Hydrated ferric sulfate catalyzed synthesis of 3-[(alkyl/arylthio) (aryl)methyl]-1*H*-indole derivatives through one-pot reaction

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Hydrated ferric sulfate catalyzed synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole derivatives through one-pot reaction[≠]

Ajaz A. Dar,[a] Shahzad Ali [a] and Abu T. Khan[a,b,*]

[a]*Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India*

[b]*Aliah University, DN 18, 8th Floor, Sector V, Kolkata-700091, West Bengal, India.*
Tel.: +91 361 2582305; fax: +91 361 2582349

atk@iitg.ernet.in (A.T. Khan)

Abstract: A wide variety of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole derivatives (**4a-z**) were synthesized through a one-pot three-component reaction from indoles, aromatic aldehydes and thiols at room temperature using hydrated ferric sulfate as a Lewis acid catalyst. The key features of the present protocol are mild and simple reaction procedure, moderate to good yields, requirement of inexpensive and reusable catalyst, no formation of dithioacetals derivatives from the corresponding aldehydes as well as *bis*-(indolyl) methane derivatives.

Keywords: Three-component reactions, Indoles, Aromatic aldehydes, Thiols, Hydrated ferric sulfate [$Fe_2(SO_4)_3$•xH_2O].

Indoles and 3-substituted indole derivatives exhibit interesting biological properties and many of them are found as such in nature.[1-3] Recently various research groups have paid considerable attention to synthesize these compounds due to their wide range of biological activities such as antioxidant, antibacterial, anti-insecticidal and anticancer activity.[4] Numerous synthetic methods have been developed for their synthesis using either indole or 3-indolecarboxaldehyde. By employing powerful carbon-carbon bond forming reactions, the synthesis of 3-substituted indole derivatives were achieved using Mannich reaction,[5] Friedel–Crafts alkylation reactions of indoles,[6] conjugate addition of indoles to unsaturated carbonyl compounds and the reaction of two equivalents of indoles with carbonyl groups in the presence of a protic acid[7] or Lewis acid.[8-10] Interestingly, 3-substituted indole derivatives containing sulfur atom is not explored yet. As a matter of fact, the synthesis of these compounds containing sulfur atom is highly desirable because they might exhibit interesting pharmacological activities.[11]

Hydrated ferric sulfate [$Fe_2(SO_4)_3 \cdot xH_2O$] has received considerable attention as a mild, inexpensive and reusable Lewis acid catalyst for various organic transformations namely tetrahydropyranylation of alcohols,[12] preparation of acylals from aldehydes,[13] 2,3-unsaturated glycosides via Ferrier rearrangement,[14] per-*O*-acetylation of sugars,[15] synthesis of tetrahydroquinoline derivatives[16] and 1*H*-pyrazole-4-carbodithioate.[17] Recently, we have developed numerous multicomponent reactions (MCRs) for the synthesis of new organic molecules.[18] We conceived that hydrated ferric sulfate can be exploited further for the synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole derivatives at room temperature from indoles, aromatic aldehydes and thiols using one-pot three-component reaction, which is shown in Scheme 1.

Scheme 1

We have chosen *p*-chlorobenzaldehyde, indole and ethanethiol as the model substrates to find out a suitable reaction condition. At first, the reaction was conducted with a mixture of *p*-chlorobenzaldehyde, indole and ethanethiol in 3 mL of ethanol in the absence of a catalyst at room temperature and the desired product, 3-[(*p*-chlorophenyl)(ethylthio)methyl]-1*H*-indole (**4b),** was isolated only in 12% yield after 12 h of stirring (Table 1, entry 1). Interestingly, when the same reactions were examined in the presence of 5, 10 and 15 mol% hydrated ferric sulfate in ethanol (3 mL) at room temperature, the required product **4b** was obtained in 42%, 73% and 74% of yields respectively (Table 1, entries 2-4). It was noted that the yield of the product **4b** did not improve significantly by further increasing the amount of catalyst. Various reactions were also scrutinized with the same combination of the substrates in presence of other Lewis acid catalysts such as anhydrous ferric chloride, hydrated ferrous chloride, ceric ammonium nitrate (CAN), nickel chloride hexahydrate and vanadyl acetylacetonate and we have isolated the product **4b** in 70%, 68%, 16%, 63% and 58% yield, respectively (Table 1, entries 5-9). To find out a suitable solvent, the same reactions were also performed in different solvents such as dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), water (H_2O), tertrahydrofuran (THF), 1,4-dioxane, dimethylformamide (DMF) and 1,2-dichloroethane ($C_2H_4Cl_2$) (Table 1, entry 9-16). Though anhydrous ferric chloride and hydrated ferrous chloride provide similar yield, we have chosen hydrated ferric sulfate because of the reusability of the catalyst. From these observations, we conclude that the best result was obtained using 10 mol% catalyst in ethanol in terms of yields and reaction time.

