Tetrahedron Letters 52 (2011) 4539–4542

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$]: an efficient heterogeneous catalyst for the synthesis of tetrahydroquinoline derivatives using Povarov reaction

Abu T. Khan *, Deb Kumar Das, Md. Musawwer Khan

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India

ARTICLE INFO

Article history:
Received 13 May 2011
Revised 17 June 2011
Accepted 19 June 2011
Available online 25 June 2011

Keywords:
Ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$]
Heterogeneous catalyst
Tetrahydroquinoline derivatives
Povarov reaction
Multicomponent reactions

ABSTRACT

$Fe_2(SO_4)_3{\cdot}xH_2O$ can be used as an efficient and reusable catalyst for the synthesis of pyrano- and furano-tetrahydroquinolines via one-pot three-component Povarov reaction involving aromatic aldehydes, aromatic amines, and cyclic enol ethers. The catalyst is recyclable, economically viable, and environmentally benign. This protocol provides good yields and diastereoselectivity as well as applicability on a wide range of substrates.

In recent years, ferric sulfate [$Fe_2(SO_4)_3{\cdot}xH_2O$] has received considerable attention as a mild, inexpensive, and reusable catalyst for various organic transformations, such as tetrahydropyranylation of alcohols,[1] preparation of acylals from aldehydes,[2] 2,3-unsaturated glycosides via Ferrier rearrangement,[3] and per-*O*-acetylation of sugars.[4] Due its wide applicability as a catalyst, we presume that it would be an efficient catalyst for the one-pot three-component synthesis of the fused tetrahydroquinoline derivatives by employing Povarov reaction.

Tetrahydroquinoline derivatives exhibit interesting biological activities. For example, 2-aryl-2,3-dihydro-4-quinolone (**1**) showed antitumor activity[5] and 2-aryl-1,2,3,4-tetrahydro-quinoline (**2**) is a core structure of the compounds possessing 5-lipoxygenase inhibitor properties as well as potential therapeutic application in asthma[6] as shown in Figure 1. Due to its pharmaceutical importance the development of new methods for the construction of a tetrahydroquinoline framework is in continuous interest to the synthetic organic chemists.[7]

Recently, multicomponent reactions (MCRs) have received considerable interest among synthetic chemists for construction of complex molecules.[8] Using this approach, fused tetrahydroquinoline derivatives can be easily accessible by employing aromatic aldehydes, aromatic amines, and 3,4-dihydropyran (DHP) or 2,3-dihydrofuran in the presence of suitable catalysts.[9] Over the years, a number of reagents have been explored as catalysts to access these compounds, such as proline triflate,[10a] 4-nitrophthalic acid,[10b] SmI_2,[10c] $NbCl_5$,[10d] TMSCl,[10e] lanthanide triflates,[10f] silica chloride or amberlyst-15,[10g] $GdCl_3$,[10h] I_2,[10i] $SbCl_3$,[10j] and Cu $(OTf)_2$.[10k] Some of these methods are associated with certain limitations such as use of excess catalyst,[10h,10i] and some of them are very expensive[10f] and non-reusable catalysts. Consequently, there is further scope to find out a greener catalyst, which provides better yields and selectivity. In this paper, we would like to report $Fe_2(SO_4)_3{\cdot}xH_2O$ as a useful catalyst for synthesis of fused tetrahydroquinoline derivatives.

For the present study, the mixture of benzaldehyde (1 mmol), aniline (1 mmol), and 3,4-dihydropyran (DHP) (1 mmol) was treated with 10 mol % of $Fe_2(SO_4)_3{\cdot}xH_2O$ in acetonitrile (4 mL) at room temperature. Pyranoquinolines **3c** and **4c** were obtained in 54% combined yield with good diastereoselectivity (30:70). The products were characterized from ^1H NMR, ^{13}C NMR spectra, and by their elemental analysis.

For optimizing the amount of catalyst and choosing the suitable solvent, various trial reactions were carried out with a combination of 4-chlorobenzaldehyde, aniline, and 3,4-dihydropyran. The results and observations are summarized in Table S1 (Supplementary data). It was noted that 10 mol % of the catalyst provides the best result for the formation of product under reflux conditions. It has also been observed that acetonitrile is conducive for the present reaction as compared to other solvents, such as ethanol, dichloromethane, dimethylformamide, toluene,
and water.

