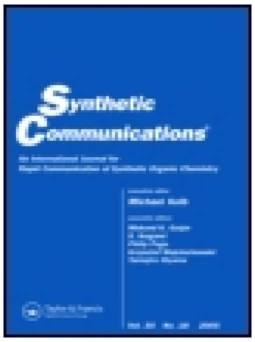

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A solvent and transition metal-free, highly efficient Brønsted acidic ionic liquid promoted one-pot three-component reactions for the synthesis of tetrasubstituted pyrroles

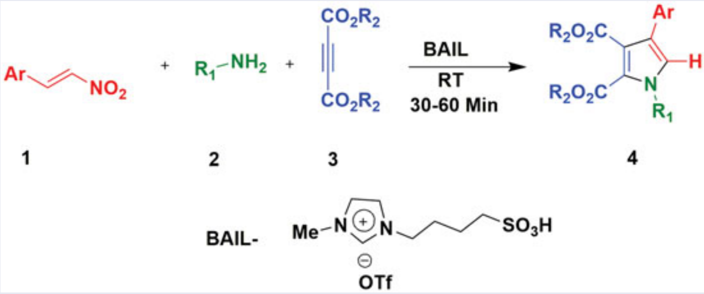
Amol Balu Atar, Eunbi Han, Dae Hyup Sohn, and Jongmin Kang

Department of Chemistry, Sejong University, Seoul, Republic of Korea

ABSTRACT

The present protocol describes a highly efficient, transition metal and solvent-free one-pot annulation of amines, dialkyl acetylenedicarboxylates and β-nitrostyrene using imidazolium Brønsted acidic ionic liquid for the synthesis of tetrasubstituted pyrroles. A diverse functionalized tetrasubstituted pyrroles derivatives were obtained with excellent yields under transition metal and solvent-free conditions. The Brønsted acidic ionic liquid can be easily recovered and reused for the next reaction without any effects on the yields of the products. This green protocol provides structurally complex, medicinally important tetrasubstituted pyrroles with various substitution patterns in a one-pot operation.

GRAPHICAL ABSTRACT



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KEYWORDS
Transition metal free;·Brønsted acid ionic liquid;·tetrasubstituted pyrroles;·Green Media ·MCRs

Introduction

Ionic liquids (ILs) as a green media has emerged powerful tool for the organic chemist in the field of modern organic chemistry and are one of the mainstream research areas of the scientific community that drives increasing efforts.[1] ILs catalyzed reactions show significant efforts in many useful organic transformations due to their unique properties such as dual role of solvent and catalyst, low vapor pressure, excellent chemical stability,

CONTACT Amol Balu Atar amol.atar@sejong.ac.kr; Jongmin Kang kangjm@sejong.ac.kr Department of Chemistry, Sejong University, Seoul 143-747, Republic of Korea.

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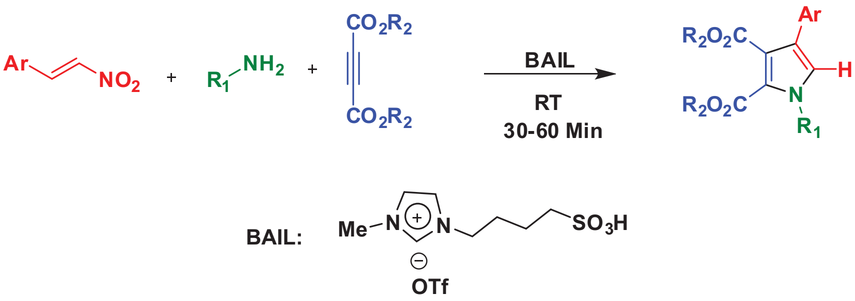
inexpensive, safe, and environmentally non-hazardous.[2] Most importantly they are immiscible with a number of organic solvents which provide nonaqueous, polar alternative for two-phase systems instead of the use of water. Recently ionic liquids have been considered as a new class of green solvents.[3] Moreover, ionic liquids have great ability to control the selectivity of chemical transformations as well as reduce the time of completion reaction. Therefore, the development of synthetically useful reactions in ILs is of considerable interest in the scientific community.[4]

