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SIMPLE AND EFFICIENT PROTOCOL FOR THE SYNTHESIS OF 1, 2, 4, 5-TETRASUBSTITUTED IMIDAZOLES PROMOTED BY BISMUTH (III) BROMIDE

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ABSTRACT

A simple and efficient protocol has been developed for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles *via* four-component using like 1,2-diketones, aryl aldehydes, aryl amines and ammonium acetate in the presence of Bismuth (III) bromide as a promoter and ethanol as a solvent and stirred at 80°C for 30 min. The reaction proceeded in short period of time with high yields using low toxicity bismuth compound.

KEYWORDS: Bismuth (III) bromide ($BiBr_3$), 1, 2, 4, 5-tetrasubstituted imidazoles, 1,2-diketones, aryl aldehydes, aryl amines and ammonium acetate.

INTRODUCTION

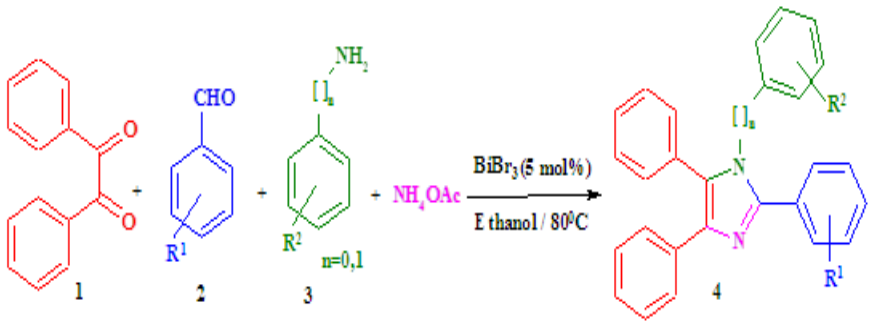
The synthesis of tetra substituted imidazoles constitutes and a substructure is a considerable interest due to their large range of biological, medicinal, physiological and pharmacologically active compounds.[1] These analogues are valuable heterocyclic molecules are present in many naturally occurring biologically active synthetic molecules such as antiallergic, analgesic[2] antifungal,[3] antibacterial, antiprotozoal, anthelmintic,[4] anti-tuberculosis, anti-inflammatory[5] and some of analogues are act as glucagon receptor, kinas inhibitor, antagonist of CB1 cannabinoid,[6] p38 MAP kinase[7] modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR).[8] These facts reflect in the field of pharmacological and medicinal potential of imidazoles derivatives as drug candidates of therapeutic significance and as intermediates in

organic synthesis. Thus the synthesis of these heterocyclic molecules has become an area of great interest.

Recently, Zare *et al*. recommended procedure of synthesizing 1,2,4,5-tetrasubstituted imidazoles derivatives, where direct condensation of 1,2-diketones with aryl aldehydes, aryl amines and ammonium acetate in presence of trityl chloride as a catalyst and reported good yield at temperature of 90°C.[9] Numerous existing reports are available in literature aforesaid sulfonic acid functionalized silica(SiO_2-Pr-SO_3H),[10] ionic liquid in green chemistry and organometallic catalysis,[11] $ZrCl_4$,[12] HY zeolite,[13] DABCO,[14] silica gel/$NaHSO_4$,[15] $HClO_4$–SiO_2,[16] PEG-400,[17] molecular iodine,[18] BF_3–SiO_2,[19] $InCl_3 \cdot 3H_2O$,[20] silica-bonded propylpiperazine N-sulfamic acid (SBPPSA),[21] potassium dodecatugstocobaltatetrihydrate ($K_5CoW_{12}O_{40} \cdot 3H_2O$),[22] nano-$TiCl_4 \cdot SiO_2$,[23] organocatalyst 2-ethylhexanoic acid,[24] Fe^{3+}-K10,[25] ionic liquid and defective keggin heteropoly acid[26] and nano Fe_3O_4@SiO_2-OSO_3H[27] have been employed to accomplish these reactions. Although, atop described protocols are valuable, yet some of the procedure use high temperature, lavish metal precursors and accession takes long time period.

