Simple Procedures for the Preparation of 1,3,5-Substituted 2,4,6-Trimethoxybenzenes

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Received: 09.07.2013; Accepted after revision: 23.07.2013

Abstract: We describe straightforward protocols for the preparation of a number of 1,3,5-substituted 2,4,6-trimethoxybenzenes. A two-step procedure for the preparation of a 1,3,5-tris-methylamino-2,4,6-trimethoxybenzene and further synthetic elaboration of this key substrate to yield a triamide, a tricarbamate and three different triureas is described. We also present a computational (DFT) study that investigates the different possible conformations of the overcrowded benzene substrate and a single-crystal X-ray structure of one of the key intermediates.

Key words: supramolecular chemistry, tripodal receptors, ureas, amides, overcrowded aromatics

The subtle interplay between rigidity and flexibility makes the design of receptors in supramolecular chemistry complex and sometimes unpredictable. Preorganization has proven a reliable strategy in receptor design, but this is only truly effective if there is a good fit with the binding partner. A particularly popular and simple scaffold that relies on preorganization is the 1,3,5-substituted 2,4,6-triethylbenzene scaffold. Receptors based on this scaffold have the unique feature that the three ethyl substituents predominantly orient themselves towards one side of the central benzene ring, while the three other substituents point towards the other side of the benzene ring. This feature has been used extensively in the preparation of receptors for a wide range of guest molecules. The central benzene ring can potentially engage in the molecular recognition events. This has inspired a renewed interest in the preparation of tripodal structures with alternative substitution patterns on the central benzene ring. This opens up new opportunities for fine-tuning the binding properties of these privileged receptor structures.

A strategy to improve the binding properties of the tripodal receptors is to modify the electronic properties of the benzene ring by changing the three ethyl substituents to three methoxy substituents. This subtle change in design provides less preorganized structures, presumably because three almost aligned O–Me dipoles in a completely alternating structure would not be favorable, and receptors based on this design would need other favorable interactions to outweigh this effect. Here we describe reliable synthetic protocols for the preparation of a series of 1,3,5-tris-substituted 2,4,6-trimethoxybenzenes. We also quantify, by means of DFT calculations, the relative energetics of the different conformations of the 1,3,5-substituted 2,4,6-trimethoxybenzenes.
Bromomethylation of 1,3,5-trimethoxybenzene (1) was performed using a modified literature procedure. Treatment of 1,3,5-trimethoxybenzene with paraformaldehyde and HBr in AcOH for three hours at 85 °C in a sealed container yielded the tris-bromomethylated product (2) in 49% yield. This procedure reliably yields >10 g of 2 as a white solid material. The transformation into the tris-methylamino compound (3) proceeded smoothly by dissolving 2 in liquid ammonia in a sealed bomb at room temperature for 18 hours. When optimized, this transformation proceeded in quantitative yield. Simple evaporation of the ammonia, addition of water and filtration yielded after concentration in vacuo the tris-hydrobromide as a pale yellow solid (Scheme 1). This protocol was concentration dependent and a concentration of the tribromide of 0.1 gram per 40 mL ammonia proved to be the optimal conditions to avoid side reactions.

With the triamine in hand, we explored the possibilities for functionalization via simple amide coupling reaction and by carbamate formation. The formation of the tris(tert-butyl)carbamate (Boc) compound 4 (Scheme 2) was effective by treatment with di-tert-butyl dicarbonate in dioxane and water, and was easily purified by column chromatography. The yield was moderate but acceptable due to the three-fold reaction (above 60% yield per carbamate formation) and easy purification protocol. We also developed conditions for the preparation of an amide, 5, by coupling of the triamine and terephthalic acid monomethyl ester and a coupling reagent (either Me3P/I2 or PYBOP) in CH2Cl2. This material was also purified by chromatography on silica revealing 66% of the triamide. Formation of amides was also attempted by an alternative route. 1,3,5-Trimethoxybenzene gave, via reaction with N-(hydroxymethyl)phthalimide, the triphthalimide 6 and ways of opening the phthalimide functionalities by reaction with amines as described by Gali et al. were attempted (Scheme 3). However, the isolated product in these attempts was the N-alkyl-substituted phthalimide of the amine.

