

Hydrated Ferric Sulfate [Fe₂(SO₄)₃·xH₂O]: An Efficient and Reusable Catalyst for One-Pot Synthesis of 2*H*-Indazolo[2,1-*b*]phthalazine-triones

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ABSTRACT. Hydrated ferric sulfate can be used as an efficient and reusable catalyst for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives *via* one-pot three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic-1,3-diketones in ethanol under reflux conditions.

Key words: Ferric sulfate hydrate [Fe₂(SO₄)₃·xH₂O], Three component reactions, Phthalhydrazide, Cyclic-1,3-diketones, 2*H*-Indazolo[2,1-*b*] phthalazine-trione derivatives

INTRODUCTION

Hydrated ferric sulfate [Fe₂(SO₄)₃·xH₂O] has been found as a catalyst for various organic transformations such as tetrahydropyranations of alcohols,¹ preparation of acylals from aldehydes,² 2,3-unsaturated glycosides *via* Ferrier rearrangement,³ per-O-acetylation of sugars,⁴ synthesis of tetrahydroquinolines⁵ through Povarov reaction and synthesis of 1*H*-pyrazole-4-carbodithioate⁶ using MCRs. The unique solubility of the catalyst in ethanol and insolubility in DCM enables its usage as both homogenous and heterogeneous catalyst; and is recoverable by DCM after the reaction. As a part of our ongoing research work by employing MCRs to synthesize new molecules,⁷ we conceived that Fe₂(SO₄)₃·xH₂O can be exploited further as a reusable catalyst for the synthesis of heterocycles by employing multicomponent reactions.

The efficient high-throughput synthesis of biologically active organic compounds is one of the most important and challenging endeavors in modern drug discovery. Organic reactions should be fast, neat and clean, and the target products should be easily separable with high purity and good yields. To cover all the above aspects, multicomponent reactions⁸ (MCRs) play an important role in combinatorial chemistry because of their ability to synthesize target molecules with greater efficiency, higher atom-economy, structural diversity and complexity in a single step from three or more reactants. These reactions are very effective for synthesizing highly functionalized organic molecules from readily available starting materials.

The synthesis of heterocyclic compounds has gained

considerable attention among synthetic organic chemists due to their immense potentiality in pharmaceuticals. Heterocyclic systems are found abundantly in nature as alkaloids, flavonoids and isoflavonoids⁹ and they are considered to be essential to life. Among various nitrogen containing heterocycles, phthalazine skeleton is present in many naturally occurring compounds and they exhibit interesting pharmacological properties (Fig. 1). The compounds having fused phthalazines possess many biological activities such as anticonvulsant,¹⁰ cardiotoxic,¹¹ vasorelaxant,¹² antimicrobial,¹³ antifungal,¹⁴ anticancer,¹⁵ and anti-inflammatory¹⁶ activities. They are also highly potent inhibitors of vascular endothelial growth factor receptor II (VEGFR-2).¹⁷⁻¹⁹ Furthermore, these compounds might be useful materials for luminescence or fluorescence studies.²⁰

The synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives have been reported involving one-pot condensation of phthalhydrazide, aldehydes and 1,3-diketones using numerous catalysts.^{21,22} Though all these protocols are quite useful, still there is a need to develop a new methodology using a reusable catalyst.

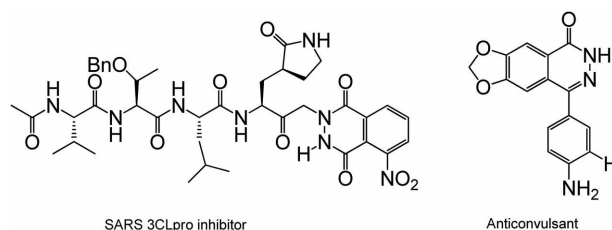
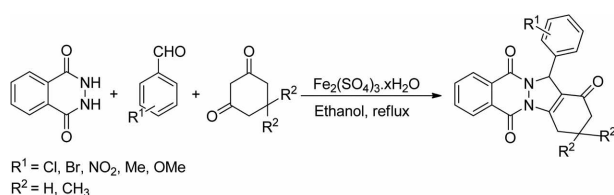


Figure 1. Some biologically active compounds having phthalazine skeleton.



Scheme 1. Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives.

In this paper, we have reported hydrated ferric sulfate catalyzed one pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives *via* three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic 1,3-dicarbonyl compounds in ethanol under reflux conditions as shown in *Scheme 1*.

