SYNTHESIS OF N-(α,α,α-TRI[^{18}F]FLUORO-m-TOLYL)PIPERAZINE. A POTENT SEROTONIN AGONIST

G. Angelini*, M. Speranza**, A. P. Wolf[a] and C.-Y. Shiue[a]

[a] Department of Chemistry, Brookhaven National Laboratory, Upton, NY 11973 USA

* Istituto di Chimica Nucleare del C.N.R., C.P. 10, 00016, Monterotondo Stazione, Rome (Italy)

** Universita' degli Studi della Tuscia, Viterbo

SUMMARY

N-(α,α,α-tri[^{18}F]fluoro-m-tolyl)piperazine (6), a serotonin agonist, was synthesized from 3-nitro-α,α,α-trichlorotoluene (1) and H[^{18}F] + Sb_2O_3 in four steps in 27% overall radiochemical yield in a synthesis time of ~ 3 hours.

Keywords: N-(α,α,α-tri[^{18}F]fluoro-m-tolyl)piperazine, H[^{18}F] + Sb_2O_3 as a new selective radiofluorinating agent, Serotonin agonist, Fluorine-18

INTRODUCTION

Serotonin is essentially localized in encephalic neurons of many vertebrate animals and develops an important activity of mediation during nervous impulse transmission. In addition, this compound also has effects on neurophysiological regulations (i.e. corporeal temperature, waking and sleeping alternation) and even on some manifestation of human and animal behaviour (i.e. aggressiveness) (1,2).

Considering the non-uniform serotonin distribution in different cerebral areas, the availability of a serotonin receptor map could be of fundamental importance for the comprehension of specific mechanisms involving this compound.

The advent of positron emission tomography (PET) has made it possible to study the dynamic physiological processes in health and disease states in the living human body utilizing radiopharmaceuticals labeled with positron emitters. For example, several glucose analogs labeled with positron emitters have been

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used to study regional brain glucose metabolism in humans (3-5). The same technique also has been used to study the neuroreceptors in the living human brain (6). While there are numerous ligands available for studying dopamine, opioid and benzodiazepine receptors, there are only a few serotonin receptor radioligands which are labeled with positron emitters and are used for PET studies. These include ^{11}C-labeled ketanserin (7), N-methylketanserin (8), N-methylbromo LSD (9) and fluorine-18 labeled setoperone (10), ritanserin (11) and altanserin (12).

N-(α,α,α-Trifluoro-m-tolyl)piperazine is a potent serotonin agonist (13). One of its structural components is α,α,α-trifluorotoluene. We recently reported a new fluorinating agent, (H[^{18}F] + Sb_2O_3), which can selectively fluorinate the side-chain of some substituted α,α,α-trihalogenotoluenes (14). We report here the application of this method to the synthesis of carrier-added (CA) N-(α,α,α-tri[^{18}F]fluoro-m-tolyl)piperazine (6) and some of its intermediates. Part of this study has appeared (15).

MATERIALS AND METHODS

Antimony trioxide was obtained from Matheson, Coleman and Bell. Aluminium trichloride, antimony trifluoride, benzotrichloride, N,N-bis(2-hydroxyethyl)amine (5a), N,N-bis(2-chloroethyl)amine (5c), methyl chloroformate, 3-nitro-α,α,α-trifluorotoluene and N-(α,α,α-trifluoro-m-tolyl)piperazine were purchased from Aldrich Chemical Company and used without further purification. Piperazine was purchased from Sigma Chemical Company.

NMR spectra were recorded with JEOL MH-100 and Varian FT-80 in chloroform-d or in water-D_2, with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standards. The mass spectra were measured with a Finnigan MAT 5100 GC/MS/DS spectrometer. High-pressure liquid chromatographic (HPLC) analyses were carried out with a Perkin-Elmer Series 2 liquid chromatograph equipped with a UV detector (254 nm) and connected to a Model LB503 Berthold flow scintillation counter. An IBM C-18 column (4.5 x 250 mm) was used. The identity of the products was established by comparison of their retention volumes with those of authentic standard samples, using at least two different solvent systems (MeOH:H_2O, 70:30 and MeOH:0.01M

$(NH_4)_2HPO_4$, 60:40) at a flow rate of 1 ml/min. Static activity analyses were carried out with NaI (Picker Nuclear Inc.) scintillation counter.

