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SYNTHESIS OF 1-[2',5'-DIMETHOXY-4'-(β-FLUOROETHYL)PHENYL]-2-AMINOPROPANE: STUDIES RELATED TO ^{18}F-LABELED SEROTONIN RECEPTOR LIGANDS

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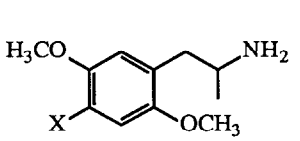
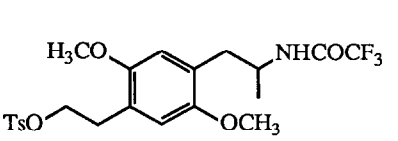
Abstract: Synthesis of the titled 2,5-dimethoxy-4-fluoroalkylamphetamine is reported. The highly functionalized aromatic nucleus of the key fluorination precursor was utimately derived from a low temperature aromatic halogen-lithium exchange reaction followed by alkylation of the resultant anion with ethylene oxide.

Molecules possessing the 1-(2,5-dimethoxyphenyl)-2-aminopropane (2,5-dimethoxyamphetamine) structural unit, which are appended with various substituents at the 4-position (para) of the aromatic nucleus are known to function as psychoactive agents in humans[1]. Included in the group of the most potent psychotomimetic amphetamines known are the para-substituted bromide **1a** (DOB) and ethyl derivative **1b** (DOET). The hypothesis that the mode-of-action of these and related para-substituted 2,5-dimethoxyamphetamines involves the stimulation of the cerebral serotonin receptor system has been tested by evaluating their *in vitro* binding affinities toward the 5-HT_2 and other serotonin receptor sub-types[2]. The potential *in vivo* assessment of serotonin receptor populations using the emerging technique of positron emission tomography[3] (PET) provides impetus to further evaluate the structure-activity relationships of molecules related to DOET, in particular para-fluoroalkyl-2,5-dimethoxyamphetamines. Fluoroalkylamphetamines which exhibit favorable *in vitro* binding properties will permit evaluation of fluorine-18 (^{18}F) radiolabeled ligands as potential PET imaging agents of the serotonin system.



1

X
a. Br
b. CH_2CH_3
c. CH_2CH_2-F

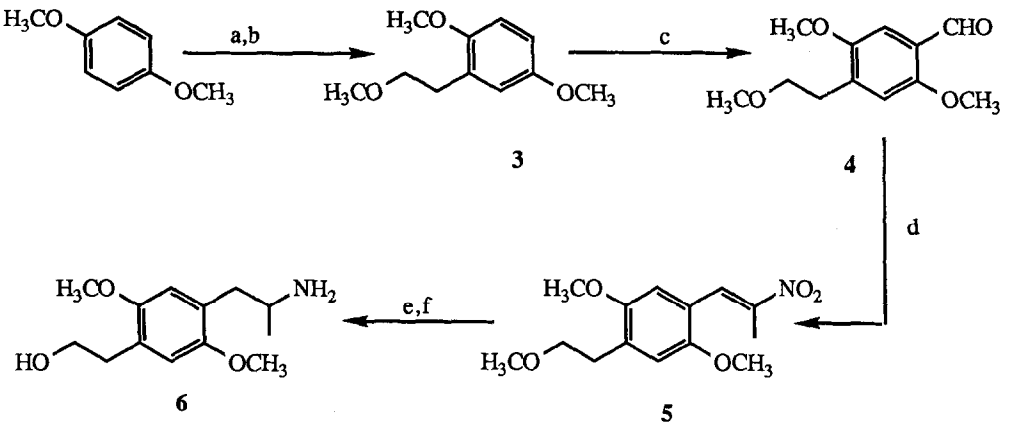


2

The biological potency of DOET **1b** coupled with the notion that fluorinated pharmaceuticals may elicit biological activities similar to the parent agents[4] has prompted the synthesis of racemic 1-[2',5'-dimethoxy-4'-(β-fluoroethyl)phenyl]-2-aminopropane (DOEF) **1c**. In this communication we describe the synthesis of **1c** employing a method which takes into account the constraints associated with the potential preparation of ^{18}F-radiolabeled[5] DOEF (^{18}F-**1c**). The short half-life of fluorine-18 (110 min) would require a late synthetic introduction of the radiofluorine atom and also that subsequent chemical transformations be rapid, convenient and efficient. Based on these criteria tosyloxytrifluoroacetamide **2** was selected as the key intermediate for DOEF production. Initally, the preparation of the highly functionalized aromatic nucleus of **2** was envisaged to follow a synthetic route similar to the one used for the formation of DOET[6], as outlined in Scheme I.

