Ionic liquid mediated and promoted one-pot green synthesis of new isoxazolyl dihydro-1H-indol-4(5H)-one derivatives at ambient temperature

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Ionic liquid mediated and promoted one-pot green synthesis of new isoxazolyl dihydro-1H-indol-4(5H)-one derivatives at ambient temperature

Nagi Reddy Modugu* and Praveen Kumar Pittala1

Abstract: We report a mild, inexpensive, fast, highly efficient, and eco-friendly protocol for the synthesis of new isoxazolyl dihydro-1H-indol-4(5H)-ones by a catalyst-free, one-pot three-component reaction of 4-amino-3-methyl-5-styrylisoxazoles, dimedone, and 2-chloroacetophenones under 1-methyl imidazolium tetrafluoroborate ([HMIm]BF4) as task-specific ionic liquid at room temperature. The important aspects of the present methodology are: use of green solvent, short reaction time, catalyst free, compatibility with wide range of substrates, ease of recovery, reusability of reaction medium, and good yields.

Subjects: Environmental Issues; Environmental Change & Pollution; Food Chemistry

Keywords: Isoxazolyl dihydro-1H-indol-4(5H)-ones; one-pot synthesis; [HMIm]BF4; green synthesis

1. Introduction

Green chemistry describes to the design of a process that reduces or minimizes the use and generation of hazardous substances to human health and environment. The development of environmentally friendly catalysts and solvents for organic chemistry and medicinal chemistry is an area of considerable importance. From both economical and environmental points of view, the use of non-volatile solvents, and green catalysts is very promising (Kamalakar, Komura, & Sugi, 2006; Sheldon, 2006).
Weingärtner & Franck, 2005). In the last a few years, room temperature ionic liquids (RTILs) have been recognized as a possible environmentally benign alternative to chemical volatile solvents because, in contrast with the conventional organic solvents, they are non-volatile, non-explosive, easy to handle, thermally robust, and recyclable (Greaves & Drummond, 2008). Accordingly, they are emerging as novel replacements for volatile organic solvents in organic synthesis (Haumann & Riisager, 2008; Martins, Frizzo, Moreira, Zanatta, & Bonacorso, 2008; Plaquevent, Levillain, Guilien, Malhiac, & Gaumont, 2008; Plechkova & Seddon, 2008). The potential of ionic liquid (IL) as green solvent has already been established in several chemical transformations (Wang, Cui, Zou, Yang, & Tang, 2006; Wu, Yang, Cui, Tang, & He, 2004). The dual role of Brensted acidic ionic liquid [HMIm]BF₄ as green solvent and catalyst was proved in a variety of organic chemical reactions (Chu, Qi, & Hao, 2007; Li, Shi, Guo, & Deng, 2004; Zhu, Yang, Tang, & He, 2003).

Multi-component reactions (MCRs), by virtue of their convergence, productivity, elegance, ease of execution, and selectivity, have become one of the most powerful platforms to access diverse complex molecules (De Greef, 2003; Dömling, 2006). Accordingly, these reactions have attracted considerable attention of medicinal chemistry, combinatorial synthesis (Alcaide et al., 2012), pharmaceutical industry (Posner, 1986; Tietze & Beifuss, 1993), and modern drug discovery and development (Estévez, Villacampa, & Menéndez, 2010; Hulme & Gore, 2003).