EXPERIMENTAL

General experimental procedure for the Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives

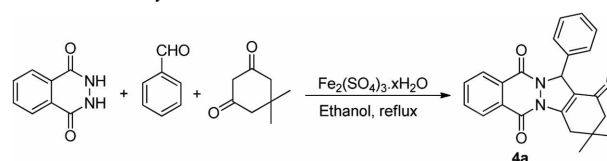
Hydrated ferric sulfate (0.20 mol, 0.084 g) was added to a mixture of an aromatic aldehyde (1.2 mmol), a cyclic 1,3-dicarbonyl compound (1.0 mmol) and phthalhydrazide (1.0 mmol) in 3 mL of ethanol. The reaction mixture was kept for refluxing in a preheated oil-bath. After completion of the reaction (as monitored by TLC), it was brought to room temperature. The solid product precipitated out after adding 6 mL of water into it and it was filtered off through a Büchner funnel. The precipitate was washed with ethanol (2 mL) and dried in a vacuum pump.

For checking reusability, a reaction mixture of phthalhydrazide (0.810 g, 5.0 mmol), 4-nitrobenzaldehyde (0.831 g, 5.5 mmol) and dimedone (0.700 g, 5.0 mmol) in presence of hydrated ferric sulfate (0.418 g, 1 mmol) was refluxed in 10 mL of ethanol. After completion of the reaction, the catalyst was recovered by removing ethanol in a rotatory evaporator followed by addition of 15 mL of CH_2Cl_2 . The catalyst was precipitated out due to its poor solubility in CH_2Cl_2 and it was filtered off through a Büchner funnel. The desired product **4b** was obtained after concentrating the organic solvent in a rotatory evaporator. The reusability of the recovered catalyst was examined for five consecutive times using the same substrates and the results are summarized in *Table 3*. We have noted that the catalyst can be reused without losing much catalytic activity.

RESULTS AND DISCUSSION

To find out suitable reaction conditions, benzaldehyde

Table 1. Optimization for one-pot condensation of phthalhydrazide, benzaldehyde and dimedone^a



Entry	Catalysts (mol%)	Solvent	Time (h)	Yield (%) ^b
1	None	Neat	10	0
2	None	EtOH	10	0
3	X (5)	Neat	10	Trace
4	X (5)	EtOH	10	40
5	X (10)	EtOH	7	56
6	X (15)	EtOH	4	70
7	X (20)	EtOH	3	87
8	X (25)	EtOH	3	88
9	X (20)	DCE	3	71
10	X (20)	MeCN	3	72
11	X (20)	H ₂ O	3	Trace
12	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (20)	EtOH	3	75
13	NiCl_2 (20)	EtOH	3	60
14	SnCl_2 (20)	EtOH	3	74
15	AcOH (20)	EtOH	3	40

^aThe reactions were carried out using phthalhydrazide (1.0 mmol), benzaldehyde (1.2 mmol) and dimedone (1.0 mmol). ^bIsolated Yield. X = $\text{Fe}_2(\text{SO}_4)_3 \cdot x\text{H}_2\text{O}$.

(1.2 mmol), dimedone (1 mmol), and phthalhydrazide (1 mmol) were chosen as the model substrates. The reactions were examined in presence of various catalysts in different solvent systems and the results are summarized in *Table 1*.

It was noted that the reaction did not provide any desired product in absence of catalyst after heating at 80 °C for 10 h either in neat or in ethanol (*Table 1*, entries 1 and 2). Interestingly, the desired product **4a** was isolated in 40% yield (*Table 1*, entry 4) when the same reaction mixture was heated in presence of 5 mol% hydrated ferric sulfate. Furthermore, we have carried out similar set of reactions in the presence of 10 mol%, 15 mol%, 20 mol% and 25 mol% (*Table 1*, entries 5-8), respectively. From these observations, we have noted that 20 mol% of the catalyst is the suitable choice to obtain best yield. For scrutinizing a suitable solvent system, the similar reaction was executed with similar boiling range of solvent such as dichloroethane, acetonitrile and water under identical reaction conditions. We found that the maximum yield of product **4a** was obtained in ethanol under reflux conditions (*Table 1*, entry 7). To examine the efficacy of the other catalysts, the similar reactions were performed in presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, NiCl_2 , SnCl_2 and CH_3COOH (*Table 1*, entries 12-15), respec-

tively and we have obtained moderate to good yield. However, we have used hydrated ferric sulfate because of its reusability.

