SciMedCentral

JSM Chemistry

Research Article

Synthesis of 2-Substituted-1H-Imidazo [4, 5-*C*] Pyridine Derivatives Catalyzed by Zinc Triflate

Srinivasulu R[1]*, Ravi Kumar K[2], Satyanarayana PVV[3] and Hari Babu B[3]

[1]*Chalapathi Institute of Engineering and Technology, Department of chemistry, India*
[2]*RA chem pharma limited, R&D division, India*
[3]*Department of Chemistry, Acharya Nagarjuna University, India*

***Corresponding author**
Srinivasulu R, Chalapathi Institute of Engineering and Technology, Department of chemistry, India

Submitted: 19 February 2014
Accepted: 21 May 2014
Published: 26 May 2014

Keywords
- 3,4-diaminopyridine
- limidazo [4,5-c] pyridine derivatives
- Aldehydes
- Methanol
- Zinc triflate

Abstract

We report a new methodology for the synthesis of 2-substituted-1H-imidazo [4,5-c] pyridine derivatives by the reaction of 3,4-diaminopyridine with substituted aryl aldehydes in the presence of zinc triflate in methanol solvent at reflux temperature.

INTRODUCTION

Diaminopyridines, imidazo [4,5-*c*] pyridines and imidazo [4,5-*b*] pyridines have been proved to be useful precursors for the synthesis of a variety of medicinal agents. The heterocycles derived from these intermediates have been evaluated as antagonists of various biological receptors. Substituted imidazo [4,5-*b*] pyridine and imidazo [4,5-*c*] pyridines derivatives have also been tested for their potential as antiviral, anticancer, inotropic agents [1-3]. Hence, the synthesis of imidazo [4,5-c] pyridine derivatives is currently of great interest. In general, imidazo [4,5-*c*] pyridine derivatives are synthesized by the reaction of 3,4-diaminopyridine with carboxylic acid derivatives or on condensation with aldehydes. However, it is noticed that all these methods are not straightforward and involve various disadvantages such as prolonged reaction times, harsh reaction conditions (above 150°C) and use of the toxic organic reagents such as $POCl_3$, Poly phosphoric acid and TMS-Cl. The major draw-back of many of these reported methods is that the synthesis involves a two step process, namely isolation of the Schiff base by condensation of Diamine with aldehyde in step one and dehydrogenative cyclization in a subsequent step to yield 1*H*- imidazo [4,5-*c*] pyridine. Therefore, it was felt that there is a strong requirement to overcome the above limitations by developing an efficient, simple and green methodology for the synthesis of 1*H*- imidazo [4,5-*c*] pyridine derivatives. Zinc (II) trifluoromethanesulphonate (zinc triflate) has recently been shown to be a versatile reagent for organic synthesis and it is used as a mild Lewis acid catalyst for wide range of organic transformations [4-6]. Zinc triflate is commercially available or it may be prepared from reacting trifluoromethanesulphonic acid reacting with zinc carbonate in methanol.[29] herein, we report a simple and efficient zinc (II) triflate (30 mol %) catalyzed synthesis of 2-substituted 1H-imidazo [4,5-c] pyridine derivatives.

RESULTS AND DISCUSSIONS

In our preliminarily investigation, we tested on the model reaction of 3,4-diamino pyridine and 4-methoxy benzaldehyde in different solvents, namely methanol, ethanol, water, THF and DMF.

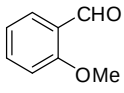
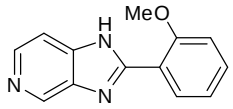
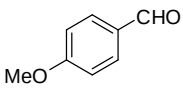
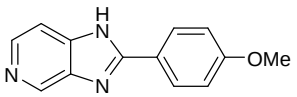
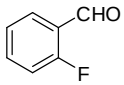
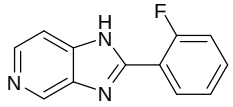
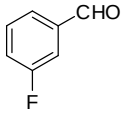
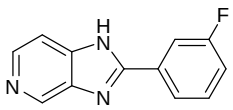
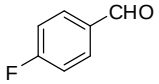
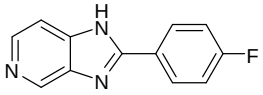
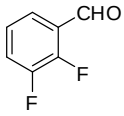
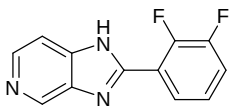
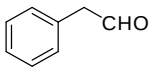
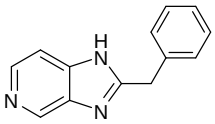
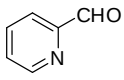
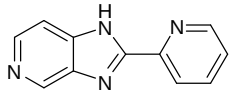
The results are shown in (Table 1). It was found that methanol was a solvent of choice for the reaction, and the desired product was obtained in better yield. In water, the desired product was formed but the reaction was incomplete even after 20h. it was observed that ethanol, THF and DMF behaved poorly in the reaction and isolated product indicating the mixture of desired compound and imine, it was confirmed by crude LCMS. In methanol solvent the reaction was tested under different mole ratios of zinc triflate and it was concluded that 30 mol% is giving better result and same time the reaction was in complete at room temperature. The reaction could be finished under very simple reaction conditions in the presence of zinc triflate in reflux of methanol solvent, which gives the desired corresponding 2-(4-methoxyphenyl)-1H-imidazo [4,5-c] pyridine product in good yield.

