Improved procedure for the preparation of 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid, key intermediate in the synthesis of novel 3-amidoindole and indolopyridone cannabinoid ligands

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Dedicated to Professor Franklin A Davis on his 70th birthday

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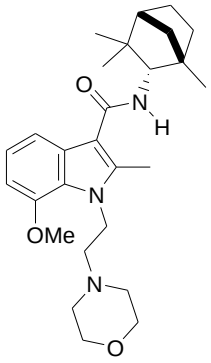
Abstract
A new efficient method was developed for the preparation of 2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid. The new method involves N-alkylation of 7-methoxy-2-methylindole with 4-(2-chloroethyl)morpholine hydrochloride followed by trichloroacetylation and hydrolysis in 3 steps and 88% overall yield.

Keywords: cannabinoid (CB2) receptor, synthesis, indole N-alkylation, indole-3-carboxylate.

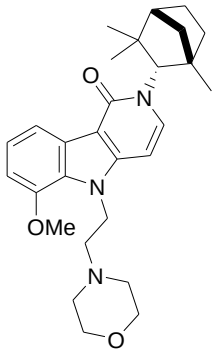
Introduction

The discovery of the human peripheral cannabinoid (CB2) receptor,[1] has stimulated a significant amount of research effort on the development of CB2 selective ligands.[2-4] In our search for novel cannabinoid receptor modulators, it was discovered that 7-methoxy-2-methyl-1-(2-morpholinoethyl)-N-((1*S*,2*S*,4*R*)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-indole-3-carboxamide **1** binds selectively to the CB2 receptor and displays excellent in vivo potency against LPS induced TNF-α release in murine models of cytokine production.[3] Further optimization led to a novel cannabinoid ligand **2** which shows high affinity for the CB2 receptor (K_i = 1.0nM) and possesses anti-inflammatory properties when administered orally in an in vivo murine inflammation model.[4] This novel C-3 amido indole and its cyclized and conformationally constrained indolopyridone cannabinoid receptor modulators **1** and **2** are derivatives of indole-3-

carboxylates. The morpholino acid, 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid (**3**) is an advanced core intermediate en route to both of these compounds.[3,4]



1



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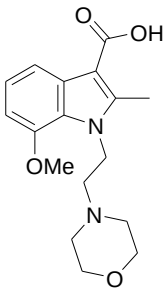
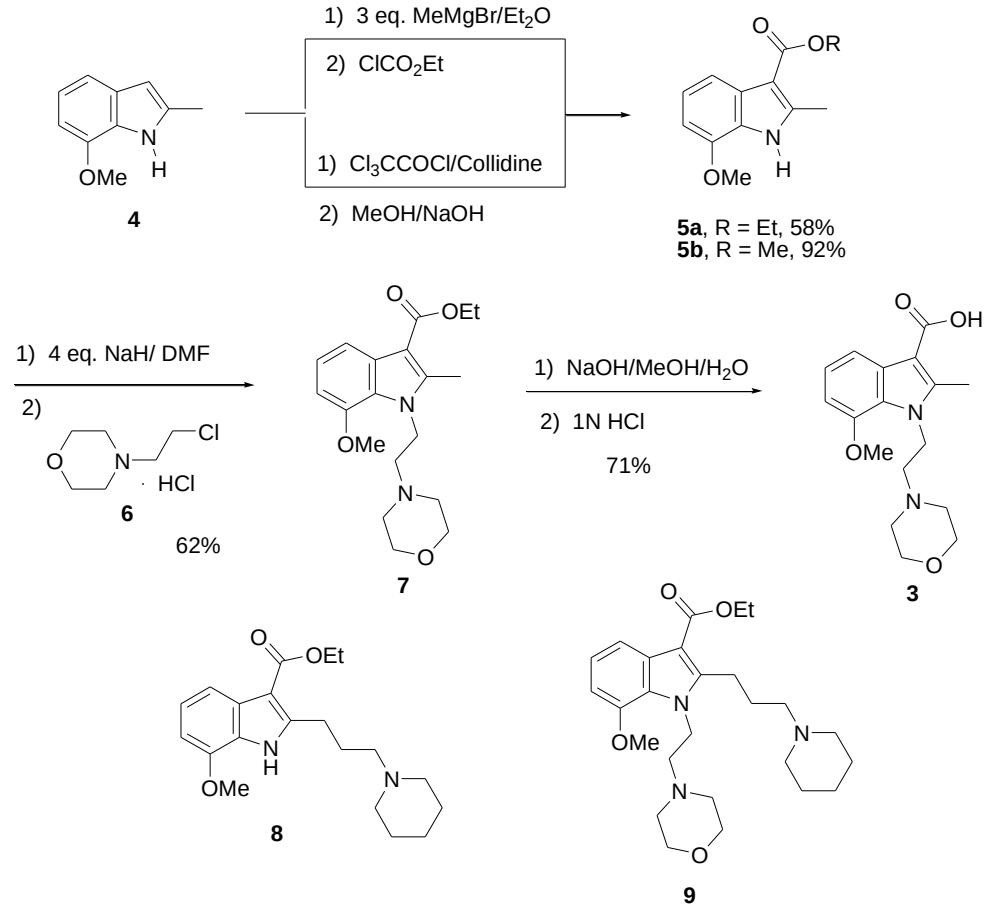


