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Tandem Synthesis of 2,3,4,5-Tetrasubstituted Pyrroles from Aromatic Aldehydes Using Diethylene Glycol-bis(3-methylimidazolium) Dihydroxide as an Efficient Catalyst

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A sequential process strategy was introduced for the synthesis of 2,3,4,5-tetrasubstituted pyrroles by the formation of benzoin from the corresponding aromatic aldehyde and followed by condensation reaction with 1,3-dicarbonyl compounds and ammonium acetate in the presence of diethylene glycol-bis(3-methylimidazolium) dihydroxide as catalyst in refluxing ethanol. The recycled catalyst could be reused four times without appreciable loss in the catalytic activity.

Keywords: Ionic liquids, Pyrroles, Sequential process synthesis, Aromatic aldehydes, Catalyst

INTRODUCTION

In recent years, ionic liquids (ILs) were used as solvents due to their particular properties, such as the ability to dissolve many organic and inorganic substances and undetectable vapour pressure [1]. Moreover, ILs as environmental friendly reaction media or catalysts, have attracted increasing attention [2-4]. Furthermore, their hydrophobicities/hydrophilicities can be tuned by appropriate modification of the cation or anion [1,2]. Therefore, room temperature ionic liquids have found wide uses in catalytic and non-catalytic reactions [5-14]. In addition, the synthesis of task-specific ionic liquids, which have a functional group in their framework, may expand the application of ionic liquids in organic chemistry [15-19].

Pyrroles represent an important class of heterocyclic compounds [20-23]. They are commonly found as structural motifs in natural (storniamide A, lamellarin R, marinopyrrole B, atorvastatin) and synthetic products (Fig. 1) [24]. Pyrrole derivatives have attracted particular attention in drug discovery due to their various pharmacological properties. Among them, lamellarins isolated from marine invertebrates, exhibit antitumor and anti-HIV activities [25].

Storniamide family are isolated from a variety of marine organisms (mollusks, ascidians, sponges) and contain 3,4-diarylpyrrole fragments. A number of o-methylated analogues of storniamide A have shown potent activity as inhibitors of the multidrug resistance (MDR) phenomenon [26], which can be considered as the main obstacle to successful anticancer chemotherapy. The marinopyrroles [27] are another important class of marine alkaloids, exemplified by the recently isolated marinopyrroles A and B. These compounds have attracted much attention because of their high activity against methicillin-resistant bacteria, an important property bearing in mind the increasing problems associated with antibiotic resistance. In this connection, some hybrid structures containing the core of bromopyrrole marine alkaloids and *N*-aryl-carbonylhydrazone moieties have recently shown good activities against methicillin-resistant Staphylococcus aureus [28]. Finally, atorvastatin, an inhibitor of HMG-CoA

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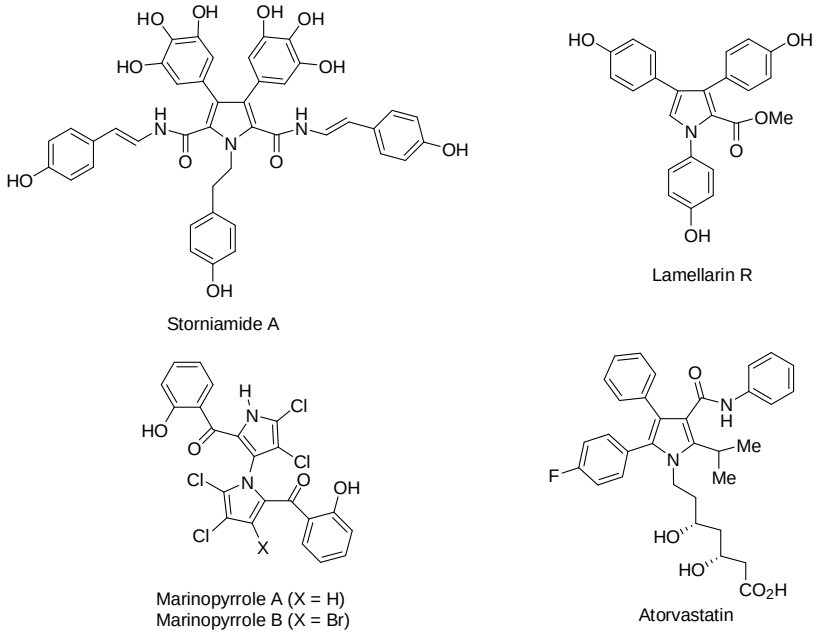


Fig. 1. Some polysubstituted pyrrole-containing bioactive natural product.

reductase, is very widely used as a cholesterol-lowering agent, being the top selling branded pharmaceutical in history.

