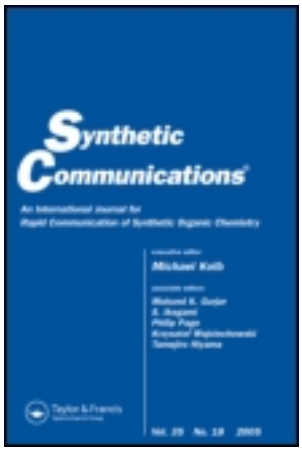

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A DIRECT IODINATION METHOD WITH IODINE AND SILVER TRIFLATE FOR THE SYNTHESIS OF SPECT AND PET IMAGING AGENT PRECURSORS

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A DIRECT IODINATION METHOD WITH IODINE AND SILVER TRIFLATE FOR THE SYNTHESIS OF SPECT AND PET IMAGING AGENT PRECURSORS

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ABSTRACT

A direct iodination method with iodine and silver triflate for the synthesis of SPECT and PET imaging agent precursors has been developed.

Iodinated aromatic compounds are essential precursors to innumerable radioiodinated tracers,[1] tritiated compounds, and several PET (positron emission tomography) imaging agents, including β-[^{11}C]CIT,[2] N-fluoroethyl β-CIT, and [^{11}C]iomazenil. The most important aromatic iodination methodologies[3] include: (a) direct iodination with I_2; a slow and reversible reaction with requires the help of an oxidant, metallic salts[4,5] or strong oxidizing acids, (b) iodination with iodide plus an oxidant or an interhalogen compound such as ICI, (c) the use of electrochemical

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reactions, or hypervalent iodine reagents,[6] (d) iododemetalation, and (e) the Sandmeyer diazotization reaction. A problem with the existing iodination procedures is that many require harsh conditions that can destroy structurally complex and sensitive drug molecules such as those containing amino and ester functions. Others utilize toxic salts of thallium or mercury which raise safety and disposal concerns. We recently (re)discovered the iodine and Silver Triflate (I_2-AgOTf) iodination system in response to frustrating and unsuccessful attempts to iodinate the phenyl tropane precursor of β-CIT by a published procedure. The reported literature method[7] using I_2 in HNO_3/H_2SO_4, gave very poor yields in our hands due to competing ring nitration and ester hydrolysis. We were familiar with the l_2-silver sulfate iodination system[4] and reasoned that substitution of the more organic-soluble AgOTf for Ag_2SO_4 might lead to faster reactions. Indeed, we found that the I_2-AgOTf reagent iodinated the β-CIT precursor in CH_2Cl_2 very smoothly at room temperature in high yield.[8] These impressive results made us wonder if others had reported the I_2-AgOTf reagent. A search found a single brief communication in 1977,[9] that has been largely overlooked in the subsequent literature.[3–6] In view of the limited amount of study of the reagent, and our favorable initial results, we decided to investigate in more detail its utility for direct iodination of a variety of compounds of interest as radiopharmaceuticals SPECT (single photon emission computed tomography) and PET imaging agents and precursors.

RESULTS AND DISCUSSION

The I_2-AgOTf reagent iodinated a variety of aromatic structures at room temperature. The progress of the iodination reaction was easily monitored through the appearance of insoluble AgI and the disappearance of the dark iodine color. Iodinations of activated molecule could be ''titrated'' by adding measured concentrations of I_2 solution to a solution of substrate and AgOTf until I_2 color just persisted. Electron rich activated molecules such as methoxybenzenes reacted almost instantaneously. In the absence of AgOTf, iodination of the same substrates was extremely slow (days) or totally unsuccessful, even if the substrates are strongly activated veratroyl derivatives. Unactivated compounds (benzene, toluene) iodinated within a few minutes. Deactivated compounds (chlorobenzene, nitroanisoles) iodinated within minutes to a few hours with I_2-AgOTf. Mono-iodination was favored over poly-iodination. In the iodination of benzilic acid esters, only monoiodo-benzilate esters were produced, even in the presence of excess I_2-AgOTf. Concerning the regiochemistry of the iodination reaction, the para position was favored over the ortho site in nearly all cases.

