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SYNTHESIS OF NEW GLYCOLURIL DERIVATIVES VIA RING-CLOSING METATHESIS

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Abstract – Tetra-*N*-allylation of glycoluril reactions followed by ring-closing metathesis has been used to generate new concave-shaped glycoluril derivatives. The advantages of this method are mild conditions, single-product formation and good yield.

Due to the growing number of applications of glycoluril derivatives in supramolecular chemistry, their synthetic study has received a great deal of attention from organic chemists.[1] Glycoluril is a fundamental component of well-known supramolecular hosts, such as cucurbiturils,[2] bambusurils,[3] molecular clips,[4] energetic materials[5] and propellanes.[6a] Also, it is a useful building block for assembling molecular machines.[6b] Moreover, copolymerized glycoluril is used for metal nanoparticles and polymeric supports.[6c] Diphenylglycoluril-based molecular clips have diverse functions including acting as receptors for resorcinols, ammonium ions, amino acids, and enzyme mimics.[7a] Glycoluril attaches precisely to different metal ions and organic compounds and these entities are found to be useful in a wide range of processes, such as catalysis, as an antibacterial, neurotropic, anxiolytic agents, explosives, flame-resistant materials and gelators.[7b-d]

Recently Chandra and co-workers reported diphenylglycoluril **1** as an organocatalyst for the chemoselective *N-tert*-butoxycarbonylation of a variety of aliphatic/aromatic/heterocyclic amines.[8] Tetranitroglycoluril (TNGU) **2** has the potential to be explosive with a high detonation velocity and useful energetic molecule with high density recorded for known C, H, N, and O-based compounds.[9] Ryzhkina *et al*. reported the pharmacological activity of glycoluril **3**, which shows a neurotropic effect[10] (Figure 1). Pentazapropellane was found to be the main structural unit of some natural products.[11] Glycoluril tetrakisbutane-1-sulfonic acid (GTBSA) **5** seems to be a reusable catalyst used for the synthesis of a range of novel mono- and bis-

spiropyrans.[12] Moreover, the Isaacs group synthesized a molecular clip such as **6** with extended ethynylated *o*-xylylene sidewalls which exhibits strong fluorescence emission.[13] In view of the varied applications of glycoluril derivatives, there is a real need to develop simple synthetic methods for new glycoluril derivatives.

