Tri(1-butyl-3-methylimidazolium) gadolinium hexachloride, ([bmim]$_3$[GdCl$_6$]), a magnetic ionic liquid as a green salt and reusable catalyst for the synthesis of tetrasubstituted imidazoles

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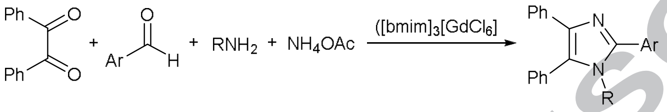

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Tri(1-butyl-3-methylimidazolium) gadolinium hexachloride, ([bmim]$_3$[GdCl$_6$]), a magnetic ionic liquid as a green salt and reusable catalyst for the synthesis of tetrasubstituted imidazoles

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ABSTRACT

The magnetic ionic liquid, tri(1-butyl-3-methylimidazolium) gadolinium hexachloride, ([bmim]$_3$[GdCl$_6$]), has been used as an efficient green catalyst for the one-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles *via* the condensation of benzil, an aromatic aldehyde, aniline and ammonium acetate. Good to excellent yield, mild reaction conditions, as well as ease of operation and work-up are some advantages of the protocol.

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1. Introduction

Imidazole derivatives have a wide range of biological activities and are used as anti-inflammatory,[1,2] antipyretic,[3] antidepressant,[4] antibacterial,[5-7] anticonvulsant,[8] antitumor,[9-12] anticancer,[13-15] antimicrobial,[3, 16, 17] antimalarial,[18] antiviral,[19] herbicide,[20] pesticide,[21] antifungal[6, 22, 23] and antioxidant agents.[24-26] A number of methods have been developed for the synthesis of 1,2,4,5-tetrasubstituted imidazoles.[27] Generally, 1,2,4,5-tetrasubstituted imidazoles are synthesized by the four-component condensations of a 1,2-diketone derivative with an aldehyde, primary amine, and ammonium acetate employing various Lewis acid catalysts, polymer-supported catalysts, zeolite supported reagents, microwave irradiation and ionic liquids.[28,29] However, there still remains the necessity of finding new methods. Ionic liquids (ILs) have recently attracted increased interest in the context of green organic synthesis.[30,31] Although ionic liquids were initially introduced as an alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility, they have since moved beyond this, showing a significant role in controlling reactions as solvent or catalysts.[32-37] Ionic liquids are used in both homogeneous and heterogeneous catalysts as well as transition metal-mediated catalysts in organometallic reactions.[38,39] Due to the high reactivity of ionic liquids, they are also applied as solvents in organic and bio-organic reactions.[40,41] Magnetic ionic liquids (MILs) are one group of room temperature ionic liquids (RTILs) which show new magnetic properties with a wide range of applications. The facile separation of MILs from the reaction media by an external magnet make them more practical than conventional ILs.[44] Del Sesto and co-workers[45,46] have described a large variety of MILs with iron, Fe(III), cobalt, Co(II), manganese, Mn(II) and gadolinium, Gd(III)-containing anions. Furthermore, the incorporation of lanthanide ions into MILs offers the advantage of a metal ion that has a considerably higher effective magnetic moment than transition metals.[47] Tri(1-butyl-3-methylimidazolium) gadolinium hexachloride, ([bmim]$_3$[GdCl$_6$]), is a representative of this class of ionic liquids (Figure 1).

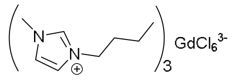


Figure 1. Chemical structure of [bmim]$_3$[GdCl$_6$].

To the best of our knowledge, ([bmim]$_3$[GdCl$_6$]) has not been used as a catalyst in organic synthesis. A one-pot multicomponent reaction for the synthesis of tetrasubstituted imidazoles catalyzed by ([bmim]$_3$[GdCl$_6$]) in excellent yields is reported herein.

