Tetrahedron Letters 51 (2010) 4328–4330

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Novel nanoscaled molecular rods consisting of seven annulated heterocycles as scaffold for multiple sugar units

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ARTICLE INFO

*Article history:*
Received 11 May 2010
Revised 4 June 2010
Accepted 8 June 2010
Available online 15 June 2010

Dedicated to Prof. Dr. Karl Gewald on the occasion of his 80th birthday

*Keywords:*
Carbohydrates
Click reaction
Condensed heterocycles
Cyclization
Cycloaddition

ABSTRACT

A nanoscaled molecular rod consisting of a novel heterocyclic system of seven annulated heterocycles was obtained in a straight forward way. It served as a scaffold for eight functionalized 1,2,3-triazoles established by multiple alkyne–azide click reaction affording nanoobjects which are surrounded by carbohydrate shells.



Nanoscaled molecular rods have gained wide interest during the last two decades.[1–3] In such scaffolds a number of stiff building blocks are connected to each other by one or two bonds. The majority of such structures comprise π-systems such as arenes, heteroaromatics, alkynes, and alkenes connected to each other by one bond thus giving larger linear products of extended π-conjugation. Similarly, also saturated cyclic building blocks can be arranged forming nanorods.[4] When spiro connection is used for the formation of nanorods two bonds starting from the same atom fix the building blocks together.[1,5] Connection of nanorod building blocks by two bonds is also possible in a ladder-like arrangement such as in [*n*]acenes, where the connecting bonds are found at adjacent atoms.[1] We disclose here a novel nanosized rod shaped system **5** consisting of seven annulated heterocycles. Because of the presence of several functional groups, this system has a potency to act as a scaffold for tethering up to eight functions to it. They can also be expected to serve as cores for dendrimer formation by covalent bonds.

We recently found a straight forward access to tetrahydropyridothienopyrimidines by constructing a pyrimidine ring starting from a piperidine-annulated 2-aminothiophene-3-carboxamide system[6] which itself was obtained by Gewald reaction.[7,8] Reaction of this system with chloroacetyl chloride led to chloroacetylation of the amino group and the resulting amide **1** was further dehydrated by catalysis with *p*-toluenesulfonic acid in refluxing toluene to the pyrimidone **2** (Scheme 1).[6] Later on, we tried to achieve similar cyclization under basic conditions by sodium ethoxide resulting in the formation of the pyrimidone ring with additional replacement of chloride by ethoxide giving the ethyl ether **3**.[6] In order to maintain the chloride for other substitution reactions we treated the chloroacetamide **1** with just one equivalent of sodium ethoxide. Remarkably, the heptacyclic annulated system **4** was obtained by forming a piperazine ring. This result can be rationalized by base-catalyzed formation of the chloromethylpyrimidone **2** which later on reacts with a second molecule of **2** to form a pyrazine ring as a linker of the two parent heterocyclic precursors. Indeed, treatment of **2** with traces of sodium ethoxide gives also the heptacyclic system **4**. The heptacyclic core of **4** represents a novel annulated heterocyclic system with the systematic name of pyrido[4′,3′:4,5]thieno[2,3-d]pyrido[4‴,3‴:4″,5″]thieno [2″,3″:4′,5′] pyrimido[1′,2′:4,5]pyrazino[1,2-*a*]pyrimidine. In this context it is worth mentioning that pyrazines are also found in naturally occurring pharmacologically active cephalostatins wherein fused carbocyclic rings are linked together by this heterocycle.[9] On the other hand, even the bispyrimidopyrazine substructure of **4** is very rare in the heterocyclic literature.[10]

Since the synthesis of the heterocyclic system **4** is straight forward and also allows to prepare larger quantities further synthetic applications were envisaged, for example, to use this system as a molecular scaffold for various functions. For such applications

