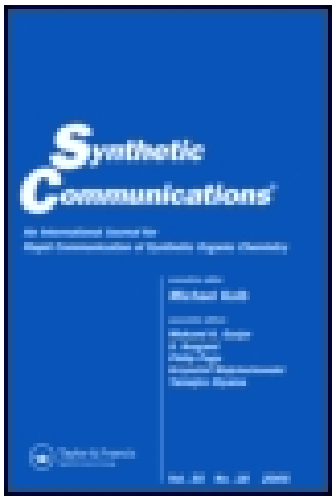

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Acid Catalyzed Silica Supported One Pot Benzoylation Route to Synthesize 2-(Substituted Phenyl)oxazolo[4,5-b]pyridines Under Ambient Conditions

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ACID CATALYZED SILICA SUPPORTED ONE POT BENZOYLATION ROUTE TO SYNTHESIZE 2-(SUBSTITUTED PHENYL)OXAZOLO[4,5-B]PYRIDINES UNDER AMBIENT CONDITIONS

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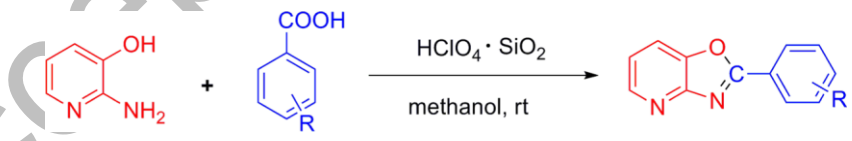
Abstract

Present paper elicits the silica supported perchloric acid catalyzed efficient protocol for the synthesis of 2-(phenyl)oxazolo[4,5-b]pyridine derivatives. The remarkable feature of this strategy embraces the high conversion, simple work-up procedures, ambient conditions, short reaction time and reusability of the catalyst. Structures of the synthesized compounds have been established on the basis of elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry). Moreover, in order to investigate the mechanistic details of the reaction and to ascertain the regioselective outcome of the product, local nucleophilicity descriptors N_k at B3LYP/6-311G++(d, p) level were determined and analyzed.



KEYWORDS: Silica supported perchloric acid ($HClO_4 \cdot SiO_2$), benzoylation, oxazolo[4,5-b]pyridine, local nucleophilicity index.

INTRODUCTION

In the present scenario one-pot reactions are quite close to "ideal synthesis"[1] as they minimize consumption of time, complex equipment, costly protection/deprotection steps, and can provide excellent yields and selectivities. Also, these are considered to be environmentally benign and atom economical.[2] Therefore, development of one-pot reactions from easily available materials is the need of the hour and highly desirable in organic synthetic chemistry.

Oxazolo[4,5-b]pyridine has emerged as a potent inhibitor of fatty acid amide hydrolase [FAAH] for pain relief, anxiety management, and treatment of sleep disorders.[3] Its pharmacological activities also include anti-pyretic, anti-inflammatory, analgesic[4] and antifungal properties.[5] These compounds also find their application as pesticides[6] and dyes.[7] Also, fluorescence emission in visible region makes them good contributors toward construction of LED devices or nonlinear optic (NLO) systems.[8] Hence considering the significant applications in the fields of pharmacology, agriculture and industrial sector there has been tremendous upsurge of interest in developing efficient methods for synthesizing oxazolo[4,5-b]pyridines.

In particular, 2-(phenyl)oxazolo[4,5-b]pyridine derivatives have been traditionally synthesized by condensation of 2-amino-3-hydroxypyridine with benzoic acid derivatives,[9] benzoic anhydride,[10] benzoyl chloride,[11] orthoesters[12] and also by direct arylation of oxazolo[4,5-b]pyridine.[13] Several catalysts have been reported in the literature for the synthesis of this moiety viz., polyphosphoric acid, trimethyl sillyl polyphosphate and silica supported sulphuric acid.[14] Moreover, C-2 arylation of oxazolo

pyridine in the presence of palladium acetate and triphenyl phospine has also been reported. However, most of these methods suffer from several bottlenecks such as tedious workup procedure, requirement of high temperature and power source and lesser yields. Also, except microwave assisted route all of them require prolonged reaction time. Therefore, search for new methods/catalysts to overcome these limitations is still an important experimental challenge to synthetic organic chemists.

