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MAGNESIUM ACETATE CATALYSED SYNTHESIS OF GLYCOLURIL DERIVATIVES VIA CYCLOCONDENSATION OF BENZIL AND UREA/THIOUREA

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ABSTRACT

An simple, efficient method for synthesis of glycoluril derivatives has been developed from Benzil and Urea in presence of a catalytic amount of magnesium acetate .The remarkable selectivity under mild, neutral and, inexpensive catalystare attractive features. This method is a very easy and rapid for synthesis of glycoluril derivative. This approach offers many advantage such as good product yields, short reaction yield, easy isolation of products.

Key words: Magnesium acetate, glycoluril, Benzil, Urea and Thiourea.

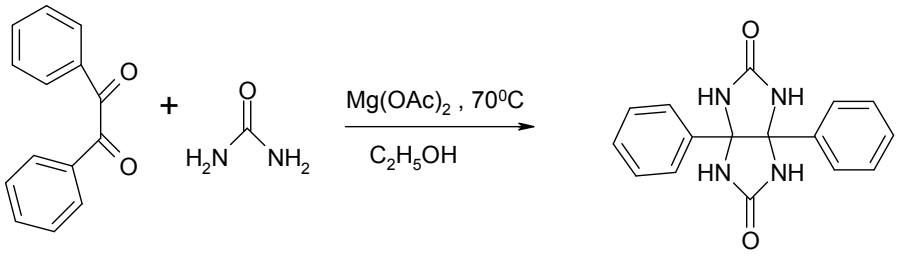
INTRODUCTION

The development of the chemistry of N-heterocycles based on urea or thiourea such as glycolurils, imidazolidine-2-ones, imidazole-2-ones, imidazolidine-2-thiones and imidazole-2-thiones is of great interest due to high physiological activity of these materials[1,2].Glycoluril as the simplest member of this class of heterobicyclic compounds was synthesized for the first time in the 19th century[3]. Glycoluril and its derivatives are the subject of many studies because of their synthetic accessibility, hydrogen-bond donat-ing/accepting ureidyl functionality, curved and rigid structure[4,5]Mebicar (2,4,6,8-tetramethyl glycoluril) as one of representatives of this class is used in medical practice as a day tranquillizer[6]. The glycolurils have been received a great deal of attention due to their practical applications such as polymer crosslinking, fertilizers, crystal engineering, explosives, stabilizer of organic compounds against photodegradation, radio iodination agents for biomoleculs, combinatorial chemistry, catalysts, bleaching activators and as monomer in supramolecular chemistry[7,8].In this study, by condensation reaction of α-diketone with urea under acidic conditions, glycoluril was prepared as the only product, while under alkaline conditions hydantoin and glycoluril were obtained as the major and minor products, respectively[4]. Imidazolidine-2-ones, imidazole-2-ones, imidazole-2-thiones and imidazolidine-2-thiones are important heterocycles with an embedded cyclic urea/thiourea scaffold, which is a core element of many pharma-ceutically relevant compounds[9]. They can exhibit a wide range of biological activities including inhibitions of the respiratory syncytial virus (RSV) fusion and NNRT (the nonnucleoside reverse transcriptase)[10]. Furthermore, these materials play important roles as progesterone receptor antagonists in the selective inhibition of farnesyltransferase (FTase) and the activation of K^+ channels[11]. Among imidazolidine-2-ones, dipheninis known as

antiepileptic drug[12].

A number of methods for synthesis of these materials have been reported[13-23].However, some of these pathways suffer from various drawbacks such as tedious work-up, unsatisfactory yields, refluxing for long periods with high boiling solvents. The aim of this work is to synthesize some glycoluril derivatives, imidazolidine-2-ones, imidazole-2-ones and imidazole-2-thiol in the presence of Magnesium acetate as a organometallic catalyst.