Indoles are one of the most widely distributed heterocyclic compounds in Nature. In many natural alkaloids, the indole nucleus is an important structural unit (Joule, 2001; Sundberg, 1996). Among the various classes of nitrogen-containing heterocycles, indoles have significant synthetic potential. Compounds carrying the indole moiety exhibit antibacterial, antifungal activities (Sundberg, 1996), CNS depressant (Arya et al., 1977), anti-inflammatory and analgesic (Biswal, Sahoo, Sethy, Kumar, & Banerjee, 2012), antiviral (Kumar, Bala, & Jeet, 2012), antihelmintic (Sharma & Jain, 2012), anticonvulsant (Panwar, Chaudhary, & Singh, 2011), cardiovascular (Kumar et al., 1981), and antihypertensive activity (Grasso et al., 1995). Similarly, the biological activity of substituted isoxazoles has made them a focus of medicinal chemistry over the years. Isoxazoles are potent analgesic, anti-inflammatory (Daidone et al., 1999), antimicrobial (Tomita et al., 1973), COX-2 inhibitory (Talley, 1999; Talley et al., 2000), antitubercular (Haripara, Patel, Joshi, & Parekh, 2004), and anticancer agents (Li et al., 2003). As a consequence, a number of methods have been reported for the construction of indoles. Recently, some functionalized indoles have been synthesized using different starting materials (Chen, Zheng, & Wu, 2011; Fu, Shi, Shi, Jiang, & Tu, 2013; Jiang, Li et al., 2012; Jiang, Yi et al., 2012; Shawkat & Talaat, 2016). However, all these procedures are not convenient from an environmental and economic point of view, as these involve toxic reagents, toxic or costly catalysts, a lack of regioselectivity, multi-step synthesis, harsh reaction conditions, hazardous organic solvents, and give poor yields of the product. So, there is still the need to develop an efficient, cost-effective, and environmentally benign methodology for the synthesis of dihydro-1H-indol-4(5H)-ones.

As a part of our continued interest in the synthesis of different heterocycles carrying isoxazole moiety of biological importance (Nagi Reddy, Praveen Kumar, & Rajanarendar, 2017; Praveen Kumar, Rajanarendar, & Nagi Reddy, 2017; Rajanarendar, Govardhan Reddy, Sivarami Reddy, & Nagi Reddy, 2012; Rajanarendar, Nagi Reddy, Govardhan Reddy, & Rama Krishna, 2012; Rajanarendar, Nagi Reddy, Rama Krishna, Rama Murthy, et al., 2012; Rajanarendar, Nagi Reddy, Rama Murthy, Surendar, et al., 2012; Rajanarendar, Raju, Nagi Reddy, et al., 2012; Rajanarendar, Nagi Reddy, et al., 2010; Rajanarendar, Raju, Siva Rami Reddy, Reddy, & Nagi Redy, 2016; Rajanarendar, Rama Murthy, Firoz, & Nagi Reddy, 2011), we report herein for the first time a simple and efficient one-pot multi-component reaction sequence to access isoxazolyl dihydro-1H-indol-4(5H)-ones from 4-amino-3-methyl-5-styrylisoxazoles, dimedone, and 2-chloroacetophenone promoted using the Brønsted acidic IL, [HMIm]BF₄, as solvent as well as catalyst under mild conditions. This reaction is an example of a Hantzsch type II synthesis (Wang, 2010).
2. Results and discussion

The reaction of 4-amino-3-methyl-5-styrylisoxazole (1a) (Murthy, Rao, & Rao, 1976) (1 mmol) with an equimolar amount of dimesedone (2) and 2-chloro-1-(4-chlorophenyl)ethanone (3h) as a simple model system was examined to establish the feasibility of the strategy and optimize the reaction conditions. It is well known that the choice of an appropriate reaction medium is of crucial importance for successful synthesis. The reaction mixture was tested under a variety of different conditions. The effects of solvent and temperature were evaluated for this reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in water without any catalyst the yield of product was very low (Table 1, entry 6). [HMIm]BF₄ provided higher yields than those using other organic solvents (Table 1, entry 7 vs. entries 1–5). Considering the toxicity of the other solvents, [HMIm]BF₄ was chosen as the solvent for all further reactions. To identify the optimum reaction temperature, the reaction was carried out at room temperature (r.t.), providing the product 4 in good yield 95% (Table 1, entry 7). The use of additives, such as L-proline, resulted in no significant improvement of the yield (Table 1, entry 8). Thus, the optimum conditions tested were at room temperature in [HMIm]BF₄ without any catalyst. To know the influence of Brønsted acidic IL [HMIm]BF₄ in this reaction, the reaction was also carried out with other ionic liquids such as [bmIm]BF₄, [bmIm]OH (Table 1, entries 9,10). In these conditions, the reaction is sluggish and the conversion only reached 70–80%, and the reaction required more time (1.5–2 h) (Table 1). It is noteworthy that [HMIm]BF₄ is highly influencing the reaction by acting as Brønsted acid catalyst as well as effective solvent media for the synthesis of title compounds. Having established that, the best solvent and catalyst is [HMIm]BF₄ for this transformation, another advantage is that it can be easily recovered after the completion of the reaction and can be reused in subsequent runs (five runs) without much loss of efficiency and with negligible loss of the IL. Listed here are the cycle number and yield of 4h (%): 1, 95; 2, 94; 3, 94; 4, 92; 5, 90. The previous reported synthesis are not convenient from an environmental and economic point of view, as those involve toxic reagents, toxic or costly catalysts, multi-step synthesis, harsh reaction conditions, hazardous organic solvents, and give poor yields of the product. Our method has a merit, where by the title compounds are being synthesized in a one-pot green method under mild conditions at ambient temperature in excellent isolated yields in short reaction time.

