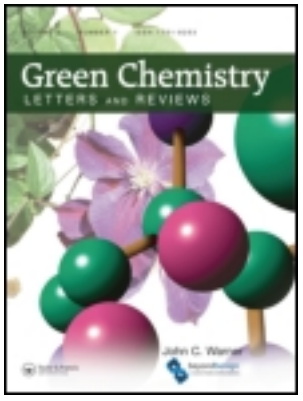

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A green synthesis of glycoluril derivatives in aqueous solution with recycle of the waste

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RESEARCH LETTER

A green synthesis of glycoluril derivatives in aqueous solution with recycle of the waste

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A series of glycoluril derivatives have been synthesized in water at room temperature from urea and 1,2-dicarbonyl compounds in the presence of phosphoric anhydride. The reaction time is about 10 minutes using one mole of 1,2-dicarbonyl compound, three moles of urea, and half mole of P_4O_{10}, but the reaction occurs also, even if with longer reaction times, with very small amounts of P_4O_{10} which is recovered at the end of reactions. In fact, several catalytic turnovers can be performed using the same reaction solution obtained after separation by simple filtration of the glycolurils.

Keywords: glycoluril; water; P_4O_{10}; green; condensation reaction

1. Introduction

In the past years the problem due to pollution is considerably increased. One of the main problems is the use of organic solvents in almost all industrial processes. The chemical community is seeking new synthetic strategies to resolve these problems. The use of water as a reaction medium seems to be one of the best choices for environmentally friendly syntheses (*1*).

Here, we report an efficient green protocol for the synthesis in aqueous medium of glycolurils that can be removed from the reaction mixture by filtration. The reuse of the remained solution permits to reduce the amount of the waste.

Glycolurils have been received a great attention due to their applications as fertilizers (*2*), psychotropic agents, stabilizers of organic compounds against photodegradation (*3*), explosives (*4*), polymer cross-linking agents (*5, 6*), catalysts, bleaching activators (*7–9*), and their use in combinatorial chemistry (*3*).

Glycolurils are also important building blocks for both molecular and supramolecular chemistry (*10*). Particular attention has been turned to cucurbiturils (*11*) (**CB**[n]) which are intriguing macrocyclic compounds, whose skeleton is constituted by glycolurils ring moieties (*12–15*).

In the past, the synthesis of glycolurils via condensation of 1,2-diketones with urea catalyzed by acids, such as H_2SO_4 (*16*), HCl (*10, 17–19*), CF_3COOH (*6, 20–23*), has been reported (Figure 1).

Recently, two new syntheses of glycolurils were reported (*24, 25*): the first catalyzed by potassium hydroxide in EtOH under ultrasound irradiation (*24*), the second catalyzed by heteropolyoxometalates in MeOH (*25*).

However, some of the reported methods suffer from limitations such as long reaction times, severe conditions, and alterations. For example, the base-catalyzed condensation of benzyl with urea gives a mixture of 3a,6a-diarylglycoluril and 5,5-diarylhydantoin in a ratio of about 1:2.

Thus, the possibility to find new efficient methods to achieve the synthesis of glycolurils with good selectivity under mild conditions, and with easy work-up, might be an important challenge.

Recently, we have reported (*26*) the facile synthesis of a series of hydantoins and thiohydantoins carried out in water at room temperature from urea (and its derivatives) and simple aldehydes (as glyoxal, and its derivatives) in the presence of phosphoric anhydride, which acts as both, condensing agent and catalyst (Figure 2).

P_4O_{10} is a reagent which can be involved in several reactions such as phosphorylation, condensation, dehydration, dealcoholysis, and many others (*27*).

The easiness of the synthesis of hydantoins depicted in Figure 2 and the mild conditions required to obtain them in good yields prompted us to try the synthesis of glycoluril derivatives.

