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Regio-selective synthesis of novel 1-*tert*-butyl-4-nitro-1*H*-pyrrole-3-carboxylic acid building block

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ABSTRACT

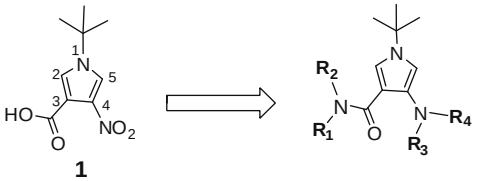
A convenient, regio-selective synthesis of novel 1-*tert*-butyl-4-nitro-1*H*-pyrrole-3-carboxylic acid was developed, utilizing the bulky *tert*-butyl moiety of 1-*tert*-butyl-1*H*-pyrrole to direct selective, un-symmetrical substitutions to the desired 3 and 4 positions.

At Locus Pharmaceuticals, we apply our computational fragment-based discovery technology, Charrette™, to design novel, small molecule antagonists or agonists for numerous biological targets. The de novo approach implemented in Charrette™ utilizes a specific fragment data set identified by our technology. Many of the fragments contained in this set, such as the 1-*tert*-butyl-4-nitro-1*H*-pyrrole-3-carboxylic acid **1**, are considered to be valuable 'chemistry ready fragments' due to the available multiple diversity points (Scheme 1). In this Letter, we wish to describe the synthetic efforts toward obtaining the above-mentioned novel building block.

We initially envisioned two general approaches to access the desired 1,3,4 tri-substituted pyrrole building block **1**. The first route involves building from a pyrrole starting material with the 3 and 4 substitutions already incorporated, and introducing the *tert*-butyl moiety at the end. We performed a quick study to evaluate the feasibility of this approach by attempting the N-*tert*-butylation of commercially available diethyl-1*H*-pyrrole-3,4-dicarboxylate, following a reported N-*tert*-butylation procedure for 1-*H*-pyrrole.[1] In this reaction (Scheme 2), imidazolium ionic liquid was used as a solvent to facilitate the N-alkylation reaction between the pyrrole and *tert*-butyl bromide. Unfortunately in our hands this key transformation was not successful making this route an unattractive option.

Alternatively, the targeted building block could potentially be made via a second route in which commercially available *N*-*tert*-butylpyrrole **2** would be used as the starting point to functionalize the 3 and 4 positions. Within this scope, there are several ways by which the 3 and 4 substitutions could be accomplished.

We first pursued one such sequence (Scheme 3), beginning with the synthesis of diethyl-1-*tert*-butyl-1*H*-pyrrole-3,4-dicarboxylate **4** by reacting *N*-*tert*-butylpyrrole **2** with excess diethyl acetylenedicarboxylate **3** at 80–130 °C under microwave irradiation. In this reported 4+2 cyclo-addition reaction to make compound **4**,[2] the initial Diels–Alder intermediate (formed at 80 °C in microwave) further undergoes a retro Diels–Alder transformation when subjected to higher temperature of 130 °C to afford the expected product in 10% yield, along with numerous unidentified by-products. The bis-ester **4** was then hydrolyzed to the bis-carboxylic acid with potassium hydroxide and subsequently converted to the cyclic-anhydride **5** in good yield. Compound **5** is essentially equivalent to the targeted building block **1** since the cyclic-anhydride could be opened with various amines to form amides at the 3 position, and the resulting carboxylic acid at the 4 position could be transformed to an amine via Curtius rearrangement and further elaborated. However, we decided not to proceed further with this reaction sequence due to the low yield and difficult purification



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Scheme 1. Potential elaborations of building block **1**.