Table 1. Optimization of the reaction conditions 4aa

| Entry | Solvent           | Temp  | Time (h) | Yieldb (%) |
|-------|-------------------|-------|----------|------------|
| 1     | THF               | reflux| 5        | 48         |
| 2     | MeCN              | reflux| 2.5      | 56         |
| 3     | DCM               | reflux| 8        | 45         |
| 4     | DMF               | reflux| 4        | 64         |
| 5     | EtOH              | reflux| 10       | 70         |
| 6     | H₂O               | reflux| 24       | 35         |
| 7     | [HMIm]BF₄         | RT    | 0.4      | 95         |
| 8     | [HMIm]BF₄ + L-proline (10 mol%) | RT | 0.5 | 94 |
| 9     | [bmIm]BF₄        | RT    | 1.5      | 80         |
| 10    | [bmIm]OH         | RT    | 2.0      | 70         |

*a*All the reactions were performed with 4-amino-3-methyl-5-styrylisoxazole (1 mmol), dimesedone (1 mmol), and 2-chloro-1-(4-chlorophenyl)ethanone (1 mmol) in 5 mL of indicated solvent at various temperatures.

*b*Isolated yields.
With the optimal conditions in hand, the versatility of the protocol was investigated for the construction of isoxazolyl dihydro-1\(H\)-indol-4(5\(H\))-one derivatives through all permutations and combinations of the substrates (Table 2, entries 1–13). Initially, from the combination of 4-amino-3-methyl-5-styrylisoxazole (1 mmol), dimedone (1 mmol), and 2-chloroacetophenone (1 mmol), under identical reaction condition (Table 2, entry 1), the desired product (4\(a\)) was obtained in 94% yield. A wide variety of reactions were examined with substituted 4-amino-3-methyl-5-styrylisoxazole (1\(\text{b}\)) and a range of 2-chloroacetophenone (1\(\text{c}\)) having both electron-withdrawing as well as electron-donating substituents at different positions on the aromatic rings of 1 and 3; the required products 4\(b\)–4\(m\) were obtained in 80–95% yields (Table 2, entries 2–13).

All the products 4 were characterized by IR, \(^1\)H NMR, \(^{13}\)C NMR, and HRMS analysis. The IR spectra of 4\(a\)–m showed absorption bands around 2,840–2,950 cm\(^{-1}\) for aliphatic CH stretching bands and 1,675 cm\(^{-1}\) for C=O functional groups, respectively. The \(^1\)H NMR spectra of 4\(a\)–m displayed the two equivalent methyl groups resonating as a singlet at \(\delta\) 0.78, and the methylene protons at C-5 and C-7 showed as two singlets at \(\delta\) 1.74 and 2.30, respectively. In addition, a characteristic singlet at \(\delta\) 6.40 ppm is ascribed to indole H-3 confirming cyclization.

