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Potassium carbonate as a base for the N-alkylation of indole and pyrrole in ionic liquids

Yogesh R. Jorapur,[a] Jae Min Jeong[b] and Dae Yoon Chi[a,*]

[a]*Department of Chemistry, Inha University, 253 Yonghyundong Namgu, Inchon 402-751, Republic of Korea*
[b]*Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul 110-744, Republic of Korea*

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Abstract—The methodology for the N-alkylation of indole and pyrrole using potassium carbonate in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] as the sustainable reaction media with acetonitrile as the cosolvent is described herein. Our approach provides good yields with alkyl halides as well as sulfonates as the electrophiles. Cesium carbonate was also found to be a consistent base in the N-alkylation. The proposed methodology is simple and mild with easy workup.

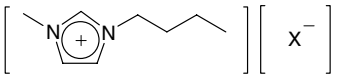
The need for indole and pyrrole research is well recognized because of their significance in the pharmaceutical area.[1] Naturally occurring substances with N-substituted indole and pyrrole assemblies are ubiquitous,[2] as inhibitors of enzymes[3] or as anti-inflammatory, analgesic, anti-rheumatic, and anti-hypertensive drugs.[4]

N-Alkylated indole and pyrrole produced by regioselective synthesis belong to an extremely attractive domain in heterocyclic chemistry as a result of their unusual bioactivities. One possible way of accomplishing the N-alkylation is by using a stoichiometric amount of a strong base. The established methods of accomplishing this include the use of alkali metals,[5] alkali metal alkoxides,[6] or potassium hydroxide in DMSO,[7] potassium super oxide in crown ethers,[8] sodium hydroxide in DMF,[9] NaH or KH in DMF,[10] HMPA,[11] Cs_2CO_3 in DMPU[12] and phase-transfer catalytic conditions.[13]

Though some of the above-mentioned methods provided good yields of N-alkylated indole and pyrrole, they also involve the use of hazardous and carcinogenic dipolar aprotic organic solvents. Moreover, during the workup, these solvents are converted into waste byproducts, making their recycling impossible. Further, some of the above-mentioned bases possess a pungent or obnoxious odor. Thus, the development of an efficient, safe, and environmentally friendly method of accomplishing the N-alkylation of indole and pyrrole constitutes an important challenge.

In recent years, ionic liquids (ILs, Fig. 1), which are usually composed of a bulky organic cation and a smaller inorganic anion, have emerged as a new, more sustainable solvent system.[14] A wide range of reactions have been reported using ILs as the reaction media,[15] including alkylation reactions, for which the use of ILs have allowed for significant advances.[16] Also, recently we reported the selective C-alkylation of pyrrole at the C2 or C5 position using ILs as the smart sustainable reaction media.[17] During our studies on pyrrole C-alkylation in ILs with 1-bromo-3-phenylpropane (**2a**, 10 mol %), we obtained pyrrole carbamate **3** and N-alkylated pyrrole **4** as the minor byproducts. The same reaction in the absence of pyrrole provided symmetrical dialkylcarbonate **6** as the sole product.[18]

These two observations diverted our attention toward the N-alkylation of pyrrole in ILs. In this work, we report on the N-alkylation of indole and pyrrole in ionic liquids using potassium carbonate as a base. The formation of pyrrole carbamate **3** (Route A) and N-alkylated



[bmim][X] {X = BF_4, PF_6, NTf_2, OTf}

Figure 1. Ionic liquids.

* Corresponding author. Tel.: +82 505 860 7686; fax: +82 32 867 5604; e-mail: dychi@inha.ac.kr

