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Research Article

Cu(II) complex based on 3-hydroxy-2-naphtoic acid (Cu-HNA) as an efficient catalyst for the one-pot multicomponent synthesis of triazolo[1,2-a]indazole-triones under solvent free conditions

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ABSTRACT

In this work, an efficient, environmentally and high yielding procedure for the one-pot, three-component synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives by condensation of dimedone, urazole, and aromatic aldehydes catalyzed by Cu (II) complex was equipped with 3-hydroxy-2-naphtoic acid ligand (Cu-HNA), as an ecofriendly catalyst with high catalytic activity and reusability at 100°C under solvent-free conditions is reported. The reaction proceeds to completion within 30–40 min in 82–92% yield.

Keywords: 3-Hydroxy-2-naphtoic acid; Triazolo[1,2-a]indazole-triones; Urazole; Multi-component reaction; One-pot; Solvent-free.

1. Introduction

Multicomponent reactions (MCRs) are important for the achievement of high levels of diversity, as they allow more than two building blocks to be combined in practical, time-saving one-pot operations, giving rise to complex structures by simultaneous formation of two or more bonds, according to the domino principle, higher productivity, simple procedures, facile execution, and play an important role in combinatorial chemistry [1-4]. MCRs contribute to the requirements of an environmentally friendly, process by reducing the number of synthetic steps, energy consumption and waste production [5]. Typical examples of MCRs are Biginelli [6], Passerini [7], Ugi [8], and Mannich [9] reactions that used successfully in many organic syntheses. Upon these facts, great efforts have been and still are being made to find and develop new MCRs.

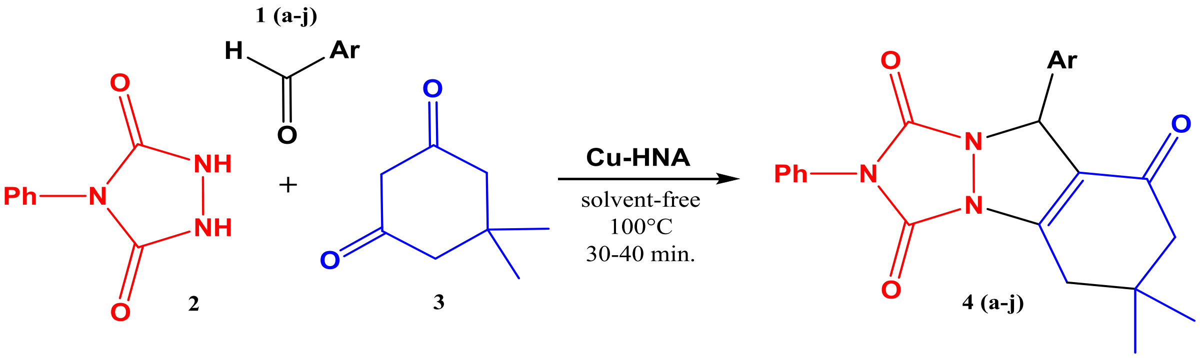
Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life [10].

Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing an urazole moiety are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful some biological as well as pharmaceutical activity [11-14].

These compounds are also used in the preparation of anti-cancer and hypolipidemic [15], herbicides [16], pesticides [17], insecticides [18], and polymeric materials with unique properties, such as heat-resistant coatings [19], tyre rubbers with high gripability [20], and melamine resins [21]. Novel methods for preparing heterocycles containing an urazole moiety have attracted much interest in recent years [22-24]. Only few methods being available for the synthesis of heterocycles containing an triazolo [1,2-a]indazole-1,3,8-trione. These compounds are synthesized by the condensation of dimedone, urazole, and aromatic aldehydes using catalysts such as sulfonated polyethylene glycol [25], mesoporous aluminosilicate [26], p-toluene sulfonic acid [27], and tungstosilicic acid [28]. These protocols have limitations such as requirement of huge amounts of catalyst, regeneration of the catalyst, the separation of the product from the reaction mixtures, purification of the products by column chromatography and the use of toxic organic solvent. Therefore, the search continues for a better catalyst for the synthesis of indazole-1,3,8-trione ring fragment.

1-hydroxy-2-naphtoic acid and 3-hydroxy-2-naphtoic acid as a ligand were applied for complexation with metal ions under different conditions [29-31]. The lanthanides were used for the indication of oxygen of hydroxyl of the –COOH group in these compounds [32, 33]. Transition metal complexes have become increasingly important in synthetic chemistry, coordination chemistry, homogeneous catalysis and biological chemistry [34]. Therefore, recently Mn2+ and Cu2+ complexes with 3-hydroxy-2-naphtoic acid have been synthesized [35, 36].