### Table 2. Substrate scope and yields of isoxazolyl dihydro-1\(H\)-indol-4(5\(H\))-one derivatives (4\(a\)–p)

| Entry | Ar   | R   | Time (min) | Yieldb (%) | Product |
|-------|------|-----|------------|------------|---------|
| 1     | \(\text{C}_6\text{H}_5\) | \(\text{C}_6\text{H}_5\) | 40         | 94        | 4\(a\)  |
| 2     | 4-CH\(_3\)\(\text{C}_6\text{H}_4\) | \(\text{C}_6\text{H}_5\) | 50         | 90        | 4\(b\)  |
| 3     | 4-OCH\(_3\)\(\text{C}_6\text{H}_4\) | \(\text{C}_6\text{H}_5\) | 45         | 92        | 4\(c\)  |
| 4     | 4-OHC\(_6\text{H}_4\) | \(\text{C}_6\text{H}_5\) | 40         | 90        | 4\(d\)  |
| 5     | 4-Cl\(\text{C}_6\text{H}_4\) | \(\text{C}_6\text{H}_5\) | 57         | 94        | 4\(e\)  |
| 6     | 4-Br\(\text{C}_6\text{H}_4\) | \(\text{C}_6\text{H}_5\) | 43         | 90        | 4\(f\)  |
| 7     | 4-N\(_2\)O\(\text{C}_6\text{H}_4\) | \(\text{C}_6\text{H}_5\) | 50         | 89        | 4\(g\)  |
| 8     | \(\text{C}_6\text{H}_5\) | 4-Cl\(\text{C}_6\text{H}_4\) | 40         | 95        | 4\(h\)  |
| 9     | \(\text{C}_6\text{H}_5\) | 4-Br\(\text{C}_6\text{H}_4\) | 45         | 92        | 4\(i\)  |
| 10    | \(\text{C}_6\text{H}_5\) | 4-N\(_2\)O\(\text{C}_6\text{H}_4\) | 55         | 90        | 4\(j\)  |
| 11    | \(\text{C}_6\text{H}_5\) | 4-CH\(_3\)\(\text{C}_6\text{H}_4\) | 40         | 94        | 4\(k\)  |
| 12    | \(\text{C}_6\text{H}_5\) | 4-OCH\(_3\)\(\text{C}_6\text{H}_4\) | 40         | 90        | 4\(l\)  |
| 13    | \(\text{C}_6\text{H}_5\) | 4-OHC\(_6\text{H}_4\) | 50         | 92        | 4\(m\)  |

*The reactions were carried out with 4-amino-3-methyl-5-styrylisoxazole (1 mmol), dimedone (1 mmol), and 2-chloroacetophenone (1 mmol) in the presence of [HMIm]BF\(_4\) at room temperature.

*Isolated yields.

With the optimal conditions in hand, the versatility of the protocol was investigated for the construction of isoxazolyl dihydro-1\(H\)-indol-4(5\(H\))-one derivatives through all permutations and combinations of the substrates (Table 2, entries 1–13). Initially, from the combination of 4-amino-3-methyl-5-styrylisoxazole (1 mmol), dimedone (1 mmol), and 2-chloroacetophenone (1 mmol), under identical reaction condition (Table 2, entry 1), the desired product (4\(a\)) was obtained in 94% yield. A wide variety of reactions were examined with substituted 4-amino-3-methyl-5-styrylisoxazole (1\(\text{b}\)) and a range of 2-chloroacetophenone (1\(\text{c}\)) having both electron-withdrawing as well as electron-donating substituents at different positions on the aromatic rings of 1 and 3; the required products 4\(b\)–4\(m\) were obtained in 80–95% yields (Table 2, entries 2–13).

All the products 4 were characterized by IR, \(^1\)H NMR, \(^{13}\)C NMR, and HRMS analysis. The IR spectra of 4\(a\)–m showed absorption bands around 2,840–2,950 cm\(^{-1}\) for aliphatic CH stretching bands and 1,675 cm\(^{-1}\) for C=O functional groups, respectively. The \(^1\)H NMR spectra of 4\(a\)–m displayed the two equivalent methyl groups resonating as a singlet at \(\delta\) 0.78, and the methylene protons at C-5 and C-7 showed as two singlets at \(\delta\) 1.74 and 2.30, respectively. In addition, a characteristic singlet at \(\delta\) 6.40 ppm is ascribed to indole H-3 confirming cyclization.