Hence, considering these challenges of synthetic protocols and in continuation of our studies on synthesis of heterocyclic compounds,[15, 16, 17] herein, we have presented a simple and convenient method to synthesize 2-(phenyl)oxazolo[4,5-b]pyridine derivatives using silica supported perchloric acid. The silica supported catalyst have high mechanical and thermal stability, low toxicity, recyclability and ease of handling.[18] A number of reactions have been cited in the literature eliciting the role of catalysts immobilized on silica.[19,20,21] In our earlier attempts, we have performed the reaction using catalyst $HClO_4 \cdot SiO_2$ at different temperatures reported in the literature for other catalyst systems. However, to our surprise upon performing the reaction at room temperature with this catalyst it took place successfully under ambient conditions. It could have happened because of the nanoparticle size of the catalyst, thereby expected to exhibit better chemical reactivity owing to the larger surface area to volume ratio.

RESULTS AND DISCUSSION

This protocol deals with the synthesis of 2-(phenyl)oxazolo[4,5-b]pyridine derivatives **3** in the presence of $HClO_4.SiO_2$ as the heterogenous and reusable nanocatalyst under ambient conditions (Scheme 1).

The transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images of catalyst reveal the nanosize and spherical surface morphology of the catalyst (Figure 1 and 2).

Initially, we have checked the feasibility of the reaction by reacting together 2-amino 3-hydroxy pyridine and benzoic acid in the presence of DMF as the solvent at room temperature which was resulted in very low yield. Afterwards, the same reaction was performed in methanol and we were amazed to see that, the reaction was carried out easily in appreciable yield and resulted in the off white solid product. Other solvents such as acetonitrile and water were also found unsuitable for this protocol. Also, when the reaction was carried out in the presence of perchloric acid alone (without silica support) the yield was satisfactory to some extent but it required enhancement in the reaction time with lack of reusability of the catalyst.

Upon optimization of reaction conditions, we found that under refluxing conditions a very low yield was obtained. For further investigations, a broad range of structurally diverse benzoic acid derivatives were used to treat with 2-amino-3-hydroxypyridine (Table 1).

Literature encompasses a number of synthetic protocols for the synthesis of oxazolo pyridine skeleton as shown in Table 2. It is reviewed that in contrast to the all reported methods, the present strategy offers certain added advantages such as ambient conditions, high product yield, simple procedure with easy workup, atom economy and most importantly the reusability of catalyst.

All the synthesized compounds were characterized by ^{1}H NMR, MASS, ^{13}C NMR and FT-IR spectroscopic data. Peaks in the IR region 1300–1000 cm^{-1} indicate the presence of C-O-C bond whereas appearance of a peak in the region 1700-1600 cm^{-1} shows the creation of C=N bond in the final compound. Molecular ion peaks in mass spectra were also consistent with the calculated values. ^{1}H NMR and ^{13}C NMR results were also in accord to the expected outcome.

Mechanistically, benzoylium ion **2** (generated *in situ* from benzoic acid) was attacked by 2-amino-3-hydroxy pyridine **1** to form benzoylated species **(a).** The cyclization followed by condensation of species **'a'** proceeds through **'b'** to **'e'** resulted in the formation of final product **3**. Interestingly the substantial increase in the rate of reaction could be attributed to the increase in surface area of the catalytic system viz., perchloric acid supported onto silica. An overview of plausible mechanism of the reaction is depicted in the Scheme 2.

The acidity of silica supported perchloric acid was investigated measuring Hammett acidity parameter (H_0)[23,24] and by titration with NaOH. The amount of H^+ obtained by titration was found to be 10.1 mmol H^+ g^{-1}.

Hammett acidity function used to express the acidic strength of an acid in aprotic organic solvent was calculated by the equation:

$H_0 = pK(ln)_{aq} + \log ([ln]_s/[Hln]_s)$

Where, $[ln]_s$ and $[Hln]_s$ are concentrations of indicator and protonated indicator, respectively that can be determined by UV-Vis spectrum. Dichloromethane was chosen as aprotic solvent and 4-nitroaniline as the basic indicator. The acidity of catalyst (H_0) was found to be 0.81.