After optimizing the reaction conditions, the mixture of benzaldehyde (1 mmol), aniline (1 mmol), and 3,4-dihydropyran (1 mmol) in acetonitrile was treated with 10 mol % $Fe_2(SO_4)_3{\cdot}xH_2O$

* Corresponding author. Tel.: +91 361 2582305; fax: +91 361 2582349.
E-mail address: atk@iitg.ernet.in (A.T. Khan).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.06.080

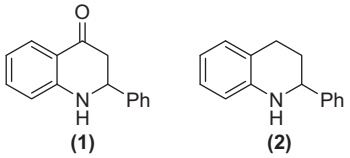


Figure 1. Biologically active tetrahydroquinoline derivatives.

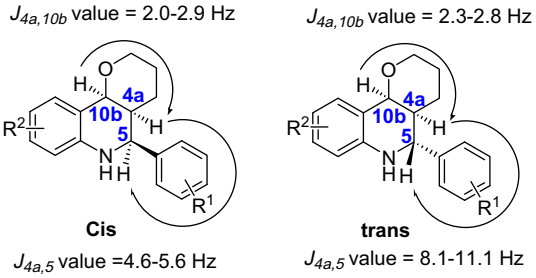


Figure 2. Coupling constant values used for determining stereochemistry.

under identical reaction conditions and the desired tetrahydroquinoline derivatives **3a** and **4a** were obtained in 87% combined yield. The stereochemistry of the fused ring junctures and other positions was established from their coupling constant values. The coupling constant between H_{4a} and H_{10b} ($J_{4a,10b}$) was found to be 2.0–2.9 Hz for all the products indicating a *cis* ring junction between the quinoline and pyran rings. Similarly, the coupling constant value between H_{4a} and H_5 ($J_{4a,5}$) was found to be 5.6 Hz in **3a** indicating the *cis* relationship, whereas the coupling constant value is 10.8 Hz in case of *trans* isomer **4a** as shown in Figure 2, which is in agreement with the reported literature value.[10d]

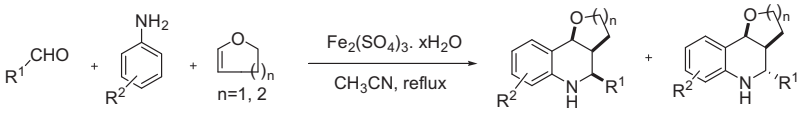
The reaction with various substituted aromatic aldehydes, such as Me, OMe, Cl, Br, and NO_2 with aniline and 3,4-dihydropyran were carried out under the same reaction conditions. The reaction time, percentage yield, and *cis:trans* ratio of the products **3** and **4** are shown in Table 1 (entries b–g). Likewise, various other aldehydes, such as 2-furaldehyde, 2-naphthaldehyde, and 3-methyl-2-thiophenecarboxaldehyde were reacted with aniline and dihydropyran under identical reaction conditions to provide the desired imino-Diels–Alder products (Table 1, entries h–j).

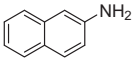
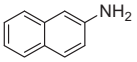
Furthermore, reactions with several substituted anilines were also studied with aromatic aldehydes and dihydropyran with the same amount of catalyst under similar reaction conditions (Table 1, entries k–o). The desired products **3k–o** and **4k–o** were obtained in good yields with similar diastereoselectivity. In the case of 2-naphthylamine, we have isolated the *trans* products **4p** and **4q** exclusively.

The structure of compound **4q** was determined through single crystal XRD data as shown in Figure 3.[12] Unfortunately, 4-hydroxybenzaldehyde did not provide the desired tetrahydroquinoline on reaction with amine and DHP under identical conditions even after prolonging the reaction for 12 h. Similarly, 4-nitroaniline also did not undergo Povarov reaction with other aromatic aldehydes. The scope of the presented protocol was verified with other enol ether, for example, 2,3-dihydrofuran (Table 1, entries r–t).

In view of a greener chemistry, the efficient recovery of the catalyst is highly desirable. In the present protocol, the catalyst $Fe_2(SO_4)_3{\cdot}xH_2O$ can be recovered conveniently from the reaction mixture at the end of the reaction. The reusability of the recovered

Table 1
Scope of various substituted pyrano/furanotetrahydroquinoline derivatives[11]