The growing importance and wide usefulness of polysubstituted pyrroles and their application in various research fields including biological science and medicinal chemistry have led to a continuing interest in developing versatile synthetic routes [24].

A variety of classical methods have been reported for the synthesis of pyrroles, such as the Barton-Zard [29], Hantzsch [30,31], Knorr [32,33], Trofimov [34], Paal-Knorr [35,36] and Clauson-Kaas [37-39] reactions and their modifications. In addition, pyrroles have also been synthesized by the Huisgen reaction [40-42], cyclization of N-propargylic derivatives [43,44], including propargyl aziridines [45,46], through the cyclocondensation of vinyl azides with 1,3-dicarbonyls [47,48], transition metal catalyzed cyclization [49], [3+2] cycloadditions [50] and multi-component reactions [24,51-58], among various other alternatives. Nevertheless, some of these methods need multiple steps, expensive or prefunctionalized substrates, and using reagents which generate halide wastes. In respect to green chemistry, the development of methods with starting from inexpensive and easy available substrates remains a demanding goal.

Tandem reactions are referred to under the nebulous phrase “multistep one-pot reactions”. Usually, using reactions in tandem is aimed at shortening syntheses process. In comparison to individual reactions, tandem reactions have several advantages such as; they allow construction of complex structures in as few steps as possible. Also, eliminate the need for a purification step (or steps). Moreover, they are easier to work with sensitive or unstable intermediates as the intermediates are not isolated in tandem reactions. They have other advantages such as; saving on cost and amounts of reagents, solvents, and reducing the amount of waste that is generated during process [59-63].

EXPERIMENTAL

General

Chemicals were purchased from Merck and Aldrich chemical companies. The products were characterized by

comparison of their spectral and physical data with those reported in the literature. For the recorded ^{1}H NMR spectra we used Bruker (400 MHZ) Avance Ultrashield in pure deuterated DMSO-d_6 and $CDCl_3$ solvents with tetra-methylsilane (TMS) as internal standards. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at 70 eV. FT-IR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer) was employed for characterization of the products. Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates. Column chromatography was carried out on columns of silica gel 60 (70-230 mesh).

Preparation of Catalyst

General procedure for the synthesis of diethylene glycol-bis(3-methylimidazolium) dibromide (3). The dicationic ionic liquid **3** was synthesized according to the literature [7,8] with slightly modification. A mixture of diethylene glycol dibromide (5.0 g, 21.56 mmol) and N-methylimidazole (3.7 g, 45.07 mmol) in acetonitrile (30 ml) was refluxed magnetically for 48 h in a two necked round bottom flask equipped with water condenser. The reaction progress was monitored by TLC. After completion of reaction, the reaction mixture was allowed to be cooled at room temperature. The solvent was evaporated under reduced pressure on rotary evaporator at 55 °C. The reaction mixture was washed with ethyl acetate (3 × 10 ml) to remove unreacted starting materials and resulting quaternized diethylene glycol-bis (3-methylimidazolium) dibromide (**3**) was obtained; yield 95% (8.1 g); thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (t, 4H, *J* = 4.0 Hz, OCH_2), 3.91 (s, 6H, NCH_3), 4.41 (t, 4H, *J* = 4.0 Hz, NCH_2), 7.82 (d, 4H, *J* = 9.6 Hz), 9.37 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.0, 48.5, 67.9, 122.4, 123.0, 136.7.

