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Synthesis of pyridine-based polyaminocarboxylic ligands bearing a thioalkyl anchor

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Abstract—A bicyclic tetraazatriacetic chelating agent containing a thioalkyl pendant group was prepared. Four synthetic routes have been investigated via a Mitsunobu reaction from 2,4-[bishydroxymethyl]-3-hydroxy-pyridine **1**. Deprotection of trityl thioether compound **5c** led to ligand **6c** in 22% overall yield from the starting 3-hydroxypyridine.

MRI is an imaging technique and now one of the most important diagnostic tools available in clinical practice. Nowadays, most of the MRI contrast agents approved for clinical use involve Gd^{3+}–poly(aminocarboxylate) complexes.[1] Among them, Gd(III)(DTPA) and Gd(III)(DOTA) are the most efficient, ensuring nontoxicity due to their kinetic inertness and high thermodynamic stability. Although it produces highly resolved images, MRI requires elevated concentrations of contrast agents. To reach the required local concentration, the majority of the potential contrast agents involves macromolecular carriers such as dendrimers,[2,3] linear polymer,[4–7] proteins,[8–10] or micelles.[11–14] Recently, we described a dithiolate DTPA derivative anchored on gold nanoparticles as a very attractive and a higher contrast agent than the Gd^{3+}–DTPA complex widely used.[15]

In order to improve these contrast-enhanced properties, we focused our attention on the synthesis of PCTA-[12] macrocycles (pyridine containing triaza macrocycle) containing a thiol group. Among the polyazamacrocyclic ligands such as 12-membered N_4 pyridine-containing macrocycles[1,16–18] (PC-type ligands), PCTA-[12][19] was already synthesised and evaluated as potential MRI contrast agent.[20] With a very high stability constant[21] ($\log_{Gd\text{–}PCTA\text{-}[12]} = 20.8$) and an improved performance in terms of relaxivity as discussed in detail in a previous review,[1] the corresponding Gd^{3+} complex was proved to be an efficient contrast agent.

Generally, the synthesis of the polyazamacrocyclic ring is the crucial step in the preparation of PCTA-[12] derivatives. Commonly, azamacrocycles were synthesised via the condensation of 2,6-bis(halomethyl)-pyridine and disodium salt of 1,4,7-trinosyl-1,4,7-triazaheptane according to the modified method of Richman and Atkins.[22] Moreover, 3-substituted-pyridine azacrowns were also prepared via this procedure.[14,23] Although effective, it suffers from a number of drawbacks involving, among others, harsh conditions of deprotection and purification of the final carboxylate derivatives. Therefore, alternative and easier strategies are desirable. The Mannich reaction was then successfully employed to obtain a 12-membered 3,5-dihydroxy pyridine-containing macrocycle[24] but was unfortunately not effective for the access to the 3-hydroxypyridine derivative. More recently, Hovinen and Sillanpää[25] proposed a new route for the synthesis of pernosylated azamacrocycles via a Mitsunobu reaction, which we chose to use for the preparation of precursors **3a**–**c** (Scheme 1).

O-Alkylation of **1**[26] in the presence of dry K_2CO_3 in DMF gave **2a**–**c** in good yields. Compounds **2a**,**b** were,

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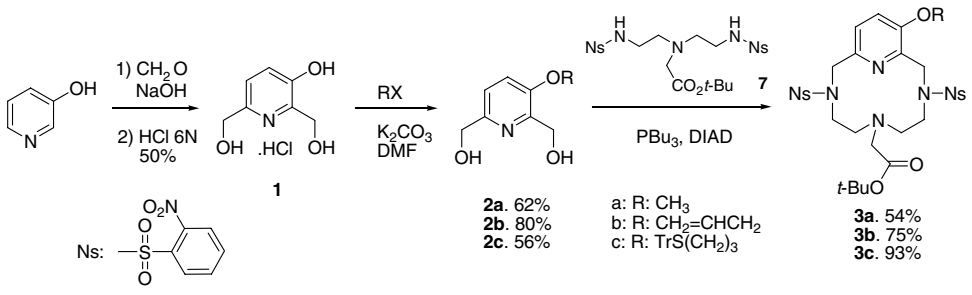


Scheme 1.

