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A CONVENIENT METHOD FOR THE CONSTRUCTION OF THE IMIDAZOLONE RING IN THE SYNTHESIS OF BENZAMIDINE DERIVATIVES

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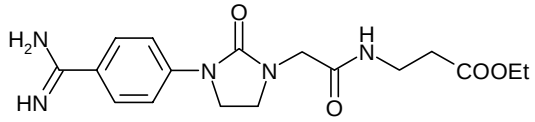
Abstract. The benzamidine derivatives containing an imidazolone ring and structural fragments of β-amino acid are known as platelet aggregation inhibitors. A new synthetic route was developed to one of them – ethyl 3-{[[(1-(4-(aminoiminomethyl)phenyl)-4,5-dihydro-2(3H)-oxo-1H-imidazol-3-yl)methyl]carbonyl]amino}propanoate. The structure of the target compound and intermediates was confirmed by ^{1}H and ^{13}C NMR analysis.

Key words: benzamidine derivatives, imidazolone ring, platelet aggregation inhibitor.

Several synthetic peptides are known to inhibit blood platelet aggregation, for example those described in [1–7]. The most promising group of these peptide analogues is amidino or guanidinoaryl substituted alkanoic acid derivatives, for example ethyl 3-{[[(1-(4-(aminoiminomethyl)phenyl)-4,5-dihydro-2(3H)-oxo-1H-imidazol-3-yl)methyl]carbonyl]amino}propanoate **1** [7].



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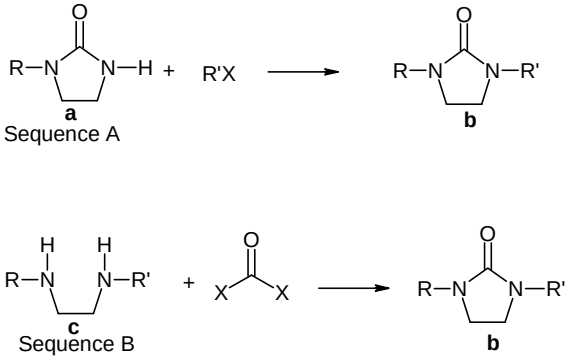
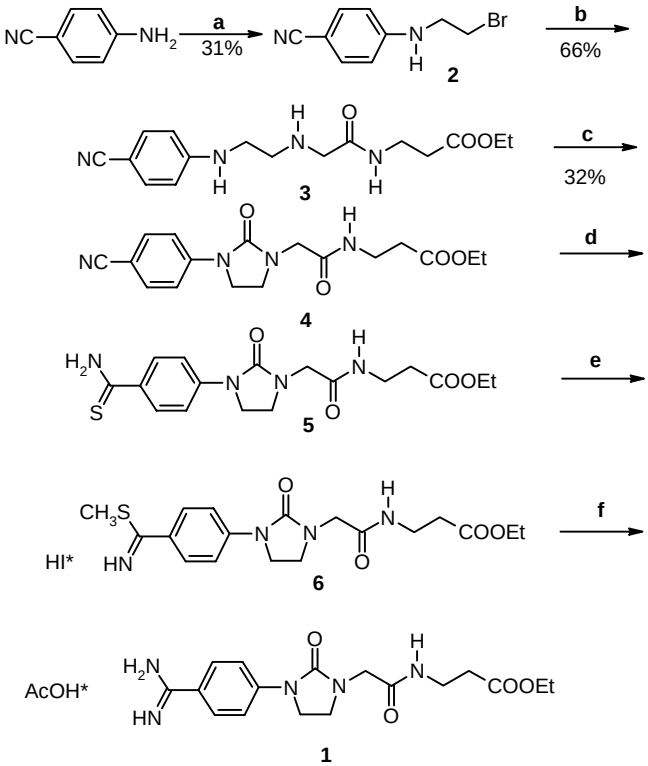
The existing synthetic route [7] is based on the following sequence: construction of a monosubstituted imidazolone ring as a key compound (compound **a** Scheme 1, Sequence A) followed by its N-alkylation with an appropriate alkylation agent resulting in the target compound **b**. Now we propose an alternative route for the preparation of **b** where the key intermediate is

diamine **c** (Scheme 1, Sequence B), and the construction of imidazolone ring is accomplished by cyclization/carbonylation step.

