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Stereospecific Synthesis of 1-Alkylimidazole Derivatives *via* Mitsunobu Reactions

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Abstract : 4,5-Dicyanoimidazole has been reacted with racemic and enantiopure alcohols **1** under Mitsunobu conditions to give 1-alkyl-4,5-dicyanoimidazole derivatives **2**, which in turn have been transformed by hydrolysis and decarboxylation into 1-alkylimidazoles **4** in good overall yield and high enantiomeric excess. The absolute stereochemistry of the compounds has been confirmed by synthesizing **4c** through an independent route.

The development of a methodology which allows the N-alkylation of imidazole derivatives with chiral alcohols in a stereocontrolled manner is of outstanding synthetic importance, in light of the interesting and usually stereochemistry-dependent antimycotic,[1] antibacterial,[2] antiprotozoal,[2] and enzyme inhibiting[3] properties of several N-alkylimidazoles.

In the last few years many research groups have been directing their efforts towards the preparation of pure enantiomers of the azole (imidazole or triazole) antifungal drugs, either by stereoselective synthesis or enantiomeric separation, but these efforts have been successful[4-6] only in few cases and never for compounds having the azole moiety directly linked to the stereogenic centre.

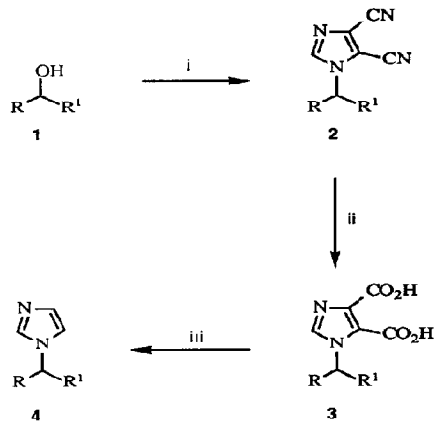
We envisaged in the Mitsunobu reaction[7] a possibility of synthesizing such compounds. Although it has been applied to a wide range of nucleophiles, including heterocyclic compounds such as purines,[8] quinazolin-4(3H)-ones,[9] and toxoflavin derivatives,[10] to our knowledge the Mitsunobu reaction has not been used for the N-alkylation of imidazole derivatives. The only information (no experimental details) in this regard concerns the reaction of both imidazole and 2-methyl-4(5)-nitroimidazole with methanol and 2-phenylethanol: while imidazole itself is unreactive under the usual reaction conditions, the nitroimidazole derivative reacts to give a mixture of N-alkyl-2-methyl-4-nitroimidazole and the corresponding 5-nitro isomer.[7]

Consequently, as part of our research project on antifungal imidazole compounds,[11] we decided to investigate the possibility of performing the alkylation of a suitable imidazole derivative with alcohols **1** *via* the Mitsunobu reaction (Scheme 1). For this purpose, we chose the commercially available 4,5-dicyanoimidazole as the imidazole substrate, since it is symmetrically substituted with two "activating", electron withdrawing groups and because of the possibility of converting the Mitsunobu reaction products **2** into the desired N-alkylimidazoles **4** by hydrolysis and decarboxylation. In order to establish the stereochemical outcome of the Mitsunobu reaction we used both racemic and enantiopure alcohols as the alkylating agents. The results of the reaction are summarized in Table 1.

When diethyl azodicarboxylate (DEAD) was added at 0 °C to a THF solution of 4,5-dicyanoimidazole, triphenylphosphine, and a primary or secondary alcohol **1**, the Mitsunobu reaction occurred readily (0.5 h) to give the alkylated products **2** in moderate to good yields.[12] The reaction did not work when tertiary alcohols

were used. Enantiomerically pure alcohols always afforded a single enantiomer of **2** in high enantiomeric excess.[13]

SCHEME 1



Reagents: i) 4,5-dicyanoimidazole, DEAD, Ph_3P; ii) NaOH, then HCl; iii) heat.
For R, R^1 and stereochemistry see Tables 1 and 2.

