A Scalable Nenitzescu Synthesis of 2-Methyl-4-(trifluoromethyl)-1*H*-indole-5-carbonitrile

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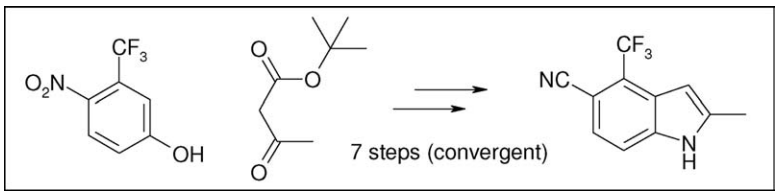

2-Methyl-4-(trifluoromethyl)-1*H*-indole-5-carbonitrile is a key intermediate in the synthesis of selective androgen receptor modulators discovered in these laboratories. A practical and convergent synthesis of the title compound starting from 4-nitro-3-(trifluoromethyl)phenol and *tert*-butyl acetoacetate was developed, including a telescoped procedure for synthesis (without isolation) and Nenitzescu reaction of 2-trifluoromethyl-1,4-benzoquinone. Conversion of the known Nenitzescu indole product to a novel triflate intermediate followed by palladium-catalyzed cyanation afforded a penultimate carbonitrile. Removal of the C-3 *tert*-butyl ester group on the indole through a decarboxylative pathway completed the synthesis of the title compound in six steps (27% overall yield) from 4-nitro-3-(trifluoromethyl)phenol (five steps, 37% overall yield from *tert*-butyl acetoacetate).

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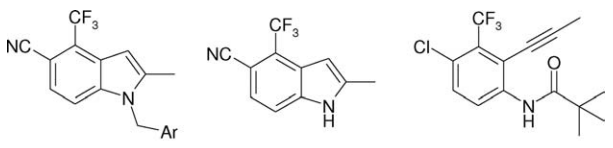
INTRODUCTION

There is significant current interest in the design and development of selective androgen receptor modulators (SARMs) as therapeutic agents for the treatment of sarcopenia and the improvement of muscle function in humans [1]. A novel series of indoles discovered in these laboratories (e.g., **1**: Ar = aryl; heteroaryl) were recently disclosed as nonsteroidal modulators of the androgen receptor [2]. In the course of this drug discovery effort, a practical synthesis of 2-methyl-4-(trifluoromethyl)-1*H*-indole-5-carbonitrile (**2**), a key synthetic intermediate in the preparation of **1**, was required.

The original medicinal chemistry route to **2** [2] entailed an indole ring synthesis from propynyl intermediate **3** [3]. This approach, although efficient, required use of propyne gas for incorporation of the alkyne moiety and very high temperatures for the cyanodechlorination reaction (copper cyanide) and removal of the pivaloyl group (180–250°C). Consequently, a more convenient and scalable synthesis of **2** was needed for large-scale applications.



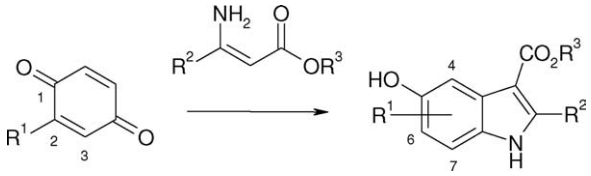
A Nenitzescu-based synthesis of **2** was developed that is amenable to multigram scale operations under relatively mild conditions. In addition, a telescoped procedure for the key Nenitzescu reaction (without isolation of the benzoquinone intermediate) is described, together with characterization of novel intermediates and the title compound (**2**).

RESULTS AND DISCUSSION

The Nenitzescu reaction [4] involves condensation of 1,4-benzoquinones with enamino esters to afford diversely functionalized 5-hydroxyindole-3-carboxylates (Scheme 1). In the case of 2-substituted-1,4-benzoquinones, the Nenitzescu reaction typically affords 6-substituted-5-hydroxyindoles (R^1 at C-6 of the indole) or mixtures of 6- and 7-substituted products [5,6]; however, there are exceptions.

Interestingly, Littell and Allen [5] discovered that the Nenitzescu reaction of 2-trifluoromethyl-1,4-benzoquinone ($R^1 = CF_3$) with 3-aminocrotonates (R^2 = Me) selectively affords the 4-substituted-5-hydroxyindole products (CF_3 at C-4 of the indole). This regioselectivity was attributed to the powerful inductive influence of the trifluoromethyl group on the 1,4-benzoquinone and the lack of a competing resonance effect with this substituent. Consequently, addition of the enamine methine carbon occurs selectively at the 3-position of the 1,4-benzoquinone. Aside from the work of Littell and Allen [5], this particular Nenitzescu synthesis of 4-trifluoromethylindoles appears to be relatively unexploited in the fields of medicinal and process chemistry.

