Organic Reactions in Ionic Liquids: A Simple and Highly Regioselective N-Substitution of Pyrrole

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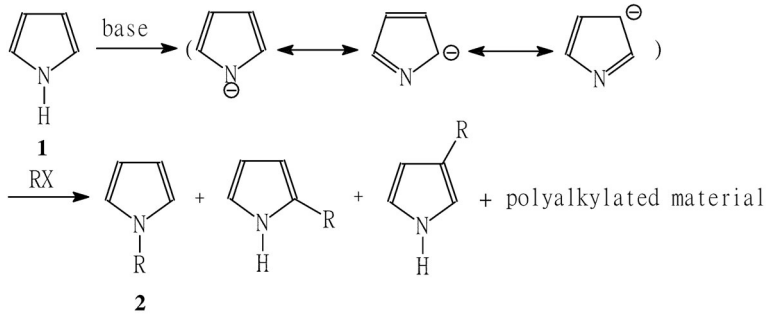
Abstract: In ionic liquids [Bmim][PF_6] or [Bmim][BF_4], pyrrole replaced the halogen atom of an alkyl halide to give the corresponding N-substituted pyrrole in excellent yield. Benzenesulfonyl chloride, *p*-methylbenzenesulfonyl chloride and benzoyl chloride reacted similarly with pyrroles to afford the N-substituted pyrroles in quantitative yield. Michael addition reaction of pyrrole with electrophilic olefins was completed in a highly regioselective manner to afford the *N*-alkylpyrroles.

Key words: pyrroles, substitution, ionic liquids, alkylation, sulfonylation, acylation

The development of simple, efficient and highly selective synthetic methods for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. The synthesis and reaction of pyrroles have been a topic of research interest for over a century because a number of their derivatives occur in nature[1] and possess a variety of important biological activities.[2] N-Substituted pyrroles are usually obtained by the reaction of pyrrolyl anion with the appropriate alkylating agents.[3] However, since the pyrroyl anion exhibits ambident behavior as nucleophile, alkylation can occur at carbon as well as at nitrogen[4] (Scheme 1). Thus, when the anion from pyrrole (**1**) is alkylated, 2- and 3-alkylpyrroles may contaminate the required product *N*-alkylpyrrole **2**. To date, several new procedures have been developed in which the N-alkylation of pyrrole can be achieved with little or no interference from C-alkylation.[5] However, these methods are limited by harsh reaction conditions, relatively long reaction time, low yield and use of toxic solvents or catalysts. Therefore, the development of a mild, efficient, and highly regioselective N-substitution of pyrrole (**1**) is still a much sought out process.

It has been demonstrated that the solvent can dramatically influence the ratio of N to C alkylation of pyrrolyl anion, and dipolar aprotic solvents can give rise to predominant N-substituted pyrrole.[4a,6] In recent years, the room temperature ionic liquids are attracting increasing interest as a 'green' recyclable alternative to classical molecular solvents in synthetic organic chemistry.[7] They appear to have solvent characteristics similar to moderately polar organic solvents and have been compared to various alcohols and dipolar aprotic solvents.[8] For example, [Bmim][PF_6] is more polar than acetonitrile and less polar than methanol.[8b] To date, some of the important reactions have been carried out and investigated, and it has been demonstrated in some cases that the reactions in ionic liquids show high selectivity or rate acceleration compared to conventional solvents.[9]

Our recent interest has been in the development of new synthetic methods using ionic liquids as reaction media and promoters.[10] As part of a program to investigate the range of organic reactions possible in ionic liquids, we examined the reactions of pyrrole (**1**) with some electro-



Scheme 1

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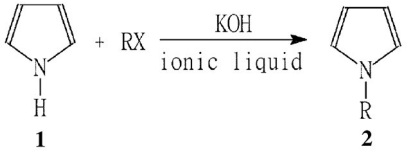
philic reagents in ionic liquids (Scheme 2), which would provide a highly regioselective synthetic method to N-substituted pyrroles **2**.



1 **2**

Scheme 2

First, we found that in the presence of KOH, the reaction of pyrrole (**1**) with methyl iodide, could proceed smoothly at 40 °C in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate, [Bmim][PF_6]. The product is *N*-methylpyrrole (**2a**) as the only isomer by GC-MS analysis and the yield is 82% (Table 1, entry 1). In a similar fashion, the reactions of pyrrole (**1**) with a variety of halogen derivatives were investigated. We found that the reaction is general and applicable to primary alkyl halides containing iodide, bromide and chloride (Table 1, entries 1,3,4,6–8). For secondary bromide, the yield is also good (Table 1, entry 2). It is noteworthy that *tert*-butyl bromide can efficiently react (Table 1, entry 5), but in the reported methods,[4a,5b] the reaction did not occur. When allyl bromide is employed as the alkylating agent, *N*-allylpyrrole (**2e**) can be produced in quantitative yield (Table 1, entry 6), and in the reported procedures,[4] a mixture of *C*- and *N*-allylpyrroles was obtained, even C-alkylated material predominated over N-alkylated material.[4c] In order to explore the generality of the method developed for the alkylation of pyrrole, we conducted experiments in which some of eletrophilic olefins, such as methyl acrylate, acrylonitrile and methyl vinyl ketone in ionic liquid [Bmim][PF_6] were employed and efficiently gave the corresponding N-substituted pyrrole derivatives as the only isomer (Table 1, entries 9–11). Furthermore, in a similar fashion we tried the reaction of pyrrole with benzenesulfonyl chloride, *p*-methylbenzenesulfonyl chloride and benzoyl chloride; here also the N-substituted pyrroles were obtained in quantitative yields (Table 1, entries 12–14). The related ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, [Bmim][BF_4], is also effective (Table 1, entries 3, 10, 12).