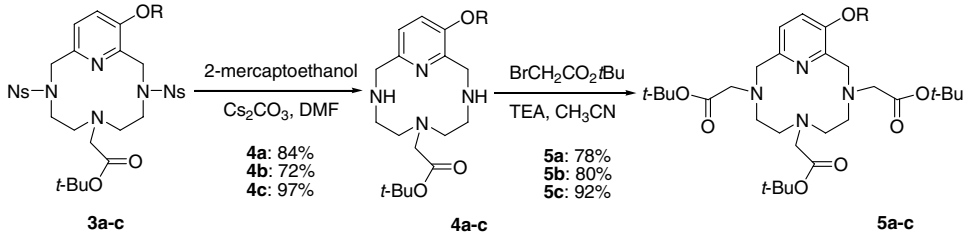
respectively, obtained from the commercially available methyl iodide and allyl bromide. Compound **2c** was obtained from bromopropylene trityl thioether.[27] Alkylation of **7**[18] with an equimolar amount of diol **2b** was preliminary performed with the classical Mitsunobu diisopropyl azodicarboxylate (DIAD)–PPh_3 tandem (3.0 equiv of each of the reagents) in THF.[25] After 4 h at room temperature, **3b** was obtained in 65% yield. 1,1′-(Azodicarbonyl)dipiperidine (ADDP)–P(*t*Bu)$_3$ combination did not have the expected efficiency[28] affording the desired product in 67% yield. Finally, the highest conversion of **2b**→**3b** was achieved (75%) when DIAD was used with PBu_3 instead of PPh_3. These conditions (DIAD–PBu_3, rt, 4 h, THF) were applied to the preparation of derivatives **3a**,**c**[29] from **2a**,**c**.

Deprotection of nosyl groups (Scheme 2) was performed with 2-mercaptoethanol in DMF and Cs_2CO_3 as bases[30] affording **4a**–**c** in good yields. Alkylation of **4a**–**c** derivatives performed with bromomethyl *tert*-butyl ester and K_2CO_3 or Ag_2CO_3 as a base gave a mixture of polyalkylated macrocycles. When triethylamine (TEA) was used, the expected product **5a**–**c** were obtained in high yields.

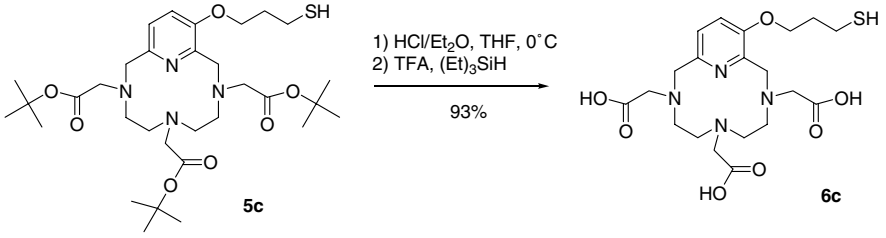
Further functionalisation of **5a** and **5b** involved the preliminary deprotection of the residual OH of the pyridine moiety. Unfortunately, whatever the conditions (TMSI or BBr_3 in chloroform) the deprotection of **5a** failed. Tested with $RhCl_3$ in ethanol[31] or Pd/C in methanol with APTS,[32] the cleavage of allyl substituent from **5b** also failed. As described by Broxterman et al.,[33] the radical addition of thiolacetic acid with AIBN on **5b** followed by the hydrolysis of the thioacetate intermediate could give the corresponding thiol derivative. Nevertheless, degradation of the starting material was solely observed under these conditions.

From **5c**, simultaneous removal of trityl and *tert*-butyl groups was also tested by the treatment with TFA/TES in THF.[34] Under these conditions, the removal of the trityl group easily occurred accompanied by a partial hydrolysis of ester functions. Even in more concentrated TFA or in longer reaction times, the monoester derivative was obtained. Finally, preliminary reaction of **5c** with HCl in ether (1 M), followed by the treatment with TFA/TES afforded macrocycle **6c** which was purified by precipitation in ether in 93% yield (Scheme 3).[35]

In conclusion, we have synthesised a new thiol PCTA type ligand in 22% overall yield from 3-hydroxypyridine in six synthetic steps via a Mitsunobu reaction and a deprotection of the thiol group. Immobilisation onto



Scheme 2.



Scheme 3.

gold nanoparticles and MRI properties are under investigations.

