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Syntheses of the tricyclic cores of clozapine, dibenzo[b,f][1,4]thiazepin-11(10H)-one, and dibenzo[b,f][1,4]oxazepin-11(10H)-one in C-14 labeled form by [^{14}C]carbonylation

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Clozapine has been demonstrated to bind covalently to proteins as a result of metabolic activation that has been proposed to be a precursor to the serious side effects including death that occur in a small percentage of the population. The covalent modification of proteins by clozapine has been studied by several groups and is well documented; therefore, the department of drug metabolism desired to use [^{14}C]clozapine as a positive control for covalent binding assays. The preparation of [^{14}C]clozapine was first conducted using a previous reported route and then using a new route that utilized [^{14}C]carbonylation as the isotope incorporating step. While this route worked, it was not deemed superior to the previous route. However, this methodology proved quite effective in preparing C-14 labeled dibenzothiazepine and dibenzoxapine ring systems.

Keywords: [^{14}C]carbonylation; clozapine; loxapine; amoxapine; tricyclic ring

Introduction

Clozapine is a tricyclic antipsychotic medication that is currently marketed for the treatment of schizophrenia.[1] It has a turbulent past that includes being withdrawn from the US market in 1975 for causing the death of several patients due to agranulocytosis.[2] In 1989, the FDA re-admitted clozapine to the US market for treatment-resistant schizophrenia and it is now used in conjunction with careful blood monitoring.[3]

Agranulocytosis occurs in 0.8–1% of the patient population and has been proposed to arise from the covalent binding of clozapine to neutrophils or their biological precursors.[4] A nitrene metabolite of clozapine or of one of clozapine's other metabolites is suspected to be the culprit, leading to the covalent modification of proteins (Scheme 1).

The generation of reactive metabolites is a major concern during the drug development process and has received considerable attention from major pharmaceutical companies over the past few years.[5] While many marketed drugs display high covalent binding to proteins, it is difficult if not impossible to predict which protein modifications will lead to toxicity. Therefore, the propensity to form reactive metabolites needs to be minimized during the compound design phase to avoid the formation of potential reactive metabolites that could lead to toxicological findings.

Many companies have implemented an assay to determine the levels of covalent binding to a biological matrix such as liver microsomes or hepatocytes. To insure the proper performance of the assay and the quality of the hepatocytes used in the assay, a substrate must be used as a positive control. Therefore, [^{14}C]clozapine was requested by the department of drug metabolism for evaluation as a positive control in covalent binding studies.

Results and discussion

Drug metabolism desired the C-14 label placed in the tricyclic core of clozapine and the amidine carbon seemed the most accessible site for radiolabeling. [^{14}C]Clozapine labeled in this location has been reported twice previously[6] and when we repeated the reported procedures, they worked admirably to prepare the compound in 30% overall yield (Scheme 2).

In an effort to improve upon this route, we envisioned the key intermediate **[^{14}C]-1** as arising from a [^{14}C]carbonylation of an aryl bromide instead.[7] This would shorten the radiochemical steps from five to two and might improve upon the radiochemical yield of 30% (47% to **[^{14}C]-1**) that was achieved when we reproduced the literature route. Therefore, bromide **3** was prepared in two steps by nucleophilic aromatic substitution to afford nitroarene **2** and subsequent reduction of the nitro group to afford aniline **3** in high yield (Scheme 3). Bromide **3** was then subjected to [^{14}C]carbonylation using standard methodology in the presence of triethylamine, but only a low yield of **[^{14}C]-1** was observed. When the base was changed from triethylamine to sodium acetate, an 83% crude yield (42% radiochemical yield) of **[^{14}C]-1** was obtained, but after preparative HPLC only a 52%

