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Multifunctionalized Glycolurils

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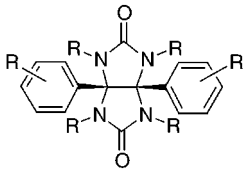
ABSTRACT



Synthetic approaches to a variety of substituted glycoluril compounds are presented herein. We have applied several of these compounds in the solution-phase synthesis of combinatorial libraries, and we have developed methods to differentiate individual reaction sites for the stepwise synthesis of individual polyfunctionalized compounds.

Glycolurils have found application in a number of settings, including light stabilization,[1] polymer cross-linking,[2] explosives,[3] and molecular recognition.[4] Previous work in this laboratory in the last of these applications[5] and in solution-phase combinatorial chemistry[6] led us to consider the glycoluril framework for use as a core molecule for the synthesis of combinatorial libraries.

We developed a series of glycoluril derivatives which allow functionalization at various positions about the core structure via amide linkages. Using either a one-pot reaction or a stepwise reaction sequence, we could synthesize either mixtures or individual compounds. The core molecules we envisioned were variously substituted glycoluril polyacids or polyacid derivatives, and three examples of such are shown in Figure 1. In each case, the bicyclic glycoluril centerpiece was formed by the condensation of 2 equiv of an appropriately substituted urea with benzil or a substituted benzil derivative.

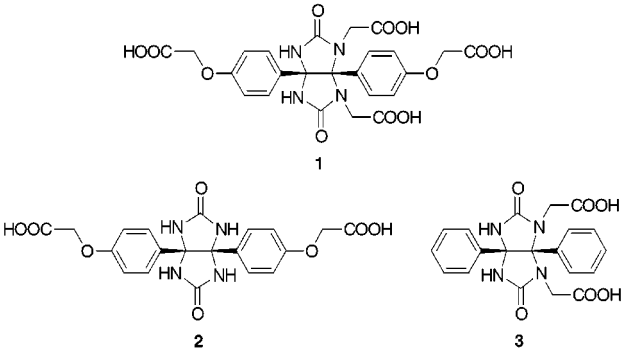


Figure 1. Three glycoluril polyacid core molecules.

The first member of this class, tetraacid **1**, can be synthesized by saponification of the corresponding tetraethyl ester. However, tetraacid **1** is so highly water soluble that

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(1) Krause, A.; Aumueller, A.; Korona, E.; Trauth, H. U.S. Patent 5,-670,613, 1997.
(2) Wang, A.; Bassett, D. U.S. Patent 4,310,450, 1982.
(3) (a) Fang, Y.; Wu, G. *Hanneng Cailiao* **1997**, *5*, 9. (b) Boileau, J.; Carail, M.; Wimmer, E.; Gallo, R.; Pierrot, M. *Propellants, Explos., Pyrotech.* **1985**, *10*, 118.
(4) (a) Dave, P. R.; Forohar, F.; Kaselj, M.; Gilardi, R.; Trivedi, N. *Tetrahedron Lett.* **1999**, *40*, 447. (b) Elemans, J. A. A. W.; de Gelder, R.; Rowan, A. E.; Nolte, R. J. M. *Chem. Commun.* **1998**, *15*, 1553. (c) Reek, J. N. H.; Wlwmans, J. A. A. W.; Nolte, R. J. M. *J. Org. Chem.* **1997**, *62*, 2234. (d) Murray, B. A.; Whelan, G. S. *Pure Appl. Chem.* **1996**, *68*, 1561. (e) Coolen, H. K. A. C.; van Leeuwen, P. W. N. M.; Nolte, R. J. M. *J. Org. Chem.* **1996**, *61*, 4739. (f) Sijbesma, R. P.; Nolte, R. J. M. *Top. Curr. Chem.* **1995**, *175*, 25.
(5) (a) Meissner, R.; Rebek, J., Jr.; de Mendoza, J. *Science* **1995**, *270*, 1485. (b) Valdez, C.; Spitz, U. P.; Toledo, L. M.; Kubik, S. W.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 12733.
(6) Pryor, K. E.; Shipps, G. W., Jr.; Skyler, D. A.; Rebek, J., Jr. *Tetrahedron* **1998**, *54*, 4107 and references therein.

