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An efficient protocol for the preparation of pyridinium and imidazolium salts based on the Mitsunobu reaction

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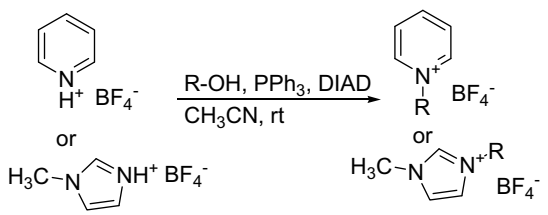
Abstract

We report herein that, in the absence of any nucleophilic counterions, tertiary nitrogen nucleophiles such as pyridines and imidazoles can be alkylated with alcohols, by simply using their ammonium form as the acidic component of the Mitsunobu reaction. This led to efficient preparation of ionic liquids under mild conditions, avoiding the usual anion exchange step.

Keywords: Mitsunobu; Pyridinium; Imidazolium; Ionic liquid; Alkylation

Imidazolium and pyridinium-based ionic liquids have been thoroughly studied over the past two decades and still receive considerable attention.[1] For example, pyridinium ionic liquids were recently used as catalysts in Morita–Baylis–Hillman reactions[2] or for asymmetric reductions of ketones.[3] The role of the counterion may also be of crucial importance, especially when the imidazolium salts are used as precursors of nucleophilic carbenes.[4] However, the quaternarization of heterocycles such as pyridine or imidazole derivatives involving alkyl halides generally requires prolonged heating[5] often incompatible with sensitive substrates. The high energy required by this reaction can also be delivered by microwave irradiation.[6] We were first intrigued by the possible application of the Mitsunobu reaction to synthesize *N*-alkylpyridinium salts under mild conditions. Recently, we reported our findings regarding this application of the Mitsunobu reaction in a synthesis of indoliziniums.[7] Since this reaction requires an acidic nucleophile (NuH), we worked out the alkylation step using pyridinium and imidazolium salts as nucleophiles. To the best of our knowledge, the Mitsunobu reaction is not used with pyridinium nor imidazolium salts as the acidic nucleophile component. Only one similar example of intramolecular N-alkylation of a pyridine–propanol scaffold showed that this reaction was made possible by the presence of an acidic NHBoc group at C6, but no pyridinium salt was used for this reaction.[8]

Our first experiment was conducted with pyridinium chloride in anhydrous methanol with a twofold excess of triphenyl phosphine PPh_3 and diisopropyl azodicarboxylate DIAD overnight at room temperature. Interestingly, N-alkylation afforded *N*-methylpyridinium chloride but in modest yield (45%). Presumably, activated methanol ($MeOP^+Ph_3$) can undergo a nucleophilic attack either by pyridine or chloride ion, thus giving chloromethane. Under the same conditions, a non-nucleophilic counterion such as



Scheme 1. Alkylation of pyridinium and *N*-methylimidazolium salts.

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tetrafluoroborate afforded a quantitative yield of the pyridinium salt. In the following experiments (Scheme 1), we used pyridinium tetrafluoroborate and *N*-methylimidazolium tetrafluoroborate as model substrates. Using 5 M equiv of methanol in acetonitrile, we were pleased to find out that the methylation of pyridinium took place quantitatively within 2 h at room temperature. Even 1.1 or 1.5 M equiv of methanol gave a satisfactory yield (see Table 1, footnotes a and b), but completion of the reaction required longer reaction times. As described in Table 1, screening various alcohols gave access to the expected *N*-alkylpyridinium salts in good yields. In addition, those salts were extracted in water, allowing an easy separation of the by-products of the Mitsunobu reaction. The same reaction conditions applied to *N*-methylimidazolium also gave good yields of quaternary products. This can lead to ionic liquids, avoiding a subsequent halide/BF_4^- exchange step, usually required in the preparation of ILs.[1]

These results show that this method constitutes a very efficient alkylation protocol and does not require harsh conditions, such as heating pyridine or *N*-methylimidazole in the presence of a large excess of the alkyl halide. Even a secondary alcohol such as isopropanol reacted under those conditions, albeit with lower yields. As far as the aqueous work-up is concerned, *n*-octyl pyridinium tetrafluoroborate and *N*-octyl-*N*′-methyl imidazolium (OMIM-BF′-methylimidazolium (OMIM–BF_4) were poorly soluble in water and were extracted at higher aqueous dilutions.