In continuation of our efforts to develop new green chemistry methods [37-42], herein we describe a simple synthesis of triazolo[1,2-a]indazole-1,3,8-triones (**4a-j**) by three-component condensation reaction of aryl aldehydes (**1a-j**), urazole (**2**), and dimedone (**3**) under solvent-free conditions using catalytic amount of Cu(II) complex based on 3-hydroxy-2-naphtoic acid (Cu-HNA) as a recyclable catalyst at 100°C (Scheme 1).



Scheme 1: Synthesis of triazolo[1,2-a]indazole-1,3,8-triones under solvent-free conditions using Cu-HNA

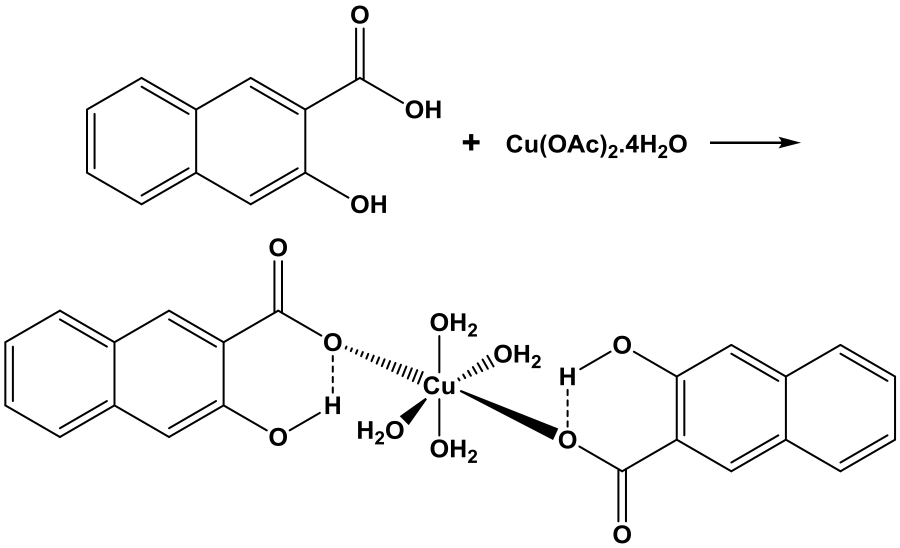
2. Experimental

2.1. Materials

Chemicals were purchased from Fluka, Merck and Aldrich Chemical Companies. Melting points were recorded with a stuart SMP3 melting point apparatus. IR measurements were carried out using KBr pellets in FTIR spectrometer. The NMR was run on Bruker-400 MHz instruments $CDCl_3$. All of the products are known and were characterized by their spectral and physical data. The monitoring of the progress of all reactions was carried out by TLC, using n-hexane/EtOAc as an eluent.

2.2. General procedure for the preparation of Cu (II) complex based on 3-hydroxy-2-naphtoic acid (Cu-HNA)

3-Hydroxy-2-naphtoicacid (2 mmol) and $Cu(OAc)_2.4H_2O$ (1 mmol) were added to the distilled water (2 ml) and the solution was stirred for 2 hours. After this time, the precipitation was obtained. The product was filtered, wash with distilled water and dry in 100°C [36]. (Scheme 2).



Scheme 2. The synthesis of Cu (II) complex based on 3-hydroxy-2-naphtoic acid (Cu-HNA)

2.3. General procedure for the synthesis of triazolo[1,2-a]indazole-1,3,8-triones (4a-j) catalyzed by Cu-HNA

A mixture of aryl aldehyde **1a-j** (1 mmol), 4-phenylurazole **2** (1 mmol), dimedone **3** (1 mmol), and Cu-HNA (0.02 g) as catalyst was heated and stirred in the oil bath at 100 °C for 30-40 min. The progress of reactions was monitored by TLC (n-hexane/EtOAc = 3:1). After completion of the reaction, the mixture was cooled to room temperature and washed with water. The solid product was purified by recrystallization from $EtOH/H_2O$ (4:1) to afford the pure product in high yields. All compounds are known and their physical and spectroscopic data were in good agreement with those of authentic samples. The catalyst was collected by filtration and washed with a small portion of hot water, and was reused for three times without any significant changes in the reaction time and the yield.

2.4. Spectral data for selected products

*9-(4-chlorophenyl)-6,6-dimethyl-2-phenyl-5,6,7,9-tetrahydro-1H,8H-[1,2,4]triazolo[1,2-a]indazole-1,3,8(2H)-trione (**4b**):*

FT-IR (νmax/cm^{-1}): 3050, 2950, 1660,1610,1200; ^{1}H NMR (ppm, $CDCl_3$): δ 1.22 (s, 6H, CH_3), 2.34 (J=19.0 Hz, 1H, CH_2), 2.39 (J=19.0 Hz, 1H, CH_2), 2.90 (J=18.5 Hz, 1H, CH_2), 2.96 (J=18.5 Hz, 1H, CH_2), 6.21 (s, 1H, CH-Ar), 7.38-7.51 (m, 9H, Ar).