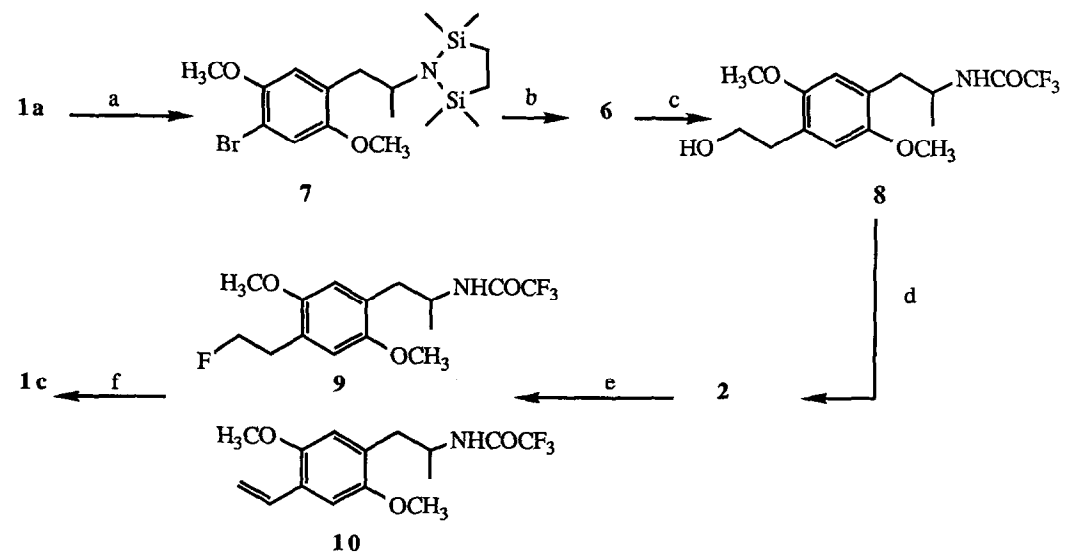
Treatment of 1,4-dimethoxybenzene with *n*-butyllithium[7] (1.1 mol, THF, 0 °C, then reflux 4.5 h) followed by ethylene oxide quench[8](1.1 mol, ether, 0 °C; hexane, reflux 5 h, 63%) afforded the corresponding

Scheme I



a. *n*-BuLi; ethylene oxide, 63%. b. NaH; CH_3I, 88%. c. $POCl_3$, $HCON(CH_3)C_6H_5$, 24%. d. NH_4OAc, $CH_3CH_2NO_2$, 70%. e. AlH_3, 93%. f. TMSCl, TMSI, 57%.

Scheme II



a. $[ClSi(CH_3)_2CH_2]_2$, 85%. b. *t*-BuLi; ethylene oxide; KOH, 75%. c. $(CF_3CO)_2O$; $NaHCO_3$, 89%. d. TsCl, 96%. e. TBAF, 55%. f. KOH, 86%.

phenylethanol which was subsequently allowed to react with sodium hydride (1.0 mol, THF, reflux, 16 h) and then with iodomethane (1.1mol, THF, 0 °C,15 min; 20 °C, 10 h, 88%) to provide methylether **3**[9,10]. Formylation of the para-position under Vilsmeier conditions[6] ($POCl_3$, $HCON(CH_3)C_6H_5$, 10 min, 100 °C, 24%) afforded para-benzaldehyde **4**. Sidechain elaboration of **4** to nitropropene **5**[11] (nitroethane 5 mol excess, cat. NH_4OAc, 100 °C, 2 h, 70 %) was followed by aluminum hydride reduction[12] (5 mol $LiAlH_4$, 100% H_2SO_4, THF, 0 °C; 20 °C, 1 h; reflux 30 min, 95 %) to yield the corresponding aminoether. Deprotection of the methylethyl ether moiety by the method of Jung[13] (TMSCl 2 mol, Et_3N, CH_2Cl_2, 20 °C, 30 min; then TMSI 1.3 mol, $CHCl_3$, 20 °C, 2 h, 57%) afforded aminoalcohol **6**. The difficulty associated with the Vilsmeier transformation[14](**3** to **4**) precluded a useful large-scale production of **6**, thus, an alternate synthesis was devised according to the route shown in Scheme II.

The facile synthesis of **6** was effected by employing the readily available starting material DOB[15]. Protection of **1a** using Magnus' reagent[16] ($[ClSi(CH_3)_2CH_2]_2$ 1 mol, Et_3N, CH_2Cl_2, 20 °C, 2 h, 85%) yielded bromodisilazane **7**. Low temperature treatment of **7** with *t*-butyllithium[7,17](2.1 mol, ether, -78 °C, 15 min) followed by addition of ethylene oxide(1.5 mol, ether, -78 °C, 1 h; then hexane, reflux, 3 h) and finally liberation of the amine functionality under basic conditions[16](10% KOH, CH_3OH, reflux, 4 h) provided aminoalcohol **6** (75% based on **7**). Subsequent formation of hydroxyacetamide **8** was carried out with a two step procedure[18]($(CF_3CO)_2O$ 2.5 mol, Et_3N, Et_2O, 0 °C; 35 °C, 1 h; then $NaHCO_3$ 1 mol, CH_3OH, H_2O, 20 °C, 3.5 h, 89%). Subjection of **8** to standard tosylation conditions (p-TsCl, py, 0 °C, 12 h, 96%) provided the desired tosylate **2**. Of the many sources of fluoride ion reported to displace sulfonate esters[19] treatment of **2** with a solution of commercially available tetrabutylammonium fluoride (TBAF)[20] (1.5 mol, THF, reflux, 30 min) afforded after separation (HPLC) fluorinated amide **9** (55%) and styrene **10**[21](18%). Subsequent hydrolysis of the trifluoroacetamide protecting group of **9** (KOH 1 mol, H_2O, iPrOH, 45 °C, 30 min, 86 %) yielded fluoroamphetamine **1c**.

In summary, the synthesis of **1c** was achieved in 8 steps starting from DOB in an overall yield of 26%. The critical transformation for the synthesis of key intermediate **2** involved a low temperature halogen-lithium exchange reaction of **7** followed by alkylation of the resultant anion with ethylene oxide. The method undoubtedly will prove valuable for the construction of other molecules containing the 1,4-dialkyl-2,5-dimethoxybezene nucleus. Furthermore, the expedient (< 75 min) and facile (47%) two-step transformation of tosylate **2** to DOEF is noteworthy, well-suited for the production of radiolabeled ^{18}F-**1c** and provides a general route to other fluoroalkylaromatic pharmaceuticals. The results of the *in vitro* receptor binding affinity of **1c** toward the 5-HT_2 serotonin receptor and also the radiosynthesis of ^{18}F-**1c** will be reported elsewhere.

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