; N, 5.17.

(*S*)-(+)-2-(2,6-Dimethylphenoxy)-1-phenylethylamine hydrochloride (4): prepared in 35% yield via method A using (*S*)-(+)-2-phenylglycinol; mp 270.3−270.9 °C ($EtOH/Et_2O$); $[\alpha]_D$ = +3.5° (*c* 0.48, MeOH). Anal. Calcd for $C_{16}H_{20}ClNO$: C, 69.18; H, 7.26; N, 5.04. Found: C, 69.08; H, 7.33; N, 5.09.

(*R*)-(−)-1-Benzyl-2-(2,6-dimethylphenoxy)ethylamine hydrochloride[9] (5): prepared in 40% yield via method A using (*R*)-(+)-2-amino-3-phenyl-1-propanol; mp 186−187 °C ($EtOH/Et_2O$);^{1}H NMR δ 2.16 (s, 6H), 3.01 (dd, J = 13.8, 9.0 Hz, 1H), 3.22 (dd, J = 13.8, 5.4 Hz, 1H), 3.65−3.93 (m, 3H), 6.92 (dd, J = 8.5, 6.1 Hz, 1H), 7.00 (br d, J = 6.9 Hz, 2H), 7.23−7.38 (m, 5H), 8.65 (br s, 3H); ^{13}C NMR δ 15.9, 34.8, 52.2, 69.8, 124.3, 127.0, 128.6, 128.9, 129.2, 130.4, 136.3, 154.3; MS m/z (%) 255 (M^+, 2), 164(100); $[\alpha]_D$ = −20.1° (*c* 0.40, MeOH). Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80. Found: C, 69.66; H, 7.53; N, 4.77.

(*S*)-(+)-1-Benzyl-2-(2,6-dimethylphenoxy)ethylamine hydrochloride (6): prepared in 28% yield via method A using (*S*)-(−)-2-amino-3-phenyl-1-propanol; mp 185−186 °C (EtOH); $[\alpha]_D$ = +24.5° (*c* 0.07, MeOH). Anal. Calcd for $C_{17}H_{22}ClNO\cdot 0.1H_2O$: C, 69.54; H, 7.62; N, 4.77. Found: C, 69.50; H, 7.66; N, 4.93.

1-(2,6-Dimethylphenoxymethyl)cyclopentylamine hydrochloride (7): prepared in 37% yield via method A using 1-amino-1-cyclopentanemethanol; mp 251−253 °C (EtOH); ^{1}H NMR δ 1.60−1.75 (m, 2H), 1.76−2.03 (m, 6H), 2.28 (s, 6H), 3.36 (s, 2H), 6.94 (dd, J = 8.4, 6.3 Hz, 2H), 7.04 (br d, J = 7.3 Hz, 1H), 8.39 (br s, 3H); ^{13}C NMR δ 16.0, 23.8, 33.4, 63.3, 73.4, 124.3, 128.9, 130.4, 153.7; MS m/z (%) 219 (M^+, 1.5), 108(100). Anal. Calcd for $C_{14}H_{22}ClNO$: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.80; H, 8.76; N, 5.42.

(*R*)-(−)-2-(2,6-Dimethylphenoxymethyl)pyrrolidine hydrochloride (8): prepared in 43% yield via method A using (*R*)-(−)-2-pyrrolidinemethanol; mp 150.9−151.3 °C (EtOAc); ^{1}H NMR δ 1.69−2.21 (m, 4H), 2.27 (s, 6H), 3.13−3.36 (m, 2H), 3.79−

3.90 (m, 1H), 3.94 (dd, J = 10.1, 4.6 Hz, 1H), 4.07 (dd, J = 10.1, 7.5 Hz, 1H), 6.94 (dd, J = 8.4, 6.4 Hz, 1H), 7.04 (br d, J = 7.3 Hz, 2H), 9.1−10.2 (m, 2H); ^{13}C NMR δ 16.1, 22.5, 26.1, 44.5, 58.8, 69.7, 124.1, 128.7, 130.3, 154.5; MS m/z (%) 205 (M^+, 3), 70 (100); $[\alpha]_D$ = −4.3° (c 0.39, MeOH). Anal. Calcd for $C_{13}H_{20}$ClNO: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.81; H, 8.31; N, 5.78.