All the products gave satisfactory mps, IR and ^{1}H NMR data, which were consistent with the literature data.

The ionic liquid can be typically recovered, after extraction of the product followed by drying under vacuum, and filtering the suspension to remove residual solid. The recovered solvent can be reused with no appreciable decrease in yield. The representative results are summarized in Table 2.

The present method has many obvious advantages, compared to those reported in literature, including high regioselectivity, generality, higher yield, being environmentally more benign, and potential for recycling of ionic liquids. In conclusion, we have demonstrated that the N-substitution of pyrrole can effectively be performed

Table 1 N-Substitution of Pyrrole in Ionic Liquids[a]

Entry	RX	Reaction Conditions	Product	Yield (%)[b]
1	CH_3I	2 h, 40 °C	**2a**	82 (80[c])
2	*i*-C_3H_7Br	2 h, 60 °C	**2b**	70 (65[c])
3	*n*-C_4H_9Br	1 h, 80 °C	**2c**	98 (95[c]) (95[d])
4	*n*-C_4H_9Cl	2 h, 80 °C	**2c**	76 (73[c])
5	*t*-C_4H_9Br	2 h, 70 °C	**2d**	57 (51[c])
6	CH_2=$CHCH_2Br$	1 h, 70 °C	**2e**	100 (96[c])
7	$C_6H_5CH_2Br$	1 h, 80 °C	**2f**	100 (98[c])
8	$C_6H_5CH_2Cl$	1 h, 80 °C	**2f**	99 (98[c])
9	CH_2=CHCN	1 h, 80 °C	**2g**	82 (80[c])
10	CH_2=$CHCO_2CH_3$	1 h, 80 °C	**2h**	78 (72[c]) (70[d])
11	CH_2=$CHCOCH_3$	1 h, 80 °C	**2i**	80 (75[c])
12	$C_6H_5SO_2Cl$	1 h, 80 °C	**2j**	100 (99[c]) (100[d])
13	*p*-$CH_3C_6H_5SO_2Cl$	1 h, 80 °C	**2k**	100 (98[c])
14	C_6H_5COCl	1 h, 80 °C	**2l**	100 (98[c])

[a] All reaction were run with pyrrole (2 mmol), RX (4 mmol), KOH (4 mmol) in ionic liquid [Bmim][PF_6] (2 mL).
[b] Determined by GC-MS (internal standard: cyclohexanone) based on pyrrole.
[c] Isolated yield.
[d] In ionic liquid [Bmim][BF_4].

in the ionic liquids [Bmim][PF_6] or [Bmim][BF_4] with high regioselectivity, which provides a simple and efficient method for the synthesis of the N-substituted pyrroles **2**.

Table 2 Recycling of [Bmim][PF_6] in N-Butylation of Pyrrole[a]

Entry	Cycle	*N*-Butylpyrrole (**2c**) Yield [b] (%)
1	1	98
2	2	96
3	3	97

[a] All reaction were run with pyrrole (2 mmol), butyl bromide (4 mmol), KOH (4 mmol) in ionic liquid [Bmim][PF_6] (2 mL) at 80 °C for 1.0 h.
[b] Determined by GC-MS based on pyrrole.

Melting points were determined on digital melting point apparatus and were not corrected. IR spectra were recorded on a Bruker VECTOR22 spectrometer. NMR spectra were recorded on Bruker Avance DMX 200 spectrometer. The ionic liquids [bmim][BF_4] and [bmim][PF_6] were synthesized according to reported procedures.[11] The other materials are commercially available and were used without further purification.

N-Substitution of Pyrrole (1); General Procedure

A mixture of pyrrole (**1**; 134.2 mg, 2 mmol), an alkyl halide (4 mmol), powdered KOH (224 mg, 4 mmol) and an ionic liquid (2 mL) was stirred for 1–2 h at 40–80 °C (for reaction conditions, see Table 1). After the reaction was complete, the mixture was extracted with Et_2O (3×5 mL). The combined Et_2O extracts were evaporated under reduced pressure and the resulting crude product was analyzed by GC-MS (HP-5, 5% phenyl methyl siloxane), or was separated by preparative TLC (silica gel). After isolation of the product, the remainder of the ionic liquid was further washed with Et_2O, followed by drying under vacuum, filtering the suspension to remove residual solid and recycled in subsequent runs (Table 1).

