A Concise and Efficient Synthesis of [2-Methyl-5-methylsulfonyl-4-(pyrrol-1-yl)benzoyl]guanidinium Methanesulfonate (Eniporide)

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A new synthesis of the benzoylguanidine-type Na^+/H^+ antiporter inhibitor eniporide (**7**) is described. Starting from 2-bromo-5-fluorotoluene (**1**), aromatic substituents were introduced by methanesulfonylation, Pd-catalyzed carboxylation with CO, and halogen–pyrrole exchange. Guanidine acylation was performed using Mukaiyama's procedure.

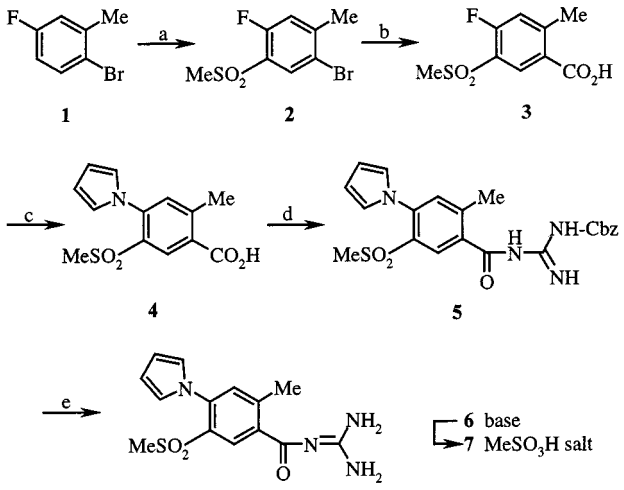
Introduction

There is convincing evidence that the Na^+/H^+ antiporter plays a pivotal role in mediating tissue injury during ischemia and reperfusion.[1] Activation of the antiporter results in a deleterious Na^+ overload and, due to coupling via the Na^+/Ca^{2+} exchanger, this causes cellular Ca^{2+} overload and serious contractile dysfunction, arrhythmia, and cellular death. Blocking the Na^+/H^+ exchange is a new strategy in cardioprotection using specific inhibitors with a benzoylguanidine structure. Two drugs of this class are under clinical investigation: cariporide[2] (Hoechst Marion Roussel, GUARDIAN trial) and eniporide (**7**, Merck KGaA, ESCAMI trial). A reduction of morbidity and mortality with patients undergoing coronary artery by-pass graft surgery and myocardial infarction patients are primary objectives of therapy.

Results and Discussion

The synthesis and structure–activity relationship of a large number of benzoylguanidine-type Na^+/H^+ antiporter inhibitors was described earlier.[3] Compound **7** was prepared starting with 4-chlorobenzoic acid. The 2-methyl group was introduced into the molecule using the *ortho*-metalation technique followed by insertion of the 5-methanesulfonyl group by a sulfochlorination, reduction, and methylation sequence. The 4-pyrrole group was built up by nucleophilic halogen displacement with benzylamine, catalytic hydrogenation, and ring formation with 2,5-dimethoxytetrahydrofuran. The benzoylguanidine side chain was prepared by treating the ester with guanidine. The free base was finally converted into the methanesulfonate salt **7**. The overall yield of the 10-step synthesis amounts approximately to 21%. Due to the high number of stages this method is not a basis for technical synthesis.

In a more straightforward conception of the synthesis, inefficient procedures such as the multistage insertion of the sulfone had to be simplified. M. Ono et al. have described a one-step Friedel–Crafts-type methanesulfonylation of deactivated benzenes.[4] In a favored procedure, methanesulfonic acid anhydride, prepared in situ from methanesulfonic acid and $SOCl_2$, was reacted with aromatic compounds in the presence of a catalytic amount of trifluoromethanesulfonic acid. Though deactivation by halogen and nitro groups is tolerated, we found 4-chloro-2-methylbenzoic acid to be totally resistant to methanesulfonylation. This led us to alter the previous strategy and to generate the methanesulfonyl group before the carboxyl group. Thus, commercially available 2-bromo-5-fluorotoluene (**1**) could be converted into 1-bromo-4-fluoro-5-methanesulfonyl-2-methylbenzene (**2**) in reasonable yield using Ono's method (Scheme 1).



