

ORGANIC CHEMISTRY | RESEARCH ARTICLE

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

Nagi Reddy Modugu and Praveen Kumar Pittala

Cogent Chemistry (2017), 3: 1318693



Received: 08 March 2017
Accepted: 10 April 2017
Published: 09 May 2017

*Corresponding author: Nagi Reddy Modugu, Division of Natural Products Chemistry (CSIR), Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad, Telangana 500007, India
E-mails: nagireddy14@gmail.com, mnreddy@iict.res.in

Reviewing editor:
Chris Smith, University of Reading, UK

Additional information is available at the end of the article

ORGANIC CHEMISTRY | RESEARCH ARTICLE

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

Nagi Reddy Modugu^{1*} and Praveen Kumar Pittala¹

Abstract: We report a mild, inexpensive, fast, highly efficient, and eco-friendly protocol for the synthesis of new isoxazolyl dihydro-1*H*-indol-4(5*H*)-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-1*H*-indol-4(5*H*)-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,



Nagi Reddy Modugu

ABOUT THE AUTHORS

Nagi Reddy Modugu was born in Hyderabad (India). He received his MSc from Kakatiya University in 2007 and PhD in Organic Chemistry from Kakatiya University, India, in 2011. He then worked as a postdoctoral fellow or research scientist at the University of Hyderabad, India and National Tsing Hua University, Taiwan. Then, he returned to India and joined as a senior scientist at CSIR-IICT Hyderabad. He has more than 10 years of research experience; he has published more than 40 papers in National and International journals. His current research interest focuses on total synthesis of bioactive natural products and synthesis of new isoxazole derivatives.

Praveen Kumar Pittala obtained his MSc degree in Organic Chemistry from Osmania University (India). He is currently a PhD student under the supervision of Nagi Reddy Modugu at CSIR-IICT Hyderabad, India. His research focuses on the development of new isoxazole derivatives and their biological activity.

PUBLIC INTEREST STATEMENT

The reported method provides wide scope and quick access to new isoxazolyl dihydro-1*H*-indol-4(5*H*)-one derivatives in good to excellent isolated yields within a short period of time from one-pot three-component reaction of 4-amino-3-methyl-5-styrylisoxazoles, dimedone, and 2-chloroacetophenones using 1-methyl imidazolium tetrafluoroborate [HMIm]BF₄ as task-specific ionic liquid at room temperature. Major advantages 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 [HMIm]BF₄ acid as an alternative solvent and catalyst. Hence, the present method meets the concept of Wender's "ideal synthesis." Finally, it is concluded that the present method is an attractive addition to the sustainable chemical processes.

2001; 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, Guillen, 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 Brønsted 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).

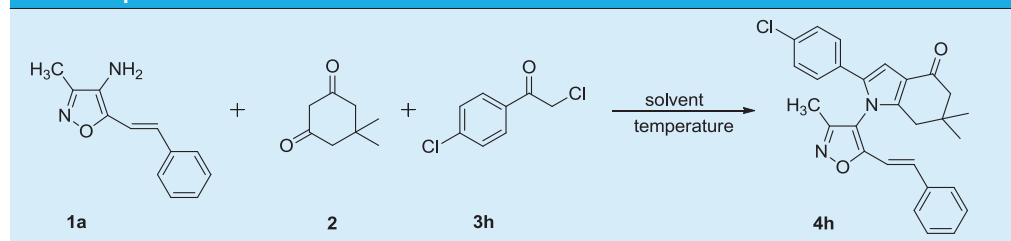
Indoles are one of the most widely distributed heterocyclic compounds in Nature. In many natural alkaloids, the indole nucleus is an important structural unit (Joule, 2001; Sundberg, 1996). Among the various classes of nitrogen-containing heterocycles, indoles have significant synthetic potential. Compounds 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), anthelmintic (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-1*H*-indol-4(5*H*)-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 Reddy, 2010; 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-1*H*-indol-4(5*H*)-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 dimedone (**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 **4a**^a