General procedure for the synthesis of diethylene glycol-bis(3-methylimidazolium) dihydroxide (4). A mixture of dicationic ionic liquid 3 (0.8 g, 2.0 mmol) and sodium hydroxide (0.5 g, 12.5 mmol) in water-ethanol [1:1] (20 ml) was stirred at room temperature. After 1 h a white precipitate was formed which filtered and washed with ethanol (3 × 10 ml). The quaternized diethylene glycol-bis(3-methylimidazolium) dihydroxide (**4**) was obtained; yield 90% (0.486 g); white solid m.p.: >250 °C; ^{1}H NMR (400 MHz, D_2O): δ 3.74-3.78 (m, 10H, NMe and OCH_2), 4.25 (t, 4H, *J* = 5.0 Hz, $^+NCH_2$), 7.31 (m, 4H, Ar), 8.32 (s, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.7, 49.0, 68.4, 123.3, 166.0, 171.1. Mass m/z (%): [M-34 (2 × OH)] 236 (22.9), 207 (14.6), 167 (22.9), 149 (58.3), 111 (14.6), 83 (33.3), 57 (base peak).

pH analysis of IL4. The pH of 4 determined by pH-ISE conductivity titration controller (Denver Instrument Model 270) was 10.23 for 0.011 g of this solid base at 25 °C.

General procedure for the synthesis of benzoins. To a mixture of aromatic aldehyde (2 mmol) and sodium hydroxide (30 mol%) in absolute ethanol (3 ml), the IL **4** (3 mol%) was added and refluxed. After 30 min the corresponding benzoins were formed. The resulting mixture was refluxed for the given times (Table 2). After completion of the reaction ethanol was evaporated and remaining was washed with water (2 × 3 ml) in order to separate IL **4**. For further purification, the corresponding benzoins were purified by flash chromatography on silica gel using hexane-ethyl acetate = 5:1 as eluent. The benzoins were compared with authentic samples [9-12].

General procedure for the synthesis of 2,3,4,5-tetra-substituted pyrroles. To a mixture of aromatic aldehyde (2 mmol) and sodium hydroxide (30 mol%) in absolute ethanol (3 ml), the IL **4** (3 mol%) was added and refluxed. After 30 min the corresponding benzoins were formed. Then, 1,3-dicarbonyl compound (1 mmol) and NH_4OAc (1.5 mmol) was added. The resulting mixture was refluxed for the given times (Table 3). After completion of the reaction the mixture was cooled to the room temperature and precipitated was filtered. The precipitates were washed with water (2 × 3 ml) in order to separate IL **4**. For further purification the precipitates were recrystallized from ethanol to give corresponding product. Some of the products (**5d**, **5g** and **5h**) were purified by silica gel column chromatography employing n-hexane/ethyl acetate as the eluent.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-yl)-ethanone (5a). White solid, recrystallized from ethanol, m.p.: 168-170

°C (Lit. [52] 170-172 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.92 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.10-7.34 (m, 10H, Ar), 8.51 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.2, 31.8, 123.5, 123.5, 127.1, 127.8, 128.0, 128.2, 129.1, 129.3, 131.9, 133.5, 137.0, 138.1, 197.6.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-carboxylic acid methyl ester (5b). White solid, recrystallized from ethanol, m.p.: 183-184 °C (Lit. [51] 178-180). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.62 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 7.11-7.26 (m, 10H, Ar), 8.29 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 15.1, 51.7, 113.3, 124.5, 127.5, 127.7, 128.1, 128.8, 129.6, 131.9, 132.2, 133.3, 136.9, 137.1, 167.1.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-carboxylic acid ethyl ester (5c). White solid, recrystallized from ethanol, m.p.: 203-204 °C (Lit. [51] 206-208). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.93 (t, 3H, J = 7.1 Hz, CH_3), 2.51 (s, 3H, CH_3), 3.97 (q, 2H, J = 7.1 Hz, OCH_2), 7.00-7.21 (m, 10H, Ar), 8.26 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 12.8, 12.9, 58.2, 111.6, 122.4, 125.3, 125.5, 125.7, 126.2, 126.6, 127.5, 129.7, 131.1, 134.4, 135.0, 164.6.