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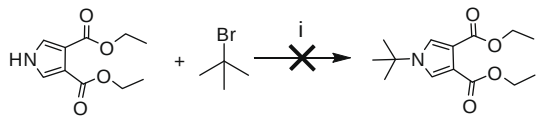
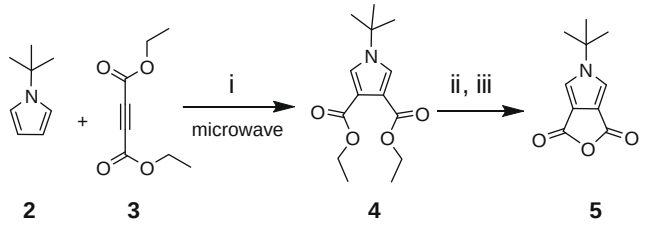


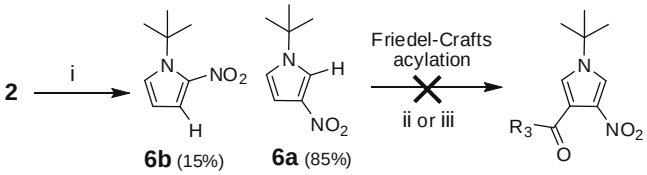
Scheme 2. Reagents and conditions: (i) KOH, 1-*N*-butyl-3-methylimidazolium hexafluorophosphate, 80 °C, 18 h.



Scheme 3. Reagents and conditions: (i) Microwave, 80–130 °C, 30 min; (ii) KOH, 3:1:1 THF/MeOH/H_2O; (iii) PCl_5, THF, 25 °C, 1 h.

process for the cyclo-addition reaction. Furthermore, this approach could limit the number of potential amide targets since it would be difficult to make those derived from less reactive anilines or sterically hindered amines.

We then attempted to introduce selective, un-symmetrical substitutions to the 3 and 4 positions starting from *N-tert*-butylpyrrole **2**. The obvious challenge was to controll the regio-selectivity of electrophilic substitution reactions to the desired 3 and 4 positions, having also the 2 and 5 positions on the pyrrole ring as potential reaction sites. There are literature examples where selective electrophilic substitution on 2,3,4,5 un-substituted pyrrole was achieved at the 3 position by having a bulky substituent or protecting groups (such as silane) on the pyrrole nitrogen.[3,4] With smaller N-substituents such as small alkyls and less sterically hindered groups, the selectivity tends to favor the 2 (or 5) position.[5,6] In our situation, we looked to utilize the bulky *tert*-butyl moiety of **2** to direct substitutions to the desired 3 and 4 positions on the pyrrole ring. We initially attempted to introduce first the nitro group,[7] then an ester via Friedel–Craft acylation (Scheme 4), based on literature precedence.[8]



Scheme 4. Reagents and conditions: (i) Acetic anhydride, nitric acid, −20 °C, 2 h; (ii) $SnCl_4$, trifluoroacetic anhydride, toluene, 0–25 °C, 16 h; (iii) $AlCl_3$, ethyl chloroformate, carbon disulfide, 0–55 °C, 16 h.

Thus, nitration of *N-tert*-butylpyrrole was accomplished with nitric acid in acetic anhydride as solvent at low temperature, affording the desired 1-*tert*-butyl-3-nitro-1*H*-pyrrole product **6a** in greater than 85% yield along with less than 15% of regio-isomer **6b**. A very small amount of bis-nitration product was also observed. NOESY proton NMR experiments were conducted to determine the regio-chemistry of the two major products. The NOESY spectrum of **6a** shows NOE correlations between the *N-tert*-butyl group proton resonance and the two most downfield of the three ring proton peaks (2 and 5 positions), as expected for the 3-nitro isomer (Fig. 1). As expected for the 2-nitro isomer **6b**, the only NOE correlation involving the *t*-butyl group is with the most downfield of the three ring proton peaks. The relative ring proton chemical shifts of **6a** versus **6b**, as well as *J* coupling analysis, also support the regio-isomer structure assignments. Compound **6a** was subsequently subjected to Friedel–Crafts acylation conditions, using either ethyl chloroformate or trifluoroacetic anhydride to incorporate the ester or carboxylic acid precursor. However, we did not observe acylation products for any of the possible positions on the ring, likely due to the combined negative effects of the bulky *tert*-butyl moiety and the electron-withdrawing nitro group.