According to this main strategy a new scheme (Scheme 2) for the synthesis of **1** was developed.

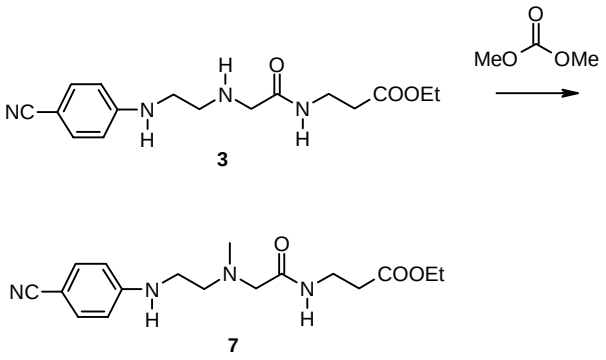


Scheme 1. Strategies for constructing target compounds.



Scheme 2. Synthesis of benzamidine derivative **1**. **a**: dibromoethane, 120 °C, 60 h; **b**: glycinyl-β-alanine ethyl ester, EtOH, K_2CO_3, 70–80 °C, 4.5 h; **c**: phosgene/toluene, CH_2Cl_2, −25 °C, 1 h; **d**: H_2S, Py/Et_3N, rt 15 h; **e**: methyl iodide, acetone, 55 °C, 2.5 h; **f**: NH_4OAc, MeOH, 60 °C, 6 h, yield **d**–**f** 67%.

The new synthesis route to **1** includes monoalkylation of 4-aminobenzonitrile with dibromoethane resulting in bromoalkylamine **2**, which may be used directly in the next step without purification. Bromide **2** reacts smoothly with glycinyl-β-alanine ethyl ester to yield the key intermediate, secondary amine **3**, which was purified by column chromatography on silica gel. For the cyclization (carbonylation) of secondary amine **3** we tried to use dimethyl carbonate, which is a non-hazardous phosgene alternative [8, pp. 411–418]. We found, however, that dimethyl carbonate in the reaction with **3** (Scheme 3) results mainly in N-methylated product **7**. The expected imidazolone compound was found only in trace amount.



Scheme 3. Reaction of diamine **3** with dimethyl carbonate.

Cyclization of **3** with phosgene results in imidazolone compound **4** in satisfactory yield (32% after purification on silica gel). Compound **4** was subjected to a standard procedure of transforming the cyano group into amidine via thioimidate salt [7], that is nitrile **4** was reacted with hydrogen sulphide affording thioamide **5**, which was converted to thioimidate salt **6** with methyl iodide. Thioimidate salt **6** was ammonolysed (with ammonium acetate) resulting in benzamidine derivative **1** in good yield (67% on three last steps).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-500 spectrometer. 2D FT methods were used for the full assignment of ^{1}H and ^{13}C chemical shifts.

HPLC analyses were carried out on a Shimadzu set (SCL-10A VP, SPD-10A VP, LC-10AT VP, FCV-10AL VP); column Waters Symmetry C-18, 5 μm, 4.6 × 250 mm; mobile phase: A – acetonitrile, B – H_3PO_4 water solution 0.5 mL/L, pH 6.67 (triethylamine), linear gradient 50–100% A in 10 min, 100% A in 10–20 min; sample 0.8 mg/mL (90% acetonitrile), 20 μL; detection at 254 nm.

Column chromatography was performed using silica gel 60–100 μm (Merck).

All solvents were treated prior to use by standard methods [9, pp. 437–445]. 4-Aminobenzonitrile was purchased from Aldrich, glycine and β-alanine ethyl ester from Reanal and used without further purification. Phosgene (in stainless steel cylinder) was purchased from AGA and used as toluene solution.