2. Results and discussion

Initially, the reaction was investigated by reacting benzil **1** (5 mmol), benzaldehyde **2a** (5 mmol), benzylamine **3a** (5 mmol), ammonium acetate **4** (5 mmol) and the magnetic ionic liquid ([bmim]$_3$[GdCl$_6$]) (1 mmol) under solvent-free conditions. This mixture was stirred at room temperature for 5 h which provided the desired 1,2,4,5-tetrasubstituted imidazole **5a** in 60% yield. When the reaction was performed at an elevated temperature (60 °C), complete conversion of the starting material to the desired product in 75% yield was achieved within 5 h, while at 120 °C the reaction was complete within 2 h in 90% yield. To optimise the reaction conditions, the temperature, and catalyst loading were then examined (Table 1). It was observed that in the absence of catalyst, the product was only detected by TLC (Table 1, entry 12). Although the reaction proceeded in solvents, the obtained yields were lower (Table 1, entries 9-11). It was found that the best conditions were 0.75 mmol of the magnetic ionic liquid under solvent-free conditions at 120 °C for 2 hours (Table 1, entry 6).

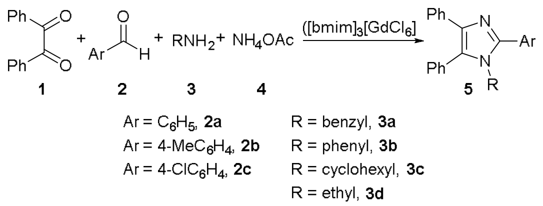


Figure 2. Reaction scope

Table 1. Optimization of the reaction conditions [a]

Entry	Catalyst (mol%)	**4** (mmol)	Temp. (°C)	Solvent	Time (h)	Yield[b] (%)
1	[bmim]$_3$[GdCl$_6$] (20)	NH$_4$OAc (5)	25	Neat	5	60
2	[bmim]$_3$[GdCl$_6$] (20)	NH$_4$OAc (5)	60	Neat	5	75
3	[bmim]$_3$[GdCl$_6$] (20)	NH$_4$OAc (5)	90	Neat	5	81
4	[bmim]$_3$[GdCl$_6$] (20)	NH$_4$OAc (5)	120	Neat	2	90
5	[bmim]$_3$[GdCl$_6$] (20)	NH$_4$OAc (7)	120	Neat	2	94
6	[bmim]$_3$[GdCl$_6$] (15)	NH$_4$OAc (7)	120	Neat	2	93
7	[bmim]$_3$[GdCl$_6$] (10)	NH$_4$OAc (7)	120	Neat	2	89
8	GdCl$_3$.6H$_2$O (15)	NH$_4$OAc (7)	120	Neat	2	76
9	[bmim]$_3$[GdCl$_6$] (15)	NH$_4$OAc (7)	80	Ethanol	5	74
10	[bmim]$_3$[GdCl$_6$] (15)	NH$_4$OAc (7)	115	Toluene	5	55
11	[bmim]$_3$[GdCl$_6$] (15)	NH$_4$OAc (7)	80	Ethyl acetate	5	77
12	None	NH$_4$OAc (7)	120	Neat	5	trace
13	[bmim]$_3$[GdCl$_6$] (15) 2nd run	NH$_4$OAc (7)	120	Neat	2	93
14	[bmim]$_3$[GdCl$_6$] (15) 3nd run	NH$_4$OAc (7)	120	Neat	2	93
15	[bmim]$_3$[GdCl$_6$] (15) 4nd run	NH$_4$OAc (7)	120	Neat	2	92
16	[bmim]$_3$[GdCl$_6$] (15) 5nd run	NH$_4$OAc (7)	120	Neat	2	92

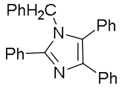
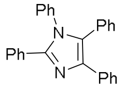
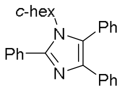
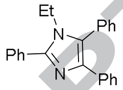
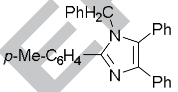
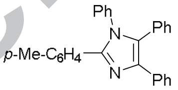
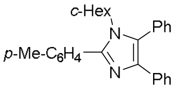
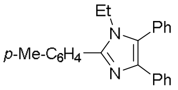
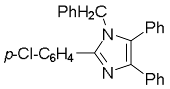
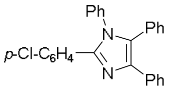
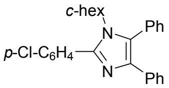
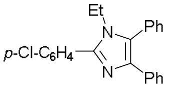
[a] Reaction conditions: **1a** (5 mmol), **2a** (5 mmol), **3a** (5 mmol) and ammonium acetate were heated with stirring, with varying catalyst loading, either in solvent or under solvent-free conditions.
[b] Isolated yield.