Table 1

After optimizing the reaction conditions, the reaction of indole, benzaldehyde and ethanethiol was performed under optimized manner and it afforded the desired product **4a** in 70% yield. In order to find the scope of the reaction a wide variety of aromatic aldehydes were treated with indole and ethanethiol under identical reaction conditions and the desired products **4c**-**h** were obtained from moderate to good yields (Table 2, entries 3-8) depending upon the type and position of substitution on the aromatic ring. It was observed that aromatic aldehydes containing electron-withdrawing groups in the ring provided better yield as compared to the aldehydes having electron-donating substituent, which may be due to low electrophilicity of the aldehyde functionality in presence of electron-rich substituent. Similarly, *ortho*-substituted aromatic aldehydes also provide lower yield due to steric hindrance. We have also examined the reactions with different aliphatic thiols namely propanethiol, benzylthiol and 2-mercaptoethanol with indole and various aromatic aldehydes under similar reaction conditions and we have isolated the desired products **4i-m** from moderate to good yields (Table 2, entries 9-13). Encouraged by these successful results, we tried to extend our protocol using various aromatic thiols. Then, a reaction was carried out with indole, benzaldehyde and thiophenol under identical reaction conditions, which gave only 24% desired product along with *bis*-(indolyl) methane derivative 30% (Table 2, entry 14). The formation of low yield of the expected product might be due to less nucleophilicity of thiophenol. However, when the reactions were executed with indole, benzaldehyde with *p*-methylthiophenol or *p*-methoxythiophenol, respectively, it afforded the desired products in 64% and 67% yield (Table 2, entries 15 & 16). From these observations, it is clear that substituted thiophenols containing electron-rich substituent in the ring provided much better yields as compared to thiophenol. It is worthwhile to mention that our protocol also provided the desired product **4q** *albeit* in low yield with aromatic thiol containing electron-withdrawing group (Table 2, entry 17). Subsequently, we have examined the reaction with indole, different aromatic aldehydes containing electron-rich as well as electron-withdrawing substituent in the ring and electron-rich thiophenols and the corresponding desired products **4r-w** from moderate to good yields. It was observed that aromatic aldehydes having electron-withdrawing substituents provided better yield as compared to the aromatic aldehydes having electron-donating substituent (Table 2, entries 18-23). Interestingly, *p*-nitrobenzaldehyde also provided the desired product **4x** in 40% yield on reaction with indole and *p*-nitrothiophenol

under the experimental conditions. Likewise, the desired product **4y** was obtained from indole, 2-naphthylaldehyde and 4-methylthiophenol under identical conditions. Apart from indole, the reaction was performed by using 5-bromoindole, *p*-chlorobenzaldehyde and ethanethiol under the experimental reaction condition the desired product **4z** was obtained in 69% yield (Table 2, entry 26). However, when a reaction was carried out with indole, cyclohexanecarboxaldehyde and *p*-methylthiophenol in 3 mL of ethanol using the same amount of catalyst under identical reaction condition, we have isolated the corresponding *bis*-(indolyl) methane derivative in 40% yield instead of the desired product.

Table 2

All the products **4a-z** were characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses. The formation of the products can be rationalized as follows: There are two possible mechanistic pathways, which are shown in Scheme 2. In ***pathway a,*** an aromatic aldehyde reacts with indole to give intermediate iminium ion **A**, which reacts with thiol immediately to furnish the final product **4**. Alternatively, a thiol may react with an aromatic aldehyde to provide a reactive sulfonium ion intermediate **B**, which may react with indole to afford the final product **4** in (***pathway b)***. However, we believe that the '***pathway a***' is more favourable as we have obtained the desired product **4q** even with a less nucleophilic aromatic thiol such as *p*-nitrothiophenol. Hydrated ferric sulphate, [$Fe_2(SO_4)_3$•xH_2O] acts as a Lewis acid in the present transformation.