Scheme 1. Nenitzescu synthesis of 5-hydroxyindole-3-carboxylates.

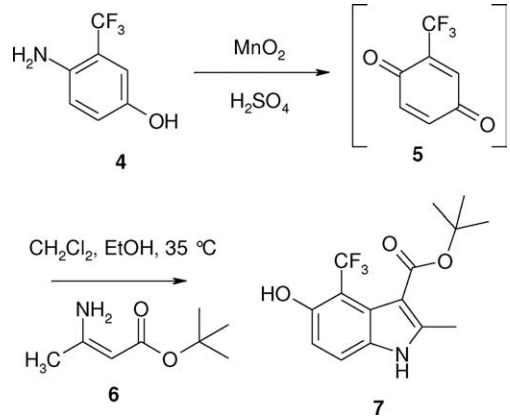


Based on this precedence, the Nenitzescu reaction appeared to have all the attributes for an efficient synthesis of **2**. In addition to being highly convergent, the Nenitzescu synthesis would incorporate the trifluoromethyl substituent at the desired 4-position of the indole along with a 5-hydroxy substituent. The latter might easily be converted to a triflate group and later substituted with a cyano substituent under palladium-catalyzed conditions. Removal of the ester moiety at C-2 of the indole through a decarboxylative pathway would then complete the synthesis of the title compound. This approach to the novel intermediate **2** was subsequently reduced to practice as outlined in Schemes 2 and 3.

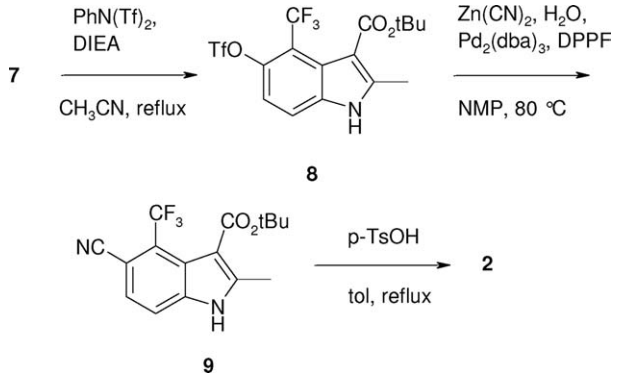
Conversion of 4-amino-3-(trifluoromethyl)phenol (**4**) to 2-trifluoromethyl-1,4-benzoquinone (**5**) and Nenitzescu reaction of **5** with 1,1-dimethylethyl (2*Z*)-3-amino-2-butenoate (**6**) are illustrated in Scheme 2. Compound **4** was prepared in quantitative yield [7] by hydrogenation of 4-nitro-3-(trifluoromethyl)phenol [8] in ethanol over palladium on carbon at atmospheric pressure. Initially, oxidation of **4** [5] with sodium dichromate in a biphasic mixture of 20% sulfuric acid and hexanes afforded **5** as a crystalline solid in 33% isolated yield.

The low yield of **5** was in accordance with the reported synthesis [5], and the material sublimed readily under relatively low-vacuum conditions. The toxicity associated with chromium salts and the volatility of **5** prompted us to explore alternative reagents for the oxidation step and a procedure that avoided isolation of **5** (i.e., a telescoped conversion of **4** → **7**). A number of oxidizing agents were evaluated qualitatively on milli-

Scheme 2. Nenitzescu indole synthesis of **7**.



Scheme 3. Synthesis of **2** from Nenitzescu indole **7**.



gram scales for conversion of **4**–**5**, including ceric ammonium nitrate, sodium (meta)periodate ($NaIO_4$), and manganese (II) oxide (MnO_2). All of these reagents gave satisfactory results; however, we favored the use of MnO_2 [9] for scale-up because of its low cost.

Adding a solution of **4** in 2.5*M* sulfuric acid to a stirred suspension of manganese dioxide in dilute sulfuric acid effected clean conversion to **5**. The manganese salts were easily removed by filtration, and extraction of both the filter cake and filtrate with dichloromethane afforded (after drying over $MgSO_4$) a clear solution of **5** (estimated yield = 78%) which could be used directly in the next step.

1,1-Dimethylethyl (2*Z*)-3-amino-2-butenoate **6** [10] was prepared in quantitative yield by treatment of *tert*-butyl acetoacetate [11] with 28–30 wt % ammonium hydroxide in MeOH. Addition of the dichloromethane solution of **5** to an ethanol solution of **6** at ambient temperature resulted in spontaneous Nenitzescu reaction to afford **7**. The reaction was mildly exothermic (10–15°C temperature rise on 0.3 mol scale) and was complete within 1 h. A solvent switch from dichloromethane/ethanol to chloroform and filtration of the resulting precipitate afforded the known indole **7** as a white solid in 64% yield (based on 3-aminocrotonate **6**). Indole **7** was used without further purification.