Currently, there has been increasing concern with regard to the tight legislation on the maintenance of "greenness" in synthetic pathways and processes. Green chemistry strongly influences chemical research, and there is an insistence on the use of "greener" reaction conditions.[5] Indeed, the use of ILs, as a green solvents, in organic reactions has improved not only the aspect of the reactions from the viewpoint of green and sustainable properties but also the synthetic efficiency by stabilizing the catalyst, changing the reaction selectivity or facilitating product isolation.[6–14] Particularly, ILs, as a green solvents, showed a great ability for multicomponent reaction (MCRs).[15] In contrast of conventional multistep synthetic protocols, the MCRs using ILs deliver outstanding benefits, such as simple experimental procedures, creation of several carbon–carbon and carbon–heteroatom bonds in a single operation, high atom economy, high yields, less formation of by products, short reaction times, and restraint of complex isolation and purification of intermediates.[16]

Pyrroles are one of the major classes of heterocyclic compounds, having increasing importance in medicinal chemistry and organic synthesis. Several pyrroles as core structures are found in natural products, bioactive compounds, drug molecules, and optoelectronic materials. The pyrroles structural motifs have shown a wide range of biological properties such as antibacterial,[17] antioxidant,[18] anti-inflammatory,[19] antifungal agents,[20] and antitumor.[21] In addition, they are used as a chromophores in an electro-optic (EO) devices. Recently Nishihara et al. showed pyrroles based π-conjugated system as a candidates for molecular flat-band ferromagnets.[22] The pyrroles derivatives have significant importance in the pharmaceutical industry and the synthesis of these novel type of heterocycles desirable. Numerous elegant approaches have been developed to access for the pyrroles derivatives. These include traditional methods such as classical Knorr reaction, the Hantzsch reaction, and the Paal – Knorr condensation reaction, multicomponent coupling, tandem reactions, transition-metal-catalyzed cyclization, and catalytic C–H bond functionalization strategies.[23]

Until now, a three-component reaction of amines, aldehydes, and β-nitrostyrene is reported to give tetrasubstituted pyrroles derivatives using $FeCl_3$ as a transition metal catalyst.[24] But unfortunately, the tetrasubstituted pyrroles derivatives has basically been catalyzed by transition metals or carried out in toxic solvents whose uses have been limited from its noncompliance with the requirements of green chemistry. Thus, the search for green solvent as well as convenient catalyst is desirable. In continuation of our ongoing research to development of greener methods for the synthesis interesting biologically active heterocycles,[25–28] we disclose herein for the first time a greener method one-pot multicomponent synthesis of tetrasubstituted pyrroles derivatives using imidazolium Brønsted acidic ionic liquid (Scheme 1).



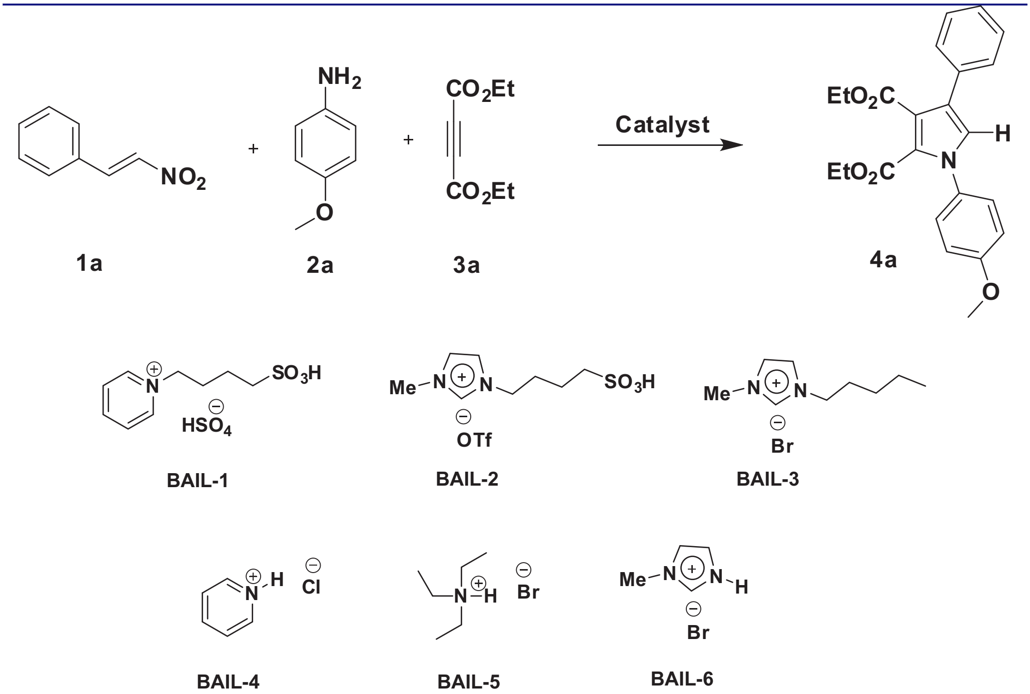
Scheme 1. BAIL-catalyzed one pot annulation for the synthesis of tetrasubstituted pyrroles derivatives.