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27. *Bromopropylene trityl thioether*: To a suspension of lithium aluminium hydride (0.38 g, 10 mmol) in 15 mL of THF was added dropwise a solution of 3-tritylsulfanyl-propionic acid (3.5 g, 10 mmol) in THF (30 mL). The mixture was then refluxed for 3 h. After cooling, 2 mL of 20% NaOH was added and the precipitate was filtered off. Pure 3-tritylsulfanyl-propanol (2.75 g, 82%) was obtained as a white solid by purification on chromatography column (SiO_2, ethyl acetate/cyclohexane: 1/2). 3-Tritylsulfanyl-propanol (0.34 g, 1 mmol) was then dissolved at 0 °C in dry CH_2Cl_2 (5 mL) with triphenylphosphine (0.29 g, 1.1 mmol). NBS (0.2 g, 1.1 mmol) was added in portion and the mixture was stirred over night at room temperature. The solvent was evaporated and the residue was treated with Et_2O. After filtration, the crude product was purified by chromatography on silica gel (CH_2Cl_2/cyclohexane: 1/1) to give the bromopropylene trityl thioether as a colorless oil (0.25 g, 62%). ^{1}H NMR ($CDCl_3$): 1.92 (q, 2H, $J = 6.78$ Hz); 2.48 (t, 2H, $J = 6.45$ Hz); 3.42 (t, 2H, $J = 6.59$ Hz); 7.31–7.61 (m, 15ArH). ^{13}C NMR: 30.82, 32.15, 32.87 (CH_2); 67.25 (C); 127.2, 128.4, 130.1 (ArCH); 145.2 (ArC).
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29. *General procedure*: **2a**–**c** (1 mmol), **7** (1 mmol) and tributylphosphine (3 mmol) were dissolved in dry THF (25 mL). DIAD (3 mmol) was added in four portions during 15 min, and the reaction was stirred at room temperature for 4 h. All volatiles were removed in vacuum, and the residue was purified by chromatography on silica gel (ethyl acetate/heptane: 1/1–100/0) to give a light yellow solid.
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35. *Synthesis of* **6c**: A solution of bromopropylene trityl thioether (0.25 g, 0.6 mmol) in 2 mL of DMF was added to a solution of **1** (0.1 g, 0.5 mmol) in 2 mL of DMF with K_2CO_3 (0.16 g, 1.1 mmol). The resulting mixture was stirred overnight at 60 °C. After cooling, the solvent was evaporated and the residue was triturated with CH_2Cl_2 and filtered. The filtrate was concentrated and purified by chromatography (SiO_2, CH_2Cl_2–CH_2Cl_2/CH_3OH: 100/2), affording pure **2c** as a white solid (0.2 g, 81%). ^{1}H NMR ($CDCl_3$): 1.85 (q, 2H, $J = 6.3$ Hz); 2.39 (t, 2H, $J = 7.07$ Hz); 3.94 (t, 2H, $J = 5.94$ Hz); 4.61 (s, 2H); 4.72 (s, 2H); 7.05 (d, H, $J = 8.28$ Hz); 7.18–7.30 (m, 10H); 7.41–7.44 (m, 6H). ^{13}C NMR ($CDCl_3$): 28.48, 28.73, 60.40, 64.96, 66.82, 67.10 (CH_2); 118.5, 120.1 (CH); 127.1, 128.3,