With this result, we decided to reverse the order of the synthetic sequence and carried out the Friedel–Crafts reaction first (Scheme 5). Compound **2** was treated with trifluoroacetic anhydride and tin chloride in toluene to give predominantly the desired regio-isomer **7** in greater than 85% yield.[9,10]

NMR experiments were conducted to confirm the regio-chemistry of product **7** (Fig. 1). The NOESY spectrum of **7** displays NOE correlations between the *N-tert*-butyl resonance and the two most downfield pyrrole proton peaks. Also, the $^{1}H/^{13}C$ gHMBC spectrum shows correlations between these two proton peaks and the *N-tert*-butyl quaternary carbon. Interestingly, J_{HF} coupling of the protons (2 and 4 positions) adjacent to the trifluoromethyl acetyl

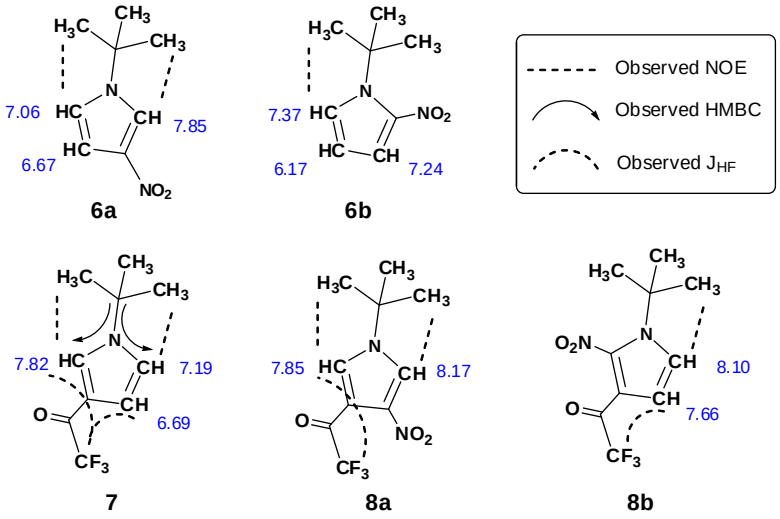
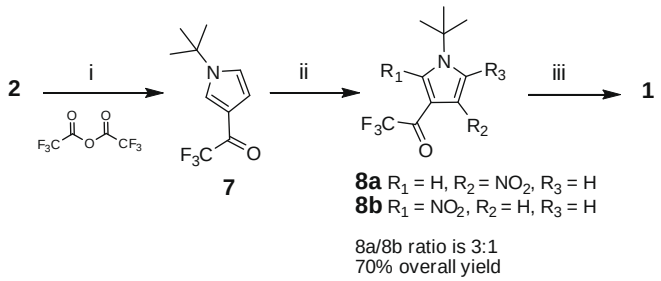


Figure 1. Summary of structurally diagnostic NMR observations.



Scheme 5. Reagents and conditions: (i) $SnCl_4$, trifluoroacetic anhydride, toluene, 0–25 °C, 6 h; (ii) acetic anhydride, nitric acid, −20 °C, 2 h; (iii) 20% aq NaOH, 120 °C, microwave, 15 min.

group with fluorine is observed as well. Subsequent nitration of **7** was carried out with nitric acid and acetic anhydride at −20 °C, affording the desired 4-nitro product **8a** as well as the regio-isomer **8b** in 3:1 ratio and 70% overall yield.[11] The desired major product **8a** was easily isolated by re-crystallization from dichloromethane/hexane. Regio-isomers **8a** and **8b** were differentiated by NOESY and ^{19}F J_{HF} coupling analysis (Fig. 1).