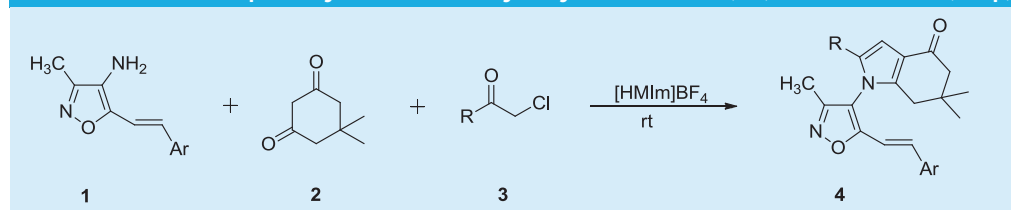


Entry	Solvent	Temp	Time (h)	Yield ^b (%)
1	THF	Reflux	5	48
2	MeCN	Reflux	2.5	56
3	DCM	Reflux	8	45
4	DMF	Reflux	4	64
5	EtOH	Reflux	10	70
6	H ₂ O	Reflux	24	35
7	[HMIm]BF ₄	RT	0.4	95
8	[HMIm]BF ₄ + <i>L</i> -proline (10 mol%)	RT	0.5	94
9	[bmIm]BF ₄	RT	1.5	80
10	[bmIm]OH	RT	2.0	70

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

^bIsolated yields.

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



Entry	Ar	R	Time (min)	Yield ^b (%)	Product
1	C ₆ H ₅	C ₆ H ₅	40	94	4a
2	4-CH ₃ C ₆ H ₄	C ₆ H ₅	50	90	4b
3	4-OCH ₃ C ₆ H ₄	C ₆ H ₅	45	92	4c
4	4-OHC ₆ H ₄	C ₆ H ₅	40	90	4d
5	4-ClC ₆ H ₄	C ₆ H ₅	57	94	4e
6	4-BrC ₆ H ₄	C ₆ H ₅	43	90	4f
7	4-NO ₂ C ₆ H ₄	C ₆ H ₅	50	89	4g
8	C ₆ H ₅	4-ClC ₆ H ₄	40	95	4h
9	C ₆ H ₅	4-BrC ₆ H ₄	45	92	4i
10	C ₆ H ₅	4-NO ₂ C ₆ H ₄	55	90	4j
11	C ₆ H ₅	4-CH ₃ C ₆ H ₄	40	94	4k
12	C ₆ H ₅	4-OCH ₃ C ₆ H ₄	40	90	4l
13	C ₆ H ₅	4-OHC ₆ H ₄	50	92	4m

^aThe 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]BF₄ at room temperature.

^bIsolated 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 (4a) was obtained in 94% yield. A wide variety of reactions were examined with substituted 4-amino-3-methyl-5-styrylisoxazole (1) and a range of 2-chloroacetophenone (3) having both electron-withdrawing as well as electron-donating substituents at different positions on the aromatic rings of 1 and 3; the required products 4b–4 m were obtained in 80–95% yields (Table 2, entries 2–13).

All the products 4 were characterized by IR, ¹H NMR, ¹³C NMR, and HRMS analysis. The IR spectra of 4a–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 ¹H NMR spectra of 4a–m displayed the two equivalent methyl groups resonating as a singlet at δ 0.78, and the methylene protons at C-5 and C-7 showed as two singlets at δ 1.74 and 2.30, respectively. In addition, a characteristic singlet at δ 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]BF₄ 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 F₂₅₄ 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, 152.0, 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, (2C), 26.3, 35.2, 44.1, 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, 156.6, 195.0. HRMS (ESI-MS) calcd for C₂₉H₂₈N₂NaO₂ (M + Na)⁺ 459.2048, found 459.2054.

Funding

Dr Nagi Reddy Modugu and Praveen Kumar Pittala thank the Department Of Science and Technology (DST), New Delhi, for supporting this work [IFA13-CH-108] [grant number GAP-0439]. We are grateful to Dr S. Chandrasekhar, Director, Indian Institute of Chemical Technology (IICT), Hyderabad, for helpful discussion and providing the research facilities.

Supplementary material

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

Supplemental data

Supplemental data for this article can be accessed at <https://doi.org/10.1080/23312009.2017.1318693>.

Author details

Nagi Reddy Modugu¹

E-mails: nagireddy14@gmail.com, mnreddy@iict.res.in

ORCID ID: <http://orcid.org/0000-0001-9019-3325>

Praveen Kumar Pittala¹

E-mail: praveen9652@gmail.com

¹ Division of Natural Products Chemistry (CSIR), Indian Institute of Chemical Technology, Uppal Road, Tarnaka, Hyderabad, Telangana 500007, India.

Citation information

Cite this article as: Ionic liquid mediated and promoted one-pot green synthesis of new isoxazolyl dihydro-1*H*-indol-4(5*H*)-one derivatives at ambient temperature, Nagi Reddy Modugu & Praveen Kumar Pittala, *Cogent Chemistry* (2017), 3: 1318693.