Scheme I



EXPERIMENTAL

General Experimental Procedure for glycoluril:

A mixture of diketone (1mmol), urea or thiourea(1mmol) and $Mg(OAc)_2$ (0.1 mmol, 30 mg) in ethanol (5ml) was stirred magnetically at 70^0c, and the progress of the reaction was monitored by thin-layer chromatography, the mixture was poured into water (50 ml) and the precipitate formed was filtered, washed with cold water, and then dried. The product was dried over anhydrous Na_2SO_4 and further recrystallization by suitable solvents.

RESULT AND DISCUSSION

The optimum condition for the synthesis of glycolurils derivatives was established by considering a reaction between benzil, and Urea/Thiourea as model reaction. It was performed in the presence of anhydrous $Mg(OAc)_2$ in C_2H_5OH as a catalyst

A proper solvent for the reaction was selected by investigating the effect of different solvents on reaction time and yield of product for model reaction. We observed that the reaction time was long and yield of the corresponding product was low when the reaction was performed in solvents of low polarity (Table 1, Entries 1 and 2). Even in CH_3CN the reaction time and yield were not satisfactory (Table 1, Entry 3). The reaction gave maximum yield of product in short time period when it was performed in polar solvent such as C_2H_5OH (Table1, Entry-4)

Table 1. Investigation of solvent effect for the synthesis of glycolurils

Entry	Catalyst	Solvent	Time (min)	Yield[a] (%)
1	anhydrous $Mg(OAc)_2$	$CHCl_3$	65	52
2	anhydrous $Mg(OAc)_2$	CH_2Cl_2	50	58
3	anhydrous $Mg(OAc)_2$	CH_3CN	55	62
4	anhydrous $Mg(OAc)_2$	C_2H_5OH	45	88

[a]Isolated Yields

On the basis of results as shown in Table 1. C_2H_5OH was selected as the most appropriated solvent for ***Scheme1.***

The efficiency of anhydrous $Mg(OAc)_2$ as a catalyst was determined with respect to its amount to be loaded in reaction mixture. There was no improvement in yield with increment in loading amount of catalyst from 0.01 mmol to 0.05 mmol. A satisfactory yield in short reaction time was obtained with 0.1 mmol of catalyst. There was no appreciable improvement in yield even if loading amount was increased to 0.2 mmol.

Table 2. Investigation of catalytic effect of anhydr. $Mg(OAc)_2$ on synthesis of glycolurils

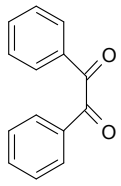
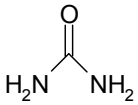
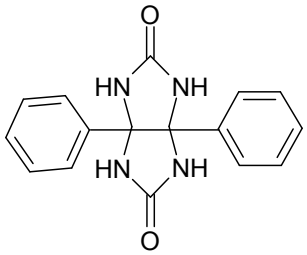
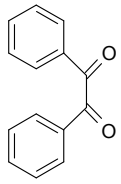
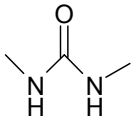
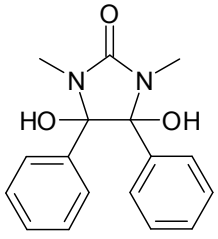
Entry	anhydrous $Mg(OAc)_2$ (mmol)	Time (min)	Yield[b] (%)
1	0.01	75	52
2	0.05	60	58
3	0.1	45	88
4	0.2	45	88

