[BMIM]BF_4: AN EFFICIENT IONIC LIQUID MEDIUM FOR ONE-POT OF 1*H*-IMIDAZOLE-5(4*H*)-ONE DERIVATIVES

V. Anitha Rani[a]* and Y. Bharathi Kumari[b]

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The environment-friendly one-pot condensation reaction of (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one with phenylhydrazine and (phenyliminomethyl)benzene in the presence of [BMIM]BF_4 as medium at 80-85 ºC for 1-1.5 h to form 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one compounds with good yields. The main advantages of this method are short reaction time, easy workup and good yields.

* Corresponding Authors
E-Mail: anitha1810@gmail.com
[a] Department of Chemistry, Institute of Aeronautical Engineering, Dundigal, Hyderabad, India
[b] Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, College of Engineering, Kukatpally, Hyderabad (A.P), India - 500 085

INTRODUCTION

Multi component and eco-friendly reactions are major techniques for the efficient and rapid synthesis of a wide variety of heterocyclic molecules. These reactions are investigated widely in heterocycles synthesis, initially due to their ability to produce complex heterocyclic compounds with functionality groups form simple starting materials via multi component one-pot reactions.[1]

In the past few decades, the preparation of new heterocyclic molecules has been the focal point of drug discovery research.[2] Among a wide variety of heterocyclic compounds, imidazole scaffold has its significance due to its promising pharmacological and biological activities.

In recent, among the other ionic liquids 1-butyl-3-methyl imidazolium salts have attracted considerable attention as an environmentally sustainable and efficient media and immense uses in various heterocyclic transformations that include hydrogenations,[3] Heck reactions,[4] Friedel-craft reactions,[5] Bishler-Napieral reactions.[6] Among these, in the last decade many applications of the ionic liquid 1-butyl-3-methyl imidazolium tetrafluoroborate ([BMIM]BF_4) in various organic conversions have been reported.[7] The weak electrostatic interactions of tetrafluoroborate with the imidazolium cation display good thermal and electrochemical stability of [BMIM]BF_4. The other favorable physical and chemical properties like lack of inflammability, neutral nature, commercial availability, low volatility, environmentally sustainable and admirable solubility with many organic products make this ionic liquid of greater use than others.[8]

Imidazolinone ring system is of biological and chemical interest since long. The imidazolinone units are found in many biologically active compounds. The imidazolone compounds having diverse bioactivities including anticancer,[9] anti-HIV agents,[10] anticonvulsant,[11] monoaminooxidase (MAO) inhibitory,[12] antiparkinsonian,[13] CNS depressant, antimicrobial, anthelmintics etc.[14]

Bearing the above results in mind, here we now wish to report synthesis of a series of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one derivatives by a one-pot three component process in [BMIM]BF_4 as medium at 80-85 ºC for 60-90 min with good yields.

EXPERIMENTAL

IR spectra were recorded with help of KBr pellets and Perkin-Elmer 1000 instrument.

^{1}H and ^{13}C NMR were recorded in DMSO-d_6 solvent in a Bruker 400 MHz spectrometer. Chemical shifts are expressed in δ ppm units using TMS as internal standard. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 value only.

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath.

General procedure of synthesis

A mixture of (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one (**1**) (10 mmol) and phenylhydrazine (**2**) (10 mmol) in [BMIM]BF_4 (4 eq.) was to heated at 80-85 ºC for 10 min. Then to this reaction mass, added (phenylimino-methyl)benzene (**3**) (10 mmol) and maintained at 50-80 min at 80-85 ºC. After completion of the reaction, as monitored by TLC, the reaction mass was cooled to 30-35 ºC, water (50 ml) was added and stirred for 15-20 min at the same temperature. A colourless solid separated out from the reaction mixture which was collected by filtration. The isolated solid was washed with water (50 ml) and dried at 50-55 ºC for 10 h. The crude product was recrystallized from ethanol to get **4**.

RESULTS AND DISCUSSION

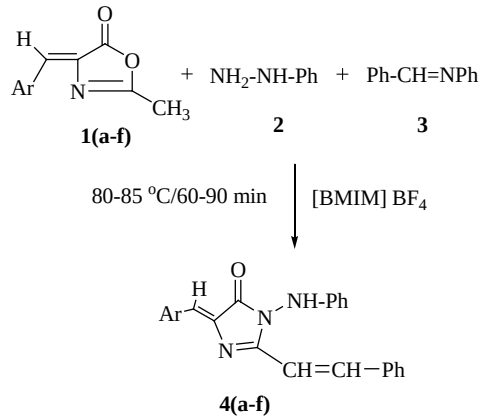
Initially, the one-pot three component reaction was initiated with (*Z*)-4-benzylidene-2-methyloxazol-5(4*H*)-one (**1a**), **2** and **3** to form 4-(benzylidene)-N-aryl amino-2-(styryl)-1*H*-imidazole-5(4*H*)-one (**4a**) in the presence of [BMIM] BF_4 as medium at 80-85 ^oC for 60 min with 80 % yield. The structure of the compound **4a** has been characterized and confirmed by ^{1}H-NMR, IR and mass spectroscopy. This model reaction was performed in different ionic liquids ([DBUH][OAc], [bmim][OH] and [bmim][Br]) at different temperatures. The results are summarized in Table 1. The best results are produced in the presence of [BMIM] BF_4 (4 eq.) as ionic liquid at 80-85 ^oC for 60 min to form title compound with 80 % yield by using **1** (1 eq.), **2** (1 eq.) and **3a** (1 eq.).

