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RADIOIODINATION *VIA* VINYLSTANNYLATED ALKYLATING AGENTS

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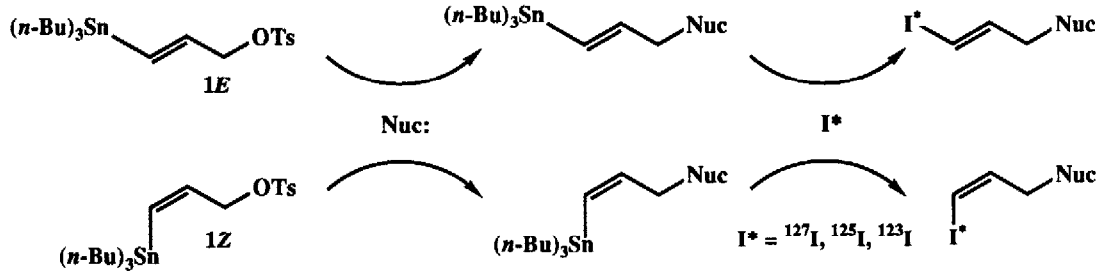
Summary: *p*-Toluenesulfonate esters of (*E*)- and (*Z*)-3-(tri-*n*-butylstannyl)-2-propen-1-ol readily react with nucleophiles to give vinylstannanes which are substrates for rapid, efficient and stereospecific radioiododestannylation at the no-carrier-added level. This general approach is illustrated by syntheses of iodinated spiperone analogs for studies of dopamine D2 receptors.

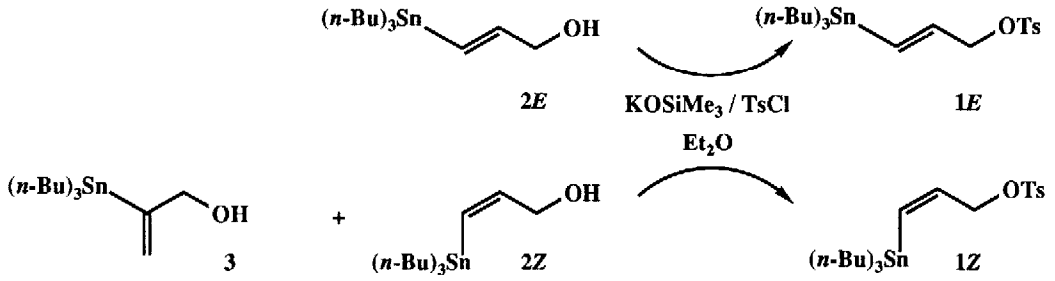
Vinylstannanes are recognized as versatile intermediates for the preparation of alkenyl halides.[1] Our interest in the design and synthesis of radioiodinated tracers for use in biomedical research has prompted us to develop novel vinylstannylated alkylating agents, **1*E*** and **1*Z***, which can be readily coupled to nucleophilic target molecules for subsequent stereospecific radioiododestannylation (Scheme 1).[2,3] These were selected for several reasons. First, in terms of chemical and biochemical stability, vinyl iodides are much less labile than aliphatic iodides and are comparable to the more widely employed aryl iodides.[4] In addition, the allylic framework initially facilitates coupling and then provides a spacer group of reasonable size and lipophilicity. Finally, halodestannylation allows efficient incorporation of radioiodine under mild conditions at the last step of the synthetic sequence.



Scheme 1.

The 3-(tri-*n*-butylstannyl)-2-propen-1-ols (**2*E*** and **2*Z***), as well as structural isomer **3** (*cf.* Scheme 2) were prepared by treatment of propargyl alcohol with tri-*n*-butyltin hydride (1.3 equiv) and a catalytic amount of azobis(isobutyronitrile).[5] Short-path chromatography on silica gel provided pure **2*E***. In accord with previous observations, **2*Z*** and **3** were obtained as an inseparable mixture. Esterification of **2*E*** with *p*-toluenesulfonyl chloride under standard Tipson conditions was uniformly unsuccessful even with work-up procedures conducted at ice bath temperatures and with the use of aqueous copper sulfate for removal of pyridine.

However, when potassium trimethylsilanolate, an organic soluble potassium hydroxide equivalent,[6] and *p*-toluenesulfonyl chloride in diethyl ether at -25 °C were employed, a 50% yield[7] of the desired tosylate **1*E*** was achieved (Scheme 2).[8] Application of this procedure to a mixture of **2*Z*** and **3** (1.1:1) allowed isolation of **1*Z*** in 42% yield (Scheme 2). Alternatively, pure **2*Z*** for tosylation can be prepared by hydroalumination of propargyl alcohol followed by stannylation with tri-*n*-butyltin triflate;[9] however, the present route allows convenient access to **1*E*** as well as **1*Z***. Once purified, **1*E*** and **1*Z*** are stable at -20 °C for at least 10 weeks.

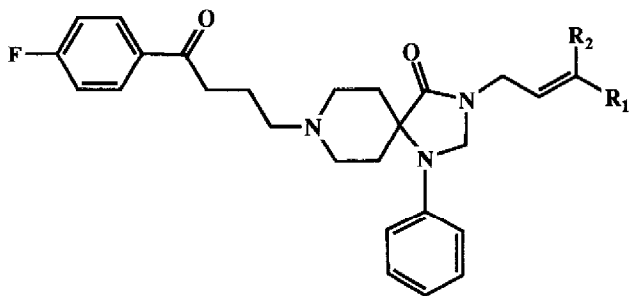


Scheme 2.