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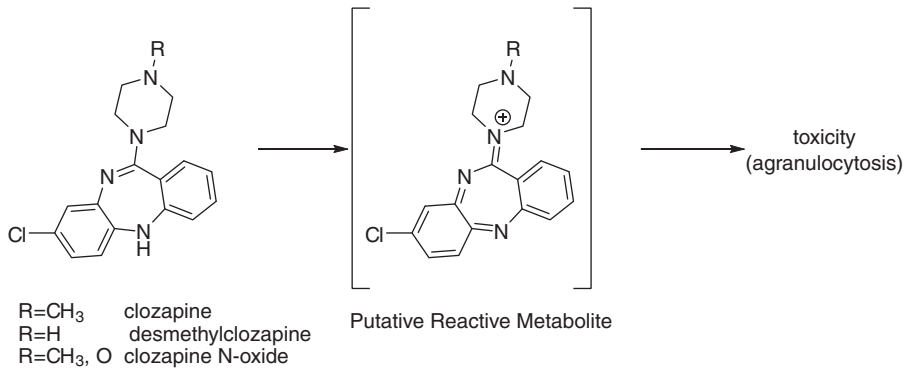
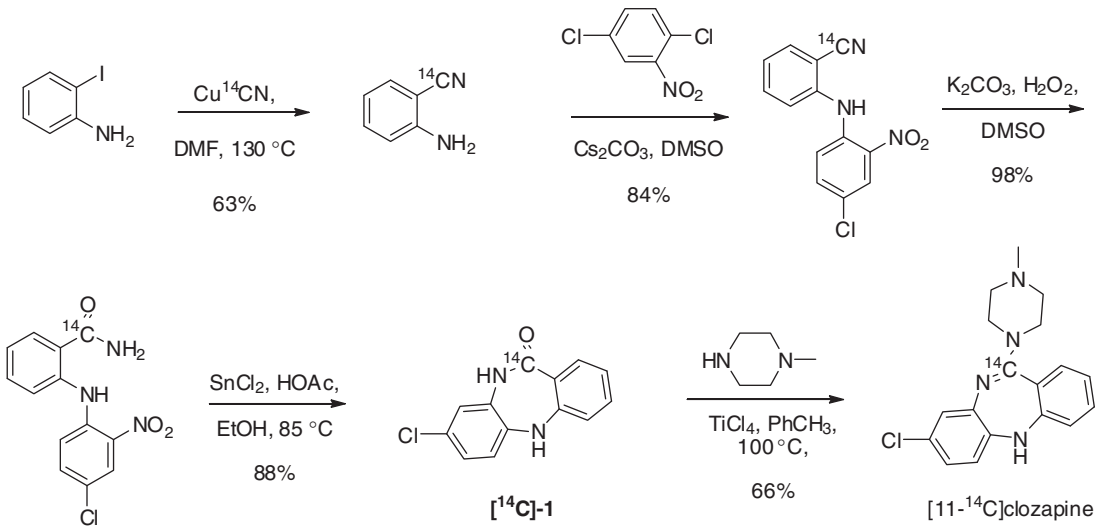
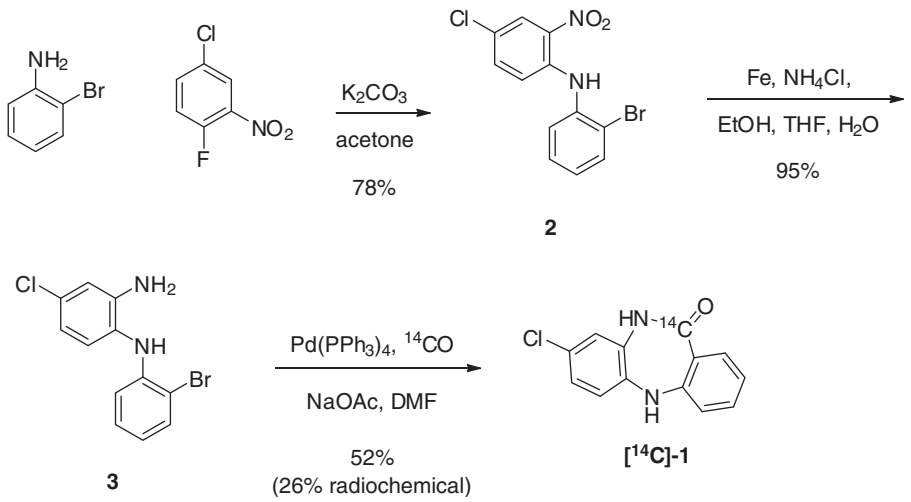


Scheme 1. Proposed metabolic process leading to toxicity of clozapine.



Scheme 2. Preparation of [^{14}C]clozapine according to the previously reported route in 30% radiochemical yield over steps steps.