Another major advantage in this method lies in the possibility of changing the counterion by simply using another strong acid in the previous protonation step. Hexafluorophosphate salts were prepared in water and freeze-dried before being redissolved in acetonitrile, whereas triflate and bis-trifluorosulfonimide salts could be directly generated in acetonitrile prior to the Mitsunobu alkylation. By using the standard conditions with *n*-butanol (Table 2), *N*-butylpyridinium and BMIM salts were obtained in good yields. As shown by these results, changing the counterions even increased the yields obtained in the quaternarization process. In particular, the bis-trifluoromethanesulfonimide is the most efficient counterion for this transformation. Nevertheless, we performed most of our study with tetrafluoroborate salts, since they are the cheapest and most used compounds in these series.

Table 1
Yields of alkylation, molar equiv alcohol/PPh_3/DIAD = 5/2/2

Alcohol R–OH	Pyridine·HBF_4	*N*-Methylimidazole·HBF_4
MeOH	100 (100)[a]	100
EtOH	100 (100)[a]	85
n-BuOH	89 (75)[b]	72
n-Octanol	86	83
CH_2=CH–CH_2OH	95 (82)[a]	100
$PhCH_2OH$	92 (85)[a]	84
i-PrOH	60	70

[a] Molar equiv alcohol/PPh_3/DIAD = 1.1/1.5/1.5.
[b] Molar equiv alcohol/PPh_3/DIAD = 1.5/2/2.

Table 2
Yields of alkylation with *n*-BuOH, different counterions

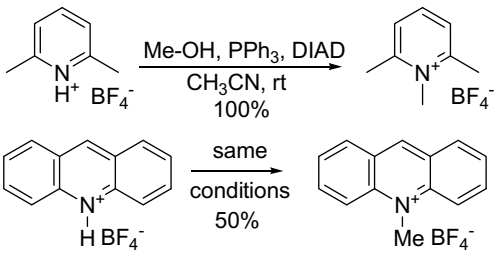
X	Pyridine·HX	MIM·HX
BF_4	89	72
PF_6	95	90
CF_3SO_2O	90	72
$(CF_3SO_2)_2N$	100	100

The choice of the counterion at the protonation stage makes this method a convenient preparation of various pyridinium and imidazolium salts in good yields.

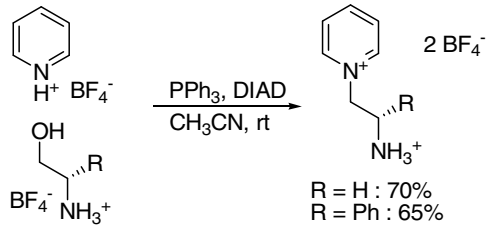
We further focused our attention towards two substrates having a very low nucleophilicity, that is, 2,6-lutidine and acridine. The latter was methylated using our standard conditions, but with longer reaction times (24 h). Acridinium gave a modest 50% yield, whereas 2,6-lutidinium was smoothly quaternarized at room temperature (Scheme 2).

An interesting feature of the Mitsunobu reaction could arise from the ammonium acidity. As depicted in Scheme 3, when both ammonium salts are present in the reaction medium, a selectivity can be obtained owing to the pK_a difference. Tuning the excess of Mitsunobu reagent afforded the selective alkylation of the most acidic ammonium salt, that is, pyridinium, while the amino group of ethanolamine was kept protected under its protonated form.

For instance, the alkylation of pyridinium tetrafluoroborate by ethanolamine tetrafluoroborate was conducted with a 1:1.5:1.5:1.2 M ratio of pyridinium: PPh_3:DIAD:alcohol and afforded a 70% yield. No alkylation occurred on the amino group of ethanolamine and no polymer nor aziridine formation was observed. A similar result was obtained with phenyl glycinol tetrafluoroborate, which was able to alkylate pyridine with a 65% yield under the same conditions. This could provide an efficient route towards various chiral ionic liquids.



Scheme 2. Alkylation of poorly nucleophilic substrates.



Scheme 3. pK_a-directed alkylation: protonation as a protection.

In summary, we have developed a very simple and efficient procedure[10] for the quaternarization of pyridiniums and *N*-methylimidazoliums. The ion-exchange step usually required in the synthesis of ionic liquids could be avoided. Other nitrogen nucleophiles are currently under investigation in our laboratory.