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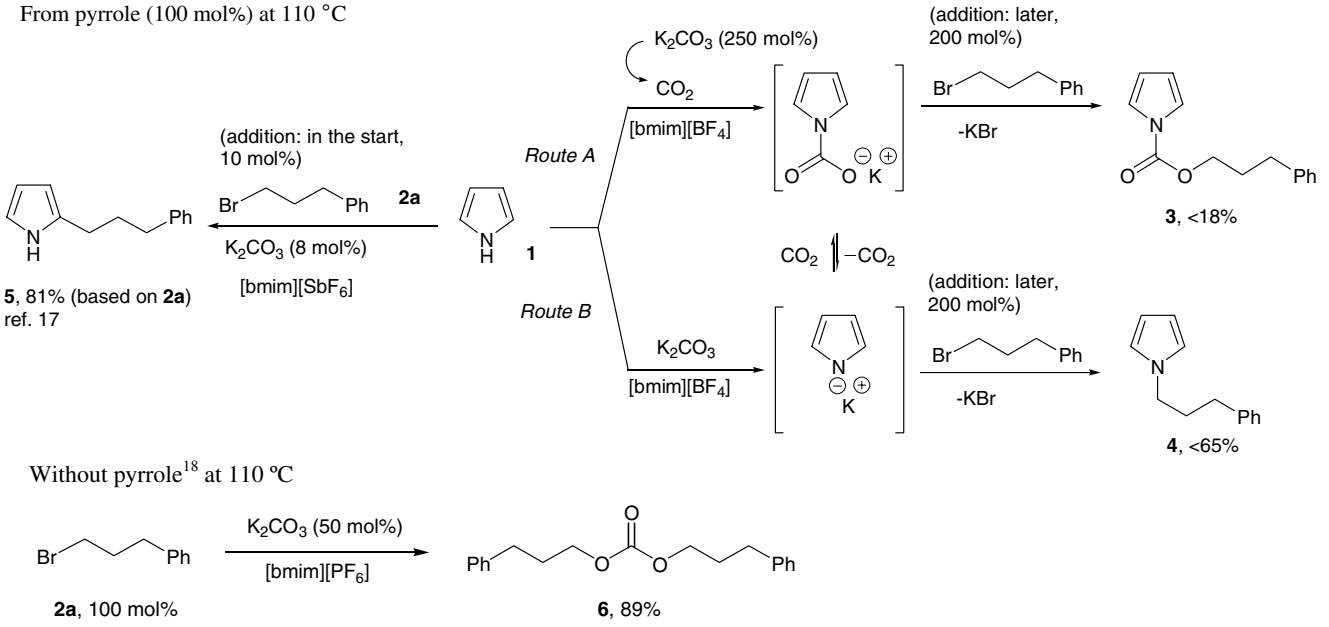


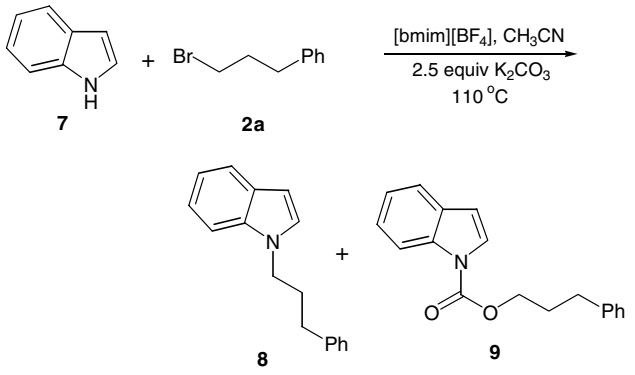
Scheme 1.

pyrrole **4** (Route B) could be explained, assuming that the reactions follow the two routes shown in Scheme 1. In addition, we have incorporated two of our recent reports on nucleophilic substitution reactions in ILs in a more simplified manner with the amounts of the reactants used in terms of mol % (Scheme 1). One might notice that three factors in these C-alkylation (reaction for compound **5**) or N-alkylation (reaction for compound **4**) from pyrrole were: (1) mole ratio of alkyl halide and pyrrole, (2) amount of potassium carbonate, and (3) interval of addition of alkyl halide. Herein, we report the optimization of these factors for the synthesis of N-alkylated and indole pyrrole in ionic liquid.

In our initial investigation designed to optimize the process of N-alkylation in ILs, we found indole to be a better candidate than pyrrole. Thus, we continued this process with indole **7** as a model nucleophile. The wide and readily accessible range of ILs offered an opportunity for the N-alkylation of indole and pyrrole. The commercial availability of potassium carbonate as a cheap, nontoxic, and weak base for the N-alkylation of indole and pyrrole in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4], is explored herein.

To begin our investigation, we first carried out the N-alkylation of indole in acetonitrile (3.0 mL) as a conventional organic solvent, which provided only 14% of 1-(3-phenylpropyl)-1*H*-indole (**8**) and 4% of 3-phenylpropyl-1*H*-indole-1-carboxylate (**9**) after 48 h (Table 1, entry 1). The same reaction with less than 1 equiv of [bmim][BF_4] (0.54 mmol, 100 μL) in CH_3CN (2.9 mL) gave 27% and 9% of **8** and **9**, respectively (entry 3). The addition of cosolvent presumably helps in decreasing the viscosity and changing the ionic conductivity of the ionic liquids, which in turn helps in accelerating the reaction. Entry 2 clearly confirmed the role played by K_2CO_3 in the generation of an ambident indolyl anion. Entry 4 with [bmim][BF_4] (2.0 mL) and CH_3CN (1.0 mL) was found to be the optimum condition, giving 82% of **8** and 3% of carbamate **9**.[19,20] Interestingly, the

