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SYNTHESIS OF 5-BENZOYL-6- TRIFLUOROMETHYL -1,2 - DIHYDRO-3*H*-PYRROLO[1,2-*a*]PYRROLE-1-CARBOXYLIC ACID

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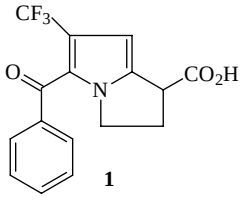
Abstract – Synthesis of the possible analgesic and/or antiinflammatory agent 5-benzoyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (**1**) was designed from the already known intermediate ester 3-methoxycarbonyl-4-trifluoromethyl-5-benzyloxycarbonylpyrrole-2-acetic acid methyl ester (**4**) wich is prepared *via* a Knorr synthesis.

INTRODUCTION

In connection with a program[1,2] related to the development of certain nonesteroidal antiinflammatory agents with fewer side effects than phenylbutazone and indomethacin, it was found that the pyrrole-2-acetic acid[3-5] (**2a**) showed good pharmacologic activity; furthermore, it was observed by the introduction of methyl groups in C4 position of the pyrrolic ring[6] and/or in the chain of the acetic acid to give the derivatives of the propionic acid (**2b,c**), the antiinflammatory activity increased; zomepirac (**2c**)[6] is one good example of this structural change. The notion that more rigid bicyclic sistems present greater analgesic and/or antiinflammatory activity, was substantiated through the pharmaceutical product ketorolac (**3a**).[7-9] The introduction of CF_3 group (comp. **2d**) in zomepirac rendered good analgesic and antiinflammatory activity;[10] thus, it was decided to carry out a synthesis of **1** to evaluate as possible analgesic and/or antiinflammatory agent.



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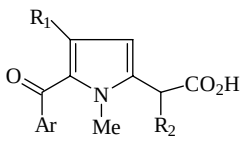
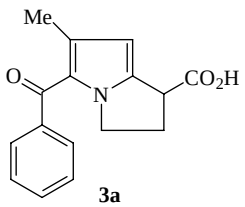


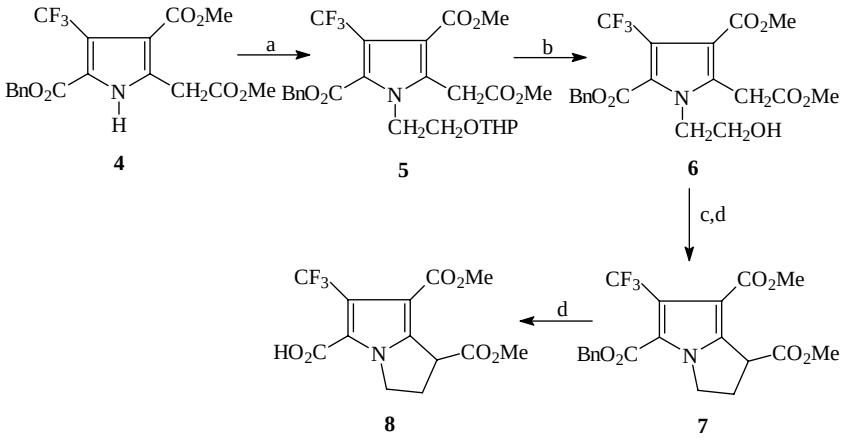
2a : R_1,R_2 = H
2b : R_1, R_2 = Me
2c : R_1 = Me, R_2 = H
2d : R_1 = CF_3, R_2 = H