1-(α,α,α-Trifluoro-m-tolyl)-4-methoxycarbonyl piperazine (7). Compound 7 was prepared according to a literature procedure (16) in 95% yield. NMR: δCCl_4 3.1 (m, 4H), 3.5 (m, 4H), 3.65 (s, 3H), 6.95 (m, 4H). MS: m/e - 288.

1-(α,α,α-Trifluoro-m-tolyl)-4-acetylpiperazine (8). A solution of N-(α,α,α-trifluoro-m-tolyl)piperazine (0.3g, 1.3 mM) in 2 ml of dioxane was added slowly to a solution of acetyl chloride (0.2g, 2.6 mM) in 2 ml of dioxane. A white precipitate was formed immediately. The mixture was stirred for 3 hours at room temperature, hydrolyzed with cold water and the solution was basified with 6N NaOH. The solution was extracted with ether and the ethereal layer was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give 300 mg (85% yield) of colorless liquid. NMR: δCCl_4 2.00 (s, 3H), 3.05 (m, 4H), 3.45 (m, 4H), 7.00 (m, 4H). M.S.: m/e = 272.

N,N-bis(2-Bromoethyl)amine Hydrobromide (5b). Compound 5b was prepared according to the literature procedure (17) in 60% yield. NMR: δD_2O 3.75 (t, 4H), 3.85 (t, 4H). The freebase of N,N-bis(2-bromoethyl)amine was obtained by careful neutralization of its hydrobromide salt with 10N NaOH. However, a rapid intramolecular nucleophilic substitution reaction occurred to give N-(2-bromoethyl)azinidine. NMR: δD_2O 1.6 (m, 2H), 1.95 (m, 2H), 2.8 (t, 2H), 3.7 (t, 2H).

N,N-bis(2-Bromoethyl)-N-methoxycarbonylamine (5e) and N,N-bis(2-chloroethyl)-N-methoxycarbonylamine (5d). Compounds 5e and 5d were prepared according to a known procedure from N,N-bis(2-bromoethyl)amine (5b) and N,N-bis(2-chloroethyl)amine (5c) in 67% and 89% yield respectively, and the structures were determined by NMR and MS. Compound 5e NMR: δCCl_4 3.55 (m, 8H), 3.65 (s, 3H). MS: m/e = 199. Compound 5d NMR: δCCl_4 3.40 (m, 8H), 3.65 (s, 3H).