Cover image

Source: Authors.

References

- Alcaide, B., Almendros, P., Aragoncillo, C., Callejo, R., Ruiz, M. P., & Torres, M. R. (2012). Diastereoselective synthesis of β -Lactam-Oxindole hybrids through a three-component reaction of azetidine-2,3-diones, α -Diazo-oxindoles, and alcohols catalyzed by $[\text{Rh}_2(\text{OAc})_4]$. *European Journal of Organic Chemistry*, 12, 2359–2366. <https://doi.org/10.1002/ejoc.v2012.12>
- Arya, P. J., Grewal, R. S., Kaul, C. L., Mizoni, R. H., Rajappa, S., & Shenoy, S. J. (1977). Synthesis and central nervous system depressant activity of some 2,3-disubstituted Indole. *Indian Journal of Chemistry*, 15B, 473–477.
- Biswal, S., Sahoo, U., Sethy, S., Kumar, H. K. S., & Banerjee, M. (2012). Indole: The molecule of diverse biological activities. *Asian Journal of Pharmaceutical and Clinical Research*, 5, 1–6.
- Chen, Z. Y., Zheng, D. Q., & Wu, J. (2011). A facile route to polysubstituted indoles via three-component reaction of 2-ethynylaniline, sulfonyl azide, and nitroolefin. *Organic Letters*, 13, 848–851. <https://doi.org/10.1021/ol102775s>
- Chu, C. D., Qi, Y. H., & Hao, W. (2007). A more efficient synthetic process of *N*-arylphthalimides in ionic liquid $[\text{bmim}][\text{BF}_4]$. *Catalysis Communications*, 8, 1527–1530.
- Daidone, G., Raffa, D., Maggio, B., Plescia, F., Cutuli, V. M. C., Mangano, N. G., & Caruso, A. (1999). Synthesis and pharmacological activities of novel 3-(isoxazol-3-yl)-quinazolin-4(3*H*)-one derivatives. *Archiv der pharmazie pharmaceutical and medicinal chemistry*, 332, 50–54. [https://doi.org/10.1002/\(ISSN\)1521-4184](https://doi.org/10.1002/(ISSN)1521-4184)
- De Greef, M. (2003). Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis*, 10, 1471–1499.
- Dömling, A. (2006). Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chemical Reviews*, 106, 17–89. <https://doi.org/10.1021/cr0505728>
- Estévez, V., Villacampa, M., & Menéndez, J. C. (2010). Multi-component reactions for the synthesis of pyrroles. *Chemical Society Reviews*, 39, 4402–4421. <https://doi.org/10.1039/b917644f>
- Fu, L. P., Shi, Q. Q., Shi, Y., Jiang, B., & Tu, S. J. (2013). Three-component domino reactions for regioselective formation of bis-indole derivatives. *ACS Combinatorial Science*, 15, 135–140. <https://doi.org/10.1021/co3001428>
- Grasso, S., Molica, C., Monforte, A. M., Monforte, P., Zappala, M., Monforte, M. T., & Trovato, A. (1995). Synthesis and antihypertensive activity evaluation of indole derivatives *n*-acetamido substituted. *Farmaco*, 50, 113–117.
- Greaves, T. L., & Drummond, C. J. (2008). Protic ionic liquids: Properties and applications. *Chemical Reviews*, 108, 206–237. <https://doi.org/10.1021/cr068040u>
- Haripara, K., Patel, S., Joshi, A., & Parekh, H. (2004). Synthesis and biological evaluation of some cyano pyridines and isoxazoles. *Indian Journal of Heterocyclic Chemistry*, 13, 221–224.
- Haumann, M., & Riisager, A. (2008). Hydroformylation in room temperature ionic liquids (rtils): Catalyst and process developments. *Chemical Reviews*, 108, 1474–1497. <https://doi.org/10.1021/cr078374z>
- Holberg, J. D., & Seddon, K. R. (1999). The phase behaviour of 1-alkyl-3-methylimidazolium tetrafluoroborates; ionic liquids and ionic liquid crystals. *Journal of the Chemical Society, Dalton Transactions*, 13, 2133–2140.