The non-transition-metal bismuth (III) compounds such as $BiCl_3$, $BiBr_3$, $Bi(OTf)_3$ and $Bi(NO_3)_3$[28] *etc*., have attracted growing interests as versatile catalysts in manifold organic synthesis attributed to their remarkable transformation relating to C-C, C-N, C-S bonds formation, in oxidation reaction, protection/deprotection of alcohols and carbonyl compounds furthermore extendable applications of organic reactions in aqueous media. $BiBr_3$ have attracted growing interests as versatile catalysts in diverse organic synthesis owing to their remarkable chemical and physical properties such as relevant stability, air- and moisture-tolerance, low toxicity compare to sodium chloride.[29-30]

In this fashion, in continuation of our efforts towards efficient synthesis of biologically important molecule[31–36], at this moment our interest drift towards the synthesis of highly functionalized piperidines derivatives. Herein, we would like to report a practical synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles derivatives **4** direct one pot condensation of 1,2-diketones **1**, aryl aldehydes **2**, aryl amine **3** ammonium acetate using a catalytic amount $BiBr_3$ catalyst, ethanol medium stirred at temperature (80^oC) to get **4a-o** desired compound in good to excellent yield it shown in **Table II**, **Scheme I**.



Scheme I.

MATERIALS AND METHODS

Experimental and characterization

Melting points were determined on a Buchi melting point apparatus and are uncorrected. IR, ^{1}H and ^{13}C NMR and LCMS were recorded on Nicolet 400DFT-IR spectrophotometer, 300 MHz Brucker spectrometer and Shimadzu LC-MS respectively. 1,2-diketones, aryl aldehydes, aryl amines, ammonium acetate and $BiBr_3$ were all commercial products and were used without further purification.

General procedure for the synthesis of 4a–o

A mixture of 1,2-diketones (10 mmol), benaldehydes (10 mmol), benzylamine (10 mmol), and ammonium acetate (30 mmol) were placed in a 50 mL round bottomed flask with ethanol (20 mL) and charged catalyst $BiBr_3$ (5 mol %) and stirred at 80^{o}C for a 3.5 hrs. The progress of the reaction was monitored by TLC (Petether: Et OAc, 2:8). After completion of the reaction, ethanol remove from reaction mass using rotary evaporator, obtained crude product was extracted with (3 × 30 mL) dichloromethane. The organic layer was washed with water and the solvent was removed at rotary evaporator. The obtained crude desired compound purified by column chromatography using dichloromethane as a gradient. After remove the solvent we got 1-*Benzyl*-2,4,5-*triphenylimidazole* (**Table II**, entry 7, **4g**). White solid: IR (KBr): ν_{max}= 2890, 1590, 1480 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 − 6.82 (m, 20H, Ar), 5.12 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.08, 138.07, 137.56, 134.46, 131.08, 131.02, 130.94, 130.05, 129.08, 128.92, 128.81, 128.61, 128.59, 128.09, 127.36, 126.78, 126.37, 126.02, 48.28.; MS m/z: 386.5; All the products prepared by this procedure were characterized by comparison of their IR, HNMR spectral and LC-MS spectral analysis with authentic samples.

RESULTS AND DISCUSSION

Initially we selected 1,2-diketones (2 eq.), benzaldehyde (2 eq.), aniline(2 eq.) and ammonium acetate (6 eq.), as a model substrate to optimize the amount of catalysts. First we conducted the reaction without catalyst stirred for 7 hrs at temperature 100^{o}C in the absence of ethanol; result is there is no desired compound **4d**. Next, run we tried with 10 mol % $BiBr_3$ with same solvent after 5 hrs stirring we got 80% of desired compound and 72% yield in methanol as solvent. Observed 5 mol % $BiBr_3$ in the presence ethanol stirred for 3.5 hrs got same 84% yield. We carried out the reaction without solvent, after 4hrs got 52% desired compound and also we monitored the reaction using different solvent like acetonitrile, methanol and dichloro methane among these, ethanol is the best solvent, is sufficient for the this method to reduce the time duration of this protocol **Table I**. These results encouraged us to extend this protocol to preparation of other piperidines derivatives. In Table II the variety of 1,2-diketones, aromatic aldehydes. Arylamine/benzylamine and ammonium acetate carrying either electron-withdrawing or electron donating substitutes affords good yields of products with purity in short reaction time. Consequently, we developed a new protocol for the synthesis of 1,2,4,5-tetrasubstituted imidazoles derivatives using $BiBr_3$ as a catalyst.