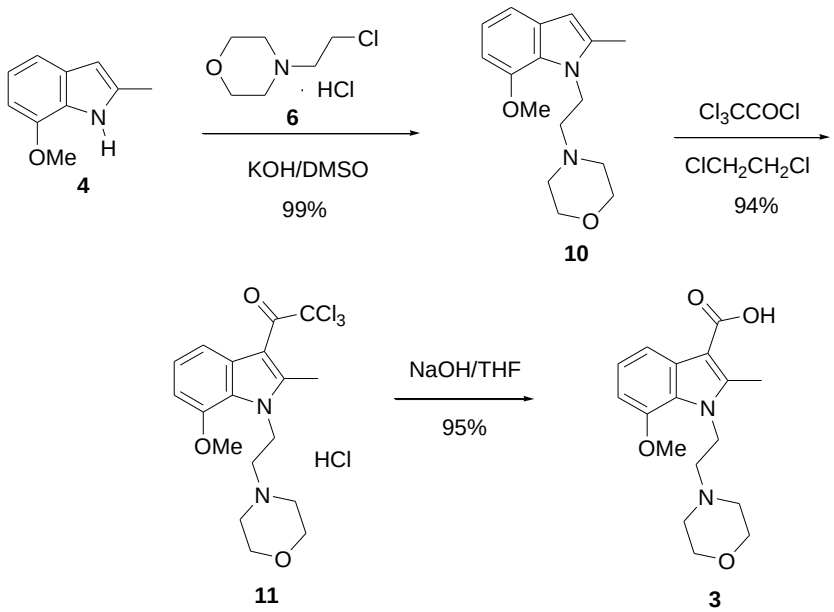
3

Previously, 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid **2** was prepared from 7-methoxy-2-methyl-1H-indole **4** as shown in Scheme 1.[3] Treatment of **4** with 3 equivalents of methylmagnesium bromide in MTBE followed by trapping the anion with ethyl chloroformate afforded ethyl indole-3-carboxylate **5a** in 58% yield after silica gel chromatography. Alternatively, the indole-3-carboxylate could be prepared by acylation of 7-methoxy-2-methyl-1H-indole **4** with trichloroacetyl chloride followed by alcoholysis.[3,5] An example of this preferred approach is the preparation of methyl indole-3-carboxylate **5b**, which was obtained in 92% yield.[3]

The introduction of the N-morpholinoethyl side chain onto the indole-3-carboxylate **5** was accomplished by treating **5** with 4-(2-chloroethyl)morpholine hydrochloride **6** in the presence of a large excess of base. Thus, treatment of ethyl indole-3-carboxylate **5a** with 4 equivalents of sodium hydride followed by addition of **6** gave ethyl 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylate **7** in 62% yield after purification by silica gel chromatography. Hydrolysis of **7** with NaOH in methanol and water and subsequent neutralization to pH 6.5-7 afforded **3** in 71% isolated yield. While this approach provided a small quantity of the desired indole-3-carboxylic acid **3** to fuel SAR studies, it was not amenable for scale-up synthesis due to the use and handling of a large excess of hazardous sodium hydride, the generation of hydrogen gas in the reaction, as well as the needs for chromatographic separation of by-products **8** and **9** resulting from the competitive C-alkylation at the 2-methyl group in **5** under the reaction conditions.[6] Herein, we report a new and improved procedure for the preparation of 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid **3** (Scheme 2).