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Aromatic compounds with electron densities equal to or greater than that of chlorobenzene could be iodinated by the I_2-AgOTf reagent. Benzophenone was not iodinated under standard conditions at room temperature; it is apparently too deactivated for the reagent. I_2-AgOTf did not react across the somewhat electron deficient double bond of azalactones. Nor was there significant iodination of unsubstituted phenyl groups in the oxazoline ring of azalactones. Molecules containing benzylic alcohol functions appeared to suffer oxidation by the I_2-AgOTf reagent. Some ethers and alcohols appear to react slowly with the reagent. Reaction solvent choices may be limited. Dichloromethane and chloroform were tried. The best solvent is dichloromethane. Iodination of radiotracers and precursor drugs containing primary, secondary, and tertiary amines occurred smoothly and in good to very good yields. Catechol derivatives were iodinated at the 6-position with I_2-AgOTf. The essentially anhydrous and neutral conditions and methylene chloride reaction medium permits application of this reagent to a wide range of organic compounds. The results are summarized in Scheme 1, 2, 3 and Table 1. All compounds made here are known compounds.

From a mechanistic point of view, we think the first process is an activation of the iodine molecule, which is polarized by the soft–soft interaction with the silver triflate, which increase the electrophilicity of the iodine and, consequently, its reactivity towards the substrate aromatic compound. This iodination obeys the orientation rule of an aromatic S_E reaction, and is assumed to take place according to the following mechanistic equations (Scheme 4).

In conclusion, we have established a mild, simple, and convenient method for the direct iodination of a wide range of aromatic compounds using a combination of iodine and silver triflate.

EXPERIMENTAL

Typical Iodination Procedure

A mixture of aromatic compound (2 mmol), silver triflate (2–4 mmol), and iodine (2–4 mmol) was stirred together in 10 mL CH_2Cl_2 in a darkened fume hood. Alternatively a solution of iodine in methylene chloride or chloroform could be added dropwise to a CH_2Cl_2 solution of the first two ingredients. If the aromatic compound contained a basic amine function, acetic acid (5 drops) was added to prevent amine-iodine complexation, or an organic-soluble acid salt form was used. Loss of iodine color and precipitation of AgI occurred as the reaction progressed. Reaction times to completion ranged from a few minutes to 12 hours, depending upon the degree

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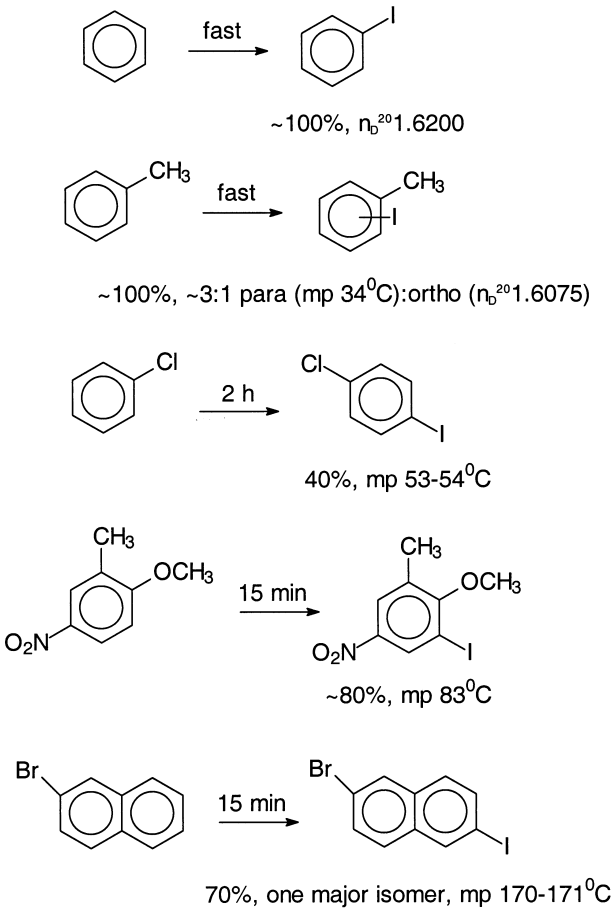
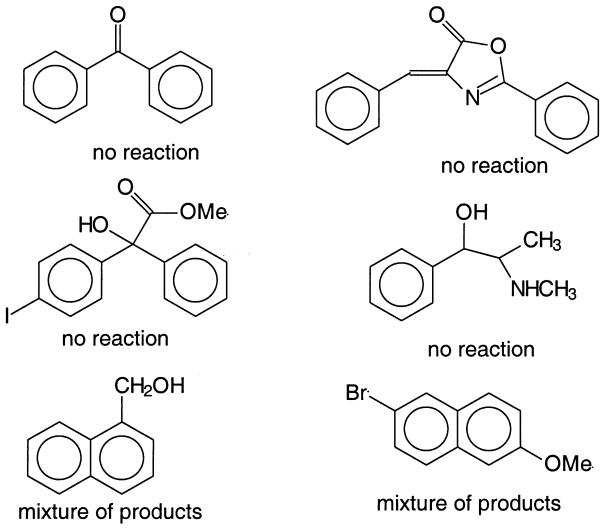