The spectrum of **8a** shows ^1H NOEs between the *N*-*tert*-butyl group and both the neighboring pyrrole protons, indicating that nitration occurred at the desired position 4. For regio-isomer **8b**, only one of the pyrrole protons (position 5) shows NOE correlation with the adjacent *N*-*tert*-butyl resonance. This pyrrole proton, however, is not coupled to fluorine, which indicates nitration at position 2 for **8b**. Finally, the conversion of **8a** to the titled compound **1** was accomplished in good yield by treatment with aqueous sodium hydroxide at 120 °C for 15 min under microwave irradiation.[12]

In conclusion, a convenient, good yielding, and regio-selective synthetic sequence was developed to access the novel 1-*tert*-butyl-4-nitro-1*H*-pyrrole-3-carboxylic acid building block. NMR studies were conducted to determine the regio-chemistry of the various electrophilic substitution products on the pyrrole ring. The *tert*-butyl moiety of *N*-*tert*-butylpyrrole **2** appeared to be instrumental in directing un-symmetrical substitutions to the desired 3 and 4 positions of the ring. With the versatile building block **1** in hand (Scheme 1), a wide range of designed amide targets deriving from sterically hindered amines and anilines were easily accessed by first activating the carboxylic acid with PCl_5. Following amide formation, the nitro group was cleanly reduced to amine with tin chloride for further elaboration.

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10. Pyrrole starting material **2** (4.87 mmol) and trifluoroacetic anhydride (4.87 mmol) were dissolved in 10 ml toluene and cooled to 0 °C. To this mixture was added drop-wise $SnCl_4$ (9.74 mmol) and stirring was continued for 1 h. Subsequently, the reaction was quenched with 1 N NaOH and extracted with ethyl acetate. The product was purified by silica column with 95:5 hexane/EtOAc to give **7** as a yellow oil (85% yield).^1H NMR (400 MHz, acetone-d_6): δ (ppm) 7.82–7.83 (m, 1H, *H*-2), 7.19 (dd, J = 3.2, 2.2 Hz, 1H, H-5), 6.68–6.70 (m(8), 1H, *H*-4), 1.63 (s, 9H, *t*-butyl).
11. Acetic anhydride (3 ml) and nitric acid (0.198 g, 3.15 mmol) were stirred at room temperature for 15 min, then this solution was added drop-wise to a solution of **7** (0.690 g, 3.15 mmol) in 10 ml acetic anhydride at −20 °C. The mixture was gradually warmed to rt and stirred for an additional 1 h, then quenched with ice and saturated $NaHCO_3$, followed by extraction with ethyl acetate. The product was re-crystallized from dichloromethane/hexane to give **8a** (0.450 g, 54% isolated yield) as a tan solid. Regio-isomer **8b** (0.11 g, 16.4% isolated yield) was an oil.^1H NMR of **8a** (400 MHz, acetone-d_6): δ (ppm) 8.17 (d, J = 2.5 Hz, 1H, *H*-5), 7.85 (m(6), J_{HH} = 2.5 Hz, J_{HF} = 1.4 Hz, 1H, *H*-2), 1.72 (s, 9H, *t*-butyl).
12. Compound **8a** (0.205 g, 0.776 mmol) was suspended in 2 ml water in a microwave reaction vial. A solution of 50% w/v aqueous NaOH (0.186 g, 2.33 mmol) was subsequently added and the reaction was heated in the microwave at 120 °C for 15 min. After cooling, the reaction was diluted with 10 ml water, neutralized with 1 N HCl, and then extracted with EtOAc. The solvent was removed to give the crude solid, which was washed with hexane, then filtered, and dried to afford the titled compound **1** as a tan solid (0.140 g, 85% yield).^1H NMR of **1** (400 MHz, acetone-d_6): δ (ppm) 10.50 (br s, 1H), 7.98 (d, J = 2.7 Hz, 1H, *H*-5), 7.61 (d, J = 2.7 Hz, 1H, *H*-2), 1.67 (s, 9H, *t*-butyl).