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1,6-Dibenzylglycoluril for synthesis of deprotected glycoluril dimer

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ABSTRACT

1,6-Dibenzylglycoluril is not accessible via classical condensation reaction between substituted urea and glyoxal. In this paper 1,6-dibenzylglycoluril was successfully prepared by alkylation of 1,6-diacetylglycoluril with benzylbromide for the first time. 1,6-Dibenzylglycoluril reacted with formaldehyde to give tetrabenzylglycoluril dimer. Deprotection of this dimer and the previously reported *o*-xylyleneglycoluril dimer was achieved by dissolving metal reduction, whereas propyleneglycoluril dimer was deprotected by action of potassium persulfate.

1. Introduction

Glycoluril[1] is a simple heterobicyclic compound, which was prepared for the first time in the 19th century. Since then, glycoluril and its derivatives have found applications in many fields of chemistry. Among others, glycoluril is used as a building block of supramolecular host molecules, molecular clips, and cucurbiturils.[2] The latter family of macrocyclic compounds is known to bind organic and inorganic cations with high affinity and selectivity. These properties made cucurbiturils one of the most promising supramolecular hosts. However, the low solubility and difficult modification represent the main drawbacks for the use of cucurbiturils. Recent approaches for the preparation of new cucurbiturils with improved properties lie in the gradual connecting of glycoluril units into acyclic structures, glycoluril oligomers, and their subsequent transformation into macrocycles.[3] Glycoluril oligomers are prepared by the acid catalyzed condensation of glycoluril and formaldehyde, which yields a statistical mixture of products with different number of glycoluril units.[4] Recently, we and others demonstrated that glycoluril dimers, trimers, and tetramers can be prepared selectively using 1,6-protected glycoluril for the termination of glycoluril oligomer.[5] However, it is important that the selectively prepared oligomers framed by the 1,6-protected glycoluril can be later deprotected, which would allow the use of the oligomers for the synthesis of macrocycles or higher oligomers. Therefore, suitable protecting groups should be found, which could be selectively introduced to the positions 1 and 6 on the glycoluril skeleton and also methods should be developed, which would enable its easy and high yielding deprotection (Fig. 1).

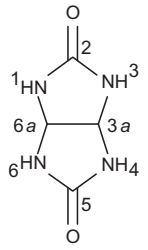

Fig. 1. Glycoluril.

A literature search gave us some inspiration,[6] for instance, Rebek and co-workers used *p*-methoxybenzyl (PMB) and *tert*-butoxycarbonyl (Boc) protecting groups in the synthesis of capsule precursors.[7] In biotin synthesis, a urea moiety was protected using benzyl substituent; deprotection was achieved by hydrobromic acid[8a] or by the dissolving metal reduction.[8b] Unfortunately, (de) protections methods were illustrated only on glycolurils bearing additional substitution in position 3*a* and 6*a*. In our work, we focus on glycoluril bearing hydrogen atoms in the central positions because of their potential use in the cucurbituril synthesis. To the best of our knowledge, the deprotection of these glycolurils has not been described in the literature until now.

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Herein we present the several methods of the preparation of 1,6-dibenzylglycoluril including the selective synthesis of this glycoluril isomer. We further demonstrate that the dimer prepared by the condensation of 1,6-dibenzylglycoluril with formaldehyde can be deprotected with high efficiency. The deprotection of the previously prepared glycoluril dimers is also discussed.

2. Results and discussion

The preparation of dibenzylglycouril was previously described;[9] nevertheless the position of substituents on the resulting product was not specified. We repeated the published procedure, which was based on the reaction between *N*-benzylurea and glyoxal and obtained a mixture in which 1,4-dibenzylglycoluril, 1-benzylhydantoin, and 3-benzylhydantoin were the main products. Only traces of desired 1,6-dibenzylglycoluril **4** were detected. This result is in agreement with the observation that an increase in the bulkiness of the substituent results in a decrease in the yield of 1,6-disubstituted glycoluril.[10] Therefore, we looked for a different preparative method. Alkylation of 1-benzylglycoluril with benzylchloride in the presence of NaH and KI resulted in the complex mixture of alkylated glycolurils. Nevertheless, we were able to isolate 1,6-dibenzylglycoluril **4** using column chromatography in an unsatisfactory yield.