Encouraged by above results, the model reaction was examined in the presence of different amount of ionic liquid [BMIM] BF_4 (2 eq., 4 eq. and 5 eq.) with respect to **1**. However, it was found that the one-pot reaction of **1** (1 eq.), **2** (1 eq.), and **3a** (1 eq.), in the presence of [BMIM]BF_4 as a medium (4 eq.) for 60 min at 80-85 ^oC gave the highest yield (80 %) (Table 1, entry 6).

Table 1. Effect of Ionic liquid (4 eq), temperature and on the yield of **4a.**

Entry	Medium, 4 eq.	Temp., °C	Time, min	4a, %
1	[BMIM] BF_4	80-85	60	80
2	[bmim][Br]	80-85	120	63
3	[DBUH][OAc]	80-85	90	61
4	[bmim][OH]	80-85	90	64
5	[BMIM] BF_4	90-95	50	75
6	[bmim][Br]	90-95	90	54
7	[DBUH][OAc]	90-95	80	50
8	[bmim][OH]	90-95	85	52

Based on optimisation condition, the scope of the one-pot three component reaction process was explored, using the best optimized conditions by changing the **1a-1f** (Table 3). The results are displayed in **Table 2.** The structures of the products were assigned on the basis of their spectral properties -IR, NMR & Mass spectra (for details, please see the supplementary material).



4(a-f)

Ar = **1a**, p-MePh; **1b**, p-MeOPh; **1c**, p-FPh
1d, p-NO_2Ph; **1e**, o-ClPh; **1d**, p-clPh

Scheme 1. Synthesis of 4-(benzylidene/substituted benzylidene)-N-aryl amino-2-(styryl/substituted styryl)-1*H*-imidazole-5(4*H*)-one derivatives.

Mechanism

Initially, nucleophilic addition of phenylhydrazine to 4-benzylidene-2-methyl oxazolin-5-one (**1**) results in the formation of (*Z*)-2-acetamido-N-phenyl-3-(phenyl/substituted phenyl)prop-2-enamides (**X**). The mechanism can be explained as Michael type addition of the active methyl group of **1** across the carbon-nitrogen double bond of the shiff bases leading to the generation of styryl group by the loss of aniline. The resulting unstable intermediates readily undergo cyclocondensation to form stable imidazolin-5-one derivatives **4**.

Table 2. Effect of quantity of ionic liquid and time on the yield of **4a.**

Entry	Quantity, eq.	Time, min	4a, %
1	3 eq.	80	80
2	4 eq.	60	80
3	5 eq.	50	78

Table 3. Synthesis of **4a-4f** from **1a-1f** with **2** and **3** in [BMIM] BF_4 at 80-85 ^oC.

Starting material	Product	Time, min	Yield %	M.P., ^{0}C
1a	**4a**	60	80	164-166
1b	**4b**	70	80	165-167
1c	**4c**	65	78	160-163
1d	**4d**	80	80	169-173
1e	**4e**	70	75	155-157
1f	**4f**	60	80	180-185