Here, we report an efficient synthetic protocol that permits to prepare glycoluril derivatives in water

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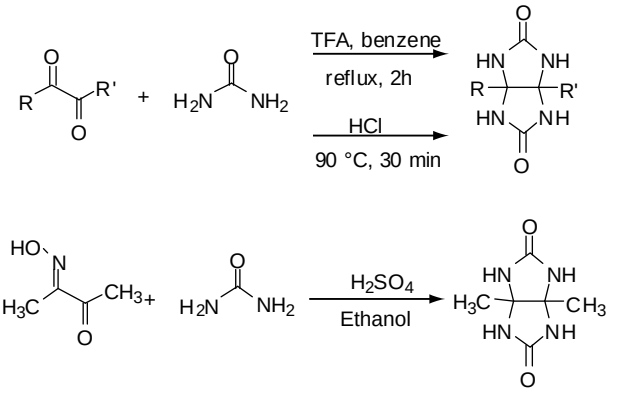

Figure 1. Examples of synthesis of glycolurils.

starting from urea, 1,2-dicarbonyl compounds, and P_4O_{10} in mild conditions and with the possibility to recycle both the solvent and the condensing agent.

2. Results and discussion

The synthesis of glycoluril derivatives **3a–g** is made in aqueous solution both adding the three reagents simultaneously and separately (Figure 3).

The best yields (52–79%) are obtained when the reagents are added separately with first addition of P_4O_{10} (1.5 mmol) to an aqueous solution of 1,2-dicarbonyl compound **1** (3.0 mmol) followed by addition of urea **2** (9.0 mmol). Lower yields (50–60%) are obtained when the reagents are dissolved simultaneously in water.

Data reported in Table 1 show that the reaction occurs under mild conditions (room temperature) in about 10 minutes giving the glycoluril derivatives **3a–g** in good yields both in the case of formation of symmetric (R = R′) and not symmetric glycolurils.

It is important to note that the work-up of these reactions and the purification of the products are very simple. Infact, glycolurils **3a–g** precipitate from the crude reaction mixture and can be recovered by simple filtration.

Importantly, the remaining aqueous solution containing P_4O_{10}[1] (as evidenced by ^{31}P NMR spectroscopy of the crude reaction mixture after filtration) can be used again for other synthetic cycles to form the same glycoluril. We have carried out four synthetic cycles and the reaction occurs in the same

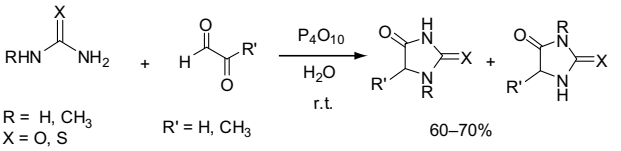

Figure 2. Synthesis of hydantoins mediated by P_4O_{10}.

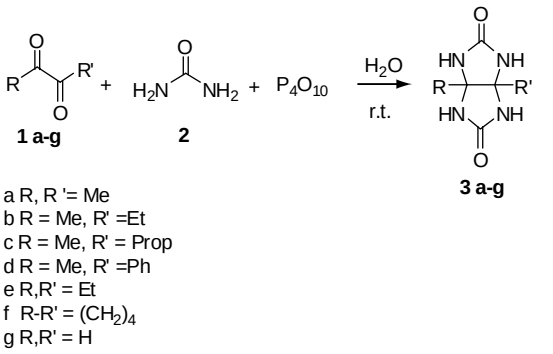

Figure 3. Synthesis of glycolurils from urea and 1,2-dicarbonyl compounds.

time with similar yields. The possibility to recycle the waste makes the whole process environmentally friendly. Thus, the method is attractive for its simplicity since the reaction goes to completeness in 10 minutes, and in all steps of the process the use of organic solvent is not required.

It has been reported (*28, 29*) that the synthesis of these compounds in aqueous solution at room temperature and in presence of mineral acids requires long reaction times (12–48 h) to obtain yields ranging from 20 to 50%. Only in one case (product **3a**) it has been reported (*30*) that the reaction occurs in 30 minutes giving the product in yield more than 96%; we repeated this experiment but, in our hands, the yield was only 40%.