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl aldehydes with 3,4-diaminopyridine. The results are shown in (Table 2). The synthesized compounds were compared (mp, MS) with authentic literature data. This comparision revealed that the compounds synthesized by this method were similar in all aspects to the reference compounds.

Table 1: Solvent effect on reaction of 3,4-diaminopyridine and 4-methoxy benzaldehyde.

S. No	Solvent	Reaction conditions		$Zn(OTf)_2$ mol %	Yield %
		Temp °C	Time hr		
01	Methanol	67	12	20	46
02	Ethanol	80	12	20	21
03	THF	68	15	20	Traces
04	DMF	100	15	20	19
05	Water	100	20	20	Not complete
06	Methanol	25-30	36	20	Not complete
07	Methanol	67	12	30	53
08	Methanol	67	12	40	52
09	Methanol	67	12	50	50

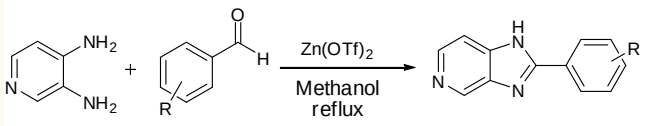
Table 2: Synthesis of 2-substituted 1H-imidazo [4,5-c]pyridine derivative from 3,4-Diamino pyridine and different substituted aldehydes[a].

Entry	aldehyde	1H-imidazo[4,5-c]pyridine	Yield[b]
1			51
2			53
3			52
4			61
5			56
6			54
7			42
8			39

CONCLUSION

In conclusion we have developed a simple and efficient method for synthesis of 2-substitued 1H-imidazo [4,5-c] pyridine derivatives from 3,4-Diamino pyridine and different substituted aldehydes by using zinc triflate as a catalyst. The use of zinc triflate as a catalyst and easy reaction conditions to deliver the target products in better yields, often in analytically pure form, suggest a good applicability of this process. We have also shown the versatility of this methodology by applying it to a wide variety of substituted aldehydes.

Scheme-1



Scheme 1

EXPERIMENTAL

All ^{1}H NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as δ value with reference to Tetra methyl silane (TMS) as an internal standard. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use.

Zinc triflate catalyzed synthesis of 2-substituted 1H-imidazo [4,5-c]pyridine derivative from 3,4-Diamino pyridine and different substituted aldehydes.

A mixture of 3,4-Diaminopyridine (1 mmol), aldehyde (1.2 mmol) and $Zn(OTf)_2$ (30 mol %) in Methanol (10 ml) was placed in a 50 ml round bottom flask and stirred at reflux for 12h. The progress of the reaction was monitored by TLC MeOH: DCM (9:1) after completion of the reaction, the reaction mixture was cooled to room temperature and concentrated under vacuum to get crude compound. The obtained crude material was diluted with water (10 ml) and stirred for 15 mins at room temperature and the product was collected by filtration, washed with water, and suck dried. The product was recrystallised from ethanol to give title compounds (entry 1-8) in 44-67% yields.

2-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 1)[7]

Off-white solid; m.p: 176-177 °C; ^{1}H NMR (DMSO-d_6): δ12.43 (s, 1H), 8.94 (s,1H), 8.38-8.29 (m, 2H), 7.62-7.51 9m, 2H), 7.27 (d, 1H, *J* = 8.4 Hz), 7.14 (t, 1H, *J* = 7.6 Hz), 4.0 (s, 3H); (LC-MS) m/*z*: 226.11 $[M+H]^+$.