Another functionality derived from amines is the urea group which has been widely used in the design of hosts towards hydrogen bond accepting guests. We studied convenient ways of converting the triamine 3 into triurea derivatives, and it was found that reaction between 3 and tert-butylisocyanate under mild conditions gave the desired triurea derivative 7. The binding properties of this compound were studied by NMR in chloroform, and the host showed a modest affinity towards chloride ions (see Supporting Information).
We studied ways to urea functionalize the triamine \( 3 \) without the need of isocyanate reagents. The compound \( 1,1' \)-carbonyldiimidazole has previously been used as an urea activating reagent by formation of an activated imidazole urea intermediate which can be reacted with a second amine giving the unsymmetrical urea.\(^{14} \) This activation method is particularly challenging with a substrate containing multiple amine functionalities because reactions between activated and non-activated amines at the early stages of the activation process can give rise to unwanted urea side products. We studied this triple activation step carefully, and under optimized conditions it was found that complete triple activation could be achieved. The optimized conditions were found by following the progress of reaction for every ten minutes using \(^{13}\)C NMR spectroscopy directly on the reaction mixture. Even in the non-deuterated reaction mixture the carbon signal originating from the methoxy \( CH_3 \) group was easily identified and could be monitored during the activation (Figure 1). As the triamine began to react with the activation reagent the overall symmetry of \( 3 \) was broken and therefore the signal split up. After 60 minutes of reaction a single signal was again obtained indicating that the overall symmetry had been reestablished due to complete activation. After complete activation, trityl-protected cysteine was added to the mixture to give the desired unsymmetrical triurea compound \( 8 \).\(^{15} \)

![Scheme 3](image)

**Scheme 3** Alternative attempts to functionalize triamine \( 3 \) with amides. *Reagents and conditions:* (a) \( N \)-hydroxymethylphthalimide, boron trifluoride etherate; (b) \( RNH_2 \).

To gain insights into the level of preorganization of the 1,3,5-tris-substituted 2,4,6-trimethoxybenzenes, we carried out a study combining single-crystal X-ray structure determination and DFT calculations. In Figure 2 the sin-
gle-crystal X-ray structure of the tribromide 2 is illustrated, showing the co-crystallization of two different conformers of 2. When the isolated crystals were dissolved in CDCl3 and analyzed by 1H NMR spectroscopy the spectrum did not show separated signals for both conformers. This indicates that the energy barrier for conformer conversion is sufficiently low to make the conformer-exchange process fast on the chemical shift time scale.

Gas-phase structure optimization and energy calculations of ten possible conformers of 2 (see Supporting Information) using DFT calculations indicate that two co-crystallizing conformers are among the three lowest energy structures. The most stable conformer was found to have all substituents located on the same plane of the benzene ring, and the highest energy structure was found to have the substituents placed alternating.

We did not succeed in obtaining crystals of sufficient quality for single-crystal X-ray determination of any of the nitrogen-containing tripodal structures. NMR data, however, was obtained and showed a number of signals only possible if either the alternating conformer or the conformer with all substituents on the same side of the benzene ring were formed exclusively or if the conformer-exchange process is fast on the chemical shift time scale.

In summary, we have presented a straightforward two-step protocol for the preparation of 1,3,5-tris(methylamino)-2,4,6-trimethoxybenzene. We have shown how this key substrate can be transformed into tricarbamates, triureas, and triureas. Despite the preorganization of these key substrate can be transformed into tricarbamates, triureas. We have shown how this key substrate can be transformed into tricarbamates, triureas. Despite the preorganization of these amides, and triureas. Despite the preorganization of these nitrogen-containing tripodal structures. NMR data, however, was obtained and showed a number of signals only possible if either the alternating conformer or the conformer with all substituents on the same side of the benzene ring were formed exclusively or if the conformer-exchange process is fast on the chemical shift time scale.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes


(7) 1,3,5-Tris(bromomethyl)-2,4,6-trimethoxybenzene (2): 1,3,5-Trimethoxybenzene (10.0 g, 59.5 mmol) and paraformaldehyde (11.0 g, 366 mmol) were suspended in 33% HBr in AcOH (85 mL) in a sealed stainless steel reaction vessel. The mixture was stirred for 3 h at 85 °C. After cooling to 25 °C CH2Cl2 (200 mL) was added, the phases were separated, and the organic phase was washed with H2O (3 × 75 mL). The CH2Cl2 phase was filtered through silica (Ø = 50 mm, h = 60 mm) and the column was flushed with further CH2Cl2 (2 × 150 mL). The solvent was removed in vacuo, and the resulting yellow oil was dissolved in a mixture of 2-propanol (100 mL) and CH2Cl2 (100 mL). White crystals were obtained by reducing the volume of the solution to 50 mL and the precipitates were filtered off and washed with 2-propanol. Yield: 13.0 g (49%); mp 125–126 °C. 1H NMR (500 MHz, CDCl3): δ = 4.60 (s, 6 H), 4.14 (s, 9 H). 13C NMR (125 MHz, CDCl3): δ = 160.3, 118.1, 63.0, 33.2. HRMS: m/z [M + H]+ calcd for C12H19O3Br3: 461.8910; found: 461.8924.