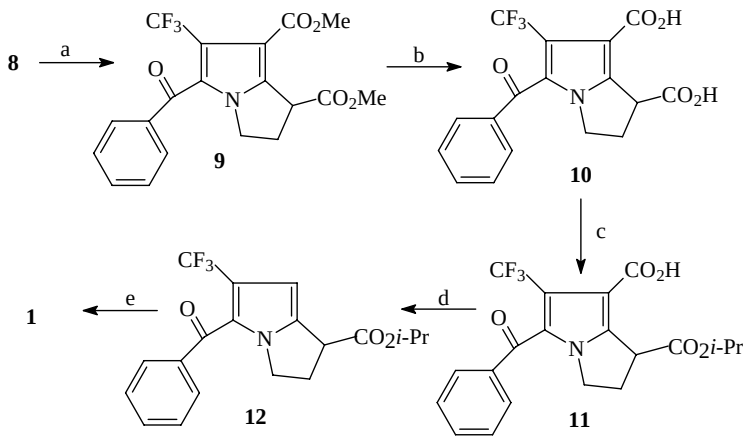
3a

RESULTS AND DISCUSSION

A synthesis of **1** was designed from the already known intermediate ester (**4**) which is prepared *via* a Knorr synthesis;[10] a synthesis is partially depicted on the **Scheme 1**. **4** was alkylated with the tetrahydropyranil ether derivative of 2-bromoethanol, NaI, and K_2CO_3 as base in dry DMF with 82 % yield; the hydrolysis to the alcohol (**6**) was achieved with a mixture of acetic acid-H_2O 6:4 at 55°C in 92 % yield. **6** was mesylated with $MeSO_2Cl$ and Et_3N in dry CH_2Cl_2 and the mesylate was intramolecularly alkylated using NaH as base in dry DMF in 86 % yield. Alternatingly we could obtain **7** directly from **4** using 1,2-dibromoethane and K_2CO_3 in dry DMF in 79 % yield, this fact conveniently placed these conditions as the best in the formation of **7**. The hydrogenolysis of the benzylic ester with 10 % Pd/C in ethyl acetate for 2 h at room temperature afforded the carboxylic acid (**8**) in quantitative yield. The synthesis continued (**Scheme 2**) with the formation of the acid

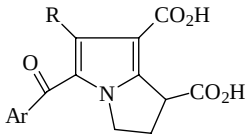


Scheme 1. a: $BrCH_2CH_2OTHP$, K_2CO_3, NaI, DMF, b: AcOH-H_2O, c: Et_3N, $MeSO_2Cl$, CH_2Cl_2, d: NaH, DMF, e: H_2, 10% Pd/C, AcOEt.



Scheme 2. a: $(COCl)_2$, PhMe, PhMgBr, $Fe(acac)_3$, THF, b: EtSLi, HMPA, c:*i*-PrOH, HCl_{gas}, d: CuO, quinoline, 215°C, e: HCO_2H, $MeSO_3H$

chloride of **8** and the subsequent treatment of the crude product with phenylmagnesium bromide and iron(III) acetylacetonate in dry THF at room temperature[11] afforded **9** in 54 % yield. The following step was the methyl esters cleavage of **9**, the hydrolysis with NaOH or KOH in MeOH:H_2O solution at reflux gave only 25 % yield of the diacid (**10**); this problem was circumvented using lithium thioethoxide in dry HMPA at room temperature.[12] furnishing the dicarboxylic acid (**10**) in 67 % yield. It is known that the compounds (**13**) undergo selective acid decarboxylation in C7 position;[13] so, it was decided to test the selective acid decarboxylation of the diacid (**10**). Decarboxylation neither was in



13

13: R = H, Me, Et, n-Bu, n-C_5H_{11}, n-C_6H_{13}, Cl, F or Br.

trifluoroacetic nor trichloroacetic acid succesful; for this reason it was prepared selectively the monoester (**11**) from **10** in dry isopropyl alcohol under Fischer conditions[14] in 75 % yield. With the antecedent pyrrole-3-carboxylic acids were decarboxylated under thermal conditions,[14] it was decided to test the thermal decarboxylation of the monoester (**11**), but it was unsuccesful; however, the decarboxylation was achieved by heating the acid with CuO/quinoline at 215°C over argon atmosphere[15] furnished the ester (**12**) in 53 % yield. Finally the ester (**12**) was hydrolized with a mixture of HCO_2H, $MeSO_3H$ and H_2O to give the acid (**1**) in 78 % yield. In conclusion, a synthesis of compound (**1**) was accomplished in seven steps from **4** in 11.4 % overall yield.

EXPERIMENTAL

Melting points were determined in a Mel-Temp melting point apparatus and are uncorrected. The IR spectra were measured with a Perkin Elmer 267 grating infrared spectrophotometer. The UV spectra were recorded on a Perkin-Elmer 402 ultraviolet visible spectrometer. The ^1H NMR spectra were measured with a Varian T-60 spectrometer and are expressed as parts per million (δ) from internal tetramethylsilane as an internal standard. The LRMS spectra were measured on, Atlas CH-4 spectrometer. The HRMS spectra were obtained with Varian-MAT 311A mass spectrometer. Column chromatography was performed over silica 60-230 mesh (MercK). Preparative TLCs were run on a Merck GF_{254} plates. The term "dried" signifies dried over Na_2SO_4 throughout the experimental section. Commercially available reagents and solvents were used without additional purification unless otherwise stated.