### 3. Conclusions

In conclusion, we have developed a novel and efficient procedure for the synthesis of isoxazolyl dihydro-1\(H\)-indol-4(5\(H\))-ones, from a wide variety of 4-amino-3-methyl-5-styrylisoxazoles, dimedone, and different substituted 2-chloroacetophenone using [HMIm]BF\(_4\) as recyclable promoter and reaction medium. The procedure offers several advantages like mild and neutral conditions, excellent yield of products, operational simplicity, and minimum environmental impact, making the technology practical, easy to perform, and facile. In addition, the ionic liquids used were found to be easily recovered and efficiently reused. The newly synthesized isoxazolyl dihydro-1\(H\)-indol-4(5\(H\))-ones might exhibit interesting pharmacology activities and may act as potential drug candidates.
4. Materials and method

4.1. Materials

All the melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F 254 silica gel plates. Visualization was done by exposing to iodine vapor. IR spectra (KBr pellet) were recorded on a Perkin-Elmer BX series FT-IR spectrometer. ¹H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. ¹³C NMR spectra were recorded on a Bruker 75 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethyl silane as internal standard. High-resolution mass spectra (HRMS) were recorded on Q-TOF Micro mass spectrometer.

4.2. General procedure for the synthesis of isoxazolyl dihydro-1H-indol-4(5H)-ones (4a–m)

A mixture of 4-amino-3-methyl-5-styrylisoxazoles 1 (1 mmol), dimedone 2 (1 mmol), and 2-chloroacetophenones 3 (1 mmol) was stirred in the presence of [HMIm]BF₄ (5 mL) at room temperature for 40 min. After completion of the reaction (confirmed by TLC), the reaction mixture was poured on to crushed ice and the separated solid product was filtered and purified by recrystallization from ethanol to give the pure products 4. The ionic liquid left over in the reaction was washed with ethyl acetate and dried at 80°C under vacuum and was reused for conducting subsequent reactions (five times). This procedure was followed for all the reactions listed in Table 2. The ILs [HMIm]BF₄, [bmIm]BF₄, [bmIm]Br, [bmIm]OH were prepared according to the reported procedures (Holberg & Seddon, 1999; Namboodiri & Varma, 2002; Ranu & Banerjee, 2005; Wu et al., 2004).

4.3. Spectral data of synthesized compounds

4.3.1. (E)-6,6-Dimethyl-1-(3-methyl-5-styrylisoxazol-4-yl)-2-phenyl-6,7-dihydro-1H-indol-4(5H)-one (4a)

Yield: 94%, mp 174–176°C. IR (KBr): 3076, 2950, 2840, 1675, 1630, 1580, 1055 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.78 (s, 6H), 1.74 (s, 2H), 2.06 (s, 3H), 2.30 (s, 2H), 6.40 (s, 1H), 6.65 (d, 1H, CH=CH, J = 12 Hz), 6.91 (d, 1H, CH=CH, J = 12 Hz), 7.02–7.80 (m, 10H); ¹³C NMR (75 MHz, CDCl₃): δ 11.4, 25.0 (2C), 34.6, 42.2, 52.4, 100.1, 106.5, 119.3, 120.4, 123.5, 125.0, 126.2, 126.8, 127.1, 127.6, 128.2, 128.8, 129.0, 129.5, 130.2, 131.6, 132.0, 134.3, 137.8, 150.2, 156.2, 194.2. HRMS (ESI-MS) calcd for C₂₈H₂₆N₂NaO₂ (M + Na)+ 445.1892, found 445.1892.

4.3.2. (E)-6,6-Dimethyl-1-(3-methyl-5-(4-methylstyryl)isoxazol-4-yl)-2-phenyl-6,7-dihydro-1H-indol-4(5H)-one (4b)

Yield: 90%, mp 192–194°C. IR (KBr): 3070, 2958, 2835, 1670, 1634, 1584, 1050 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.86 (s, 6H), 1.80 (s, 2H), 2.08 (s, 3H), 2.20 (s, 2H), 2.5 (s, 3H), 6.60 (s, 1H), 6.73 (d, 1H, CH=CH, J = 12 Hz), 6.89 (d, 1H, CH=CH, J = 12 Hz), 7.00–7.78 (m, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 10.8, 24.4, 26.3, 35.2, 41.4, 51.6, 100.9, 105.3, 119.7, 120.8, 122.2, 125.7, 126.3, 127.4, 127.9, 128.0, 128.6, 129.2, 129.7, 130.3, 131.5, 132.4, 134.0, 135.0, 138.1, 152.3, 156.2, 156.6, 195.0. HRMS (ESI-MS) calcd for C₂₉H₂₈N₂NaO₂ (M + Na)+ 459.2048, found 459.2054.

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Supplementary material

Full Characterization data for new compounds are provided in supporting information.

Supplemental data

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