Scheme 2

Moreover, the structure of **4e** was further confirmed by single XRD crystallographic data.

Figure 1

The catalyst [$Fe_2(SO_4)_3$•xH_2O] was recovered conveniently from the reaction mixture at the end of the reaction after each cycle. After completion of the reaction, the ethanol was removed in a rotatory evaporator and the crude residue was dissolved in 10 mL of dichloromethane. On adding dichloromethane, the catalyst was separated out and it was filtered off through a Büchner funnel. The required product **4c** was isolated after concentrating dichloromethane followed by purification through a silica gel column chromatography. The reusability of the recovered catalyst was

examined for another four successive cycles with a similar set of reactions and the results are shown in Table 3. Due to loss of the catalyst in each cycle, the yield decreased relatively.

Table 3

In summary, we have achieved the synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole derivatives from indoles, aromatic aldehydes and various aliphatic/aromatic thiols using a catalytic amount of hydrated ferric sulfate at room temperature. We did not observe the formation of *bis*-(indolyl) methane derivatives as well as dithioacetals derivatives of the corresponding aromatic aldehydes in the present protocol. This reaction strategy involves use of a cheap and non-toxic hydrated ferric sulfate as the catalyst. Using this method, we are able to synthesize numerous 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indole derivatives from indoles, aromatic aldehydes and a wide variety of thiols.

Acknowledgements

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Supplementary data

Supplementary data (detailed experimental procedures, Crystallographic data in CIF, ^{1}H, ^{13}C NMR Spectra and spectral data for all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/.....

References and notes

≠ This work is dedicated to Late Dr. Uttara Debi who was compassionate and amicable in nature**.**

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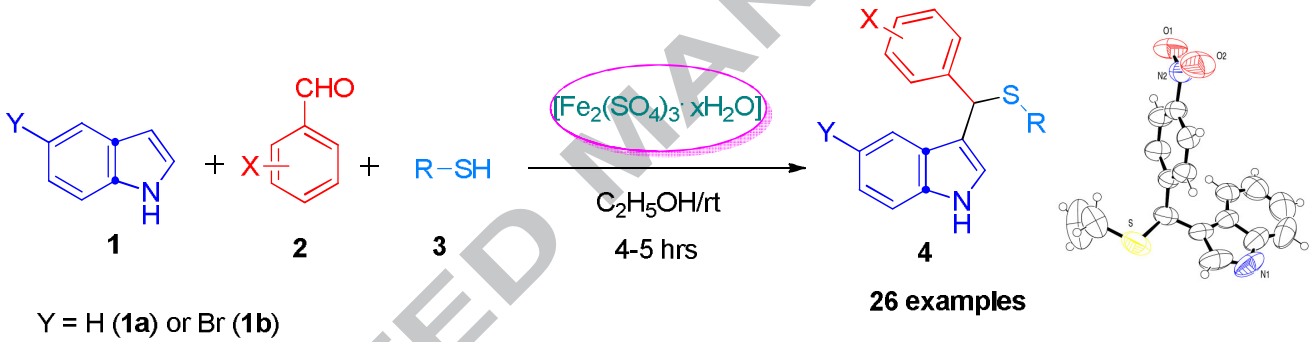
19. *General procedure*: Hydrated ferric sulfate (0.042 g, 0.1 mmol) was added to a stirred mixture of indole (1 mmol) and aldehyde (1 mmol) in 3 mL of ethanol at room temperature. Subsequently, thiol (1.2 mmol) was added into it and stirring was further continued. After completion of the reaction as monitored by TLC, ethanol was removed in rotary evaporator and the crude residue was extracted with dichloromethane (2 × 15 mL). The organic layer was washed with water followed by brine solution. The organic extract was dried over anhydrous sodium sulfate and it was concentrated in a rotary evaporator. Finally, the crude residue was passed through a silica gel column to obtain the desired pure product. All the desired products were eluted with ethyl acetate: hexane (1:9) mixture during column chromatography except for the compounds **4m** and **4x,** which were eluted with 1:1 mixture of the same solvent system.