We carried out the reaction depicted in Figure 3 using a large excess (12 mmol) of aqueous 85% H_3PO_4 instead of P_4O_{10}, but we obtained the products, after 2 h, in lower yields (45–55%), with respect to those obtained in the presence of P_4O_{10}. We tested also the reaction without P_4O_{10} but it does not occur.

All (already known) products have been identified by ^1H, ^{13}C NMR and ESI–MS spectroscopy and their spectral data have been compared with those reported in the literature (*31, 32*).

Table 1. Glycolurils from 1,2-dicarbonyl compounds and urea.[a]

Entry	1,2–dicarbonyl compound	Products (Yield %[b])
1	**1a**	**3a** (79)
2	**1b**	**3b** (75)
3	**1c**	**3c** (71)
4	**1d**	**3d** (76)
5	**1e**	**3e** (70)
6	**1f**	**3f** (52)
7	**1g**	**3g** (70)

[a]Reaction carried out at room temperature for 10 minutes.
[b]Obtained by filtration from the crude reaction mixture.

The course of this simple reaction can be rationalized taking into account that P_4O_{10} as a polycyclic structure and that cyclic phosphorus compounds show a different behavior with respect to acyclic ones. In particular, it is known that cyclic phosphorus compounds containing a phosphoryl group react with a nucleophile faster (of a factor of 10^{6-8}) with respect to the corresponding acyclic compound, to give the relative pentacoordinate species (*33*). This is due to the major stability of this cyclic pentacoordinated intermediate than the corresponding acyclic pentacoordinated intermediate.

Based on the above considerations, since P_4O_{10} has a polycyclic structure while H_3PO_4 has an acyclic structure (Figure 4), we can explain why P_4O_{10} reacts faster than H_3PO_4.

For the synthesis of glycolurils, herein reported, we proposed the reaction mechanism shown in Figure 5.

The initial step probably involves the hydration of the carbonyl groups and then the phosphorylation by P_4O_{10} of two hydroxyl groups with formation of the intermediate **A**-like. It is important to emphasize that in the case of P_4O_{10} this step is very fast, although, when H_3PO_4 is used, this kind of intermediate is disfavored because the corresponding intermediate **A**-like is not a cyclic pentacoordinated intermediate, as in the case of that formed using P_4O_{10}, which is stabilized (*33*) by a factor of 10^{6-8} with respect to the corresponding acyclic intermediate. The subsequent nucleophilic attack of urea gives condensation and cyclization with probable formation of an intermediate **B**-like which reacts with P_4O_{10} giving, after addition of urea, glycolurils **3a–g**. In the process there is reformation of P_4O_{10}, as shown for the decomposition of intermediate **C**. This is supported by the fact that in the ^{31}P NMR spectrum of the reaction mixture we noted always the signal of P_4O_{10} ($\delta = -23$ ppm), also at the end of the reaction. Only after several hours (4–6 h) we noted the signal of H_3PO_4 due to the partial hydrolysis of P_4O_{10}.

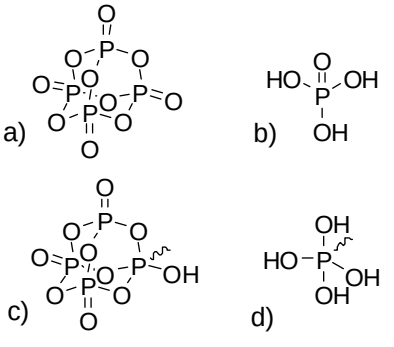

Figure 4. Structure of P_4O_{10} and H_3PO_4 and their related pentacoordinate forms.

