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Mitsunobu alkylation of imidazole: a convenient route to chiral ionic liquids

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Abstract—The Mitsunobu protocol offers a convenient route from imidazole to N-alkyl-substituted imidazoles, precursors to imidazolium-based ionic liquids, and is particularly useful for preparing chiral ionic liquids.

Imidazole functional group plays important roles in numerous bioactive compounds.[1] Recently, the interest in this heterocyclic system has widened as it is a precursor to a class of compounds called room temperature ionic liquids.[2] Ionic liquids, of which imidazolium salts are most widely used, have gained initial notice of synthetic chemists as environmentally friendly 'green' organic solvents, and continue to hold their attention as reaction catalysts or promoters.[3] While imidazolium-based ionic liquids are generally of type that includes two different unfunctionalized alkyl substituents—methyl and butyl, for example—on N(1) and N(3), and a variety of counter anions, interests in catalytic and promoting activities of these salts have prompted syntheses of novel imidazolium structures containing functionalized alkyl substituents.[4] Of these, chiral ionic liquids have a potential to be used as asymmetric organocatalysts.[5] While initial results of asymmetric inductions by some of the earlier chiral ionic liquid compounds were not particularly encouraging,[6] more recent reports using well designed salts show some promises.[7] As a general rule, a study of asymmetric catalysts is logically conducted using chiral counterparts that faithfully represent the structures of established symmetric (achiral) catalysts. In imidazolium-based ionic liquids, either of the two N-substituents would be a good place to insert a chirality. Therefore, synthetic routes yielding such N-substituted imidazole precursors are sought after.

Imidazoles are generally synthesized via condensation reactions of ring fragments, each at an appropriate oxidation level.[1] A typical example for N(1)-alkylimidazoles is those involving glyoxal [providing C(4) and C(5)], formaldehyde [C(2)] an amine and ammonia.[8] An alkyl substituent on N(1) of imidazoles would come in the form of the amine employed in this approach. A convenient alternative toward N-alkyl-substituted imidazoles would be an alkylation of imidazole nitrogen with suitable electrophiles. The cheap price of imidazole would certainly make this alternative approach seem desirable. Usual S_N2-type alkylations with alkyl halides are, however, not very reliable due to frequent bis-alkylation problems (yielding symmetrical imidazolium salts).[9]

The pK_a of imidazole is ca. 14.5, placing it below carboxylic acids, phenols and imides in the acidity scale.[1] Imidazole would, therefore, be less reactive than these typical nucleophiles in a Mitsunobu-type alkylation. On the other hand, the substrate (imidazole) is cheap, and alcohols, the electrophilic partner in the Mitsunobu-type alkylation and through which the N-substituent would be introduced, occur with a wider diversity than amines or alkyl halides in terms of functionality and chirality, rendering the Mitsunobu approach worth exploring.[10]

When imidazole was reacted with representative alcohols under the usual Mitsunobu conditions, (PPh_3–DEAD or –DIPAD [diethyl or diisopropyl azodicarboxylate]), the N-alkylimidazoles were obtained in yields around 20%. Through the optimization of the reaction

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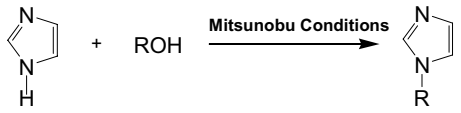
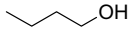
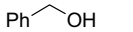
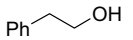
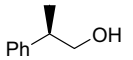
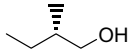
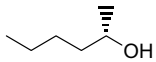
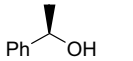
Table 1. Mitsunobu alkylation of imidazole



A: PPh_3-DIPAD (10 eq.) **C:** PBu_3-TMAD (10 eq.)
B: PBu_3-ADDP (1 eq.) **D:** PBu_3-CMBP (10 eq.)

Entry	ROH	Conditions	Yield (%)
1		A	63
2		C	89
3		A	78
4		A	62
5		B	71
6		C	94
7		A	37
8		B	57
9		C	76
10		D	70
11		A	39
12		B	65
13		C	94
14		D	79
15		A	61[a]
16		C	75[a]
17		D	18
18		A	72[b]
19		C	88
20		D	41

[a] With inversion of configuration (>99% ee).
[b] With inversion of configuration (86% ee).

conditions, improved yields were obtained. The results are summarized in Table 1.