Graphical abstract

Hydrated ferric sulfate catalyzed synthesis of 3-[(alkyl/arylthio) (aryl)methyl]-1H-indole derivatives through one-pot reaction

Ajaz A. Dar, Shahzad Ali and Abu T. Khan*



Y = H (**1a**) or Br (**1b**)

X = H, F, Cl ,Br, NO_2, Me, OMe, CN

2 = 2-Naphthaldehyde

R = Et, Pr, $HOCH_2CH_2$, Ph, $PhCH_2$, *p*-MeOPh, *p*-MePh, p-NO_2Ph

Formation of one C-C and one C-S bonds and one stereocentre in a single operation

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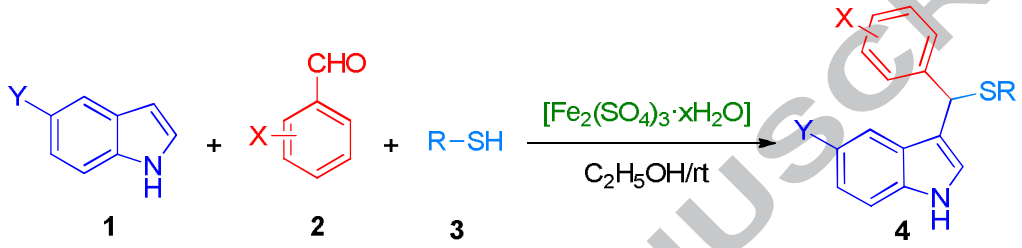

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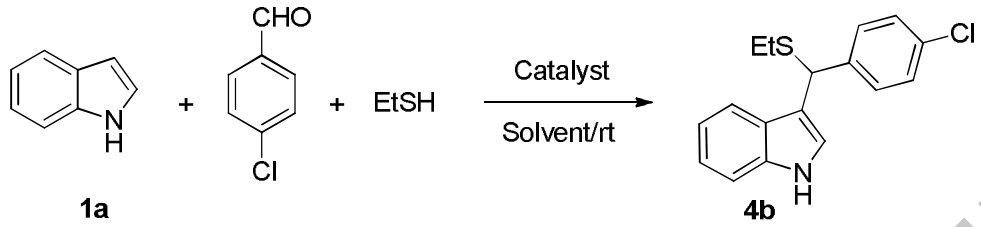
X = H, F, Cl ,Br, NO_2, Me, OMe, CN

2 = 2-Naphthaldehyde

R = Et, Pr, $HOCH_2CH_2$, Ph, $PhCH_2$, *p*-MeOPh, *p*-MePh, *p*-NO_2Ph

Scheme 1. Synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles

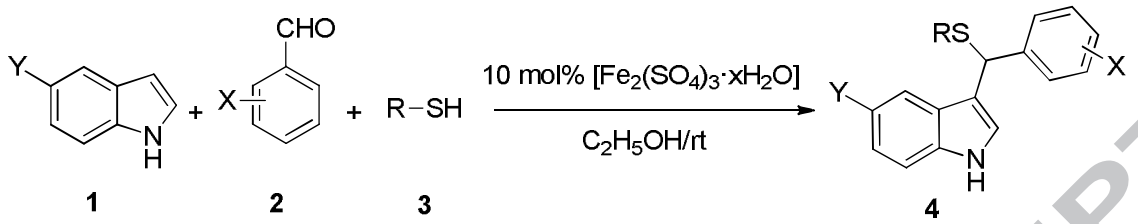
Table 1. Optimization for reaction conditions[a]