The other approach we tested for the preparation of 1,6-dibenzylglycoluril **4** was based on the 1,3,4,6-tetraacetylglycoluril.[11] **1**. This compound was previously prepared by Kühling and it was used by him[11] and others[12] as a mild acylating reagent. Kühling shown that the reaction between **1** and 2 equiv of monofunctional nucleophiles results in the formation of the acetylated nucleophiles and 1,4-diacetylglycoluril **2a**. However, our aim was to prepare 1,6-diacetylglycoluril **2b** isomer, which can later serve for the preparation of **4**. Clearly, the selective formation **2a** is caused by the different reactivity of acetyl groups of **1** with nucleophiles. To understand different reactivity of acetyl groups of **1**, we prepared 1,3,4,6-tetraacetylglycoluril and obtained its monocrystals suitable for the X-ray measurement.

The crystal structure of **1** revealed that acetyl groups are attached to glycoluril unit with the different degree of twisting relative to the planes of the corresponding ureido moieties (Fig. 2). This is illustrated by different values of dihedral angles comprising acetyl groups: 141.35° (O3–C5–N1–C1), −167.86° (O4–C7–N2–C1), −172.33° (O5–C9–N3–C2), and 157.39° (O6–C11–N4–C2). The listed values demonstrate that the acetyl groups bound in the positions N1 and N4 are more twisted compared to those in positions N3 and N2, which can rationalize their higher reactivity with nucleophiles.[13]

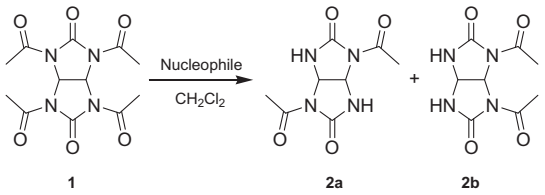
We envisioned that when bifunctional instead of monofunctional nucleophiles will be used, they could react with acetyl groups on one face of **1** yielding 1,6-diacetylglycoluril **2b**. Therefore, we tested **1** in the reactions with several bifunctional nucleophiles (Table 1). The bifunctional reagents with the nucleophilic groups directly attached to aromatic ring did not satisfy our expectation as only undesired isomer **2a** was formed. In these reagents the rigid arrangement and lower reactivity of nucleophilic groups, caused by their direct attachment to the aromatic system, probably hinder reaction of both nucleophilic groups with acetyl groups on one face of **1**. On the other hand, primary diamines with more flexible structure and higher nucleophilicity furnished 1,6-diacetylglycoluril **2b** in acceptable yields.

Table 1
Reaction of bifunctional nucleophiles with **1** at room temperature

Nucleophile	**2a**/**2b**[c]
Pyrocatechol, K_2CO_3[a]	100:0
o-Phenylenediamine[b]	100:0
m-Xylylenediamine[b]	55:45
Ethylenediamine[b]	59:41

[a] In CH_3CN.
[b] In CH_2Cl_2.
[c] Product ratio based on NMR.

Separation of **2b** from 1,4-diacetylderivative **2a** was achieved by the fractional crystallization from glacial acetic acid (Scheme 1). This simple separation procedure allows the preparation of desired product on a multigram scale.



Scheme 1. Reaction of **1** with nucleophilic reagent.

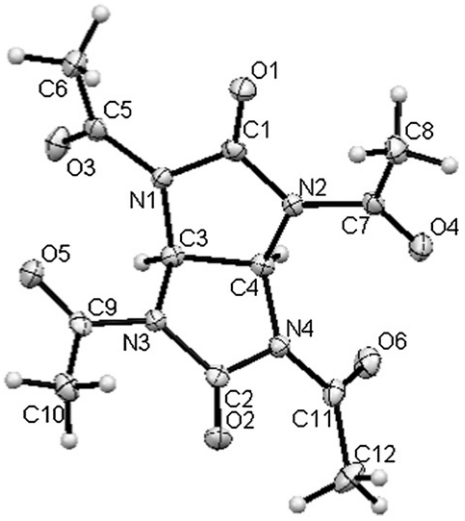
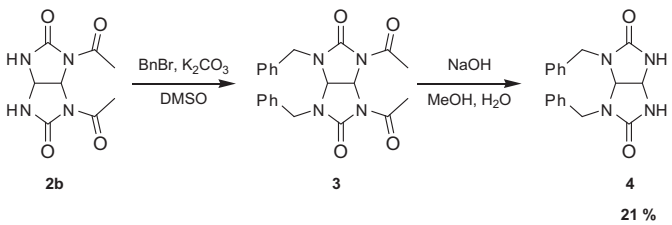