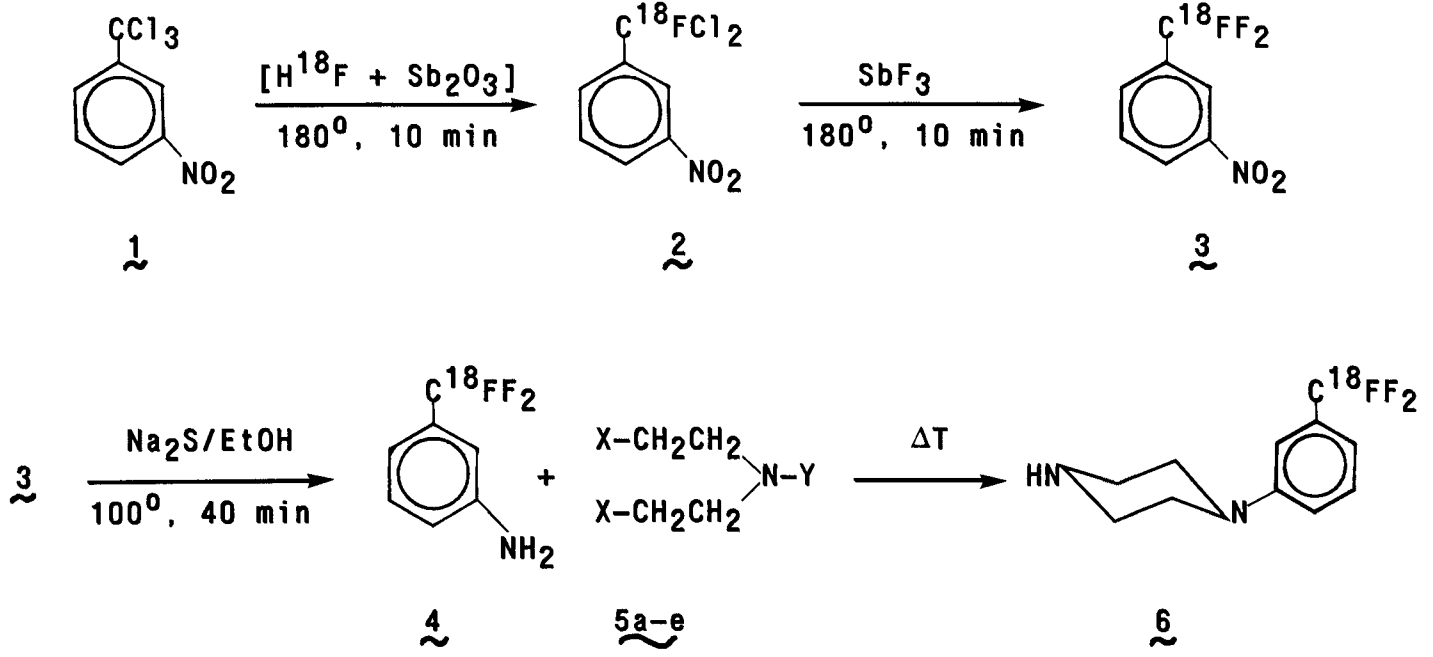
3-Nitro-α,α,α-tri[^{18}F]fluorotoluene (3). Antimony trioxide (1 mg) was added to 0.1 ml of aqueous no-carrier-added H[^{18}F] solution (30 mCi) in a screw capped glass vial. The suspension was warmed in an 100°C oil bath under vigorous stirring for 3 minutes, evaported and coevaporated with CH_3CN (3 x 0.5 ml) to dryness at 130°C under a slow stream of nitrogen. 3-Nitro-α,α,α-trichlorotoluene

(1) (47 mg, 0.2 mmol) was added to the resulting white powdered solid residue, the solution was stirred at 180°C for 10 minutes and then cooled to room temperature. Antimony trifluoride (20 mg, 0.12 mmol) was added to the cold solution and was heated again at 180°C for an additional 10 minutes. At the end of the reaction, 0.1 ml of CH_3OH and 5 ml of H_2O were added and the resulting solution was passed through a C18 Sep-Pak cartridge. The cartridge was washed with 5 ml of H_2O and the washings were discarded. The products were eluted with toluene and analyzed by HPLC. Compound 3 was isolated in 75% radiochemical yield.

α,α,α-Tri[^{18}F]fluoro-m-toluidine (4). Sodium sulfide (0.3g, 2.3 mmol) was added to a solution of carrier-added 3-nitro-α,α,α-tri[^{18}F]fluorotoluene (3) (0.3g, 1.6 mM, 17.4 mCi) in 6 ml of ethanol. The mixture was kept at 100°C for 40 minutes and was cooled to room temperature. The resulting sulfur was separated from the reaction mixture by centrifugation, the supernant was acidified with 2N HCl and evaporated to dryness to give a slushy white solid. Two milliliters of H_2O were added and the suspension was filtered to give a colorless solution which was passed through a C18 Sep-Pak cartridge. The hydrochloric salt of 4 was eluted with 3 ml of H_2O, whereas unreacted 3 remained on the cartridge. The aqueous solution was neutralized with 6N NaOH and extracted with ether (2 x 2 ml). The ethereal layer was dried (Na_2SO_4) and evaporated to give 170 mg, 8.3 mCi (69% chemical yield, 70% radiochemical yield) of α,α,α-tri[^{18}F]fluoro-m-toluidine (4). The identity of compound 4 was confirmed by HPLC and NMR. NMR: δCCl_4 5.6 (s, 2H); 7.00 (m, 4H).