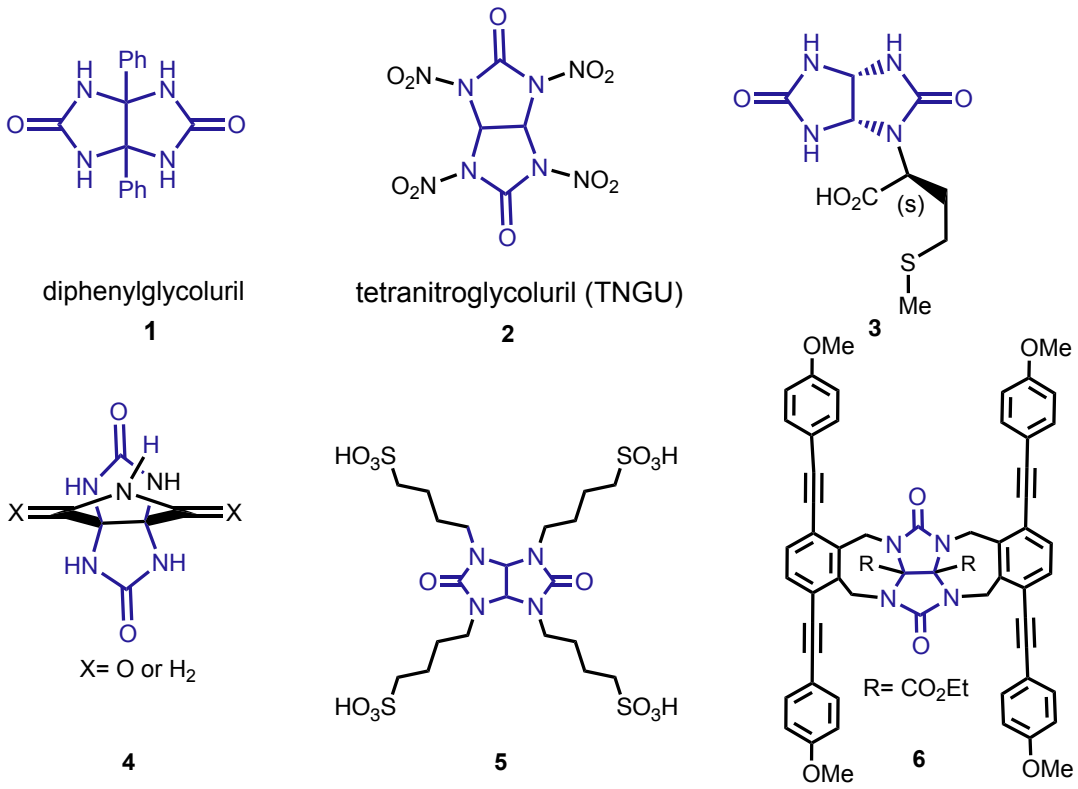
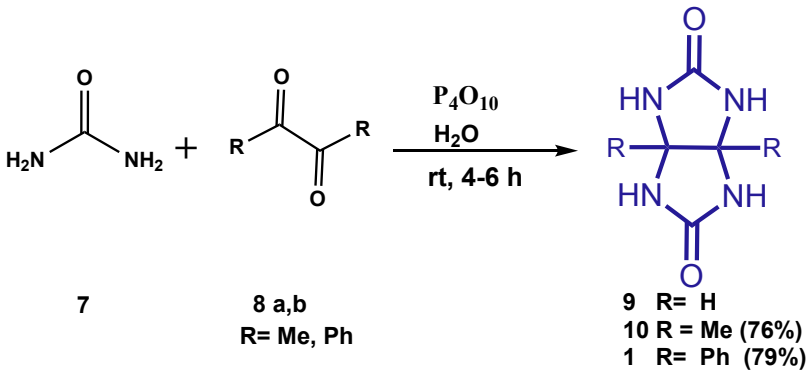


Figure 1. Glycoluril containing useful materials

In view of our interest in preparing carbocycles and heterocycles via C-C bond formation,[14a] we identified metathesis strategy is suitable for assembling new glycoluril-based molecules. Our study relies on the mild reaction conditions for synthesizing new symmetrical glycoluril scaffolds via ring-closing metathesis (RCM) as a key step.[14c,d] The double bond generated at the end of the metathesis sequence can be useful for further synthetic manipulation. It can be used as an additional handle for introducing other functional groups.

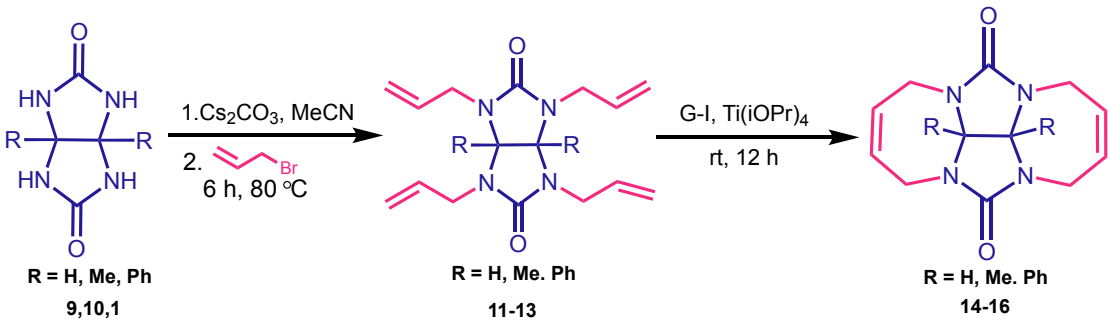
Our journey started with the preparation of various glycoluril derivatives based on the reported procedure.[15] This procedure involves the usage of water at room temperature where urea and 1,2-dicarbonyl compounds such as **8a, b** were reacted in the presence of phosphoric anhydride, which has a dual role as a condensing agent and a catalyst. The best yields (76% and 79%) were obtained when the reagents were added separately with the first addition of P_4O_{10} (1.5 mmol) to an aqueous solution of 1,2-dicarbonyl compounds **8a, b** (3.0 mmol) followed by the addition of urea **7** (9.0 mmol). Lower yields (50-60%) were obtained when the

reagents were dissolved simultaneously in water (Scheme 1).



