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(*S*)-Ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-iodo-4,5-methylenedioxyphenyl)propanoate

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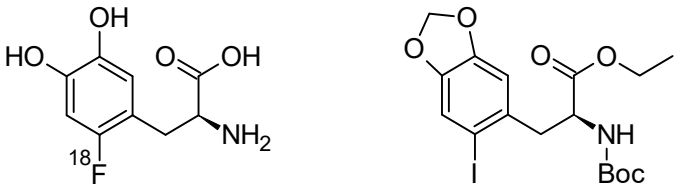
Abstract: A multistep gram-scale synthesis of (*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-iodo-4,5-methylenedioxyphenyl)propanoate (**2**) has been developed. The title compound was prepared starting from commercially available L-DOPA which was *O*- and *N*-protected before undergoing iodination by CF_3CO_2Ag/I_2. The structure of the target compound was confirmed using IR, ^{1}H-NMR, ^{13}C-NMR, 2D (COSY, HSQC) NMR spectroscopy, as well as ESI-MS and HRMS.

Keywords: phenylalanine; L-DOPA; iodination; medicinal chemistry

1. Introduction

3,4-Dihydroxy-6-[^{18}F]fluoro-L-phenylalanine—6-[^{18}F]fluoro-L-DOPA or 6-[^{18}F]fluoro levodopa (**1**, Figure 1)—is a positron emission tomography (PET) diagnostic radiotracer [1,2], useful to detect pathological loss of dopaminergic neuron terminals in the striatum. Thus, 6-[^{18}F]fluoro-L-DOPA is used for the diagnosis of Parkinson's disease (PD) and distinction between essential tremor and parkinsonian syndromes (PS), especially at the PS onset [3]. 6-[^{18}F]Fluoro-L-DOPA is also useful to detect tumors with an increase intracellular transport and decarboxylation of L-DOPA. In fact, 6-[^{18}F]fluoro-L-DOPA has a privileged role in the diagnosis of pheochromocytoma, paraganglioma, and brain tumors [4]. Other possible applications include psychiatric [5,6] and age-related neurodegenerative disorder diagnoses [7].



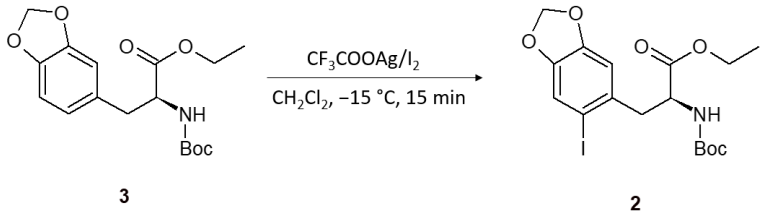
1 **2**

Figure 1. 6-[^{18}F]Fluoro levodopa (**1**) and (*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-iodo-4,5-methylenedioxyphenyl)propanoate (**2**).

Several synthetic routes to **1** have been reported in the literature [8–16]. However, most of them suffer from limitations such as the formation of regioisomers as reaction by-products, long reaction times, and low overall yield. Thus, herein we report on the synthesis and structural identification of an intermediate suitable for a gram-scalable nucleophilic fluorination of levodopa.