Scheme 1. Iodination of simple compounds.

of activation of the aromatic ring. Workup: AgI was removed by filtration and washed with 4×3 mL CH_2Cl_2. The combined CH_2Cl_2 solution was washed with dilure NH_4OH, dilute Na_2SO_3, and water, then dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give the crude product. Crude products were analyzed by TLC, HPLC or in some cases GC. Products were further purified, if necessary, by flash chromatography with silica gel and hexane/Et_2O/iPr_2NH mixtures as eluent. Product percentages were given representative isolated yields. Final products were



Scheme 2. Substrates which failed to iodinate or gave complex mixtures with I_2-AgOTf.

characterized by some relevant analytical data such as n_D,[20] mp or ^{1}H NMR (Bruker QE 300, TMS as an internal standard, $CDCl_3$ as solvent) in comparison with the compounds which are known from the literature.

Analytical data for the compounds in Scheme 3 were listed as below. β-**CIT**, ^{1}H NMR ($CDCl_3$), δ 7.60 (d, 2H, J = 8.4 Hz), 7.02 (d, 2H, J = 8.1 Hz), 3.73–3.58 (m, 1H), 3.50 (s, 3H), 3.38–3.35 (m, 1H), 2.95–2.86 (m, 2H), 2.60–2.54 (m, 1H), 2.23 (s, 3H), 2.16–2.13 (m, 2H), 1.84–1.75 (m, 3H). β-**CINT**, ^{1}H NMR ($CDCl_3$), δ 7.77–7.67 (m, 3H), 7.41–7.38 (m, 3H), 3.60–3.59 (m, 1H), 3.43 (s, 3H), 3.41–3.39 (m, 1H), 3.18–3.12 (m, 1H), 3.03–3.02 (m, 1H), 2.78–2.66 (m, 1H), 2.24 (s, 3H), 2.28–2.06 (m, 2H), 1.85–1.58 (m, 3H). **I-MDM**, ^{1}H NMR ($CDCl_3$), δ 7.60–7.24 (m, 9H), 4.23 (s, 1H), 3.86 (s, 3H). **I-QNB**, ^{1}H NMR ($CDCl_3$), δ 7.71–7.65 (m, 2H), 7.41–7.21 (m, 7H), 4.98–4.91 (m, 1H), 3.20–3.08 (dd, 1H, J = 15.8, 2.0 Hz), 2.95–2.45 (m, 6H), 2.00–1.98 (m, 1H), 1.64–1.24 (m, 4H). **I-TRB**, ^{1}H NMR ($CDCl_3$), δ 7.65–7.32 (m, 9H), 5.20–5.16 (m, 1H), 3.25–3.18 (m, 2H), 2.42 (s, 3H), 2.14–2.08 (m, 1H), 1.96–1.68 (m, 4H), 1.60–1.47 (m, 4H). **I-PB**, ^{1}H NMR ($CDCl_3$), δ 7.58–7.36 (m, 9H), 5.10–5.04 (m, 1H), 3.49–3.40 (m, 1H), 2.88–2.72 (m, 1H), 2.53–2.48 (m, 4H), 1.83–1.79 (m, 4H).