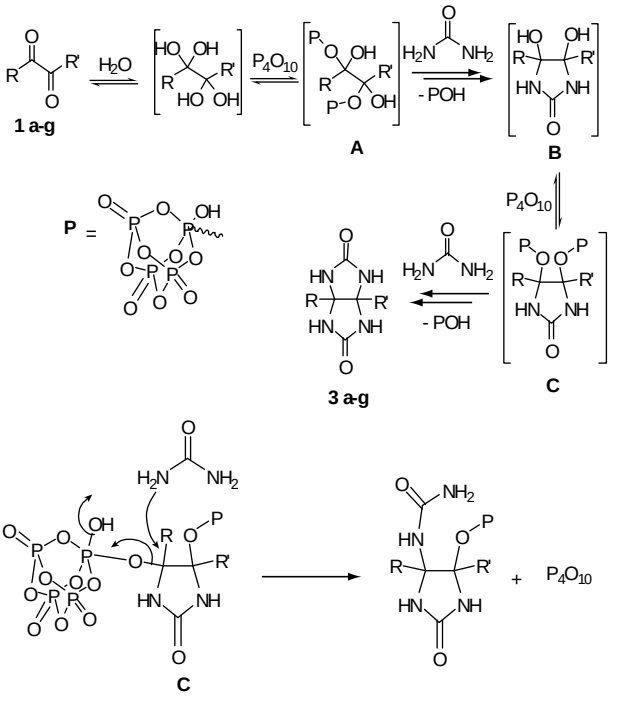

Figure 5. Hypothesized reaction mechanism.

In addition, the reaction goes to completeness giving the same product yield even when it is carried out with only 0.1 eq. of P_4O_{10}.

3. Experimental

3.1. General

^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 400, 100.56, and 161.89 MHz, respectively. Chemical shifts are referenced to the solvent (DMSO-d_6). *J* values are given in Hz. ESI–MS analysis was recorded with WATERS 2Q 4000 instrument.

3.2. General procedure

To a water (5 mL) solution of 1,2-dicarbonyl compound **1** (3.0 mmol), P_4O_{10} (1.5 mmol, 426 mg) was added and the mixture was stirred for 5 minutes. After this time urea **2** (9.0 mmol, 540 mg) was added. After 10 minutes the solution became cloudy and the product precipitates. The product was collected by filtration on a Buckner funnel and the solid was washed with cold water and dried. The products were characterized by ^1H and ^{13}C NMR spectroscopy.

3a,6a-dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (3a) (*31*): white solid; m.p. $>300^\circ C$ (Lit. $348^\circ C$); ^1H NMR (DMSO-d_6) δ 7.08 (br. s, 4*H*, NH), 1.32 (s, 6*H*, CH_3); ^{13}C NMR (DMSO-d_6) δ 159.4 (C=O), 75.3 (C), 21.9 (CH_3); ESI–MS: 171 [$M^+ + 1$], 193 [$M^+ + Na$].

3a-ethyl-6a-methyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (3b) (*17–19*): white solid; m.p. > 300°C (Lit. 320–321°C); ^{1}H NMR (DMSO-d_6) δ 7.17 (br. s, 2*H*, NH), 7.06 (br. s, 2*H*, NH), 1.62 (q, $J = 7.04$ Hz, 2*H*, CH_2–CH_2), 1.33 (s, 3*H*, CH_3), 0.93 (*t*, $J = 7.04$ Hz, 3*H*, C–CH_2–CH_3); ^{13}C NMR (DMSO-d_6) δ 159.6 (C = O), 77.8 (C) 75.4 (C), 28.1 (CH_2–CH_3), 21.5 (CH_3), 7.6 (CH_2–CH_3); ESI–MS: 185 [$M^+ + 1$], 207 [$M^+ + Na$].