Entry	R^1	2	*n*	Time (h)	Yield[a] (%)	Ratio[b] (**3**:**4**)
a	Ph	$PhNH_2$	2	1.5	87	22:78
b	4-MeC_6H_4	$PhNH_2$	2	1.0	91	20:80
c	4-ClC_6H_4	$PhNH_2$	2	1.5	87	19:81
d	4-BrC_6H_4	$PhNH_2$	2	1.5	89	22:78
e	4-$MeOC_6H_4$	$PhNH_2$	2	1.0	88	19:81
f	3-$NO_2C_6H_4$	$PhNH_2$	2	1.5	84	23:77
g	4-$NO_2C_6H_4$	$PhNH_2$	2	1.5	86	18:82
h	2-furyl	$PhNH_2$	2	1.5	82	21:79
i	2-naphthyl	$PhNH_2$	2	1.5	86	21:79
j		$PhNH_2$	2	1.5	78	0:100
k	Ph	4-$MeC_6H_4NH_2$	2	1.0	92	20:80
l	Ph	4-$ClC_6H_4NH_2$	2	1.5	89	14:86
m	Ph	4-$MeOC_6H_4NH_2$	2	1.0	91	21:79
n	Ph	4-$BrC_6H_4NH_2$	2	1.5	87	17:83
o	4-ClC_6H_4	4-$ClC_6H_4NH_2$	2	1.0	91	20:80
p	Ph		2	2.5	82	0:100
q	2-naphthyl		2	1.5	85	0:100
r	4-MeC_6H_4	$PhNH_2$	1	1.5	87	23:77
s	2-furyl	$PhNH_2$	1	1.5	82	22:78
t	Ph	4-$ClC_6H_4NH_2$	1	1.5	85	21:79

[a] Isolated yields.
[b] The product ratio was determined from crude ^1H NMR spectra.

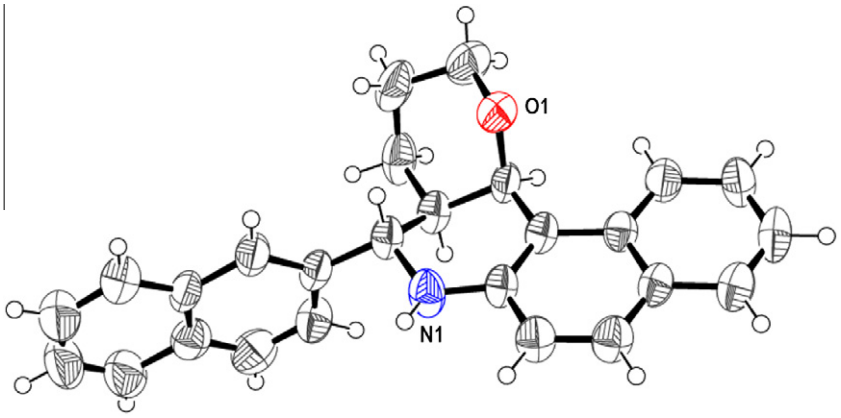
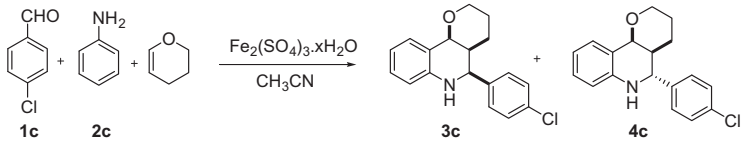


Figure 3. Single crystal X-ray structure of **4q** (CCDC No. 793766).

Table 2
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)	Ratio[b] **3c**:**4c**	Yield[c] (%)
1	415	1.5	19:81	87
2	410	1.5	21:79	86
3	405	1.6	20:80	84

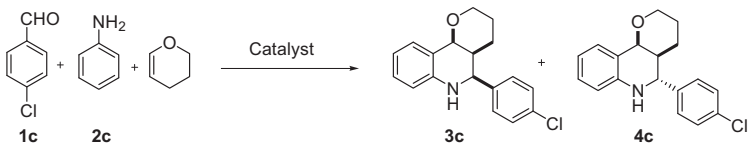
[a] Reaction was carried out with 10 mmol scale.
[b] The product ratio was determined from ^{1}H NMR spectra.
[c] Isolated yields.

catalyst was examined and the results are summarized in Table 2. It clearly indicates that the catalyst can be reused for three successive times without losing activity.

The efficiency and generality of the present protocol can be realized at a glance by comparing our results with those of some reported procedures as shown in Table 3. The results have been compared with respect to the mole percent of the catalyst used, yields, and diastereoselectivity. The similar Povarov reaction was reported by Laszlo and co-workers using $FeCl_3$ in combination of other co-catalyst.[13] It is worthy to mention that the present protocol provides better diastereoselectivity and avoidance of co-catalyst as compared to $FeCl_3$ method. Considering all these parameters, we believe that $Fe_2(SO_4)_3{\cdot}xH_2O$ is a better catalyst for Povarov reaction.