Scheme 3. Preparation of diazepine **[^{14}C]-1** via [^{14}C]carbonylation.

yield (26% radiochemical) of the target was obtained. This yield is about half that of the previously reported route owing partially to the necessity of performing preparative HPLC to remove some close eluting non-radioactive impurities from the sample. Thus, despite being only one radiochemical step, this route suffers from the need to use an excess of the C-14 reagent and thus from a significantly lower radiochemical yield than that reported by Matloubi and co-workers. However, it does allow for

the utilization of non-radioisotope using groups to prepare the [^{14}C]carbonylation precursor and for the long-term storage of the non-radioactive intermediate **3**.

We then extended our investigation to other tricyclic ring systems; first turning our attention to the synthesis of oxepine **[^{14}C]-4**, which is the tricyclic core of [^{14}C]loxapine and [^{14}C]amoxapine. The bromo precursor for the [^{14}C]carbonylation was synthesized in a manner analogous to that described for **3** in moderate yield, and the [^{14}C]carbonylation afforded a 57% crude yield of the target compound (Scheme 4). After preparative HPLC, a 36% yield (26% radiochemical yield) of oxepine **[^{14}C]-4** was obtained. Despite the low yield this does provide a rapid synthesis of the oxepine core.

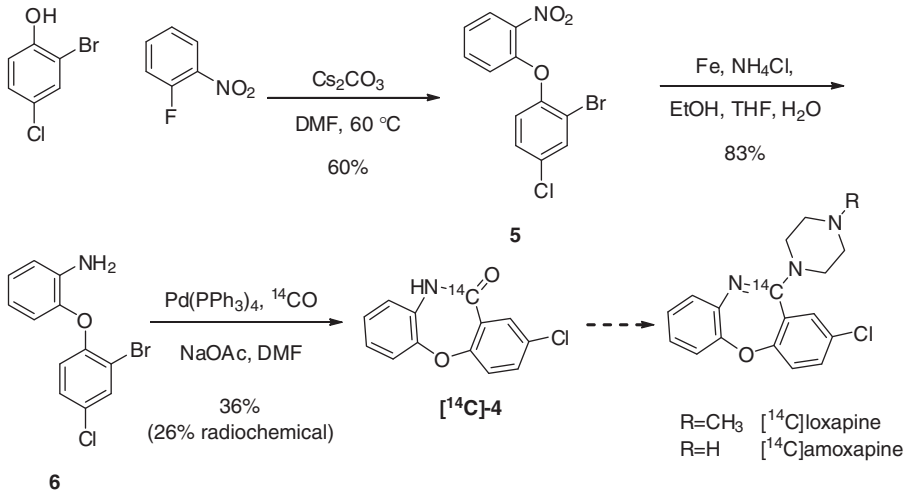
Finally, we turned our attention to the thiazepine ring system. We had previously prepared **[^{14}C]-7** using a route similar to that published for [^{14}C]clozapine (Scheme 5). Carboxylation of the dianion formed from thiophenol afforded the thiol **[^{14}C]-8** in low yield. The low yield may have been due to the formation of phenylthioester or disulfide of **[^{14}C]-8** with the excess thiophenol in the reaction mixture. Attempts at converting the thioester to **[^{14}C]-8** were unsuccessful. Thiol **[^{14}C]-8** was then coupled with 2-chloronitrobenzene to give the acid that was esterified to give **[^{14}C]-9**. Nitroarene **[^{14}C]-9** was reduced with zinc metal to give aniline **[^{14}C]-10** and the aniline was cyclized using trimethylaluminum to afford the thiazepine **[^{14}C]-7** in 15% overall yield from Ba^{14}CO$_3$.

The [^{14}C]carbonylation substrate was prepared in a manner analogous to that previously described for **3** to give bromide precursor **12** (Scheme 6). The [^{14}C]carbonylation was initially performed with triethylamine, and this reaction afforded a 20% isolated yield of **[^{14}C]-7**. Switching to sodium acetate dramatically improved the yield to give 50% isolated yield (32% radiochemical yield). This improvement in yield with the use of NaOAc was also observed in the synthesis of **[^{14}C]-1**.