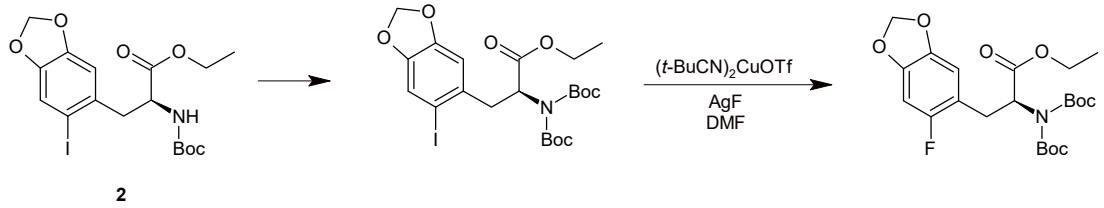
2. Results and Discussion

The synthesis of (*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-iodo-4,5-methylenedioxyphenyl) propanoate (**2**, Scheme 1) was performed starting from commercially available levodopa which was reacted with thionyl chloride in EtOH to give the corresponding ethyl ester, whose amino group was in turn protected by BOC. The protection of catechol hydroxyl groups with CH_2I_2 in the presence of Cs_2CO_3 gave the benzodioxole derivative **3** (see Scheme 1) which was in turn submitted to an iodination reaction at the *C*-6 position. A similar synthetic strategy was previously reported in a Chinese patent [17] where the iodination step was performed using $PhI(O_2CCF_3)_2/I_2$. We chose CF_3CO_2Ag/I_2 [18] as the iodinating reagent since it is cheaper and more atom efficient than $PhI(O_2CCF_3)_2/I_2$. Furthermore, CF_3CO_2Ag/I_2 should allow easier product purification since the chosen iodination promoter does not liberate iodobenzene in the reaction crude. Finally, the reaction time was reduced from overnight to 15 minutes in our conditions, nevertheless ensuring a comparable yield (73%, 70% [17]).



Scheme 1. Preparation of (*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-iodo-4,5 methylenedioxyphenyl)propanoate (**2**).

Through a procedure recently proposed for the synthesis of [^{18}F]labeled compounds for PET imaging [19], a copper-mediated nucleophilic fluorination of **2** could be carried out. In order to avoid a possible hydro-dehalogenation caused by the relatively acidic *N*H carbamate proton, the Boc-derivative of **2** should be synthesized should be previously synthesized (Scheme 2).



Scheme 2. Copper-mediated fluorination of **2**.

The structure of the synthesized compound **2** has been confirmed using NMR spectroscopy and mass spectrometry. Likely as a consequence of a hindered rotation around some Csp^3–Csp^3 and Csp^3–Csp^2 bonds, a mixture of rotamers of **2** in ^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$. A variable-temperature ^{1}H-NMR study in CD_3OD was then performed in the range of temperature 25–50 °C. In particular, at 50 °C a coalescence of signals occurred allowing more sharp and detectable signals (see ^{1}H-NMR spectra in Figures S3, S5). On the basis of homonuclear (COSY) and heteronuclear (HSQC) experiments, it was possible to assign all ^{1}H and ^{13}C chemical shifts of **2** (see Figures S8, S9). The ^{1}H and ^{13}C-NMR spectra recorded in CD_3OD at 50 °C will be described.

3. Materials and Methods

3.1. General Information

Unless otherwise specified, yields refer to purified products and were not optimized. The structures of the compounds were confirmed using routine spectrometric analyses. Only spectra

for compounds never previously described, to our knowledge, are given. Compounds used as starting materials were purchased from either Aldrich (Chemical Co., Milwaukee, WI, USA) or Lancaster (Synthesis, Inc., Frankfurt, Germany) and were used without any further purification. Solvents were RP grade, unless otherwise indicated. ^{1}H 500-MHz and ^{13}C 125-MHz spectra were recorded on an Agilent 500-vnmrs500 spectrometer (Agilent Technologies, Palo Alto, CA, USA). Chemical shifts are reported in ppm using solvent resonance [(residual non-deuterated solvent for ^{1}H-NMR): CD_3OD, δ 3.30 (^{1}H-NMR) and δ 47.8 (^{13}C-NMR)] as reference. *J* absolute values are given in Hz. $ESI^{+/-}$/MS/MS analyses were performed with an Agilent 1100 series LC-MSD trap system VL Workstation (Agilent Technologies, Palo Alto, CA, USA). HRMS analyses were performed using a Bruker microTOF QII mass spectrometer (Bruker, Bremen, Germany) equipped with ESI operating in positive ion mode. The IR were recorded on a Perkin-Elmer Spectrum One FT spectrophotometer (Perkin Elmer Corporation, Norwalk, CT, USA) and band positions are given in reciprocal centimeters (cm^{-1}). Eluting solvent, to isolate the product, is indicated in parentheses and was determined using TLC, performed on precoated silica gel on aluminum sheets (Kieselgel 60 F254, Merck, Darmstadt, Germany). TLC plates were visualized with UV light and/or in an iodine chamber. Column chromatography was performed on ICN silica gel 60 Å (63–200 μm) as a stationary phase. The weight of the silica gel was approximately 100 times that of the substance.