Table I: Optimization for the 1,2,4,5-tetrasubstituted imidazoles[a].

Entry	$BiBr_3$ mol %	Time (hrs)	Yield[b] (%)	Solvent
1[c]	No catalyst	7	00	Neat
2	10	5	80	Ethanol
3	10	5	72	Methanol
4	5	3.5	84	Ethanol
5	5	3.5	75	Methanol
6	5	3.5	65	Acetonitrile
7[d]	5	3.5	58	Dichloromethane
9	5	4	52	Neat

[a]1,2-diketones, aniline, benzaldehyde and ammonium acetate were taken in 2:2:2:6 ratio in presence of various $BiBr_3$ mol % at 80^{o}C; [b]Isolated yields; [c]Reaction was carried out at 100^{o}C and 55^{o}C[d].

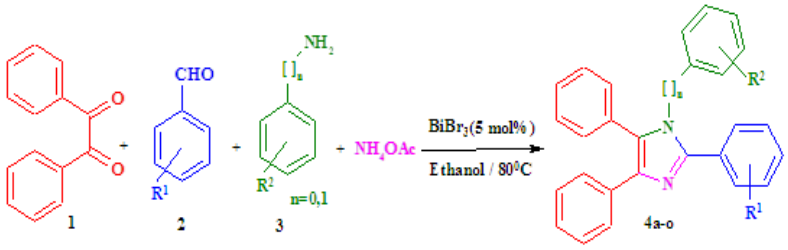


Table II Synthesis of 1,2,4,5-tetrasubstituted imidazoles (4a-o) catalyzed by $BiBr_3$ (5.0 mol %).

Entry	R^1 Arylaldehyde	R^2 Arylamine/benzylamine	Product	Yield (%)	mp(°C) Observed	mp(°C) Literature[ref.]
1	H	H	**4a**	84	215−216	214−216[25]
2	4-CH_3	H	**4b**	86	189−191	189−190[10]
3	3-NO_2	H	**4c**	82	243−244	242−244[25]
4	4-Cl	H	**4d**	85	158−160	157−159[10]
5	4-OCH_3	H	**4e**	80	182−184	181−183[10]
6	4-NO_2	H	**4f**	81	191−193	192−194[27]
7	H	CH_2	**4g**	85	160−161	159−161[26]
8	4-CH_3	CH_2	**4h**	87	165−166	164−166[26]
9	3-Br	CH_2	**4i**	86	148−149	148−150[26]
10	4-Cl	CH_2	**4j**	83	163−164	163−165[25]
11	4-NO_2	CH_2	**4k**	71	171−173	170−172[26]
12	2-OCH_3	CH_2	**4l**	82	187−189	188−190[26]
13	2-NO_2	CH_2	**4m**	80	153−155	154−155[25]
14	4-$N(CH_3)_2$	CH_2	**4n**	78	149−151	149−150[10]
15	3,4-OCH_3	CH_2	**4o**	85	184−186	182−184[10]

[a]All the products are known, characterized by IR, LCMS and NMR spectral analysis and compared with the authentic samples. [b]Isolated yields

CONCLUSION

In conclusion, we have developed a novel protocol for the synthesis of 1,2,4,5-tetrasubstituted imidazoles via condensation of 1,2-diketones, benzyl amine with various aryl aldehydes, aryl amines and ethanol using $BiBr_3$ as catalyst. This protocol offers several advantages including good to excellent yield, simple work-up procedure, and inexpensive, environmental friendly catalyst.

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