Moreover, this mechanism is also supported by theoretical calculations which were carried out using the GAUSSIAN 03 program in continuation of our research work.[25, 26] The standard split valence basis set, 6-311G ++(d, p) was used for the optimization. Fukui functions were calculated using natural population analysis (NPA) schemes, and the outcome of such NPA[27] results are reported in all the cases at DFT/B3LYP/6-311++G(d, p) level.[28, 29]

Analysis of site selectivity for electrophilic attack on 2-amino 3-hydroxy pyridine shows that the local Nucleophilicity[30] $\mathbf{N_k}$ is higher at the amine nitrogen (N) (0.706) position than the phenolic oxygen (O) (0.346) which allows electrophile to preferably attack on N

in a regioselective manner **(**Table 3). Consequently, the local nucleophilicity parameters are very useful in identifying electrophilic/nucleophilic sites within a static reactivity picture to understand the regioselectivity pattern.

Furthermore, the recyclability/reusability of catalyst is an important factor from economical and environmental points of view. Therefore, keeping these issues under consideration, it was our endeavour to recover and check the reusability of the catalyst. Therefore, after the initial first run catalyst was recovered with the help of chloroform, washed with dry ether and subjected to drying under low pressure and was subjected again to the reaction (upto five runs) under similar conditions. The comparable yields of the product showed no significant loss in catalytic activity. The results of reusability of the catalyst are summarized in Figure 3. Such recyclability allows the repetitive use of minimal amount of catalyst in several run.

CONCLUSION

In conclusion, we have developed an efficient synthetic protocol for the synthesis of oxazolo[4,5-*b*]pyridines from benzoic acid and its substituted derivatives. The use of silica supported perchloric acid as a highly efficient, inexpensive, easy to handle, non-toxic and reusable catalyst makes the present procedure eco-friendly and economically acceptable. Furthermore, ambient conditions, high yields of products, less reaction time, and easy work-up procedure are other noteworthy advantages which make this method a fair contribution to the existing methodologies.

EXPERIMENTAL

All chemicals were purchased from Sigma Aldrich, India and used without further purification. The reactions were performed in aerobic atmosphere without any specific precautions. Melting points were determined with open capillary tube on a Veego melting point apparatus and were uncorrected. FT-IR spectra were recorded as KBr pellets within the range of 4400-400 cm^{-1} using Perkin Elmer spectrum RX1. The ^{1}H NMR spectra of the synthesized compounds were recorded at 400 MHz using BRUKER AVANCE II 400 NMR spectrometer in DMSO solvent and the chemical shifts were expressed in parts per million. Spin multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). ^{13}C NMR was recorded at 100 MHz using BRUKER AVANCE II 100 MHz spectrometer in DMSO. Mass analysis was performed on quadruple-time of flight (Q-TOF) mass spectrometer (MICROMASS) using electrospray ionization (ESI) in positive mode. Scanning electron microscopy (SEM) of the catalyst was carried out using a Jeol JSM 6100 instrument. Transmission electron microscopy (TEM) analysis was performed by Hitachi (H-7500) 120 kV instrument. TLC is performed using precoated aluminium sheets with silica gel 60 F254.

Preparation Of Silica Supported Perchloric Acid

The silica supported $HClO_4$ was prepared as per the procedure reported by Khan, *et al*.[31] Silica gel 200-400 mesh (25 g) was added to 75 mL of diethylether. To the suspension thus obtained, 12.5 mmol of $HClO_4$ (70% aq solution) was added. The mixture was concentrated and the residue was heated at 100°C for 72 h under inert N_2 atmosphere.

Free flowing off white powder of perchloric acid supported onto Silica ($HClO_4.SiO_2$) was obtained.