Scheme 1. (a) $MeSO_3H$, $SOCl_2$, CF_3SO_3H, 125 °C; (b) CO, DMSO, H_2O, KOAc, $Pd(OAc)_2$, dppf, 25 atm., 82 °C; (c) pyrrole, NaH, DMSO; (d) 2-chloro-1-methylpyridinium iodide, NMP, *N*-Cbz-guanidine, $(iPr)_2NEt$; (e) H_2, Pd/C, Me_2CO

The conversion of the bromide into a carboxylic acid was the next step. The plan to do this by halogen–metal exchange and carbon dioxide trapping of the lithium salt failed because the primary attack occurred at the methanesulfonyl group. Palladium-catalyzed carboxylation with carbon monoxide,[5] however, gave 4-fluoro-2-methyl-5-methanesulfonylbenzoic acid (**3**)[3] in high yield. The pre-

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catalyst chosen was the 1,1′-bis(diphenylphosphanyl)-ferrocene complex with palladium(II) acetate. The reaction was performed in a steel vessel and addition of water was necessary to release the acid from the putative intermediate acyl bromide.

Aromatic halides can be displaced with an alkali metal salt of pyrrole.[6] With compound **3** the nucleophilic reaction is favored by the two electron-withdrawing groups in the *ortho* and *para* positions, as well as by the choice of the leaving group. Actually the F−pyrrole exchange **3** → **4** in DMSO took place in high yield at room temperature while the corresponding 4-chloro-2-methyl-5-methanesulfonylbenzoic acid required prolonged heating at 65 °C.

Esters, acid chlorides, and imidazolides were the activated acid derivatives of choice in the preparation of benzoylguanidines.[3] The yield of the reaction **4** → **6** was not fully satisfactory and was obviously diminished by oxidative and hydrolytic secondary processes. When Mukaiyama's procedure[7] with its outstanding mild conditions was used a partial double acylation of guanidine could not be prevented. Cbz-protected guanidine,[8] however, gave pure and stable **5** in high yield. Simple process handling as well as the development of a continuous flow technique enabled scale-up.

The Cbz group was split off by catalytic hydrogenation in acetone. The reaction conditions used prevented any oxidative and hydrolytic attacks on the sensitive base **6**. After removal of the catalyst, the methanesulfonate **7** was precipitated from the hydrogenation solution without isolating the base. The purity of the material thus produced was >99.5%. The use of protected guanidine increased the number of stages by one, but this disadvantage was made up for by a simpler and safer procedure, protection of the base **6**, and last but not least by a higher overall yield for the conversion of the acid **4** into the benzoylguanidine salt **7**.

In summary, this new concise synthesis is feasible for large-scale preparation of eniporide **(7)**. The number of stages was reduced from ten to five, while the overall yield could roughly be doubled. The early methanesulfonylation in one step as well as the direct halogen−pyrrole exchange are of particular importance. In contrast to the old process, no low-temperature technique was required here.

Experimental Section

Melting points were determined with a Büchi 535 melting point apparatus and are uncorrected. − IR, NMR, and MS spectra are consistent with the structures cited and were recorded on a Bruker IFS 48 IR spectrophotometer, a Bruker AM 250 NMR spectrometer, and a Vacuum Generators VG 70 E or 70−250 SE mass spectrometer, respectively. All NMR spectra were recorded in [D_6]DMSO, and chemical shifts given in parts per million (δ) downfield from tetramethylsilane. − Microanalyses were obtained with an elementar vario EL analyzer.