- Hulme, C., & Gore, V. (2003). Multi-component reactions: Emerging chemistry in drug discovery from xylocain to crivivan. *Current Medicinal Chemistry*, 10, 51–80. <https://doi.org/10.2174/0929867033368600>
- Jiang, B., Li, Y., Tu, M. S., Wang, S. L., Tu, S. J., & Li, G. (2012). Allylic amination and *n*-arylation-based domino reactions providing rapid three-component strategies to fused pyrroles with different substituted patterns. *Journal of Organic Chemistry*, 77, 7497–7505. <https://doi.org/10.1021/jo301323r>
- Jiang, B., Yi, M. S., Shi, F., Tu, S. J., Pindi, S., McDowell, P., & Li, G. (2012). A multi-component domino reaction for the direct access to polyfunctionalized indoles via intermolecular allylic esterification and indolation. *Chemical Communication*, 48, 808–810. <https://doi.org/10.1039/C1CC15913E>
- Joule, J. A. (2001). In E. J. Thomas (Ed.), *Science of synthesis* (Vol. 10, p 361). Stuttgart: Thieme.
- Kamalakar, G., Komura, K., & Sugi, Y. (2006). Tert-butylation of phenol over ordered solid acid catalysts in supercritical carbon dioxide: Efficient synthesis of 2,4-di-tert-butylphenol and 2,4,6-tri-tert-butylphenol. *Industrial & Engineering Chemistry Research*, 45, 6118–6126. <https://doi.org/10.1021/ie060440k>
- Kumar, A., Agarwal, J. C., Nath, C., Gurtu, S., Sinha, J. N., Bhargava, K. P., & Shanker, K. (1981). Synthesis and biological activity of 2-substituted-3-ethyl-*N*-alkyl/arylindoles. *Journal of Heterocyclic Chemistry*, 18, 1269–1271. <https://doi.org/10.1002/jhet.v18.6>
- Kumar, L., Bala, S., & Jeet, K. (2012). The diverse pharmacological importance of indole derivatives: A review. *International Journal of Research in Pharmacy and Science*, 2, 23–33.
- Li, W.-T., Hwang, D.-R., Chen, C.-P., Shen, C.-W., Huang, C.-L., Chen, T.-W., ... Chen, C.-T. (2003). Synthesis and biological evaluation of *N*-Heterocyclic Indolyl Glyoxylamides as orally active anticancer agents. *Journal of Medicinal Chemistry*, 46, 1706–1715. <https://doi.org/10.1021/jm020471r>
- Li, D., Shi, F., Guo, S., & Deng, Y. (2004). One-pot synthesis of silica gel confined functional ionic liquids: Effective catalysts for deoxygenation under mild conditions. *Tetrahedron Letters*, 45, 265–268. <https://doi.org/10.1016/j.tetlet.2003.10.175>
- Martins, M. A. P., Frizzo, C. P., Moreira, D. N., Zanatta, N., & Bonacorso, H. G. (2008). Ionic liquids in heterocyclic synthesis. *Chemical Reviews*, 108, 2015–2050. <https://doi.org/10.1021/cr078399y>
- Murthy, K., Rao, N. V. S., & Rao, K. S. R. K. M. (1976). Microwave-induced acetoacetylation of isoxazolyl amines with β -keto esters. *Journal of Indian Chemical Society*, 53, 1047–1050.
- Nagi Reddy, M., Praveen Kumar, P., & Rajanarendar, E. (2017). A fast and highly efficient one-pot synthesis of novel isoxazolylpyrido[2,3-*b*][1,4]oxazin-2(3*H*)-ones via smiles rearrangement using task-specific ionic liquid $[\text{HMIm}][\text{BF}_4]$ as green solvent. *Green Chemistry Letters and Reviews*, 10, 48–53. <https://doi.org/10.1080/17518253.2017.1285966>
- Namboodiri, V., & Varma, R. S. (2002). Solvent-free sonochemical preparation of ionic liquids. *Organic Letters*, 4, 3161–3163. <https://doi.org/10.1021/ol026608p>
- Panwar, H., Chaudhary, N., & Singh, S. (2011). Synthesis, characterization and biological activity of some substituted pyrazolyl and pyrazolyl-1,3,4-thiadiazino(6,5-*b*)indoles. *Rasayan Journal of Chemistry*, 4, 371–380.