In conclusion, we have demonstrated $Fe_2(SO_4)_3{\cdot}xH_2O$ can be used for one-pot Povarov reaction for the synthesis of pyrano- and furano[3,2-c]quinoline derivatives. In comparison to other Lewis acids catalyst, it has been found to be effective, mild, and less expensive. In addition, it requires shorter reaction times, providing good yields and diastereoselectivity. Moreover, due to its recyclability, the present method may open up an environmentally benign pathway for the synthesis of fused pyrano- and furanotetrahydroquinolines.

Table 3
Comparison of our result with other results using different catalysts



Entry	Catalyst	Amount	Condition	Time (h)	Ratio[a] (3a:4a)	Yield[b,c]
1	$FeCl_3$	10 mol %	rt	6	50:50	82[13]
2	Proline triflate	5 mol %	rt	5	25:75	85[10a]
3	4-Nitrophthalic acid	25 mol %	50 °C	3.5	39:61	90[10b]
4	I_2	30 mol %	rt	3	23:77	84[10i]
5	$Fe_2(SO_4)_3{\cdot}xH_2O$	10 mol %	reflux	1.5	19:81	87[d]

[a] The product ratio was determined from ^{1}H NMR spectra.
[b] Isolated yields.
[c] Reported method with other catalysts.
[d] The present protocol.

Acknowledgments

D.K.D. is thankful to IIT Guwahati for his research fellowship. M.M.K. acknowledges UGC for his research fellowship. We are thankful to D.S.T. for providing XRD facility under the FIST programme.

Supplementary data

Supplementary data (optimization table, X-ray crystallographic data (CIF file) of **4q**, spectral data of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.080.