Acknowledgements

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10. The following procedure for the synthesis of BMIM·BF_4 is illustrative: An ice-cold methanolic solution of *N*-methylimidazole was treated with an equimolar amount of aqueous HBF_4. After stirring 15 min at rt, the solvents were removed in vacuo. The salt obtained can be either taken-up in water and freeze-dried or dried under vacuum. 1 mmol of this salt was dissolved in anhydrous acetonitrile (10 mL). Triphenylphosphine (2 mmol) and *n*-butanol (5 mmol) were added, followed by a dropwise addition of diisopropyl azodicarboxylate (2 mmol). The resulting pale orange solution was stirred 15 h at rt and concentrated in vacuo. The residue was extracted with water (10 mL), the aqueous layer washed with ether (4 × 10 mL). Evaporation to dryness or freeze-drying afforded BMIM·BF_4 as a colourless oil. In case of residual starting *N*-methylimidazolium salt, the ionic liquid can be dissolved in dichloromethane and filtered through a pad of potassium carbonate. Although most of these compounds were already described in the literature, we have listed below their NMR data in D_2O, as their spectra are often given in different solvents such as acetone-d_6, CD_2Cl_2 or $CDCl_3$/DMSO-d_6. Purities were checked with BMIM, BF_4 and *N*-butylpyridinium, BF_4, as satisfactory elemental analyses were obtained for these compounds.
N,N′-Dimethylimidazolium tetrafluoroborate:[9a] ^{1}H NMR (D_2O, 300 MHz): 3.76 (s, 6H), 7.28 (s, 2H), 8.50 (s, 1H); ^{13}C NMR (D_2O, 75 MHz): 35.5, 123.3, 136.5.
N-Ethyl, N′-ethylimidazolium tetrafluoroborate (EMIM, BF_4):[9a] ^{1}H NMR (D_2O, 300 MHz): 1.45 (t, $J = 7.4$ Hz, 3H), 3.84 (s, 3H), 4.18 (t, $J = 7.4$ Hz, 2H), 7.37 (s, 1H), 7.44 (s, 1H), 8.65 (s, 1H).
N-Butyl, N′-methylimidazolium tetrafluoroborate (BMIM, BF_4):[6b] ^{1}H NMR (D_2O, 300 MHz): 0.87 (t, $J = 7.4$ Hz, 3H), 1.26 (hex, $J = 7.7$ Hz, 2H), 1.79 (quint, $J = 7.0$ Hz, 2H), 3.83 (s, 3H), 4.14 (t, $J = 7.0$ Hz, 2H), 7.36 (d, $J = 1.5$ Hz, 1H), 7.41 (d, $J = 1.5$ Hz, 1H), *H-2 exchanged in D_2O*; ^{1}H NMR (acetone-d_6, 300 MHz): 0.92 (t, $J = 7.4$ Hz, 3H), 1.36 (hex, $J = 7.7$ Hz, 2H), 1.90 (quint, $J = 7.4$ Hz, 2H), 4.02 (s, 3H), 4.33 (t, $J = 7.3$ Hz, 2H), 7.70 (s, 1H), 7.77 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (acetone-d_6, 75 MHz): 13.2, 19.4,32.2, 36.0, 49.6, 122.8, 124.2, 137.1.
N-Methyl, N′-octylimidazolium tetrafluoroborate (OMIM, BF_4): ^{1}H NMR (D_2O, 300 MHz): 0.81 (t, $J = 6.6$ Hz, 3H), 1.15–1.3 (m, 10H), 1.81 (quint, $J = 7.2$ Hz, 2H), 3.84 (s, 3H), 4.13 (t, $J = 7.0$ Hz, 2H), 7.38 (s, 1H), 7.42 (s, 1H), 8.65 (s, 1H).
N-Allyl, N′-methylimidazolium tetrafluoroborate:[9b] ^{1}H NMR (D_2O, 300 MHz): 3.83 (s, 3H), 4.74 (d, $J = 6.2$ Hz, 2H), 5.30 (d, $J = 18.6$ Hz, 1H), 5.38 (d, $J = 10.4$ Hz, 3H), 5.90–6.05 (m, 1H), 7.38–7.40 (m, 2H), 8.66 (s, 1H).