- Plaquet, J.-C., Levillain, J., Guillen, F., Malhiac, C., & Gaumont, A.-C. (2008). Ionic liquids: New targets and media for α -amino acid and peptide chemistry. *Chemical Reviews*, 108, 5035–5060. <https://doi.org/10.1021/cr068218c>
- Plechkova, N. V., & Seddon, K. R. (2008). Applications of ionic liquids in the chemical industry. *Chemical Society Reviews*, 37, 123–150. <https://doi.org/10.1039/B006677J>
- Posner, G. H. (1986). Multi-component one-pot annulations forming 3 to 6 bonds. *Chemical Reviews*, 86, 831–844. <https://doi.org/10.1021/cr00075a007>
- Praveen Kumar, P., Rajanarendar, E., & Nagi Reddy, M. (2017). Ionic liquid [HMIm]BF₄ mediated and promoted eco-friendly one-pot sequential synthesis of new isoxazolyl quinazolin-4(3H)-ones. *Chemistry Select*, 2, 2651–2654.
- Rajanarendar, E., Nagi Reddy, M., Govardhan Reddy, K., & Rama Krishna, S. (2012). L-Proline catalyzed efficient one-pot three-component aza-Diels-Alder reactions on nitrostyrylisoxazoles: A facile synthesis of new isoxazolyl tetrahydroquinolines and isoxazolo[2,3-*a*]pyrimidines. *Tetrahedron Letters*, 53, 2909–2913. <https://doi.org/10.1016/j.tetlet.2012.04.002>
- Rajanarendar, E., Nagi Reddy, M., Murthy, K., Reddy, K., Raju, S., Srinivas, M., ... Rao, M. (2010). Synthesis, antimicrobial, and mosquito larvicidal activity of 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6,10b-tetrahydro-1*H*-pyrimido[5,4-*c*]quinolin-5-ones. *Bioorganic & Medicinal Chemistry Letters*, 20, 6052–6055. <https://doi.org/10.1016/j.bmcl.2010.08.060>
- Rajanarendar, E., Nagi Reddy, M., Rama Murthy, K., Surendar, P., Reddy, R.N., & Reddy, Y. N. (2012). Synthesis and *in vitro* and *in vivo* anticancer activity of novel phenylmethylene bis-isoxazolo[4,5-*b*]azepines. *Bioorganic & Medicinal Chemistry Letters*, 22, 149–153. <https://doi.org/10.1016/j.bmcl.2011.11.044>
- Rajanarendar, E., Nagi Reddy, M., Rama Krishna, S., Rama Murthy, K., Reddy, Y. N., & Rajam, M. V. (2012). Design, synthesis, antimicrobial, anti-inflammatory and analgesic activity of novel isoxazolyl pyrimido[4,5-*b*]quinolines and isoxazolyl chromeno[2,3-*d*]pyrimidin-4-ones. *European Journal of Medicinal Chemistry*, 55, 273–283. <https://doi.org/10.1016/j.ejmech.2012.07.029>
- Rajanarendar, E., Govardhan Reddy, K., Sivarami Reddy, A., & Nagi Reddy, M. (2012). Brønsted acidic ionic liquid [HMIm]BF₄ promoted simple and efficient one-pot green synthesis of isoxazolyl-1,3-benzoxazines at ambient temperature. *Green Chemistry Letters and Reviews*, 5, 699–705.
- Rajanarendar, E., Raju, S., Siva Rami Reddy, A. S., Reddy, K. G., & Nagi Reddy, M. (2010). A fast and highly efficient protocol for synthesis of pyrrolo[2,3-*d*]isoxazoles and a new series of novel benzyl bis-pyrrolo[2,3-*d*]isoxazoles using task-specific ionic liquids as catalyst and green solvent. *Chemical and Pharmaceutical Bulletin*, 58, 833–839. <https://doi.org/10.1248/cpb.58.833>
- Rajanarendar, E., Raju, S., Nagi Reddy, M., Krishna, S. R., Kiran, L. H., Narasimha Reddy, A. R., Reddy, Y. N., & Reddy, Y. N. (2012). Multi-component synthesis and *in vitro* and *in vivo* anticancer activity of novel arylmethylene bis-isoxazolo[4,5-*b*]pyridine-*N*-oxides. *European Journal of Medicinal Chemistry*, 50, 274–279. <https://doi.org/10.1016/j.ejmech.2012.02.004>
- Rajanarendar, E., Rama Murthy, K., Firoz, P. S., & Nagi Reddy, M. (2011). A fast, highly efficient and green protocol for Michael addition of active methylene compounds to styrylisoxazoles using task-specific basic ionic liquid [bmIm]OH as catalyst and green solvent. *Indian Journal of Chemistry*, 50B, 587–592.
- Ranu, B. C., & Banerjee, S. (2005). Ionic liquid as catalyst and reaction medium. the dramatic influence of a task-specific ionic liquid, [bmim]oh, in michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles. *Organic Letters*, 7, 3049–3052. <https://doi.org/10.1021/ol051004h>
