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LARGE SCALE PREPARATION OF PROTECTED 4-AMINOMETHYLBENZAMIDINE. APPLICATION TO THE SYNTHESIS OF THE THROMBIN INHIBITOR, MELAGATRAN

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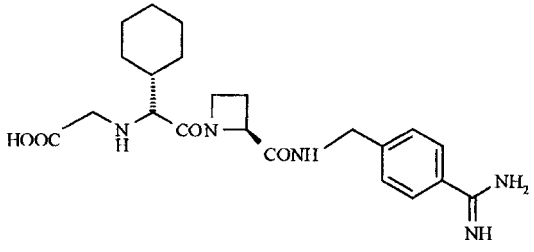
Abstract: To allow the preparation of melagatran on a multigram scale, we have investigated several approaches for the synthesis of the key intermediate 4-aminomethylbenzamidine. The only industrially suitable pathway relies on the preparation of an N-hydroxyimino intermediate.

In connection with our on-going research program on orally active thrombin inhibitors, we were faced with the preparation of melagatran **1**.[1] This potent and selective thrombin inhibitor (Ki thrombin = 0.002 mmol/l)[2] showed oral



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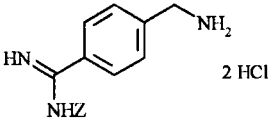
*To whom correspondence should be addressed

bioavailability in several models of thrombosis in rat and dog, and is currently under extensive clinical trials.

One of the key intermediates in the preparation of melagatran is the dihydrochloride of [(4-aminomethyl-phenyl)-iminomethyl]-carbamic acid benzyl ester **2**. A preparation of the corresponding free base is reported in the Astra patent[1] (Scheme 1).



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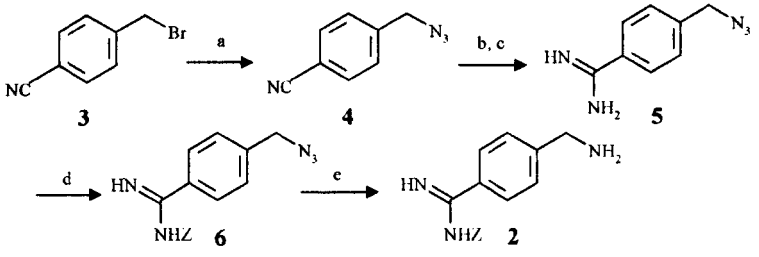
The first disadvantage of this synthetic pathway is the use of a potentially explosive reagent, the azido derivative **4**. Secondly, eliminationof the triphenylphosphine oxides formed in the last steps proved to be quite tedious, since only silicagel chromatography could afford relatively pure protected benzamidine **2** as the free base; finally, a significant instability of **2** was observed on silicagel.

Scheme 1

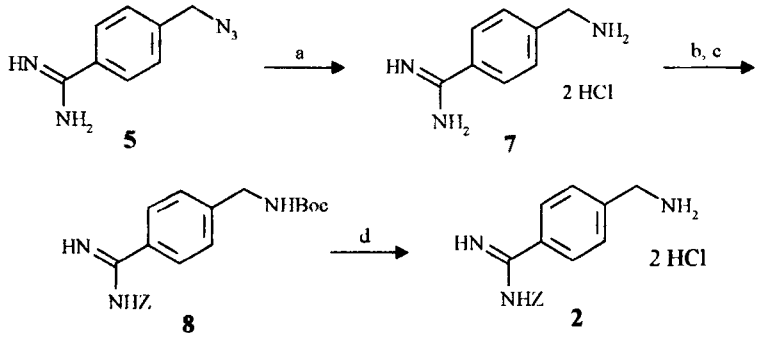


Reagents:(a) NaN_3, THF-water; (b) EtOH, HCl, toluene; (c) NH_3, EtOH, NaOH (57-65% for 3 steps); (d) benzyl chloroformate, Et_3N, CH_2Cl_2 (91%); (e) PPh_3, H_2O-THF.

Pure intermediate **2** could be effectively obtained by adding a few steps to the previous synthetic route (Scheme 2): intermediate **5** was directly

hydrogenated using palladium on carbon to give the totally deprotected benzamidine **7**, as the dihydrochloride salt (90%). Protection was effected, taking advantage of the difference of basicity between the primary benzylic amine and the benzamidine: treatment with one equivalent of triethylamine-$(Boc)_2O$ gave the Boc-protected benzylamine as the sole product, which was not isolated. Reaction with sodium hydroxyde-benzyl chloroformate yielded the protected benzamidine **8** with a 61% yield. Finally, treatment with gaseous HCl in anhydrous ethyl acetate quantitatively effected the removal of the Boc protecting group to give pure **2**. The total yield for this route was 35%, starting from 4-cyano benzyl bromide **3**.