Result and discussion

To optimize the best reaction conditions, we started our study by reacting trans β-nitrostyrene **1a**, 4-methoxyaniline **2a** and diethyl acetylenedicarboxylate **3a** as the model substrates by using various parameters like different catalysts, temperature, and solvents were carried out (Table 1). Initially, using model substrate, the reaction was carried out in water as a green solvent at room temperature. The result shows that there was no any product formation and TLC indicating only starting materials (Table 1, entry 1). Then, further using water as solvent, reaction was carried out at refluxed condition. These results show that there is no any progress in reaction and indicated that need catalyst to proceed the reaction (Table 1, entry 2). Then, we screened different acid promoter catalysts for this one-pot annulation using water as a solvent. Unfortunately, when various acid promoters catalysts, such as TsOH, HCl, TFA, HOAc, and CF_3COOH (Table 1, entries 3–7), were evaluated as highly efficient promoters for the reaction, the desired product was obtained only in 12–34% yields.

Next, we decided to investigate to use different Brønsted acidic ionic liquid as a catalyst as well as solvent. To our surprise, when **BAIL-1** used as catalyst and solvent for this one-pot annulation using model substrates, the desired product **4a** was obtained in 54% yield at room temperature (Table 1, entry 8). Inspired by this result, we screened different types of Brønsted acidic ionic liquid for this one-pot reaction (Table 1). Among all screened Brønsted acidic ionic liquid imidazolium-based **BAIL-2** as a catalyst as well as solvent for the model reaction, and gratifyingly, 98% of the desired product **4a** was obtained within 30 min (Table 1, entry 9). In contrast, another Brønsted acidic ionic liquid was not highly effective for this transformation (Table 1, entries 10–13). Also, we screened different temperature system, and room temperature was best system in term of yield of desired product and reaction time (Table 1, entries 8, 14, and 15). The acid strength values (H_0) of the ionic liquids were determined using the UV-visible spectroscopy combined with Hammett indicator (p-nitroaniline) method at room temperature. The acidity of **BAIL** decreases in the order: **BAIL-2** > **BAIL-6**≈ **BAIL-3**> **BAIL-1**> **BAIL-4**> **BAIL-5**. It is concluded that the sequence of the catalytic performance observed for the synthesis of tetrasubstituted pyrroles derivatives is in good agreement with the Brønsted acidity order determined by the Hammett method, and **BAIL-2** was determined to be the most suitable catalyst for this one-pot reaction. We also checked the effect of amount of **BAIL-2** loaded for this reaction. When 5, 10, and

Table 1. Screening of various types of catalysts and solvents for the synthesis of compound **4a**.[a]



Entry	Catalyst (10 mol%)	Solvent	Temperature	Time	Yield[b] (%)
1	—	Water	RT	24 h	0[c]
2	—	Water	Reflux	24 h	0[c]
3	TsOH	Water	Reflux	12 h	17
4	HCl	Water	Reflux	16 h	15
5	TFA	Water	Reflux	24 h	12
6	HOAc	Water	Reflux	20 h	34
7	CF_3COOH	Water	Reflux	18 h	22
8	BAIL-1	—	RT	2 h	54
9	BAIL-2	—	RT	30 min	98
10	BAIL-3	—	RT	40 min	62
11	BAIL-4	—	RT	70 min	50
12	BAIL-5	—	RT	100 min	45
13	BAIL-6	—	RT	80 min	66
14	BAIL-2	—	50 °C	30 min	85
15	BAIL-2	—	80 °C	30 min	78
16	BAIL-2 (5 mol%)	—	RT	30 min	96
17	BAIL-2 (20 mol%)	—	RT	30 min	95

[a] Reactions and conditions: The reactions were carried out in a pressure vial in the presence of trans *β*-nitrostyrene **1a** (1 mmol), 4-methoxyaniline **2a** (1 mmol) and diethyl acetylenedicarboxylate **3a** (1 mmol).

