ARTICLE IN PRESS

Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient method for the cycloaminomethylation of glycoluril

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ARTICLE INFO

Article history:
Received 8 February 2016
Revised 2 March 2016
Accepted 3 March 2016
Available online xxxx

Keywords:
Synthesis
Cycloaminomethylation
Glycoluril

ABSTRACT

The efficient method for the cycloaminomethylation of glycoluril to yield 2,6-di*tert*-butylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-dione is described. The material is synthesized employing water as the solvent, and is isolated by filtration. This is an improvement over the previous reported synthetic method, which relied on the use of samarium trichloride catalysis, as well as silica gel column chromatographic purification to obtain the target product.

Introduction

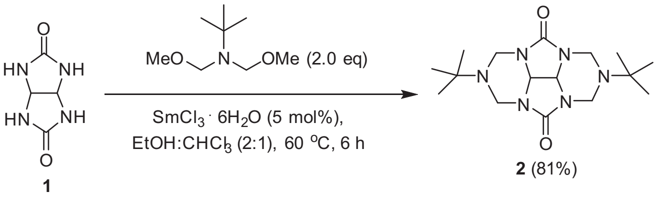
Glycoluril and/or its derivatives have been used in water treatment,[1] paints, and coatings,[2] as a slow-release nitrogen fertilizer,[3] in the synthesis of the hydrolytically unstable explosives dinitroglycoluril (DNGU)[4] and tetranitroglycoluril (TNGU).[5] In connection with an ongoing search to synthesize new energetic materials at the US Army Research Laboratory (ARL), attention has been focused on the synthesis of polynitrogen, tetracyclic compounds. The main compound of interest at this time is the glycoluril-derived tetracycle 2,6-di-*tert*-butylhexahydro-1*H*,5*H*-2,3a,4a,6,7a,8a-hexaazacyclopenta[*def*]fluorene-4,8-dione. Khairullina and coworkers reported that this aforementioned bis-1,3,5-triazinane fused aza heterocyclic compound could be synthesized by reacting glycoluril and *N*,*N*-bis(methoxymethyl)*tert*-butylhexanamine in the presence of catalytic samarium trichloride ($SmCl_3 \cdot 6H_2O$) to obtain the desired product.[6]

In synthesizing new materials at ARL, it is important that the materials can be prepared on a large scale in an efficient and cost-effective manner. Preferably, avoiding the use of organic solvents, expensive catalysts, and flash chromatography on silica gel would be ideal in achieving a cost-effective synthesis. With this in mind, we sought to develop an alternative synthesis to make fused aza heterocycles containing the bis-1,3,5-triazinane core unit.

Existing synthesis of bis-1,3,5-triazinane compounds

The synthesis of di-*tert*-butyl-bis-1,3,5-triazinane **2** was previously synthesized from glycoluril and *N*,*N*-bis(methoxymethyl) *tert*-butylhexanamine in the presence of catalytic $SmCl_3{\cdot}6H_2O$ (Scheme 1)[6] on a 10 mmol scale. Although no procedure and yield for the synthesis of *N*,*N*-bis(methoxymethyl)*tert*-butylhexanamine was given, it is assumed that this material was synthesized from *tert*-butylamine, formaldehyde, methanol, and KOH at refluxing temperatures.[7] In the Khairullina synthesis, silica gel column chromatography was required to obtain **2**.

Although the target molecule was prepared by this method, the presence of chlorinated organic solvents, the use of the samarium trichloride catalyst, and the need to use silica gel chromatography to purify the compound presents limitations from producing **2** economically on a large scale.



Scheme 1. Samarium trichloride-mediated synthesis of di-*tert*-butyl-bis-1,3,5-triazinane **2**.

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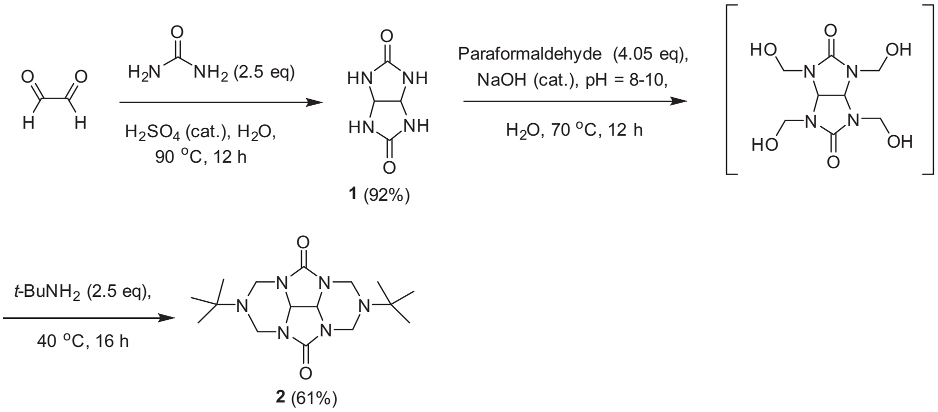
http://dx.doi.org/10.1016/j.tetlet.2016.03.013
0040-4039/Published by Elsevier Ltd.

Please cite this article in press as: Wingard, L. A.; et al. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2016.03.013



Scheme 2. Samarium-free synthesis of **2**.

Optimized synthesis of di-*tert*-butyl-bis-1,3,5-triazinane 2

The optimized synthesis commenced with an acid-catalyzed condensation of glyoxal and urea to afford glycoluril (**1**) in high yield after filtration. Rather than employing $SmCl_3 \cdot 6H_2O$ in the presence of *N*,*N*-bis(methoxymethyl)*tert*-butylhexanamine, glycoluril and paraformaldehyde were suspended in water, treated with a catalytic amount of NaOH, and heated to produce tetramethylol glycoluril. This material was not isolated, though addition of *tert*-butylamine and gentle heating led to the formation of **2**. Gratifyingly, this material did not require column chromatography for purification, but could simply be isolated by filtration without the need for further purification. The synthesis of **2** was carried out on a 176 mmol scale to yield 36 g of product on multiple occasions (see Scheme 2).

When synthesizing the tetramethylolglycoluril intermediate, pH control is essential. A pH of 8–10 is the best to achieve optimal yields. No reaction occurred if the pH was 7 and below. When the pH rose to 11 and above, poor yields of **2** were obtained.

Conclusions

In summary, an optimized and cost-efficient synthesis of **2** is described. Unlike the previous synthetic methodology, the new method detailed in this paper allows **2** to be synthesized from inexpensive commercially available starting materials. The use of *N*,*N*-bis(methoxymethyl)*tert*-butylhexanamine, $SmCl_3 \cdot 6H_2O$, chlorinated organic solvents and silica gel column chromatography is avoided. The aforementioned compound has been reproducibly synthesized on a 36 g scale. Although outside the scope of our current research interests, it is believed that the new methodology could be applied toward synthesizing other bis-1,3,5-triazinanes through the employment of other primary amines during the cyclization step.

Acknowledgments

Research was sponsored by the Army Research Laboratory was accomplished in part under Cooperative Agreement Number W911NF-12-2-0019. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing official policies, either expressed or implied, of the Army Research Laboratory or the U.S. Government. The U.S. Government is authorized to reproduce and distribute reprints for Government purposes notwithstanding any copyright notation herein.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.013.

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Please cite this article in press as: Wingard, L. A.; et al. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2016.03.013