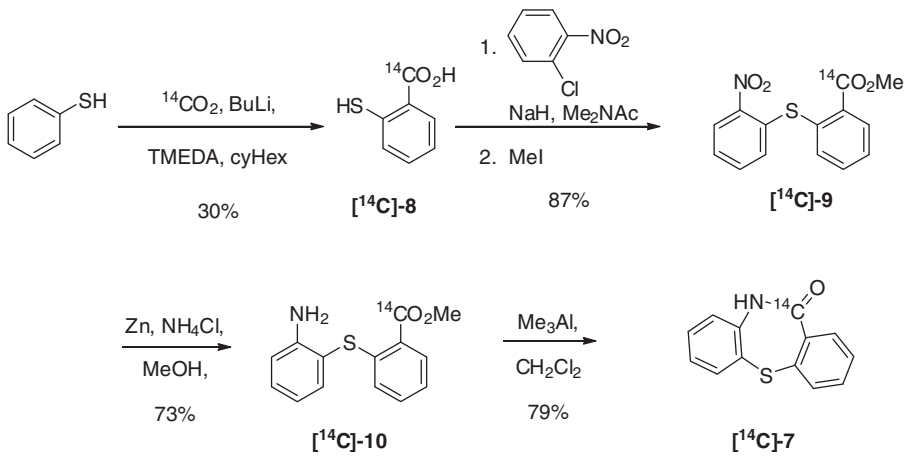
Experimental

General

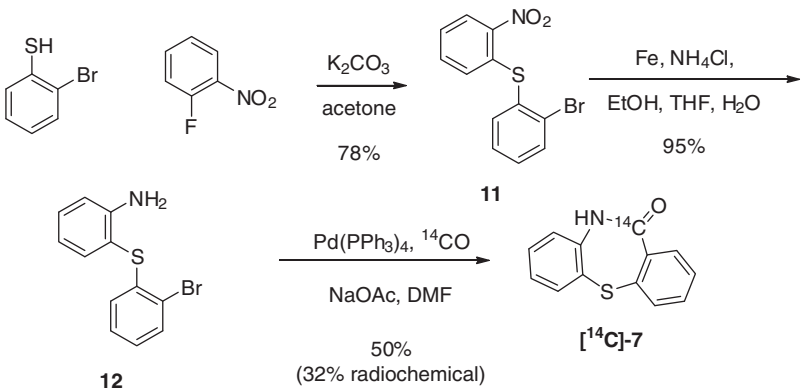
Pd(PPh$_3$)$_4$ was obtained from Strem Chemical Company and Na^{14}CO$_2$H (57 mCi/mmol) and Ba^{14}CO$_3$ (57 mCi/mmol) were obtained from American Radiolabeled Chemicals, Inc. All other reagents were obtained from Acros and Aldrich and were used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 500 and Avance 600 with Dual Cryoprobe spectrometers in $CDCl_3$ and were referenced to the



Scheme 4. Preparation of oxepine **[^{14}C]-4** as an intermediate toward [^{14}C]lox pine or [^{14}C]amoxapine.



Scheme 5. Preparation of thiazepine **[^{14}C]-7** by carboxylation.



Scheme 6. Preparation of thiazepine **[^{14}C]-7** by [^{14}C]carbonylation.

residual solvent peak (7.26 and 77.00 ppm). LC/MS analyses were performed on an HP MSD-1100 using a Luna-C18(2) column, with a 10–100% gradient of MeOH-0.1% aqueous formic acid over 10 min and electrospray ionization. HPLC analyses were performed using a Agilent 1100 series HPLC system using either method A (10/90 to 100/0 MeOH/0.1% aqueous TFA gradient elution over 20 min, Phenomenex Polar-RP), method B (10/90 to 100/0 MeCN/0.1% aqueous TFA gradient elution over 10 min, Phenomenex Luna C-18(2)), or method C (50/50 to 100/0 MeOH/0.1% TFA over 20 min, Phenomenex Polar-RP). All HPLC analyses were conducted using a flow rate of 1 mL/min on 4.6 × 100 mm columns heated to 30°C and concluded with a 5 min wash of 100% MeOH or MeCN. Preparative HPLC was conducted on a 21.2 × 250 mm 5 μ Thermo Scientific Hypersil Gold C18 column using MeOH-0.1% aqueous TFA with a flow rate of 15 mL/min and a gradient elution of 50 to 100% over 40 min. GC/MS analyses were conducted with a Hewlett Packard 6890 GC system and 5973 Mass Selective Detector using a temperature gradient of 70–260°C over 20 min.