Entry	Catalyst	Solvent	Catalyst (mol %)	Time/h	Yield (%)[b]
1	No catalyst	Ethanol	0	12	12
2	$Fe_2(SO_4)_3.H_2O$	Ethanol	5	6.0	42
3	$Fe_2(SO_4)_3.H_2O$	Ethanol	10	4.0	73
4	$Fe_2(SO_4)_3.H_2O$	Ethanol	15	4.0	74
5	$FeCl_3$	Ethanol	10	5.0	70
6	$FeCl_2.xH_2O$	Ethanol	10	5.0	68
7	CAN	Ethanol	10	5.0	16
8	$NiCl_2.6H_2O$	Ethanol	10	5.0	63
9	$VO(acac)_2$	Ethanol	10	5.0	58
10	$Fe_2(SO_4)_3.H_2O$	CH_2Cl_2	10	4.0	66
11	$Fe_2(SO_4)_3.H_2O$	CH_3CN	10	4.0	68
12	$Fe_2(SO_4)_3.H_2O$	H_2O	10	5.0	27
13	$Fe_2(SO_4)_3.H_2O$	THF	10	5.0	67
14	$Fe_2(SO_4)_3.H_2O$	Dioxane	10	5.0	25
15	$Fe_2(SO_4)_3.H_2O$	DMF	10	5.0	30
16	$Fe_2(SO_4)_3.H_2O$	$C_2H_4Cl_2$	10	5.0	65

[a]All the reactions were carried out using indole (1 mmol), *p*-chlorobenzaldehyde (1 mmol) and ethanethiol (1.2 mmol) in 3 mL of solvent at room temperature. [b]Isolated yield.

Table 2. $Fe_2(SO_4)_3.xH_2O$ catalyzed synthesis of substituted 3-thiolalkyl/arylated indoles