5-Benzyloxycarbonyl-3-methoxycarbony-4-trifluoromethyl-1-tetrahydropyranyloxyethyl)pyrrole -2-acetic acid methyl ester (5). 4 (198 mg, 0.496 mmol), dry DMF (7.5 mL), dry K_2CO_3 (216 mg, 1.7 mmol), dry NaI (150 mg, 1 mmol) and 2-bromotetrahydropyraniloxyethane (224 mg, 1.07 mmol) were

heated under N_2 atmosphere to 95°C for 2 h, with magnetic stirring. The reaction mixture was poured into water (50 mL) and the product was extracted into ether (3 x 20 mL). The extract was washed with H_2O (5 mL) and then it was dried and evaporated in vacuo. The residue was purified by column chromatography on silica gel (8 g) using hexane-acetone (90:10) to elute the desired material as yellow oil (**5**) (209 mg, 80 %). UV (MeOH) λ max (log ε) 213 (4.35), 263 (3.85); IR ($CHCl_3$) 1730, 1070, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (s, 5H), 5.28 (2, 2H), 4.20-4.45 (m, 3H, NCH_2, CH), 4.10 (s, 2H), 3.97 (m, 4H), 3.73 (s, 3H), 3.62 (s, 3H). MS (m/z, %) 527 (M^+, 1), 443 (2), 392 (9), 336 (3), 91 (100), 85 (54). Anal. Calcd for $C_{25}H_{28}NO_8F_3$: C, 56.87; H, 5.30; N, 2.65; F, 10.80. Found: C, 56.88; H, 5.21; N, 2.58; F, 10.72.

5-Benzyloxycarbonyl-3-methoxycarbonyl-4-trifluoromethyl-1-(ω-hydroxyethyl)pyrrole-2-acetic acid methyl ester (6). **5** (7.42 g 14 mmol), H_2O (40 mL) and AcOH (60 mL) were heated to 55-60°C with magnetic stirring for 1.75 h. After the mixture was poured into H_2O (250 mL) and the product was extracted into ether (3 x 80 mL). The extract was washed with H_2O (2 x 20 mL) and then it was dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (260 g) using hexane-AcOEt (7.5:2.5) to elute **6** as yellow oil (5.97 g, 91 %). UV (MeOH) λ max (log ε) 216 (4.22), 247 (3.82), 264 (3.87); IR $CHCl_3$) 3640, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (s, 5H), 5.32 (s, 2H), 4.23 (t, 2H, J=7.1 MHz), 4.08 (2, 2H), 3.80 (s, 3H), 3.77 (t, 2H, J=7.1 MHz), 3.70 (s, 3H), 2.25 (m, 1H); MS (m/z, %) 443 ($M,^+$ 2), 411 (6), 323 (3), 91 (100). Anal. Calcd for $C_{20}H_{20}NO_3F_3$: C, 54.13; H, 4.51; N, 3.15; F, 12.85. Found: C, 54.01; H, 4.42; N, 3.08; F, 12.81.

5-Benzyloxycarbonyl-3-methoxycarbonyl-4-trifluoromethyl-1-(ω-methanesulfonyloxyethyl)-pyrrole-2-acetic acid methyl ester (7). A mixture of **6** (26 g, 58 mmol) and Et_3N (12.4 mL, 87 mmol) in dry CH_2Cl_2 (260 mL) was cooled with magnetic stirring to 0°C. $MeSO_2Cl$ (5.6 mL, 70 mmol) was added at a rate such that the reaction temperature did not exceed 10°C. The reaction mixture was stirred for 1 h at rt. The solution was poured into H_2O (250 mL), extracted with CH_2Cl_2, and the extract was dried. The solvent was removed *in vacuo* and the residue was dissolved in dry DMF (220 mL), this mixture was cooled to 5°C and NaH (2.38 g, 59.5 mmol, 60 %) was added under N_2 atmosphere. The mixture was stirred for 30 min at rt and then was poured into H_2O (1.2 L) and the product was extracted into ethyl acetate (3 x 150 mL). The extract was washed with H_2O (40 mL) and then it was dried and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (1 Kg) using hexane-acetone (9:1) to elute **7** as oil (20.80 g, 83.4 %).