*N-(2-Bromophenyl)-4-chloro-2-nitroaniline (**2**)*

A slurry of 2-bromoaniline (0.670 g, 3.89 mmol), 4-chloro-1-fluoro-2-nitrobenzene (0.394 g, 2.24 mmol), and Cs_2CO_3 (0.756 g, 2.32 mmol) in 6 mL of DMF was stirred overnight under N_2 at 100°C. The solvent was removed and the residue partitioned between 10 mL of water and 10 mL of CH_2Cl_2. The layers were separated and the aqueous layer extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated to dryness to give 523 mg of a brown oil. The oil was purified by silica gel chromatography (0–100% Hex-EtOAc over 25 min) and the product containing fractions were combined and concentrated to dryness to afford 294 mg (40%) of a red solid. ^{1}H NMR δppm 7.05 (d, J = 9.2 Hz, 1H), 7.12 (td, J = 7.5, 1.5 Hz, 1H), 7.34 (dd, J = 9.0, 2.6 Hz, 1H), 7.36 (d, J = 7.3 Hz, 1H), 7.40 (dd, J = 7.9, 1.5 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 9.38 (br. s., 1H). ^{13}C NMR δppm 117.6, 119.8, 123.1, 125.2, 126.0, 127.1, 128.4, 134.0, 135.7, 137.2, 140.5 (HMBC shows that the peak at 134.0 has two overlapping carbons). GC/MS: 328 (100%), 326 (80%), 324 (26%).

*N1-(2-Bromophenyl)-4-chlorobenzene-1,2-diamine (**3**)*

A solution of nitroaniline **2** (172 mg, 0.53 mmol) in 10 mL of ethanol, 6 mL of THF, 2 mL of water, and 1 mL of saturated aqueous NH_4Cl was stirred vigorously under N_2 as iron powder (1.16 g, 20.7 mmol) was added. The resulting slurry was warmed to 85°C and was stirred overnight. After cooling to room temperature, the slurry was filtered through celite and the filtrate was diluted with 100 mL of water, 100 mL of CH_2Cl_2 and 50 mL of saturated $NaHCO_3$. The layers were separated and the aqueous layer was extracted three times with 50 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and filtered and the resulting solution was concentrated to give 177 mg of a brown oil. Purification by silica gel chromatography (10–60% over 20 min) afforded 105 mg of an off white solid (67%). ^{1}H NMR δppm 6.54 (dd, J = 8.1, 1.1 Hz, 1H), 6.69 (td, J = 7.3, 1.5 Hz, 1H), 6.73 (dd, J = 8.4, 2.3 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 7.11 (td, J = 7.5, 1.2 Hz, 1H), 7.50 (dd, J = 7.9, 1.2 Hz, 1H). ^{13}C NMR δppm 110.4, 114.2, 115.6, 118.8, 119.9, 125.1, 128.3, 128.4, 132.3, 132.7, 142.8, 144.4. GC/MS: 298 (100%), 296 (81%), 300 (26%).

*[11-^{14}C]8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11(10H)-one (**[^{14}C]-1**)*

A three-necked, round-bottom flask containing sodium [^{14}C] formate (5.6 mg, 4.5 mCi, 0.08 mmol) was fitted with a septum, a vacuum outlet and a 90° bent adapter to which was attached a round-bottom flask containing a solution of bromide **3** (11 mg, 0.04 mmol), $Pd(PPh_3)_4$ (22 mg, 0.02 mmol), and NaOAc (95 mg, 1.16 mmol) in 7 mL of DMF. The apparatus was evacuated to approx. 1 mm Hg and the valve leading the vacuum was closed. Sulfuric acid (24 mL) was added through the septum to the sodium [^{14}C]formate, and the resulting solution was stirred for 1 h at 120°C. The DMF solution was warmed to 100°C and was stirred overnight. The sample was removed from the apparatus to give 4 mCi (43% radiochemical purity) and was purified by preparative HPLC to give 1.2 mCi (52%, 26% radiochemical) at a radiochemical purity of 98% (method C). ^{1}H NMR ppm 6.97 (d, J = 8.5 Hz, 1H), 7.07 (dd, J = 8.5, 1.8 Hz, 1H), 7.15 (d, J = 1.8 Hz, 1H), 7.44 (m, 2H), 7.50 (m, 1H), 7.55 (m, 1H), 7.72 (br. s, 1H), 8.70 (br. s., 1H). LC/MS (M+H): 247 (100%), 249 (32.1%), 248 (13.7%), 244 (8.1%).