N-Benzyl, N′-methylimidazolium tetrafluoroborate:[9c] ^{1}H NMR (D_2O, 300 MHz): 3.82 (s, 3H), 5.32 (s, 2H), 7.25–7.40 (m, 7H), 8.69 (s, 1H).
N-Isopropyl, N′-methylimidazolium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 1.48 (d, $J = 6.8$ Hz, 6H), 3.82 (s, 3H), 4.56 (hept, $J = 6.6$ Hz, 1H), 7.36 (d, $J = 1.7$ Hz, 1H), 7.48 (d, $J = 1.7$ Hz, 1H), 8.70 (s, 1H).
N-Methylpyridinium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 4.38 (s, 3H), 8.03 (t, $J = 6.7$ Hz, 2H), 8.52 (t, $J = 7.8$ Hz, 1H), 8.76 (d, $J = 6.3$ Hz, 2H); ^{13}C NMR (D_2O, 75 MHz): 48.4, 128.2, 145.3, 145.6.
N-Ethylpyridinium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 1.60 (t, $J = 7.4$ Hz, 3H), 4.61 (q, $J = 7.4$ Hz, 2H), 8.02 (t, $J = 6.8$ Hz, 2H), 8.50 (t, $J = 7.8$ Hz, 1H), 8.82 (d, $J = 5.7$ Hz, 2H); ^{13}C NMR (D_2O, 75 MHz): 15.5, 57.2, 128.1, 143.8, 145.3.
N-Butylpyridinium tetrafluoroborate:[9d] ^{1}H NMR (D_2O, 300 MHz): 0.91 (t, $J = 7.3$ Hz, 3H), 1.32 (hex, $J = 7.5$ Hz, 2H), 1.96 (quint, $J = 7.5$ Hz, 2H), 4.58 (t, $J = 7.3$ Hz, 2H), 8.03 (t, $J = 6.8$ Hz, 2H), 8.51 (td, $J = 7.8$, 1.1 Hz, 1H), 8.80 (d, $J = 5.5$ Hz, 2H); ^{13}C NMR (D_2O, 75 MHz): 12.5, 18.6, 32.5, 61.6, 128.1, 144.1, 145.3.
N-Octylpyridinium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 0.82 (t, $J = 6.4$ Hz, 3H), 1.5–1.7 (m,10H), 1.99 (quint, $J = 7.5$ Hz, 2H), 4.58 (t, $J = 7.3$ Hz, 2H), 8.03 (t, $J = 7.1$ Hz, 2H), 8.51 (t, $J = 7.9$ Hz, 1H), 8.80 (d, $J = 5.6$ Hz, 2H).
N-Allylpyridinium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 5.21 (d, $J = 6.2$ Hz, 2H), 5.46 (d, $J = 17.4$ Hz, 1H), 5.53 (d, $J = 10.4$ Hz, 1H), 6.15 (m, 1H), 8.07 (t, $J = 7$ Hz, 2H), 8.55 (t, $J = 7.8$ Hz, 1H), 8.82 (d, $J = 4.9$ Hz, 2H); ^{13}C NMR (D_2O, 75 MHz): 63.4, 122.9, 128.2, 129.9, 144.2, 145.8.
N-Benzylpyridinium tetrafluoroborate:[2] ^{1}H NMR (D_2O, 300 MHz): 5.74 (s, 2H), 7.42 (m, 5H), 7.99 (t, $J = 7.1$ Hz, 2H), 8.48 (t, $J = 7.9$ Hz, 1H), 8.83 (d, $J = 5.5$ Hz, 2H); ^{13}C NMR (D_2O, 75 MHz): 64.5, 128.2, 129.0, 129.4, 129.8, 132.6, 144.2, 145.8.
N-Isopropylpyridinium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 1.63 (d, $J = 6.8$ Hz, 6H), 4.90 (hept, $J = 6.6$ Hz, 1H), 8.05 (d, $J = 6.7$ Hz, 2H), 8.59 (t, $J = 7.5$ Hz, 1H), 8.87 (d, $J = 5.6$ Hz, 2H).
N-Methyl-2,6-lutidinium tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 2.77 (s, 6H), 4.05 (s, 3H), 7.69 (d, $J = 7.9$ Hz, 2H), 8.15 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (D_2O, 75 MHz): 21.0, 39.7, 127.0, 143.9, 155.8.
N-(2-Aminoethyl)pyridinium bis-tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 3.70 (t, $J = 6.4$ Hz, 2H), 4.90 (t, $J = 6.4$ Hz, 2H), 8.15 (t, $J = 6.2$ Hz, 2H), 8.64 (t, $J = 6.6$, 1H), 8.93 (d, $J = 6.5$ Hz, 2H).
N-[(2S)-2-Amino-2-phenylethyl]pyridinium bis-tetrafluoroborate: ^{1}H NMR (D_2O, 300 MHz): 4.17 (d, $J = 7.7$ Hz, 2H), 6.25 (t, $J = 7.7$ Hz, 1H), 8.11 (t, $J = 6.8$ Hz, 2H), 8.59 (t, $J = 6.7$, 1H), 9.04 (d, $J = 6.0$ Hz, 2H).