General Procedure For Synthesis Of 3a-J: 2-Phenyloxazolo[4,5-B]Pyridine (3a)

In a 100 c.c. round bottom flask, to the mixture of benzoic acid (0.24 g, 2 mmol) and 2-amino-3-hydroxypyridine (0.11 g, 1 mmol), $HClO_4.SiO_2$ nanoparticles (5 mol%) in 3 mL methanol as a solvent was added under stirring at room temperature. Progress of the reaction was continuously monitored by TLC (n-hexane and ethyl acetate in 2:1). After the completion of process as marked by TLC the solid was recovered by rotatory evaporator. The beauty of the process lies in the easy recovery of the catalyst by adding excess of chloroform. The product was recrystallised from acetonitrile and then washed with dichloromethane (2 x 5 mL). Off white solid; m.p. 132-134 °C; IR (KBr, cm^{-1}) 3052, 1678, 1595, 1554, 1490, 1260, 1065, 662; ^{1}H NMR (400 MHz, DMSO) δ 6.45-6.48 (t, 1H), 7.02-7.04 (d, 1H), 7.41-7.52 (m, 1H), 7.51-7.60 (m, 2H), 7.68-7.70 (d, 1H), 7.93-8.03 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 114.5, 116.2, 119.3, 122.6, 127.6, 136.1, 138.4, 143.2, 156.8, 159.5; HRMS (ESI) *m/z* $[M+H]^+$: 197.067; Anal. Calcd for $C_{21}H_{15}N$: C, 73.51; H, 4.34; N, 13.98. Found: C, 73.58; H, 4.45; N, 13.84.

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carry out this work on GAUSSIAN 03 program. All the authors have no conflict of interest.

SUPPLIMENTARY INFORMATION

Full experimental detail, IR, ^{1}H NMR spectra and HRMS data can be accessed on the publisher's website.

REFERENCES

1. Domling, A.; Ugi, I. *Angew*. *Chem*. *Int*. *Ed*. **2000**, 39, 3168.
2. Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J*. *Am*. *Chem*. *Soc*. **2009**, 131, 4598.
3. Maryanoff, B. E.; Costanzo, M. J. *Bioorg*. *Med*. *Chem*. **2008**, 16, 1562.
4. Marie-Claude, V.; Patricia, J.; Marie-Laure, B.; Laurence, S.; Gerald, G. *Tetrahedron* **1997**, 53, 5159.
5. Duchowicz, P. R.; Vitale, M. G.; Castro, E. A.; Fernandez, M.; Caballero, J. *Bioorg*. *Med*. *Chem*. **2007**, 15, 2680.
6. Mincheva, Z.; Courtois, M.; Andreu, F.; Rideau, M.; Viaud- Massuard, M. C. *Phytochemistry* **2005**, 66, 1797.
7. Barni, E.; Pasquino, S.; Savarino, P.; Di Modica, G.; Giraudo, G. *Dyes Pigments* **1985**, 6, 1.
8. Mac, M.; Baran, W.; Uchacz, T.; Baran, B.; Suder, M.; Lesniewski, S. *J*. *Photochem*. *Photobiol*. *A* **2007**, 192, 188.

9. Clark, R. L.; Pessolano, A. A.; Witzel, B.; Lanza, T.; Shen, T. Y.; Van Arman, C. G.; Risley, E. A. *J. Med. Chem.* **1978**, 21, 1158.

10. Shen, T. Y.; Clark, R. L.; Pessolano, A. A.; Witzel, B. E.; Lanza, T. J. *US Patent* **1977**, US4038396 A.

11. Guillaumet, G.; Flouzat, C. *US Patent* **1991**, US 5077408 A.

12. Doise, M.; Dennin, F.; Blondeau, D.; Sliwa, H. *Tetrahedron Lett*. **1990**, 31, 1155.

13. Zhuravlev, F. A. *Tetrahedron Lett*. **2006**, 47, 2929.

14. Baltorka, I. M.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Zolfigol M. A.; Hojati, S. F. *J. Iran. Chem. Soc*. **2008**, 5, S65.

