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SYNTHESIS OF 7-[^{123}I]IODOTACRINE: A POTENTIAL SPECT AGENT TO MAP ACETYLCHOLINESTERASE

Murthy R. Akula and George W. Kabalka*

*Departments of Chemistry and Radiology
University of Tennessee
Knoxville, TN 37996-1600 USA;
Phone: (423)974-3260 Fax: (423)974-2997

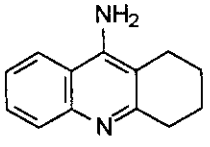
SUMMARY

9-Amino-1,2,3,4-tetrahydroacridine (Tacrine), a cognitive enhancer, is an inhibitor of the enzyme acetylcholinesterase. The synthesis of no-carrier-added 7-[^{123}I]iodotacrine, was accomplished in four steps for potential use in mapping acetylcholinesterase.

Keywords: [^{123}I]Iodotacrine, acetylcholinesterase, SPECT, 2-cyanoaniline, radioiodination, Radio-TLC.

INTRODUCTION

Alzheimer's disease (AD) affects four million elderly Americans and is one of the most debilitating ailments. AD is currently recognized as a major cause of memory loss (1). As general health care has improved, the proportion of senile population has continued to increase and diseases affecting cognition have assumed ever-increasing prominence (2). As a result, extensive research is currently underway with the goal of finding effective diagnostic methods and treatments for AD and related cognitive disorders. Tacrine, **1**, a cognitive enhancer in AD patients was recently approved for patient use. This drug is a very potent



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(IC_{50} = 0.319 μM) and selective acetylcholinesterase inhibitor (3). Our research efforts have focused on synthesizing a no carrier-added radioiodinated analogue of tacrine for use as a SPECT imaging agent to map acetylcholinesterase receptor sites.

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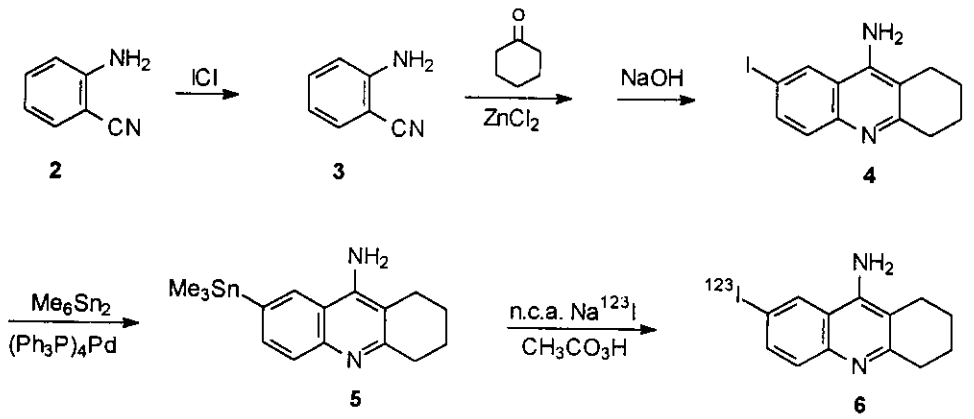
RESULTS AND DISCUSSION

The synthesis of no-carrier-added 7-[^{123}I]iodotacrine, **6**, is outlined in the Scheme. 2-Cyanoaniline, **2**, was converted into the requisite tin precursor **5** in three steps. An attempted

Scheme



2 **3** **4** **5** **6**

iodination of 2-cyanoaniline using a solution of iodine monochloride in methylene chloride did not furnish the required compound and the starting material was recovered. However, iodination of substituted aniline **2** according to the method of Wallington and Krueger (4) using iodine monochloride in water afforded the isomerically pure 2-cyano-4-iodoaniline, **3**, in 81% yield, m.p. = 85-87 °C. 2-Cyano-4-iodoaniline **3** was heated with an excess of cyclohexanone at 140 °C and an equimolar amount of zinc chloride to isolate the zinc complex of tricyclic amine **4** (5). Free amine **4** was generated by treating the complex with sodium hydroxide to obtain a colorless solid which was recrystallized from chloroform in 91% yield, m.p. = 252 -254 °C. 7-Iodotacrine, **4**, was then subjected to a palladium catalyzed deiodostannylation. The reaction of **4** with hexamethylditin and tetrakis(triphenylphopshine)palladium(0) in refluxing dioxane for 0.5 h gave 7-trimethylstannyl tacrine, **5** in 55% yield. The tin precursor was

purified using silica gel column chromatography to afford white solid, m.p. = 205-207 °C. No-carrier-added radioiodination of 7-trimethylstannyl tacrine **5** was conducted by conventional electrophilic idodestannylation using Na^{123}I and dilute peracetic acid.