Scheme 2



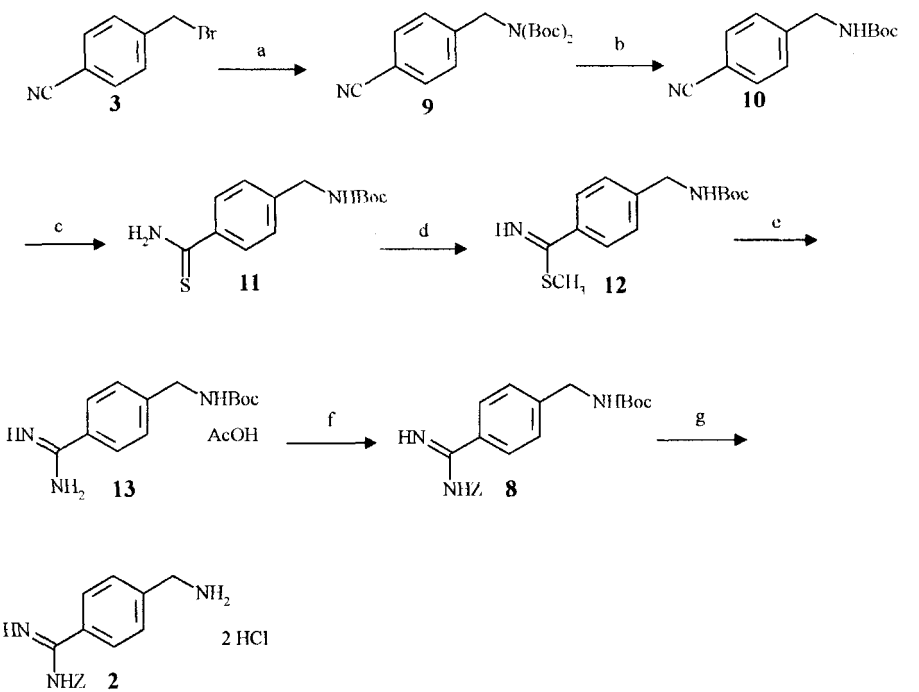
Reagents: (a) H_2, 10% Pd-C, methanol-chloroform (90%); (b) Et_3N, Boc_2O, H_2O, THF; (c) benzyl chloroformate, NaOH, H_2O-THF (61% for two steps); (d) gas HCl, anh. EtOAc (100%).

Obviously, this pathway did not suppress the use of the azido **4**. For this reason, we set up another strategy described in Scheme 3, which circumvented the use of this hazardous intermediate: diBoc-derivative **9** was obtained by condensation of bromide **3** with ditertbutylimino dicarboxylate in strong basic conditions. Mono-deprotection gave the Boc-protected amine **10**. Elaboration of the amidino moiety was sequentially effected, first by treating the

cyano group with H_2S in pyridine, followed by alkylation with methyliodide, and finally substitution using ammonium acetate. Protection of the resulting benzamidine **13** with benzylchloroformate was followed by deprotection of the benzylamine with hydrochloric acid in anhydrous ethyl acetate to give **2**.

The overall yield for this pathway was 46%. Unfortunately, even if this chemical route avoided the use of the azido derivative **4**, methylation of the thioamidine **11** liberated methyl mercaptan, a highly toxic gas, the generation of which was not recommended from an industrial point of view.

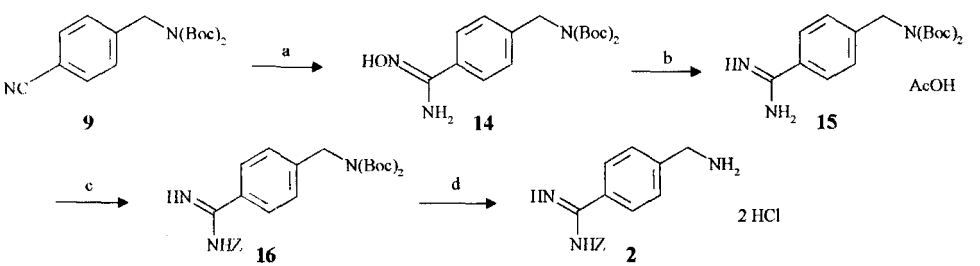
Scheme 3



Reagents: (a) NaH, $(BOC)_2NH$, THF (96%); (b) NaOH, methanol-THF; (c) H_2S, pyridine; (d) CH_3I, acetone (84% for two steps); (e) CH_3COONH_4, methanol (94%); (f) NaOH, benzyl chloroformate H_2O-THF (61%); (g) gas. HCl, anh. EtOAc (100%).