1,7-Dimethoxycarbonyl-5-benzyloxycarbonyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (7). **4** (0.735 g, 1.84 mmol), dry K_2CO_3 (0.88 g, 6.35 mmol) and 1,2-dibromoethane (0.32 mL, 3.7 mmol) in dry DMF (10 mL) were heating at 95°C with magnetic stirring for 70 min. The mixture was poured into H_2O (60 mL) and extracted with ether (3 x 15 mL). Dried, filtration and

concentration of the organic layer gave a residue which was subjected to column chromatography on silica gel (34 g), the compound as yellow oil (**7**) (0.62 g, 79 %) being eluted with 10 % ethyl acetate in hexane. UV (MeOH) λ max (log ε) 214 (4.35), 268 (4.12); IR (neat) 1740, 1705, cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (s, 5 H), 5.32 (s, 2H), 4.10-4.47 (m, 3H, NCH_2, CH), 3.80 (s, 3H), 3.70 (s, 3H), 2.52-2.98 (m, 2H); MS m/z (rel intensity) 335 ($M,^+$ 14), 394 (3), 318 (6), 291 (7), 91 (100). Anal. Calcd for $C_{20}H_{18}NO_6F_3$: C, 56.47; H, 4.23; N, 3.29; F, 13.41. Found: C, 56.36; H, 4.09; N, 3.45; F, 13.28.

1,7-Dimethoxycarbonyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-a]pyrrole-5-carboxylic acid (8). 7 (17 g, 0.04 mol) and Pd/C (10 %, 1.7 g) in ethyl acetate (250 mL) were hydrogenolized at atmospheric pressure for 2 h. The mixture was filtered through a pad of celite with the aid of two 50 mL portions of ethyl acetate and then concentrated to afford in quantitative yield **8** as a white solid. mp: 179-180°C (ethyl acetate:hexane); UV (MeOH) 212 nm (ε 15490), 265 nm (ε 9120); IR (KBr) 3520, 1740, 1700 cm^{-1}; ^1H NMR δ 7.80 (br s, 1H), 4.20-4.39 (m, 3H, CH, CH_2N), 3.80 (s, 3H), 3.73 (s, 3H), 2.50-3.00 (m, 2H); MS (m/z, %) 335 ($M,^+$ 24), 303 (18), 276 (100), 236 (12). Anal. Calcd for $C_{13}H_{12}NO_6F_3$: C, 46.56; H, 3.58; N, 4.17; F, 17.01. Found: C, 46.39; H, 3.73; N, 4.19; F, 16.83.

1,7-Dimethoxycarbonyl-5-benzoyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole (9). 8 0.315 g, 0.94 mmol) and oxalyl chloride (1.41 mmol, 0.18 g) in dry toluene were refluxed for 2 h. The solvent was removed *in vacuo*, the residue was dissolved in dry THF (4 mL) and iron(III) acetylacetonate (`10 mg, 0.028 mmol) was added and the mixture was stirred (inert atmosphere). Phenylmagnesium bromide (0.94 mmol, 0.91 M) was added dropwise. After 20 min, the mixture was poured into aqueous HCl (10 mL, 5%) and extracted with ether (3 x 20 mL). The organic layer was washed with saturated aqueous NaCl solution, then with H_2O and finally it was dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (25 g) with acetone:hexane (14:86) as eluant affording **10** as yellow oil (0.202 g, 54%). UV (MeOH) λmax (log ε) 218 (4.04), 255 (4.00), 282 (3.86); IR ($CHCl_3$) 1735, 1705, 1645 cm^{-1}; H^1 NMR ($CDCl_3$) δ 7.28-7.90 (m, 5H), 4.05-4.42) (m, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 2.46-3.05 (m, 2H); MS (m/z, %) 395 ($M,^+$84), 336 (100), 318 (21), 290 (17), 105 (90), 77 (90). Anal. Calcd for : $C_{19}H_{16}NO_5F_3$: C, 57.72; H, 4.05: N, 3.54; F, 14.43. Found: C, 57.63; H, 3.97; N, 3.58; F, 14.35.

5-Benzoyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1,7-dicarboxylic acid (10). 9 (2 g, 5.06 mmol) was dissolved in dry HMPA (30 mL), and with magnetic stirring lithium thioethoxide (2.8 g, 41.6 mmol) in portionwise was added in 7 h. After 2 h cold water (90 mL) and aqueous HCl (10 %, 20 mL) were added, the mixture was extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with saturated aqueous NaCl solution (2 x 20 mL) and dried. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (70 g) using CH_2Cl_2-MeOH-HCO_2H (198 mL:1.8 mL:0.1 mL) to elute the product, the diacid (**10**) was

obtained in 67 % (1.2 g). mp: 201-203°C (ethyl acetate-hexane); UV (MeOH) λ max (log ε) 211 (4.08), 252 (4.07), 295 (3.84); IR (KBr) 2500-3550, 1705, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (br s, 2H), 7.46-8.00 (m, 5H), 3.92-4.52 (m, 3H, NCH_2, CH), 3.92-4.52 (m, 3H), 2.52 (m, 2H); MS (m/z, %) 367 ($M,^+$ 1), 323 (39), 303 (80), 262 (24), 105 (72), 77 (100). Anal. Calcd for $C_{17}H_{12}NO_5F_3$: C, 55.54; H, 3.26; N, 3.81; F, 15.51. Found: C, 55.49; H, 3.21; N, 3.79; F, 15.47.