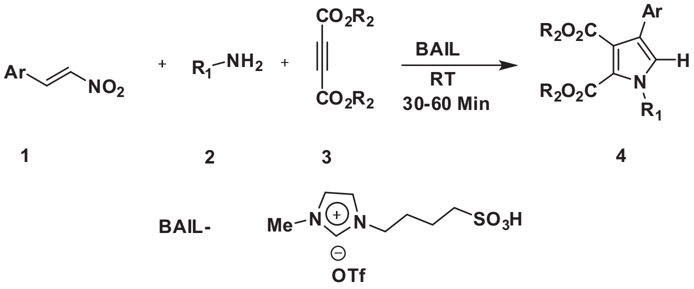
[b] Isolated yields.

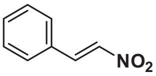
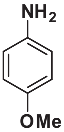
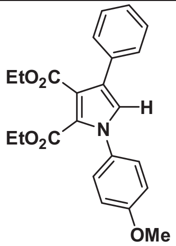
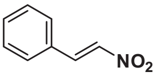
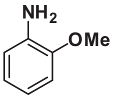
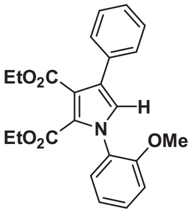
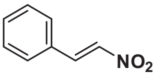
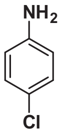
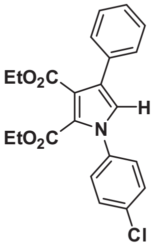
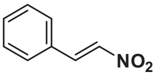
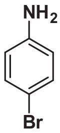
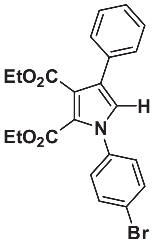
[c] Starting material recovered.

20 mol% of **BAIL-2** were used, the yields were obtained 96, 98, and 95%, respectively (Table 1, entries 9, 16, and 17). This results show that 10 mol% of **BAIL-2** was sufficient and optimal quantity for the completion of the reaction (Table 1, entry 9).

Under the above-optimized conditions, the substrate scope of this reaction was examined by using various aryl substituted β-nitrostyrene, amines, and dialkyl acetylenedicarboxylate (Table 2). The results show that aryl substituted β-nitrostyrene substituted with

Table 2. One pot annulation of amines, dialkyl acetylenedicarboxylate and β-nitrostyrenes for the synthesis of tetrasubstituted pyrroles derivatives catalyzed by BAIL.[a]



No.	β-nitrostyrene	R_1	R_2	Product	Time(Min)	Yield[b]
4a					30	98%
4b					30	95%
4c					25	96%
4d					35	92%

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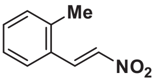
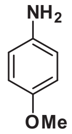
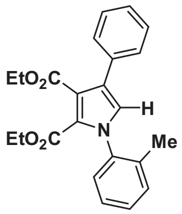
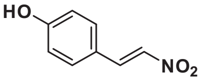
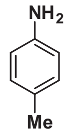
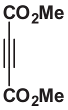
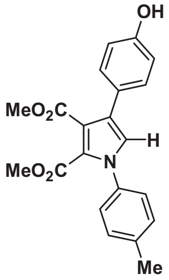
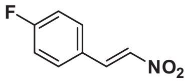
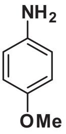
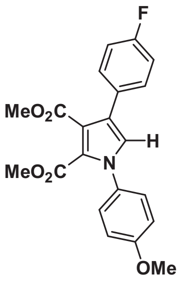
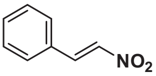
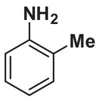
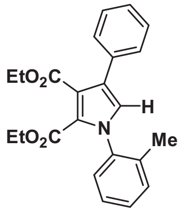
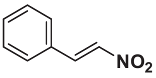
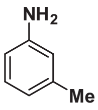
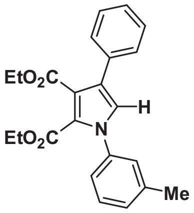
4e					50	96%
4f					45	90%
4g					50	93%
4h					60	89%
4i					55	85%