*2-Bromo-4-chloro-1-(2-nitrophenoxy)benzene (**5**)*

A slurry of 2-bromo-4-chlorophenol (1.48 g, 7.12 mmol) and Cs_2CO_3 (3.91 g, 12.00 mmol) in 20 mL of DMF was treated with 1-fluoro-2-nitrobenzene (956 mg, 6.78 mmol) as described for **2** to afford 1.334 g (60%) of a solid. ^{1}H NMR δppm 6.88 (dd, J = 8.2, 1.1 Hz, 1H) 6.95 (d, J = 8.7 Hz, 1H) 7.24 (td, J = 7.8, 1.2 Hz, 1H) 7.29 (dd, J = 8.7, 2.4 Hz, 1H) 7.52 (ddd, J = 8.2, 7.0, 1.6 Hz, 1H) 7.66

(d, J = 2.4 Hz, 1H) 7.99 (dt, J = 8.2, 0.9 Hz, 1H). ^{13}C NMR δppm 115.7, 119.4, 121.6, 123.8, 126.1, 129.1, 130.9, 133.7, 134.4, 140.8, 149.8, 151.2. GC/MS: 329 (100%), 327 (78%), 331 (25%).

*2-(2-Bromo-4-chlorophenoxy)aniline (**6**)*

A slurry of nitroarene **5** (603 mg, 1.84 mmol) and iron powder (2.31 g, 41.3 mmol) in 8 mL of EtOH, 8 mL of THF, and 2 mL of a solution of saturated aqueous NH_4Cl, and was reacted as described for **3** to give 457 mg (83%) of a clear oil, which solidified upon standing. ^{1}H NMR δppm 3.80 (m, 2H), 6.71 (td, J = 7.6, 1.6 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.4, 1.8 Hz, 1H), 6.82 (dd, J = 8.0, 1.5 Hz, 1H), 7.00 (td, J = 7.7, 1.5 Hz, 1H), 7.16 (dd, J = 8.8, 2.7 Hz, 1H), 7.60 (d, J = 2.5 Hz, 1H). ^{13}C NMR δppm 113.7, 116.7, 118.5, 118.8, 119.7, 125.6, 128.5, 128.6, 133.1, 138.4, 142.6, 152.9. GC/MS: 299 (100%), 297 (80%), 301 (26%).

*[11-^{14}C]Dibenzo[b,f][1,4]oxazepin-11(10H)-one (**[^{14}C]-4**)*

Sodium [^{14}C]formate (10.3 mg, 0.15 mmol, 8.4 mCi), bromide **6** (32 mg, 0.11 mmol), $Pd(PPh_3)_4$ (22 mg, 0.02 mmol), NaOAc (134 mg, 1.63 mmol) and 5 mL of DMF were reacted as described for **[^{14}C]-1** to give 4.5 mCi (65% radiochemical purity, method C). Purification by preparative HPLC afforded 2.2 mCi (36% yield, 26% radiochemical yield) with a radiochemical purity of 99.6% (method C). ^{1}H NMR δppm 7.02 (m, 1H) 7.15 (ddd, J = 7.3, 5.2, 1.8 Hz, 2H), 7.19 (d, J = 8.9 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H) 7.46 (dd, J = 8.5, 2.7 Hz, 1H) 7.91 (d, J = 2.4 Hz, 1H). ^{13}C NMR δppm 121.3, 121.8, 122.4, 126.16, 126.21, 126.23, 130.00, 130.04, 130.8, 131.7, 134.3, 150.7, 158.1. LC/MS: 248 (100%), 250 (31%), 249 (14%), 246 (8.3%).