(±)-2-[2-(2,6-Dimethylphenoxy)ethyl]piperidine hydrochloride (9): prepared in 48% yield via method A using (±)-2-piperidineethanol; mp 205.7−206.3 °C (CH_3CN); ^{1}H NMR δ 1.42−1.82 (m, 5H), 1.89−2.03 (m, 2H), 2.17−2.31 (m, 1H), 2.23 (s, 6H), 2.80−2.92 (m, 1H), 3.18−3.31 (m, 2H), 3.82−3.89 (m, 2H), 6.91 (dd, J = 8.3, 6.5 Hz, 1H), 7.02 (br d, J = 7.5 Hz, 2H), 9.19 (br s, 2H); ^{13}C NMR δ 16.4, 22.1, 28.2, 33.9, 44.1, 53.8, 68.0, 124.2, 129.1, 130.7, 155.7; MS m/z (%) 233 (M^+, 6), 84 (100). Anal. Calcd for $C_{15}H_{24}$ClNO: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.91; H, 8.83; N, 5.09.

(*S*)-(−)-2-(2,6-Dimethylphenoxymethyl)-1-methylpyrrolidine hydrochloride (10): prepared in 38% yield via method A using (*S*)-(−)-1-methyl-2-pyrrolidinemethanol; mp 184.1−184.6 °C (EtOAc); ^{1}H NMR (MeOH-d_4) δ 2.05−2.28 (m, 3H), 2.32 (s, 6H), 2.33−2.49 (m, 1H), 3.14 (s, 3H), 3.21−3.34 (m, 1H), 3.71−3.90 (m, 2H), 4.13 (br d, J = 4.4 Hz, 2H), 6.95 (dd, J = 8.5, 6.3 Hz, 1H), 7.04 (br d, J = 7.6 Hz, 2H); ^{13}C NMR (MeOH-d_4) δ 16.6, 22.5, 27.2, 40.7, 58.3, 68.9, 69.6, 125.8, 130.2, 131.6; CI-MS m/z 220 (MH^+); $[\alpha]_D$ = −26.9° (c 0.35, MeOH). Anal. Calcd for $C_{14}H_{22}$ClNO: C, 65.74; H, 8.67; N, 5.48. Found: C, 65.48; H, 8.56; N, 5.37.

(±)-2-[2-(2,6-Dimethylphenoxy)ethyl]-1-methylpyrrolidine hydrochloride (11): prepared in 33% yield via method A using (±)-1-methyl-2-pyrrolidineethanol; mp 159.8−160.4 °C; ^{1}H NMR δ 1.71−2.10 (m, 4H), 2.23 (s, 6H), 2.22−2.48 (m, 2H), 2.83 (br s, 3H), 2.97−3.10 (m, 1H), 3.40−3.60 (m, 2H), 3.81 (br t, J = 6.6 Hz, 2H), 6.92 (dd, J = 8.3, 6.5 Hz, 1H), 7.03 (br d, J = 7.5 Hz, 2H), 10.71 (br s, 1H); ^{13}C NMR δ 17.0, 22.0, 30.2, 31.5, 39.2, 55.9, 66.5, 69.4, 124.8, 129.7, 131.3, 156.2; MS m/z (%) 233 (M^+, 15), 84 (100). Anal. Calcd for $C_{15}H_{24}$ClNO: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.74; H, 8.91; N, 4.99.