With **1*E*** and **1*Z*** in hand, we turned our attention toward alkylation of the amide nitrogen of spiperone, a potent butyrophenone neuroleptic with high affinity for dopamine D_2 receptors. This target was selected because of the great interest in the development of [^{123}I]-labelled tracers for localization of dopamine D_2 receptors in living human brain by single photon emission computed tomography[10] and because of the substantial bulk tolerance, with respect to dopamine D_2 receptor binding, at this position of spiperone.[11] The reaction of spiperone (98 mg) with sodium hydride (6 equiv) and **1*E*** (1.2 equiv) in dry DMF for 5 minutes at ambient temperature rendered **4*E*** in 47% yield (Figure 1).[12] In similar fashion, **4*Z*** was prepared from spiperone and **1*Z*** in 48% yield. Conversion of **4*E*** and **4*Z*** to the corresponding vinyl iodides, **5*E*** (40%) and **5*Z*** (84%), was accomplished for each case by treatment with iodine (1.05 equiv) in dichloromethane at ambient temperature for 1.5 hours (Figure 1). The nature of the double bond was confirmed by high-field (300 MHz) ^{1}H NMR spectroscopy which clearly defined appropriate vicinal couplings for **5*E*** (^{3}J = 14.6 Hz) and **5*Z*** (^{3}J = 7.3 Hz). Although **5*E*** and **5*Z*** proved inseparable by reverse-phase HPLC under a variety of conditions, further evidence for stereochemical integrity was obtained by normal-phase HPLC which allowed baseline resolution of the two isomers with hexane / ethyl acetate (1:1) containing 1% triethylamine as eluent.

Having established the identity of the non-radioactive standards, we investigated the radioiodination of **4*E*** and **4*Z*** under no-carrier-added conditions. **5*E*** and **5*Z*** labelled with iodine-125 are obtained from the appropriate stannylated precursor (0.25 - 1.5 mg) after a one minute incubation with sodium [^{125}I]-iodide (2 mCi, *ca.* 1 nmol in 20μL 0.1 N NaOH) and chloramine-T (20 μL, 4.4 mM) at ambient temperature in a solvent mixture of acetonitrile (65

μL) and 10% aqueous sulfuric acid (35 μL). The incorporation of radioiodine is essentially quantitative, and is not dependent upon the concentration of precursor employed over the 6-fold range studied. Excellent isolated radiochemical yields of ligand are obtained after semi-preparative reverse-phase HPLC purification. No significant chemical or radiochemical impurities were detected by analytical reverse-phase HPLC (*vide infra*). For typical preparations of [^{125}I]-labelled ligands, high specific activities (1450 - 1860 mCi/μmol) were ascertained by comparison of the ultraviolet absorbance HPLC peak area of carrier ligand in an aliquot of known radioactivity to the peak area of a standard sample. These radioiodinations proceeded with retention of configuration based on normal-phase HPLC studies. On a 10 mCi scale with sodium [^{123}I]-iodide, 13.3 hour half-life, [^{123}I]-labelled **5*E*** (3600 mCi/μmol) was obtained in a sterile, pyrogen-free formulation within 1.5 hours in 50% radiochemical yield (not decay corrected). Following intravenous administration to rodents, radioiodinated (*E*)- and (*Z*)-(N-iodoallyl)spiperones label cerebral dopamine D_2 receptors with high specificity.[2]



Compound	*R1*	*R2*
4*E*	Sn(*n*-Bu)3	H
4*Z*	H	Sn(*n*-Bu)3
5*E*	I	H
5*Z*	H	I
6*E*	Cl	H
6*Z*	H	Cl
7	H	H

Figure 1.

To verify that the radioligands were not contaminated with "pseudo-carrier" substances, we also synthesized the most likely side products expected during radioiodination. The chloro-analogs, **6*E*** and **6*Z*** (Figure 1), which would result from oxidant-promoted chlorodestannylation, were prepared by treatment of spiperone with a mixture of (*E*)- and (*Z*)-1,3-dichloropropene in DMF containing sodium hydride. The allyl derivative **7**, which would result from simple protodemetallation, was prepared in similar fashion by N-alkylation of spiperone with allyl bromide (Figure 1). During radiolabelling, **7** was found as the major non-labelled product while the chlorinated materials were not observed. Since **7** was well resolved from **5*E*** and **5*Z*** by reverse-phase HPLC, it was not detected in purified samples of the radioligands. In agreement with studies of aromatic systems,[13] iododestannylation of the vinyl system is so facile that it is not adversely affected by protodestannylation.

Vinylstannanes have previously served for introduction of labelled halovinyl groups,[4,14] and the utility of the present approach rests in the capacity of the stannylated alkylating agents **1*E*** and **1*Z*** to provide convenient entry into a variety of "active series." For example, we recently alkylated a secondary amine, N6 of [nor-(cyclopropylmethyl)]-diprenorphine, with **1*E*** as a prelude to the synthesis of a radioiodinated bioisosteric analog of diprenorphine for *in vivo* studies of opiate receptors. Further, we have established conditions for stereospecific radioiododestannylation of vinylstannanes with retention of configuration. The procedure is fast and reliable, gives excellent yields and high specific activities, and is amenable to the efficient preparation of either [^{125}I]- or [^{123}I]-labelled tracers without requiring extensive time to optimize reaction conditions. Vinylstannanes available through this general strategy also should be suitable precursors to radiobrominated and radiofluorinated tracers as well as to non-labelled vinyl halides.

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