Scheme 1



Scheme 2

Results and Discussion

Our rationale for developing the new and improved synthesis of 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid **3** as shown in Scheme 2 was based on the following considerations. First, we believed that the undesired competitive C-alkylation at the 2-methyl group in **5** in the previous synthesis (scheme 1) was a result from increase of acidity of the 2-methyl group, a consequence of the introduction of the 3-carboxylate group in **5** through a vinylogous carbonyl effect. We envisioned that if the indole N-alkylation was carried out prior to introduction of the 3-carboxylate group, the undesired competitive C-alkylation at the 2-methyl group would disappear. Second, we would like to take advantage of the much more desired non-metallic method that we developed earlier for the synthesis of indole-3-carboxylate **5b** using trichloroacetyl chloride.

Thus, treatment of 7-methoxy-2-methyl-1H-indole **4** with 1.4 equivalents of 4-(2-chloroethyl)morpholine hydrochloride **6** in DMSO using 4 equivalents KOH as base gave 4-(2-(7-methoxy-2-methyl-1H-indol-1-yl)ethyl)morpholine **10** smoothly (Scheme 2). The use of a strong base such as NaH was found to be unnecessary for this reaction and the concerns of handling NaH and generation of hydrogen gas on scale-up were eliminated. More importantly, by using a weaker base (KOH), the undesired C-alkylations were not observed, resulting in higher yield and simpler product isolation and purification. After extractive workup to remove the water soluble inorganic salts and excess 4-(2-chloroethyl)morpholine, the desired product **10** was obtained in essentially quantitative yield whithout chromatographic purification.

With an efficient approach to intermediate **10** in hand, our next goal was the introduction of the 3-carboxylate group to **10**. The 3-acylation was initially tried using the trichloroacetyl chloride and collidine as the base. The reaction took place to give the desired product, but it was sluggish. After 2 hours of refluxing, the desired product **11** was formed in 28% by LC/MS. Longer heating resulted in decomposition of the product. Considering the fact that the starting compound **10** has a basic nitrogen in the morpholine ring, we decided to run the acylation reaction without the use of external base. To our delight, the reaction was fast and completed in 6-8 hours under reflux in 1,2-dichloroethane. The reaction was also very clean, resulting in again a very simple work-up and product isolation and purification. After cooling the reaction mixture to room temperature, the desired product **11** was isolated in 94% yield as a hydrochloride salt after filtration of the resulting slurry. Final hydrolysis of **11** to 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid **3** was uneventful. By running the reaction with aqueous 1N NaOH in THF, 7-methoxy-2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid **3** was isolated in 95% yield after pH adjustment of the reaction mixture using HCl.

Conclusions

In summary, a new and efficient method was developed for the preparation of 2-methyl-1-(2-morpholinoethyl)-1H-indole-3-carboxylic acid. The new method involves N-alkylation of 7-methoxy-2-methylindole with 4-(2-chloroethyl)morpholine hydrochloride followed by trichloroacetylation and hydrolysis in 3 steps and 88% overall yield. The new process was readily scaled-up and no chromatographic separation of products was involved. The new method was successfully applied to the synthesis of novel 3-amidoindole and indolopyridone cannabinoid ligands. Furthermore, it is expected that this new method can be applied to the preparation of other aminoalkylindoles, biologically important and medicinally useful agents.