EXPERIMENTAL

Melting points were recorded on an Electrothermal Digital Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 MHz NMR spectrometer. The chemical shift values are expressed in part per million (δ) scale relative to tetramethylsilane. Radio thin layer chromatography was carried out using a radio-TLC scanner (Bioscan, Autochanger 300, system imaging scanner). The starting materials were purchased from Aldrich Chemical Company. All the reactions were carried out using dry solvents under inert atmosphere. Na^{123}I was purchased from Nordion Inc., Vancouver Canada.

2-Cyano-4-iodoaniline (3). 2-Cyanoaniline (5.0 g, 42 mmol) was dissolved in a mixture of water (125 mL) and concentrated hydrochloric acid (12 mL) contained in a 1L beaker and the solution was cooled to 20 °C. A solution of iodine monochloride (6.9 g, 42 mmol) was prepared in a mixture of water (25 mL) and concentrated hydrochloric acid (7 mL) contained in a 250 mL beaker at 5 °C. The iodine monochloride solution was added rapidly to the cyanoaniline solution at 20 °C. 2-Cyano-4-iodoaniline separated almost immediately as a granular white precipitate. The mixture was stirred for one hour and allowed to warm to room temperature prior to filtration using a Büchner funnel. The product was washed with three portions of cold water (3 x 100 mL) and dried to obtain 9.8 g of crude product which was crystallized from ethanol. Yield = 8.8 g (81%). M.p. = 85-87 °C. ^{1}H NMR ($CDCl_3$), δ, 4.49 *(bs,* 2H, amine), 6.54 (*d*, $J_{6,5}$ = 7.5 Hz, 1H, H-6), 7.53-7.57 (*dd*, $J_{5,3}$ = 2 Hz, $J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.63-7.64 (*d*, $J_{3,5}$ = 2 Hz, 1H, H-3). ^{13}C NMR($CDCl_3$), δ, 98.10 (C-4), 115.94 (C-6), 116.99 (C-5), 139.63 (C-3), 142.36 (C-2) and 148.97 (C-1). Anal: $C_7H_6N_2$ requires C, 34.45, H, 2.06. N, 11.48. Found: C, 34.60, H, 2.01, N, 11.48.

9-Amino-7-iodo-1,2,3,4-tetrahydroacridine (4). Zinc chloride (4.0 g, 30 mmol) was added to a solution of 2-cyano-4-iodoaniline (3.6 g, 15 mmol) in cyclohexanone (15 mL) and the resulting mixture was stirred at 145-150 °C for 30 min. After cooling, the material was broken into small lumps and agitated in ethyl acetate. The solid zinc complex was filtered and washed with ethyl acetate (2 x 50 mL). The complex was suspended in water (100 mL), 6*N* sodium hydroxide (15 mL) was then added and the mixture heated at 60 °C for 1 hr. The mixture was filtered and the solid was thoroughly washed with water. The product was air dried and recrystallized from chloroform to obtain colorless needles. Yield = 4.4 g (91%). M.p. = 252-254 °C. NMR (DMSO -d_6), δ, 1.85 (*t*, 4H, H-2 and H-4), 2.50 (*t*, 2H, H-1), 2.85 (*t*, 2H, H-4), 6.42 (*bs*, 2H, amine), 7.35 (*d*, $J_{5,6}$ = 7.5 Hz, 1H, H-5), 7.75 (*d*, $J_{6,5}$ = 7.5 Hz, 1H, H-6) and 8.65 (*s*, 1H, H-8). ^{13}C NMR (DMSO-d_6), δ, 22.10, 22.53 (C-2, C-3), 25.15 (C-1), 26.26 (C-4), 93.41 (C-7), 126.20, 129.84, 130.91, 138.42, 140.64, 146.42 (aromatic carbons), 161.28 (C-9). Anal: $C_{13}H_{13}N_2I$ requires C, 48.17, H, 4.04, N, 8.64. Found: C, 47.88, H, 4.04, N, 8.50.

