# Ionic liquid-accelerated *N*-arylation of benzoazoles with diaryliodonium salts, an efficient method for the synthesis of *N*-aryl azoles

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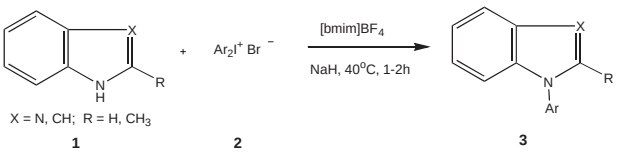
*N*-Arylation of benzoazoles with diaryliodonium salts can be performed in good yields in the room-temperature ionic liquid 1–butyl–3–methylimidazolium tetrafluoroborate ([bmim]$BF_4$), which provides an efficient method for the synthesis of *N*-arylbenzoazoles. The ionic liquid can be recycled and reused.

**Keywords:** ionic liquids, indoles, benzimidazoles, diaryliodonium salts, *N*-arylation of azoles

The *N*-arylbenzoazole moiety is a structural element present in many biologically active and pharmaceutically important compounds.[1] Benzoazole-containing compounds are of interest as antifungals,[2] antagonists,[3] and synthetic intermediates used in the preparation of other biologically active heterocyclic products.[4] The direct *N*-arylation of N–H containing heteroarenes has been brought about by the traditional Ullmann coupling.[5] Other methods, that utilize aryl bismuths,[6] aryl leads,[7] arylboronic acids[8] and aryl siloxanes[9], have been developed. The palladium-catalysed *N*-arylation of mono-nitrogen azoles is an important alternative.[10] Finally, the arylation of indole-like heteroarenes by nucleophilic aromatic substitution of aryl halides activated by electron-withdrawing substituents represents an alternative route to *N*-arylbenzoazoles.[11] While all of these methods have their uses, most of them suffer from limitations such as the need to employ harsh reaction conditions, the use of difficultly accessible or toxic reagents, and the necessary presence of a metal catalyst.

Room temperature ionic liquids (RTILs), especially those based upon the 1-*n*-alkyl-3-methylimidazolium cation, have attracted growing interest in the last few years.[12] They offer an alternative and environmentally advantageous reaction medium, compared to conventional organic liquids, as they are non-volatile, recyclable, thermally robust and excellent solvents for a wide range of organic or inorganic materials. These media have been applied to non-catalytic[12,13] and catalytic reactions[12] as well as to selective extraction.[14]




**Scheme 1**

Recently, our research interest has been in the application of hypervalent iodine compounds in organic synthesis. Our previous works have shown that diaryliodonium salts are efficient arylating reagents.[15] As part of a program to investigate the range of organic reaction possible in ionic liquids, coupled with high reactivity of diaryliodonium salts, we examined the reaction of benzoazoles with diaryliodonium salts in the ionic liquid 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]$BF_4$). Here we report the ionic-liquid-accelerated *N*-arylation of benzoazoles with diaryliodonium salts for the synthesis of *N*-arylbenzoazoles (Scheme 1).

We have found that *N*-arylation of benzoazole **1** with diaryliodonium salts **2** in the presence of NaH in [bmim]$BF_4$ occurs readily, reaching completion within 1–2h at 40 °C, and giving the corresponding *N*-arylbenzoazoles **3** in good yields. The results are summarised in Table 1. All products were characterised by m.p., IR, $^1$H NMR, and mass spectra.

As can be seen in Table 1, the present method shows an efficient entry to *N*-arylated benzoazoles, allowing the

**Table 1** *N*-Arylation of benzoazoles with diaryliodonium salts in [bmim]$BF_4$

| Entry | Ar | X | R | Product | M.P. (°C) | Lit. M.P. | Yield [a]/% |
|---|---|---|---|---|---|---|---|
| 1 | Ph | CH | H | *N*-Phenylindole (**3a**) | Oil | Oil [5c] | 85 |
| 2 | Ph | CH | H | **3a** | | | 82[b] |
| 3 | *p*-$MeC_6H_4$ | CH | H | *N*-(4-Methylphenyl)indole (**3b**) | Oil | Oil [5c] | 86 |
| 4 | *p*-$MeC_6H_4$ | CH | H | **3b** | | | 85[c] |
| 5 | *p*-$MeOC_6H_4$ | CH | H | *N*-(4-Methoxyphenyl)indole (**3c**) | 56–58 | 57–58[5c] | 79 |
| 6 | *p*-$ClC_6H_4$ | CH | H | *N*-(4-Chlorophenyl)indole (**3d**) | 67–68 | 64–66[5c] | 90 |
| 7 | *p*-$BrC_6H_4$ | CH | H | *N*-(4-Bromophenyl)indole (**3e**) | 65–66 | 64–65[15g] | 83 |
| 8 | *m*-$NO_2C_6H_4$ | CH | H | *N*-(3-Nitrophenyl)indole (**3f**) | 65–67 | 67–68[5d] | 74 |
| 9 | Ph | N | H | 1-Phenylbenzimidazole (**3g**) | 93–94 | 95–96[5f] | 82 |
| 10 | Ph | N | H | **3g** | | | 80[b] |
| 11 | *p*-$MeC_6H_4$ | N | H | 1-(4-Methylphenyl)benzimidazole (**3h**) | Oil | Oil[7a] | 76 |
| 12 | *p*-$MeC_6H_4$ | N | H | **3h** | | | 75[c] |
| 13 | *p*-$MeOC_6H_4$ | N | H | 1-(4-Methoxyphenyl)benzimidazole (**3i**) | 96–98 | 99[16a] | 72 |
| 14 | *p*-$ClC_6H_4$ | N | H | 1-(4-Chlorophenyl)benzimidazole (**3j**) | 90–91 | 92[16a] | 69 |
| 15 | *p*-$BrC_6H_4$ | N | H | 1-(4-Bromophenyl)benzimidazole (**3k**) | 112–113 | 112–113[15h] | 65 |
| 16 | *m*-$NO_2C_6H_4$ | N | H | 1-(3-Nitrophenyl)benzimidazole (**3l**) | 149–150 | 151–152[5e] | 54 |
| 17 | Ph | N | Me | 2-Methyl-1-phenylbenzimidazole (**3m**) | 90–91 | 92[16a] | 83 |
| 18 | *p*-$ClC_6H_4$ | N | Me | 1-(4-Chlorophenyl)-2-methylbenzimidazole (**3n**) | 158–160 | – | 72 |
| 19 | *p*-$BrC_6H_4$ | N | Me | 1-(4-Bromophenyl)-2-methylbenzimidazole (**3o**) | 120–122 | 119–121[16c] | 70 |