3a-methyl-6a-propyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (3c) (*34*)**:** white solid; m.p. > 300°C (Lit. 312–312.5°C); ^{1}H NMR (DMSO-d_6) δ 7.16 (br. s, 2*H*, NH), 7.06 (br. s, 2*H*, NH), 1.61–1.50 (m, 2*H*, CH_2–CH_2–CH_3), 1.46–1.27 (m, 2*H*, CH_2–CH_2–CH_3), 1.32 (s, 3*H*, CH_3), 0.87 (t, $J = 7.47$ Hz, 3*H*, CH_2–CH_2–CH_3); ^{13}C NMR (DMSO-d_6) δ 159.6 (C = O), 77.3 (C) 75.5 (C), 37.6 (CH_2–CH_2–CH_3), 21.5 (CH_3), 16.0 (CH_2–CH_2–CH_3), 14.2 (CH_2–CH_2–CH_3); ESI–MS: 199 [$M^+ + 1$], 221 [$M^+ + Na$].

3a-methyl-6a-phenyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (3d) (*32*)**:** white solid; m.p. > 300°C (Lit. 348°C); ^{1}H NMR (DMSO-d_6) δ 7.58 (br. s, 2*H*, NH), 7.41 (m, 5*H*, Ar), 7.29 (br. s, 2*H*, NH), 0.78 (s, 3*H*, CH_3); ^{13}C NMR (DMSO-d_6) δ 159.9 (C = O), 138.7 (C Ar), 128.4 (CH Ar), 128.1 (CH Ar), 126.8 (CH Ar), 79.9 (C), 76.6 (C), 23.7 (CH_3); ESI–MS: 247 [$M^+ + 1$], 269 [$M^+ + Na$].

3a,6a-diethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (3e): white solid; m.p. > 300°C; ^{1}H NMR (DMSO-d_6) δ 7.20 (br. s, 4*H*, NH), 1.60 (q, $J = 7.48$ Hz, 4*H*, CH_2–CH_3), 0.94 (t, $J = 7.48$ Hz, 6*H*, CH_2–CH_3); ^{13}C NMR (DMSO-d_6) δ 159.9 (C = O), 78.0 (C), 27.5 (CH_2–CH_3), 7.5 (CH_2–CH_3); ESI–MS: 199 [$M^+ + 1$], 221 [$M^+ + Na$].

(3a*s*,7a*s*)-tetrahydro-1*H*-3a,7a-(epiminomethanoimino)benzimidazole-2,9-dione (3f) (*35*)**:** white solid; m.p. > 300°C (Lit. 319–320°C); ^{1}H NMR (DMSO-d_6) δ 7.01 (br. s, 4*H*, NH), 1.69 (t, $J = 6.25$ Hz, 4*H*, C–CH_2–CH_2), 1.39 (t, $J = 6.25$ Hz, 4*H*, CH_2–CH_2); ^{13}C NMR (DMSO-d_6) δ 160.3 (C = O), 73.6 (C–CH_3), 31.5 (C–CH_2–CH_2), 17.6 (CH_2–CH_2); ESI–MS: 197 [$M^+ + 1$], 219 [$M^+ + Na$].

tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione (3g) (*36*)**:** white solid; m.p. > 300°C (Lit. 360°C); ^{1}H NMR (DMSO-d_6) δ 7.16 (br. s, 4*H*, NH), 5.24 (s, 2*H*, CH); ^{13}C NMR (DMSO-d_6) δ 160.3 (C = O), 64.6 (CH); ESI–MS: 133 [$M^+ + 1$], 155 [$M^+ + Na$].

4. Conclusions

In summary, we have found a facile, atom economic, fast, and highly efficient protocol for the synthesis at room temperature and in aqueous solution of a series of glycoluril derivatives from urea and 1,2-dicarbonyl compounds in the presence of P_4O_{10} which acts as a catalyst. The glycolurils are separated by simple filtration and their aqueous solution can be used again for several other reactions thus giving the possibility to considerably reduce the waste amount.

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Note

1. ^{31}P NMR spectroscopy of a solution of P_4O_{10} in water showed a signal at −23 ppm together with other little signals attributable to hydrolysis products, and the spectrum remains unchanged for at least 5 hours. A similar ^{31}P NMR spectrum was obtained for the residue solution of the reaction that evidenced the presence of P_4O_{10} in the waste solution.

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