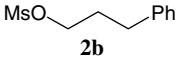
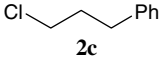
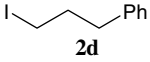
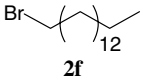
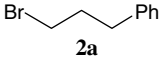
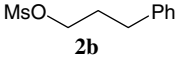
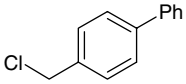
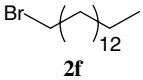
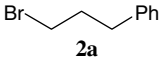
Table 1. N-Alkylation of indole with 1-bromo-3-phenylpropane in the presence of K_2CO_3 under various reaction conditions[a]



Entry	[bmim][X] (mL)	CH_3CN (mL)	Time (h)	Yield (%)[b]		
				7	**8**	**9**
1	—	3.0	48	76	14	4
2[c]	[BF_4] 3.0	—	48	92	—	—
3	[BF_4] 0.1	2.9	48	55	27	9
4	[BF_4] 2.0	1.0	34	—	82	3
5[d]	[BF_4] 2.0	1.0	34	—	80	5
6[e]	[BF_4] 2.0	1.0	34	—	80	3
7[e]	[BF_4] 2.0	1.0	36	—	82	4
8	[PF_6] 2.0	1.0	34	—	80	4
9	[NTf_2] 2.0	1.0	48	12	58	18
10	[OTf] 2.0	1.0	48	8	62	16

[a] All reactions were carried out on a 1.0 mmol reaction scale of indole **7** with 2.0 mmol of 1-bromo-3-phenylpropane **2a** and 2.5 mmol of K_2CO_3 at 110 °C.
[b] Isolated yields.
[c] Reaction was carried out in the absence of K_2CO_3.
[d] Reaction was carried out using 2.5 mmol of Cs_2CO_3.
[e] Reaction with recycled [bmim][BF_4], runs 2 and 3, respectively.

Table 2. N-Alkylation with various alkyl halides and mesylates in [bmim][BF_4][a]

Entry	Nucleophile	RX	Time (h)	Product (yield,[b] %)	
				NR	NCO_2R
1	Indole	 **2b**	32	**8** (68)	**9** (14)
2	Indole	 **2c**	72	**8** (38)	**9** (10)
3	Indole	 **2d**	26	**8** (71)	**9** (4)
4	Indole	CH_3I **2e**	28	**8e** (55)	—
5	Indole	 **2f**	72	**8f** (65)	—
6	Pyrrole	 **2a**	30	**4** (65)	**3** (18)
7	Pyrrole	 **2b**	28	**4** (62)	**3** (20)
8	Pyrrole	 **2g**	48	**10** (56)	—
9	Pyrrole	 **2f**	72	**11** (62)	—
10	Pyrrole	CH_3I **2e**	26	**12** (52)	—
11[c]	Carbazole **13**	 **2a**	72	**14** (20)	—

[a] Reactions were carried out on a 1.0, 2.0, and 1.0 mmol reaction scale of indole, pyrrole, and carbazole, respectively, with 2.0, 4.0, and 2.0 mmol of the electrophiles, respectively, and 2.5 mmol of K_2CO_3 at 110 °C in a solvent system consisting of a mixture of [bmim][BF_4] (2.0 mL) and CH_3CN (1.0 mL).

[b] Isolated yields.

[c] Unreacted carbazole recovered (<75%).

use of Cs_2CO_3 gave approximately the same results, affording 80% of the N-alkylated compound **8** (entry 5). The ILs can be recycled and reused without any degradation (entries 6 and 7).[20]

We next screened the reaction with the three other ILs. In the case of entries 8–10, [bmim][PF_6], [bmim][NTf_2], and [bmim][OTf] were used as the ILs, and 80%, 58%, and 62% of the desired product **8** was obtained, respectively.

We further examined the reactivity by using a series of different electrophiles, namely simple alkyl halides and sulfonates (Table 2). In entry 1, mesylate **2b** reacted within 32 h to yield 68% of **8** and in entry 3, iodide **2d** gave 71% of the desired product **8** within 26 h, whereas, as expected, the reaction with the chloride **2c** was found to be sluggish (entry 2). Finally, we applied our green protocol to the N-alkylation of pyrrole and carbazole. In the case of pyrrole, these conditions did not give reproducible yields of the products, and a variable ratio of the N-alkylated pyrrole **4** and pyrrole carbamate **3** was observed (entries 6 and 7), whereas N-alkylation of carbazole **13** was found to be very slow affording 20% of **14** (entry 11).