We then envisioned to modify the preparation of the amidino functionality, as illustrated in Scheme 4. This was done according to the recent paper by Judleins *et al.*:[3] diBoc-derivative **9**, already described in Scheme 3, was condensed with hydroxylamine in basic aqueous medium (reflux 3 hours) to give the N-hydroxy imino derivative. The crude reaction mixture was cooled to allow the N-hydroxyimino containing derivative **14** to precipitate. Hydrogenolysis gave the diBoc-protected benzamidine **15**, which was protected on the benzamidine moiety by reaction with benzylchloroformate in aqueous sodium hydroxyde. Finally, the desired benzamidine **2** was efficiently obtained by deprotection of the primary benzylic amine under acidic conditions. **2** has been conveniently prepared on a kilogram scale using this five steps synthesis (total yield 43%).

Scheme 4



Reagents: (a) $NH_2OH.HCl$, Na_2CO_3, H_2O, EtOH (80%) (b) H_2, 10% Pd-C, acetic acid/acetic anhydride (86%); (c) benzylchloroformate, 4N NaOH, THF (60%); (d) gas. HCl, anh. EtOAc (100%).

Using this latest pathway allowed the preparation of melagatran on a multigram scale, first by coupling **2** with Boc-azetidine-OH, followed by deprotection and coupling with Boc-cyclohexylglycine. Removal of the Boc group was followed by alkylation of the terminal amino group with benzylbromoacetate and general deprotection gave melagatran, with a purity higher than 98%; moreover, the IC_{50} value for thrombin inhibition was found to be 2.9 nM, a result comparable to the Ki value of 2 nmol/l given in the literature.

Experimental

4-Aminomethyl-benzamidine 7:

10.5 g (0.06 mol) of the azide **5** obtained according Scheme 1 were hydrogenated in 200mL of methanol and 40 mL of chloroform on 10% Pd/C at ambient temperature and pressure. After 24 hours, the catalyst was filtered and the solvents were evaporated to give 12 g (90%) of the benzamidine derivative as the dihydrochloride. mp > 260° C. IR (nujol, cm^{-1}) 3400-2100, 1683. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 4.15 (s, 2H), 7.75 (d, 2H), 7.90 (d, 2H), 8.50-10.00 (broad s, 5H). Found: C, 43.35; H, 6.03; N, 17.84; Cl^-, 30.47. $C_8H_{11}N_3$, 2HCl (222.12) requires C, 43.26; H, 5.90; N, 18.92; Cl^-, 31.92.

[(4-*Tert*-butoxycarbonylaminomethyl-phenyl)-iminomethyl]-benzyl carbamate 8:

11.1 g (0.05 mol) of compound **7** were dissolved in 220 mL of a 1:1 mixture of THF-water. Triethylamine (6.24 mL, 0.045 mol) was added, followed by Boc_2O (10.9 g, 0.05 mol). The reaction mixture was stirred overnight, then evaporated to give a crude residue (14.2 g) which was used without any further purification in the next reaction. This residue was dissolved in THF (110 mL), and 125 mL (0.5 mol) of 4N NaOH were added. At 0-5°C, be vigorously stirred at room temperature overnight. The THF was then evaporated and the aqueous residue extracted with ethyl acetate. The organic layer was washed with brine and dried over calcium sulfate. Evaporation of the solvent gave 31.8 g of a crude solid. This solid was taken up with 50 mL of diethyl ether and the resulting solid was rinced three times with 10 mL of diethyl ether to give 11.7 g (61%) of a white solid.mp 130° C. IR (nujol, cm^{-1}) 3300-2500, 1709, 1610. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.35 (s, 9H), 4.20 (d, 2H), 5.15 (s, 8H), 7.40 (m, 7H), 7.45 (t, 1H), 7.95 (d, 2H), 9.20 (broad s, 2H). Found: C, 65.48; H, 6.58; N, 10.17. $C_{21}H_{25}N_3O_4$ (383.45) requires C, 65.78; H, 6.57; N, 10.96.

[(4-Aminomethyl-phenyl)-iminomethyl]-benzyl carbamate 2:

Gaseous HCl was bubbled at 0°C for one hour through a solution of benzamidine **16** (56 g, 0.12 mol) in a mixture of anhydrous methanol-ethyl acetate 900:750 mL.

