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FeF_3 MEDIATED SYNTHESIS OF 3,4-DIHYDRO-3-PYRIDYL-2*H*-NAPHTHA[2,1-*E*][1,3]OXAZINE DERIVATIVES

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ABSTRACT
Biologically active 3,4-dihydro-3-substituted-2H-naphtho [2,1-e][1,3]oxazine derivatives were synthesized using environmentally benign and economically feasible Lewis acid FeF_3. They are characterized by FT-IR, HNMR and Mass spectroscopic methods.

INTRODUCTION
1,3-oxazine derivatives, especially, when they were condensed with aromatic rings displayeddiverse biological properties, such as antibacterial, anticancer, anti-fungal, analgesic, anticonvulsant and anti-tubercular activities.[i,ii] Moreover, trifluoromethyl-1,3-oxazine-2-one is highly active against various HIV-1 mutant strains, since, they are non-nucleoside reverse transcriptase inhibitors that have an ability to bind and block HIV reverse transcriptase. Further, naphthoxazine derivatives showed high-level potential for the treatment of Parkinson's disease**.**[iii,iv] They wereshown to be anti-inflammatoryagents. They were also used for treating allergies, ulcers, asthma, diabetes, and arthritis. 1,3-Oxazines have been used as key intermediates in the synthesis of thrombolytic agents, chiral auxiliaries in organic synthesis and liquid crystal devices.[v]In a comprehensive survey of literature, it was found that naphth-1,3-oxazine derivatives were conventionallyprepared using 2-naphthol, and various substituted aryl and heteroaryl aldehydes in the presence of dry methanolic ammonia. Further, the multi-component condensation of phenols or naphthols with primary amines (or ammonia) and two equivalents of aldehydes led to these target molecules. Similarly,condensation of derivatives of Betti base with aromatic aldehydes led to the formation of the corresponding 1,3-oxazine with varied biological properties.[vi] Yet another method involves using the condensation reaction of salicylaldehyde with a primary amine, followed by reduction and then cyclizationreaction with a suitable aldehyde. The oxazines containing six-membered ring nitrogen and oxygen was constructed by a type of Mannich reaction, in which zirconyl(IV)

chloride enhances the reaction. Synthesized compounds were investigated against Gram-positive Bacillus subtilis,Gram-negative Escherichia coli, and two fungi Candida albicans and Aspergillus niger, in comparison with standard drugs, indicating that these compounds possess significant antibacterial and antifungal activity.[vii,viii]

A series of novel naphtho[1,2-e][1,3]oxazines bearing arylsulfonamide moiety were synthesized via a one-pot approach and in a green reaction medium. They were examined for their in vitro anticancer activity against breast (MCF-7), colon (HCT116), and B-Celllymphoma(Waco3-CD5) cancers.[ix]The synthesis of 1,2-dihydro-1-arylnaphtho[1,2-e]oxazine-3-one using the three-component system (*β*-naphthol, benzaldehyde, and urea) was achieved in presence of $HClO_4$-SiO_2.[x] Moreover,another oxazine derivative (1,3-diphenyl-1H-naphtho[1,2-e]oxazine) was developed by the reaction of N-arylidene-1-(*α*-aminoarylbenzyl)-2-naphthol with iodobenzene diacetate.[xi] Nevertheless, all the above methods require expensive reagents and tedious work-up procedures.

In order to overcome this, the development of environmentally friendly and economically inexpensive processes for the synthesis of biologically active heterocycles, using readily available and cheap reagents,becomes an important goal of current organic synthesis**.**Our present aim is to synthesize 3,4-dihydro-3-substituted-2*H*-naphtho [2,1-e][1,3]oxazine derivatives using environmentally benign,economically feasible Lewis acid FeF_3.

EXPERIMENTAL

All the chemicals were purchased from Sigma–Aldrich and were used without any further purification. The progress of the reactions waschecked on TLC and spots were observed under the UV light. Products were confirmed by Proton and Carbon NMR spectra, performed on Gemini Varian-VXR-unity (400 MHz, 300 MHz) instrument. Chemical shifts (d) are reported in ppm from TMS as internal standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector.

GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUNDS (4a-g):

A mixture of formalin (0.2 mol), aromatic amine (0.1 mol), 1-naphthol (0.1 mol) and Lewis acid (0.15 mol) was stirred at room temperature for 1hr. After the completion of reaction, the reaction mixture was extracted with DCM. The solvent was removed under reduced pressure. The obtained product waspurified by column chromatography on silica gel by hexane: ethyl acetate as eluent.

3,4-dihydro-3-(pyridin-4-yl)-2*H*-naphtho[2,1-e][1,3]oxazine (4a):IR: 1050 (C-O-C),1198 (C-O-C);^{1}HNMR (DMSO-d_6, ppm) δ = 4.86 (s, 2H), 5.40 (s, 2H), 6.84-7.56 (m, 9H), 8.41 (d, 1H);MS: m/z263$(M+1)^+$;

3,4-dihydro-3-(pyridin-3-yl)-2*H*-naphtho[2,1-e][1,3]oxazine (4b):^{1}HNMR (DMSO-d_6, ppm) δ = 4.77 (s, 2H), 5.40 (s,2H), 6.80-7.52 (m, 8H),8.43 (m, 2H);MS: m/z 262.9$(M+1)^+$;

3,4-dihydro-3-(pyridin-2-yl)-2*H*-naphtho[2,1-e][1,3]oxazine (4c). ^{1}HNMR (DMSO-d_6, ppm) δ = 4.74 (s, 2H), 5.39 (s, 2H), 6.83-7.52 (m, 9H), 8.36 (d, 1H);MS: m/z263.4$(M+1)^+$;

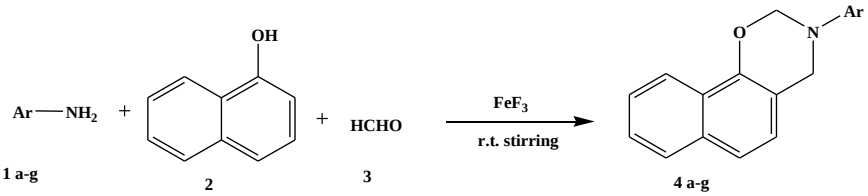
3,4-dihydro-3-(6-methylpyridin-2-yl)-2*H*-naphtho[2,1-e][1,3]oxazine (4d). ^{1}HNMR (DMSO-d_6, ppm)δ = 2.48 (s, 3H), 4.81 (s, 2H), 5.44 (s, 2H), 6.85-7.54 (m, 9H); MS: m/z 277.1$(M+1)^+$;

3,4-dihydro-3-(5-methylpyridin-2-yl)-2*H*-naphtho[2,1-e][1,3]oxazine (4e). ^{1}HNMR (DMSO-d_6, ppm) δ = 2.41 (s, 3H), 4.75 (s, 2H), 5.44 (s, 2H), 6.88-7.61 (m, 8H), 8.43 (d, 1H);MS: m/z 277.2$(M+1)^+$;

3,4-dihydro-3-(4-methylpyridin-2-yl)-2*H*-naphtho[2,1-e][1,3]oxazine (4f). ^{1}HNMR (DMSO-d_6, ppm)δ = 2.40 (s, 3H), 4.76 (s, 2H), 5.46 (s, 2H) 6.90-7.61 (m, 8H), 8.43 (d, 1H);MS: m/z 276.7$(M+1)^+$;

3-(5-chloropyridin-2-yl)-3,4-dihydro-2*H*-naphtho[2,1-e][1,3]oxazine (4g). ^{1}HNMR (DMSO-d_6, ppm)δ = 4.76 (s, 2H), 5.43 (s, 2H) 6.84-7.52 (m, 8H), 8.44 (d, 1H);MS: m/z 297.8$(M+1)^+$;

Scheme



Ar = 4-pyridyl, 3-pyridyl, 2-pyridyl, 2-(6-methylpyridyl), 2-(5-methylpyridyl), 2-(4-methylpyridyl), 2-(5-chloropyridyl)

Results and Discussion

We wish to report the synthesis of 3,4-dihydro-3-pyridyl-2*H*-naphtho[2,1-*e*][1,3]oxazine derivatives promoted by ionic liquid as a catalyst (Scheme 1). We have considered the reaction of aromatic amine, 1-naphthol and formalin at room temperature with continuous stirring condition as the model reaction.

