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Simple and Efficient One-Pot Synthesis of Imidazo[1,2-*a*]pyridines Catalyzed by Magnetic Nano-Fe₃O₄-KHSO₄·SiO₂

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Abstract: The present report highlights a magnetic nano-Fe₃O₄– KHSO₄·SiO₂ catalyzed synthesis of imidazo[1,2-*a*]pyridines. The synthetic strategy adopted is expedient, versatile, and offers good to excellent yields from readily available starting materials.

Key words: multicomponent reactions, transition metals, heterocycles, heterogeneous catalysis, iron

Multi-component reactions (MCRs) constitute one of the most promising synthetic strategies, that have transformed the art of organic synthesis.¹ Due to their convergent nature and high bond-forming index (BFI), these reactions are capable of constructing a synthetic hub of divergent molecules in an efficient fashion.² Of special interest are compounds which possess the molecular skeleton found in natural products and drug-like molecules.³ Since the vast majority of natural products and drug-like compounds possess heterocyclic subunits, the ability to synthesize diverse heterocyclic compounds efficiently is critical. Imidazo[1,2-a]pyridines are important fused heterocycles due to their potential biological activities. They have been used for the treatment of septic acute lung injury (ALI), osteoporosis, and are extensively employed as PI3Ka inhibitors, mGlu2 receptors, anti-viral, anti-cancer, anxyolytic, and anti-herpes drugs (Figure 1).⁴

Different methods have been applied for the synthesis of imidazo[1,2-*a*]pyridines. Among these, only a few reports deal with the one-pot synthesis of imidazo[1,2-*a*]pyridine scaffolds employing different catalytic systems.⁵ Thus, there is scope for developing operationally simple and efficient synthetic strategies. Magnetic Fe₃O₄ nanoparticles have recently emerged as an attractive catalyst for various synthetic transformations because of their easy recyclability, reusability, high surface area, low toxicity, and excellent activity.⁶ An up-to-date literature survey reveals that

there is no report on iron-catalyzed synthesis of imidazo[1,2-*a*]pyridines. In context of the above and as a part of our current research interest,⁷ we report herein a facile and straightforward synthesis of imidazo[1,2-*a*]pyridines by a magnetic nano-Fe₃O₄–KHSO₄·SiO₂ catalyzed onepot three-component reaction of 2-aminopyridine, aldehyde, and alkyne (Scheme 1).





Figure 1 Biologically active imidazo[1,2-a]pyridine derivatives

In order to achieve a practical protocol for the one-pot synthesis of imidazo[1,2-a]pyridines, the effect of a number of parameters such as catalysts, additives, and solvents was screened for the model reaction employing 2-amino-pyridine (1), benzaldehyde (2a), and phenylacetylene (3a).⁸ The results are presented in Table 1.



 $R^2 = aryl, alkyl$

Scheme 1 One-pot synthesis of imidazo[1,2-a]pyridines

SYNLETT 2012, 23, 2635–2638 Advanced online publication: 01.10.2012 DOI: 10.1055/s-0032-1317323; Art ID: ST-2012-D0659 © Georg Thieme Verlag Stuttgart · New York

Table 1 Screening of Reaction Conditions^a

Entry	Catalyst (mol%)	Additive	Solvent	Yield (%) ^b
1	CdI ₂ (10)	_	toluene	trace
2	CdI ₂ (10)	Et ₃ N	toluene	23
3	$ZrOCl_2 \cdot 8H_2O(10)$	_	toluene	_
4	SbCl ₅ (10)	_	toluene	_
5	NiCl ₂ ·6H ₂ O (10)	_	toluene	_
6	TiO ₂ (10)	_	toluene	_
7	Yb(OTf) ₃ (10)	_	toluene	32
8	Yb(OTf) ₃ (10)	Et ₃ N	toluene	35
9	Yb(OTf) ₃ (10)	_	BMIM[BF ₄]	30
10	Yb(OTf) ₃ (10)	TFA	toluene	40
11	$Fe_{3}O_{4}(5)$	_	toluene	43
12	Fe ₃ O ₄ (10)	_	toluene	57
13	Fe ₃ O ₄ (12)	_	toluene	57
14	Fe ₃ O ₄ (10)	KHSO ₄ ·SiO ₂	toluene	89
15	Fe ₃ O ₄ (10)	$KHSO_4$ ·SiO ₂	PhCl	78
16	Fe ₃ O ₄ (10)	$NaHSO_4 \cdot SiO_2$	toluene	72
17	Fe ₃ O ₄ (10)	L-proline	toluene	59
18	Fe ₃ O ₄ (10)	K-10	toluene	68
19	Fe ₃ O ₄ (10)	P_2O_5	toluene	64

^a Using **1** (1 mmol), **2a** (1 mmol), **3a** (1.2 mmol) at 110 °C for 24 h. ^b Isolated yield after column chromatography.