After stirring overnight at room temperature, solvents were evaporated. The residue was taken up several times with anhydrous ethyl acetate to eliminate the residual hydrochloric acid. Trituration with diethyl ether, followed by filtration and washings afforded 44.3 g (100%) of a white solid, as the hydrochloride. Decomposition at temperature > 260°C. IR (nujol, cm^{-1}) 1761, 1741, 1617. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 4.15 (d, 2H), 5.30 (s, 2H), 7.40 (m, 5H), 7.75 (d, 2H), 7.90 (d, 2H), 8.80, 10.40, 11.00-11.50 (3 broad s, 3H). Found: C, 53.80; H, 5.48; N, 11.33. Cl^-, 19.02. $C_{16}H_{17}N_3O_2$, 2HCl (356.25) requires C, 53.94; H, 5.38; N, 11.80, Cl^-, 19.90.

4-Di-*tert*-butoxycarbonylaminomethyl-benzonitrile 9:

To 210 mL of anhydrous THF was added 8.7 g (0.345 mol) of NaH, then 61.5 g (0.314 mol) of 4-bromomethyl benzonitrile in 240 mL of anhydrous THF were rapidly added under nitrogen at room temperature. A solution of ditertbutylimino-dicarboxylate (75 g, 0.345 mol) in 150 mL of anhydrous THF was then added dropwise at room temperature (the reaction is slightly exothermic). Stirring was continued for 18 hours, and the solvent was evaporated. The crude residue was taken up with water and diethyl ether. The organic layer was washed with water, brine, dried over sodium sulfate and evaporated. The resulting solid was triturated with hexane to yield 100.2 g (96%) of a pale brown solid, mp 119-121°C. IR (nujol, cm^{-1}) 2228, 1761, 1730, 1691. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.47 (s, 9H), 4.83 (s, 2H), 7.39 (d, 2H), 7.62 (d, 2H). Found: C, 64.90; H, 7.40; N, 8.37. $C_{18}H_{24}N_2O_4$ (332.40) requires C, 65.04; H, 7.28; N, 8.43.

4-*Tert*-butoxycarbonylaminomethyl-benzonitrile 10:

36.4 g (0.105 mol) of compound **9** were dissolved in 185 mL of THF, and a solution of sodium hydroxyde (4.2 g, 0.105 mol) in 370 mL of methanol was added dropwise. The reaction was stirred overnight. Partial evaporation of the methanol was followed by addition of water to give white crystals, which were filtered and washed with water.

22.5 g (93%). mp 111-113° C. IR (nujol, cm^{-1}) 3353, 2227, 1677. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.35 (s, 9H), 4.20 (d, 2H), 7.40 (d, 2H), 7.80 (d, 2H). Found m/z 232.1206. $C_{13}H_{16}N_2O_2$ requires m/z 232.1206.

(4-Thiocarbamoyl-benzyl)-carbamic acid *tert*-butyl ester 11:

22.5 g (0.097 mol) of the nitrile **10** were dissolved in 575 mL of pyridine. 57.7 mL (0.42 mol) of triethylamine were added and H_2S was bubbled for 1 hour. Stirring was continued overnight. The reaction was then diluted with 2.3 L of water and extracted with ethyl acetate. The organic layer was washed with water, brine, and dried over calcium sulfate. Evaporation of the solvent gave 31.6 g of the desired compound as a brown oily residue containing 20% of pyridine. IR (nujol, cm^{-1}) 3360, 3313-3160, 1677. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.40 (s, 9H), 4.15 (d, 2H), 7.25 (d, 2H), 7.5 (broad s, 1H), 7.85 (d, 2H), 9.4-9.8 (2 broad s, 2H).

[4-(Amino-methylsulfanyl-methyl)benzyl]-carbamic acid *tert*-butyl ester 12:

Crude **11** was dissolved in 1150mL of acetone, 250 mL of CH3I were added, and the reaction was refluxed for two hours. After cooling, the excess reactant and the solvent were evaporated. The residue was taken up with water and diethyl ether, the aqueous phase was treated with sodium bicarbonate, and extracted with diethyl ether. The organic layer was washed with water, brine, and dried over calcium sulfate. Filtration and evaporation gave 22.9 g (84%) of the desired compound. mp 114-115°C. IR (nujol, cm^{-1}) 3311, 1682, 1587. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.40 (s, 9H), 2.40 (s, 3H), 4.15 (d, 2H), 7.30 (d, 2H), 7.40 (t, 1H), 7.65-7.80 (2d, 2H), 10.1-10.4 (2s, 2H). Found m/z 280.1241. $C_{14}H_{20}N_2O_2S$ requires m/z 280.1240.