(8) (2,4,6-Trimethoxybenzene-1,3,5-triyl)trimethanamine Hydrobromide (3): 1,3,5-Tris(bromomethyl)-2,4,6-trimethoxybenzene (401 mg, 0.898 mmol) and liquid NH3 (98%); mp 176 °C (dec.). 1H NMR (500 MHz, D2O): δ = 4.60 (s, 6 H), 4.14 (s, 9 H). 13C NMR (125 MHz, CDCl3): δ = 160.3, 118.1, 63.0, 33.2. HRMS: m/z [M + NH4]+ calcd for C12H19O3Br3N+: 511.3239; found: 511.3239.

(9) Tri-tert-butyl[(2,4,6-Trimethoxybenzene-1,3,5-triyl)methylene]tricarbamate (4): The tribromide 2 (1.80 g, 4.02 mmol) was dissolved in THF–EtOH (100 mL; 1:1) and concentrated aq NH3 (80 mL) was added. The reaction mixture was stirred for 14 h whereafter the solvent was removed in vacuo. The residue was dissolved in dioxane–H2O (70 mL, 1:1) and NaOH (0.80 g, 20 mmol) was added. Boc-O (5.76 g, 26 mmol) in dioxane (20 mL) was slowly added at 0 °C and the reaction was stirred for an hour at 0 °C and 5 h at 25 °C. H2O was added and the solution was extracted with CH2Cl2 (3 × 60 mL). The organic phase was dried over Na2SO4, filtered and concentrated in vacuo. The product was further purified by dry column chromatography (Ø = 60 mm, h = 50 mm, heptane with 0.1% Et3N to EtOAc with 0.1% Et3N with 5% gradient), followed by...
Preparation of 1,3,5-Substituted 2,4,6-Trimethoxybenzenes

(13) Diness, F.; Beyer, J.; Meldal, M.

(14) 1H NMR (500 MHz, CDCl₃): δ = 5.15 (s, 6 H), 3.88 (s, 9 H), 3.83 (s, 9 H). 13C NMR (125 MHz, CDCl₃): δ = 158.5, 155.1, 122.6, 79.1, 62.4, 34.8, 28.6. HRMS: m/z [M + Na]+ calcd for CₓHᵧNₒOₘNa⁺: 578.3048; found: 578.3069.

(15) 2.2′,2′′-[[[(2,4,6-Trimethoxybenzene-1,3,5-)
triy][tris(methylene)][tris(azanediyl)][tris(carbonyl)][tris(
azaenyl)][tris(tritylthio)propanoic Acid] (8): The triamine 3 (100 mg, 0.200 mmol) was dissolved in DMF (10 mL) and a solution of 1,1′-carbonyldimidazole (100.9 mg, 0.622 mmol) in MeCN (10 mL) was added. The reaction mixture was stirred for an hour and 2-tritylcysteine (233.5 mg, 0.643 mmol) and Et₃N (0.142 mL, 1 mmol) were added. The reaction mixture was stirred overnight whereafter the volatiles were removed. The residue was redissolved in CHCl₃, and washed with 0.5 M HCl (3 × 50 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The product was further purified by preparative HPLC to give a white solid material. Yield: 121 mg (45%); mp 177–179 °C. 1H NMR (500 MHz, DMSO-d₆): δ = 12.70 (s, 3 H), 7.17–7.40 (m, 45 H), 6.42 (d, J = 8.3 Hz, 3 H), 6.30 (t, J = 5.4 Hz, 3 H), 4.25 (d, J = 5.4 Hz, 4 H), 4.20 (dd, J = 8.3, 6.8, 5.1 Hz, 3 H), 3.72 (s, 9 H), 2.41 (dd, J = 11.7, 6.8 Hz, 3 H), 3.23 (dd, J = 11.7, 5.1 Hz, 3 H). 13C NMR (125 MHz, DMSO-d₆): δ = 172.60, 150.04, 156.69, 144.16, 129.00, 128.03, 126.78, 122.54, 61.50, 34.31, 33.03. HRMS: m/z [M + H]+ calcd for CₓHᵧNₒOₘSₚ: 1423.4913; found: 1423.4884.