In conclusion, we emphasize that our IL methodology constitutes a highly useful method of N-alkylation of indole and pyrrole, because of its ease, simplicity, and the mildness of the conditions. Our protocol does not use a strong base or the conventional organic solvents such as DMSO or DMF with their high water solubility and high boiling points (over 100 °C) leading to complexities during workup. Moreover, our method is devoid of any inert condition and can be performed without any special equipment or precaution. Thus, we expect that our sustainable approach will find many applications in organic synthesis.

Acknowledgments

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carried out at the Korea Basic Science Institute (Daegu, Korea).

Supplementary data

Characterization of all compounds including ^{1}H and ^{13}C NMR spectra (16 pages). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.129.

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19. Typical procedure: Potassium carbonate (345 mg, 2.5 mmol), indole (**7**, 1.0 mmol), [bmim][BF_4] (2.0 mL), and CH_3CN (1.0 mL) were stirred over 10 h at 110 °C. The reaction mixture was cooled to room temperature. 1-Bromo-3-phenylpropane (**2a**, 398 mg, 2.0 mmol) was added to the reaction mixture and stirred for another 24 h at 110 °C. The reaction was monitored by thin layer chromatography (TLC) until trace or no indole was observed. The reaction mixture was extracted from ionic liquid phase with ethyl ether (10 mL × 5). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/Hx) to obtain 193 mg (82%) of 1-(3-phenylpropyl)-1*H*-indole (**8**) as colorless oil. In case of pyrrole N-alkylation the procedure was the same except pyrrole (**1**, 2.0 mmol), and 1-bromo-3-phenylpropane (**2a**, 796 mg, 4.0 mmol) were used. Reaction mixture was stirred over 30 h at 110 °C.
1-(3-Phenylpropyl)-1*H*-indole (**8**): Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (quin, $J = 7.2$ Hz, 2H), 2.65 (t, $J = 7.6$ Hz, 2H), 4.15 (t, $J = 7.2$ Hz, 2H), 6.52 (d, $J = 2.0$ Hz, 1H), 7.10–7.34 (m, 9H), 7.66 (d, $J = 4.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 32.9, 45.6, 101.0, 109.3, 119.2, 120.9, 121.3, 126.1, 127.7, 128.4, 128.5, 128.6, 135.9, 140.9; MS (EI) 235 (M^+), 130 (100). Anal. Calcd: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.73; H, 7.22; N, 6.35.
3-Phenylpropyl-1*H*-indole-1-carboxylate (**9**): Colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18 (quin, $J = 8.0$ Hz, 2H), 2.83 (t, $J = 8.0$ Hz, 2H), 4.46 (t, $J = 6.8$ Hz, 2H), 6.61–6.62 (m, 1H), 7.20–7.38 (m, 9H), 8.19–8.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3, 32.2, 66.4, 108.0, 115.1, 121.0, 123.0, 124.5, 125.5, 126.2, 128.4, 128.45, 130.5, 135.2, 140.8, 151.0; MS (EI) 279 (M^+), 91 (100). HR MS (EI) calcd for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1262.
1-Biphenyl-4-ylmethyl-1*H*-pyrrole (**10**): White solid; mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 2H), 6.22 (t, $J = 2.4$ Hz, 2H), 6.74 (t, $J = 2.0$ Hz, 2H), 7.18–7.20 (m, 2H), 7.35–7.37 (m, 1H), 7.42–7.46 (m, 2H), 7.54–7.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.03, 108.5, 121.1, 127.0, 127.3, 127.4, 127.45, 128.8, 137.2, 140.6; MS (EI) 233 (M^+), 167 (100). Anal. Calcd: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.81; H, 6.72; N, 6.35.
9-(3-Phenylpropyl)-9*H*-carbazole (**14**): Yellow solid; mp 111–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (quin, $J = 7.6$ Hz, 2H), 2.70 (t, $J = 8.0$ Hz, 2H), 4.30 (t, $J = 7.2$ Hz, 2H), 7.15–7.46 (m, 11H), 8.09–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 33.3, 42.4, 108.6, 118.8, 120.3, 122.8, 125.5, 126.1, 128.3, 128.4, 140.3, 141.0; MS (EI) 285 (M^+), 180 (100). Anal. Calcd: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.14; H, 6.99; N, 4.61.
20. Ionic liquid recycling procedure: To the ionic liquid phase ethyl acetate (5.0 mL) was added and filtered. The filtrate was washed with water (2.0 mL × 4). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. Ionic liquid was further dried under high vacuum at 80 °C overnight and used for the next run.