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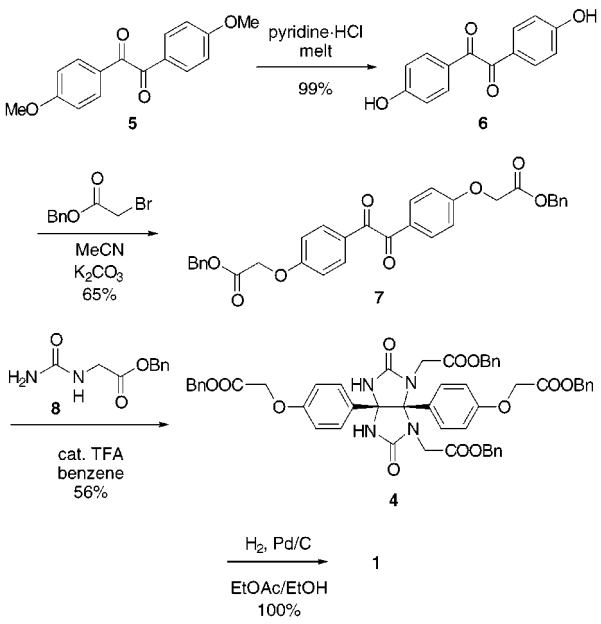
separation of the compound from the salt byproducts of the reaction was impossible. By replacing the ethyl esters with benzyl esters (compound **4**) and performing a hydrogenolysis instead of a saponification, we were able to access **1** cleanly and in high yield. This optimized procedure is shown in Scheme 1.

Scheme 1

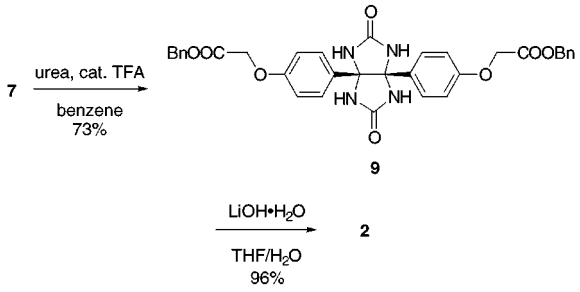


Following a published procedure, we demethylated commercially available anisil **5** with pyridine·HCl.[7] The resulting 4,4′-dihydroxybenzil **6** was then alkylated with benzyl bromoacetate to provide the requisite diketone **7** for condensation. The other partner in the condensation, benzyl hydantoate **8**,[8] is prepared in two steps from glycine by initial esterification with benzyl alcohol followed by conversion of the amino functionality into a urea upon reaction with KOCN in EtOH/H_2O. The TFA-catalyzed condensation is performed with azeotropic removal of water, and the resulting tetraester **4** is converted in quantitative yield to tetraacid **1** by catalytic hydrogenolysis.

Mindful of the remarkable water solublity of **1**, initial syntheses of other analogues with fewer acid substituents were originally based on the hydrogenolysis of the corresponding benzyl esters, as well. However, issues of solubility and product recovery limited yields for this step in both cases to approximately 35−55%.

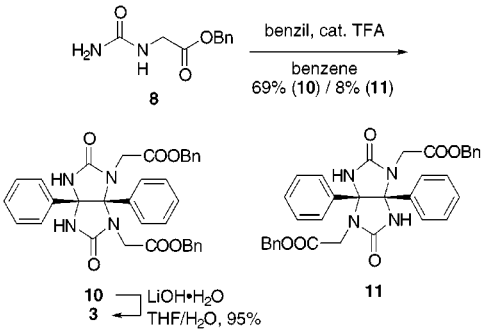
Fortunately, subsequent trials proved that the diacids were also less soluble in water than the tetraacid, so saponification of either the ethyl or benzyl esters was a viable option; yields of the saponification reactions are routinely greater than 90%. Condensation of substituted benzil **7** with urea yields glycoluril diester **9** (Scheme 2). Saponification of the diester with LiOH yields diacid **2**, which precipitates immediately upon pouring the reaction mixture into 1 M HCl.

Scheme 2



Similarly, benzyl hydantoate **8** can be condensed with benzil[9] to yield diester **10** (Scheme 3). Diacid **3** crystallizes upon chilling after pouring the reaction mixture into 1 M HCl after saponification of diester **10** with LiOH.

Scheme 3

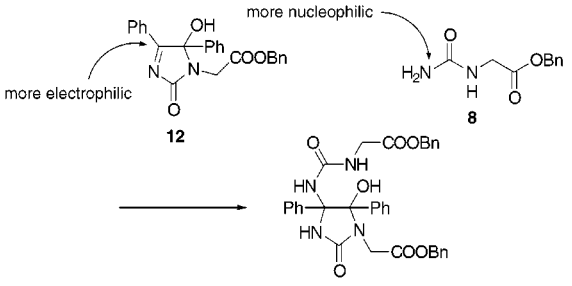


The *cis*-substituted product **10** is isolated in 63% yield, while the corresponding *trans*-substituted product **11** is produced in only 8% yield.[10] The two isomers can be isolated from the crude reaction mixture (after aqueous extraction) by selective crystallization.