***N*-Methylpyrrole (2a)**
Oil.[12]

IR (film): 2942, 2907, 2810, 1508, 1418, 1386, 1327, 1286, 1088, 1060, 968, 819, 723, 664, 606 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.40 (t, *J* = 2.4 Hz, 2 H), 6.10 (t, *J* = 2.4 Hz, 2 H), 3.60 (s, 3 H).

***N*-Isopropylpyrrole (2b)**
Oil.[12]

IR (film): 2955, 2811, 1510, 1418, 1386, 1375, 1286, 1088, 1059, 968, 819, 722, 664 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.60 (t, *J* = 2.4 Hz, 2 H), 6.15 (t, *J* = 2.4 Hz, 2 H), 3.76 (q, *J* = 7.2 Hz, 1 H), 1.71 (t, *J* = 7.2 Hz, 6 H).

***N*-Butylpyrrole (2c)**
Oil.[12]

IR (film): 3118, 2967, 1565, 1465, 1498, 1282, 1117, 1090, 718 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.61 (t, *J* = 2.4 Hz, 2 H), 6.17 (t, *J* = 2.4 Hz, 2 H), 3.82 (t, *J* = 6.8 Hz, 2 H), 1.70 (m, 2 H), 1.27 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

***N*-*tert*-Butylpyrrole (2d)**
Oil.[12]

IR (film): 3123, 2984, 1530, 1481, 1375, 1267, 1094, 713 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.65 (t, *J* = 2.4 Hz, 2 H), 6.09 (t, *J* = 2.4 Hz, 2 H), 1.42 (s, 9 H).

***N*-Allylpyrrole (2e)**
Oil.[12]

IR (film): 3118, 2967, 1498, 1282, 1090, 718 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.56 (t, *J* = 2.4 Hz, 2 H), 6.12 (t, *J* = 2.4 Hz, 2 H), 5.64–6.06 (m, 1 H), 4.84–5.30 (m, 2 H), 4.42 (m, 2 H).

***N*-Benzylpyrrole (2f)**
Oil.[12]

IR (film): 3118, 3018, 2918, 1656, 1495, 1452, 1208, 1065, 775, 745, 718 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.25 (m, 3 H), 7.08 (m, 2 H), 6.64 (t, *J* = 2.6 Hz, 2 H), 6.17 (t, *J* = 2.6 Hz, 2 H), 4.96 (s, 2 H).

***N*-(2-Cyanoethyl)pyrrole (2g)**
Oil.[5c]

IR (film): 2950, 2925, 2250, 1500, 1290 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.71 (t, *J* = 2.2 Hz, 2 H), 6.20 (t, *J* = 2.2 Hz, 2 H), 4.17 (t, *J* = 6.8, 2 H), 2.69 (t, *J* = 6.8, 2 H).

Methyl 3-(1-Pyrrolidyl)propionate (2h)
Oil.[5c]

IR (film): 2962, 1757, 1451, 1345, 1194, 1089, 724 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.68 (t, *J* = 2.2 Hz, 2 H), 6.19 (t, *J* = 2.2 Hz, 2 H), 3.86 (t, *J* = 7.4 Hz, 2 H), 3.68 (s, 3 H), 2.76 (t, *J* = 7.4 Hz, 2 H).

(1-Pyrrolidyl)butan-2-one (2i)
Oil.[5c]

IR (film): 2990, 1730, 1366, 1174, 1088, 723 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.67 (t, *J* = 2.2 Hz, 2 H), 6.17 (t, *J* = 2.2 Hz, 2 H), 3.85 (t, *J* = 7.4 Hz, 2 H) 2.40 (t, *J* = 7.4 Hz, 2 H), 1.89 (s, 3 H).

***N*-Phenylsulfonylpyrrole (2j)**
Mp 90 °C (Lit.[3d] mp 89–89.5 °C).

IR (KBr): 3077, 1576, 1454, 1393, 1059, 730, 622 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.3–8.3 (m).

***N*-(*p*-Methylbenzenesulfonyl)pyrrole (2k)**
Mp 104–105 °C (Lit.[3d] mp 104.5 °C).

IR (KBr): 3076, 2957, 1574, 1454, 1393, 1059, 859 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.3–8.3 (m, 8 H), 2.42 (s, 3 H).

***N*-Benzoylpyrrole (2l)**
Oil.[13]

IR (KBr): 3074, 1698, 1600, 1455, 724 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.94 (d, *J* = 6.8 Hz, 2 H), 7.64 (m, 1 H), 7.51 (m, 2 H), 7.12 (t, *J* = 2.2 Hz, 2 H), 6.20 (t, *J* = 2.2 Hz, 2 H).

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