- Sharma, K., & Jain, R. (2012). Synthesis, reactions and anthelmintic activity of 1-[benzimidazol-2-yl]-4-formyl-3-[2'-substituted phenyl]indole-3-yl]-pyrazoles. *Indian Journal of Chemistry*, 51B, 1462–1469.
- Shawkat, A. M., & Talaat, E. E. (2016). A facile one-pot synthesis of novel 1-substituted 2-(8-hydroxyquinolin-5-yl)-1,5,6,7-tetrahydro-6,6-dimethyl-4*H*-indol-4-one derivatives. *Arxiv.org*, iv, 4, 184–192.
- Sheldon, R. (2001). Catalytic reactions in ionic liquids. *Chemical Communications*, 232399–2407. <https://doi.org/10.1039/b107270f>
- Sundberg, R. J. (1996). *The chemistry of indole*. New York, NY: Academic.
- Talley, J. J. (1999). Selective inhibitors of cyclooxygenase-2 (COX-2). *Progress in Medicinal Chemistry*, 36, 201–234. [https://doi.org/10.1016/S0079-6468\(08\)70048-1](https://doi.org/10.1016/S0079-6468(08)70048-1)
- Talley, J. J., Brown, D. L., Carter, J. S., Graneto, M. J., Koboldt, C. M., Masferrer, J. L., ... Seibert, K. (2000). 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: A potent and selective inhibitor of COX-2. *Journal of Medicinal Chemistry*, 43, 775–777. <https://doi.org/10.1021/jm990577v>
- Tietze, L. F., & Beifuss, U. (1993). Sequential transformations in organic chemistry: A Synthetic strategy with a future. *Angewandte chemie international edition in English*, 32, 131–163. [https://doi.org/10.1002/\(ISSN\)1521-3773](https://doi.org/10.1002/(ISSN)1521-3773)
- Tomita, K., Takahi, Y., Ishizuka, R., Kamamura, S., Nakagawa, M., Ando, M., ... Udaira, H. (1973). *Ann Sankyo Res Lab*, 1, 25. *Chemical Abstract*, 80, 120808.
- Wang, Z. (2010). Hantzsch pyrrole synthesis. *Comprehensive Organic Name Reactions and Reagents*, 1326–1329. doi:10.1002/9780470638859.conrr295
- Wang, H., Cui, P., Zou, G., Yang, F., & Tang, J. (2006). Temperature-controlled highly selective dimerization of α -methylstyrene catalyzed by Brønsted acidic ionic liquid under solvent-free conditions. *Tetrahedron*, 62, 3985–3988. <https://doi.org/10.1016/j.tet.2006.02.025>
- Weingärtner, H., & Franck, E. U. (2005). Supercritical water as a solvent. *Angewandte Chemie International Edition*, 44, 2672–2692. <https://doi.org/10.1002/anie.v44:18>
- Wu, H.-H., Yang, F., Cui, P., Tang, J., & He, M.-Y. (2004). An efficient procedure for protection of carbonyls in Brønsted acidic ionic liquid [Hmim]BF₄. *Tetrahedron Letters*, 45, 4963–4965. <https://doi.org/10.1016/j.tetlet.2004.04.138>
- Zhu, H. P., Yang, F., Tang, J., & He, M.-Y. (2003). Brønsted acidic ionic liquid 1-methylimidazolium tetrafluoroborate: A green catalyst and recyclable medium for esterification. *Green Chemistry*, 5, 38–39. <https://doi.org/10.1039/b209248b>



© 2017 The Author(s). This open access article is distributed under a Creative Commons Attribution (CC-BY) 4.0 license.

You are free to:

Share — copy and redistribute the material in any medium or format.

Adapt — remix, transform, and build upon the material for any purpose, even commercially.

The licensor cannot revoke these freedoms as long as you follow the license terms.

Under the following terms:

Attribution — You must give appropriate credit, provide a link to the license, and indicate if changes were made.

You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use.

No additional restrictions.

You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits.



Cogent Chemistry (ISSN: 2331-2009) is published by Cogent OA, part of Taylor & Francis Group.

Publishing with Cogent OA ensures:

- Immediate, universal access to your article on publication
- High visibility and discoverability via the Cogent OA website as well as Taylor & Francis Online
- Download and citation statistics for your article
- Rapid online publication
- Input from, and dialog with, expert editors and editorial boards
- Retention of full copyright of your article
- Guaranteed legacy preservation of your article
- Discounts and waivers for authors in developing regions

Submit your manuscript to a Cogent OA journal at www.CogentOA.com

