Synthesis of ({8-[4,6-Bis-(bis-pyridin-2-ylmethyl-amino)-[1,3,5]triazine-2-ylamino]-octyl}—ethoxycarbonylmethyl-amino)-acetic acid ethyl ester

Daniel Vomasta and Burkhard König *

Institute of Organic Chemistry, University of Regensburg, D-93040 Regensburg, Germany
* Author to whom correspondence should be addressed. E-mail: Burkhard.koenig@chemie.uni-regensburg.de

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Combination of recognition units in synthetic receptors typically increases binding constants, if cooperativity occurs. Dipicolylamine (Dpa) bis-zinc complexes are known to bind phosphate-dianions under physiological conditions with good affinities, whereas metal(II)-iminodiacetate (M(II)-IDA) complexes (metal(II) = copper(II), nickel(II) or zinc(II)) show affinity to N-terminal histidine. Combining both units may lead to a selective binding of phosphorylated amino acid bearing N-terminal histidine. We report here a general synthetic route to ligands bearing a Dpa and an Ida site for metal ion complexation. The use of 6-chloro-N,N,N',N'-tetrakis-pyridin-2-ylmethyl-[1,3,5]triazine-2,4-diamine (1) in nucleophilic aromatic substitution provides a practical and versatile access to a variety of such two-prong Dpa receptors, which is exemplarily shown on the preparation of compound 3.

\[
\begin{align*}
&\text{1} & \text{2} & \xrightarrow{K_2CO_3} \text{3} \\
\text{6-Chloro-N,N,N',N'-tetrakis-pyridin-2-ylmethyl-[1,3,5]triazine-2,4-diamine (0.29 g, 1 mmol) was dissolved in dioxane (10 mL) and 0.5 g (1 mmol) of [(8-amino-octyl)-ethoxycarbonylmethyl-amino]-acetic acid ethyl ester (2) was added together with 0.27 g (2 mmol) of } K_2CO_3. \text{ The mixture was refluxed for 2 d, filtered and evaporated. The crude product was purified by column chromatography (silica gel, ethyl acetate / ethanol 2:1, } R_f = 0.27 \text{) to yield 0.2 g (27 %) of 3 as a pale yellow oil.}
\end{align*}
\]
\[\text{ES-MS (acetonitrile/TFA): } m/z \text{ (%) = 395.9 (100) [M+2H}^+\text{], 264.3 (40) [M+3H}^+\text{], 790.6 (2) [MH}^+\text{].}\]

IR (neat): \(n (\text{cm}^{-1}) = 3941 (\text{w}), 3573 (\text{w}) 3437 (\text{s}), 3054 (\text{m}), 2982 (\text{m}), 2932 (\text{m}), 2857 (\text{m}), 2306 (\text{w}), 1732 (\text{s}), 1594 (\text{s}), 1543 (\text{s}), 1487 (\text{s}), 1429 (\text{s}), 1411 (\text{s}), 1360 (\text{m}), 1319 (\text{m}), 1266 (\text{s}), 1188 (\text{m}), 1096 (\text{m}), 1026 (\text{m}), 942 (\text{w}), 893 (\text{w}), 810 (\text{m}), 736 (\text{s}).\]

HR-MS (EI-MS, 70 eV): \(m/z\) : calc.: 789.4438; found: 789.4427.

\[(8-Amino-octyl)-ethoxycarbonylmethyl-amino]-acetic acid ethyl ester (2):

To a solution of 5 g (34.7 mmol) of 1,8-diaminooctane in 50 mL of CHCl₃ at 0°C was added 2.36 g (11.6 mmol) of boc-Eanhydride in 14 mL of CHCl₃ dropwise during 0.5 h. The reaction mixture was stirred at room temp. for 2 d, the solvent was evaporated, the residue was taken up with ethyl acetate (200 mL), washed with brine (100 mL, 3x), dried over Na₂SO₄ and evaporated to give 2.3 g (85%) of 8-(amino-octyl)-carbamic acid tert.butyl ester [5] as a colourless oil.