9-Amino-7-trimethylstannyl-1,2,3,4-tetrahydroacridine (5). Hexamethylditin (1.7 g, 5.2 mmol) and iodotacrine **4** (1.1 g, 3.4 mmol) were added sequentially to a suspension of tetrakis-triphenylphosphinepalladium(0) (0.15 g, 0.12 mmol) in anhydrous 1,4-dioxane (25 mL). The reaction mixture was stirred at reflux under nitrogen for 0.5 h. After cooling, the mixture was filtered, the insoluble black material was washed with dioxane (25 mL), and the dioxane layers combined. Removal of the dioxane solvent gave a gummy residue which was purified by chromatography (silica gel, chloroform/methanol = 9/1 (v/v). The solid product was recrystallized from ethyl acetate/petroleum ether to furnish **3**. Yield = 0.67 g (55%). M.p. = 205-207 °C. ^{1}H NMR ($CDCl_3$), δ, 0.32 [*s* with Sn satellites, J_{Sn-H} = 54 Hz, 9H, $Sn(CH_3)_3$], 1.83 (*t*, 4H, H-2 and H-3), 2.50 (*t*, 2H, H-1), 2.90 (*t*, 2H, H-4), 7.75 (*d*, $J_{5,6}$ = 7.8 Hz, 1H, H-5), 7.85 (*d*, Sn satellites J_{Sn-H} = 47 Hz, 1H, H-6), 8.15 (*bs*, 2H, amine), 8.52 (*s*, Sn satellites J_{Sn-H} = 47 Hz, 1H, H-8). Anal: $C_{16}H_{22}N_2Sn$ requires C, 53.22, H, 6.12, N, 7.76. Found: C, 52.88, H, 6.46, N, 7.34.

9-Amino-7-[^{123}I]iodo-1,2,3,4-tetrahydroacridine (6). No-carrier-added Na^{123}I (1 mCi, specific activity ~250 Ci/μM) dissolved in 40 μL of methanol was placed in a 1 mL Wheaton vial containing a solution of tin precursor **5** (50 μL of a 5.2 x10^{-2} M solution in MeOH). Peracetic acid (100 μL, 0.3% solution in methanol) was added over a one minute period. The vial was gently shaken and allowed to stand for 3 minutes. A drop of saturated aqueous sodium thiosulphate was added to destroy excess iodine. Volatile solvents were removed using a stream of nitrogen and the residue dissolved in a 2:1 (v/v) mixture of chloroform:methanol (0.2 mL). **6** was purified by passing it through two alumina Sep-pak cartridges in series using chloroform: methanol (4:1) as eluent. The radiochemical purity of **6** was verified by radio-TLC using an aluminum backed silica gel plate utilizing chloroform:methanol = 4:1 as the solvent system (Figure, R_f = 0.61). Both the chemical and radiochemical purities were >99% and the decay corrected radiochemical yield of **6** was 32%. The average time of synthesis and purification was 20 min.

CONCLUSION

In summary, a no-carrier-added iodine-123 labeled tacrine, **6**, a potential SPECT agent for mapping acetylcholinesterase receptor sites, was synthesized via iododestannylation in good yield and high radiochemical purity. Biodistribution studies are currently underway and the synthesis of F-18 labeled analogue is being developed.

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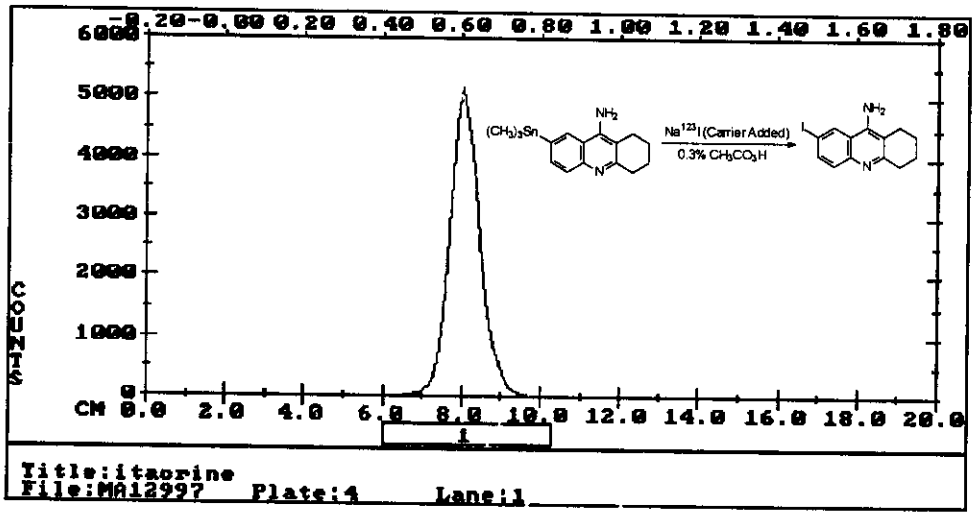

Figure: Radio-TLC of 9-Amino-7-[^{123}I]iodo-1,2,3,4-tetrahydroacridine (6)

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