(16) 3,3′,3″-[[[(2,4,6-Trimethoxybenzene-1,3,5-
triy][tris(methylene)][tris(azanediyl)][tris(carbonyl)][tris(
azaenyl)][tris(tritylthio)propanoic Acid] (9): The triamine 3 (202 mg, 0.406 mmol) was dissolved in DMF (20 mL) and a solution of 1,1′-carbonyldimidazole (3.1 equiv, 204 mg, 1.26 mmol) in MeCN (20 mL) was added. The reaction mixture was stirred for an hour at r.t. 1-Aminobenzoic acid (3.2 equiv, 178 mg, 1.30 mmol), Et₃N (21.2 equiv, 1.2 mL, 8.6 mmol) and DMAP (0.1 equiv, 5.1 mg, 0.042 mmol) were added and the reaction mixture was stirred for 3 d. Thereafter, the reaction mixture was poured into an ice-cold solution of 2 M HCl, the precipitate was filtered off and dried in vacuo. Finally, the crude product was washed once with 2 M NaOH (20 mL), recrystallized with 2 M HCl, filtered and dried in vacuo. Yield: 62.9 mg (21%). 1H NMR (500 MHz, DMSO-
δ): δ = 9.24 (s, 3 H), 8.06 (s, 3 H), 7.58 (d, J = 7.7 Hz, 3 H), 7.44 (d, J = 7.7 Hz, 3 H), 7.31 (t, J = 7.7 Hz, 3 H), 6.57 (s, 3 H), 4.38 (s, 6 H), 3.84 (s, 9 H). 13C NMR (125 MHz, DMSO): δ = 167.36, 158.22, 154.79, 140.90, 131.19, 128.78, 122.34, 121.73, 121.48, 118.00, 62.37, 32.98. HRMS: m/z [M + H]+ calcd for CₓHᵧNₒOₘSₚ: 745.2464; found: 745.2489.

(17)Trimethyl 2,2′,2′′-[[[(2,4,6-Trimethoxybenzene-1,3,5-
triy][tris(methylene)][tris(azanediyl)][tris(carbonyl)][tris(
azaenyl)][tris(4-methoxybenzyl)thio]propanoate] (10): The PMB-protected cysteine (234 mg, 0.830 mmol) was dissolved in DMF (20 mL) and a solution of 1,1′-carbonyldimidazole (143.1 mg, 0.883 mmol) in MeCN (20 mL) was added. The mixture was stirred for 30 min and the triamine 3 (100 mg, 0.201 mmol) and imidazole (136 mg, 2.00 mmol) were added. The reaction mixture was stirred overnight whereafter the volatiles were removed. The residues were redissolved in CHCl₃ (80 mL) and washed with 0.5 M HCl (3 × 50 mL) and 0.5 M NaOH (20 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated in vacuo. The product was further purified by preparative HPLC to give a white solid material. Yield: 65 mg (28%); mp 185 °C (dec.). 1H NMR (500 MHz, DMSO-d₆): δ = 3.97 (t, J = 8.7 Hz, 6 H), 3.69 (d, J = 8.7 Hz, 6 H), 2.65 (dd, J = 13.6, 6.8 Hz, 3 H). 13C NMR (125 MHz, DMSO-d₆): δ = 173.18, 148.38, 137.60, 124.83, 123.50, 121.87, 117.47, 110.84, 70.20, 58.70, 43.38, 34.92, 31.79. HRMS: m/z [M + Na]+ calcd for CₓHᵧNₒOₘSₚNa⁺: 553.3717; found: 553.3717.

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Synlett 2013, 24, 2437–2442

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MHz, DMSO-\textit{d}_{6}); \delta = 172.14, 158.16, 158.05, 156.72, 129.95, 129.79, 122.47, 113.73, 62.10, 55.00, 52.41, 51.91, 34.79, 33.07, 33.00. HRMS: \textit{m}/\textit{z} [M + H]\^+ \text{calcd} for C_{51}H_{67}N_{6}O_{15}S_{3}^+: 1099.3821; \text{found: } 1099.3853.

(18) C_{12}H_{15}Br_{3}N_{3}; M = 446.97; monoclinic; a = 9.9840(8) Å, b = 16.845(2) Å, c = 18.806(2) Å, \alpha = 90^\circ, \beta = 112.224(8)^\circ, \gamma = 90^\circ; V = 2927.8(5) Å³; T = 122 K; space group P2_{1}/c; Z = 8; \mu(\text{Mo–K}\_\lambda) = 0.07 \text{ mm}^{-1}; 94511 \text{ reflections measured, 11105 independent reflections (} R_{\text{int}} = 0.112\text{). The final } R_1 \text{ values were } 0.039 \text{ [}\text{\textit{F}_2} > 2\sigma(\text{\textit{F}_2})\text{]}. The final } R_1 \text{ values were } 0.0688 \text{ (all data). The final } wR(\text{\textit{F}_2}) \text{ (all data) values were } 0.110. \text{ The goodness of fit on } F^2 \text{ was } 1.163. \text{ The structure of the tribromide 2 has been submitted to the Cambridge Crystallographic Data Centre (CCDC) as CCDC 947822.}