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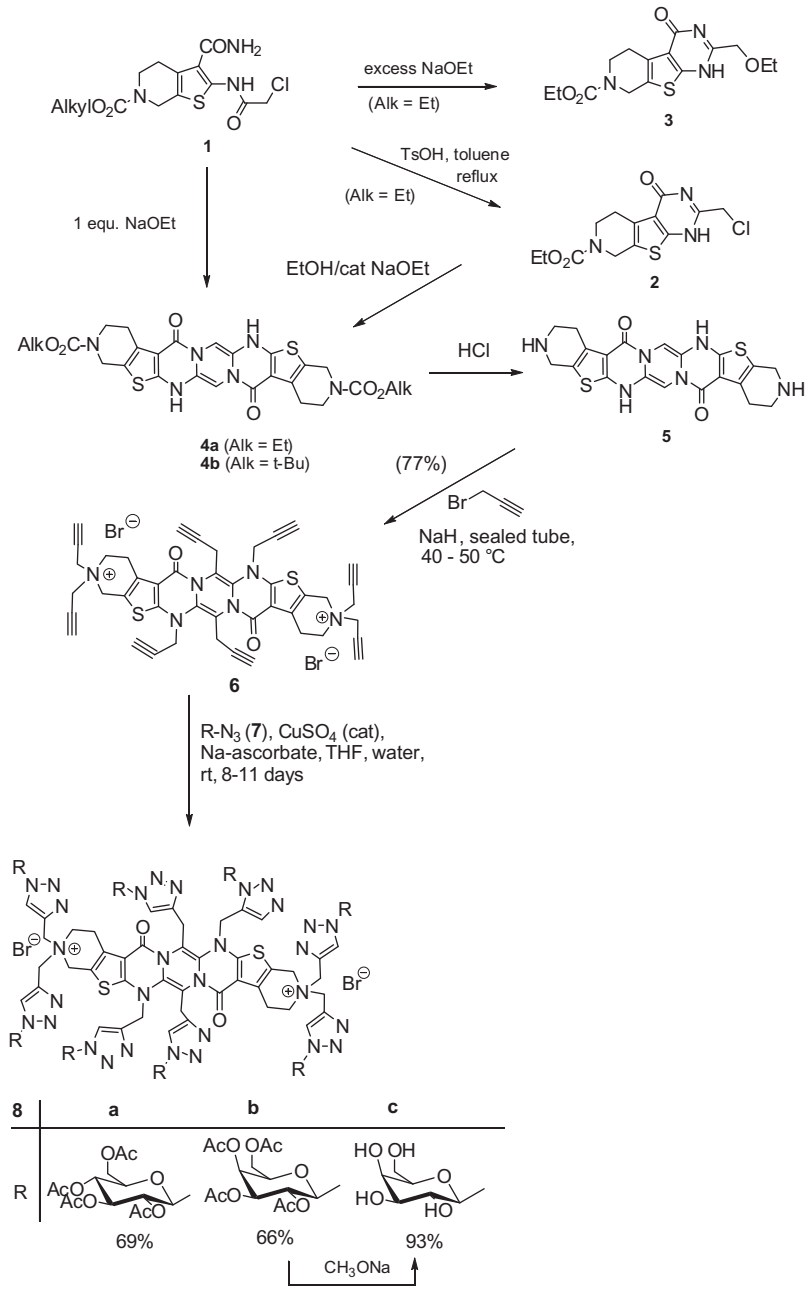
doi:10.1016/j.tetlet.2010.06.040




**Scheme 1.** Synthesis of carbohydrate-heterocycle conjugates **8**.

reactive nucleophilic sites are available at the N-atoms of the pyrimidine and/or the CH-positions of the pyrazine rings. One could further think of increasing the number of nucleophilic tethering sites at the heptacyclic system **4** by N-deprotecting of the tetrahydropyridine moieties (Scheme 1). This turned out to be difficult with the ethyl carbamate **4a** (Alk = Et) whereof only mixtures of products were obtained under basic conditions containing the expected product **5** together with the starting material and the monodeprotected derivative. On the other hand, acid treatment (diluted HCl or TFA) of the Boc-protected heptacycle **4b** (Alk = *t*-Bu) provided high yields of the envisaged product **5**. According to MM2-calculations this heptacyclic system **5** exceeds 1.5 nm in its largest extension. In order to enable tethering of functionalities by Cu-catalyzed alkyne–azide cycloaddition propargyl functions were introduced into **5**. The eightfold propargylated dicationic ammonium salt **6** was obtained by reaction with propargyl bromide in the presence of sodium hydride in a sealed tube. The placement of the eight propargyl groups in the highly symmetric structure **6** is confirmed by the NMR spectra wherein three types of propargyl signals are found in a ratio of 2:2:4.[11] With the alkyne **6** in hand we pursued linking monosaccharides as first examples of biomolecules to the heptacyclic core system by Cu-catalyzed cycloaddition with azides **7** to obtain octaglycosyl products **8** (Scheme 1). Excess of azides **7** was used and reaction times had to be sufficiently long (9–11 days) to omit isolation of mixtures of **8** and intermediates wherein not all propargyl groups of **6** had been transformed into 1,2,3-triazoles. The possibility of splitting off the acetyl groups from products **8** to deliberate the free OH groups of the sugar units was checked with the galactose derivative **8b**. Treatment with catalytic amounts of sodium methoxide in methanol at room temperature gave rise to the formation of the envisaged product **8c** in excellent yield.[12] Products **8** appeared