\[1H-NMR (300 MHz, CDCl₃): \delta \text{ = 1.20-1.33 (m, 12 H, CH}₃\text{), 1.42 (s, 9 H, boc-CH}₃\text{), 2.65 (m, 2 H, CH}₂\text{), 3.10 (m, 2 H, CH}₂\text{), 4.55 (bs, 1 H, NH).}\]

\[\text{8-(Amino-octyl)-carbamic acid tert-butyl ester (2.26 g, 9.8 mmol) was dissolved in 100 mL of MeCN and 3.58 g (21.6 mmol) of KI, 4.07 g (29.4 mmol) of K}_{2}\text{CO₃ and 2.4 mL (3.6 g, 21.6 mmol) of ethylbromo acetate were added to the solution. The mixture was refluxed for 2 d and the solvent was evaporated. The residue was taken up with ethyl acetate (200 mL) and washed with water (100 mL, 3x), sat. NaHCO₃-solution (100 mL, 2x) and finally with brine (100 mL, 2x). The combined organic phases were dried over Na₂SO₄, filtered and evaporated to yield 2.7 g (69%) of } (8-(tert-butoxycarbonylamino-octyl)-ethoxycarbonylmethyl-amino)-acetic acid ethyl ester\] as orange oil. The compound was used without further purification.

\[1H-NMR (300 MHz, CDCl₃): \delta \text{ = 1.14-1.28 (m, 14 H, CH₃, CH₂), 1.30-1.46 (m, 13 H, CH₃, CH₂), 2.56-2.65 (m, 2 H, CH₂), 2.95-3.07 (m, 2 H, CH₂), 3.46 (s, 4 H, CH₂), 4.10 (quart, 4 H, CH₂), 4.56 (bs, 1 H, NH).}\]
\[^{13}\text{C}]\text{-NMR}\ (75\text{ MHz, }\text{CDCl}_3): \delta = 14.1\ (+, 2\text{ C}), 26.7-27.1\ (-, 3\text{ C}); 28.4\ (+, 3\text{ C}), 29.2\ (-, 2\text{ C}), 29.9\ (-, 1\text{ C}), 40.6\ (-, 1\text{ C}), 54.3\ (-, 1\text{ C}), 55.1\ (-, 2\text{ C}), 60.5\ (-, 2\text{ C}), 155.9\ (C_{\text{quat}}, 1\text{ C}), 171.3\ (C_{\text{quat}}, 2\text{ C}), 171.6\ (C_{\text{quat}}, 1\text{ C}).

ES-MS (DCM/MeOH + 10 mmol/l NH_4Ac): m/z (\%) = 417.4\ (100) [MH^+], 361.3\ (10) [MH^+-C_4H_8].

IR (neat): n (cm\(^{-1}\)) = 3445\ (s), 3055\ (w), 2982\ (m), 2932\ (m), 2857\ (w), 2209\ (w), 1655\ (s), 1615\ (w), 1502\ (w), 1446\ (w), 1367\ (m), 1265\ (s), 1175\ (s), 1030\ (s), 867\ (w), 739\ (s).

HR-MS (EI-MS 70 eV): m/z (\%) calc.: 416.2886; found: 416.2878.

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\[^1\text{H}]\text{-NMR}\ (300\text{ MHz, }\text{CDCl}_3): \delta = 1.17-1.26\ (m, 14\text{ H, }\text{CH}_3, \text{CH}_2), 1.33-1.49\ (m, 4\text{ H, }\text{CH}_2), 2.13\ (bs, 2\text{ H, }\text{NH}), 2.57-2.68\ (m, 4\text{ H, }\text{CH}_2), 3.46\ (s, 4\text{ H, }\text{CH}_2), 4.83\ (quart., J = 7.1\text{ Hz, }4\text{ H, }\text{CH}_2).

\[^{13}\text{C}]\text{-NMR}\ (75\text{ MHz, }\text{CDCl}_3): \delta = 14.2\ (+, 2\text{ C}), 26.7-28.3\ (-, 3\text{ C}), 29.4\ (-, 2\text{ C}), 33.1\ (-, 1\text{ C}); 42.0\ (-, 1\text{ C}); 54.4\ (-, 1\text{ C}); 55.1\ (-, 2\text{ C}); 60.6\ (-, 2\text{ C}); 171.4\ (C_{\text{quat}}, 2\text{ C}).

CI-MS (NH_3): m/z (\%) = 317.2\ (100) [MH^+].

IR (neat): n (cm\(^{-1}\)) = 3414\ (s), 2984\ (w), 2933\ (w), 2875\ (w), 2084\ (w), 1735\ (s), 1655\ (s), 1535\ (w), 1371\ (w), 1266\ (m), 1192\ (s), 1123\ (w), 1029\ (m), 736\ (s).

HR-MS (EI-MS, 70 eV): m/z (\%) calc.: 316.2362; found: 316.2353.

References and Notes


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