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Synthesis of Glycoluril Derivatives Catalyzed by Some Heteropolyoxometalates

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ABSTRACT

An environmentally benign green protocol is introduced for the synthesis of simple derivatives of glycolurils through condensation of vicinal diketones, as well as glyoxal, with urea and methylurea by the mediation of a catalytic amount of simple acidic and anionic heteropolyoxometalates. $H_3PW_{12}O_{40}$ *and* $H_4SiMo_3W_9O_{40}$ *(Keggin types),* $H_{14}NaP_5W_{30}O_{110}$ *(Preyssler type), and* $K_6P_2Mo_{18}O_{62}$ *(Wells-Dawson type) revealed the best catalytic activity in the reaction of urea with 2,3-butanedione and led to the corresponding glycoluril quantitatively after 5.5 h.*

Keywords Glycoluril, Heteropoly acid, Heteropolyoxometalates, Condensation.

INTRODUCTION

Glycolurils (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-diones) have been received much attention due to their industrial applications, such as fertilizers, polymer crosslinking, explosives, stabilizers of organic compounds, and combinatorial chemistry.[1] Moreover, they exhibited a broad spectrum of biological activities such as minor tranquilizer.[2]

The glycoluril skeleton has served as an important building block for the preparation of a wide variety of supramolecular systems, including molecular clips, the cucurbit[n]uril family, and molecular capsules.[3] Glycoluril was shown to be a molecular template for intramolecular Claisen-type condensations. The synthesis of glycolurils *via* condensation of vicinal diketones with urea and its derivatives catalyzed by classical acid, such as H_2SO_4, HCl, and CF_3COOH has already been claimed.[4] However, in spite of their potential utility, some of the reported methods suffer from drawbacks such as longer reaction times, harsh conditions and corruption.

The development of inexpensive reagents and efficient catalytic synthethic routes is of great importance for industrial activities. The catalytic function of *Keggin* heteropolycompounds has attracted much attention, particularly because of their great potential economic reward and green benefits.[5] These compounds have a very strong, approaching the superacid region, Brönsted acidity.

Herein, we report the synthesis of some glycolurils catalyzed by some heteropoly compounds *via* condensation of glyoxal and/or vicinal diketones with urea and methylurea.

EXPERIMENTAL SECTION

Materials and methods

All reagents were commercial products and were used as received. All products were characterized by comparison of their spectral and physical data with those of authentic samples. Melting points were recorded on an Electrothermal type 9200 melting point apparatus and are uncorrected. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. Heteropolyoxometalates were prepared according to the literature or were purchased commercially.

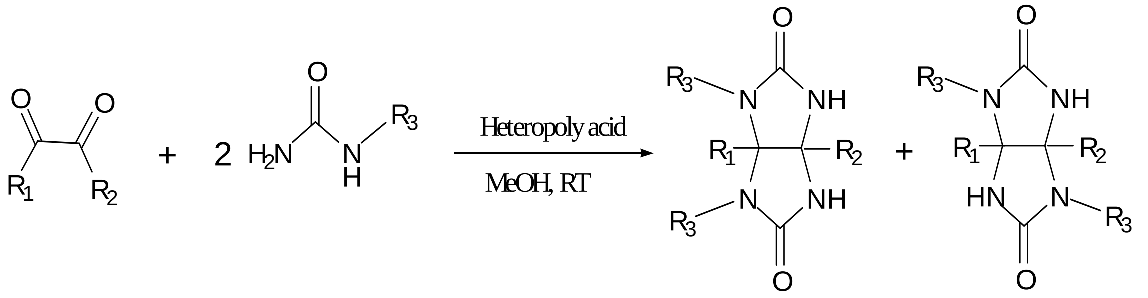
General procedure for synthesis of the glycolurils

A 5 ml round flask was charged with compound **1** (1.15 mmol), urea (2.53 mmol), heteropolyacid catalyst (0.011 mmol), and MeOH (1 cm^3). The reaction was carried out at ambient temperature and its progress was monitored by TLC. After completion of the reaction, the reaction mixture was poured into water (10 cm^3) and filtered. The solid product was washed by water and subsequently ether to give the pure product. All glycolurils were known and their authenticity were established by comparison of their spectral and physical data with those of authentic samples.

RESULTS AND DISCUSSION

The condensation reaction of dicarbonyl compounds **1a-d** with ureas **2a,b** in MeOH with $H_3PW_{12}O_{40}$ as a strong heteropolyacid catalyst at ambient temperature yielded the glycoluril derivatives **3, 4** (Scheme 1).

Table 1 describes cyclocondensation of glyoxal (**1a**) and three vicinal diketones, 2,3-butanedione (**1b**), 2,3-hexanedione(**1c**), and 2,3-heptanedione (**1d**) with urea and methylurea to form the corresponding glycolurils. Compound **1a** produced **3a** in the reaction with urea with 75 % of conversion after 2 h. On the other hand, methylurea did not afford the desired solid product in a considerable amount compared to urea under the same conditions. The decrease in conversion would be due to steric hindrance induced by the methyl group of methylurea. 2,3-butanedione, **1b,** reacted with urea and produced **3c** quantitatively after 5.5h. Whereas, methylurea showed lower reactivity and led to 50% of product after 48 h. 2,3-hexanedione, **1c,** was also subjected to the reaction with urea and methylurea. **1c** produced the corresponding glycoluril with 83% yield after 48 h. Methylurea showed higher activity in the reaction with **1c** and resulted in complete conversion after 24 h. 2,3-Heptanedione (**1d**) showed lower activity toward urea and gave 48% of product after 36 h. Presumably, both electronic and steric effects exerted by the methyl substituent(s) around the carbonyl groups and methylurea affect on their reactivity and therefore reaction rate.