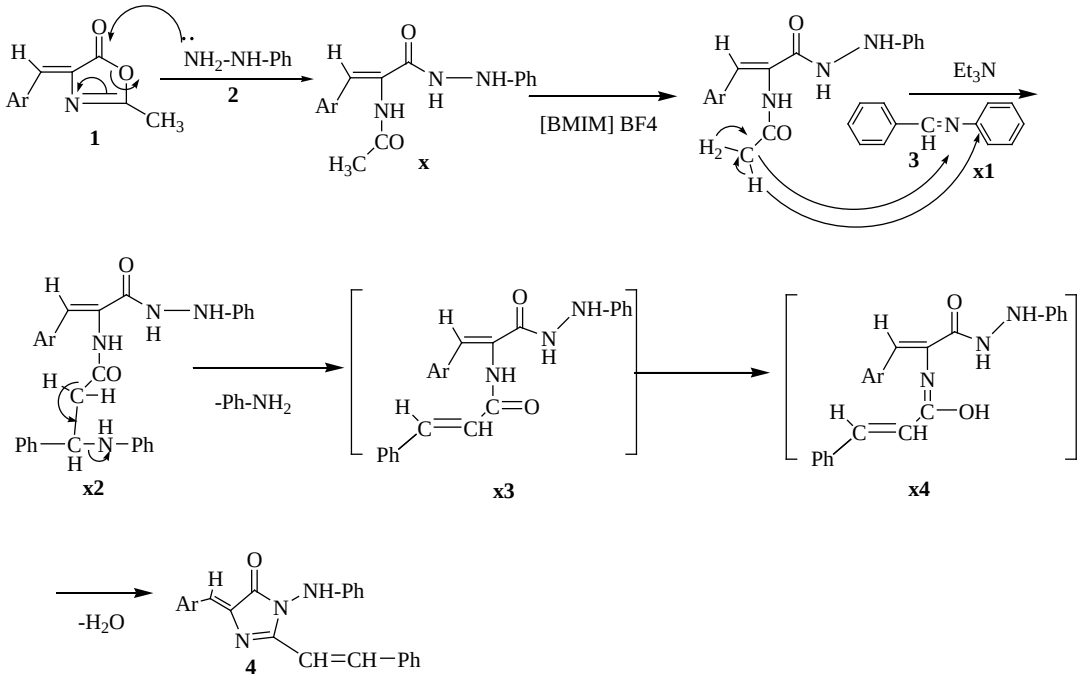
Spectral analysis of 4a-4f

4a: IR (KBr): 3444 (-NH), 1668 (-C=O), 3252(Ar), 1595(C=C),1256(C-N) cm^{-1}. ^{1}H NMR δ= 6.8 (d, 2H, HC=CH), 7.4-8.0(m,15H, Ar-H), 8.0-8.2 (s, 1H(-NH), 8.4 (s, 1H, NH).δ 8.4 (s, 1H, NH). ^{13}C NMR (100MHz) δ = 116(-C=C), 119 (-C=C), 123(-C=C)Ar, 137(C-N), 141(-C=N), 167 (C=O). Mass (*m/z*) = 366 (M+1) (100 %).

4b: IR (KBr): 3436 (-NH), 1674 (-C=O), 3250(Ar), 1590(C=C),1254(C-N) cm^{-1}. ^{1}H NMR δ = 4.2 (s,3H,-OCH_3), 6.7 (d, 2H, HC=CH), 7.4-8.0 (m, 14H, Ar-H), 8.0-8.2(s, 1H(-NH), 8.4 (s, 1H, NH). ^{13}C NMR δ = 116 (-C=C), 118 (-C=C), 122 (-C=C)Ar, 138(C-N), 143 (-C=N), δ 166 (C=O). Mass (*m/z*): 396 (M+1) (100 %).

4c: IR (KBr): 3423 (-NH), 1661(-C=O) 3166 (Ar), 1555 (C=C), 1262 (C-N) cm^{-1}. ^{1}H NMR δ= 6.9 (d, 2H, HC=CH), 7.4-8.0 (m,14H, Ar-H), 8.0-8.2 (s, 1H(-NH), 8.4 (s, 1H, NH). ^{13}C NMR δ= 117 (-C=C), 118 (-C=C), 121 (-C=C)Ar, 137 (C-N), 144 (-C=N), 166 (C=O). Mass (*m/z*): 385 (M+1) (100 %).

4d: IR (KBr): 3455 (-NH), 1662 (-C=O) 3064(Ar), 1598(C=C), 1272(C-N) cm^{-1}. ^{1}H NMR δ 6.8 (d, 2H, HC=CH), 7.5-8.0(m, 14H, Ar-H), 8.0-8.2(s, 1H(-NH), δ 8.4 (s, 1H, NH). ^{13}C NMR δ 116 (-C=C), 118 (-C=C), 123 (-C=C) Ar, 138 (C-N), 145 (-C=N), 167 (C=O). Mass (*m/z*): 411 (M+1) (100 %).



Scheme 2. Mechanism of the formation **4**.

4e: IR (KBr): 3434 (-NH), 1693 (-C=O) 3146(Ar),1570(C=C),1265(C-N) cm^{-1}. ^1H NMR δ = 6.9 (d, 2H, HC=CH), 7.5-8.0 (m,14H, Ar-H), 8.0-8.2 (s,1H(-NH), 8.4 (s, 1H, NH). ^{13}C NMR δ = 117 (-C=C), (-C=C), 124 (-C=C) Ar, 137 (C-N), 144 (-C=N), 168 (C=O). Mass (*m/z*): 400 (M+1) (100 %).

4f: IR (KBr): 3434 (-NH), 1653 (-C=O) 3250(Ar), 1593(C=C), 1254(C-N) cm^{-1}. ^1H NMR δ= 6.8 (d, 2H, HC=CH), 7.4-7.9 (m,14H, Ar-H), 8.0-8.2(s, 1H(-NH), δ 8.4 (s, 1H, NH). ^{13}C NMR δ= 116 (-C=C), 118 (-C=C), 123 (-C=C)Ar, 138 (C-N), 145 (-C=N), 167 (C=O). Mass (*m/z*): 400 (M+1) (100 %).

CONCLUSION

In conclusion we have developed an efficient and environmental benign protocol for the synthesis of title compounds using ionic liquid and green principles. This one-pot three component reaction proceeded in short time with high yields, straightforward work-up procedure and no need to use column purifications.

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