References and notes

1. Li, L.; Zhu, L.; Zhang, X.; Zhang, G.; Qu, G. *Can. J. Chem.* **2005**, *83*, 1120.
2. Zhang, X.; Li, L.; Zhang, G. *Green Chem.* **2003**, *5*, 646.
3. Zhang, G.; Liu, Q.; Shi, L.; Wang, J. *Tetrahedron* **2008**, *64*, 339.
4. Shi, L.; Zhang, G.; Pan, F. *Tetrahedron* **2008**, *64*, 2572.
5. Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Hackl, T.; Lee, K. H. *J. Med. Chem.* **1998**, *41*, 1155.
6. Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669.
7. Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.
8. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2006.
9. Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789.
10. (a) Li, J.; Li, J.; Su, W. *J. Chem. Res.* **2009**, 499; (b) Srinivasa, A.; Mahadevan, K. M.; Hulikal, V. *Monatsh Chem.* **2008**, *139*, 141; (c) Zhou, Z.; Xu, F.; Han, X.; Han, X.; Zhou, J.; Shen, Q. *Eur. J. Org. Chem.* **2007**, 5265; (d) da Silva-Filho, L. C.; Junior, V. L.; Constantino, M. G.; da Silva, G. V. J. *Synthesis* **2008**, 2527; (e) More, S. V.; Sastry, M. N. V.; Yao, C. *Synlett* **2006**, 1399; (f) Makioka, Y.; Shindo, T.; Taniguchi, Y.; Takaki, K.; Fujiwara, Y. *Synthesis* **1995**, 801; (g) Das, B.; Reddy, M. R.; Holla, H.; Ramu, R.; Venkateswarlu, K.; Rao, Y. K. *J. Chem. Res.* **2005**, 793; (h) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J.Org. Chem.* **1999**, *64*, 6462; (i) Xia, M.; Lu, Y. D. *Synlett* **2005**, 2357; (j) Maiti, G.; Kundu, P. *Tetrahedron Lett.* **2006**, *47*, 5733; (k) Bohorquez, A. R. R.; Kouznetsov, V. V.; Doyle, M. P. *Lett. Org. Chem.* **2011**, *8*, 5.
11. *General procedure for the synthesis of tetrahydroquinoline derivatives:* Into a 25 mL round bottomed flask, a mixture of anilines (1 mmol) and aromatic aldehydes (1 mmol) in acetonitrile (2 mL) was taken and left for stirring for 10 min at room temperature. Then, both enol ether (1 mmol) and the catalyst ferric sulfate (0.042 g, 10 mol %) were added successively into the above reaction mixture. Finally, the reaction flask is fitted with a reflux condenser and kept for refluxing in an oil-bath. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by filtration and usual work-up procedure was followed to obtain the crude products. The products **3** and **4** were eluted in ethyl acetate/hexane (05:95) in 78–92 yield after column chromatographic separation. Spectral data of some selected compounds: Compound **3d**: White solid (0.067 g, 20%); mp 124 °C; R_f (5% ethyl acetate/hexane) 0.34; IR (KBr): 3445, 3379, 2932, 2851, 1605, 1482 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (2H, dd, J = 6.4, 2.4 Hz), 7.42 (1H, d, J = 7.6 Hz), 7.30 (2H, d, J = 8.4 Hz), 7.10 (1H t, J = 7.6 Hz), 6.81 (1H, t, J = 7.6 Hz), 6.60 (1H, d, J = 8.0 Hz), 5.31 (1H, d, J = 5.6 Hz), 4.65 (1H, d, J = 2.0 Hz), 3.82 (1H, br s), 3.61–3.57 (1H, m), 3.42 (1H, td, J = 11.6, 2.0 Hz), 2.12–2.11 (1H, m), 1.57–1.42 (3H, m), 1.30–1.25 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 140.4, 131.7, 128.7, 128.4, 127.8, 121.4, 120.2, 118.8, 114.8, 72.8, 60.8, 59.1, 39.1, 25.6, 18.2. Anal. Calcd for $C_{18}H_{18}BrNO$ (344.25): C, 62.80; H, 5.27; N, 4.07. Found: C, 62.98; H, 5.19; N, 4.01. Compound **4d**: White solid (0.239 g, 69%); mp 133 °C; R_f (5% ethyl acetate/hexane) 0.23; IR (KBr): 3312, 2937, 2838, 1613, 1487 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (2H, d, J = 8.4 Hz), 7.30 (2H, d, J = 7.6 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.10 (1H, t, J = 7.6 Hz), 6.72 (1H, t, J = 7.6 Hz), 6.53 (1H, d, J = 8.4 Hz), 4.69 (1H, d, J = 10.8 Hz), 4.38 (1H, d, J = 2.4 Hz), 4.11–4.08 (1H, m), 4.03 (1H, br s), 3.72 (1H, td, J = 11.2, 2.0 Hz), 2.05–2.02 (1H, m), 1.83–1.75 (1H, m), 1.71–1.61 (1H, m), 1.47–1.42 (1H, m), 1.37–1.33 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 141.5, 131.9, 131.0, 129.6, 129.5, 121.7, 120.8, 117.8, 114.4, 74.5, 68.7, 54.4, 39.0, 24.2, 22.1. Anal. Calcd for $C_{18}H_{18}BrNO$ (344.25): C, 62.80; H, 5.27; N, 4.07. Found: C, 62.61; H, 5.19; N, 4.22. Compound **4q**: White solid (0.310 g, 85%); mp 214 °C; R_f (5% ethyl acetate/hexane) 0.19; IR (KBr): 3391, 3055, 2931, 2900, 2839, 1620, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.82 (5H, m), 7.64 (1H, d, J = 8.0 Hz), 7.56 (2H, t, J = 8.4 Hz), 7.50–7.42 (3H, m), 7.20 (1H, t, J = 7.6 Hz), 6.69 (1H, d, J = 8.8 Hz), 4.96 (1H, s), 4.26 (1H, br s), 4.17 (1H, dd, J = 10.8, 3.6 Hz), 3.83 (t, J = 11.2 Hz, 1H), 2.30–2.20 (m, 1H), 1.97–1.87 (qt, J = 4.0 Hz, 8.8 Hz, 1H), 1.70 (1H, tt, J = 9.2, 4.4 Hz), 1.51–1.45 (1H, m), 1.34–1.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 139.5, 133.9, 133.5, 133.4, 130.2, 128.7, 128.5, 128.1, 128.0, 127.9, 127.5, 127.2, 126.4, 126.2, 125.6, 122.0, 121.7, 117.9, 111.2, 71.4, 69.0, 54.9, 38.7, 24.3, 22.1. Anal. Calcd for $C_{26}H_{23}NO$ (365.18): C, 85.45; H, 6.34; N, 3.83. Found: C, 85.14; H, 6.39; N, 3.71.
12. *Crystallographic data.* The X-ray crystal structures were determined with a Siemens P-4 diffractometer. Complete crystallographic data of **4q** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 793766. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).
13. Cabral, J.; Laszlo, P. *Tetrahedron Lett.* **1989**, *30*, 7237.