2-Methyl-4,5-diphenyl-1H-pyrrole-3-yl)-phenyl-methanone (5d). Yellow solid, purified by column chromatography on silica gel, m.p.: 218-219 °C (Lit. [51] 223-225). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3H, CH_3), 6.95-7.37 (m, 15H, Ar), 11.65 (s, H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 12.7, 121.0, 122.0, 125.7, 126.3, 126.8, 127.1, 127.6, 127.8, 128.9, 129.6, 130.2, 131.3, 132.2, 134.0, 135.6, 139.7, 192.8.

2-Methyl-4,5-di-p-tolyl-1H-pyrrole-3-yl)-ethanone (5e). White solid, recrystallized from ethanol, m.p.: 237-238 °C (Lit. [51] 237-238). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.74 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 6.99-7.05 (m, 4H, Ar), 7.09 (d, 2H, J = 7.6 Hz, Ar), 7.17 (d, 2H, J = 8.0 Hz, Ar), 11.52 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.8, 20.6, 20.8, 30.5, 121.5, 122.0, 126.4, 126.5, 128.7, 128.9, 129.4, 130.6, 134.0, 134.8, 135.3, 135.7, 194.5.

2-Methyl-4,5-di-*p*-tolyl-1*H*-pyrrole-3-carboxylic acid methyl ester (5f). White solid, recrystallized from ethanol, m.p.: 175-176 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.21 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.47 (s, 3H, OCH_3), 6.97-7.07 (m, 8H, Ar), 11.47 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.3, 20.6, 20.8, 50.0, 111.0, 121.9, 126.7, 127.1, 128.1, 128.7, 129.4, 130.4, 133.3, 134.8, 135.3, 135.3, 165.1. MS: m/z (%): 320 (M^++1, 22.6), 319 (M^+, 45.9), 244 (17.4), 149 (52.2), 83 (base peak). Anal. Calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39; found: C, 78.74; H, 6.67; N, 4.21.

2-Methyl-4,5-di-*p*-tolyl-1*H*-pyrrole-3-yl)-phenyl-methanone (5g). Yellow solid, purified by column chromatography on silica gel, m.p.: 220-221 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.16 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.82-7.52 (m, 13H, Ar), 11.53 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.7, 20.6, 120.9, 121.5, 126.8, 127.0, 127.8, 128.2, 128.8, 129.4, 130.0, 131.3, 132.6, 133.4, 134.4, 135.5, 139.8, 192.8. MS: m/z (%): 366 (M^++1, 10.8), 365 (M^+, 34.8), 279 (17.4), 167 (30.4), 149 (base peak), 57 (80.7). Anal. Calcd. for $C_{26}H_{23}NO$: C, 85.45; H, 6.34; N, 3.83; found: C, 85.18; H, 6.38; N, 3.61.

1-[4,5-Bis-(4-fluoro-phenyl)-2-methyl-1*H*-pyrrole-3-carboxylic acid methyl ester (5h). Yellow solid, purified by column chromatography on silica gel, m.p.: 211-213 °C (Lit. [58] 215-218). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.49 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 7.08-7.15 (m, 8H, Ar), 11.64 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 13.3, 50.06, 114.25, 115.03, 115.25, 115.45, 115.54, 127.24, 127.33, 128.79, 128.87, 132.17 ($^1J_{C\text{-}F}$ = 120.0 Hz), 132.39, 135.79, 164.89. MS: m/z (%): 329 (M^++2, 3.6), 328 (M^++1, 35.5), 327 (M^+, base peak), 312 (55.5), 296 (49.1), 266 (69.1), 253 (16.3), 95 (5.5).

1-[4,5-Bis-(4-chloro-phenyl)-2-methyl-1H-pyrrole-3-yl]-ethanone (5i). White solid, recrystallized from ethanol, m.p.: 230-232 °C (Lit. [52] 234-235 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.90 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 6.99-7.01 (m, 2H, Ar), 7.17-7.19 (m, 4H, Ar), 7.31-7.33 (m, 2H, Ar), 8.55 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.8, 31.4, 122.2, 128.4, 129.2, 129.3, 130.6, 132.5, 133.1, 133.7, 135.1, 196.0.