Experimental Section

General. Proton NMR spectra were recorded with a Bruker DRX-400 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for proton NMR. All other reagents and solvents were commercial products and were used as received unless otherwise noted. All reactions were monitored by HPLC using a Shimadzu LC-10AS system and YMS ODS-A S5 4.6x50mm column with linear gradient system of H_2O-MeOH-H_3PO_4 90:10:0.2 to 10:90:0.2 over 4 min. and at a flow rate of 4 mL/min. All compounds were of >99% purity by analytical HPLC analyses. Melting points are uncorrected.

Preparation of 1-[2-(4-morpholino)ethyl)-2-methyl-7-methoxyindole 10. To a stirred suspension of 130.2 g (0.7 mol) of N-(2-chloroethyl)morpholine hydrochloride **6** in 1 L of DMSO was added 132 g (2 mol) of 85% powdered KOH. After the suspension was stirred for 5 minutes, a solution of 80.6 g (0.5 mol) of 2-methyl-7-methoxyindole **4**[7] in 200 mL of DMSO was added. After stirring for 10 minutes, the reaction mixture was heated to 100°C and stirred at this temperature for 3.5 hours. The reaction mixture was cooled to ambient temperature and diluted with 1 L of water and 2 L of MTBE. The organic layer was separated and aqueous layer was extracted with MTBE (2x1 L). The organic layers were combined, washed with brine (1 L). The solvent was removed under reduced pressure to give 135.9 g product **10** as a light yellow oil (99%). ^{1}H NMR ($CDCH_3$) δ 2.42 (s, 3H), 2.52 (m, 4H), 2.62 (t, *J*=7.1Hz, 2H), 3.75 (m, 4H), 3.90 (s, 3H), 4.42 (t, *J*=7.1Hz, 2H), 6.17 (s, 1H), 6.55 (d, *J*=7.8Hz, 1H), 6.90 (dd, *J*=7.8, 8.0Hz, 1H), 7.10 (d, *J*=8.0Hz, 1H). MS calcd for $C_{16}H_{22}N_2O_2$ [M+H] 275.168, found 265.169. Anal. HPLC tr = 2.19 min.

Preparation of 1-[2-(4-morpholino)ethyl)-2-methyl-3-trichloroacetyl-7-methoxyindole hydrochloride 11. To a solution of **10** (132 g, 0.48 mol) in 1,2-dichloroethane (2 L) was added trichloroacetyl chloride (262.4 g, 1.44 mol). The solution was refluxed for 6-8 h and then cooled to ambient temperature. The resulted slurry was filtered, washed with MTBE(2xl L) and dried to

give 205.8 g of product **11** (94%). ^{1}H NMR ($CDCl_3$) δ 0 2.85 (s, 3H), 2.95 (m, 2H), 3.30 (m, 2H), 3.55 (m, 2H), 4.05 (m, 5H), 4.32 (m, 2H), 5.15 (m, 2H), 6.75 (d, *J*=7.8Hz, 1H), 7.15 (dd, *J*=7.8, 8.0Hz, 1H), 7.85 (d, *J*=8.0Hz, lH). MS calcd for $C_{18}H_{21}Cl_3N_2O_3$ [M+H] 419.061, found 419.065. Anal. HPLC tr = 2.77 min.

Preparation of 1-[2-(4-morpholino)ethyl)-2-methyl-7-methoxyindole-3-carboxylic acid 3. To a solution of **11** (182.45 g, 0.4 mol) in THF (1 L) was added NaOH solution (1 L, 1N, 1 mol). The reaction mixture was stirred about 1-2 h. The pH of the reaction solution was adjusted to 4 with HCl (6N). The slurry was filtered, washed with MTBE (2x500 mL) and water. The solid was dried to give product **3** (120.58 g, 95%). ^{1}H NMR (DMSO-d_6) δ 2.44 (s, 3H), 2.58 (s, 2H), 2.72 (s, 4H), 3.56 (s, 4H), 3.90 (s, 3H), 4.42 (s, 2H), 6.67 (d, *J*=7.8Hz, 1H), 7.00 (dd, *J*=7.8, 8.0Hz, 1H), 7.65 (d, *J*=8.0Hz, 1H). 318.158. MS calcd for $C_{17}H_{22}N_2O_4$ [M+H] 319.158, found 319.162. Anal. HPLC tr = 1.43 min.

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