Green Ecofriendly synthesis of Glycoluril derivatives via Cyclocondensation of Benzil and urea/thiourea

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Abstract
A green, simple, efficient method for manufacturing of glycoluril derivatives has been developed from Benzil and Urea without solvent and catalyst. This method is a very easy and rapid for synthesis of glycoluril derivatives.

This approach offers many advantages such as eco-friendly, environ friendly, good product yields, easy isolation of products with green approach.

Keywords: Ecofriendly, envirofriendly, glycoluril, benzil, urea and thiourea.

Introduction

Due to high physiological activity of N-heterocycles such as glycolurils based on urea or thiourea, imidazolidine-2-ones, imidazole-2-ones, imidazolidine-2-thiones and imidazole-2-thiones is of great interest[2,10].

Glycoluril was synthesized in the 19th century which is simplest member of this class of N-heterocycles compounds[13]. Glycoluril had good synthetic accessibility, hydrogen-bond donating/accepting ureidyl functionality, curved and rigid structure.[1,15]

Mebicar (2,4,6,8-tetramethyl glycoluril) as one of representatives of this class is used in medical practice as a day tranquillizer[11]. It can exhibit a wide range of biological activities including inhibitions of the respiratory syncytial virus (RSV) fusion and NNRT (the nonnucleoside reverse transcriptase)[12].

Furthermore, these materials play important roles as progesterone receptor antagonists in the selective inhibition of farnesyltransferase (FTase) and the activation of K^+ channels[17]. Among imidazolidine-2-ones, dipheninis is known as antiepileptic drug[3].

A number of methods for synthesis of these materials have been reported[4-9,14,16,19]. In our previous work we reported the synthesis of glycoluril using catalyst and ethanol as solvent.[18]

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 overcome these drawbacks and have eco-friendly, green synthesis of some glycoluril derivatives, imidazolidine-2-ones, imidazole-2-ones and imidazole-2-thiol without catalyst and solvents.

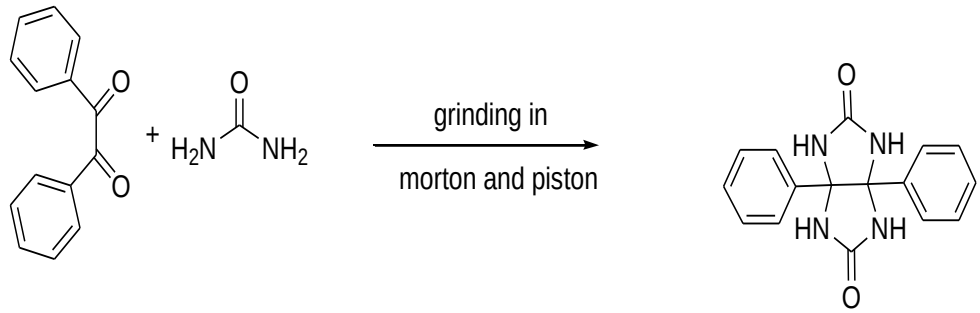
Material and Methods

General Experimental Procedure for glycoloril: A mixture of diketone (1mmol), urea or thiourea (1mmol) was grinned at room temp in the mortem and piston 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.