1-[4,5-Bis-(4-chloro-phenyl)-2-methyl-1H-pyrrole-3-carboxylic acid ethyl ester (5j). White solid, recrystallized from ethanol, m.p.: 155-157 °C (Lit. [52] 155-156 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.08 (t, 3H, J = 5.6

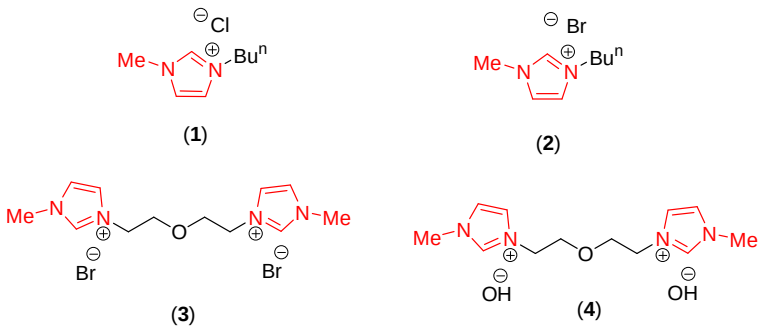
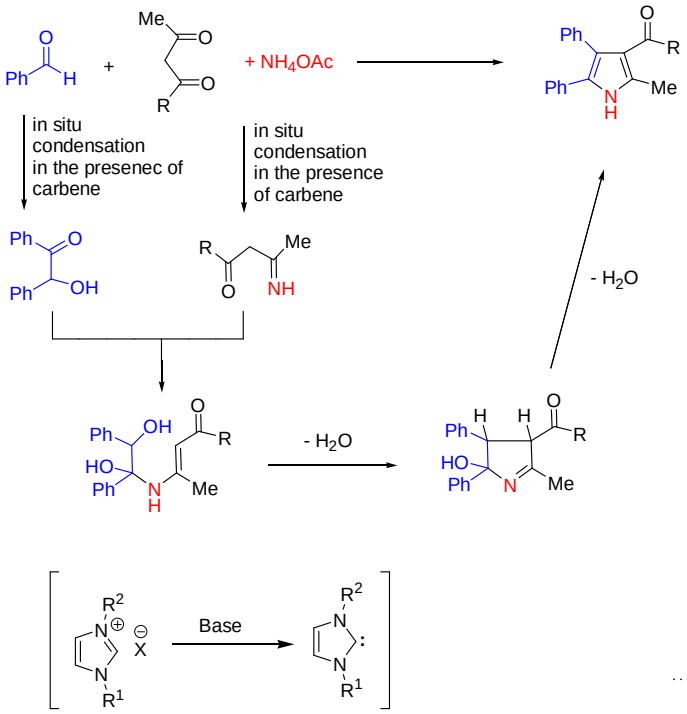


Fig. 2. The structure of ionic liquids **1-4**.



Scheme 1. A tandem condensation reaction and cyclization to access pyrroles

Hz, CH_3), 2.58 (s, 3H, CH_3), 4.09 (q, 2H, J = 5.6 Hz, OCH_2), 6.99-7.01 (m, 2H, Ar), 7.14-7.19 (m, 4H, Ar), 7.24-7.26 (m, 2H, Ar), 8.41 (s, 1H, NH).

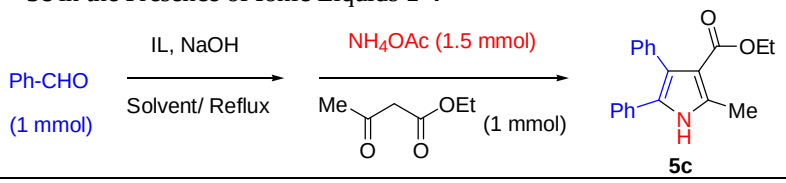
RESULTS AND DISCUSSION

Recently, Tamaddon reported a one pot synthesis for *tetra*-substituted pyrroles *via* preparing the benzoins from the reaction of aromatic aldehydes and toxic NaCN followed by condensation with 1,3-dicarbonyl compounds and ammonium acetate [58].