*6,6-dimethyl-9-(4-nitrophenyl)-2-phenyl-5,6,7,9-tetrahydro-1H,8H-[1,2,4]triazolo[1,2-a]indazole-1,3,8(2H)-trione (**4g**):*

FT-IR (νmax/cm^{-1}): 3040, 2960,1730, 1660, 1610, 1520, 1410, 1390, 1350; ^{1}H NMR (ppm, $CDCl_3$): δ 1.21 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.35 (J=18.5 Hz, 1H, CH_2), 2.42 (J=18.5 Hz, 1H, CH_2), 2.91 (J=18.5 Hz, 1H, CH_2), 2.98 (J=18.5 Hz, 1H, CH_2), 2.89-3.00 (m, 2H, CH_2), 6.32 (s, 1H, CH-Ar), 7.47 (s, 1H, Ar), 7.53 (s, 4H, Ar), 7.75 (d, J=7.6 Hz, 2H, Ar), 8.27 (d, J=7.6 Hz, 2H, Ar).

3. Results and discussion

For the primary study and optimization of the three-component reaction, as a model, first the condensation of 4-chlorobenzaldehyde, 4-phenylurazole, and dimedone was tested using different conditions.The results presented in Table 1 indicate that solvents affected the efficiency of the catalyst. Yields were lower in acetonitrile, ethanol, chloroform, ethyl acetate, and water (Table 1, entries 1-5). However, the best results were obtained under solvent-free conditions at 100°C (Table 1, entry 10-14). Next, the optimum amount of Cu-HNA was evaluated. In order to establish the true effectiveness of the catalyst, reaction was performed at 100°C without catalyst under solvent-free conditions. It was found that no conversion to triazolo[1,2-a]indazole1,3,8-trione occurred after 60 min of heating (Table 1, entries 9). The highest yield was obtained with 0.02 g of the catalyst (Table 1, entries 12). A further increase in the amount of Cu-HNA did not have any significant effect on the product yield.

Table 1. Optimization conditions of Cu-HNA catalyzed the synthesis of triazolo[1,2-a]indazole1,3,8-trione[a]

Entry	Condition/ Temp. (°C)	Catalyst amount (g)	Time (min)	Yield[b] (%)
1	CH_3CN/Reflux	0.02	60	42
2	EtOH/Reflux	0.02	60	30
3	$CHCl_3$/Reflux	0.02	60	27
4	EtOAc/Refiux	0.02	60	31
5	H_2O/Refiux	0.02	60	trace
6	Solvent-free/r.t	0.02	60	–
7	Solvent-free/50	0.02	60	trace
8	Solvent-free/70	0.02	60	43
9	Solvent-free/100	-	60	–
10	Solvent-free/100	0.01	60	55
11	Solvent-free/100	0.02	60	87
12	Solvent-free/100	0.02	40	88
13	Solvent-free/100	0.02	20	63
14	Solvent-free/100	0.04	40	90

[a] Condensation reaction between 4-chlorobenzaldehyde (1 mmol), urazole (1 mmol) and dimedone (1 mmol) in different conditions.
[b] Isolated yield.

The generality of this reaction was examined using different aldehydes having electron-donating as well as electron-withdrawing groups. Substituents on the aromatic ring had no obvious effect on yield or reaction time under the above optimal conditions. In all cases, the reactions gave the corresponding products in good yields and short reaction times (Table 2). This method offers significant improvements with regard to the scope of the transformation, simplicity and green aspects by avoiding toxic solvents.