Scheme 1

Having prepared two different glycoluril derivatives, the stage was set for *N*-allylation. An earlier report used a strong base such as *t*-BuOK in DMSO for tetra-allylation. Extraction of compound **11** from DMSO is a tedious task due to its high boiling point and water solubility. Therefore, we searched an alternative and mild conditions for this purpose. For tetra-*N*-allylation, we used mild conditions and the reaction of glycoluril was performed in acetonitrile in the presence of a weak base such as cesium carbonate (5 equiv), allyl bromide (4.50 equiv) to afford tetra-allyl products **11-13** in 6 h as a single product in 57% -74% yield. Olefin metathesis has received a great deal of attention over the last two decades due to the wide range of applications that are possible with commercially available and easy-to-handle catalysts. A variety of retrosynthetic paths are opened to carbocycles, polycyclics, and macrocycles by incorporating the RCM in their synthetic sequence.[16]

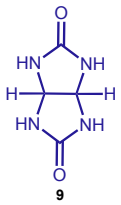
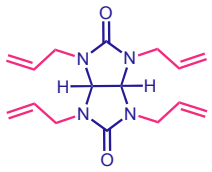
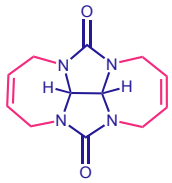
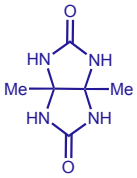
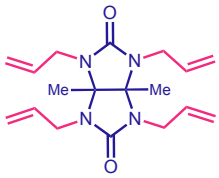
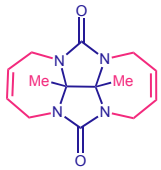
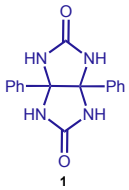
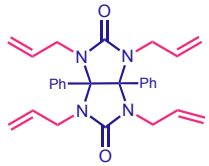
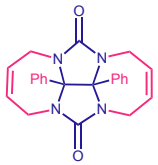


Scheme 2

Later RCM of tetra-allyl derivatives resulted in ring closure products such as **14**, **15** and **16**. Based on the above considerations, we prepared the tetra-allyl-glycoluril derivatives **11-13** which were further subjected to RCM using Grubbs first generation catalyst (G-I) in anhydrous DCM at rt in an inert atmosphere for 12-18 h resulting in low yield of the ring closure products (25%). A catalytic amount of Ti(*i*OPr)$_4$ was found

to be useful in generating the RCM products in an improved yield and obtained the products **14**, **15**, and **16** in better yield (73-77%) and required less reaction time. (Scheme 2) The interesting features of Ti(*i*OPr)$_4$ are; its inhibition of chelate formation between the substrate and catalyst and use of chelation to acquire suitable conformation of the substrate for cyclization.[17]

Table 1. Synthesis of glycoluril derivatives via RCM strategy

S.No.	Substrate	Allyl products	RCM products
1	 **9**	 **11 (65%)**	 **14** (72%)
2	 **10**	 **12 (57%)**	 **15** (68%)
3	 **1**	 **13 (68%)**	 **16** (77%)

The structures of compounds **11-16** were supported by NMR spectral data. The ^{1}H NMR spectrum of compound **14** contains a doublet proton signal due to the presence of CH_2 groups (3.67 and 4.47 ppm), a singlet signal of 4 -CH protons (5.71 ppm), and a singlet proton signal of 2x (-CH) groups (5.30 ppm). The ^{13}C NMR spectrum contains signals at δ127.1 (CH), 156.3 (CO), 69.1 (CH_2), and 41.6 ppm (CH) indicating the presence of symmetry element in the product. Later, the structure and stereochemistry of compound **14** were confirmed by single-crystal X-ray diffraction (XRD) study. (Figure 2)