15. Bandyopadhyay, P.; Prasad, G. K.; Sathe, M.; Sharma, P.; Kumar, A.; Kaushik, M. P. *RSC Adv*. **2014**, 4, 6638.

16. Bandyopadhyay, P.; Sathe, M.; Prasad, G. K.; Sharma, P.; Kaushik, M. P. *J. Mol. Catal. A* **2011**, 341, 77.

17. Sharma, P.; Kumar, A.; Sharma, M. *J. Mol. Catal. A* **2005**, 237, 191.

18. Shukla, P. K.; Verma, A.; Pathak, P. *Arch. Appl. Sci. Res*. **2014**, 6, 18.

19. Zolfigol, M. A.; Veisi, H.; Mohanazadeh, F.; Sedrpoushan, A. *J. Heterocyclic Chem*. **2011**, 48, 977.

20. Veisi, H. *Tetrahedron Lett*. **2010**, 51, 2109.

21. Shirini, F.; Zolfigol, M. A.; Salehi, P. *Curr. Org. Chem*. **2006**, 10, 2171.

22. Ge, F.; Wang, Z.; Wan, W.; Lu, W.; Hao, J. *Tetrahedron Lett*. **2007**, 48, 3251.

23. Zhao, Y.; Long, J.; Deng, F.; Liu, X.; Li, Z.; Xia, C.; Peng, J. *Catal. Commun.* **2009**, 10,732.

24. Pourjavadi, A.; Hosseini, S.H.; Soleyman, R. *J. Mol. Catal. A* **2012**, 365, 55.

25. Sharma, P.; Kumar, A.; Sahu, V. *J*. *Phys*. *Chem*. *A* **2010**, 114, 1032.

26. Sharma, P.; Ahuja, M.; Kumar, A.; Sahu, V. *Chem*. *Phys*. *Lett*. **2015**, 628, 85.

27. Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J*. *Chem*. *Phys*. **1985**, 83, 735.

28. Becke, A. D. *Phys*. *Rev*. *A* **1998**, 38, 3098.

29. Lee, C.; Yang, W.; Parr, R. G. *Phys*. *Rev*. *B* **1988**, 37, 785.

30. Perez, P.; Domingo, L. R.; Duque-Norena, M.; Chamorro, E. *J*. *Mol*. *Struct*. *THEOCHEM*. **2009**, 895, 86.

31. Khan, A. T.; Choudhury, L. H.; Ghosh, S. *J*. *Mol*. *Catal*. *A* **2006**, 255, 230.

Table 1. Synthesis of 2-(phenyl)oxazolo[4,5-b]pyridine derivatives from 2-amino-3-hydroxypyridine and substituted benzoic acids

S. no.	Entry	R	Yield[a] (%)
1	3a	H	90
2	3b	2-Cl	89
3	3c	2-OMe	92
4	3d	3-OMe	92
5	3e	3-Cl	90
6	3f	3-Br	88
7	3g	4-Me	96
8	3h	4-OMe	94
9	3i	4-Cl	87
10	3j	4-CF_3	86

[a]Yields are those of pure isolated product.

Table 2. Comparison of various protocols for the synthesis of 2-(phenyl)oxazolo[4,5-b]pyridine derivatives

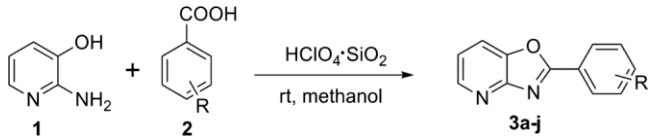
Entry	Precursor	Catalyst	Condition	Time	Yield (%)	Ref.
1.	Benzoic acid	Polyphosphoric acid	185°C	35 min.	3-60	[9]
2.	Aryl halide	$Pd(OAc)_2/PPh_3/Cs_2CO_3$	30°C	24 h.	33-67	[13]
3.	Benzoic anhydride	-	Reflux temperature	Several min.	34	[10]
4.	Benzoic acid	PPh_3, Et_3N(excess)	Reflux temperature	-	72-98	[22]
5.	Orthoester	p-Toluenesulfonic acid	145-180°C	-	30-60	[12]
6.	Benzoyl chloride	Trimethyl silyl polyphosphate	Reflux temperature	15 h.	-	[11]
7.	Benzoic acid	$HClO_4.SiO_2$	Room temperature	15-30 min.	86-96	Our work

Table3. Local Nucleophilicity Index of 2-amino-3-hydroxypyridine

Reactant	**N**	$\mathbf{f_k^-}$		$\mathbf{N_k}$	
2-amino-3-hydroxypyridine	3.238	O	N	O	N
		0.107	0.218	0.346	0.706

*k defines the site in the molecule where the property is being evaluated.