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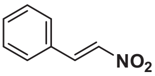
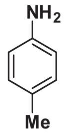
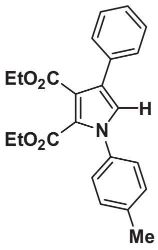
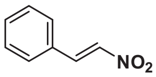
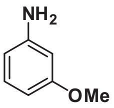
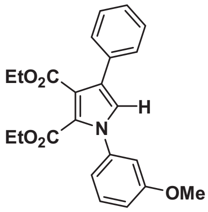
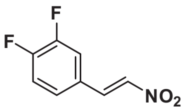
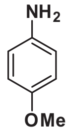
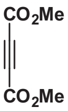
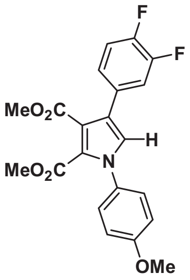
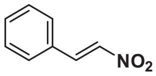
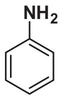
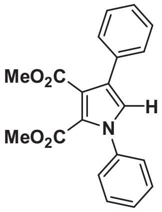
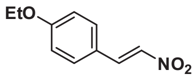
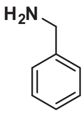
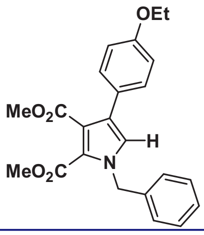
4j					40	88%
4k					35	91%
4l					35	91%
4m					60	84%
4n					60	80%

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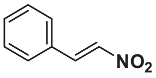
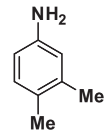
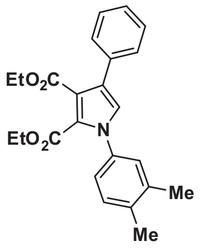
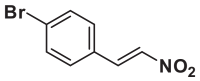
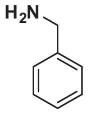
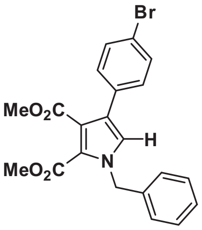
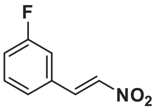
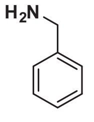
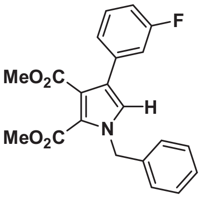
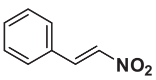
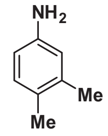
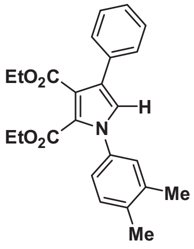
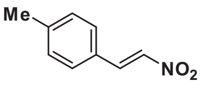
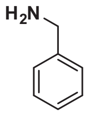
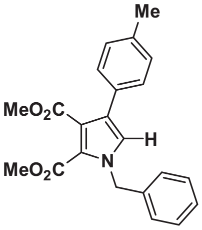
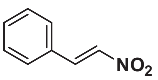
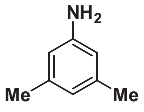
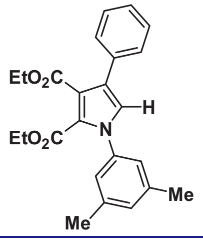
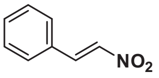
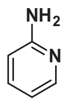
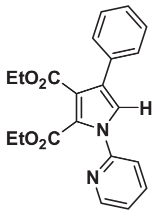
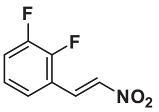
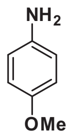
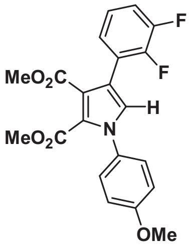
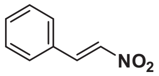
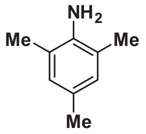
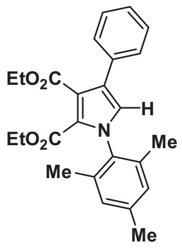
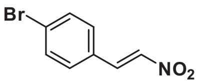
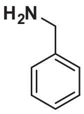
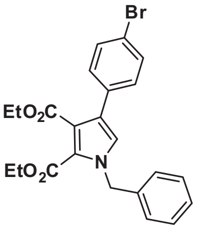
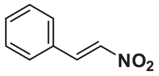
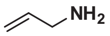
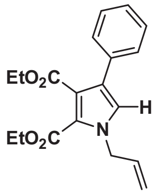
either electron-donating or electron-withdrawing groups proceeded the reaction smoothly and gave the products in good yields (Table 2, entries **4a**, **4e**, **4f**, **4g**, **4l**, **4n**, **4p**, **4s**, and **4v**). The present methods also work well both aromatic and aliphatic amines as well as dialkyl acetylenedicarboxylate (Table 2, entries **4a**, **4x**, and **4y**). We did not observe much difference in the yield of **4**, obtained by electron-donating