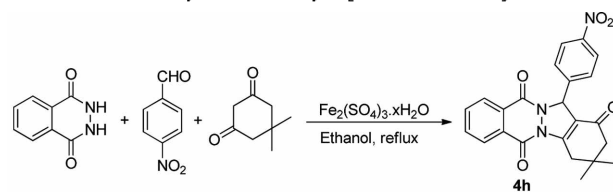
To generalize our protocol, a wide variety of aromatic aldehydes having electron-donating and electron-withdrawing substituents in the aromatic ring were reacted with phthalhydrazide, and dimedone under similar reaction condition and the desired 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives (**4b-o**) were obtained in good yields. Likewise, cyclohexane-1,3-dione also provided the desired 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives **4p-u** in good yields under identical reaction conditions. It is worthwhile to mention that aromatic aldehydes having electron-withdrawing group require relatively shorter reaction time as well as also provide good yields. Unfortunately, the similar kind of cyclized product was not obtained when the reaction carried out with acyclic 1,3-diketones. All the successful results (Table 2) clearly demonstrate that hydrated

Table 2. Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

Entry	R ¹	R ²	Time (h)	Product ^a	Yield (%) ^b
1	H	CH ₃	3	4a	87
2	4-OCH ₃	CH ₃	4	4b	83
3	2-OCH ₃	CH ₃	4	4c	81
4	3,4-(OCH ₃) ₂	CH ₃	4	4d	86
5	3,4,5-(OCH ₃) ₃	CH ₃	4	4e	84
6	4-OH-3-OCH ₃	CH ₃	4	4f	85
7	4-CH ₃	CH ₃	4	4g	84
8	4-NO ₂	CH ₃	2	4h	93
9	3-NO ₂	CH ₃	2	4i	92
10	2-NO ₂	CH ₃	2	4j	87
11	4-Cl	CH ₃	2	4k	89
12	2-Cl	CH ₃	2	4l	84
13	4-Br	CH ₃	2	4m	90
14	3-Br	CH ₃	2	4n	91
15	3-OH	CH ₃	4	4o	80
16	H	H	3	4p	86
17	4-Cl	H	2	4q	89
18	4-NO ₂	H	2	4r	90
19	4-OCH ₃	H	4	4s	83
20	4-OH-3-OCH ₃	H	4	4t	79
21	2-OCH ₃	H	4	4u	80

^aAll the reactions were carried out using phthalhydrazide (1.0 mmol), aromatic aldehydes (1.2 mmol) and dimedone (1.0 mmol)/cyclohexane-1,3-dione (1.0 mmol) using 0.2 mmol of catalyst. ^bIsolated yield.

Table 3. Reusability of the catalyst [Fe₂(SO₄)₃·xH₂O]

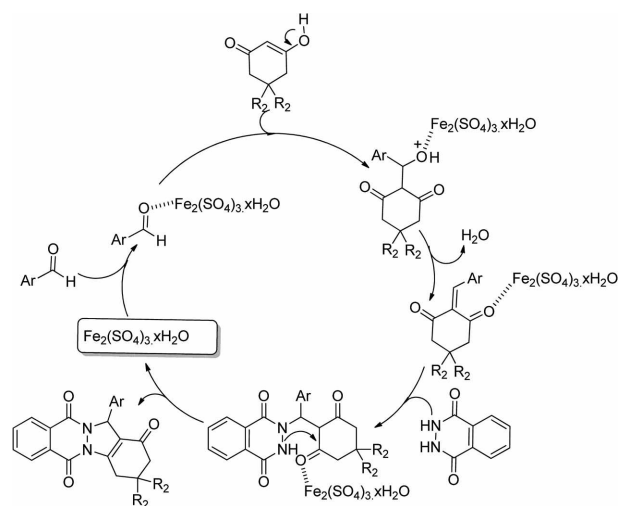


Round	Catalyst recovered (mg)	Reaction time (h)	Yield ^b (%)
1	418	3	94
2	413	3	92
3	403	3	91
4	395	3	90
5	388	3	89

^aThe same set of reaction was performed with phthalhydrazide (5.0 mmol), 4-nitrobenzaldehyde (5.5 mmol) and dimedone (5.0 mmol) in each time. ^bIsolated yield.

ferric sulfate is an efficient catalyst for this three-component reaction.

The probable mechanism for the formation of product may be rationalized as follows: Aromatic aldehyde reacts with dimedone to provide Knoevenagel product 2-benzyldene-5,5-dimethylcyclohexane-1,3-dione in the presence of hydrated ferric sulfate. Then the intermediate undergoes 1,4-Michael addition with phthalhydrazide followed by concomitant cyclization to give the desired product (Scheme 2).



Scheme 2. Probable mechanism for the formation of product.

RECYCLING OF THE CATALYST

In view of greener chemistry, efficient recovery and reuse of the catalyst are highly desirable. As a matter of fact, the catalyst Fe₂(SO₄)₃·xH₂O was recovered conveniently

from the reaction mixture at the end of the reactions and it was reused another four times for the same set of reaction.

CONCLUSION

In summary, we have shown that hydrated ferric sulfate is an efficient and reusable catalyst for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives via one-pot three-component condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic-1,3-diketones in ethanol under reflux conditions.

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