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PRELIMINARY NOTE

Use of Diethylaminosulfur Trifluoride in an Efficient Synthesis of (S)-N-[(1-Ethyl-2-Pyrrolidinyl)Methyl]-5-(3-Fluoropropyl)-2-Methoxybenzamide

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SUMMARY

Diethylaminosulfur trifluoride (DAST) was used to prepare 2,6-dimethoxybenzoyl fluoride, which on reaction with (S)-N-ethyl-2-aminomethylpyrrolidine gave (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide in >95% yields. A three-step efficient synthesis of the fluorinated benzamide neuroleptic, (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(3-fluoropropyl)-2-methoxybenzamide was then carried out using DAST in an essential step. 3-(4-Methoxyphenyl)-1-propanol was converted to 5-(3-hydroxypropyl)-2-methoxybenzoic acid with n-butyllithium and CO_2 in 80-90% yields. The acid was then reacted with DAST to provide 5-(3-fluoropropyl)-2-methoxybenzoyl fluoride, which was then treated with (S)-N-ethyl-2-aminomethylpyrrolidine to give the fluorinated benzamide in >90% yields.

Substituted benzamides have been developed as selective, high affinity, reversible antagonists for the D_2 receptor [1]. One such derivative, raclopride, has been labeled with carbon-11 and used in imaging of primates and humans by positron emission tomography (PET) [2]. Due to the very short half-life of carbon-11 (20.4 min), attempts towards development of a fluorine-18 (110 min) labeled derivative of raclopride as a PET radiotracer have attracted much attention [3].

We have developed a new class of fluorinated benzamide neuroleptics which show high affinity for the D_2 receptor and are therefore good candidates for use in PET when labeled with fluorine-18. The synthesis of these derivatives involves use of diethylaminosulfur trifluoride (DAST) for the simultaneous conversion of an alcoholic hydroxyl and a carboxylic acid group to a fluoroalkyl group and an acyl fluoride, respectively. Use of DAST

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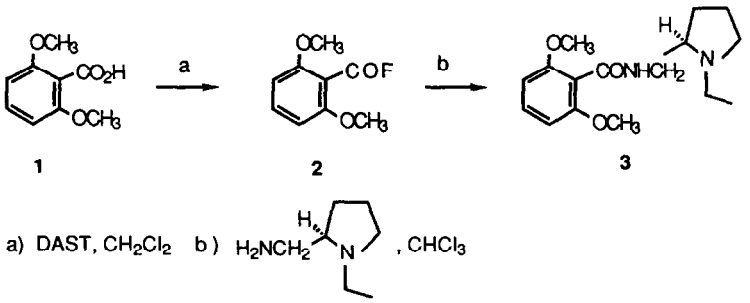
has been reported for the synthesis of acyl fluorides via acids [4] and also in the preparation of fluorides from alcohols [5].

Reported methods for the preparation of these substituted benzamides employ the acid chloride coupling with the amine [6]. We have investigated the synthesis of these substituted benzamides using coupling of the substituted benzoyl fluoride with (S)-N-ethyl-2-aminomethylpyrrolidine. Use of the acid fluoride rather than the corresponding acid chloride as reported, therefore provides efficient and rapid synthesis of these fluorinated benzamide derivatives. As a pilot investigation, synthesis of (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide was carried out by using 2,6-dimethoxybenzoyl fluoride. Based on the results of this synthesis, an efficient three-step synthesis of (S)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-(3-fluoropropyl)-2-methoxy benzamide was carried out.

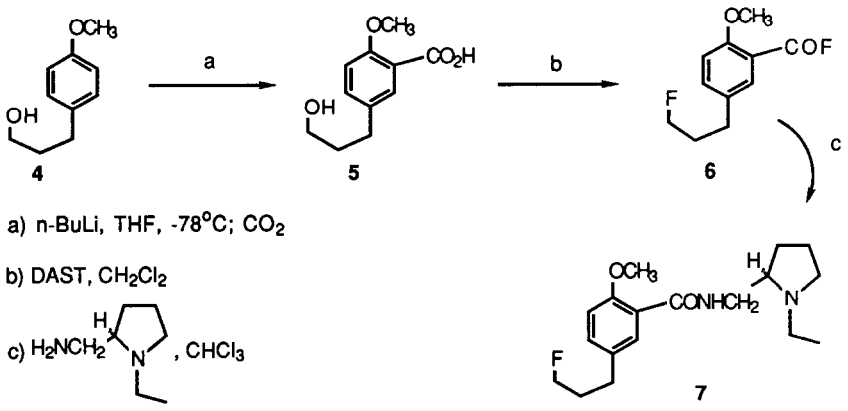
As shown in Scheme 1, 2,6-dimethoxybenzoic acid **1** was converted to acid fluoride **2** by treatment with an equimolar amount of DAST in dichloromethane at 0-5°C (reaction was complete in 15 minutes). The reaction mixture was washed with water (no hydrolysis of the acid fluoride was observed), and the organic layer was separated and dried over magnesium sulfate Acid fluoride **2** (m.p. 57-59°C) was obtained in >95% yield. Into a chloroform solution of acid fluoride **2**, an equimolar amount of (S)-N-ethyl-2-aminomethylpyrrolidine was added at ambient temperature. The reaction was complete in less than 5 minutes to provide benzamide **3** in >95% yield, m.p. 180-182°C (hydrochloride salt), lit. m.p. 182-184°C [7].



Scheme 1.

Following the successful synthesis of **3**, 3-(4-Methoxyphenyl)-1-propanol **4** (Scheme 2) in tetrahydrofuran was treated with two equivalents of n-butyllithium at -78°C for 30 minutes and then allowed to warm up to ambient temperature and stirred for another hour. The mixture was then poured over dry ice in ether to provide **5** in 80-90% yields. DAST in dichloromethane was cooled to 0-5°C into which a dichloromethane solution

of acid **5** was added dropwise over a period of 15 minutes. The reaction was continued at 0-5°C for two hours. Unreacted DAST was removed by washing the organic layer with water and removal of dichloromethane *in vacuo* provided acid fluoride **6** as a yellow oil. Into a chloroform solution of acid fluoride **6**, a solution of (S)-N-ethyl-2-amino-methylpyrrolidine in chloroform was added and in less than 10 minutes the reaction was complete to provide benzamide **7**, isolated in >90% yield as a light yellow oil (^{1}H NMR, ∂ ppm: 8.38, hump, 1H, CONH; 8.05, d, 1H, H-6; 6.8-7.35, dd, 2H, H-3 and H-4; 4.65-4.9, t, 1H of CH_2F and 3.9-4.15, t, 1H of CH_2F, $^2J_{HF}$= 45.3 Hz; 3.9, s, 3H, OCH_3; 2 6-2.85, t, 2H, benzylic CH_2; 1.55-2.5, m, 13H; 1.0-1.28, t, 3H, CH_3).



Scheme 2 .

The acyl fluoride provides reproducible, high yields and the amination is very facile (5-10 minutes at ambient temperature). The reaction of acid **5** with two equivalents of DAST leads cleanly to the acyl fluoride as well as converting the alcohol to the desired fluoride. This route therefore provides an efficient synthesis of these fluorinated benzamide neuroleptics.

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