1-Isoproppoxycarbonyl-5-benzoyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-7-carboxylic acid (11). 10 (0.90 g, 2.45 mmol) in dry *i*-PrOH (10 mL) was cooled to 0°C and HCl gas was bubbled through the *i*-PrOH until saturation was achieved. The solution was then left at ambient temperature and stirred for 2 h and then the solvent was evaporated to dryness *in vacuo*. Benzene was added to the residue and the mixture was evaporated to dryness *in vacuo* again and the solid was then crystallized from hexane-ethyl ether (2:1) affording **11** (0.76 g, 75 %). mp: 184-186°C; UV (MeOH) λ max (log ε) 212 (4.07), 252.5 (4.07) 296 (3.85); IR ($CHCl_3$) 2500-3550, 1730, 1700, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.62 (br s, 1H), 7.30-8.10 (m, 5H), 5.05 (hep, 1H, J=7.10 Hz), 4.05-4.50 (m, 3H), 2.42-3.12 (m, 2H), 1.29 (d, 6H, J=7.10 Hz); MS (m/z, %) 409 ($M,^+$ 40), 350 (5), 322 (100), 105 (24), 77 (21). Anal. Calcd for : $C_{20}H_{18}NO_5F_3$: C, 58.66; H, 4.39; N, 3.42; F, 13.93. Found: C, 58.60; H, 4.31; N, 3.37; F, 13.87.

5-Benzoyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid isopropyl ester (12). 11 (41 mg, 0.1 mmol), dry quinoline (1 mL) and CuO (50 mg) were heated under argon atmosphere to 215°C for 15 min. The reaction mixture was cooled at rt and poured into aqueous HCl (15 mL, 15%), extracted with ether (3 x 10 mL), the organic layer was separated, dried, filtered and concentrated. The residue was purified by column chromatography of silica gel (1.5 g) using hexane-acetone (9:1) as eluant, **12** (19.5 mg, 53%) was obtained as yellow oil. UV (MeOH) UV (MeOH) λ max (log ε) 209 (3.91), 242 (3.93), 294 (3.98); IR ($CHCl_3$) 1730, 1635, 1385, 1368 cm^{-1}; ^1HNMR ($CDCl_3$) δ 7.14-7.87 (m, 5H), 6.33 (s, 1H), 5.00 (hept, 1H, J=7.1 Hz), 3.78-4.45 (m, 2H, NCH_2, CH), 2.37-3.05 (m, 2H), 1.26 (d, 6H, J=7.1 Hz). MS (m/z, %) 365 ($M,^+$ 27), 278 (100), 105 (34), 77 (37). Anal. Calcd for $C_{19}H_{18}NO_3F_3$: C, 62.40; H, 4.92; N, 3.83; F, 15.60. Found: C, 62.32; H, 4.79; N, 3.78; F, 15.47.

5-Benzoyl-6-trifluoromethyl-1,2-dihydro-3*H*-pyrrolo[1,2-*a*]pyrrole-1-carboxylic acid (1). 12 (73 mg, 0.20 mmol), MsOH (0.04 mL, 70%), HCO_2H (2 mL, 97 %) were heated to 55°C with magnetic stirring for 16 h, and then poured into water (20 mL), extracted with ethyl acetate (4 x 10 mL). The organic layer was separated, dried, filtered, and concentrated. The residue was purified by crystallization from hexane-ethyl ether (2:1) affording **1** (50.3 mg, 78 %).mp: 135-136°C; UV (MeOH) λ max (log ε) 214 (3.87), 252 (3.94), 312 (4.00); IR ($CHCl_3$) 2500-3550, 1720, 1630 cm^{-1}; ^1H NMR

($CDCl_3$) δ 8.25 (br s, 1H), 7.20-7.90 (m, 5H), 6.45 (s, 1H), 3.90-4.62 (m, 3H, NCH_2, CH), 2.60-3.22 (m, 2H); MS (m/z, %) 323 ($M,^+$ 39), 279 (86), 218 (24), 105 (77), 77 (100); HRMS m/z Calcd for: $C_{16}H_{12}NO_3F_3$ (M^+) 323.0769. Found: 323.0751. Anal. Calcd for: $C_{16}H_{12}NO_3F_3$: C, 59.44; H, 3.71; N, 4.33; F, 17.64. Found: C, 59.64; H, 3.82; N, 4.31; F, 16.93.

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