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NEW SYNTHETIC REACTIONS BASED ON 1-METHYL-2-FLUOROPYRIDINIUM SALTS. STEREOSPECIFIC PREPARATION OF PRIMARY AMINES FROM ALCOHOLS

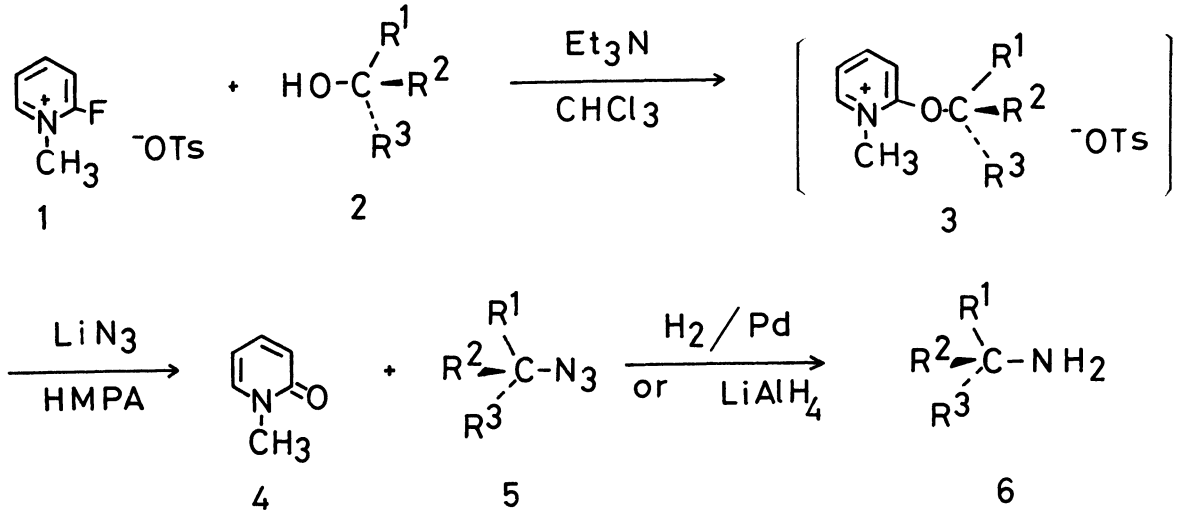
Ko HOJO, Susumu KOBAYASHI, Kenso SOAI, Shigeru IKEDA, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Treatment of various alcohols with 1-methyl-2-fluoropyridinium salt and lithium azide afforded corresponding alkyl azides, which were converted to primary amines by reduction. The overall reactions proceeded with inversion of configuration.

Sterically controlled introduction of amino group is of special synthetic importance, and extensive investigations have been conducted in recent years.[1] We now wish to report stereospecific two-step synthesis of primary amines starting from alcohols using 2-fluoropyridinium salt.[2]

2-Alkyloxpyridinium salt formed 'in situ' from alcohols and 2-fluoropyridinium salts reacted with azide ion to give the corresponding alkyl azides in good yields.[3] The method seems to have general applicability in the synthesis of various primary amines, since the conversion of alkyl azides to primary amines is well known to be effected under a variety of mild reductive conditions where most of the functional groups present in a molecule remain intact.[4]

High stereospecificity was observed in the reaction of optically active alcohols; for instance, (R)-(-)-2-octanol, $[\alpha]_D^{20}$ -9.7° (neat), when treated with 1 and lithium azide, and then reduced with $LiAlH_4$, afforded (S)-(+)-2-amino-octane in good yields; $[\alpha]_D^{19}$ +6.08° (c 1.30, benzene), lit: $[\alpha]_D$ +6.59° (c 5.95, benzene).[5] Acetyl derivative ; $[\alpha]_D^{24}$ -23.3° (c 0.658, benzene).



Typical experimental procedure is illustrated below; to a stirred suspension of 1-methyl-2-fluoropyridinium tosylate (312mg, 1.1mmol) in dry $CHCl_3$ (6ml) were added 1-dodecanol (186mg, 1.0mmol) and triethylamine (110mg, 1.1mmol) in $CHCl_3$ (6ml). A homogeneous solution was stirred at room temperature for 30 min under an argon atmosphere. Chloroform was evaporated in vacuo, and to the residual solid were added dry HMPA (5ml) and anhyd. LiN_3 (97.8mg, 2.0mmol). The solution was kept at 80°C for one hour with stirring. The reaction mixture was cooled, and poured to water, and 1-azidododecane was extracted with ether. The extracts were washed with brine to remove 1-methyl-2-pyridone and HMPA, dried, and concentrated in vacuo. The $LiAlH_4$ reduction of the crude products in ether at room temperature, followed by purification of the products as hydrochloride provided 1-aminododecane (181mg, 94%); Acetyl derivative; mp 55.5-56.5°C; IR (KBr) 3300, 1635cm^{-1}.

Various primary amines prepared according to the present procedure are recorded in the table.

Table. Preparation of primary amines from alcohols.

Entry No.	ROH	RNH_2	Isolated overall yield (%)	
1	$CH_3(CH_2)_{10}CH_2OH$	$CH_3(CH_2)_{10}CH_2NH_2$	94	
2	$C_6H_5CH_2OH$	$C_6H_5CH_2NH_2$	77	
3	$C_6H_5CH=CHCH_2OH$	$C_6H_5CH=CHCH_2NH_2$	78	
4	dl-$C_6H_5CH(CH_3)OH$	dl-$C_6H_5CH(CH_3)NH_2$	75	
5	(R)-(-)-2-octanol	(S)-(+)-2-aminooctane	77	
6	3β-cholestanol	3α-aminocholestane	77	Ac. der. mp 212-213°C[6]

It is noted that alicyclic alcohol such as 3β-cholestanol was also successfully converted to the corresponding amines with invertion of configuration.

Further investigations are in progress.

References and Note

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