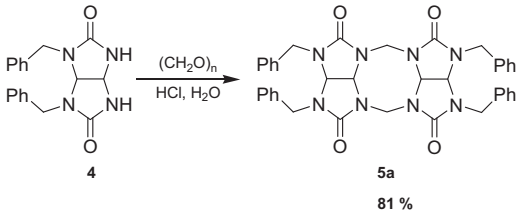
Fig. 2. ORTEP representation of the crystal structures of **1**.[14]

Glycoluril **2b** was used for the synthesis of 1,6-dibenzylglycoluril **4**. First, it was alkylated with benzylbromide in the presence of K_2CO_3 in DMSO (Scheme 2). Resulting acetylglycoluril **3** was subsequently hydrolyzed without the isolation to furnish 1,6-dibenzylglycoluril **4**. Note that the use of stronger base (*t*-BuOK) in the alkylation step resulted in the rearrangement and 1,4-dibenzylglycoluril was formed as a side-product.



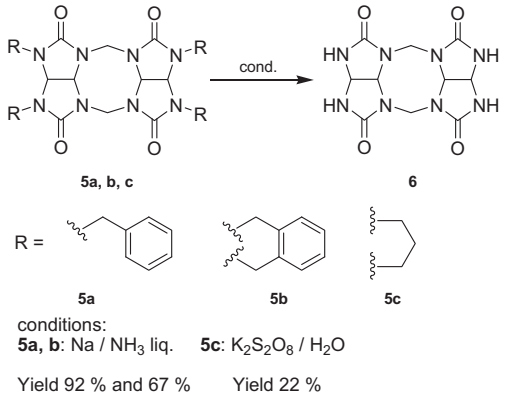
Scheme 2. Synthesis of 1,6-dibenzylglycoluril **4**.

Since we had a relatively high yielding method for the preparation of 1,6-dibenzylglycoluril **4**, we prepared the smallest glycoluril oligomer, the dimer, reaction between glycoluril **4** and paraformaldehyde in concd HCl resulted in the formation of dimer **5a** in 81% yield (Scheme 3).



Scheme 3. Preparation of protected glycoluril dimer **5a**.

Deprotecting of the dimer **5a** was achieved by the dissolving metal reduction using sodium in liquid ammonia (Scheme 4). This methodology is commonly used for the deprotection of benzylamides.[6] Deprotected dimer[4b,5e] **6** was isolated in 92% yield. The same deprotecting protocol could be used also in the case of *o*-xylyleneglycoluril dimer **5b**. Dimer **5b** was originally suggested as an easily accessible protected dimer,[5b] and deprotected dimer **6** was obtained in 67% yield.



Scheme 4. Deprotection of protected dimers.

During our previous work on the synthesis of glycoluril dimers, we prepared propyleneglycoluril dimer **5c**.[5b] Simple alkyl groups are not generally considered as protecting groups. Nevertheless, few examples could be found in literature.[15] It is also known that simple alkylamides are dealkylated by the action of potassium persulfate ($K_2S_2O_8$).[16] We have found, that $K_2S_2O_8$ could be also used for deprotecting of **5c**. Deprotected dimer **6** was easily isolated by filtration from water soluble side-products. Unfortunately, the yield is rather low. Based on HPLC–HRMS studies we determined that those water soluble side-products corresponds to propyleneglycoluril dimers substituted in positions 3*a* and 6*a* with hydroxyl groups. Major product was tetrahydroxylated and trihydroxylated propyleneglycoluril dimer. Minor product was dihydroxylated dimer, while monohydroxylated dimer was present only in traces. Formation of these side-products was not surprising as similar reaction conditions were used by Kim and co-workers for the preparation of hydroxylated cucurbiturils.[17]

Please note that the deprotected dimer **6** can be easily obtained by the condensation of glycoluril and formaldehyde.[4b,5e] Nevertheless, the direct preparation of higher deprotected glycoluril oligomers is very difficult compared to the easy preparation of the protected analogs e.g., *o*-xylyleneglycoluril trimer.[5c] Therefore, the demonstrated deprotection should be understood as a proof of the concept for future applications.