When imidazole (20 equiv) was reacted with *n*-butanol in the presence of excess PPh_3–DIPAD (10 equiv each), *N*-butylimidazole was obtained in 63% yield (entry 1). The reaction conditions (*Conditions A*) were devised so that an excessive use of inactive but cheap imidazole substrate and the Mitsunobu reagents would drive the reaction to a maximum extent with a potentially valuable alcohol as the limiting agent. After the reaction was complete, most of the by-products and the unreacted reagents were sufficiently removed through simple acid–base aqueous extractions, and a subsequent flash silica chromatography afforded the desired product in pure form. Under these conditions (*A*), other primary alcohols reacted similarly to give the corresponding N-alkylimidazoles (entries 3 and 4). Chiral primary alcohols with the stereogenic center at the β-position reacted under the *Conditions A* to produce the desired *N*-alkylimidazoles in yields lower than 40% (entries 7 and 11), while chiral secondary alcohols with the stereogenic center at the carbinol carbon fared better under these conditions (*A*) to yield the corresponding chiral imidazoles in 60–70% (entries 15 and 18).

In order to further improve the yields of the reactions, a range of sets of variant Mitsunobu reagents were employed. Empolying PBu_3–ADDP (1,1′-azodicarbonylpiperidine, 1 equiv each, *Conditions B*), the modified protocol developed for Mitsunobu alkylations of nitrogen nucleophiles, the yield with a primary alcohol improved a little (entry 5), while those with the β-branched alcohols improved to ca. 60% (entries 8 and 12).[11] On the other hand, the *Conditions B* were not effective at all with secondary alcohols.

PBu_3–TMAD (*N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide) protocol, a more recent variant, has been known to be particularly effective for less reactive Mitsunobu nucleophiles (with larger pK_a) and sterically bulky alcohols.[12] The results of primary alcohols were similar with PBu_3–TMAD (1 equiv each) to those obtained under the *Conditions B*, while with secondary alcohols the TMAD protocol did produce the desired products, albeit in low yields. Big improvements were observed throughout the every class of alcohols when the PBu_3–TMAD reagents were employed in excess (10 equiv each, *Conditions C*). Yields around 90% were obtained with achiral primary alcohols (entries 2 and 6), while with chiral β-branched primary alcohols (entries 9 and 13) and chiral α-branched secondary alcohols (entries 16 and 19), the yields ranged 75–94%. The product isolation was again very simple under the *Conditions C*. After the reaction was complete, TMAD–H_2 formed was precipitated and filtered off, and the filtrate was subjected to simple acid–base aqueous extractions to remove most of the by-products and the unreacted reagents.

PBu_3–CMBP (cyanomethylenetributylphosphorane) protocol, reported to be effective for Mitsunobu alkylations of nitrogen nucleophiles,[13] resulted in slightly lower yields with chiral β-branched primary alcohols (entries 10 and 14), or much lower yields with chiral secondary alcohols with the stereogenic center at the carbinol carbon (entries 17 and 20) than the PBu_3–TMAD conditions (*C*).

The configuration of the stereogenic carbinol carbon had been inverted in the process of the reaction, which was confirmed by comparing with authentic samples independently prepared with corresponding chiral amines via condensation procedure. In the case of 2-hexanol, the inversion of configuration was virtually complete so that (*R*)-*N*-*sec*-hexylimidazole was produced in >99% ee from (*S*)-2-hexanol (entries 15 and 16). On the other hand, the reaction at the benzylic site was not completely stereoselective and (*S*)-*N*-*sec*-phenethylimidazole of 86% ee was produced from enantio-pure (*R*)-α-methylbenzyl alcohol (entry 18).

N-Substituted imidazoles thus prepared can be converted to imidazolium salts by simple alkylation with appropriate electrophiles. Two of the chiral N-substituted imidazoles prepared in this study, namely *N*-*sec*-hexylimidazole and *N*-*sec*-phenethylimidazole, both having the stereogenic center adjacent to the ring nitrogen, were reacted with MeI to produce the corresponding imidazolium salts in quantitative yields. Both these salts are liquids at room temperature. Further studies

with these and other chiral ionic liquids will be reported in due course.

In conclusion, the Mitsunobu protocol, specifically that using PBu_3–TMAD in excess, offers a convenient route from imidazole to N-alkyl-substituted imidazoles, precursors to imidazolium-based ionic liquids, and is particularly useful for preparing chiral ionic liquids.

Representative procedure of the Mitsunobu alkylation (Conditions C): PBu_3 (10 mmol) and imidazole (20 mmol) were placed in a dry flask. Benzene (30 mL) was added followed by (*S*)-2-hexanol (1 mmol). The mixture was cooled in an ice bath. TMAD (10 mmol) was added. The mixture was stirred at 0 °C for 10 min, then heated to 60 °C overnight. The reaction mixture was diluted with hexane (30 mL) and filtered. The filtrate was extracted with 1 N HCl (2×60 mL). The combined aq phases were washed with EtOAc (2×60 mL). The aq phase was made basic (pH $\sim$ 13) by adding 2 N NaOH. It was then extracted with chloroform (3×60 mL). Drying and concentration of the organic phase yielded the crude product, which was then purified on a flash silica column (EtOAc–MeOH 9:1) to afford (*R*)-*N*-*sec*-hexylimidazole in 75% yield.

Acknowledgements

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