Herein, we investigated the effect of some ionic liquids **1-4** for the synthesis of benzoins and 2,3,4,5-*tetra*-substituted pyrroles (Fig. 2). Previously, significant improvements on the synthesis of benzoins were reported by using ionic liquids as catalysts [9-12].

Based on previous works in this area, we decided to combine both benzion and finally pyrrole synthesis in a sequential process strategy. At first aromatic aldehyde was converted into corresponding benzoin in the presence of ILs

Table 1. Investigation the Effect of Solvents and Conditions on the Synthesis of Pyrrole **5c** in the Presence of Ionic Liquids **1-4**



5c

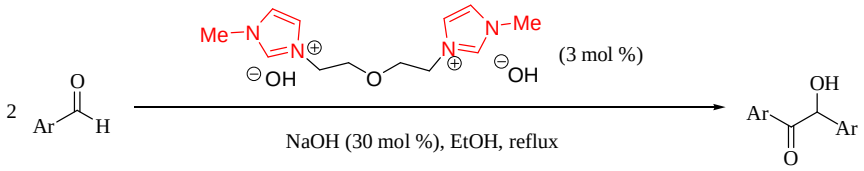
Entry	IL (mol%)	Solvent	NaOH (mol%)	Time (min)[a]	Time (min)[b]	Yield (%)[c]
1	**1** (3)	THF	40	30	30	90
2	**1** (5)	THF	40	30	30	91
3	**1** (3)	THF	20	30	35	88
4	**1** (3)	EtOH	40	40	35	87
5	**1** (5)	H_2O	40	100	-	-
6	**2** (3)	THF	40	30	35	89
7	**2** (3)	EtOH	40	40	40	85
8	**2** (5)	H_2O	40	100	-	-
9	**3** (3)	EtOH	40	30	30	88
10	**3** (3)	THF	40	40	40	86
11	**3** (5)	H_2O	40	100	-	-
12	**4** (3)	EtOH	30	30	30	89
13	**4** (3)	THF	30	40	35	87
14	**3** (5)	H_2O	40	100	-	-

[a]The time related to benzoin formation. [b]The time related to pyrrole formation. [c]Yield of isolated product of pyrrole

in basic media. Then, condensation reaction with 1,3-dicarbonyl compounds and ammonium acetate was carried out in a sequential process for the synthesis of pyrroles. Proposed mechanism for the synthesis of 2,3,4,5-*tetra*-substituted pyrroles has been described in Scheme 1 [9-12,53,54,58]. This should be possible by the formation of benzoin in the presence of *N*-heterocyclic carbenes (IL and sodium hydroxide) [9-12]. Then, the reaction of benzoin was taken placed with enamines or imines. The sequential condensation reaction between benzoin and imine in the presence of *N*-heterocyclic carbenes should result in substituted pyrroles.

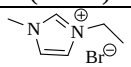
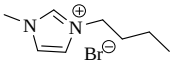
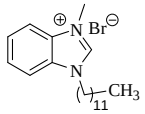
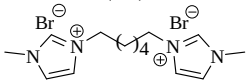
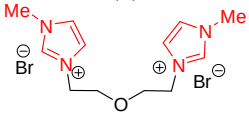
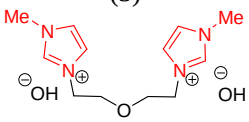
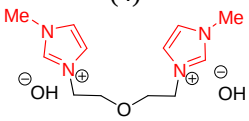
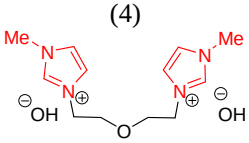
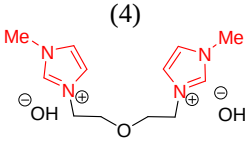
With this hypothesis in mind, we initiated a study by testing the reaction of benzaldehyde with sodium hydroxide (30-40 mol%) in the presence of ionic liquids **1-4** in different solvents and conditions, followed by sequential reaction with ethyl acetoacetate and ammonium acetate as model reaction (Table 1). It importance to mentioning, the benzoin formation step was accomplished without using toxic NaCN.