*2-Mercapto[^{14}C]benzoic acid (**[^{14}C]-8**)*

A solution of TMEDA (697 mg, 6 mmol) in 6 mL of cyclohexane was stirred at 0°C as 3.8 mL of 1.6 M (6 mmol) *n*-BuLi in hexane was added followed by dropwise addition of thiophenol (330 mg, 3.0 mmol) in 1.25 mL of cyclohexane. After complete addition, the solution was warmed to room temperature and stirred for 24 h. The solution was then cooled in liquid nitrogen and was evacuated. $^{14}CO_2$ (97 mCi, 1.7 mmol, generated from 336 mg (1.7 mmol) of $Ba^{14}CO_3$) was transferred into the reaction flask. The reaction was warmed to room temperature and was stirred for 16 h. The solution was then diluted with 10 mL of 2 M HCl and was extracted five times with 25 mL of Et_2O to give 75 mCi in the combined organic extracts (45% radiochemical purity, method B). The organic extracts were extracted ten times with 5 mL of 5% $NaHCO_3$ and the combined aqueous layers were extracted with Et_2O after acidification with HCl. The combined organic layer was washed with an aqueous solution of saturated NaCl and was then dried ($MgSO_4$). Filtration gave a Et_2O solution that contained 33.9 mCi of **[^{14}C]-8** at a radiochemical purity of 87% (method B, 30% yield corrected for purity). LC/MS (M-H): 155 (100%), 153 (7.2%), 156 (6.8%).

*Methyl 2-(2-nitrophenylthio)[^{14}C]benzoate (**[^{14}C]-9**)*

A solution **[^{14}C]-8** (34 mCi, 87% radiochemical purity, 0.52 mmol) in 1.5 mL of dimethylacetamide was added to a slurry of 60% NaH dispersion in oil (48 mg, 1.2 mmol) and the resulting slurry was stirred for 30 min under Ar at room temperature. A solution of 2-chloronitrobenzene (116 mg, 0.74 mmol) in 1 mL of dimethylacetamide was added and the solution was warmed to 75°C and stirred overnight. After cooling to room temperature, MeI (173 mg, 1.22 mmol) was added and the solution was stirred for 3 h. It was then poured into 100 mL of water and was extracted twice with 50 mL of EtOAc. The combined organic layers were washed with 50 mL of saturated aqueous NaCl and were then dried ($MgSO_4$). The solution was concentrated to dryness to give 177 mg (34 mCi, 85% radiochemical purity (method B), 92% yield) of a yellow solid.

*Methyl 2-(2-aminophenylthio)[^{14}C]benzoate (**[^{14}C]-10**)*

A solution of ester **[^{14}C]-9** (33 mCi, 0.48 mmol, 85% radiochemical purity) and NH_4Cl (65 mg, 1.2 mmol) in 3.6 mL of MeOH was stirred as zinc powder (799 mg, 12.2 mmol) was added and the reaction mixture was then warmed to reflux for 4 h. The slurry was diluted with hot methanol and was filtered while still warm through a pad of celite to give a yellow solution. The MeOH was removed, and the solution was partitioned between 10% aqueous acetic acid and EtOAc. The layers were separated and the aqueous layer extracted four times with 50 mL EtOAc. The combined organic layers were dried ($MgSO_4$) and filtered to give 25 mCi with a radiochemical purity of 82% (method B, 73% yield). LC/MS (M+H) 262 (100%), 263 (15.5%), 260 (8.4%).

*[11-^{14}C]Dibenzo[b,f][14]thiazepin-11(10H)-one (**[^{14}C]-7**)*

A solution of aniline **[^{14}C]-10** (25 mCi, 82% radiochemical purity, 0.36 mmol) in 12 mL of CH_2Cl_2 was cooled to 0°C and stirred under Ar as 225 μL of a 2 M (0.45 mM) solution of trimethylaluminum in hexanes was added. The solution was stirred for 30 min at 0°C and then at room temperature overnight. It was then cooled to 0°C and 2.1 mL of 1 M aqueous HCl was added and after 10 min, 20 mL of water. The solution was then extracted three times with 50 mL of CH_2Cl_2 and the combined organic layers were washed with 50 mL of saturated aqueous NaCl. The solution was dried ($MgSO_4$) and then filtered to give 25 mCi at a radiochemical purity of 65% (method B, 79% yield). LC/MS: 252 (100), 253 (15%), 250 (9%).

