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Mono- and Dialkylations of Pyrrole at C2 and C5 Positions by Nucleophilic Substitution Reaction in Ionic Liquid

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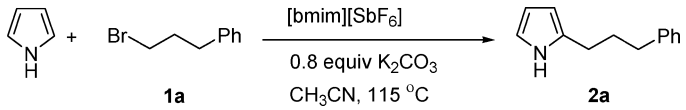
ABSTRACT



A novel ionic liquid methodology for pyrrole C-alkylation is described. The pyrrole alkylation is achieved with various simple alkyl halides and mesylates selectively at C2 and C5 positions in good yields with minimal byproducts under relatively mild conditions in various ionic liquids. 2-(3-Phenylpropyl)pyrrole (2a) was synthesized from pyrrole and 1-bromo-3-phenylpropane in a mixture solvent system, [bmim][SbF_6] and CH_3CN, in 81% yield at 115 °C for 44 h with 5% yield of dialkylated compound 3a.

Alkylation reactions, particularly of π-rich heteroaromatics,[1] are frequently used for the construction of molecular frameworks. Surprisingly, however, relatively few strategies have been established despite the widespread availability of electron-rich five-membered aromatics and the chemical utility of the accompanying products.[2] The synthesis and reactions of pyrroles[2] have attracted much research interest for over a century because of their importance as precursors in the synthesis of pharmaceutically useful compounds.[3] To date, pyrrole reactions remain a challenge for synthetic chemists because of pyrrole's sensitivity to acids and air.[4] Mono C-alkylation of π-rich heteroaromatic pyrrole by the Friedel−Crafts approach is impractical because the Brønsted or Lewis acid catalysts employed induce polyalkylation, ring opening, and polymerization.[1] Generally, *C*-alkyl pyrroles are synthesized[5] by Vilsmeier−Haack formylation followed by Wolff−Kishner reduction.[6] The other approach involves the isomerization of *N*-alkylpyrrole by thermal rearrangement at a very high temperature with no regioselectivity.[7] Alternatively, *C*-alkyl pyrroles are prepared using pyrrolylmagnesium halides.[8] These indirect approaches are not suitable, as they need harsh conditions and use of hazardous and often expensive acid catalysts. Moreover, these above-mentioned processes are usually carried out in polar solvents such as THF, DMF, and DMSO, leading to complex isolation and recovery procedures. Thus, the regioselective alkylation of pyrrole has been a stubborn problem.

Room-temperature ionic liquids[9,10] have increasingly attracted attention as the green, high-tech reaction media of

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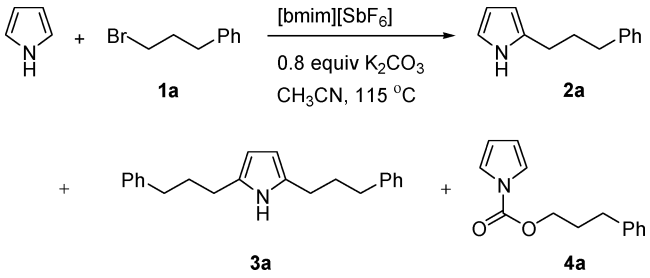
the future. It has also been reported that ionic liquids containing imidazolium cations can act as a powerful media in some catalytic organic reactions not only for the facilitation of the catalyst recovery but also for the acceleration of the reaction rate and improvement of selectivity. Recently, we reported highly efficient nucleophilic substitution reactions in ionic liquids, which are valuable platforms for the development of practical methodology.[11] Although the C-alkylations of pyrrole on C2 position from reactive halide moieties such as allyl, benzyl, and acetate have been reported,[12] to the best of our knowledge, there is no report on regioselective one-pot pyrrole alkylation from simple alkyl halides or alkyl mesylates either in ionic liquids or others. Herein, we report that by employing an ionic liquid as a solvent, significant rate enhancement of the C-alkylation of pyrrole at the C2 position can be accomplished from alkyl halides or alkyl mesylates. In this novel methodology, preferential introduction of an alkyl substituent at the C2 position of pyrrole can be achieved with minimal formation of other products, including dialkylated product.

