Volume 65, Issue 8, 2021
Journal of Scientific Research
of
The Banaras Hindu University

Ecofriendly Synthesis of Pyridine Derivatives Using Activated Fly Ash as an Efficient and Reusable Catalyst

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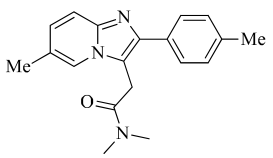
Abstract: Synthesis of imidazo [1, 2-a] pyridines derivatives were reported from 2-aminopyridine and various substituted phenacyl bromide using Activated Fly Ash as an efficient, eco-friendly, and reusable catalyst. The present protocol offers various advantages, such as the use of less hazardous solvent, high yield, and operationally simple procedure.

Index Terms: **Activated Fly Ash, imidazo [1, 2-a] pyridines; 2-amino pyridine; phenacyl bromides.**

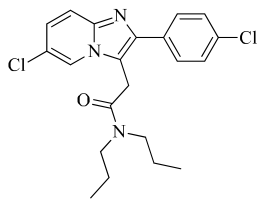
I. INTRODUCTION

Fused heterocyclic compounds containing nitrogen have received considerable attention due to their wide biological activities (Heravi, M.M,2015). Imidazo [1, 2-a] pyridine scaffolds are more attractive due to their applications in pharmaceuticals such as antiviral(Gueiffier,1998; Lhassani, M.,2010; Chaouni-Benabdallah,2001), antibacterial(Lv, K.; Li, L,2017), antifungal (Husain, 2013), anticancer (Romagnoli, R,2016; Ye, Z,2020) and anti-inflammatory (Almasirad,2014) agents. Imidazo [1, 2-a] pyridine as a core structure represents leading drugs in the market such as zolpidem (I), alpidem (II), olprinone (III), minodronic acid (IV), zolimidine (V), saripidem (VI), and miroprofen (VII) (Fig. 1) (Aakash, D,2017; Nisha, D,2016). Several reports on the synthesis of imidazolo [1, 2-a] pyridine proceed through the condensation reaction of various substituted α-bromo carbonyl compounds with 2-amino pyridine the presence of a variety of catalyst. The importance of the Imidazo [1, 2-a] pyridine scaffold as biologically active compounds and ligands for metal catalysts makes it an attractive moiety for the development of a new synthetic method for their preparation. Cyclization of 2-aminopyridines with phenacyl bromide is the classical method for the synthesis of substituted imidazo [1,2-a]pyridine. The method utilizes various catalyst which includes iodine(Xing, M.-M,2016) hypervalent iodine(Huang, H.-Y,2004), SnCl2(Shaabani, A, 2009),MgO(Patil, S.V,2016), gold(Talbot, E.P.A,2014) ,copper NPs(Sun, W,2018), Pd(II)(Wang, Y,2014), DBU(Veer, B,2019), DABCO(Murthy,S.N,2010). Non-conventional heating methods, which include microwave(Mert-Balci,F,2012),grinding(Zhu,D,2009), and ultrasound(Vieira, B.M,2019), are also successfully reported. However, these reported methodologies suffer from some drawbacks like high temperatures, long reaction times, and toxic metal catalysts, expensive, harmful reagents, and solvents. Despite these efforts, it is still a challenge to synthesize the functionalized Imidazo [1, 2-a] pyridines from the readily available starting materials.

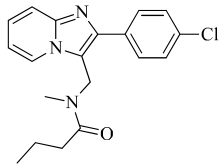
In continuation of our previous work here, we employed copper Activated Fly Ash as a heterogeneous catalyst to develop a rapid and efficient process for the synthesis of imidazo [1, 2-a] pyridines (Ajit, K. Dhas,2019)



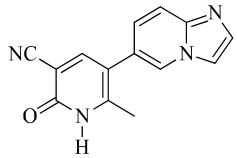
Zolpidem (sedative)
(I)



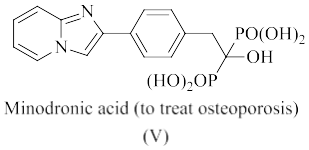
Alpidem (anxiolytic drug)
(II)