3. Conclusions

In conclusion, we have developed method for the preparation of 1,6-diacetylglycoluril. This glycoluril derivative was used for the selective preparation of 1,6-dibenzylglycoluril. New methods for the deprotection of glycoluril dimers have been also demonstrated.

4. Experimental section

4.1. General

All reagents were purchased from commercial sources and were used without further purification. Melting points were determined using Kofler block. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance 300 spectrometer. Chemical shifts were measured using the δ scale with TMS or residual solvent signal as a standard. LC-HRMS measurements were performed with Waters Micromass Q-TOF micro spectrometer. IR spectra were recorded using Mattson ATI Genesis FT-IR spectrometer. X-ray diffraction data were collected on a KUMA KM-4 κ-axis CCD diffractometer with Mo Kα radiation (λ=0.71073 Å). The temperature during data collection was 120(2) K. The structure was solved by direct methods and refined by full-matrix least-squares methods using ShelXTL software. The thermal ellipsoids in figure were drawn at the 50% probability level.

*4.1.1. 1,3,4,6-Tetraacetylglycoluril (**1**).* $HClO_4$ (70% aqueous solution; 3.5 mL) was added dropwise to the suspension of glycoluril[1c] (50.0 g; 0.35 mol) in Ac_2O (331 mL; 357.3 g; 3.5 mol; 10 equiv) under cooling with water bath. The temperature did not exceed 40 °C, and the solids gradually dissolved to form yellow solution. Reaction mixture was stirred at room temperature, under a calcium chloride stopper overnight. Separated solid material was filtered off and washed three times with 100 mL of water, affording of a 64.6 g white crystalline solid. A second crop was obtained by concentration of the mother liquor to approx. 2/3 of the volume followed by overnight crystallization providing an additional 22.6 g. Total yield 80%. Mp dec above 180 °C (lit.[11a] 234–238 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ=6.55 (s, 2H, CH), 2.54 (s, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.6 (C=O acetyl), 150.7 (C=O glycoluril), 61.9 (CH), 24.9 (CH_3). IR (Nujol): ν=2973, 2879, 2839, 1805, 1753, 1733, 1702, 1436, 1361, 1297, 1266, 1216, 1189, 1097, 1035, 987, 921, 779 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $[C_{12}H_{14}N_4O_6+H]^+$ 311.0992, found 311.0967.

*4.1.2. 1,4-Diacetylglycoluril (**2a**).* 1,3,4,6-Tetraacetylglycoluril **1** (22.6 g; 72.8 mmol) was dissolved in dichloromethane (400 mL). A solution of ethylenediamine (5.42 mL; 4.87 g; 81.0 mmol; 1.1 equiv) in dichloromethane (30 mL) was added dropwise over 15 min, and the resulting mixture was stirred at room temperature for 3 days. The resulting solid was filtered off, washed three times with 80 mL of water and once with 40 mL of acetone to remove acetylated ethylenediamine. The dried solid (13.4 g) was recrystallized from 200 mL of glacial acetic acid, filtered off and washed with Et_2O, affording a white crystalline solid 5.03 g (30%). Analytical sample was recrystallized from glacial acetic acid. Mp >300 °C (lit.[11a] 328–330 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ=8.85 (s, 2H, NH), 5.66 (s, 2H, CH), 2.35 (s, 6H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ=169.6 (C=O acetyl), 153.8 (C=O glycoluril), 61.8 (CH), 23.1 (CH_3). IR (Nujol): ν=3269, 2965, 2944, 2886, 2869, 2844, 1760, 1667, 1445, 1380,

1346, 1320, 1239, 1163, 1071, 974, 872, 770, 724 cm^{-1}. HRMS (ESI^+) *m/z* calcd for $[C_8H_{10}N_4O_4+H]^+$ 227.0780, found 227.0773.