40					45	83%
4p					40	90%
4q					60	81%
4r					60	79%
4s					30	95%
4t					30	86%

(continued)

4u					60	nr
4v					60	81%
4w					60	78%
4x					35	91%
4y					45	84%

[a] Reactions and conditions: The reactions were carried out in a pressure vial in the presence of trans *β*-nitrostyrene **1** (1 mmol), amines **2** (1 mmol) and dialkyl acetylenedicarboxylate **3** (1 mmol)

[b] Isolated yields. Figure 1 illustrated the plausible mechanism of this one-pot reaction is expected on the basis of the reported literature.[16] Initially, enaminone **A** was formed by reaction of amines **2** with dialkyl acetylenedicarboxylate **3**. Then *β*-nitrostyrene **1** undergo the nucleophilic addition with enaminone to form intermediate **B**. The subsequent cyclization of intermediate **B** to form **C** adduct. Finally, the title compounds **4** were formed by removal of nitro group by oxidative aromatization.

and-withdrawing amines. When we used *-o*, *-m*, and *-p* substituted amines for the reaction, an excellent yield of **4** was obtained in each case (Table 2, entries **4a**, **4b**, **4c**, **4d**, **4h**, **4i**, **4k**, **4o**, and **4w**). Furthermore, these methods extended to heterocyclic amines, but unfortunately, the reaction was not worked (Table 2, entry **4u**).

Table 3. Recycling and reuse of imidazolium Brønsted acidic ionic liquid.

Entry	Reaction cycle	Yielda (%)
1	First (fresh run)	98
2	Second cycle	96
3	Third cycle	95
4	Fourth cycle	95

[a]Isolated yield.

The reusability of the imidazolium Brønsted acidic ionic liquid is also important from the perspective of commercial applications. Therefore, the recovery and reusability of the catalyst were explored for the synthesis of **4a** by using model reaction (Table 3). After completion of the reaction as monitored using TLC, the crude product was extracted with ether. The recycled catalyst was washed with ether and dried under vacuum. The recovered catalyst could be recycled efficiently without any remarkable loss in catalytic activity. Recycling and reuse of the catalyst show had high activity and gave the desired product in excellent yield (Table 3).

The synthesized title compounds were further characterized by their spectral properties (^{1}H, 13C NMR, and HRMS).

Experimental

Material and methods

Chemicals were purchased from Aldrich and Alfa Aesar chemical companies and used as it is. The NMR spectra were recorded in $CDCl_3$ on a Jeol JNMECP 400 NMR instrument using TMS as an internal standard. The HRMS was recorded on a Jeol JMS-700 mass spectrometer.

General procedure for the synthesis of fully substituted pyrrole functionalities

To a mixture of amines (1 mmol), dialkyl acetylenedicarboxylates (1 mmol) and β-nitrostyrene (1 mmol) were added 10 mol % BAIL, and the reaction mixture was kept room temperature with constant stirring for stipulated time (see Table 2). After completion of the reaction as monitored using TLC, the crude product was extracted with ether. The combined organic layers were washed with brine solution and dried over Na_2SO_4. The Na_2SO_4 was filtered off and the solvent was removed under vacuum. The crude product obtained was then purified using silica gel column chromatography (100–200 mesh) using ethyl acetate: hexane as eluent to get corresponding products. The spectral and analytical data of the model representative compound is given here:

4a. Diethyl 1-(4-methoxyphenyl)-4-phenyl-1H-pyrrole-2, 3-dicarboxylate

Yellow sticky liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46–7.43 (m, 2H), 7.35 (t, *J* = 12Hz, 2H), 7.29–7.24 (m, 3H), 6.96–6.92 (m, 3H), 4.34–4.28 (m, 2H), 4.19–4.14 (m, 2H), 3.83 (s, 3H), 1.28 (t, *J* = 12Hz, 3H), 1.17 (t, *J* = 12Hz, 3H); 13C NMR ($CDCl_3$, 100 MHz) δ (ppm) 166.31, 159.92, 159.49, 133.33, 132.49, 128.47, 127.74, 127.42, 127.00,