Scheme 1. Synthesis of 2-(phenyl)oxazolo[4,5-b]pyridine derivatives using $HClO_4 \cdot SiO_2$ as supported catalyst.



Scheme 2. Schematic diagram of a plausible mechanism.

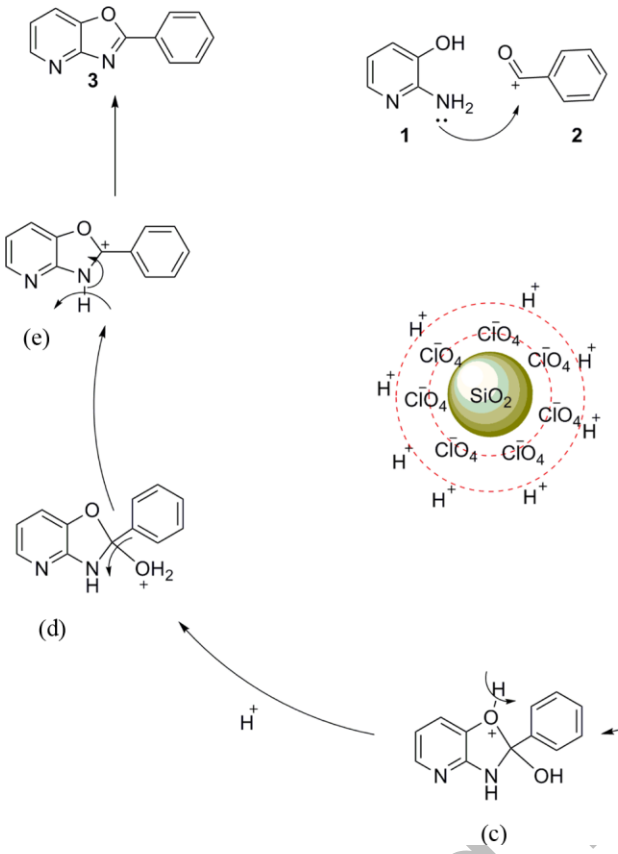


Figure 1. TEM image of silica supported perchloric acid.

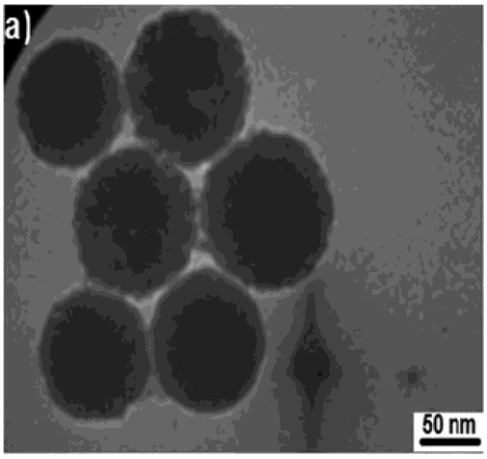


Figure 2. SEM images of silica supported perchloric acid.

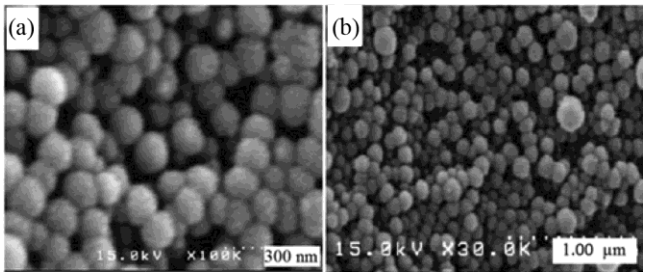


Figure 3. Representation of reusability of catalyst.