*4.1.3. 1,6-Diacetylglycoluril (**2b**).* The acetic acid mother liquor from the previous reaction (**2a**) was evaporated to dryness (Caution, foaming!). The resulting solid (8.45 g) was recrystallized from glacial acetic acid (100 mL), filtered off, washed with Et_2O and recrystallized from glacial acetic acid, affording a white crystalline solid 3.40 g (21%). Attempts to isolate more of the 1,6-derivative from mother liquor by repeated crystallization failed. Mp dec above 210 °C ^1H NMR (300 MHz, DMSO-d_6): δ=8.69 (s, 2H, NH), 6.44 (d, *J*=7.2, 1H, CH), 5.25 (d, *J*=7.2, 1H, CH), 2.31 (s, 6H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=168.9 (C=O acetyl), 154.7 (C=O glycoluril), 65.9 (CH), 59.0 (CH), 24.1 (CH_3) ppm. IR (Nujol): ν=3268, 3218, 2976, 2923, 2881, 2835, 1776, 1754, 1694, 1462, 1381, 1328, 1235, 1152, 1076, 978, 865, 782, 737 cm^{-1}. HRMS (ESI^+) *m/z* calcd for $[C_8H_{10}N_4O_4+H]^+$ 227.0780, found 227.0781.

*4.1.4. 1,6-Dibenzylglycoluril (**4**). Method A*: 1-Benzylglycoluril[18] (2.50 g, 10.7 mmol) was dissolved in dry DMF (110 mL). NaH (60% dispersion in mineral oil, 0.40 g, 10.7 mmol, 1 equiv) was added, and the resulting mixture was stirred at room temperature until the evolution of gas ceased. Benzylchloride (1.35 mL, 1.50 g, 11.8 mmol, 1.1 equiv) was added followed by KI (1.78 g, 10.7 mmol, 1 equiv), and the reaction mixture was heated to 80–90 °C for 12 h. DMF was evaporated and residue was separated by column chromatography (silica, CH_2Cl_2/MeOH 10:1) affording 0.25 g of a yellowish crystalline solid (7%), which was recrystallized from MeOH.

Method B: 1,6-Diacetylglycoluril **2b** (0.50 g, 2.21 mmol) was dissolved in dry DMSO (5 mL). Benzylbromide (0.55 mL, 0.79 g, 4.64 mmol, 2.1 equiv) was added, followed by K_2CO_3 (0.64 g, 4.64 mmol, 2.1 equiv). The reaction mixture was heated to 80 °C under an argon atmosphere for 17 h, diluted with EtOAc (50 mL) and washed three times with water (50 mL) and once with brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated to give 0.62 g of yellow oil, which was redissolved in methanol (20 mL). A solution of NaOH (0.30 g, 7.5 mmol) in water (20 mL) was added, and the resulting mixture was heated to reflux for 2.5 h. Methanol was evaporated and the resulting crystalline material was filtered off and washed with water. White to yellow crystals (0.15 g, 21%). Mp 197–200 °C ^1H NMR (300 MHz, DMSO-d_6): δ=7.64 (s, 2H, NH), 7.33–7.08 (m, 10H, CH arom.), 5.26 (d, *J*=8.5, 1H, CH), 4.98 (d, *J*=8.5, 1H, CH), 4.48 (d, *J*=16.1, 2H, CH_2), 3.98 (d, *J*=16.1, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=159.7 (C=O), 137.5 (C arom.), 128.5 (CH arom.), 127.2 (CH arom.), 127.1 (CH arom.), 70.7 (CH), 60.4 (CH), 45.1 (CH_2) ppm. IR (Nujol): ν=2970, 2923, 2907, 2880, 2838, 1719, 1694, 1455, 1375, 1351, 1239, 1127, 1072, 960, 885, 720, 700 cm^{-1}. HRMS (ESI^+) *m/z* calcd for $[C_{18}H_{18}N_4O_2+H]^+$ 323.1508, found 323.1507.