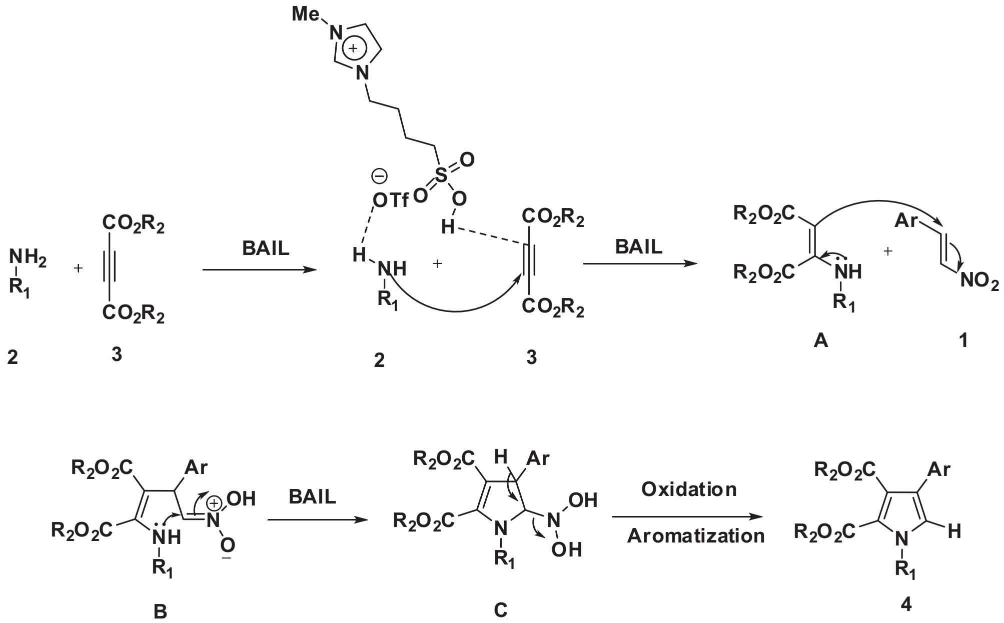


Figure 1. Plausible mechanism for the formation of substituted pyrrole derivatives **4**.

126.04, 124.46, 123.41, 121.77, 61.26, 60.74, 55.50, 14.05, 13.95; HRMS m/z calcd for $C_{23}H_{23}NO_5$ [M+] 393.4324, found 393.4321.

Conclusion

In summary, we have disclosed greener method of a three component one pot coupling reaction of amines, dialkyl acetylenedicarboxylate, and β-nitrostyrene for the synthesis of tetrasubstituted pyrroles derivatives using imidazolium Brønsted acidic ionic liquid as a catalyst as well as solvent. The present protocol demonstrated a clean reaction, a transition metal-free and solvent-free process, easily accessible reactants, and environmentally friendly reaction conditions. Further application of this green method for the synthesis of various biologically important and optoelectronic relevant heterocyclic compounds are ongoing in our laboratory.

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References

[1] Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2084. DOI: 10.1021/cr980032t.
[2] Chen, L.; Huang, B.; Nie, Q.; Cai, M. *Appl. Organometal. Chem.* **2016**, *30*, 446–450. DOI: 10.1002/aoc.3453.

[3] Plechkova, N. V.; Seddon, K. R. *Chem. Soc. Rev.* **2008**, *37*, 123–150. DOI: 10.1039/b006677j.

[4] Sheldon, R. *Chem. Commun.* **2001**, *23*, 2399–2407. DOI: 10.1039/b107270f.

[5] Deb, M. L.; Borpatra, P. J.; Baruah, P. K. *Green Chem.* **2019**, *21*, 69–74. DOI: 10.1039/C8GC03507E.

[6] Myles, L.; Gore, R.; Spulak, M.; Gathergood, N.; Connon, S. *Green Chem.* **2010**, *12*, 1157–1162. DOI: 10.1039/c003301d.