1-Bromo-4-fluoro-2-methyl-5-(methylsulfonyl)benzene (2): A mixture of methanesulfonic acid (162 mL, 2.50 mol) and $SOCl_2$ (72.6 mL, 1.00 mol) was heated under reflux for 1 h. To the reaction mixture, cooled to 25 °C, were added 2-bromo-5-fluorotoluene (**1**; 100 g, 529 mmol) and trifluoromethanesulfonic acid (8.80 mL, 100 mmol). The mixture was heated at 125 °C for 3 h, cooled, poured into ice water (600 mL), and extracted with EtOAc (2 × 400 mL). The organic phase was washed with 1 N NaOH (3 × 300 mL), dried, and evaporated. Recrystallization of the residue from Et_2O gave pure **2** (92.2 g, 65%) as white crystals, m.p. 113−114 °C. − IR (KBr): $\tilde{\nu}$ = 1313, 1145, 1085, 517, 508 cm^{-1}. − ^1H NMR: δ = 2.45 (s, 3 H, Me), 3.33 (s, 3 H, SO_2Me), 7.62 (d, *J* = 10.2 Hz, 1 H, Ar 3-H), 7.92 (d, *J* = 6.7 Hz, 1 H, Ar 6-H). − EI-MS (70 eV): *m*/*z* (%) = 266/268 (96/95) [M^+], 251/253 (43/45) [$M^+ - CH_3$], 203/205 (54/52) [$M^+ - SOCH_3$], 187/189 (50/48) [$M^+ - SO_2CH_3$], 108 (100) [$M^+ - SO_2CH_3 - Br$], 107 (78) [$M^+ - SO_2CH_3 - HBr$]. − $C_8H_8BrFO_2S$ (267.1): calcd. C 35.97, H 3.02, Br 29.91, S 12.00; found C 36.00, H 2.90, Br 29.80, S 12.00.

4-Fluoro-2-methyl-5-(methylsulfonyl)benzoic Acid (3): A 750-mL steel autoclave equipped with a magnetic stirrer, Teflon insert, temperature sensor, CO inlet, and a manometer was charged with DMSO (200 mL), H_2O (40 mL), KOAc (34.0 g, 346 mmol), 1-bromo-4-fluoro-5-methanesulfonyl-2-methylbenzene (**2**, 44.8 g, 168 mmol), $Pd(OAc)_2$ (1.20 g, 5.35 mmol), and dppf (5.60 g, 10.1 mmol). The vessel was closed and CO (25 atm.) was introduced. The stirred mixture was autoclaved at 82 °C for 89 h, while the pressure rose to 30 atm. during the reaction. With occasional ice cooling the solution was then mixed with EtOAc (1 L), extracted with 2 N NaOH (2 × 320 mL), and the combined aqueous phases were acidified with concentrated HCl. The white crystals separated on cooling were collected, washed with water (200 mL), and air-dried to give the title compound **3** (36.0 g, 92%), m.p. 212−214 °C. The m.p. given in ref.[3] is incorrect.

2-Methyl-5-methylsulfonyl-4-(pyrrol-1-yl)benzoic Acid (4): Pyrrole−Na was prepared by adding NaH (60% in mineral oil, 808 mg, 20.2 mmol) to a solution of pyrrole (1.40 mL, 20.2 mmol) in DMSO (20 mL). In parallel, the acid **3** (3.60 g, 15.5 mmol) was also treated with NaH (620 mg, 15.5 mmol) in DMSO (20 mL). After stirring for 1 h at room temperature, the second mixture was added dropwise to the first one, and stirring was continued for an additional 3 h under N_2 protection. The solution was poured into ice-cold diluted HCl (150 mL H_2O + 150 mL 1 N HCl) and the white crystals of the title compound which separated were collected and dried at 50 °C (3.34 g, 77%). An analytical sample was prepared by recrystallization from PhMe, m.p. 192 °C. − IR (KBr): $\tilde{\nu}$ = 1697 (CO_2H), 1304, 1263, 1153, 737 cm^{-1}. − ^1H NMR: δ = 2.65 (s, 3 H), 2.67 (s, 3 H), 6.33 (t, *J* = 2 Hz, 2 H, pyrrole 3-H), 7.08 (t, *J* = 2 Hz, 2 H, pyrrole 2-H), 7.52 (s, 1 H, Ar 3-H), 8.50 (s, 1 H, Ar 6-H), 13.45 (s br, 1 H, H/D exchangeable). − EI-MS (70 eV): *m*/*z* (%) = 279 (100) [M^+], 262 (7) [$M^+ - OH$], 214 (33) [$M^+ - C_4H_3N$], 154 (14) [$M^+ - SO_2CH_3 - HCO_2H$]. − $C_{13}H_{13}NO_4S$ (279.3): calcd. C 55.89, H 4.70, N 5.02, S 11.48; found C 56.01, H 4.84, N 5.00, S 11.51.