Note: In the case of larger charges, the final product may contain 1-benzylglycoluril as an impurity. This impurity could be easily removed by trituration with boiling water.

*4.1.5. Tetrabenzylglycoluril dimer (**5a**).* Concentrated hydrochloric acid (4 mL) was added to the mixture of 1,6-dibenzylglycoluril **4** (0.36 g, 1.11 mmol) and paraformaldehyde (33.5 mg, 1.11 mmol). The resulting mixture was heated to 80 °C (bath temperature) with stirring for 1.5 h (After approx. 20 min yellow gummy material formed.) The mixture was then evaporated and residue was triturated with toluene (60 mL). The resulting solid was filtered off, washed with toluene and Et_2O, to give 0.30 g of an off-white solid (81%). Mp 288–289 °C (dec). ^1H NMR (300 MHz, DMSO-d_6): δ=7.35–7.11 (m, 20H, CH arom.), 5.80 (d, *J*=14.7, 2H, NCH_2N), 5.46 (d, *J*=8.7, 2H, CH), 5.05 (d, *J*=8.7, 2H, CH), 4.46 (d, *J*=16.2, 4H, CH_2 benzyl), 4.27 (d, *J*=14.7, 2H, NCH_2N), 4.07 (d, *J*=16.2, 4H, CH_2 benzyl) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=156.9 (C=O), 136.9 (C arom.), 128.5 (CH arom.), 127.3 (CH arom.), 127.2 (CH arom.), 70.8 (CH), 67.9 (CH), 52.6 (NCH_2N), 46.1 (CH_2 benzyl) ppm. IR (Nujol): ν=2953, 2925, 2854, 1710, 1474, 1451, 1382, 1320, 1220, 1130, 955, 807, 793, 737 cm^{-1}. HRMS (ESI^+) *m/z* calcd for $[C_{38}H_{36}N_8O_4+H]^+$: 669.2938, found: 669.2952.

*4.1.6. Glycoluril dimer (**6**). Method A*: Glycoluril dimer **5a** or **5b**[5b] (0.39 mmol) was added to liquid ammonia (20 mL) and the resulting mixture was cooled to −40 to −45 °C. Sodium metal (0.28 g, 12.48 mmol, 32 equiv) was added portionwise over 5 min. The resulting dark blue mixture was stirred with a glass coated magnetic stirring bar at −45 to −40 °C for additional time (30 min–1 h), before solid NH_4Cl (0.66 g) was slowly added. (The temperature did not exceed −35 °C during addition of NH_4Cl.) The reaction mixture was left to reach room temperature, the resulting white solid was mixed with water, filtered off, washed with water, acetone, and Et_2O. Yield 92% and 67%, respectively.

Method B: Propyleneglycoluril dimer[5b] **5c** (0.2 g; 0.515 mmol) was mixed with a solution of $K_2S_2O_8$ (0.69 g; 2.57 mmol; 5 equiv) in 25 mL of water. A slow stream of nitrogen was passed through the resulting mixture for 1 h. Then, the mixture was heated to 80 °C for 16 h under nitrogen, the resulting solid was filtered off and washed with water and acetone. 35 mg Beige solid (22%). Mp >300 °C. ^1H NMR (300 MHz, DMSO-d_6): δ=7.60 (s, 4H, NH); 5.60 (d, *J*=14.5, 2H, CH_2), 5.35 (d, *J*=8.5, 2H, CH), 5.23 (d, *J*=8.5, 2H, CH), 4.03 (d, *J*=14.5, 2H, CH_2) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=157.8 (C=O), 74.1 (CH), 60.1 (CH), 51.2 (CH_2) ppm. IR (Nujol): ν=3599, 3534, 3214, 3079, 2921, 2825, 1760, 1704, 1491, 1404, 1329, 1293, 1243, 1189, 1108, 959, 884, 800, 724 cm^{-1}. HRMS (ESI^+) *m/z* calcd for $[C_{10}H_{12}N_8O_4+H]^+$ 309.1060, found 309.1055.

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Supplementary data

^1H and ^{13}C NMR spectra of compounds **1**, **2a**, **2b**, **4**, **5a**, **6** and cif of **1**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.097.

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