As shown in Table 1, the catalytic amounts of 3 mol% of the ILs **1-4** as catalysts in refluxing absolute ethanol give the corresponding product **5c** in the range of 85-88% yields. Also, the synthesis of pyrrole **5c** was achieved in the presence of ILs **1** and **2** and in THF in shorter reaction times and higher yields than ethanol. While the results for ILs catalysts **3** and **4** were inversed. In water as solvent the benzoin formation did not proceed. Although the catalytic effects of ionic liquids **1** and **2** were reported for the synthesis of benzoins previously [10] but, the ILs **3** and **4**



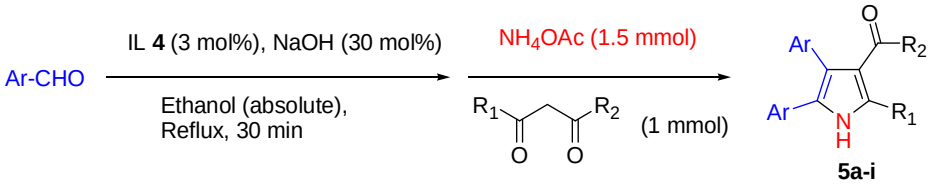
Scheme 2. Synthesis of some benzoin derivatives in the presence of IL **4**

Table 2. Comparison the Effect of IL **4** with those ILs Reported on the Formation of Benzoins

Entry	Ar	IL (mol%)	Condition	Time (min)	Yeild (%)[a]	Ref.
1	C_6H_5-	 (10)	CH_2Cl_2/ K_2CO_3/rt	720	86	[11]
2	C_6H_5-	 (1)	THF/NaOH/ reflux	31	76	[11]
3	C_6H_5-	 (20)	H_2O/TEA/rt	1200	99	[10]
4	C_6H_5-	 (1)	THF/NaOH/ reflux	1440	82	[12]
5	C_6H_5-	 (3)	EtOH/NaOH/ reflux	30	90	This work
6	C_6H_5-	 (4)	EtOH/NaOH/ reflux	30	91	This work
7	4-Me-C_6H_4-	 (4)	EtOH/NaOH/ref lux	30	90	This work
8	4-F-C_6H_4-	 (4)	EtOH/NaOH/ reflux	30	88	This work
9	4-Cl-C_6H_4-	 (4)	EtOH/NaOH/ reflux	30	89	This work

[a]Yield of isolated product of benzoin.

Table 3. Synthesis of 2,3,4,5-Tetrasubstituted Pyrroles Using IL **4** as Catalyst



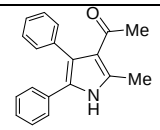
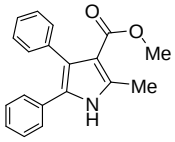
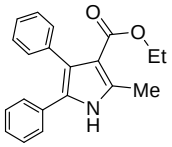
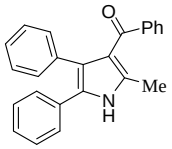
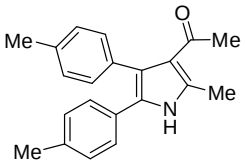
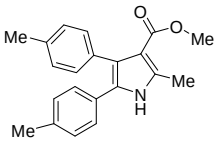
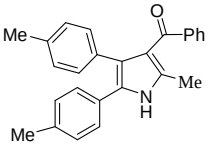
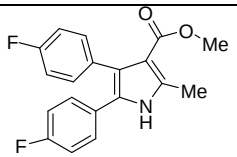
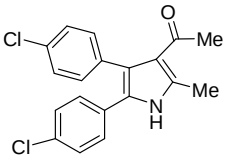
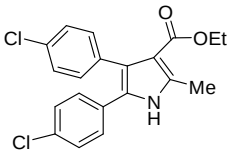
Entry	Ar	R_1	R_2	Product	Time (min)[a]	Yeild (%)[b]
1	C_6H_5-	Me	Me	 **5a**	35	90
2	C_6H_5-	Me	OMe	 **5b**	35	88
3	C_6H_5-	Me	OEt	 **5c**	30	89
4	C_6H_5-	Me	Ph	 **5d**	50	85
5	4-Me-C_6H_4-	Me	Me	 **5e**	40	91
6	4-Me-C_6H_4-	Me	OMe	 **5f**	40	90
7	4-Me-C_6H_4-	Me	Ph	 **5g**	50	87