Synthesis of the title compound (**2**) from indole **7** is illustrated in Scheme 3. We opted to perform triflate formation prior to *tert*-butyl ester removal in order to maintain protection of the indole's potentially reactive C-3 position. Initially, reaction of **7** with triflic anhydride and 2,6-lutidine in dichloromethane at 0°C generated the novel triflate **8**; however, the reaction was accompanied by formation of several unidentified by-products. Alternatively, reaction of **7** with *N*-phenyl-bis(trifluoromethane)sulfonimide and Hunig's base in acetonitrile at reflux gave a much cleaner reaction mixture. The sulfonamide by-product was removed from the reaction mixture on workup (dilute sodium hydroxide wash), and the product (**8**) was crystallized from *tert*-butyl methyl ether in 75% yield.

Limited examples of palladium-catalyzed couplings of zinc cyanide with *ortho*-trifluoromethyl substituted aryl halides and aryl triflates are described in the patent literature [12]. We explored coupling of 8 with zinc cyanide using tris[dibenzylideneacetone]-di-palladium(0) catalyst and 1,1′-bis(diphenylphosphino)-ferrocene ligand in wet 1-methyl-2-pyrrolidinone (NMP) [13]. Heating the batch to 125°C effected a 50% conversion of 8 to the desired 5-cyanoindole 9 during which time the reaction stalled and turned very dark both observations consistent with catalyst deactivation. Interestingly, if the reaction was performed under the same conditions, but at lower temperature (80°C), the results were dramatically improved. Under these conditions, the reaction mixture maintained a light amber appearance and was complete within a few hours. The novel nitrile product (**9**) was obtained in 85% yield following workup and trituration with *tert*-butyl methyl ether.

Completion of the synthesis entailed removal of the *tert*-butyl ester group of **9** with *para*-toluenesulfonic acid in refluxing toluene [5]. Following workup and crystallization from toluene, the novel indole **2** was obtained in 87% yield as an off-white crystalline solid.

In summary, a scalable synthetic pathway to the novel indole **2**, an important intermediate in the preparation of nonsteroidal androgen receptor modulators (**1**), was achieved in six steps and 27% overall yield from 4-nitro-3-(trifluoromethyl)phenol (five steps and 37% overall yield from *tert*-butyl acetoacetate). This chemistry was subsequently adapted to kilo-lab preparations of the title compound. The medicinal chemistry synthesis of **3** and the structure activity relationships of SARMs derived from **2** are planned for future publications.

EXPERIMENTAL

1,1-Dimethylethyl 5-hydroxy-2-methyl-4-(trifluoromethyl)-1*H*-indole-3-carboxylate (7). A solution of **4** [7] (70 g, 0.40 mol) in 2.5*M* H_2SO_4 (720 mL) was added dropwise to a stirred suspension of MnO_2 (78 g, 0.9 mol) in 2.5*M* H_2SO_4 (720 mL) with external cooling; the reaction mixture temperature was maintained between 6°C and 8°C during this addition. After stirring an additional 30 min, the mixture was filtered and the cake washed several times with CH_2Cl_2. The organic phase of the filtrate was separated, dried over $MgSO_4$, filtered through a small plug of silica gel and concentrated to a volume of about 300 mL at atmospheric pressure (to avoid sublimation of **5**). The resulting CH_2Cl_2 solution of **5** (about 0.31 mol, 78% yield) was added dropwise to a stirred solution of **6** [10] (47.6 g, 0.3 mol) in EtOH (100 mL) at room temperature (rt) (internal temperature rose to +35°C during this addition). After stirring the reaction mixture for 1 h at ambient temperature, the solvent was removed by rotovap and replaced with $CHCl_3$. The stirred mixture was cooled to 0°C and indole **7** [5] was collected by filtration as an off-white solid (62 g, 66% yield from **6**) and used without further purification; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 1.45 (s, 9H), 2.37 (s, 3H), 6.76 (d, 1H, J = 9 Hz), 7.33 (d, 1H, J = 9 Hz), 9.68 (br s, 1H), 11.55 (s, 1H); Anal. Calcd. for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.11; N, 4.44. Found: C, 56.80; H, 5.02; N, 4.34.