4-*Tert*-butoxycarbonylaminomethyl-benzamidine 13:

22.9 g (0.082 mol) of compound **12** were dissolved in 390 mL of anhydrous methanol. 13.9 g (0.18 mol) of ammonium acetate were added and the reaction mixture was refluxed for 6 hours. After cooling, the solution was flushed with nitrogen in order

to eliminate the methanethiol which is formed during the reaction ; sodium hydroxyde and sodium hypochlorite containing flasks were placed at the outlet of the nitrogen circulation. The excess of ammonium acetate was eliminated by sublimation during the evaporation of the methanol to give 23.8 g (94%) of the desired compound as a white solid. mp 222°C. IR (nujol, cm^{-1}) 3450-2400, 1686. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.35 (s, 9H), 4.20 (d, 2H), 7.40 (d, 2H), 7.50 (broad s, 1H), 7.75 (d, 2H). Found m/z 249.1464. $C_{13}H_{19}N_3O_2$ requires m/z 249.1472.

4-Di-*tert*-butoxycarbonylaminomethyl-N-hydroxy-benzamidine 14:

To a suspension of nitrile **9** (94.8 g, 0.285 mol) in water-ethanol 700:1800 mL, were added hydroxylamine hydrochloride (71.34 g, 1.03 mol) and sodium carbonate (66.5 g, 0.63 mol). The reaction mixture was refluxed for three hours. Ethanol was evaporated, and the aqueous residue was taken up twice with methylene chloride. The organic layer was washed with water, brine, dried over sodium sulfate and evaporated to give 89.8 g (75%) of a pale yellow amorphous solid. IR (nujol, cm^{-1}) 3458, 3363, 3217, 1780-1731, 1690-1650, 931. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.4 (s, 18H), 3.31-5.77 (2s, 2H), 4.69 (s, 2H), 7.20 (d, 2H), 7.65 (d, 2H), 9.56 (d, 1H). Found: C, 59.06; H, 7.32; N, 13.53. $C_{18}H_{27}N_3O_5$ (365.43) requires C, 59.16; H, 7.45; N, 11.50. MS (DCP + NH_3) m/z 366 ($M + H^+$). $C_{18}H_{27}N_3O_5$ requires m/z 365.

Depending on the reaction conditions, the corresponding monoboc-derivative can be formed; rather than performing a tedious separation of the two analogs at this stage, it is more advantageous to continue the synthesis with the mixture diboc + monoboc, which will finally give compound **2** after hydrochloric acid deprotection.

4-Di-*tert*-butoxycarbonylaminomethyl-benzamidine acetate 15:

Acetic anhydride (35 mL, 0.368 mol) was added to a solution of benzamidoxime **14** (89.7 g, 0.245 mol) in 1 L of glacial acetic acid. After stirring 10 minutes at room temperature, the catalyst (10% Pd/C) was added and hydrogenation was

performed at room temperature and pressure for 18 hours. After filtration and evaporation of the acetic acid, the residue was taken up three times with n-heptane to eliminate the residual acetic acid, then triturated in diethyl ether to give a white amorphous solid (86.4 g, 86%). IR (nujol, cm^{-1}) 1755-1707, 1608. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.42 (s, 18H), 1.70 (s, 3H), 3.32 (broad s, 1H), 4.77 (s, 2H), 7.38 (d, 2H), 7.77 (d, 2H), 10.0-10.5 (broad s, 2H).MS (DCI + NH3) m/z 350 ($M + H^+$). $C_{18}H_{27}N_3O_4$ requires m/z 349.

[(4-Di-*tert*-butoxycarbonylaminomethyl-phenyl)-iminomethyl]-benzyl carbamate 16:

To a suspension of benzamidine acetate **15** (85.8 g, 0.21 mol) in 470 mL of THF was added 524 mL (2.09 mol) of 4N NaOH. At 5°C, benzyl chloroformate (75 mL, 0.52 mol) was added dropwise, and stirring was continued overnight at room temperature. After decantation, the organic layer was evaporated, and the residue was taken up with ethyl acetate. The resulting amorphous solid was filtered, washed with ethyl acetate, and dried to give 60.9 g (60%). IR (nujol, cm^{-1}) 1778, 1663-1631. ^1H NMR (300 MHz, d_6-DMSO) δ (ppm) 1.42 (s,18H), 4.76 (s, 2H), 5.12 (s, 2H), 7.32 (d, 2H), 7.40 (m, 5H), 7.96 (d, 2H), 9.12 (broad s, 1H). Found: C, 64.47; H, 6.94;N, 8.68. $C_{26}H_{33}N_3O_6$ (483.57) requires C, 64.58; H, 6.88; N, 8.69.

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