2-(4-methoxyphenyl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 2)[7]

Off white solid; m.p.: 268-274 °C. ^{1}H NMR (DMSO-d_6): δ 13.20 (s, 1H), 8.90 (s, 1H), 8.29 (d, 1H, *J* = 5.2 Hz), 8.17 (d, 2H, *J* = 8.8 Hz), 7.56 (m, 1H), 7.14 (d, 2H, *J* = 8.8 Hz), 3.85 (s, 3H); (LC-MS) m/*z*: 226.18 $[M+H]^+$

2-(2-fluorophenyl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 3)[7]

Light brown colour solid ; m.p: 236-240 °C; ^{1}H NMR (DMSO-d_6): δ 13.01 (s, 1H), 9.0 (s, 1H), 8.35 (d, 1H, J = 5.2 Hz), 8.26 (t, 1H, J = 7.6 Hz), 7.64-7.51 (m, 2H), 7.48-7.41 (m, 2H); (LC-MS) m/*z*: 214.16 $[M+H]^+$

2-(3-fluorophenyl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 4)[7]

Light brown colour solid; m.p: 266-269 °C; ^{1}H NMR (DMSO-d_6): δ 13.47 (s, 1H), 8.97 (s, 1H), 8.33 (d, 1H, J = 5.2 Hz), 8.08 (d, 1H, J= 8.0 Hz), 8.01 (d, 1H, J = 10 Hz), 7.67-7.62 (m, 2H), 7.44-7.39 (m, 1H); (LC-MS) m/*z:* 214.0 $[M+H]^+$

2-(4-fluorophenyl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 5) [7]

Off white solid; m.p: above 300 °C; ^{1}H NMR (DMSO-d_6): δ13.38 (s, 1H), 8.94 (s, 1H), 8.32-8.25 (m, 3H), 7.60 (s, 1H), 7.47-7.42 (m, 2H); (LC-MS) m/*z:* 213.9 $[M+H]^+$

2-(2,3-difluorophenyl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 6)

Light brown colour solid; m.p: above 300°C; ^{1}H NMR (DMSO-d_6): δ 13.20 (s, 1H), 9.01 (s, 1H), 8.35 (d, 1H, J = 5.6 Hz), 8.03 (t, 1H, J = 7.2 Hz), 7.68-7.62 (m, 2H), 7.45-7.40 (m, 1H); (LC-MS) m/*z:* 232.09 $[M+H]^+$

2-benzyl-1H-imidazo[4,5-c]pyridine (Table 2, entry 7) [8]

Off white solid; m.p: 148-152 °C; ^{1}H NMR (DMSO-d_6): δ 12.74 (s, 1H), 8.81 (s, 1H), 8.25 (d, 1H, J = 5.2 Hz), 7.34-7.30 (m, 1H), 7.26-7.12 (m, 5H), 4.23 (s, 2H); (LC-MS) m/*z:* 209.80 $[M+H]^+$

2-(pyridin-2-yl)-1H-imidazo[4,5-c]pyridine (Table 2, entry 8)

Light yellowish solid; m.p: 196-198 °C; ^{1}H NMR (DMSO-d_6): δ 13.5 (s, 1H), 8.98 (s, 1H), 8.79 (d, 1H, J= 4.8 Hz), 8.39 (d, 1H, J = 8 Hz), 8.34 (d, 1H, J = 5.6 Hz), 8.05 (t, 1H, J = 7.6 Hz), 7.61-7.58 (m, 2H); (LC-MS) m/*z:* 197.19 $[M+H]^+$

ACKNOWLEDGMENTS

The authors are very much grateful to the management of Chalapathi Institute of Engineering and Technology, Guntur, A.P, India, for providing moral support in carrying out this work.

REFERENCES

1. Kale, R.P.; Shaikh, M. U.; Jadhav, G. R.; Gill, C. H. *Tetrahedron Lett*. 2009, 50, 1780-1782.
2. Temple, C. Jr.; Rose, J. D.; Comber, R. N.; Rener, G. A. *J. Med. Chem*. 1987, 30, 1746-1751.
3. Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Wyss, V. L.; Hayes, J. S. *J. Med. Chem*. 1985, 28, 717-727.
4. Lekhok, K. C.; Bhuyan, D.; Prajapati, D.; Boruah, R. C. *Mol. Divers*. 2010, 14, 841-846.
5. Kumar, V. N.; Sridhar, G.; Laxminarayana, E.; Mallaiah, B.; Giri, T. *J. Drug. Chem*. (IJPI) 2012, 2, 10.
6. Atukuri, D.; Ravindra, R. K.; Pramod, P. K. *Lett. Org. Chem*. 2013, 10, 510-517.
7. Robertson, D. W.; Beedle, E. E.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Wyss, V. L.; Hayes, J. S. *J. Med. Chem*. 1985, 28, 717-727.
8. Berner, H.; Reinshagen, H.; Koch, M. A. *J. Med. Chem. 1973, 16, 1296-1298.*

Cite this article

Srinivasulu R, Ravi Kumar K, Satyanarayana PVV, Hari Babu B (2013) Synthesis of 2-Substituted-1H-Imidazo [4, 5-C] Pyridine Derivatives Catalyzed by Zinc Triflate. JSM Chem 2(1): 1009.