Table 1 illustrates the pyrrole alkylation with 1-bromo-3-phenylpropane **1** in the presence of K_2CO_3 and [bmim]-[SbF_6] under various reaction conditions.[13] Whereas the pyrrole alkylation with halide **1a** in the presence of K_2CO_3 in an organic solvent such as CH_3CN at 115 °C (in a pressure vial) hardly occurred even after 7 days (entry 9), the same reaction in [bmim][SbF_6] as a reaction media was complete within 44 h, affording the desired product **2a** (71% yield) together with the dialkylated product **3a** (10% yield) (entry 1). The reaction without the addition of K_2CO_3 went to completion within 48 h in similar yield (entry 2).

Moreover, entries 3−5 show that the use of acetonitrile as a cosolvent did not affect the reactivity of the alkylation. However, only 10−30% acetonitrile was desirable for solublizing the salt formed during the reaction. In addition, as shown in entries 6−8, the use of lesser amounts of [bmim]-[SbF_6] had influenced the reactivity of pyrrole alkylation. The use of 0.1 equiv of [bmim][SbF_6] in entry 8 showed sluggish behavior, affording a small amount of the desired product **2a** (22% yield), together with **3a** (4% yield) and **4a** (5% yield). A comparison of entries 6 and 8 demonstrates that when 1.0 equiv of the ionic liquid [bmim][SbF_6] was used, pyrrole alkylation proceeded much faster than using only 0.1 equiv of the ionic liquid.

Table 1. Reductive Alkylation of Pyrrole with 1-Bromo-3-phenylpropane (**1a**) in the Presence of K_2CO_3 under Various Reaction Conditions[a]



entry	[bmim] [SbF_6] mL (equiv)	CH_3CN (mL)	time (h)	yield of product (%)[b] 1a	2a	3a	4a
1	3 (13.92)		44		71	10	
2[c]	3		48		74	8	
3	2.7 (12.53)	0.3	44		77	7	
4	2.4 (11.14)	0.6	44		81	5	
5	2 (9.28)	1	48		77	6	
6	1 (4.64)	2	72	29	43	10	trace
7	0.5 (2.32)	2.5	72	36	34	11	trace
8	0.1 (0.46)	2.9	7 days	55	22	4	5
9[d]		3	7 days	85	5	4	trace

[a] All reactions were carried out on a 1.0 mmol reaction scale of bromide **1a** with 10.0 equiv of pyrrole and 0.8 mmol K_2CO_3 at 115 °C. [b] Isolated yield. [c] Reaction was carried out in the absence of K_2CO_3, and 4% yield of the hydroxylated compound, 1-hydroxy-3-phenylpropane, was detected by ^{1}H NMR. [d] Trace of 1-(3-phenylpropyl)-1*H*-pyrrole was detected by ^{1}H NMR.

To determine whether other ionic liquids enhanced the reactivity and selectivity significantly in acetonitrile and other cosolvents, we next carried out the pyrrole alkylation of **1a** under the same conditions as for entry 4 in Table 1, except for the use of the four other ionic liquids instead of [bmim]-[SbF_6] and two other cosolvents instead of acetonitrile. In entries 1 and 2 (Table 2), using [bmim][PF_6] and [bmim]-[NTf_2], we obtained astonishing results with the formation of carbamate **4a** (21 and 24% yields, respectively), a trace of 1-(3-phenylpropyl)-1*H*-pyrrole (**3a**), and slightly lower yields of **2a** (68 and 65%, respectively). Similarly, in entry 4, using [bmim][BF_4], we obtained an unexpected major amount of 1-(3-phenylpropyl)-1*H*-pyrrole (62% yield) and a lower yield of the desired product **2a** (25%), together with **3a** (2% yield) and dialkylated product **4a** (2% yield). However, the pyrrole alkylation using [bmim][OTf] showed very slow reactivity, affording the desired product **2a** (51% yield) after 72 h. Toluene and 1,4-dioxane were found to be unsatisfactory cosolvents, as undesirable elimination of **1a** to alkene occurred (entries 5 and 6).

To explore a new approach to the synthesis of C-alkylated pyrrole, we have investigated the alkylation of pyrrole with

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(13) 1-*n*-Butyl-3-methylimidazolium hexafluoroantimonate is abbreviated as [bmim][SbF_6]. **Typical Procedure.** 1-Bromo-3-phenylpropane (**1a**, 199 mg, 1.0 mmol) was added to a mixture of K_2CO_3 (111 mg, 0.8 mmol), pyrrole (0.7 mL, 10.0 mmol), and [bmim][SbF_6] (2.4 mL) in acetonitrile (0.6 mL). The mixture was stirred over 44 h at 115 °C. The reaction mixture was extracted from ionic liquid phase with ethyl ether (10.0 mL × 5). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel) (5% EtOAc/hexanes) to obtain of 2-(3-phenylpropyl)-1*H*-pyrrole (**2a**, 149 mg, 81%) and 2,5-bis-(3-phenylpropyl)-1*H*-pyrrole (**3a**, 15 mg, 5%) as a colorless oil.