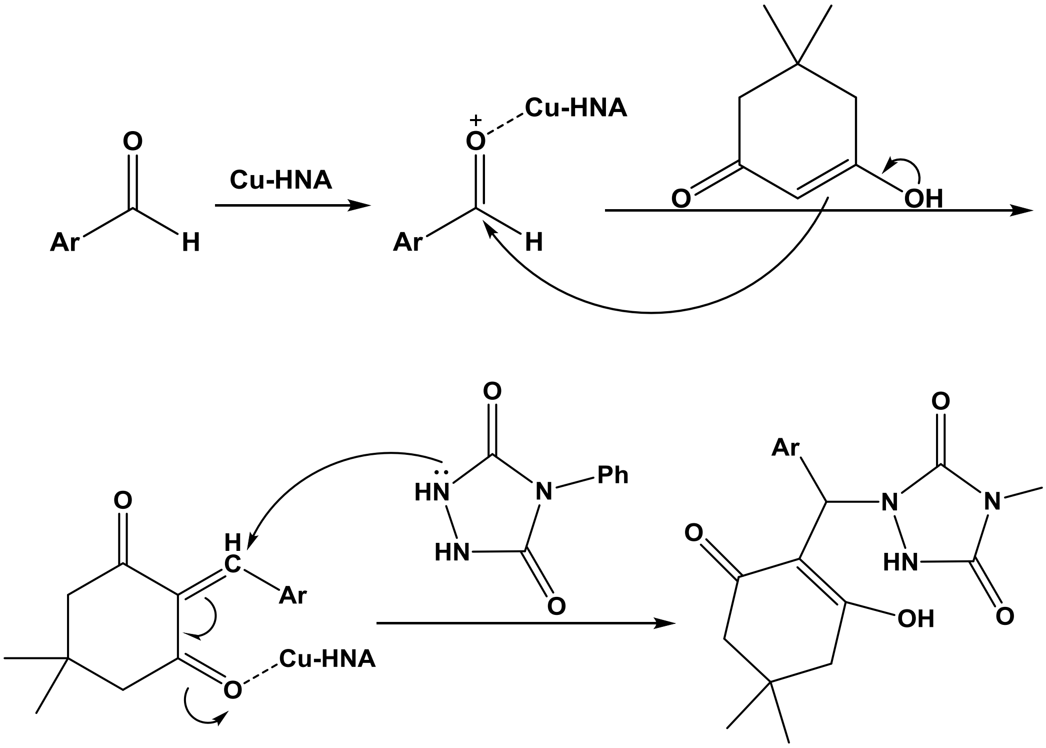
Table 3. Synthesis of triazolo[1,2-a]indazole1,3,8-trione[a]

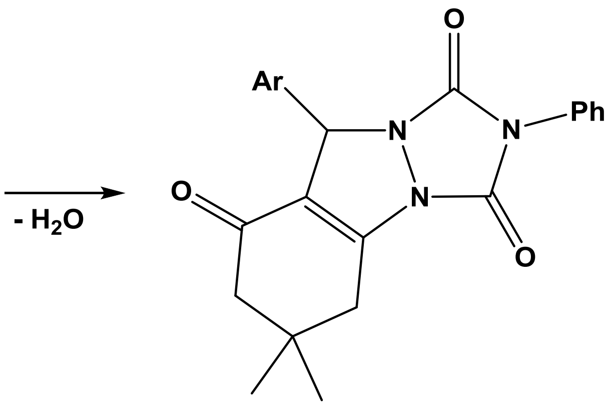
Entry	Ar	Product	Time (min)	Yield[b] (%)	M.P. °C Found	M.P. °C Reported[lit]
1	C_6H_5	**4a**	40	85	181-183	186-188[28]
2	4-ClC_6H_4	**4b**	40	88	170-172	166-168[28]
3	4-BrC_6H_4	**4c**	30	85	180-182	184-187[28]
4	3-BrC_6H_4	**4d**	40	90	165-168	160-162[28]
5	2-ClC_6H_4	**4e**	40	82	172-174	175-177[28]
6	3-OMeC_6H_4	**4f**	30	92	110-112	106-104[25]
7	4-$NO_2C_6H_4$	**4g**	30	90	124-126	126-128[28]
8	3- $NO_2C_6H_4$	**4h**	30	87	132-134	131-133[25]
9	4-MeC_6H_4	**4i**	40	84	162-164	163-164[25]
10	4-CNC_6H_3	**4j**	40	85	236-238	240-242[25]

[a] Condensation reaction between aldehyde (1 mmol), urazole (1 mmol), dimedone (1 mmol) and Cu-HNA (0.02 g) in solvent-free condition and 100°C.

[b] Isolated yield.

A possible mechanism for the formation of the products is shown in Scheme 3. The reaction occurs via initial formation of heterodiene by standard Knoevenagel condensation of aldehyde and dimedone. Subsequent Michael-type addition of the urazole to followed by cyclization affords the corresponding product (Scheme 3).





Scheme 3. The plausible mechanism for the condensation reaction of aryl adehyde, urazole, and dimedone catalyzed by the Cu-HNA complex.

4. Conclusions

In conclusion, an extremely efficient method has been developed for the synthesis of triazolo[1,2-a]indazole-triones via a one-pot three component condensation reaction using Cu-HNA as an eco-friendly catalyst. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, cost efficiency, use of solvent-free and mild conditions, simple workup, high yields and usage in synthesis of complex molecules. The Cu-HNA catalyst can be recycled and used at least three times without any substantial reduction in its catalytic activity.

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