Once the synthesis of the polyacids was accomplished, it became necessary to develop methodology to couple building

(7) Somin, I. N.; Kuznetsov, S. G. *Khim. Nauka I Prom.* **1959**, *4*, 801.
(8) Previously reported in Kotani, T.; Ishii, A.; Nhagaki, Y.; Toyomaki, Y.; Yago, H.; Suehiro, S.; Okukado, N.; Okamoto, K. *Chem. Pharm. Bull.* **1997**, *45*, 297.

(9) Substituted benzils have also been used to incorporate additional functional groups in the core molecules; see Supporting Information for an example.
(10) This is thought to be the result of the production of intermediate **12**, which, particularly under acidic conditions, reacts with a second equivalent of benzyl hydantoate **8** to preferentially form the *cis*-isomer.

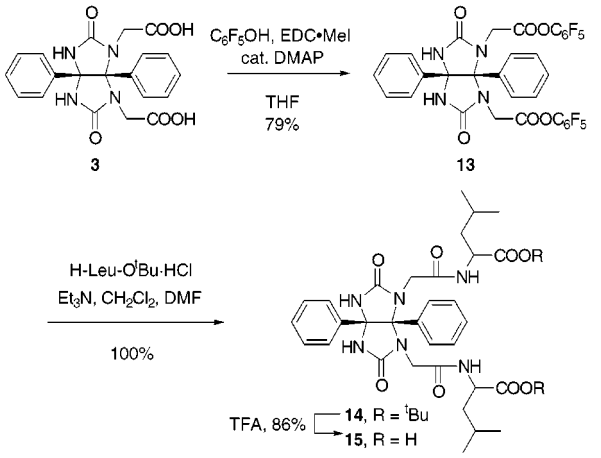


blocks to them in a clean, efficient manner. Historically,[6] activation of core acids as acid chlorides has been a simple, effective way to accomplish this goal. In the case of the glycoluril core molecules, however, the presence of the urea functionality precludes activation as acid chlorides.

Alternatives to acid chloride activation are, happily, numerous. One option is to make use of a coupling reagent to directly couple the amine building blocks to the polyacid core. Another option is to activate the acids on the core as some functional group other than as acid chlorides and isolate the activated core for use in a subsequent amidation step.

Exemplifying the latter route, we activated diacid **2** as the bis(pentafluorophenyl ester) **13** by coupling the diacid and pentafluorophenol with EDC·MeI and catalytic DMAP in THF (see Scheme 4).[11] The resulting active ester reacts

Scheme 4



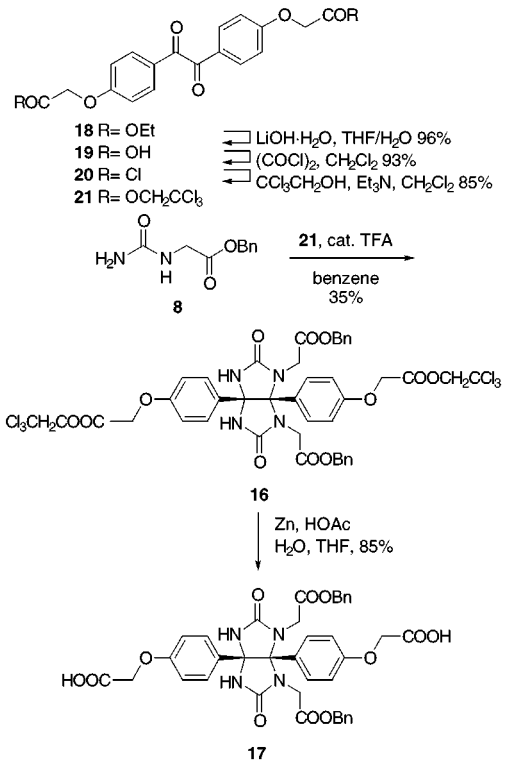
readily with a variety of amines, including relatively unreactive anilines.[12] Additionally, both unreacted excess amines and pentafluorophenol can be removed by aqueous extraction during workup. The glycoluril core is unaffected by the reaction conditions used for deprotection of *tert*-butyl ester derivatives of amino acids used as building blocks (neat TFA, 12 h), as demonstrated by the synthesis of bis(leucine *tert*-butyl ester) derivative **14** and its subsequent TFA deprotection to yield diacid **15**.