[a]Isolated yield based on diaryliodonium salts. [b]Using [bmim]$PF_6$. [c] Using recovered [bmim]$BF_4$.

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preparation of *N*-arylbenzoazoles bearing various substituents such as methyl, methoxy, bromo, chloro and nitro groups on the phenyl ring. The ionic liquid [bmim]$BF_4$ can truly be compared with classical molecular solvents, with the advantage of rate acceleration and reduction in reaction temperature. For example, in our previously reported methods,[15g-h] the *N*-arylation of indole with diaryliodonium salts in the presence of copper catalyst needs heating in DMF at 140–150 °C for 6–7h, *N*-arylation of benzimidazole needs heating at 80 °C for 2.5–3h, but the same reaction was successful in [bmim]$BF_4$ at 40 °C in only 1–2h. Moreover, the copper catalyst was not needed. On the other hand, the ionic liquid ([bmim]$BF_4$) can typically be recovered by extracting to isolate the product and filtering to remove insoluble sodium bromide, followed by vacuum drying. The recovered solvent can be reused with no appreciable decrease in yield (entries 4 and 12). Further studies indicate that the related ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]$PF_6$ is also an efficient solvent for *N*-arylation of benzoazoles with diphenyliodonium bromide (entries 2 and 10).

In conclusion, we have demonstrated that *N*-arylation of benzoazoles with diaryliodonium salts can effectively be performed in the room-temperature ionic liquid [bmim]$BF_4$, which provides a simple and efficient method for the synthesis of *N*-arylbenzoazoles. The present method has many obvious advantages, both environmental and in practical operation, requiring mild reaction conditions, and offering simplicity of procedure, ease of product isolation and the potential for recycling of the ionic liquid.

## Experimental

$^1$H NMR spectra were recorded on an Avance-400 spectrometer using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were determined on a PE-683 Infrared spectrophotometer, with KBr pellets for solid materials. Mass spectra were measured on a HP-5989B mass spectrometer. Elemental analyses were performed on an EA1110 analyser.

**General procedure for the preparation of *N*-arylbenzoazoles**

NaH (1.5 mmol) was added to a stirred solution of benzoazole **1** (1.5 mmol) in [bmim]$BF_4$ (4 ml), and the mixture was warmed at 40 °C until the solids were dissolved. The iaryliodonium salt **2** (1 mmol) was added. The mixture was stirred at 40 °C for 1–2h. The resulting solution was cooled to room temperature and extracted with diethyl ether (10 ml × 3). The combined ether extracts were concentrated *in vacuo* to leave a residue which was chromatographed on silica gel plate, using petroleum ether for **3a–3e**, cyclohexane/ethyl acetate (20:1) for **3f**, cyclohexane/ethyl acetate (2:1) for **3g–3o** as the developer, to give pure products. After filtering off the salt by-product, the rest of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs.

All products except **3n** are known, and their physical and spectroscopic data are in full agreement with expected and/or reported values.

*1-(4-Chlorophenyl)-2-methylbenzimidazole* (**3n**): white solid, m.p. 158–160 °C; $^1$H NMR $\delta_H$: 2.81(s, 3H), 7.25(m, 3H), 7.35–7.38 (m, 3H), 7.66–7.69 (m, 2H); IR $\nu_{max}$/cm$^{-1}$: 3079, 3025, 1560, 1456, 1300, 1233, 997, 860, 726; MS *m/z* (%): 242 ($M^+$, 1.3), 132(100), 131(75), 104(13), 65(17), 63(28), 52(17); Anal: calcd. for $C_{14}H_{11}ClN_2$: C, 69.35; H, 4.53; N, 11.55. Found: C, 69.12; H, 4.57; N, 11.69 %.

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