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PRELIMINARY NOTE

Fluoroalkylbenzenes: Synthesis of (S)-2,3-Dimethoxy-5-[(3-fluoro)propyl]-6-hydroxy-N-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide

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SUMMARY

The synthesis of the titled fluoropropylsalicylamide (**2**) was achieved by a route which avoided the intramolecular cyclization reactions of *ortho*-[(3-fluoro)propyl]phenol substrates.

The study of fluorinated analogues of biologically important molecules [1] including derivatives in which aromatic halogen substituents have been replaced with fluoroalkyl groups [2] and the recent report that the *ortho*-halogenated bromo-salicylamide (**1**) functions as a potent dopamine D-2 receptor antagonist [3] makes the fluoropropylsalicylamide (**2**) a logical and highly desirable synthetic target for *in vivo* and *in vitro* studies [2]. The novel *ortho*-[(3-fluoro)propyl]phenol structural feature of (**2**) is without literature precedent and is anticipated under certain reaction conditions to lead to loss of fluorine and intramolecular cyclization to provide benzopyran-type products [4]. Additionally, functional groups of penta-substituted aromatic substrates are known to possess increased reactivity profiles as a result of steric crowding [1]. Thus before we could develop an efficient synthesis of (**2**), a preliminary investigation of the reactivity of several *ortho*-[(3-fluoro)propyl]phenols was undertaken.

(1) R = Br
(2) R = $CH_2CH_2CH_2F$

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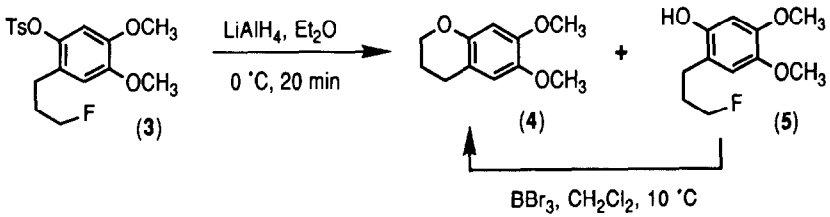
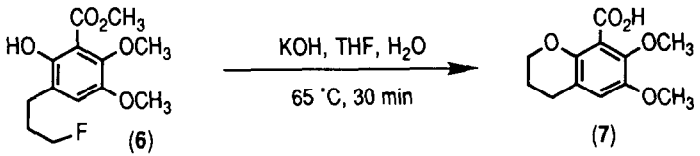
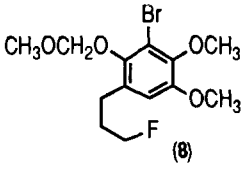




Preliminary synthetic studies revealed that *ortho*-[(3-fluoro)propyl]phenols cyclize either under Lewis acid or aqueous base reaction conditions. For example, reduction of the tosylate (**3**)* with lithium aluminum hydride at 0°C afforded the cyclized benzopyran (**4**) (53 %) and the fluoropropylphenol (**5**) (34 %). The phenol (**5**) was converted to the pyran (**4**) by treatment with boron tribromide in dichloromethane at 10 °C (63 %)[1]. Furthermore, *ortho*-fluoropropylsalicylic ester (**6**) rapidly cyclized to afford the benzopyran acid (**7**) (76 %) when treated with potassium hydroxide in aqueous THF at 65 °C for 30 min [5]. Indeed, the labile nature of these *ortho*-[(3-fluoro)propyl]phenols to these reaction conditions required that traditional salicylamide reaction sequences [3,6] be avoided for the preparation of (**2**). We therefore selected intermediate (**8**) as the critical precursor for the synthesis of (**2**). The requisite benzoic acid for amide formation could potentially be afforded from the corresponding aryl bromide by a regiospecific heteroatom-facilitated lithium-for-bromine exchange reaction followed by trapping with carbon dioxide [7], and the methoxymethyl ether of the phenol moiety could be unmasked under mild noncyclizing aqueous acid conditions.