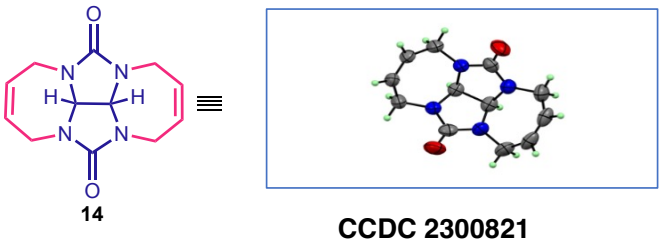


Figure 2. Single-crystal XRD structure of compound **14**

In conclusion, the synthesis of a novel class of glycoluril derivatives is realized. The aim of this strategy is to use mild reaction conditions to generate interesting glycoluril derivatives. Simple reactions like allylation and metathesis were used to create new molecules containing glycoluril unit. Moreover, the advantages of this method are a simple reaction sequence, easy-to-handle reaction conditions and good yield. The compounds prepared here are useful in material science and also in supramolecular chemistry.

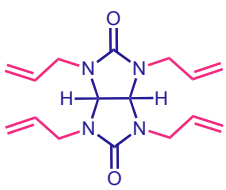
EXPERIMENTAL

Reactions involving air-sensitive reagents or catalysts were conducted in anhydrous and degassed solvents. Dichloromethane (DCM) was distilled over P_2O_5. The commercial-grade reagents were used without further purification. All the reactions were monitored by thin-layer chromatography alumina merck plates using appropriate solvent systems. All the compounds were purified by column chromatography using silica gel (100–200 mesh) and the yields refer to the chromatographically isolated yield. The NMR spectral analysis was done using $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm (δ scale) and coupling constants (J) are reported in Hz. The standard abbreviations s, d, t, q, and m refer to the singlet, doublet, triplet, quartet and multiplet, respectively. All NMR spectroscopic data were recorded with Bruker (AVANCE IIITM) 500 MHz and 400 MHz spectrometers. High-resolution mass spectrometric (HRMS) measurements were recorded with Bruker (Maxis Impact) or Micromass Q-ToF spectrometers, The melting points of unknown compounds were recorded with a Veego melting point apparatus.

General procedure for *N*-allylation

A two-neck 100 mL flask was flushed with argon. MeCN (20 mL) was added and compounds **9**, **10**, and **1** (1.0 equiv) were dissolved. Then cesium carbonate (5 equiv) was gradually added and the reaction mixture was further stirred for 1 h. Allyl bromide (4.50 equiv) was injected into the reaction mixture and the reaction was performed at 80 ºC for 6 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with water. EtOAc (100 mL) was used to extract the mixture and the organic phase was washed by saturated NaCl aqueous solution (100 mL) three times. The organic layer was dried by $MgSO_4$, the solvent was removed. Products **11**, **12** and **13** were obtained after purification over a silica column with the eluent of EtOAc /petroleum ether (30: 70).

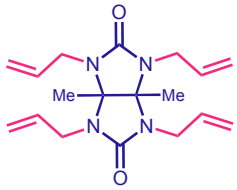
1,3,4,6-Tetraallyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (11)



Prepared according to the general procedure of allylation. The crude reaction mixture was purified using silica gel column chromatography to give compound as a pale-yellow oil (207 mg, 65%); R_f 0.45 (30% EtOAc/petroleum ether); ^{1}H NMR δ 5.77 (m, 4H, -CH), 5.23-5.14 (m, 10H, -CH_2 and -CH), 4.22-4.18 (m, 4H, -CH_2), 3.73-

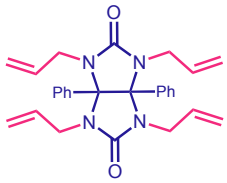
3.68 (m, 4H, -CH_2); ^{13}C NMR δ 158.4, 133.0, 118.2, 67.5, 45.7; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{16}H_{22}N_4O_2$ $[M+H]^+$ 303.1816, found 303.1815.