Table 3. Continued

8	4-F-C_6H_4-	Me	OMe	 **5h**	30	89
9	4-Cl-C_6H_4-	Me	Me	 **5i**	30	90
10	4-Cl-C_6H_4-	Me	OEt	 **5j**	30	88

[a]The time related to pyrrole formation step. [b]Yield of isolated pyrrole product.

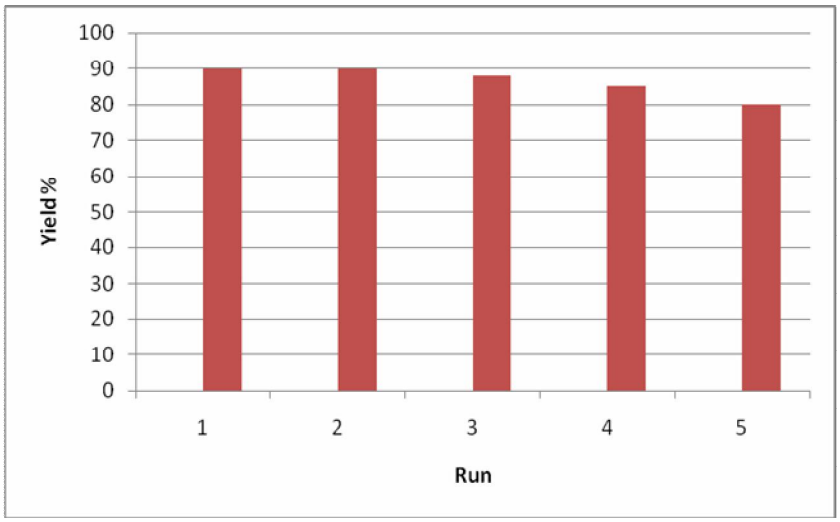


Fig. 3. Reusability of IL **4** in the reaction of benzeldehyde with sodium hydroxide in refluxing ethanol for 30 min followed by adding ethyl acetoacetate and ammonium acetate further 30 min at reflux conditions.

were used for the first time. So, we examined the catalytic activity of IL **4** *via* the reaction of benzaldehyde or some benzaldehyde derivatives with NaOH (30 mol%) in refluxing ethanol for the synthesis of corresponding benzoins (Table 2 and Scheme 2).

Also, the catalytic activity of IL **4** was compared with some other ILs which previously reported (Table 2, entries 1-4). The results show that our method is quite comparable with the former methods in the yields and reaction times.

As shown in Table 3, it was found that this method works with an aromatic aldehyde bearing electron-donating or halogen groups such as Me, F and Cl. In addition, 1,3-

dicarbonyl compounds such as acetyl acetone, benzoyl acetone, methyl acetoacetate and ethyl acetoacetate reacted under optimized conditions and corresponding products were obtained in high yields.

The possibility of recycling the catalyst **4** was examined using the reaction of benzaldehyde and sodium hydroxide in refluxing ethanol followed by the condensation with ammonium acetate and ethyl acetoacetate under optimized conditions. Upon completion, the reaction mixture was cooled to room temperature and the precipitates were filtered. The precipitates were washed with water (2 × 3 ml) to separate IL **4**. The catalyst **4** was recycled by evaporating the aqueous phase under reduced pressure and washing with ethyl acetate. The recycled catalyst could be reused four times without any treatment (Fig. 3).

CONCLUSIONS

In conclusion, we introduced a strategy for the synthesis of *tetra*-substituted pyrroles *via* a sequential process from an aromatic aldehyde. Aromatic aldehydes are available starting materials. Those bearing electron-donating such as Me and halogens such as F and Cl were converted into the corresponding products when using ILs (**1-4**) as catalyst in refluxing ethanol in good to high yields. Also, in this method, using toxic NaCN is avoided.

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