# Regioselective alkylation in ionic liquids

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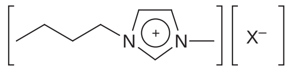
**The room temperature ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF$_6$], is used as a 'green' recyclable alternative to dipolar aprotic solvents for the regioselective alkylation at the heteroatom of indole and 2-naphthol.**

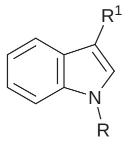
Efficient alkylation of the ambident nucleophiles indole **1** or 2-naphthol **4** is usually achieved by pre-formation of the ambident indolyl[1] or 2-naphtholate[2] anions and subsequent treatment with alkyl halide. Regioselective alkylation at the heteroatom for these anions is solvent dependant and can be achieved by use of a dipolar aprotic solvent such as DMF.[2,3] The procedure of Heaney and Ley for *N*-alkylation of indoles in DMSO with solid KOH is probably the most convenient method known and obviates the need for strong bases such as NaH or alkyllithiums.[4] However, despite the well known ability of solvents such as DMSO and DMF to accelerate nucleophilic displacements,[5] the relatively high boiling points of these solvents, their thermal instability, considerable odour problems and miscibility with both aqueous and organic phases can make product isolation difficult and solvent recovery almost impossible.

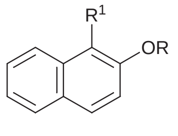
The introduction of air and moisture stable ambient temperature ionic liquids by Wilkes and Zaworotko[6] in 1992 considerably widened the possible applications of ionic liquid systems as solvents and reagents for organic synthesis. Recently room temperature ionic liquids have been reported as solvents for polymerisation,[7] hydrogenation[8] and as catalysts for the Diels–Alder reaction.[9] The ionic liquid [bmim][PF$_6$] is conveniently prepared,[10] fluid at room temperature, moisture stable and has no detectable vapour pressure. It is an excellent solvent for carbonyl compounds, alkyl halides, alcohols and amines, but is immiscible with saturated hydrocarbon solvents, dialkyl ethers and water. The unique solvating properties of this moisture stable ionic liquid makes it a strong candidate as a recyclable solvent.[11] Our recent interest has been in the area of clean synthesis[12] and as part of a programme to investigate the range of organic reactions possible in ionic liquids, we were interested in the reactions of **1** and **4** with alkyl halides in [bmim][PF$_6$].



[bmim][PF$_6$] X = PF$_6$

[bmim][BF$_4$] X = BF$_4$





**1** R = R$^1$ = H
**2** R = Et, Bu, Me or PhCH$_2$, R$^1$ = H
**3** R = R$^1$ = Et, Bu, Me or PhCH$_2$

**4** R = R$^1$ = H
**5** R = Et, Bu, Me or PhCH$_2$, R$^1$ = H
**6** R = R$^1$ = Et, Bu, Me or PhCH$_2$

The reaction of **1** with simple alkyl halides at room temperature was examined in [bmim][PF$_6$] using solid KOH as base; the products were conveniently extracted with Et$_2$O, and almost exclusive *N*-alkylation to form **2** was seen in all cases. The results for the alkylation of **1** with four typical alkyl halides in this solvent are outlined in Table 1. These reactions were carried out, typically as 10% w/v solutions of **1** in [bmim][PF$_6$] using 1.3 to 2 equiv. of alkyl halide and 2 equiv. of KOH. Reactions were complete in 2–3 h with almost quantitative extraction of products. The dialkylated products **3** were identified from the proton NMR spectra of the crude extracts and were only observed for the more reactive alkyl halides, PhCH$_2$Br and MeI. Analogous results were seen for the alkylation of 2-naphthol, **4**, to give predominantly *O*-alkylated products **5** (Table 1). The solvent can be typically recovered by filtering to remove residual insoluble KOH and precipitated potassium halide followed by vacuum drying. The NMR spectra ($^1$H, $^{13}$C, $^{19}$F) of recovered solvent indicate no evidence of ionic liquid degradation during the course of the reactions and the recovered solvent has been recycled numerous times with no appreciable decrease in yield or regioselectivity, with only small mechanical losses. The ionic liquid [bmim][PF$_6$] can truly be compared with classical molecular solvents, with the added advantage of *in situ* generation of anion, and the non-nucleophilic hexafluorophosphate anion avoids problems associated with halide exchange which had been encountered by Brunet and co-workers in their study.[13] Further studies indicate that the related ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF$_4$][14] is also an efficient solvent for alkylation of **1** and **4**.

In conclusion, room temperature ionic liquids are an attractive clean synthetic alternative to classical dipolar aprotic solvents for alkylation of ambident nucleophiles. There are many obvious advantages including simplicity of the methodology, the ease of product isolation, the lack of measurable solvent vapour pressure, the regioselectivity and the potential for recycling. Room temperature ionic liquids are neoteric solvents, and studies are underway to demonstrate their obvious potential as an alternative to classical molecular solvents for organic synthesis.

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**Table 1** Data for the reaction of indole, **1**, and 2-naphthol, **4**, with a selection of alkyl halides in the room temperature ionic liquid [bmim][PF$_6$]

| Substrate | Alkyl halide | Yield (%)[a] | Products | Ratio[b] |
|---|---|---|---|---|
| **1** | EtBr | 92 | **2**+**3** | > 99 : 1 |
| **1** | BuBr | 93 | **2**+**3** | > 99 : 1 |
| **1** | MeI | 91 | **2**+**3** | 93 : 2 |
| **1** | BnBr | 94 | **2**+**3** | 95 : 5 |
| **4** | EtBr | 94 | **5**+**6** | > 99 : 1 |
| **4** | BuBr | 98 | **5**+**6** | > 99 : 1 |
| **4** | MeI | 97 | **5**+**6** | 97 : 3 |
| **4** | BnBr | 95 | **5**+**6** | 95 : 5 |

[a] Isolated yield. [b] The ratio of either **2** : **3** or **5** : **6** was determined by $^1$H NMR and gas chromatographic analysis.

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## Notes and References

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