1,1-Dimethylethyl 2-methyl-4-(trifluoromethyl)-5-{[(trifluoromethyl)-sulfonyl]oxy}-1*H*-indole-3-carboxylate (8). A stirred solution of **7** (62 g, 0.197 mol), *N*, *N*-diisopropyl ethylamine (DIEA) (56 mL, 0.321 mol), and $PhN(Tf)_2$ (78 g, 0.218 mol) in CH_3CN (300 mL) was heated at reflux temperature for 2 h. The reaction mixture was cooled to ambient temperature, diluted with EtOAc, and washed with water; the layers were separated and the aqueous phase was extracted with EtOAc. The combined EtOAc layers were washed with 0.1*N* NaOH, 2*M* H_3PO_4, and water. The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated, and the resulting material crystallized from *tert*-butyl methyl ether (MTBE) to afford **8** as a white crystalline solid (66 g, 75% yield), mp 161–163°C; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 1.48 (s, 9H), 2.48 (s, 3H), 7.29 (d, 1H, J = 9 Hz), 7.77 (d, 1H, J = 9 Hz), 12.39 (s, 1H); ^{13}C NMR (101 MHz, dimethylsulfoxide-d_6) δ 13.6, 28.4, 81.0, 109.3, 112.6 (q, J_{CF} = 33 Hz), 115.8, 117.45, 120.3 (q, J_{CF} = 321 Hz), 122.8 (q, J_{CF} = 2 Hz), 123.6 (q, J_{CF} = 275 Hz), 135.5, 141.2 (q, J_{CF} = 2 Hz), 145.5, 165.0; ESMS (negative mode): m/z 446 $(M-H)^-$; Anal. Calcd. for $C_{16}H_{15}F_6NO_5S$: C, 42.96; H, 3.38; N, 3.13; S, 7.17. Found: C, 42.94; H, 3.46; N, 3.23; S, 7.12.

1,1-Dimethylethyl 5-cyano-2-methyl-4-(trifluoromethyl)-1*H*-indole-3-carboxylate (9). To a stirred solution of **8** (20.2 g, 45.2 mmol) in NMP (150 mL) was added deionized water (8 mL), and N_2 was passed through the solution for 10 min. 1,1′-Bis(diphenylphosphino)ferrocene (2.49 g, 4.49 mmol) and tris(dibenzylidineacetone)-dipalladium(0) (2 g, 2.18 mmol) were added, and the solution was stirred under N_2 atmosphere at rt for 15 min. Zinc cyanide (3.95 g, 33.6 mmol) was added and the mixture was stirred an additional 10 min at rt. The reaction mixture was heated to 80°C and maintained at this temperature for 3 h. After cooling to 35°C, the mixture was diluted with MTBE and washed with water. The aqueous layer was extracted with MTBE, and the combined MTBE layers were washed with water and dried over $MgSO_4$. The organic phase was filtered and the MTBE filtrate was stirred over decolorizing charcoal for 15 min. The charcoal mixture was filtered through a plug of silica gel (75 g), and the filtrate was concentrated at reduced pressure. The remaining material was triturated with hot MTBE, then diluted with *iso*-octane, cooled to −15°C and filtered to afford **9** as a beige solid (12.5 g, 85% yield), mp 220–222°C (dec); ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ 1.49 (s, 9H), 2.50 (s, 3H), 7.70 (1H, d, J = 8 Hz), 7.77 (1H, d, J = 8 Hz), 12.54 (s, 1H); ESMS (negative mode): m/z 323 $(M-H)^-$; Anal. Calcd. for $C_{16}H_{15}F_3N_2O_2$: C, 59.26; H, 4.66; N, 8.64. Found: C, 59.26; H, 4.70; N, 8.46.

2-Methyl-4-(trifluoromethyl)-1*H*-indole-5-carbonitrile (2). A rapidly stirred mixture of **9** (12.5 g, 38.54 mmol), *para*-toluenesulfonic acid monohydrate (0.71 g, 3.7 mmol), and toluene (110 mL) was heated at reflux for 1 h. The mixture was cooled to ambient temperature, diluted with EtOAc, and washed with saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$, filtered, and concentrated at reduced pressure; the remaining material was crystallized from toluene to provide **2** as an off-white solid (7.5 g, 87% yield), mp 191–192°C; ^{1}H NMR (400 Mz, dimethylsulfoxide-d_6) δ 2.45 (s, 3H), 6.43 (br

s, 1H), 7.58 (d, 1H, $J = 8$ Hz), 7.69 (d, 1H, $J = 8$ Hz), 12.07 (br s, 1H); ^{13}C NMR (101 MHz, dimethylsulfoxide-d_6) δ 13.9, 99.3 (q, $J_{CF} = 3$ Hz), 99.7 (q, $J_{CF} = 3$ Hz), 115.5, 118.4, 121.6 (q, $J_{CF} = 32$ Hz), 124.7 (q, $J_{CF} = 275$ Hz), 125.9, 126.1 (q, $J_{CF} = 2$ Hz), 139.5, 142.9; ESMS (negative mode): *m/z* 223 $(M-H)^-$; Anal. Calcd. for $C_{11}H_7F_3N_2 \cdot (0.2\ H_2O)$: C, 58.00; H, 3.27; N, 12.30. Found: C, 58.04; H, 3.05; N, 12.34.

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