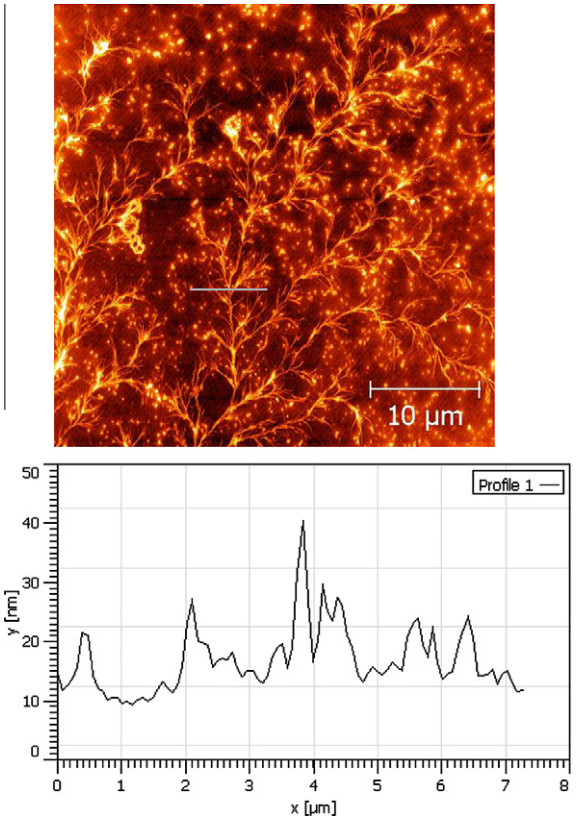



**Figure 1.** AFM-image of **8c** on glass (sample obtained from aqueous solution).

as colorless solids and were characterized by HPLC–HRMS and NMR spectroscopy. MM2 geometry-optimized structure of the octagalactosyl product **8c** revealed a flat rod-like structure (not shown), which ranges over approximately 3 nm in its largest extension. Its rim is almost entirely covered by the carbohydrate moieties. As compared with a recently published 'hard-core sugar ball' also consisting of a heterocyclic core and sugar molecules at the periphery our compounds exceed those structures by the number of sugar molecules considerably.[13] First AFM-investigations revealed that the octagalactose derivative **8c** forms interesting supramolecular structures resembling dendritic patterns on glass surfaces obviously by diffusion-controlled growth (Fig. 1). As can be seen in the profile these structures are not flat but three-dimensional reaching a maximum height of about 30 nm in the investigated region.

In summary, a novel nanorod-like heptacyclic condensed heterocyclic system **5** could be synthesized in a straight forward manner. This core could be equipped with eight tethering sites by propargylation having the potential to attach eight functions by Meldal–Sharpless click reaction. This potential was demonstrated as first example by tethering eight carbohydrate units to give novel monosaccharide conjugates **8**. Our ongoing activities are focused on the investigation of the properties of the new compounds **8**, such as the ability to capture ions or other polar species or to interact with surfaces. We further prove the possibility of linking other functions, for example, catalytic moieties or peptides to the heptacyclic heterocyclic scaffold **4** or **5**. In addition, the possibility to use the heptacyclic heterocyclic molecular rod **5** as cores for dendrimers by introducing oligofunctional moieties or to apply them as repeating units in the establishment of nanorods of extended sizes by reaction with suitable bifunctional electrophiles is under investigation.

## Acknowledgments

We thank Professor Dr. Klaus Rademann, Humboldt University, Berlin for providing AFM facilities. Donations of chemicals by Bayer Services GmbH & Co. OHG, BASF AG, and Sasol GmbH are gratefully acknowledged.