129.9 (ArCH); 145.1 (ArC), 148.0, 149.9, 150.9 (C). Compound **3c** then was prepared as described in Ref. 29 from **7**. Yield: 93%. ^{1}H ($CDCl_3$) NMR: 1.32–1.35 (m, 27H); 1.62–1.68 (m, 2H); 2.28 (t, 2H, $J = 6.78$); 2.35 (t, 2H, $J = 7.73$); 2.55 (t, 2H, $J = 7.64$); 3.10–3.14 (s+t, 4H); 3.27 (t, 2H, $J = 7.71$); 3.80 (t, 2H, $J = 6.12$); 4.43 (s, 2H); 4.49 (s, 2H); 7.05–7.20 (m, 10H); 7.30–7.35 (m, 7H); 7.50–7.64 (m, 6H); 7.89–7.95 (m, 2H). ^{13}C NMR ($CDCl_3$): 28.46 (CH_3); 27.32, 28.13, 44.38, 45.47, 49.74, 50.30, 51.04, 51.88, 54.35, 57.90, 67.11, 67.17 (CH_2); 81.48 (C); 120.3, 126.1 (CH); 124.5, 124.65, 127.1, 128.3, 130.0, 131.0, 131.2, 131.9, 132.1, 133.7, 134.0 (ArCH); 143.6, 145.2, 146.0, 148.6, 148.7, 154.0 (C); 171.4 (C=O). To a solution of **3c** (1.5 g, 1.5 mmol) in 5 mL DMF were added Cs_2CO_3 (1.15 g, 3.5 mmol) and 2-mercaptoethanol (0.57 g, 7.3 mmol). The resulting mixture was stirred for 2 h. The solvent was evaporated in vacuum and the residue was triturated with CH_2Cl_2. After filtration, pure **4c** was obtained by chromatography (SiO_2, CH_2Cl_2/CH_3OH: 10/1—CH_3OH—CH_3OH/NH_3 aq: 10/1) as a yellow oil (0.93 g, 97%). ^{1}H NMR ($CDCl_3$): 1.48 (s, 9H); 1.84 (t, 2H, $J = 6.32$ Hz); 2.39 (t, 2H, $J = 6.87$ Hz); 2.62 (s, br, 4H); 2.79–2.84 (m, 4H); 3.51 (s, 2H); 3.90–3.94 (m, 4H); 4.07 (s, 2H); 7.01 (s, 2H); 7.18–7.30 (m, 9ArH); 7.40–7.43 (m, 6H). ^{13}C NMR ($CDCl_3$): 28.55 (CH_3); 28.47, 28.73, 47.60, 48.71, 48.94, 51.93, 53.90, 56.60, 57.54, 59.96, 64.22, 66.75, 68.46 (CH_2); 118.5, 120.7 (CH); 127.0, 128.2, 129.8 (ArCH); 145.1 (ArC); 147.4, 151.7 (C);171.7 (C=O). To a solution of **4c** (0.93, 1.4 mmol) in 20 mL CH_3CN, were added triethylamine (0.44 g, 4.4 mmol) and *tert*-butyl bromoacetate (0.85 g, 4.4 mmol). The resulting mixture was stirred at 70 °C for 1 h and evaporated in vacuum. The residue was dissolved in CH_2Cl_2 and the organic layer was washed with water and brine. The solution was dried over Na_2SO_4 and evaporated to dryness to give pure **5c** as a yellow solid (1.16 g, 92%). ^{1}H NMR ($CDCl_3$): 1.32–1.43 (m, 27H); 1.71 (t, 2H, $J = 6.5$ Hz); 2.28 (t, 2H, $J = 6.87$ Hz); 3.09–3.11 (br, 4H); 3.32 (s, 4H); 3.61 (t, 2H, $J = 5.28$ Hz); 3.79–3.89 (m, 8H); 4.26 (s, 2H); 6.97 (s, 2H); 7.11–7.22 (m, 9H); 7.30–7.35 (m, 6H). ^{13}C NMR ($CDCl_3$): 28.46, 28.51 (CH_3); 28.74, 50.13, 50.72, 51.14, 53.08, 53.68, 54.24, 55.43, 56.85, 58.75, 59.14, 67.15, 67.38 (CH_2); 82.32, 84.51 (C); 119.4, 121.7 (CH); 127.1, 128.3, 129.9 (ArCH); 145.1 (ArC); 148.6, 149.1, 151.7 (C); 166.1, 170.3, 170.4 (C=O). 35 mL of a solution of HCl in diethylether was added dropwise to a solution of **5c** (0.6 g, 0.68 mmol) in 10 mL of anhydrous THF. The reaction mixture was stirred overnight and the white precipitate was filtered off. The residue was then dissolved in 3 mL of TFA. After 1 h, 0.32 mL of triethylsilane was added and the mixture was stirred for 1 h. Pure **6c** was obtained by the addition of diethylether, filtration of the precipitate and washing with diethylether. Compound **6c** was obtained as a light yellow solid (0.3 g, 93%). ^{1}H NMR (CD_3OD) : 2.11–2.26 (m, 2H); 2.71–2.77 (m, H); 2.92–2.97 (m, H); 3.24 (s, 4H); 3.47–3.54 (m, 4H); 3.89 (s, 2H); 4.06–4.10 (m, 4H); 4.25 (s, 2H); 4.52 (s, 2H); 4.62 (s, 2H); 7.41 (s, lH); 7.57 (d, H). ^{13}C NMR (CD_3OD): 28.27, 30.13; 51.42, 51.98, 52.09, 52.30, 52.42, 52.95, 54.63, 56.34, 56.55, 57.86, 65.66, 66.96, 67.04 (CH_2); 119.9, 121.5 (CH); 147.9, 149.0, 151.0 (C); 168.0, 172.3 (C=O). MS: ESI: 471.2 [M+H].