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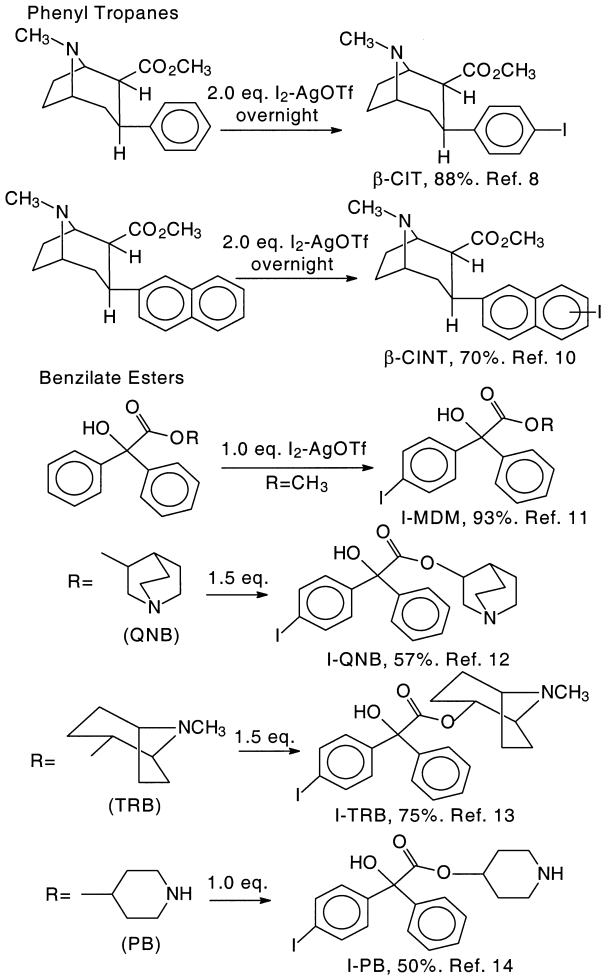

Scheme 3. Iodination of radiotracer precursors.

Analytical data for the products in Table 1 were listed as below. Entry 1 Product, ^{1}H NMR ($CDCl_3$), δ 7.70 (s, 1H), 6.92 (s, 1H), 5.95 (s, 2H), 3.78 (s, 2H), 1.45 (s, 2H). Entry 2 Product, ^{1}H NMR ($CDCl_3$), δ 7.70 (s, 1H), 6.94 (s, 1H), 5.96 (s, 2H), 3.85–3.76 (m, 2H), 2.98–2.90 (m, 2H), 1.43 (s, 2H). Entry 3 Product, ^{1}H NMR ($CDCl_3$), δ 7.71 (s, 1H), 6.93 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83–3.80 (m, 2H), 2.96–2.93 (m, 2H), 1.45 (s, 2H). Entry 4 Product, ^{1}H NMR ($CDCl_3$), δ 7.70 (s, 1H), 6.94 (s, 1H), 5.97 (s, 2H), 3.66–3.61 (m, 2H), 3.03 (s, 1H), 2.94–2.89 (m, 2H), 2.88 (s, 3H). Entry 5

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Product, ^{1}H NMR ($CDCl_3$), δ 7.24 (s, 1H), 6.70 (s, 1H), 6.50 (brs, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.61 (dt, 2H, J = 6.5, 6.5 Hz), 2.98 (t, 2H, J = 6.5 Hz). Entry 6 Product, ^{1}H NMR ($CDCl_3$), δ 7.73 (s, 1H), 7.50–7.34 (m, 5H), 6.93 (s, 1H), 5.95 (s, 2H), 3.60–3.55 (m, 2H), 3.01 (s, 1H), 2.94–2.91 (m, 2H), 2.72 (s, 2H). Entry 7 Product, ^{1}H NMR ($CDCl_3$), δ 8.11 (s, 1H), 7.71 (s, 1H), 6.92

Table 1. Catechol Derivatives Iodinate at the 6-Position[a]