A tentative mechanism for this multicomponent reaction was proposed (Figure 3). Initially the counter-cation, bmim$^+$, of the ionic liquid, [bmim]$_3$[GdCl$_6$], acts as a Lewis acid, catalysing the condensation of the NH$_2$ group of substrate **2** with the carbonyl group of aldehyde **1** to furnish intermediate **3**. The ionic liquid also acts as a Lewis acid, catalysing the condensation of the NR$_2$ group of substrate **4** with the carbonyl group of 1,2-dicarbonyl **5** to furnish intermediate **6**, and catalyses the condensation of the NH$_2$ group of substrate **6** with the carbonyl group to furnish intermediate **7.** In the next step, the reaction can also proceed in an E1 like fashion (**7**), with the elimination of oxygen occurring at the same time as the counter-anion deprotonates the nitrogen so it can form a new N=C bond, forming the imine which after tautomerism gives **9**.

Figure 3. Plausible mechanism for the formation of tetrasubstituted imidazoles

The suitability of this method was investigated for several aromatic aldehydes and amines (Table 2). It was clearly observed that substitution of the aldehyde did not appreciably affect the yield of the desired product. In all cases, the products were characterized by ^{1}H and ^{13}C NMR, FT–IR and CHN analyses.

Table 2. Synthesis of tetra substituted imidazole derivatives[a]

Entry	Reactant		Product **5**	Time (h)	Yield[b] (%)
1	**2a**	**3a**		2.5	94[48]
2	**2a**	**3b**		2.5	95[49]
3	**2a**	**3c**		2.5	91[49]
4	**2a**	**3d**		2.5	92
5	**2b**	**3a**		2.5	94[48]
6	**2b**	**3b**		2.5	93[49]
7	**2b**	**3c**		2.5	90[49]
8	**2b**	**3d**		2.5	88[48]
9	**2c**	**3a**		2.0	94
10	**2c**	**3b**		2.0	92[50]
11	**2c**	**3c**		2.0	90
12	**2c**	**3d**		2.0	91[51]

[a] benzil (5 mmol), aldehyde (5 mmol), amine (5 mmol), ammonium acetate (7 mmol), [bmim]$_3$[GdCl$_6$] (0.75 mmol), 120°C, 2 h.[52]

[b] Isolated yield.

The recyclability of the catalyst was also studied in the synthesis of 1,2,4,5-tetrasubstituted imidazoles **5a** under the optimized conditions. The recycled catalyst could be reused 5 times without appreciable loss in the catalytic activity of magnetic ionic liquid (Table 1, entry 13-16).

Conclusions

An efficient, solvent-free, one-pot, multicomponent reaction, catalyzed by a magnetic ionic liquid, tri(1-butyl-3-methylimidazolium) gadolinium hexachloride was described for the synthesis of 1,2,4,5-tetrasubstituted imidazoles derivatives. The catalyst could be readily separated by use of magnetic force and reused without any significant loss of catalytic activity after 5 runs. This method offers several advantages including good to excellent yield, short reaction time, mild reaction condition, simple work-up procedure, ease of separation, green process, and recyclability of the magnetic catalyst, as well as the ability to tolerate a wide variety of substitution in the starting materials.

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52 *General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles*: Benzil (5 mmol), aldehyde (5 mmol), amine (5 mmol), ammonium acetate (7 mmol), and the magnetic ionic liquid ($[bmim]_3[GdCl_6]$) (0.75 mmol) were added to a round bottom flask. This mixture was heated at 120 °C for 2 h. After reaction completion, EtOAc (20 mL) was added to the reaction mixture. The magnetic ionic liquid was magnetically separated from the product solution, washed with EtOAc (20 mL), and used for subsequent reactions after drying under vacuum at 45 °C for 6 h. Tetrasubstituted imidazoles were obtained by evaporation of the solvent, followed by recrystallization from ethanol.