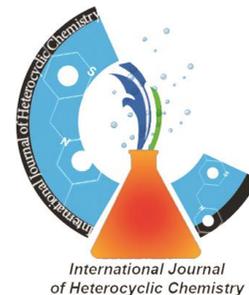

Research article

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One-pot synthesis of triazolo[1,2-a]indazole-triones catalyzed by a novel magnetically and reusable green catalyst of Preyssler

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Abstract:

An atom-efficient, eco-friendly, solvent-free, high yielding, multicomponent green strategy to synthesize triazolo[1,2-a]indazole-triones derivatives by the one-pot condensation of aldehyde, dimedone, and phenyl urazole under microwave irradiation is presented. Reactions catalyzed by a novel nanomagnetic organic-inorganic hybrid catalyst (Fe@Si-Gu-Prs) was prepared by the chemical anchoring of Preyssler heteropolyacid ($H_{14}[NaP_5W_{30}O_{110}]$) onto the surface of modified Fe_3O_4 magnetic nanoparticles with guanidine-propyl-trimethoxysilane linker. A series of different substituted aromatic aldehydes including either electron-withdrawing or electron-donating groups used in this reaction participated well and gave the corresponding products in good to excellent yield. In this method, catalyst was isolated and reused several times, at least four times without significant loss of activity.

Keywords: one-pot multicomponent reaction, magnetic nanoparticles, microwave irradiation, triazoloindazole, Preyssler

Introduction

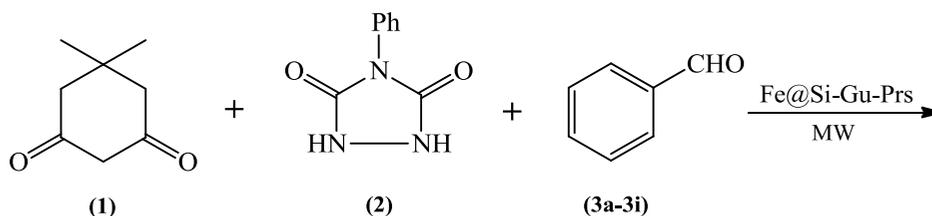
Multi-component reactions (MCRs) have emerged as an efficient and powerful method in modern organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very rapidly and in an efficient manner without the isolation of intermediates [1-3]. MCRs contribute to the principles of an environmentally friendly process by reducing the number of steps, energy consumption and production of waste. Therefore, the discovery for new MCRs and improvement of previously known MCRs with recyclable catalysts are of considerable interest [4-5].

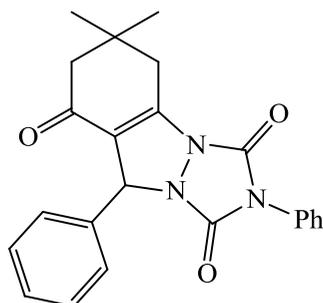
Heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals and biologically active pharmaceuticals vital for enhancing the quality of life [6]. Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing a urazole (1,2,4-triazolidine-3,5-diones) moiety are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [7]. Urazole derivatives also exhibit anticonvulsant or fungicidal activity as well as catalytic activity in radical polymerization [8].

In recent decades, magnetic nanoparticles (MNPs) have been widely studied for various biological and medical applications [9]. They have been shown to be promising supports for the immobilization of catalysts because magnetic catalysts can be easily separated from the reaction medium by an external magnet, which provides a simple separation of the catalyst without the need for filtration, centrifugation, or other tedious workup processes [10]. This separation technique has a special importance for nanosized catalyst supports where filtration methods result in the loss of catalyst particles and product contamination. Apart from an easy separation, an interesting property of MNPs is that an appropriate surface modification provides a wide range of magnetic-functionalized catalysts that show equal and sometimes higher activity than their homogeneous catalysts in organic transformations. In recent years, MNPs as catalyst or catalyst support have been widely used in a variety of important organic reactions including C-C coupling, reduction, oxidation and multicomponent reactions with high activity [11].

The Preyssler ($H_{14}NaP_5W_{30}O_{120}$) is a heteropoly acid (HPA) which has significant advantages, such as 14 acidic protons, high thermal stability, high hydrolytic stability ($0 < \text{pH} < 12$), regenerability and safety [12]. Owing to the low surface area ($7\text{--}10 \text{ m}^2/\text{g}$) and high solubility of HPAs in polar solvents, it is preferable to use them in supported form. These catalysts can be supported on neutral solids, such as silica, activated carbons, or zeolites and acidic ion exchange resins [13]. Recently, we functionalized Fe_3O_4 MNPs with 3-chloropropyl-trimethoxysilane and guanidine, respectively, and then Preyssler HPA immobilized via non-covalent interactions ($Fe@Si\text{-}Gu\text{-}Prs$) [14].

In a continuation of our achievements in the preparation of novel catalysts and based on our previous success in the preparation of MNPs as catalysts [15-20], in this study, we wish to report catalytic activity of this novel nanomagnetically recoverable catalyst ($Fe@Si\text{-}Gu\text{-}Prs$) as a heterogeneous and novel acidic catalyst in the synthesis of triazolo[1,2-a]indazole-trione derivatives by the one-pot condensation of aldehyde, dimedone, and phenyl urazole under microwave irradiation (Scheme 1).





(4a-4i)

Scheme 1. Synthesis of triazolo[1,2-a]indazole-trione derivatives using Fe@Si-Gu-Prs as a nano magnetic catalyst.