Table 1. Mitsunobu Reaction of Alcohols 1 with 4,5-Dicyanoimidazole

Compd[a]	R	R^1	configuration of starting **1**	yield of **2** (%)[b]	$[\alpha]_D^{20}$[c]	ee (%)[d]
2a	H	H		45		
2b	Me	n-Hexyl	R,S	68		
2c	Me	n-Hexyl	R	65	+1.1 (c=2.91)[e]	97
2d	Me	n-Hexyl	S	67	-1.0 (c=2.18)[e]	97
2e	Me	Benzyl	R,S	40		
2f	Me	Benzyl	R	39	+58.8 (c=0.85)	98
2g	Et	Phenyl	R,S	55		
2h	Et	Phenyl	R	55	-44.3 (c=2.82)	41

[a]The reactions were performed in THF at 0°C to room temperature for 0.5 h with equimolar amounts of all the reagents. [b]Not optimized yields referring to isolated and purified materials. [c]Measured in chloroform solution. [d]The enantiomeric excess (ee) was determined by 300-MHz ^1H NMR analysis in the presence of the chiral shift reagent Eu(hfc)$_3$. [e]Determined with a mercury lamp at 546 nm.

When (R)-(+)-1-phenyl-1-propanol was tested, a 7:3 mixture of enantiomers **2h** was obtained, probably as a consequence of a reaction pathway involving partial retention of configuration at the benzylic carbon atom.[14,15]

Next we examined the hydrolysis-decarboxylation procedure. For this purpose, the dicyanoimidazole derivatives **2b,c,e,f,g,h** were treated with 10 N NaOH in EtOH under reflux for 24 h, followed by acidification of the solution, to give the dicarboxylic acids **3b,c,e,f,g,h**. Usual methods of decarboxylation[16] did not give good results: finally we found out that a clean conversion of **3b,c,e,f,g,h** to **4b,c,e,f,g,h** could be performed in good yield by simply heating them in diphenyl ether at reflux for 0.5 h. ^{1}H NMR analysis in the presence of chiral shift reagents[13] showed ees ≥ 97% for compounds **4c** and **4f**, revealing that no racemisation had occurred during both the final steps, while compound **4h** was obtained in racemic form (Table 2).

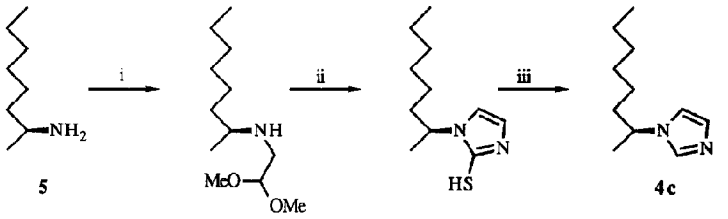
Table 2. Synthesis of 1-Alkylimidazoles 4

Compd	R	R^1	absolute configuration of 4	overall yield of 4 (%)[a]	$[\alpha]_D^{20}$[b]	ee (%)[c]
4b	Me	n-Hexyl	R,S	62		
4c	Me	n-Hexyl	S	50	+16.0 (c=1.1)[d]	97
4e	Me	Benzyl	R,S	44		
4f	Me	Benzyl	S	40	+93.3 (c=0.75)	98
4g	Et	Phenyl	R,S	25		
4h	Et	Phenyl	S	28	0	**0**

a-d: see *b-e* in Table 1

To establish the absolute configuration of the products, we synthesized **4c** starting from (S)-(+)-2-octylamine **5**,[7] by an independent route (Scheme 2).

SCHEME 2



5 **4c**

Reagents: i) bromoacetaldehyde dimethyl acetal; ii) KSCN, HCl; iii) Ni/Ra

Compound **4c** was prepared in good overall yield and was shown to be identical (^{1}H NMR, IR, MS,

optical rotation) to the product obtained by the Mitsunobu-hydrolysis-decarboxylation procedure. It is interesting to note that the sequence reported in Scheme 2 could be an interesting alternative way to prepare chiral 1-alkylimidazoles; more work in this direction is under study in our laboratory.

In conclusion, we have demonstrated that N-alkylimidazoles can be prepared in good overall yield through a three-step sequence starting from 4,5-dicyanoimidazole and alcohols. This procedure has a major advantage over more conventional routes (i.e. alcohol → alkyl halide → N-alkylimidazole) in that it allows the unprecedented preparation of enantiomerically pure derivatives with an absolute configuration opposite to that of the starting alcohols, as expected on the basis of the Mitsunobu reaction mechanism. In contrast, benzylimidazole derivatives racemise during the final step.

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12) Not optimized yields refer to isolated and purified materials. All the compounds gave satisfactory microanalyses and showed spectroscopic data in accordance with the assigned structures.

13) The enantiomeric excess (ee) was determined by 300-MHz ^{1}H NMR analysis ($CDCl_3$) in the presence of the chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] [Eu(hfc)$_3$]. In the case of **4f**, europium(III) tris(*d,d*-dicampholylmethanate) has been used.

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