1-(Benzyloxycarbonyl)-3-[2-methyl-5-methylsulfonyl-4-(pyrrol-1-yl)-benzoyl]guanidine (5): Compound **4** (2.75 g, 9.85 mmol) was treated with 2-chloro-1-methylpyridinium iodide (2.81 g, 11.0 mmol) in *N*-methyl-2-pyrrolidone (28 mL) for 90 min at room temperature. The reddish-brown solution was cooled, *N*-Cbz-guanidine[8] (2.31 g, 12.0 mmol) and $(iPr)_2NEt$ (5.00 mL, 29.4 mmol) were consecutively added, and stirring continued for an additional 2 h at room temp. The mixture was poured into ice/water (100 mL) and the solid which separated was recrystallized from *i*PrOH (75 mL) to give **5** (3.9 g, 87%) as a light beige powder, m.p. 163 °C. − IR (KBr): $\tilde{\nu}$ = 1694 (C=O), 1268, 1116 cm^{-1}. − ^1H NMR: δ = 2.60 (s, 3 H), 2.66 (s, 3 H), 5.22 (s, 2 H, OCH_2), 6.30 (t, *J* = 2 Hz, 2 H, pyrrole 3-H), 7.07 (t, *J* = 2 Hz, 2 H, pyrrole 2-H), 7.33−7.45 (m, 5 H, Ar-H),

7.43 (s, 1 H, Ar 3-H), 8.47 (s, 1 H, Ar 6-H), 8.81 (s br, 1 H, NH, H/D exchangeable), 9.67 (s br, 1 H, NH, H/D exchangeable), 11.33 (s br, 1 H, NH, H/D exchangeable). − FAB-MS: *m/z* (%) = 455 (100) $[M + H]^+$, 411 (40) $[(M + H)^+ - CO_2]$, 262 (36) $[(M + H)^+ - Cbz-CH_4N_3]$. − $C_{22}H_{22}N_4O_5S$ (454.5): calcd. C 58.14, H 4.88, N 12.33, S 7.05; found C 58.11, H 4.99, N 12.33, S 7.10.

[2-Methyl-5-methylsulfonyl-4-(pyrrol-1-yl)benzoyl]guanidinium Methanesulfonate (7, Eniporide): The foregoing Cbz-protected compound **5** (16.5 g, 36.3 mmol) was hydrogenated with a Pd/C catalyst (5%, 4 g) in Me_2CO (400 mL) at atmospheric pressure for 9.5 h at room temperature. The catalyst was removed over a suitable fine filter. $MeSO_3H$ (4.00 mL, 61.6 mmol) was added to the resulting clear solution of the base **6** and white crystals of the methanesulfonate **7** (14.8 g, 95%) were allowed to separate with stirring in an ice bath for 1 h. They were then vacuum-dried at room temperature, m.p. 273 °C. − IR (KBr): $\tilde{\nu}$ = 3399 (NH), 1719 (C=O), 1695 (C=O), 1293, 1182 cm^{-1}. − ^1H NMR: δ = 2.09 (s, Me_2CO), 2.39 (s, 3 H, *Me*SO_3H), 2.55 (s, 3 H, Me), 2.71 (s, 3 H, SO_2Me), 6.34 (t, *J* = 2 Hz, 2 H, pyrrole 3-H), 7.11 (t, *J* = 2 Hz, 2 H, pyrrole 2-H), 7.60 (s, 1 H, Ar 3-H), 8.30 (s, 1 H, Ar 6-H), 8.43 (s br, 4 H, NH_2, H/D exchangeable), 11.73 (s, 1 H, $MeSO_3H$, H/D exchangeable). − EI-MS (70 eV): *m/z* (%) = 320 (100) $[M^+]$, 303 (26) $[M^+ - NH_3]$, 278 (30) $[M^+ - NH_2CN]$, 262 (40) $[M^+ - N=C(NH_2)_2]$, 261 (60) $[M^+ - HN=C(NH_2)_2]$, 154 (37) $[M^+ - MeSO_2 - HN=C(NH_2)_2 - CO]$, 96 (11) $[MeSO_3H^+]$, 86 (40) $[(NH_2)_2C=NCO^+]$. − $C_{14}H_{16}N_4O_3S·CH_4O_3S·0.25C_3H_6O$ (431.00): calcd. C 43.89, H 5.03, N 13.00, S 14.88; found C 43.98, H 4.99, N 12.78, S 15.16.

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