Glycinyl-β-alanine ethyl ester was prepared according to [10, pp. 14, 143, 153].

2-Bromoethyl(4-cyanophenyl)amine (2)

6.0 g of 4-aminobenzonitrile (50 mmol) in 50 mL of dibromoethane was heated at 120 °C for 60 h. The reaction mixture was diluted with dichloromethane (100 mL) and the precipitate was filtered off (5.4 g of 4-aminobenzonitrile hydrobromide, 27 mmol, 53% from starting material). The filtrate was evaporated, dissolved in 50 mL toluene, filtered through celite, and evaporated. The crude product was purified by column chromatography on silica gel using petrol ether : ethyl acetate : triethyl amine (10 : 1 : 0.1) as the eluent. Yield 3.5 g of **2** (31%), purity 94 % (HPLC).

^{1}H NMR ($CDCl_3$): δ 3.56 (t, J = 5.5 Hz, CH_2Br), 3.62 (q, J = 5.6 Hz, CH_2N), 4.64 (t, J = 5.6 Hz, NH), 6.62 (d, J = 8.7 Hz, *ortho* to NH), 7.45 (d, J = 8.7 Hz, *ortho* to CN).

^{13}C NMR ($CDCl_3$): δ 30.91 (CH_2Br), 44.40 (CH_2N), 99.68 (**C**CN), 112.46 (*ortho* to NH), 120.10 (CN), 133.80 (*ortho* to CN), 150.23 (CNH).

Ethyl 3-{[[[(2-((4-cyanophenyl)amino)ethyl)amino]methyl]carbonyl]amino}-propanoate (3)

The mixture of 5.5 g of N-glycinyl-β-alanine ethyl ester (32 mmol), 3.4 g of **2** (15.1 mmol), 7.5 g of K_2CO_3, and 15 mL of ethanol was stirred at 70–80 °C for 4.5 h, filtered through celite, and evaporated. Column chromatography on silica gel (ethyl acetate : ethanol gradient from 25 : 1 to 5 : 1) yielded 3.17 g of **3** (66%), purity 95% (HPLC).

^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.1 Hz, CH_3), 2.51 (t, J = 6.1 Hz, CH_2COO), 2.92 (t, J = 5.5 Hz, $CH_2C\mathbf{H}_2NHCH_2$), 3.28 (q, J = 5 Hz, $PhNHC\mathbf{H}_2$), 3.36 (s, NCH_2CO), 3.49 (q, J = 6 Hz, $CONHC\mathbf{H}_2$), 3.8 (bs, $CH_2N\mathbf{H}CH_2$), 4.13 (q, J = 7.1 Hz, OCH_2), 5.18 (t, J = 5 Hz, PhNH), 6.63 (d, J = 8.7 Hz, *ortho* to NH), 7.38 (d, J = 8.7 Hz, *ortho* to CN), 7.72 (t, J = 6 Hz, CONH).

^{13}C NMR ($CDCl_3$): δ 14.05 (CH_3), 33.74 (CH_2COO), 34.41 ($CONH\mathbf{C}H_2$), 42.20 ($PhNHCH_2$), 48.26 ($PhNHCH_2\mathbf{C}H_2$), 51.73 ($NH\mathbf{C}H_2CO$), 60.84 (OCH_2), 98.39 (**C**CN), 112.17 (*ortho* to NH), 120.43 (CN), 133.56 (*ortho* to CN), 151.33 (CNH), 170.44 (CONH), 172.73 (COO).