Attempts to synthesize libraries by the direct reaction between the polyacid cores and amine building blocks using coupling reagents have been stymied in many cases by our inability to clean the library of byproducts sufficiently. A number of coupling reagents have been used to test their efficacy, including DCC, EDC·MeI, PyBOP, PyBrOP, and DPPA. Many of the reactions worked fairly well, but it was impossible to purify the products completely without resorting to chromatography.[13]

To synthesize smaller libraries and individual compounds with the tetrasubstituted core molecule **1**, it is necessary to incorporate different protecting groups into the molecule that would allow orthogonal deprotection under conditions that would not epimerize amino acid substituents. The bis(2,2,2-trichloroethyl ester)/bis(benzyl ester) **16** provides us with this ability. Deprotection of the trichloroethyl esters yields the diacid/diester **17**; subsequent derivatization at the acid positions, followed by mild hydrogenolysis, yields a diacid for further reaction.

A synthetic scheme for diester/diacid **17** is shown in Scheme 5. The diethyl ester substituted benzil **18**[14] is

Scheme 5



saponified to **19** in almost quantitative yield with LiOH in aqueous THF. Conversion of this diacid to the diacid chloride **20** was accomplished using oxalyl chloride in good yield. Esterification with 2,2,2-trichloroethanol provided the protected dione **21**.

The dione was condensed with benzyl hydantoate **8** to yield the differentially protected glycoluril **16**. Deprotection of the trichloroethyl esters was accomplished by treatment with zinc and acetic acid to give the diacid **17**. Attempts to condense the free diacid **19** in a glycoluril-forming reaction

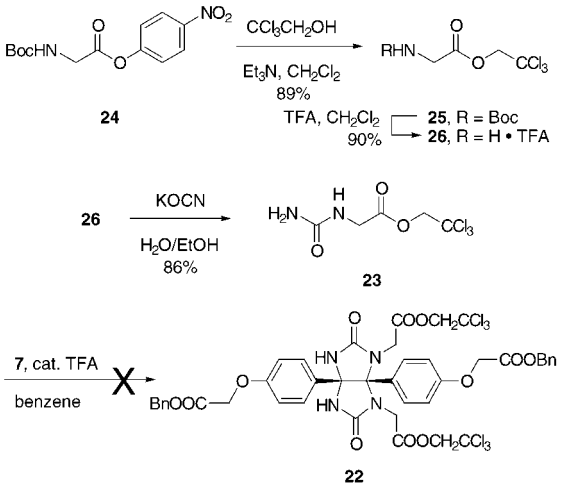
(11) Similar methodology can be applied to other polyacid glycoluril core molecules, as described in the Supporting Information.

(12) Mass spectroscopy of libraries formed by the reaction of the glycoluril core with aniline and several other single amines showed that all three masses expected for the two homo- and the heterosubstituted products were present.

(13) The synthesis of bis(leucine) adduct **14** by reaction of diacid **2** with H-Leu-O^{t}Bu·HCl under the action of DPPA is described in the Supporting Information. In this and a few other cases (with other cores, amines, and coupling reagents), the reaction was sufficiently clean to allow nonchromatographic workup.

(14) Diethyl ester **18** is prepared in a manner similar to that of dibenzyl ester **7**, with the substitution of ethyl bromoacetate as the alkylating agent. The dibenzyl ester should be able to be used interchangeably in this reaction.

Scheme 6



only met with success when unsubstituted urea was used, yielding glycoluril diacid **2**.[15] In several attempts with benzyl hydantoate, the acid-catalyzed cyclization of the hydantoate to give hydantoin proceeded to the exclusion of the desired condensation; it is thought that the poor solubility of diacid **19** in the reaction medium is to blame.

(15) See Supporting Information.

A synthesis of the "reverse" glycoluril **22** (Scheme 6), in which the benzyl and trichloroethyl esters are switched relative to compound **16**, also met with failure. The trichloroethyl hydantoate **23** (available in three steps from *N*-α-Boc-L-glycine-4-nitrophenyl ester **24**) is more labile to hydantoin formation than the benzyl analogue, and glycoluril formation was not competetive in this case, despite the favorable solubility properties of the reactants.

In summary, we have developed methodologies for the preparation of a variety of differently substituted glycolurils and have applied these methods in the construction of solution-phase combinatorial libraries. Glycoluril intermediates with orthogonal protecting groups for the synthesis of individual compounds have also been produced. Current progress in our laboratory is directed toward the expansion of the linker chemistries available for the introduction of building blocks on the glycoluril skeleton and will be reported in due course.

Acknowledgment. We thank the Skaggs Research Foundation and Novartis AG for financial support.

Supporting Information Available: Experimental procedures and analytical information for compounds **1**−**4**, **7**−**11**, **13-21**, **23**, **25**, and **26** and glycolurils with other substitutions. This material is available free of charge via the Internet at http://pubs.acs.org.

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