1,3,4,6-Tetraallyl-3a,6a-dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (12)



Pale-yellow oil (132 mg, 57%); R_f 0.45 (30% EtOAc/petroleum ether); ^{1}H NMR δ 5.81-5.76 (m, 4H, -CH), 5.13 (d, J = 16.6 Hz, 8H, -CH_2), 3.97-3.79 (m, 8H, -CH_2), 1.43 (S, 6H, -CH_3); ^{13}C NMR δ 156.9, 135.1, 116.1, 79.9, 43.1, 17.8; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{18}H_{26}N_4O_2$ $[M+H]^+$ 330.2005, found 330.2005.

1,3,4,6-Tetraallyl-3a,6a-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (13)

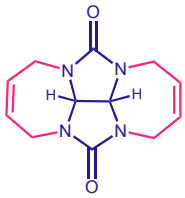


Crystalline solid (165 mg, 68%); R_f 0.35 (20% EtOAc/petroleum ether); mp 89-91 ^{o}C; ^{1}H NMR δ 7.12 (t, J = 7.19 Hz, 2H, -CH) 7.04 (t, J = 8.12 Hz, 4H, -CH), 6.79 (d, J = 7.55 Hz, 4H, -CH) 5.98-5.90 (m, 4H, -CH), 5.18-5.15 (m, 8H, -CH_2), 3.93-3.89 (m, 4H, -CH_2), 3.71 (dd, J = 5.23, 16.43 Hz, 4H, -CH_2); ^{13}C NMR δ 159.7, 134.1, 132.7, 129.2, 128.5, 128.4, 116.7, 88.7, 45.2; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{28}H_{30}N_4O_2$ $[M+H]^+$ 477.2269, found 477.2269.

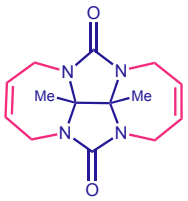
General procedure for RCM

To a stirred solution of RCM precursors, **11-13** (1 equiv) in dry DCM (30 mL) was degassed with nitrogen for 10 min, and then the G-I catalyst (10 mol%) was added. Later on, the reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (by TLC monitoring) the solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography using 50% of EtOAc/petroleum ether as an eluent to deliver the RCM products **14**, **15** and **16**.

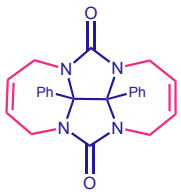
Compound 14- Prepared according to the general procedure for RCM. The crude mixture was purified using column chromatography to give the compound as crystalline solid (30 mg, 72%); R_f 0.45 (50% EtOAc/petroleum ether); mp 86-88 ^{o}C; ^{1}H NMR δ 5.71 (s, 4H, -CH), 5.30 (s, 2H, -CH), 4.47 (d, J = 9.98 Hz, 4H, -CH_2), 3.67 (d, J = 16.95 Hz, 4H, -CH_2); ^{13}C NMR δ 156.3, 127.1, 69.1, 41.6; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{12}H_{15}N_4O_2$ $[M+H]^+$ 247.1189, found 247.1190.



Compound 15- white solid; (56 mg, 68%); R_f 0.38 (50% EtOAc/petroleum ether); mp 110-112 ^{o}C; ^{1}H NMR δ 5.61 (d, J = 5 Hz, 4H, -CH), 4.46-4.40 (m, 4H, -CH_2), 3.57 (d, J = 16.88 Hz, 4H, -CH_2), 1.51 (s, 6H, -CH_3); ^{13}C NMR δ 155.6, 126.7, 77.7, 39.5, 14.9; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{14}H_{18}N_4O_2$ $[M+H]^+$ 275.1430, found 275.1431.



Compound 16- crystalline solid (32 mg, 77%); R_f 0.41 (30% EtOAc/petroleum ether); mp 108-111 °C; ^{1}H NMR δ 7.55-7.37 (m, 10 H, -CH), 5.98 (s, 4H, -CH), 4.20 (s, 8H, -CH_2); ^{13}C NMR δ 152.6, 131.2, 129.3, 128.2, 125.5, 120.9, 43.5; HRMS (ESI, Q-ToF): *m/z* calcd for $C_{24}H_{22}N_4O_2$ $[M+H]^+$ 398.1410, found 398.1410.



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