*2-Bromophenyl)(2-nitrophenyl)sulfane (**11**)*

2-Bromobenzenethiol (0.919 g, 4.86 mmol), 1-fluoro-2-nitrobenzene (0.915 g, 6.48 mmol), and potassium carbonate (987 mg, 7.14 mmol) in 50 mL of acetone was reacted as described for compound **2** to give 1.41 g of a yellow solid. ^{1}H NMR indicated a purity of 84% with the remaining 16% being residual 2-fluoronitrobenzene (78% yield corrected for purity). ^{1}H NMR δppm 6.77 (d, J = 8.2 Hz, 1H) 7.25 (tt, J = 7.7, 1.1 Hz, 1H) 7.35 (m, 1H) 7.37 (m, 1H) 7.42 (tt, J = 7.5, 1.1 Hz 1H) 7.72 (dd, J = 7.6, 1.5 Hz, 1H) 7.77 (dd, J = 7.9, 1.2 Hz, 1H) 8.25 (dd, J = 8.2, 1.2 Hz, 1H). 13C NMR δppm 125.4, 125.9, 128.1, 128.8, 131.1, 131.7, 132.5, 133.6, 134.3, 137.3, 138.0, 145.3. GC/MS: 311 (100%), 309 (98%), 312 (15%).

*(2-Bromophenyl)(2-aminophenyl)sulfane (**12**)*

A slurry of nitroarene **11** (609 mg, 1.96 mmol), 12 mL of EtOH, 12 mL of THF, 4 mL of water, 4 mL of saturated aqueous NH_4Cl and iron powder (2.45 g, 44.7 mmol) were reacted as described for **3** to give 701 mg (2.5 mmol, 95% yield) of a white solid. ^{1}H NMR äppm 6.62 (d, J = 7.9 Hz, 1H) 6.78 (td, J = 7.5, 1.1 Hz, 1H) 6.81 (d, J = 8.5 Hz, 1H) 6.96 (t, J = 7.6 Hz, 1H) 7.09 (t, J = 7.6 Hz, 1H) 7.27(m, 1H) 7.45 (d, J = 7.9 Hz, 1H) 7.51 (d, J = 7.9 Hz, 1H). 13 C

NMR δppm 113.2, 115.7, 119.0, 120.8, 126.2, 126.4, 127.8, 131.8, 132.8, 137.9, 138.0, 149.2. GC/MS: 281 (100), 279 (99%), 282 (15%).

*[11-^{14}C]Dibenzo[b,f][14]thiazepin-11(10H)-one (**[^{14}C]-7**)*

Sodium [^{14}C]formate (11 mg, 0.16 mmol, 8.8 mCi, 56 mCi/mmol), bromide **12** (28 mg, 0.10 mmol), $Pd(PPh_3)_4$ (13 mg, 0.01 mmol), NaOAc (88 mg, 1.1 mmol) and 3 mL of DMF were reacted according to the procedure reported for **[^{14}C]-1** to give 4.0 mCi (90% radiochemical purity by HPLC, method C). Purification by preparative HPLC afforded 2.8 mCi (0.05 mmol, 56 mCi/mmol, 50% yield, 32% radiochemical yield) at a radiochemical purity of 97% (method C). ^{1}H NMR δppm 7.10 (dd, J = 7.9, 1.1 Hz, 1H) 7.14 (td, J = 7.6, 1.3 Hz, 1H) 7.30 (td, J = 7.8, 1.4 Hz, 1H) 7.37 (td, J = 7.5, 1.5 Hz, 1H) 7.40 (td, J = 7.3, 1.7 Hz, 1H) 7.51 (dd, J = 7.6, 1.4 Hz, 1H) 7.57 (dd, J = 7.7, 1.3 Hz, 1H) 7.84 (dd, J = 7.6, 1.8 Hz, 1H). LC/MS: 252 (100), 253 (15%), 250 (9%).

Conclusion

We have demonstrated that [^{14}C]carbonylation can be an effective means of incorporating C-14 into tricyclic ring systems, which are present in a significant number of antipsychotics. Although the yields are modest and the purification can be difficult, the routes given here provide rapid access to the C-14 labeled thiazepine, diazepine and oxepine ring systems. This method reduces the number of radiochemical steps and the amount of radiochemical waste generated during the synthesis.

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