N-(α,α,α-Tri[^{18}F]fluoro-m-tolyl)piperazine (6). A mixture of α,α,α-tri[^{18}F]fluoro-m-toluidine (4) (170 mg, 1.04 mmol, specific activity 8 Ci/mol) and N,N-bis(2-bromoethyl)-N-methoxycarbonylamine (5e) (435 mg, 1.48 mmol) in a small vial was heated for 2 hours at 150°C under vigorous agitation. After cooling, 4.0 ml H_2O were added and the resulting emulsion was neutralized with 6N NaOH. The products were extracted with CCl_4 (2 x 3.0 ml), dried (Na_2SO_4) and evaporated to give 330 mg of a residue. Radio HPLC analyses of the residue revealed complete absence of the starting compound 4.

A fairly good yield of compound 6 (1.9 mCi, yield: 51%) was obtained,



	X	Y
a	OH	H
b	Br	H
c	Cl	H
d	Cl	CO_2CH_3
e	Br	CO_2CH_3

Scheme 1 Synthesis of N-(α,α,α-Tri[^{18}F]fluoro-m-tolyl)piperazine

together with a limit amount (0.15 mCi) of carbamate derivative 7. Moderate yields (0.50 mCi) of an intermediate compound, i.e. N(2-bromoethyl)-N'[m-[^{18}F]-(trifluoromethyl)phenyl]ethylenediamine were observed, together with significant quantities (0.90 mCi) of an unknown compound.

RESULTS AND DISCUSSION

Recently, we reported that H[^{18}F] + Sb_2O_3 can selectively introduce fluorine-18 into a trihalogenomethyl group in 20-50% yield (14). However, attempts to directly label N-(α,α,α-trifluoro-m-tolyl)piperazine (6) with this reagent does not undergo any measurable ^{18}F-to-^{19}F exchange reaction even at relatively high temperature (200°C). Neither the addition of a small amount of anhydrous $AlCl_3$ to the reaction mixture nor the employment of the analogs of 6 with an electron-withdrawing group (eg. CO_2CH_3, $COCH_3$) on the secondary nitrogen of 6 (compounds 7 and 8) promoted any incorporation of ^{18}F into trifluoromethyl group. We therefore have synthesized ^{18}F-labeled 6 from 3-nitro-α,α,α-trichlorotoluene (1) in four steps in 27% radiochemical yield (Scheme 1).

Fluorination of 3-nitro-α,α,α-trichlorotoluene (1) with H[^{18}F] + Sb_2O_3 and antimony trifluoride gave 3-nitro-α,α,α-tri[^{18}F]fluoro-m-toluidine (4) in 70% yield. Reactions of 4 with a series of N,N-bis(2-haloethyl)amine or its analogs (5a-e) were investigated. However, only the reaction of 4 with N,N-bis(2-bromoethyl)-N-methoxycarbonylamine (5e) gave N-(α,α,α-tri[^{18}F]fluoro-m-tolyl)piperazine (6) in reasonable yield (51%). The remaining reactants studied (5a-d) were not suitable for preparing compound 6 due to either long reaction time or undesired side products.

Thus, this reaction sequence provides a general method to prepare N-(α,α,α-tri[^{18}F]fluoro-m-tolyl)piperazine (6) and related compounds. Because of its low specific activity, the utility of compound 6 synthesized by this method remains to be seen. The specific activity of 6, however, probably can be imporved by the reaction of α-chloro-α,α-difluoro-m-nitrobenzene with H[^{18}F]-Sb_2O_3.

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