(±)-2-(2,6-Dimethylphenoxymethyl)-1-methylpiperidine hydrochloride[10] (12): prepared in 63% yield via method A using (±)-1-methyl-2-piperidinemethanol; mp 173.2−173.7 °C (EtOAc) (lit.[10] mp 171−173 °C); ^{1}H NMR δ 1.46−2.16 (m, 6H), 2.28 (s, 6H), 2.97 (br s, 3H), 3.02−3.19 (m, 1H), 3.38−3.51 (m, 2H), 3.86−3.97 (m, 1H), 4.05−4.17 (m, 1H), 6.97 (dd, J = 8.5, 7.0 Hz, 1H), 7.06 (br d, J = 7.4 Hz, 2H), 10.28−10.47 (m, 1H); ^{13}C NMR δ 16.2, 21.3, 22.4, 26.3, 41.0, 55.3, 63.5, 69.9, 124.3, 128.9, 130.2, 154.5; CI-MS m/z 234 (MH^+). Anal. Calcd for $C_{15}H_{24}$ClNO: C, 66.77; H, 8.97; N, 5.19. Found: C, 66.58; H, 8.68; N, 4.92.

(±)-3-(2,6-Dimethylphenoxy)-1-methylpiperidine hydrochloride (13): prepared in 67% yield via method B using (±)-3-hydroxy-1-methylpiperidine; mp 157.0−158.5 °C; ^{1}H NMR δ 1.60−1.80 (m, 1H), 1.85−2.10 (m, 2H), 2.15−2.26 (m, 1H), 2.38 (br s, 6H), 2.90 (br s, 3H), 2.90−3.10 (m, 1H), 3.10−3.28 (m, 1H), 3.40−3.50 (m, 1H), 3.60−3.72 (m, 1H), 4.38−4.52 (m, 1H), 7.09 (dd, J = 8.3, 6.5 Hz, 1H), 7.19 (br d, J = 7.5 Hz, 2H), 11.5 (br s, 1H); ^{13}C NMR δ 18.6, 22.1, 30.3, 44.3, 54.4, 57.3, 75.6, 125.8, 130.9, 132.3, 155.4; MS m/z (%) 219 (M^+, 10), 98 (100), 70 (18). Anal. Calcd for $C_{14}H_{22}$ClNO: C, 65.74; H, 8.67; N, 5.48. Found: C, 66.01; H, 8.86; N, 5.66.

***endo*-3-(2,6-Dimethylphenoxy)-8-methyl-8-azabicyclo-[3.2.1]octane hydrochloride (14):** prepared in 66% yield via method B using *endo*-3-tropanol; mp >280 °C; ^{1}H NMR (DMSO-d_6/TFA-d_1) δ 2.24 (s, 6H), 2.15−2.30 (m, 4H), 2.40−2.60 (m, 4H), 2.69 (s, 3H), 3.77−3.93 (m, 2H), 3.97 (br t, J = 5 Hz, 1H), 6.86 (br t, J = 7.4 Hz, 1H), 6.99 (br d, J = 7.4 Hz, 2H); ^{13}C NMR δ 18.1, 23.3, 35.3, 38.1, 61.3, 74.0, 123.2, 129.3, 129.6, 156.7; MS m/z (%) 245 (M^+, 12), 124 (100), 96 (12). Anal. Calcd for $C_{16}H_{24}$ClNO: C, 68.19; H, 8.58; N, 4.97. Found: C, 68.22; H, 8.52; N, 5.21.

(±)-3-(2,6-Dimethylphenoxy)-1-azabicyclo[2.2.2]octane hydrochloride (15): prepared in 61% yield via method B using (±)-3-quinuclidinol; mp 254.5−255.5 °C; ^{1}H NMR (DMSO-d_6/TFA-d_1) δ 1.60−1.92 (m, 3H), 2.22 (s, 6H), 2.25−2.45 (m, 2H), 2.95−3.50 (m, 5H), 3.69−3.80 (m, 1H), 4.20−4.27 (m, 1H), 6.93 (dd, J = 8.2, 6.6 Hz, 1H), 7.04 (br d, J = 7.5 Hz, 2H); ^{13}C NMR δ 16.4, 16.8, 20.0, 25.3, 44.6, 45.5, 52.4, 75.5, 123.7, 129.0, 129.9, 155.1; MS m/z (%) 231 (M^+, 35), 110 (100). Anal. Calcd for $C_{15}H_{22}$ClNO: C, 67.28; H, 8.28; N, 5.23. Found: C, 67.04; H, 8.18; N, 5.43.

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