Saripidem (anxiolytic drug)
(III)

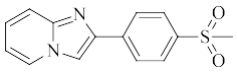


Olprinone (PDE-III inhibitor)
(IV)



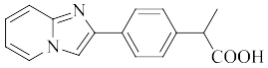
Minodronic acid (to treat osteoporosis)

(V)



Zolimidine (to treat peptic ulcer)

(VI)



Miroprofen (analgesic)

(VII)

II. MATERIALS AND METHODS

All Chemicals were purchased from SD Fine and spectrochem used without further purification. Melting points of the products were recorded in open capillaries in a liquid paraffin bath and are uncorrected. The reaction was monitored by thin-layer chromatography (TLC) in 20 % (ethyl acetate: n-hexane) on silica gel precoated aluminum foil (Merck). IR spectra were recorded in KBr disc on Shimadzu-FT-IR Spectrophotometer, and absorption bands are expressed in cm-1. 1H spectra were recorded on a Bruker Avance Neo 500 NMR Spectrometer instrument in DMSO-d6 as solvent and TMS as the internal standard. Mass spectra were recorded on Waters Q-TOF micromass spectrophotometer.

General procedure for the synthesis of Imidazo [1, 2-a] pyridines derivatives.

In a round bottom flask, 2-amino pyridine (1 mmole), substituted phenacyl bromide (1 mmole) (2a-k), and Activated Fly Ash catalyst (10 mole %) was added to 5 ml ethanol. The reaction mixture was refluxed, and the progress of the reaction was monitored by thin-layer chromatography using hexane: ethyl acetate (8:2) as a mobile phase. After completing the reaction, the reaction mixture was filtered to isolate the catalyst and then poured over crushed ice to obtain a solid product. The isolated crude product was purified by recrystallization using hot ethanol. Other analogs of this series were prepared, and tabulated data of various derivatives is mention in Table 4. Their structures have been confirmed by analytical methods such as mp, 1H NMR, Mass Spectra, and IR spectra.

Spectral data:

Synthesis of 2-(4-methoxyphenyl)imidazo[1,2-a]pyridine (3c), Yield 89%; MP 132- 134 0C; 1H NMR (500 MHz, DMSO-d6) δ 8.9 (d, 1H), 8.7 (s, 1H), 7.95 (d, 2H), 7.90 (d, 2H),7.52-7.49 (m, 1H), 7.18 (d, 2H), 3.85 (s, 3H); IR(KBr, cm-1): 3363(C-H), 3132(Ar-H),1665(C=N), 1550(C=C), 1257 (C-O), 760(C-H bend); [M+1]+ - 225.51 Synthesis of 2-(4-nitrophenyl)imidazo[1,2-a]pyridine (3b), Yield 95%; MP 203-2070C;1H NMR (500 MHz, DMSO-d6) δ 8.65 (s, 1H), 8.58 (d, 1H), 8.31 (d, 2H), 8.23 (d, 2H), 7.63 (d, 1H), 7.30 – 7.27 (m, 1H), 6.96 (m, 1H); IR(KBr, cm-1): 3350(C-H), 3140(ArH), 1670(C=N), 1500(N-O stretch), 1220 (C-N), 740(C-H bend); [M+1]+ - 240.07

III. RESULT AND DISCUSSION

The reaction of 2-amino pyridine (1) and phenacyl bromide (2a) is considered as a model reaction (Figure 2) for the development of methodology. The model reaction was investigated with various catalysts few of them are mentioned in Table 1. The lesser yield was observed when the reaction was carried out without catalyst (Table 1, entry 1). Low yields were found when the reaction was catalyzed by a basic catalyst such as DBU and NaHCO3 (Table 1, entries 2, 3). Marginal improvement in the yield of the product was observed in the presence of Lewis acid catalysts such as ZnO, FeCl3, and AlCl3 (Table 1, entries 4, 5, and 6). We observed the best results when the reaction was catalyzed by Activated Fly Ash (Table 1, entry 7). This finding shows that the reaction was effectively catalyzed by Activated Fly Ash.