Conclusion

3,4-dihydro-3-substituted-2H-naphtho [2,1-e][1,3] oxazine derivatives were synthesized using reagent FeF_3. All the above synthesized derivatives were characterized by FT-IR, HNMR and Mass spectroscopic methods. The peaks of oxazine ring were observed in the range ofδ 4.7-4.8 and δ 5.3-5.4 ppm, respectively, indicates the presence of NCH_2 and OCH_2 groups, which confirms the formation of benzoxazine ring.

References

i. Chylin´ska, J.B., Urban´ski, T., Mordarski, M., 1963. Dihydro-1,3-oxazine derivatives and their antitumor activity. J. Med. Chem. 6,484–487.

ii. Didwagh, S.S., Piste, P.B., 2013. Novel one-pot synthesis andantimicrobial activity of 6-chloro-2,4- diphenyl 3,4-dihydro-2H-1,3-benzoxazine derivatives. Int. J. Chem. Tech. Res. 5, 2199–2203.

iii. Zuhal Turgut *,EmelPelit, AdemKöycü, Synthesis of New 1,3-Disubstituted-2,3-dihydro-1H-naphth[1,2e][1,3]oxazines.*Molecules* 2007, *12*(3), 345-352.

iv. Suryakant B. Sapkal,Kiran F. Shelke,Amol H. Kategaonkar, Murlidhar S. Shingare, Dual role of ammonium acetate for solvent-free synthesis of 1,3-disubstituted-2,3-dihydro-1H-naphth-[1,2e] [1,3]-oxazine.Green Chemistry Letters and Reviews: 2009, 2,2.

v. NiloZanatta*, Adriana M. C. Squizani, Leonardo Fantinel, Fabiane M. Nachtigall, Deise M. Borchhardt, Helio G. Bonacorso and Marcos A. P. Martins Synthesis of N-substituted 6-trifluoromethyl-1,3-oxazinanes. J. Braz. Chem. Soc., Vol. 16, No. 6A, 1255-1261, 2005

vi. Valmik D. Dhakane , Somnath Gholap, Umesh P. Deshmukh, Babasaheb P. Bandgar,An efficient and green method for the synthesis of [1,3]oxazine derivatives catalyzedby thiamine hydrochloride (VB1) in water; ComptesRendusChimie; 2014, 17(5):431–436.

vii. Kategaonkar, A.H., Sonar, S.S., Pokalwar, R.U., Kategaonkar, A.H.,Shingate, B.B., Shingare, M.S., 2010. An efficient synthesis of 3,4-dihydro-3-substituted-2H-naphtho[2,1-e][1,3]oxazine derivatives catalyzed by zirconyl(IV) chloride and evaluation of its biologicalactivities. Bull. Korean Chem. Soc. 31, 1657–1660.

viii. Mathew, B.P., Kumar, A., Sharma, S., Shukla, P.K., Nath, M., 2010.An eco-friendly

synthesis and antimicrobial activities of dihydro-2H-benzo- and naphtho-1,3-oxazine derivatives. Eur. J. Med.Chem. 45, 1502–1507.

ix. Saved Gholamhossein Mansouri Hassan Zali-BoeiniKamiarZomorodianBahmanKhalvatiRazieHelaliPargali Ali DehshahriHadi Amiri Rudbari Mehdi Sahihi Zahra Chavoshpour,Synthesis of novel naphtho [1,2-e][1,3]oxazines bearing an aryl sulfonamide moiety and their anticancer and antifungal activity evaluations , Arabian Journal of Chemistry, 2020, 13: 1271-1282.

x. Mayekar, A.N., Yathirajan, H.S., Narayana, B., Sarojini, B.K.,SuchethaKumari, N., Harrison, W.T.A., 2011. Synthesis andantimicrobial study of new 8-bromo-1,3-diaryl-2,3-dihydro-1H-naphtho[1,2e][1,3]oxazines. Inter. J. Chem. 3, 74–86.

xi. V. Verma, K. Singh, D. Kumar et al., "Synthesis, antimicrobial and cytotoxicity study of 1, 3-disubstituted-1H-naphtho[1, 2-e][1, 3]oxazines," European Journal of Medicinal Chemistry, vol. 56, pp. 195–202, 2012.

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