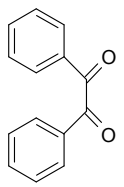
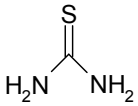
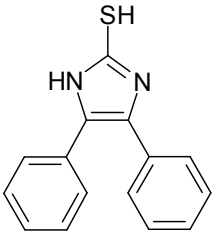
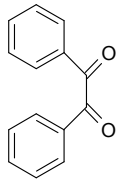
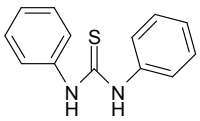
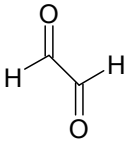
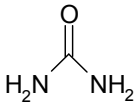
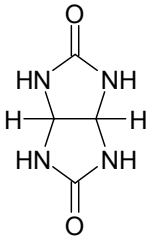
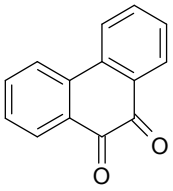
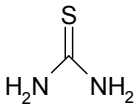
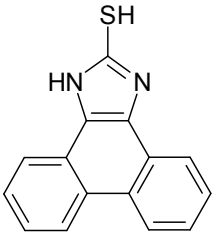
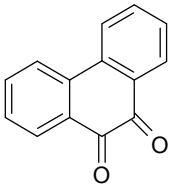
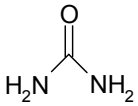
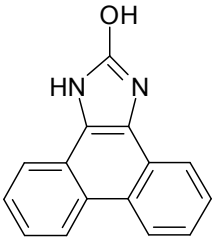
[b]Isolated yields

Thus, the most appropriate loading amount for anhydrous $Mg(OAc)_2$ as a catalyst was found to be 0.1 mmol as per results summarized in Table 2.

After optimization of reaction conditions, we examined the generality of this procedure for other substrates using *α*-diketone compounds and urea/thiourea derivatives (table 3). In the case of the urea derivatives such as N,N–dimethyl urea and with *α*-diketone, the major product was not a glycoluril derivative and the product was imidazolidine-2-one or imidazole-2-one (table 3, entries1,2,5,7). So, the major product for reaction of thiourea and with *α*-diketone was imidazole-2-thiol (table 3, entries 3,6), and in the case of the N,N'-diphenylthiourea condensation with benzil did not observe any reaction (table 3, entry 4).

Table- 3. Synthesis of glycoluril catalysed by Magnesiumacetate[a]

Entry	α-diketone[a]	Urea derivatives	Product[b]	Time	Yield[c]
1				45	78
2				40	89

3				50	72
4			No reaction	----	0
5				45	76
6				50	69
7				55	71

[a] diketone (1 mmol), urea or thiourea (1 mmol) and $Mg(OAc)_2$ (0.1 mmol) Ethanol (5ml) was stirred magnetically at 70^0c
[b] All products were identified by their IR and ^{1}H NMR spectra
[c] Isolated yields.

Compound characterization

Tetrahydro-3a,6a-diphenylimidazo[4,5-d] imidazole-2,5(1H,3H)-dione (table 3, entry 1): Yield 0.21 g(72%), m.p>300° C, IR (KBr, cm^{-1}): 1687, 1710, 2847, 3070, 3230; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.05–7.07 (10H, m, Ar–H), 7.74 (4H, brs, NH, D_2O-exchangable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 82.2, 127.4, 127.8, 128.2, 138.7, 161.2 (C=O); *Anal*. Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.17; H, 4.86; N, 18.87.

4,5-Diphenyl-1H-imidazole-2-thiol (table 3, entry 3): Yield 0.17 g (68%), m.p>300°C, IR (KBr, cm^{-1}):1209, 1498, 1674, 2748, 3013, 3161; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.33–7.35 (10H, m, Ar– H), 12.54 (2H, brs, NH, SH (Tautomerization), D_2O-Exchangable); ^{13}C

NMR (75 MHz, DMSO-d_6): δ 125.2, 127.9, 128.6, 128.8, 129.2, 160.4; *Anal*. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Found: C, 71.31; H, 4.85; N, 11.01; S, 12.80.

1H-phenanthro [9,10-d] imidazole-2-thiol (table 3,entry 6): Yield 0.16 g (64%), m.p>300°C, IR (KBr,cm^{-1}): 1195, 1502, 1620, 2759, 2946, 3165; *Anal*. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19; S, 12.81. Found: C, 72.24; H, 4.16; N, 10.98; S, 12.77.

CONCLUSIONS:

In conclusion, we successfully developed a simple and highly efficient one-pot synthesis of glycoluril derivatives from easily available starting material using magnesium acetate as an organometallic catalyst. This protocol is attractive in terms of atom economy, short reaction time, simple, easy work-up make this procedure a useful addition to modern synthetic methods.

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