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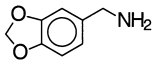
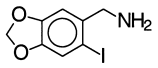
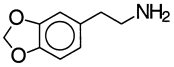
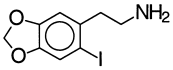
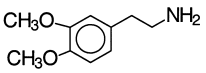
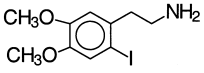
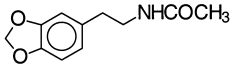
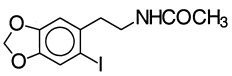
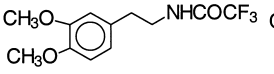
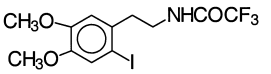
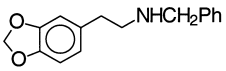
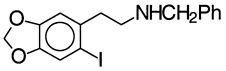
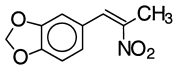
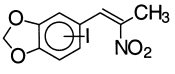
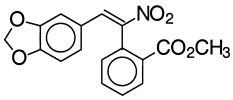
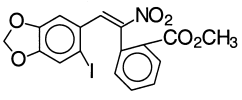
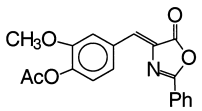
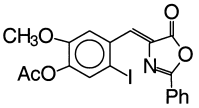
1.			65	15
2.			61	16
3.			73	17
4.			78	17
5.			>90	18
6.			67	17
7.			>90 (2:1 6-iodo:2-iodo)	19
8.			87	20
9.			90	21

(*continued*)

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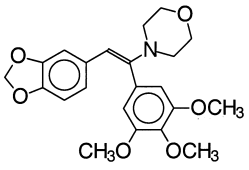
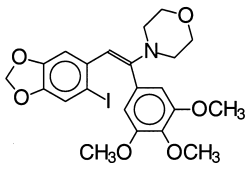
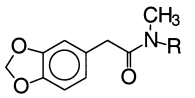
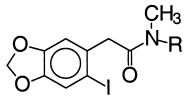
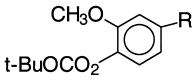
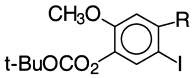
Table 1. Continued

Entry	Substrate	Product	Yield[b]	Ref.
10.			83	22
11.	 R=CH_2OSiMe_2t-Bu		57	23
12.	 R=$CH_2CH(NHCO_2t\text{-}Bu)CO_2CH_3$		60	24

[a]Reaction conditions: 1 : 1 :1 :1 substrate/I_2/AgOTf, CH_2Cl_2, R. T., in a darkened fume hood; [b]isolated yield.

$$CF_3SO_3Ag + I_2 \rightleftharpoons CF_3SO_3I + AgI$$
$$CF_3SO_3I \rightleftharpoons CF_3SO_3^- + I^+$$
$$I^+ + ArH \longrightarrow ArI + H^+$$
$$CF_3SO_3^- + H^+ \rightleftharpoons CF_3SO_3H$$

Scheme 4. Mechanistic equation of iodinatior.

(s, 1H), 5.98 (s, 2H), 2.46 (s, 3H). Entry 8 Product, ^{1}H NMR ($CDCl_3$), δ 7.98 (s, 1H), 7.70 (s, 1H), 7.50–7.35 (m, 4H), 6.94 (s, 1H), 5.95 (s, 2H), 3.81 (s, 3H). Entry 9 Product, ^{1}H NMR ($CDCl_3$), δ 7.77 (s, 1H), 7.58 (s, 1H), 7.50–7.39 (m, 5H), 6.93 (s, 1H), 3.47 (s, 3H), 3.02 (s, 3H). Entry 10 Product, ^{1}H NMR ($CDCl_3$), δ 7.23 (s, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 6.77 (s, 2H), 5.97 (s, 2H), 3.89 (s, 6H), 3.86 (s, 3H), 3.75–3.68 (m, 4H), 2.59–2.51 (m, 4H). Entry 11 Product, ^{1}H NMR ($CDCl_3$), δ 7.23 (s, 1H), 6.98 (s, 1H), 5.97 (s, 2H), 4.02 (s, 2H), 3.33 (s, 2H), 2.80 (s, 3H), 0.93 (s, 9H), 0.11 (s, 6H). Entry 12 Product, ^{1}H NMR ($CDCl_3$), δ 7.33 (s, 1H), 6.95 (s, 1H), 3.82

(s, 3H), 3.65 (t, 1H, J = 8.1 Hz), 3.40 (s, 3H), 3.13 (s, 1H), 2.96 (d, 2H, J = 7.0 Hz), 1.13 (s, 9H), 1.10 (s, 9H).

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