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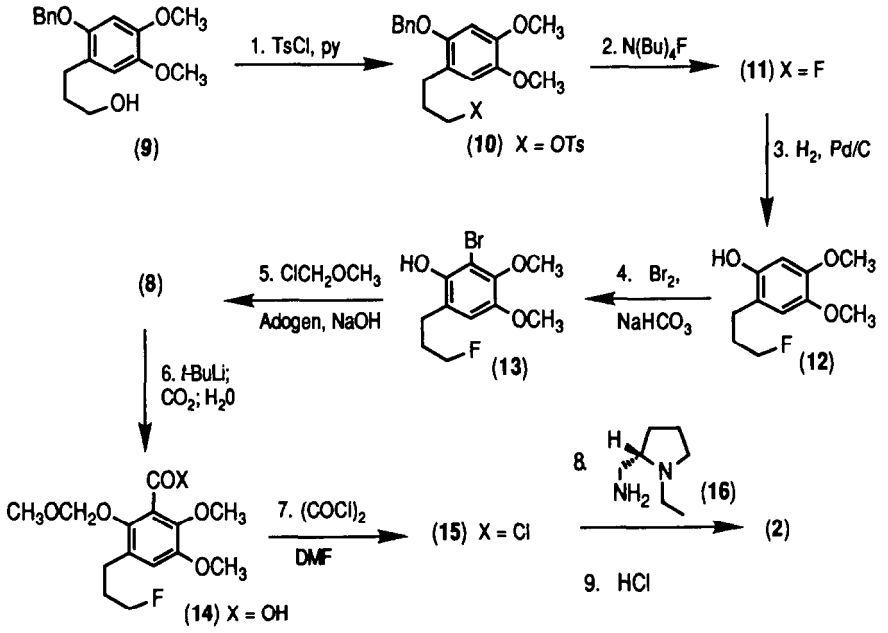
* Preparation of a detailed account of the syntheses and chemistry of the new molecules reported here as well as other molecules possessing the *ortho*-[(3-fluoro)propyl]phenol structural unit is currently in progress. The spectroscopic qualities (^1H and ^{19}F NMR, and IR) and elemental analyses of all new compounds are in agreement with the assigned structures.

The intermediate (**8**) was synthesized from the previously reported 3-[4,5-dimethoxy-2-(phenylmethoxy)benzene]propanol (**9**) (Scheme 1) [8]. Treatment of alcohol (**9**) with *p*-toluenesulfonyl chloride and pyridine in dichloromethane at 0 °C afforded the tosylate (**10**) (91%), which was converted to the fluoropropylbenzene (**11**) with tetrabutylammonium fluoride in refluxing tetrahydrofuran (93%). Removal of the benzyl ether protecting group by hydrogenolysis over palladium on carbon in methanol at 20 °C yielded the corresponding fluoropropylphenol (**12**) (100 %) which underwent regiospecific bromination with bromine buffered with sodium bicarbonate in carbon tetrachloride at 0 °C to afford (89 %) the penta-substituted bromophenol (**13**). Protection of the phenol group as the methoxymethyl (MOM) ether using chloromethyl methyl ether and mild phase transfer conditions [9] afforded (87%) the key intermediate (**8**). Bromine-for-lithium exchange of (**8**) with *t*-BuLi in ether at -78 °C



Scheme 1. Synthesis of Fluoroalkylsalicylamide (**2**).

and then reaction of the aryl anion with carbon dioxide in ether at - 78 °C followed by water quench [7] provided (68 %) the fluoropropylbenzoic acid (**14**). Elaboration of (**14**) to the desired salicylamide (**2**) was achieved by first generating the corresponding acid chloride (**15**) with oxalyl chloride and dimethylformamide in dichloromethane at 0 °C (not isolated),

followed by treatment with (S)-N-ethyl-2-(aminomethyl)pyrrolidine (**16**) [7] in dichloromethane (20 °C), and then removal of the MOM ether group with aqueous methanolic HCl at 20 °C (78 %, **14**→2).

The synthesis of (**2**) from alcohol (**9**) was accomplished in nine steps in an overall yield of 35 %. It is apparent that molecules with the novel *ortho*-[(3-fluoro)propyl]phenol structural unit can be obtained in synthetically useful yields by employing reaction conditions which do not favor intramolecular etherification processes. The initial screening of *in vitro* biological activity has revealed that fluoroalkylsalicylamide (**2**) is a potent dopamine D-2 antagonist similar to the bromosalicylamide (**1**). A full description biological properties of salicyclamide (**2**) will be published elsewhere.

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