[7] Sajjadifar, S.; Mohammadi-Aghdam, S. *Asain J. Green Chem.* **2017**, *1*, 1–15. DOI: 10.22631/ajgc.2017.46496.

[8] Rezayati, S.; Nezhad, E. R.; Hajinasiri, R. *Chinese Chem. Lett.* **2016**, *27*, 974–978. DOI: 10.1016/j.cclet.2016.02.015.

[9] Youseftabar-Miri, L.; Hosseinjani-Pirdehi, H. *Asian J. Green Chem.* **2017**, *1*, 56–68.

[10] Rezayati, S.; Salehi, E.; Hajinasiri, R.; Sharif, S. A. *Comptes Rendus Chimie* **2017**, *20*, 554–558. DOI: 10.1016/j.crci.2016.07.004.

[11] Das, P. J.; Das, D. *Asain J. Green Chem.* **2018**, *2*, 11–24. DOI: 10.22631/ajgc.2017.95985.1019.

[12] Rezayati, S.; Sheikholeslami-Farahani, F.; Hossaini, Z.; Hajinasiri, R.; Abad, S. A. S. *Comb. Chem. High Throughput Screening* **2016**, *19*, 720–727. DOI: 10.2174/1386207319666160709191851.

[13] Poyafar, F.; Fallah-Mehrjardi, M.; Banitaba, S. H. *Asian J. Green Chem.* **2018**, *2*, 96–106.

[14] Rezayati, S.; Hajinasiri, R.; Abbaspour, S. *Asian Journal of Green Chemistry* **2018**, *2*, 268–280.

[15] Isambert, N.; Duque, M. D. M. S.; Plaquevent, J. C.; Nisson, Y. G.; Rodriguez, J.; Constantieux, T. *Chem. Soc. Rev.* **2011**, *40*, 1347–1357. DOI: 10.1039/c0cs00013b.

[16] Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. DOI: 10.1021/cr950027e.

[17] Daidone, G.; Maggio, B.; Schillaci, D. *Pharmazie* **1990**, *45*, 441–442.

[18] Demir, A. S.; Akhmedov, I. M.; Sesenoglu, O. *Tetrahedron* **2002**, *58*, 9793–9799. DOI: 10.1016/S0040-4020(02)01298-X.

[19] Kaiser, B.; Glenn, D. G. E. M. *J. Pharm. Sci.* **1972**, *61*, 1908–1912. DOI: 10.1002/jps.2600611205.

[20] Meshram, H. M.; Prasad, B. R. V.; Kumar, D. A. *Tetrahedron Lett.* **2010**, *51*, 3477–3480. DOI: 10.1016/j.tetlet.2010.03.036.

[21] Davis, F. A.; Bowen, K.; Xu, H.; Velvadapu, V.; Ballard, C. *Tetrahedron* **2008**, *64*, 4174–4182. DOI: 10.1016/j.tet.2008.02.102.

[22] Yamanoi, Y.; Takahashi, K.; Hamada, T.; Ohshima, N.; Kurashina, M.; Hattori, Y.; Kusamoto, T.; Sakamoto, R.; Miyachi, M.; Nishihara, H. *J. Mater. Chem. C* **2015**, *3*, 4316–4320. DOI: 10.1039/C4TC02941K.

[23] Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633–4657. DOI: 10.1039/c3cs60015g.

[24] Ghabraie, E.; Balalaie, S.; Bararjanian, M.; Bijanzadeh, H. R.; Rominger, F. *Tetrahedron* **2011**, *67*, 5415–5420. DOI: 10.1016/j.tet.2011.05.076.

[25] Atar, A. B.; Jeong, Y. S.; Jeong, Y. T. *Tetrahedron* **2014**, *70*, 5207–5213. DOI: 10.1016/j.tet.2014.05.094.

[26] Atar, A. B.; Jeong, Y. T. *Tetrahedron Lett.* **2013**, *54*, 1302–1306. DOI: 10.1016/j.tetlet.2012.12.105.

[27] Atar, A. B.; Jeong, Y. T. *Tetrahedron Lett.* **2013**, *54*, 5624–5628. DOI: 10.1016/j.tetlet.2013.08.016.

[28] Atar, A. B.; Lee, S. D.; Cho, B. G.; Cho, D. W.; Jeong, Y. T. *Res. Chem. Intermed.* **2016**, *42*, 1707–1728. DOI: 10.1007/s11164-015-2113-3.