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11. *Octapropargyl product* **6**: 77% yield, mp 199 °C (dec). $^1$H NMR (DMSO-$d_6$): $\delta$ 2.95 (t, 4H, $J$ = 2.6 Hz, 4C–C*H*), 3.39 (br s, 4H, H-4,13), 3.76 (dd, 4H, $J_1$ = 2.2 Hz, $J_2$ = 2.6 Hz, 2C*H*$_2$–C–CH), 4.02 (m, 8H, H-3,12, 2C*H*$_2$–C–CH), 4.23 (t, 4H, $J$ = 2.2 Hz, 4C–C*H*), 4.69 (s, 8H, 4C*H*$_2$–C–CH), 5.05 (s, 4H, H-1,10). $^{13}$C NMR (DMSO-$d_6$): $\delta$ 20.9 (8C*H*$_2$–C), 27.8 (C-4,13), 49.6 (8C*H*$_2$–C), 54.3 (C-3,12), 55.6 (C-1,10), 67.5 (8CH$_2$–*C*), 70.7, 75.8, 77.7, 83.7 (8C–*C*H), 92.1 (C-7,16), 119.2 (C-4b,13b), 123.5 (C-9a,18a), 127.5 (C-4a,13a), 151.7 (C-8a,17a), 156.8 (C-7a,16a), 161.1 (C=O). HRMS (ESI): $m/z$ calcd $C_{44}H_{36}N_6O_2S_2$ [$M^{2+}$]: 372.1165, found: 372.1167.
12. *Octagalactose derivative* **8c**: Dry sodium methoxide/MeOH solution (0.1 equiv) (freshly prepared 1.0 M solution) was added to a stirred solution of the peracetylated galactose derivative **8b** (1 mmol) in MeOH at room temperature. The mixture was stirred overnight. The reaction was monitored by HPLC. Neutralization by addition of DOWEX 50 × 8 ion-exchange resin (pH 6) followed by filtration and evaporation of the filtrate to dryness afforded the pure unprotected product **8c** as colorless crystals (93%), mp 184–185 °C. $^1$H NMR ($D_2O$): $\delta$ 3.45–4.03 (m, 60H, H-1,10, 8C*H*$_2$–C$_{triazole}$, 8C$_5$H–C*H*$_2$–OH, 8C$_5$*H*–CH$_2$–OH, 8C$_2$*H*, 8C$_3$*H*), 4.27 (t, 4H, $J$ = 9.4 Hz, 4C$_4$*H*), 4.95 (m, 12H, H-3,12,4,13, 4C$_4$*H*), 5.38 (d, 2H, $J$ = 9.2 Hz, 2C$_1$H–N$_{triazole}$), 5.43 (d, 2H, $J$ = 9.2 Hz, 2C$_1$H–N$_{triazole}$), 5.79 (d, 4H, $J$ = 9.2 Hz, 4C$_1$H–N$_{triazole}$), 7.74 (s, 2H, 2CH$_{ar\text{-}triazole}$), 7.83 (s, 2H, 2CH$_{ar\text{-}triazole}$), 8.83 (s, 4H, 4CH$_{ar\text{-}triazole}$). $^{13}$C NMR ($D_2O$): $\delta$ 21.9 (C-4,13), 32.5 (2C*H*$_2$–C$_{triazole}$), 33.3 (2C*H*$_2$–C$_{triazole}$), 53.6 (C-3,12), 55.1 (4C*H*$_2$–C$_{triazole}$), 56.3 (C-1,10), 60.6, 60.7, 60.9 (8C$_5$H–C*H*$_2$–OH), 68.3, 68.5 (8C$_4$H), 69.4, 69.6, 69.8 (8C$_2$H), 72.9 (8C$_3$H), 77.9, 78.4 (8C$_5$H), 87.7, 87.8, 88.2 (8C$_1$H–N$_{triazole}$), 107.9 (C-7,16), 120.9 (C-4b,13b), 124.6 (4CH$_{ar\text{-}triazole}$), 124.7 (C-9a,18a), 127.4, 128.9 (4CH$_{ar\text{-}triazole}$), 135.1 (C-4a,13a), 141.2, 141.4 (8C$_{q\text{-}triazole}$), 151.7 (C-8a,17a), 159.6 (C-7a,16a), 162.0 (2C=O). HRMS (ESI): $m/z$ calcd $C_{92}H_{124}N_{30}O_{42}S_2$ [$M^{2+}$]: 1192.3960, found: 1192.3997.
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