Results and Discussion

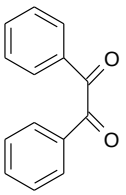
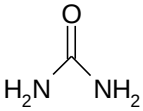
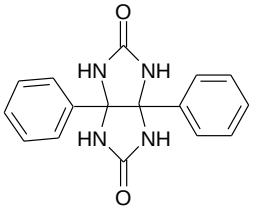
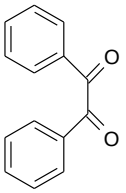
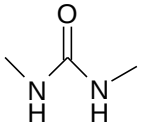
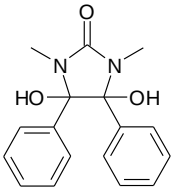
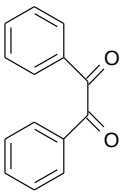
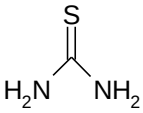
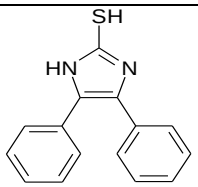
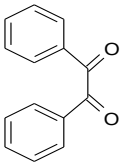
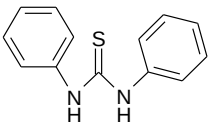
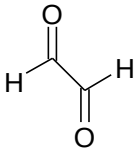
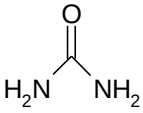
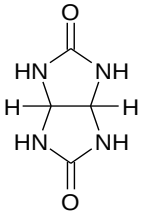
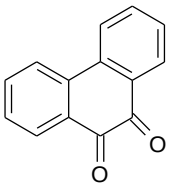
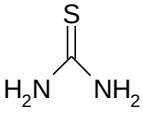
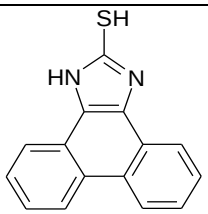
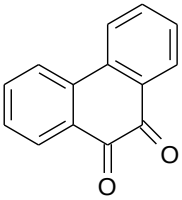
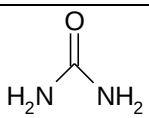
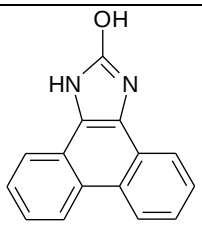
We examined the generality of this procedure for other substrates using α-diketone compounds and urea/thiourea derivatives (table 1). In the case of the urea derivatives such as N,N–dimethyl urea and with α-diketone, the major product was not a glycoluril derivative and the product was imidazolidine-2-one or imidazole-2-one (table 1, entries 1,2,5,7).

So, the major product for reaction of thiourea and with α-diketone was imidazole-2-thiol (table 1, entries 3,6) and in the case of the N,N'-diphenyl thiourea condensation with benzil did not observe any reaction (table 1 , entry 4).



Scheme I

Table 1
Synthesis of glycoluril without catalyst and solvent[a]

Entry	α-diketone[a]	Urea derivatives	Product[b]	Time	Yield[c]
1				25	82
2				20	91
3				30	78
4			No reaction	50	26
5				25	86
6				35	75
7				30	82

[a] diketone (1 mmol), urea or thiourea (1 mmol) was grined at room temperature
[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 1, entry 1)*: Yield 0.24 g(72%), m.p>300° C, IR (KBr, cm^{-1}): 1672, 1695, 2832, 3215, 3055; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.10–7.12 (10H, m, Ar–H), 7.79 (4H, brs, NH, D_2O-exchangable); ^{13}C NMR (65 MHz, DMSO-d_6): δ 72.2, 117.4, 117.8, 118.2, 128.7, 151.2 (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 1, entry 3): Yield 0.195 g (78%), m.p>300°C, IR (KBr, cm^{-1}):1224, 1512, 1689, 2763, 3028, 3176; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.38–7.40 (10H, m, Ar– H), 12.59 (2H, brs, NH, SH (Tautomerization), D_2O-Exchangable); ^{13}C NMR (75 MHz, DMSO-d_6): δ 115.2, 117.9, 118.6, 118.8, 119.2, 150.4; *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 1,entry 6): Yield 0.19 g (75%), m.p>300°C, IR (KBr,cm^{-1}): 1210, 1517, 1635, 2774, 2961, 3180; *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.

Conclusion

In conclusion, we successfully developed a simple green eco-friendly, environment friendly and highly efficient one-pot synthesis of glycoluril derivatives from easily available starting material. This protocol is attractive in terms of atom economy, short reaction time, simple and easy work-up.

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