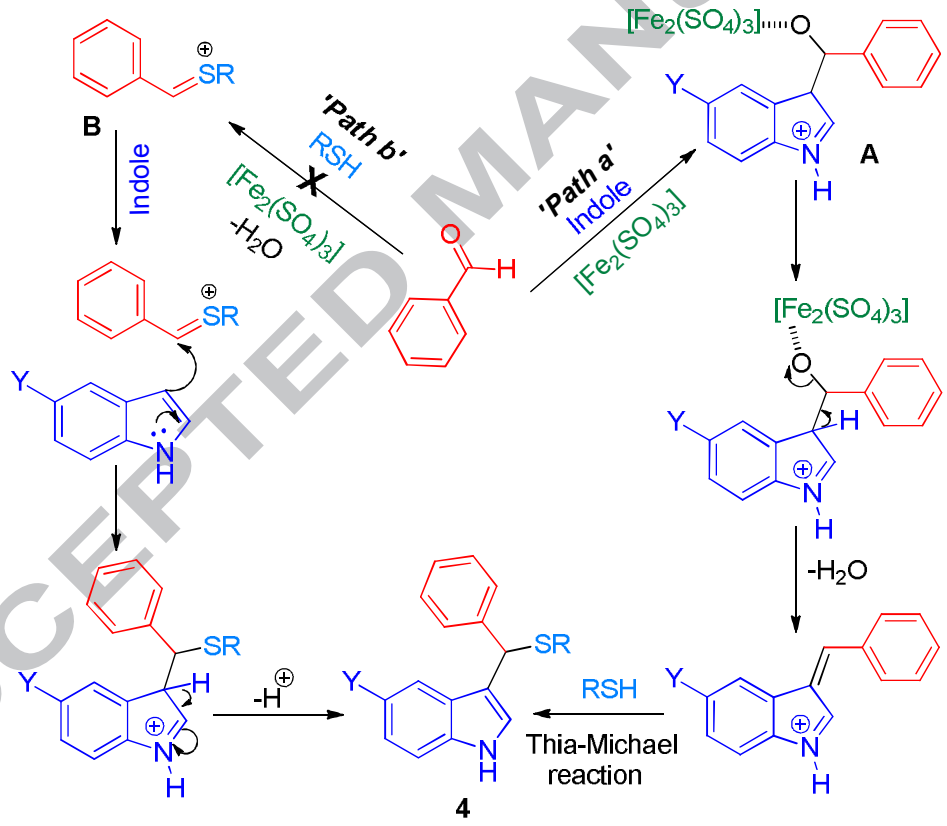


1 2 3 4

Entry	Indole	Aldehyde	Substituent/R	Product[a]	Yield (%)[b]
1	**1a**	Benzaldehyde	Et	**4a**	70
2	**1a**	*p*-Chlorobenzaldehyde	Et	**4b**	73
3	**1a**	*p*-Bromobenzaldehyde	Et	**4c**	72
4	**1a**	*p*-Methoxybenzaldehyde	Et	**4d**	53
5	**1a**	*p*-Nitrobenzaldehyde	Et	**4e**	74
6	**1a**	*o*-Chlorobenzaldehyde	Et	**4f**	25
7	**1a**	*o*-Nitrobenzaldehyde	Et	**4g**	30
8	**1a**	*m*- Nitrobenzaldehyde	Et	**4h**	75
9	**1a**	Benzaldehyde	Pr	**4i**	69
10	**1a**	*p*- Chlorobenzaldehyde	Pr	**4j**	71
11	**1a**	*p*- Methylbenzaldehyde	Pr	**4k**	51
12	**1a**	Benzaldehyde	$C_6H_5CH_2$	**4l**	61
13	**1a**	Benzaldehyde	$HOCH_2CH_2$	**4m**	62
14	**1a**	Benzaldehyde	C_6H_5	**4n**	24
15	**1a**	Benzaldehyde	*p*-MeC_6H_4	**4o**	64
16	**1a**	Benzaldehyde	*p*-$MeOC_6H_4$	**4p**	67
17	**1a**	Benzaldehyde	*p*-$NO_2C_6H_4$	**4q**	20
18	**1a**	*p*- Bromobenzaldehyde	*p*-MeC_6H_4	**4r**	68
19	**1a**	*p*- Methylbenzaldehyde	*p*-MeC_6H_4	**4s**	49
20	**1a**	*p*- Methoxybenzaldehyde	*p*-MeC_6H_4	**4t**	46

21	**1a**	*p*- Nitrobenzaldehyde	*p*-$MeOC_6H_4$	**4u**	71
22	**1a**	*p*- Cyanobenzaldehyde	*p*-MeC_6H_4	**4v**	70
23	**1a**	*p*-Fluorobenzaldehyde	*p*-$MeOC_6H_4$	**4w**	66
24	**1a**	*p*- Nitrobenzaldehyde	*p*-$NO_2C_6H_4$	**4x**	40
25	**1a**	2-Naphthaldehyde	*p*-MeC_6H_4	**4y**	68
26	**1b**	*p*-Chlorobenzaldehyde	Et	**4z**	69

[a]All the reactions were performed using **1** (1 mmol), aldehyde (1 mmol) and thiol (1.2 mmol). [b]Isolated yield.



Scheme 2. Plausible mechanism for the formation of the product **4.**

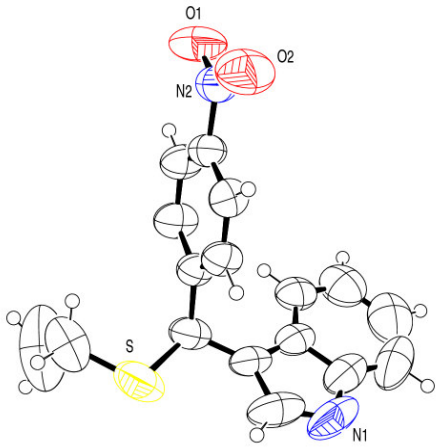
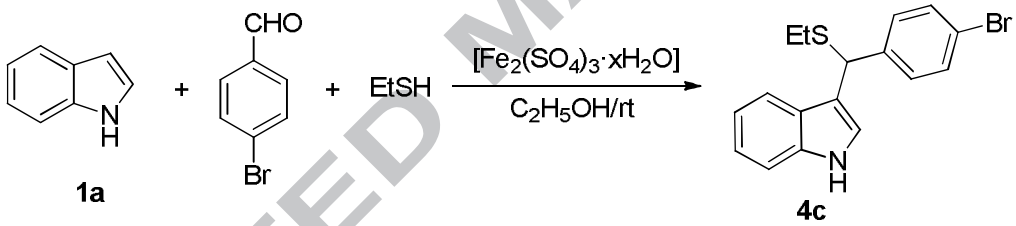


Figure 1. X-ray structure of compound **4e** (CCDC 930601)

Table 3. Results of the study on the recovery and reusability of $[Fe_2(SO_4)_3 \cdot xH_2O]$[a]



Round	Catalyst recovered/mg	Reaction time (h)	Yield (%)[b]
1	126	4.0	72
2	121	4.0	70
3	117	4.0	67
4	113	4.0	61
5	106	4.0	55

[a] All the reaction were performed with 3 mmol scale of the reactants using 9 mL of ethanol at room temperature. [b] Isolated yield.