Ethyl 3-{[[(1-(4-cyanophenyl)-4,5-dihydro-2(3H)-oxo-1H-imidazol-3-yl)methyl]-carbonyl]amino}propanoate (4)

The solution of 3.1 g **3** (9.7 mmol), 3.0 mL triethylamine, and 25 mL CH_2Cl_2 was cooled to –25 °C. Phosgene solution (3.0 mL, 35%) in toluene was added at

once and the mixture was stirred for 1 h at 0 °C. The traces of phosgene were destroyed by adding 20 mL of ethanol. The mixture was evaporated to dryness and the residue treated with 50 mL of ethyl acetate. The insoluble amine salt was separated by filtration and the filtrate concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate : ethanol from 25 : 1 to 5 : 1). Yield 1.07 g (32%) of **4**, purity 99% (HPLC).

^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7.1 Hz, CH_3), 2.52 (t, J = 6.1 Hz, CH_2COO), 3.52 (q, J = 6.1 Hz, $NHCH_2$), 3.62 (t, J = 7.9 Hz, CH_2N), 3.87 (t, J = 7.9 Hz, CH_2N), 3.92 (s, NCH_2CO), 4.10 (q, J = 7.1 Hz, OCH_2), 6.79 (t, J = 6 Hz, NH), 7.56 (d, J = 8.7 Hz, *ortho* to CN), 7.63 (d, J = 8.7 Hz, *ortho* to NCO).

^{13}C NMR ($CDCl_3$): δ 14.04 (CH_3), 33.76 (CH_2COO), 34.81 ($NHCH_2$), 42.08 and 42.51 (CH_2N), 47.84 (NCH_2CO), 60.70 (CH_2O), 104.95 (CCN), 116.86 (*ortho* to NCO), 119.07 (CN), 132.91 (*ortho* to CN), 143.79 ($C_{arom.}N$), 157.12 (NCON), 167.95 (NHCO), 172.31 (COO).

Ethyl 3-{[[(1-(4-(aminoiminomethyl)phenyl)-4,5-dihydro-2(3H)-oxo-1H-imidazol-3-yl)methyl]carbonyl]amino}propanoate (1)

The cyano compound **4** was converted to amidine according to a standard procedure [7]. Yield 66%, purity 95% (HPLC). The product was recrystallized from ethanol to afford 98% purity.

^{1}H NMR (CD_3OD + δ DMSO – d6): δ 1.23 (t, J = 7.1 Hz, CH_3), 1.87 (s, CH_3CO), 2.53 (t, J = 6.7 Hz, CH_2COO), 3.46 (t, J = 6.7 Hz, $NHCH_2$), 3.61 and 3.96 (m, NCH_2CH_2N), 3.93 (s, NCH_2CO), 4.11 (q, J = 7.1 Hz, OCH_2), 7.79 and 7.83 (m, aromatic H).

^{13}C NMR (CD_3OD + δ DMSO – d6): δ 14.41 (CH_3), 24.20 (**C**H_3CO), 34.75 (CH_2COO), 36.21 ($NHCH_2$), 43.40 (N**C**H_2**C**H_2N), 47.61 (NCH_2CO), 61.51 (OCH_2), 117.96 (*ortho* to NCO), 121.85 (**C**CNH), 129.77 (*ortho* to CNH), 146.95 (**C**NCO), 158.96 (NCON), 167.31 (CONH), 170.57 (CNH), 173.07 (COO), 180.02 (CH_3**C**O).

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MUGAV MEETOD IMIDASOLOONI TSÜKLI SAAMISEKS BENSAMIDIINI DERIVAATIDE SÜNTEESIL

Veiko ALLIKMAA, Margus EEK, Tõnis PEHK ja Margus LOPP

Mitmed imidasolooni tsüklit ja β-aminohappe struktuurielemente sisaldavad bensamidiini derivaadid on vereliistakute agregatsiooni inhibiitorid. Artiklis on kirjeldatud ühe sellise ühendi – etüül 3-{[[(1-(4-(aminoiminometüül)fenüül)-4,5-dihüdro-2(3H)-okso-1H-imidasool-3-üül)metüül]karbonüül]amino}propanaadi alternatiivset sünteesi. Lõpp-produkti ja vaheühendite struktuur on identifitseeritud ^{1}H ja ^{13}C TMR-analüüsi abil.