1a $R_1, R_2 = H$
1b $R_1, R_2 = Me$
1c $R_1, R_2 = Et$
1d $R_1 = Me; R_2 = n\text{-}Pr$

2a $R_3 = H$
2b $R_3 = Me$

3a $R_1, R_2, R_3 = H$
3b $R_1, R_2 = H; R_3 = Me$
3c $R_1, R_2 = Me; R_3 = H$
3d $R_1, R_2, R_3 = Me$
3e $R_1, R_2 = Et, R_3 = H$
3f $R_1, R_2 = Et, R_3 = Me$
3g $R_1 = Me; R_2 = n\text{-}Pr; R_3 = H$
3h $R_1, R_3 = Me; R_2 = n\text{-}Pr$

4b $R_1, R_2 = H; R_3 = Me$
4d $R_1, R_2, R_3 = Me$
4f $R_1, R_2 = Et, R_3 = Me$
4h $R_1, R_3 = Me; R_2 = n\text{-}Pr$

Scheme 1

Table 1 Reaction of the carbonyl compounds 1a-d with ureas 2a,b

	Urea			Methylurea		
Compound	Conv. %	Time (h)	Product(s)	Conv. %	Time (h)	Product(s)
1a	75	2	**3a**	a	-	-
1b	100	5.5	**3c**	50	48	**3d**, **4d**
1c	83	48	**3e**	100	24	**3f**, **4f**
1d	48	36	**3g**	b	-	-

a: No precipitate after several hours b: Highly impure red residue after 36 h (unable to be purified).

The reaction of **1b** with urea was used as a model reaction to obtain further insights on the role of kind and concentration of catalyst in the introduced condensation protocol. Therefore, a solution of compound **1b** (1.15 mmol) reacted with urea (2.53 mmol) in MeOH (1 ml) at room temperature in the presence of different heteropoly acid catalysts (0.011 mmol) (Table 2). First of all, **1b** led to 10-15% of product in the absence of catalyst after 24 h. Findings revealed that the examined heteropoly acids exhibited different catalytic activities. Among various heteropolyoxometalates introduced in Table 2, $H_3PW_{12}O_{40}$, and $H_4SiMo_3W_9O_{40}$ (K*eggin*), $H_{14}NaP_5W_{30}O_{110}$ (*Preyssler*), and $K_6P_2Mo_{18}O_{62}$ (*Wells-Dawson*) reacted quantitatively with urea after 5.5 h.

Other investigated heteropolyoxometalates displayed lower catalytic activity and led to 30-80% of product under similar reaction conditions after 5.5 h. Clearly, W-substituted polyoxometalates showed higher catalytic activity than Mo counterparts. Additionally, heteropoly compounds in their acidic forms where more effective than their corresponding soluble ionic salts. $H_3PMo_{12}O_{40}$ as a strong heteropoly acid was obviously less efficient than $H_3PW_{12}O_{40}$. The first, led to 60% of product; whereas, $H_3PW_{12}O_{40}$ gave complete conversion during the same time. V-substituted heteropolyoxometalates, which are interesting catalysts in organic synthesis, disclosed less catalytic activity and resulted in <55% of the corresponding glycoluril.

Table 2 Reaction of 2,3-butanedione with urea in the presence of different heteropoly acids

Heteropoly acid	Conv. %	Time (h)
Without	10-15	24
$H_3PW_{12}O_{40}$	100	5.5
$H_3PMo_{12}\ O_{40}$	60	5.5
$H_{14}NaP_5W_{30}O_{110}$	100	5.5
$Na_3PW_9Mo_3O_{40}$	50	5.5
$K4SiW_9Mo_2O_{39}$	80	5.5
$K_6P_2Mo_{18}O_{62}$	95	5.5
$K_{14}NaP_5W_{30}O_{110}$	40	5.5
$H_5PMo_{11}VO_{40}$	30	5.5
$H_7SiV_3Mo_9O_{40}$	25	5.5
$(TBA)_7PW_{11}O_{39}$	10	5.5
$H_4SiMo_3W_9\ O_{40}$	100	5.5
$H_5SiMo_2VW_9\ O_{40}$	55	5.5

A set of experiments where carried out using different mol% of $H_3PW_{12}O_{40}$ in the reaction of **1b** (1.15 mmol) with urea (2.53 mmol) under the standard reaction condition in MeOH (1 ml) at room temperature (Table 3). As mentioned earlier, the catalytic system was inefficient in the absence of catalyst and <10% of product was obtained after 2 h. A clear increase in yield % occurred in the presence of 0.5 mol % of $H_3PW_{12}O_{40}$ and 42% of glycoluril produced during the same time. Higher amount of catalyst, resulted in a smooth increase in conversion % and 55-65% of conversions were obtained in the presence of 1 and 1.5 mol % $H_3PW_{12}O_{40}$, respectively, after 2 h.

Table 3 Reaction of 1b with urea using different quantities of $H_3PW_{12}O_{40}$

$H_3PW_{12}O_{40}$(% mol)	Conv. %	Time (h)
0.0	< 10	2
0.5	42	2
1.0	55	2
1.5	65	2

Table 4 Reaction of 1b with urea in different solvents

Solvent	Conv. %	Time (h)
MeOH	100	5.5
MeCN	75	5.5
H_2O	85	5.5
CH_3COCH_3	85	5.5
EtOAc	80	5.5
EtOH	65	5.5

Additional experiments were performed to find the best solvent for the reaction of **1b** with urea. As shown in Table 4, methanol was the best solvent and conducted the reaction of **1b** with urea satisfactorily; whereas, other polar solvents showed lower efficacy toward the condensation reaction. Interestingly, 85% of **3c** provided in normal drinking water. Therefore, this solvent would be a good choice for synthetic purposes from the green points of view.

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