Experimental

The materials were purchased from Sigma-Aldrich and Merck and were used without any additional purification. Melting points were determined on an Electrothermal type 9100 melting point apparatus. IR spectra were recorded on a Thermo Nicolet AVATAR-370 FT-IR spectrophotometer and ^1H NMR spectra were recorded on a Bruker DRX400 spectrometer. The nanomagnetic Fe@Si-Gu-Prs catalyst was synthesized according to our previous reports [14].

synthesis of triazolo[1,2-a]indazole-triones

The Fe@Si-Gu-Prs catalyst (0.1 g) was added to a mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol) and phenyl urazole (1 mmol) under microwave Irradiation for 15min. Upon completion, the reaction mixture was allowed to cool to room temperature and the catalyst was separated from the reaction mixture by an external magnet and thoroughly washed and dried to be reused in the next run. Cold water (20 mL) was added to the reaction mixture (without a catalyst) and after stirring for a few minutes, the solid product formed was filtered off and washed several times with cold ethanol and water. The resulting crude product was recrystallized from ethanol and gave compounds **4a-i** in high yields.

Results and discussion

For optimized the variables (amount of catalyst, and the time) the reaction of benzaldehyde (**3a**) was chosen as a model system under MW irradiation. We first examined the reaction of benzaldehyde (1 mmol), dimedone (1 mmol), and phenyl urazole (1 mmol) in the presence of catalytic amount of several acid catalysts. The results are summarized in Table 1. As it is observable, the best results obtained using 0.1 g of nanomagnetic Fe@Si-Gu-Prs catalyst (entry 4). It is noteworthy that the reactions were completed after about 15 min, and increasing the amount of the catalyst (entry 5) and the time (entry 6) did not affect on the reaction process.

Table 1. Optimization of reactions under microwave irradiation (400 W).

Entry	Catalyst (g)	Time (min)	Yield (%)
1	-	30	trace
2	Fe@Si-Gu-Prs (0.01)	30	trace

3	Fe@Si-Gu-Prs (0.05)	20	35
4	Fe@Si-Gu-Prs (0.1)	15	70
5	Fe@Si-Gu-Prs (0.2)	15	72
6	Fe@Si-Gu-Prs (0.1)	30	71
7	H ₁₄ NaP ₅ W ₃₀ O ₁₂₀	20	58
8	(0.1)	20	45
	H ₃ PW ₁₂ O ₄₀ (0.1)		

Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), and phenyl urazole (1 mmol).

Also, the effect of various solvents on the rate of the reaction was studied (Table 2). As can be seen, MW irradiation was favorable conditions for this synthesis.

Table 2. Effect of various conditions on triazolo[1,2-a]indazole-triones synthesis.

Entry	Conditions	Time (min)	Yield (%)
1	Reflux/CH ₃ CN	60	56
2	Reflux/EtOH	60	60
3	Reflux/CHCl ₃	60	50
4	Reflux/H ₂ O	60	trace
5	MW	15	70

Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), and phenyl urazole (1 mmol) in presence of 0.1 g of Fe@Si-Gu-Prs catalyst.

After optimizing the conditions, we next examined the generality of these conditions to other substrates (aldehydes). The results are summarized in Table 3. It could be seen that by using this nanomagnetic catalyst (Fe@Si-Gu-Prs), the aromatic aldehydes containing electron donating and electron withdrawing groups afforded the products with good to excellent yields. Compounds **4a–i** are stable solids whose structures were established by IR, and ¹H-NMR spectroscopy.

Table 2. Synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives using Fe@Si-Gu-Prs nanomagnetic catalyst.

Entry	Aldehyde	Product	Yield ^a (%)	m.p.
1	C ₆ H ₅ CHO	4a	70	187-190
2	4-ClC ₆ H ₄ CHO	4b	81	165-168
3	4-BrC ₆ H ₄ CHO	4c	72	180-183
4	4-FC ₆ H ₄ CHO	4d	82	104-107
5	4-NO ₂ C ₆ H ₄ CHO	4e	83	173-176

6	4-CH ₃ C ₆ H ₄ CHO	4f	71	158-161
7	2-ClC ₆ H ₄ CHO	4g	71	170-173
8	4-	4h	75	178-181
9	CH ₃ OC ₆ H ₄ CHO	4i	77	130-133
	4-OHC ₆ H ₄ CHO			

Reaction conditions: benzaldehyde (1 mmol), dimedone (1 mmol), and phenyl urazole (1 mmol) in presence of 0.1 g of Fe@Si-Gu-Prs catalyst, under microwave irradiation after 15 min.

We think Fe@Si-Gu-Prs catalyst is a good proton source in terms of convenience, cheapness, and easy production. The cheapness and availability of the reagents, easy procedure and facile work-up make this method attractive for the large-scale operations. This nanomagnetic particle not only exhibits excellent activity in this one-pot reaction, but also simplifies recycling and reuse of the catalyst.

This magnetic catalyst can be easily removed from the reaction mixture by an external magnet, and it was reused several times without loss of catalytic activity.

Conclusions

In conclusion, we have used Fe@Si-Gu-Prs as an efficient, reusable, and green solid acid catalyst for synthesis of triazolo[1,2-a]indazole-1,3,8-trione derivatives that were prepared *via* one-pot three component reaction of aryl aldehydes, dimedone, and phenyl urazole under microwave irradiation conditions. Excellent yields, enhanced reaction rates and short reaction times, simplicity of operation, and easy workup are some advantages of this protocol.

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