Table 2. Alkylation of Pyrrole with Alkyl Bromide **1a** in the Presence of K_2CO_3 in Various Ionic Liquids and Cosolvents[a]

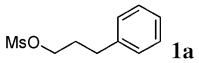
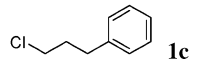
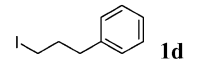
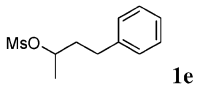
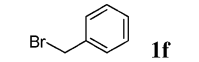
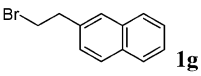
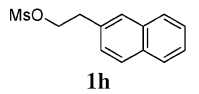
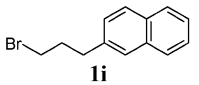
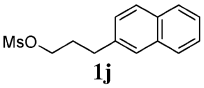
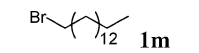
entry	[bmim] [X]	cosolvent	time (h)	yield of product (%)[b] **1a**	**2a**	**3a**	**4a**
1[c]	PF_6	CH_3CN	46		68	2	21
2[c]	NTf_2	CH_3CN	48		65	3	24
3	OTf	CH_3CN	72	35	51	2	4
4[d]	BF_4	CH_3CN	45		25	2	2
5[e]	SbF_6	toluene	46		57	10	2
6[e]	SbF_6	1,4−dioxane	46		60	8	2

[a] All reactions were carried out on a 1.0 mmol reaction scale of alkyl bromide **1a**, with 10.0 equiv of pyrrole and with 0.8 mmol K_2CO_3 in 2.4 mL of ionic liquid and 0.6 mL of cosolvent at 115 °C. [b] Isolated yield. [c] Trace of the 1-(3-phenylpropyl)-1*H*-pyrrole was detected by ^{1}H NMR. [d] 1-(3-Phenylpropyl)-1*H*-pyrrole (62% yield) and the eliminated compound, allylbenzene (2% yield), were detected by ^{1}H NMR. [e] Allylbenzene (12% yield for entry 5, 10% yield for entry 6) and hydrolyzed compound, 3-hydroxypropylbenzene (2% yield), were detected by ^{1}H NMR.

primary, secondary, and benzylic halides or mesylates. The results displayed in Table 3, clearly show that the method is highly efficient. The yields of the pyrrole-α-alkylated products range from 55 to 82%. The success of this reaction is most likely due to the relatively mild conditions used. The pyrrole alkylation with the primary mesylates and chloro and iodo alkanes under these conditions provided **2a** in good yields (74, 55, and 64%, entries 1−3, respectively). Chlorides afforded slow reactivity in comparison to iodo and mesylates. The secondary mesylate gave product **2e** (71% yield) and 8% yield of 3-(1-methyl-3-phenylpropyl)-1*H*-pyrrole without formation of any N-alkylated and eliminated compounds (entry 4). However, being an active halide, the alkylation of benzyl bromide took place at 80 °C to afford **2f** (71% yield) and **3f** (9% yield) (entry 5).[14] Interesting results were observed in the case of entries 7 and 9 where, along with **2h** (72% yield) and **2j** (70% yield), 18 and 20% yields of fluorinated compounds[11a] were obtained, respectively. The alkylation of pyrrole with long-chain alkyl halide was found to react slowly to yield **2m** (73%) because of its poor solubility in ionic liquid. The displacements of aromatic ethyl bromides or mesylates generally gave eliminated products as major products. It was reported that ionic liquids reduced the elimination. In these cases, only 2 (entry 6) and 5% yields (entry 8) of alkenes were formed.