The investigation was initiated by examining the effect of various unexplored catalysts for the aforementioned model reaction. Out of all the trials, ZrOCl₂·8H₂O, SbCl₅, NiCl₂·6H₂O, and TiO₂ did not result in the formation of the product (entries 3-6). CdI₂ alone produced only a trace of the product, although a CdI₂-Et₃N combination brought about 23% product yield (entries 1 and 2). Yb(OTf)₃, Yb(OTf)₃-Et₃N, and Yb(OTf)₃-TFA afforded lower yields (entries 7, 8 and 10); nevertheless an $Yb(OTf)_3$ -[BMIM][BF₄] combination resulted in 30% yield (entry 9). Nano-Fe₃O₄ (10 mol%) notably gave the product in 57% yield (entry 12). Further increase in the catalyst mol% did not improve the yield (entry 13). The amino-imino tautomerism in 2-aminopyridine and the soft acidic centers of nano-iron did not appear to favor formation of imine, which may be the reason for low yields obtained in the presence of nano-Fe₃O₄ alone. To achieve increased conversion, attention was directed towards the use of additives and solvents, which conclusively provided Fe_3O_4 -KHSO₄·SiO₂ in toluene as the best combination (entry 14).⁹ The KHSO₄·SiO₂ additive is assumed to promote the formation of imine considerably to facilitate nucleophilic attack of the C–H activated phenylacetylene to the intermediate imine. The propargylamine, thus formed, subsequently underwent nano-Fe₃O₄ catalyzed 5-*exo*-dig cyclization. Other additives such as L-proline, K-10, and P₂O₅ did not improve the yield (entries 17–19).

With the optimized conditions in hand, the scope of this methodology was extended to the reaction of a wide range of aldehydes and alkynes with 2-aminopyridine to afford a variety of imidazo[1,2-a]pyridines (Table 2). The findings revealed that a range of reactant combinations afforded good to excellent product yield, except the combination of 2-aminopyridine, 4-(dimethylamino)benzaldehyde, and phenylacetylene which led to no product (entry 8), possibly due to the coordination of the NMe_2 group with Fe_3O_4 . Among the aromatic aldehydes, benzaldehyde and halo-substituted benzaldehydes showed excellent reactivity in this cyclization (entries 1– 6); whereas those bearing strong electron-donating and electron-withdrawing groups showed appreciable lowering of yield (entries 7, 10, 11 and 14). The reaction was also feasible with an aliphatic aldehyde, but it required an excess of KHSO₄·SiO₂ (entry 12). Furfural, a representative heterocyclic aldehyde, also participated in the reaction with reasonably good yield (entry 13). It is worth mentioning that the nano-Fe₃O₄ could be magnetically recovered by an external magnetic field and could be reused six times without significant loss of activity (Figure 2).¹⁰

In conclusion, we have demonstrated the catalytic use of magnetic nano-Fe₃O₄–KHSO₄·SiO₂ for an efficient onepot synthesis of imidazo[1,2-*a*]pyridines. The approach is convenient, practical, versatile, and may be used as an alternative to the existing synthetic methodologies.