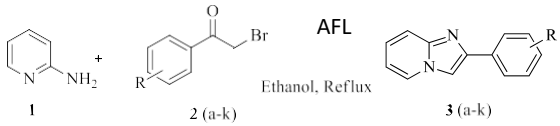


Figure 2. Synthesis of substituted imidazo [1, 2-1].

In order to study the screening of solvent, the model reaction was carried out in various solvents. Moderate yields were observed when the reaction was carried out in less polar solvents such as dichloromethane and toluene (Table 2, entries 1 and 2). At the same time, significant improvement in the yield of the product was observed in polar solvents such as methanol and acetonitrile (Table 2, entries 3 and 4). The lesser yield was reported in the presence of water (Table 2, entry 6). The best results were obtained in ethanol as a solvent at reflux condition, making it the most suitable solvent for the reaction (Table 2, entry 5).

Subsequently, we investigated the optimal concentration of catalyst in the model reaction; lowering the amount of catalyst to 5 mole % lowers the desired product's yield to 69% (Table 3, entry 1). However, optimal results were obtained with 10 mole % catalyst loading (Table 3, entry 2).

Based on the optimized reaction conditions, we performed the reactions of various substituted phenacyl bromide 2(a-k) to expand the method's applications. The results are summarized in Table 4.

In order to make the process useful for large scale preparation, we examined the recycling of the catalyst. After

completing the reaction, the catalyst was recollected using an external magnet from the reaction mixture, washed, dried, and reused for the next cycle, indicating a slight decrease in the yield of the product up to the third cycle, then after the yield decreases considerably.

Entry	Catalysts	Solvent	Temperature (^{0}C)	Time (h)	Yield (%)
1	--	Ethanol	Reflux	8	45
2	DBU	Ethanol	Reflux	4	60
3	NaHCO3	Ethanol	Reflux	6	65
4	ZnO	Ethanol	Reflux	4	72
5	FeCl3	Ethanol	Reflux	4	75
6	AlCl3	Ethanol	Reflux	3	69
7	AFLA	Ethanol	Reflux	1.5	94

Table 1. Screening of various catalysts for the synthesis of Imidazo [1, 2-a] pyridines derivatives.

Entry	Solvent	Catalyst (%)	Time (h)	Yield (%)
1	Dichloro methane	10	7	58
2	Toluene	10	7	58
3	Methanol	10	5	72
4	Acetonitrile	10	5	84
5	Ethanol	10	1.5	94
6	Water	10	5	30

Table 2. Screening of various solvents for the synthesis of Imidazo [1, 2-a] pyridines derivatives at reflux temperature.

Entry	Catalyst (Mole %)	Solvent	Time (h)	Temperature (^{0}C)	Yield (%)
1	5	Ethanol	3.5	Reflux	75
2	10	Ethanol	1.5	Reflux	94
3	15	Ethanol	1.5	Reflux	94

Table 3. Effect of concentration of catalyst for the synthesis of Imidazo [1, 2-a] pyridines derivatives.

Entry	Compound	Aldehyde (2a-k)	Time (h)	Yield (%)	M. P. (^{0}C)
1	3a	-H	1.5	94	134-137
2	3b	4-NO2	1	95	203-207
3	3c	4-OCH3	2	89	132-134
4	3d	4-Cl	2	86	206-208
5	3e	3-CH3	2	88	100-103
6	3f	4-F	1.5	83	161-164
7	3g	4-CH3	2.5	90	145-147
8	3h	3-NO2	2	87	202-205
9	3i	4-Br	2.5	88	209-213
10	3j	2-Br	2.5	85	84-88
11	3k	2-OH	2.5	85	141-145

Table 4. Synthesis of Imidazo [1, 2-a] pyridine derivatives.

IV. Conclusion

Herein we describe an efficient synthesis of imidazo [1, 2-a] pyridine from 2- aminopyridines and various substituted phenacyl bromide catalyzed by Activated Fly Ash. The work offers several practical advantages: short reaction time, less hazardous solvent, and high yield. Moreover, the present protocol is operationally simple and could be applied for large scale synthesis.

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