Furthermore, after finding the significance of ionic liquids in pyrrole alkylation, we next attempted to selectively synthesize either homo- or hetero-2,5-dialkylated pyrrole. First, we followed route A (one-pot synthesis) in Scheme 1 with a 1:2 ratio of pyrrole and alkyl bromide **1a**. However, the reaction did not go to completion even after 48 h at 115 °C, giving a poor yield of 2,5-dialkylated pyrrole **3a** (20−25%), so the reaction conditions[15] were modified. We obtained 54% yield of 2,5-dialkylated pyrrole **3a**. The alternative strategy was route B (step-by-step synthesis) in

Table 3. Alkylation of Pyrrole with Various Alkyl Halides and Mesylates in [bmim][SbF_6][a]

entry	compound	time (h)	yield (%)[b] **2**	**3**	comment
1	 **1a**	44	74	8	2% *N*-alkylated
2	 **1c**	48	55	5	trace *N*-alkylated
3	 **1d**	36	64	12	
4	 **1e**	72	71		8% 3-(1-methyl-3-phenylpropyl)-1*H*-pyrrole
5[c]	 **1f**	3	71	9	
6	 **1g**	58	82	-	2% alkene and trace fluorinated
7	 **1h**	56	72	-	18% fluorinated and trace alkene
8	 **1i**	62	82	-	5% alkene and trace fluorinated
9	 **1j**	60	70	-	20% fluorinated and trace alkene
10[d]	 **1m**	72	73		

[a] All reactions were carried out on a 1.0 mmol reaction scale of alkyl bromides or mesylates **1**, with 10.0 equiv of pyrrole and with 0.8 mmol K_2CO_3 in 2.4 mL of ionic liquid and 0.6 mL of cosolvent at 115 °C. [b] Isolated yield. [c] Reaction was carried out at 80 °C. [d] Starting material (20%) was isolated.

Scheme 1. The isolated[13] monoalkylated pyrrole **2a** was allowed to react with 2.0 equiv of alkyl bromide **1a** at 115 °C for 48 h. Unfortunately, we obtained similar results, with 30−35% yield of 2,5-dialkylated pyrrole **3a** and recovery of unreacted monoalkylated pyrrole **2a**; hence, we modified the route B reaction conditions.[16] We obtained 73% yield of 2,5-dialkylated pyrrole **3a**, and unreacted monoalkylated compound **2a** was recovered. Our observation was that the reaction from mono to dialkylated pyrrole is sluggish.

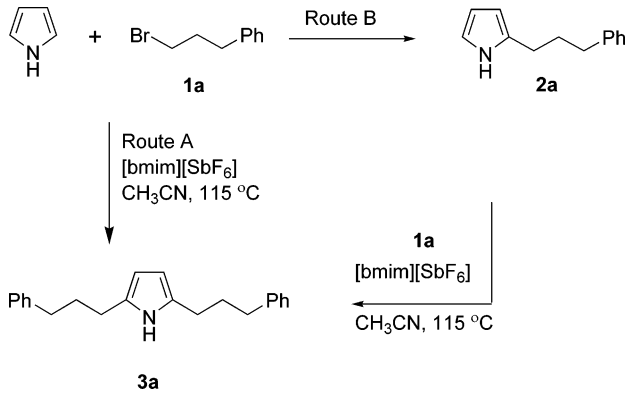
In summary, ionic liquids act as an important driving force in the regioselective alkylation of pyrrole. The experimental procedure is very simple and convenient, and in addition,

(14) Reaction mixture turned dark after 1 h at 80 °C due to the high reactivity of benzyl bromide.

(15) Reaction was carried out on a 2.0 mmol reaction scale of pyrrole with 5.0 equiv of bromide (**1a**) and without K_2CO_3 at 115 °C for 48 h.

(16) Reaction was carried out on a 1.0 mmol reaction scale of 2-(3-phenylpropyl)-1*H*-pyrrole (**2a**) with 5.0 equiv of bromide **1a** and without K_2CO_3 at 115 °C for 48 h.

Scheme 1. Dialkylation of Pyrrole with 1-Bromo-3-phenylpropane (**1a**) in Ionic Liquids



our methodology did not require any aqueous workup, thereby avoiding the generation of toxic waste. It is noteworthy that our procedure does not require any Lewis acid/base catalyst. Further studies on the development of a more efficient green protocol (lower reaction temperature, shorter reaction time, etc.) for pyrrole alkylation using ionic liquids as well as polymer-supported ionic resin[17] are in progress in our laboratories.

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Supporting Information Available: Experimental procedures, including characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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