Figure 2 Recyclability of nano-Fe₃O₄

Entry	Aldehyde 2		Alkyne 3		Product 4		Time (h)	Yield (%) ^b
1		2a	=	3 a	N N Ph	4a	24	89
2	CI	2b		3a	N Ph	4b	20	86
3	CI	2c	$\equiv -\langle \rangle$	3a	N N Ph	4c	20	84
4	Br	2d	=	3a	N Ph	4d	20	83
5	Br	2e	$\equiv -\langle \rangle$	3a	N -3-BrC ₆ H ₄	4e	20	82
6	Br	2f		3a	N Ph	4f	20	83
7	MeO	2g	$\equiv -\langle \rangle$	3a	N -4-MeOC ₆ H ₄	4g	24	75
8	Me ₂ N	2h		3 a	N Ph	4h	24	n.r.
9		2i		3a	N 4-MeC ₆ H ₄	4i	20	79
10	0 ₂ N	2ј		3a	N Ph	4j	24	69
11	NO ₂	2k		3a	N 2-O ₂ NC ₆ H ₄	4k	24	65
12	~0	21	$\equiv -\langle \rangle$	3 a		41	17	70°
13	() o	2m		3a		4m	17	72
14	HO MeO O	2n		3a		4n	24	55

 Table 2
 One-Pot Three-Component Coupling of 2-Amino Pyridine, Aldehyde, and Alkyne^a

Table 2 One-Pot Three-Component Coupling of 2-Amino Pyridine, Aldehyde, and Alkyne^a (continued)



^a Using 1 (1 mmol), 2 (1 mmol), 3 (1.2 mmol), nano-Fe₃O₄ (0.1 mmol) and KHSO₄·SiO₂ (150 mg) at 110 °C in anhyd toluene.

^b Isolated yield after column chromatography.

^c Using KHSO₄·SiO₂ (175 mg).

Acknowledgement

We thank the Council of Scientific and Industrial Research (CSIR), New Delhi for financial assistance.

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- (8) General Experimental Procedure: To an oven-dried 25 mL round-bottom flask containing a magnetic stir bar was added 2-aminopyridine (1 mmol, 94.1 mg), aldehyde (1 mmol), KHSO₄·SiO₂ (150 mg, 0.032 mmol with respect to KHSO₄), and anhyd toluene (2 mL). The mixture was stirred for 15 min and to it was then added alkyne (1.2 mmol) and nano-Fe₃O₄ [<50 nm particle size, \geq 98% trace metals basis (Aldrich)] (0.1 mmol, 23.2 mg). The total reaction mixture was refluxed at 110 °C for the appropriate time. After completion of the reaction (monitored by TLC), EtOAc was added (10 mL), the magnetic Fe₃O₄ nanoparticles were collected on the magnetic stir bar, and the mixture was filtered through a porous plug. The filtrate was concentrated under reduced pressure and the crude product thus obtained, was purified by silica gel column chromatography (EtOAchexane, 1:9). The pure products were characterized based upon their physical and spectroscopic properties. Spectroscopic Data of the Representative Compounds: 3-Benzyl-2-(3-chlorophenyl)imidazo[1,2-a]pyridine (4c): White solid; mp = 141-142 °C. ¹H NMR (300 MHz, $CDCl_3$): $\delta = 7.77$ (s, 1 H), 7.65–7.53 (m, 3 H), 7.27–7.22 (m, 4 H), 7.21–7.10 (m, 2 H), 7.07 (d, J = 6.6 Hz, 2 H), 6.68– 6.64 (m, 1 H), 4.42 (s, 2 H) ppm. ¹³C NMR (75 MHz, $CDCl_3$): $\delta = 143.7, 142.2, 136.1, 135.9, 134.4, 132.0, 129.9,$ 129.6, 129.3, 128.1, 127.9, 127.7, 126.9, 126.3, 124.8, 123.3, 118.0, 117.7, 112.4, 29.9 ppm. 3-Benzyl-2-(4-tolyl)imidazo[1,2-a]pyridine (4i): Pale yellow solid; mp = 160–161 °C. ¹H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (t, J = 8.1 Hz, 4 H), 7.26 (br s, 5 H), 7.16– 7.13 (m, 3 H), 6.70 (br s, 1 H), 4.49 (s, 2 H), 2.39 (s, 3 H) ppm. ¹³C NMR (75 MHz, CDCl₃): $\delta = 144.6$, 144.0, 137.7, 136.6, 131.9, 129.0, 128.9, 128.2, 127.6, 126.7, 124.1, 123.1, 117.5, 117.3, 112.0, 30.1, 21.1 ppm.
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- (10) Reusability of magnetic nano-Fe₃O₄: After completion of the reaction EtOAc was added and the Fe₃O₄-nanoparticles were recovered by the application of an external magnet. The recovered nanoparticles were thoroughly washed with Et₂O, dried at 130 °C for 1 h and then reused for a new catalytic cycle.

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