3.2. (S)-Ethyl 2-(tert-butoxycarbonylamino)-3-(2-iodo-4,5-methylenedioxyphenyl)propanoate (**2**)

CF_3COOAg (0.67 g, 3.05 mmol) and I_2 (0.78 g, 3.05 mmol) were added to a solution of **3** (0.79 g, 2.34 mmol) in CH_2Cl_2 (28 mL) at −5 °C. After stirring at −5 °C for 15 min, the resulting AgI precipitate was filtered and the filtrate was washed with saturated aqueous $Na_2S_2O_3$ solution. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure affording 0.99 g of a yellowish oil which was purified through column chromatography (EtOAc/hexane 2:8) which gave 0.79 g (73%) of the desired product as a colorless oil: $[\alpha]_D^{20}$ = +103 (*c* 1, EtOH); ^{1}H-NMR (CD_3OD, 50 °C): δ 1.24 (t, *J* = 7.0 Hz, 3H, C*H*$_3$), 1.38 (s, 9H, *t*-Bu), 2.92 (t, *J* = 11.0 Hz, C*H*H), 3.20 (dd, *J* = 14.1, 5.9 Hz, 1H, CH*H*), 4.16 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 4.39 (dd, *J* = 9.1, 5.9 Hz, 1H, C*H*), 5.89–5.96 (m, 2H, OC*H*$_2$O), 6.79 (s, 1H, Ar*H*), 7.24 (s, 1H, Ar*H*); ^{13}C-NMR [attached proton test (APT), CD_3OD, 50 °C] δ 13.0 (OCH$_2$*C*H$_3$), 27.2 (3 x *C*H$_3$), 42.0 (CH*C*H$_2$), 53.9 (*C*HCH$_2$), 60.9 (O*C*H$_2$CH$_3$), 79.3 (*C*(CH$_3$)$_3$), 87.5 (*C*$_{Ar}$I), 101.7 (OCH$_2$O), 110.2 (H*C*$_{Ar}$), 118.1 (H*C*$_{Ar}$), 133.1 (*C*$_{Ar}$), 147.6 (O*C*$_{Ar}$), 148.5 (O*C*$_{Ar}$), 154.7 (NH*C*=O), 172.0 (O*C*=O); FT-IR (neat, cm^{-1}): 3392, 2977, 2917, 1795, 1707, 1475, 1390, 1228, 1162, 1036, 931, 858; ESI^+/MS *m*/*z* 486 $[M + Na]^+$; ESI^+/MS/MS *m*/*z* 386 (100); HRMS [direct analysis in real time (DART), *m*/*z*] Calcd. for $C_{17}H_{22}INO_6$: 486.0384 ($[M + Na]^+$); found: 486.0379.

4. Conclusions

In conclusion, (*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-iodo-4,5-methylenedioxyphenyl)propanoate (**2**) has been successfully synthesized starting from commercially available L-DOPA and using CF_3CO_2Ag/I_2 as the iodinating reagent. The title compound is a suitable intermediate for the synthesis of 6-fluoro-L-DOPA and certain derivatives by cross-coupling reactions.

Supplementary Materials: ^{1}H and ^{13}C-NMR spectra of compounds **2** and **3** are available online.

Author Contributions: Conceptualization, G.L. and A.S.; writing—original draft preparation, G.L. and M.M.C.; writing—review, M.M.C.; synthesis of the intermediate **3**, G.F.; synthesis of the target compound, M.M.C. and L.D.; spectral data, L.D. and F.P.; supervision and project administration, A.S. All authors read and approved the final manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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