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A novel reduction of pyridinemethanols by samarium diiodide

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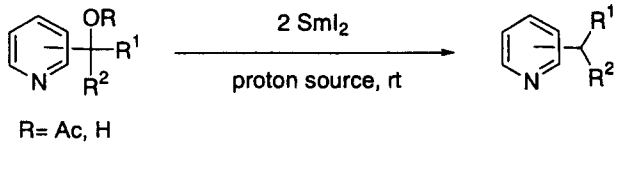
Abstract

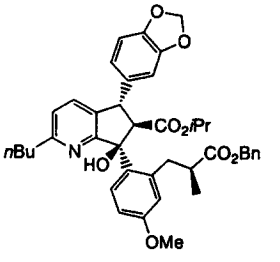
An efficient synthesis of alkylpyridine derivatives by SmI_2 mediated deoxygenation of pyridinemethanol derivatives is described.

Keywords: Samarium diiodide; deoxygenation; pyridinemethanols; alkylpyridine.

Alkylpyridine derivatives are important and common building blocks for drug candidates.[1] Deoxygenation of pyridinemethanol derivatives is frequently employed in order to prepare these compounds.[1c,2] However, in some cases it is difficult to reduce the sterically hindered hydroxy group. In fact, the deoxygenation of the pyridinemethanol **1**, which is the intermediate for an endothelin antagonist,[3] could not be achieved by known methods such as hydrogenation or various combinations of a Lewis acid and a hydride.[4] Although SmI_2 mediated deoxygenation has been widely reported as an extremely mild and powerful method, it is limited to α-oxygenated carbonyl compounds or nitriles,[5] and their related compounds.[6] Consideration of the mechanism prompted us to extend the use of SmI_2 to the reduction of pyridinemethanols. In this communication, we wish to report a mild and effective SmI_2 mediated deoxygenation of pyridinemethanol derivatives and its application to the complex molecule **1**.



R= Ac, H



1

The direct dehydroxylation of pyridinemethanols was carried out at room temperature by using 2.5 equiv. of an SmI_2–THF solution in the presence of HMPA and 1.3 equiv. of pivalic acid. As shown in

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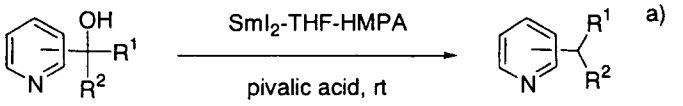
Table 1
Deoxygenation of pyridinemethanols

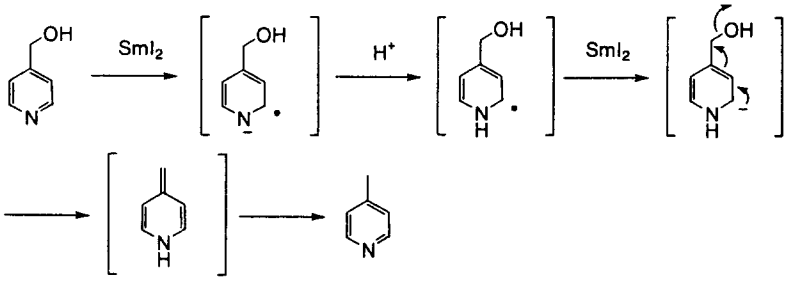


Run	pyridine	R^1	R^2	Reaction time	Yield(%)
1	4-	H	H	<10 min	60
2	4-	H	H	<10 min	59 b)
3	4-	Ph	H	<10 min	63
4	4-	Ph	H	<10 min	38 b)
5	2-	Ph	H	<10 min	49
6	2-	Ph	H	12 h	no reaction b)
7	4-	Ph	Me	<10 min	58
8	2-	Ph	Me	<10 min	54
9	4-	nBu	Me	<10 min	62
10	2-	nBu	Me	12 h	5

a) A pivalic acid - THF solution (0.17 mol dm^{-3}, 0.96 mmol) was added dropwise to a mixture of pyridinemethanols (0.754 mmol), HMPA (1.13ml), and a SmI_2-THF solution (0.1 mol dm^{-3}, 1.89 mmol) at room temperature. b) A SmI_2-THF solution (0.1 mol dm^{-3}, 3.0 eq.) was added to a mixture of pyridinemethanol and tBuOH (1.5 eq.).

Table 1, 2- and 4-pyridine derivatives were smoothly deoxygenated within 10 min in moderate yield except for 2-(1-hydroxy-1-methylpentyl)pyridine (run 10). In this case, some decomposition took place, and the product was obtained in only 5% yield together with 23% of the unreacted substrate after 12 h. Neither 3-pyridyl nor phenyl analogues were deoxygenated under the reaction conditions. Similar to the case of deoxygenation of α-hydroxy esters,[7] the yield was lower (run 4) or the reaction did not proceed (run 6) when *t*BuOH was used as a proton source instead of pivalic acid without HMPA.

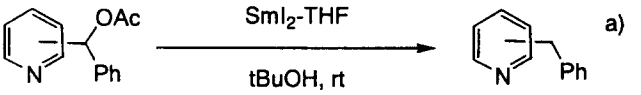
The reaction might go through the path as shown in Scheme 1. Initial electron transfer to the 2-position of the pyridine ring followed by successive protonation and another electron transfer gave the corresponding carbanion which might induce elimination of the hydroxy group to give the deoxygenated compound.[8]



Scheme 1.

The deoxygenation of acetoxy derivatives was also examined. The reaction was run at room temperature by using 3.0 equiv. of an SmI_2–THF solution in the presence of 1.5 equiv. of *t*BuOH. As shown in

Table 2
Deoxygenation of pyridylmethyl acetates

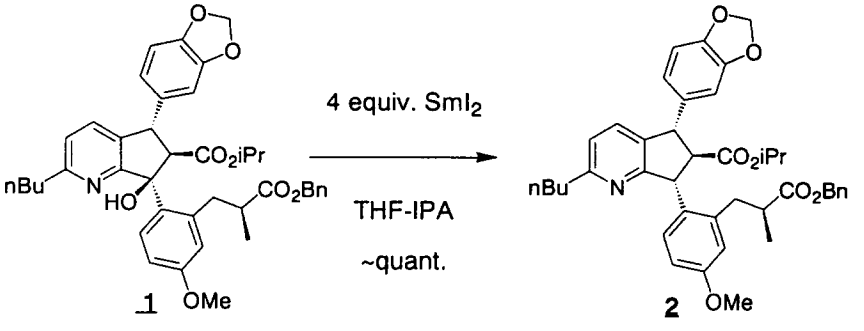


Run	pyridine	Reaction time	Yield(%)
1	4-	<10 min	82
2	3-	30 min	56
3	2-	<10 min	78

a) A SmI_2-THF solution (0.1 mol dm^{-3}, 3.0 eq.) was added to a mixture of pyridylmethyl acetates and tBuOH (1.5 eq.).

Table 2, 2- and 4-pyridyl derivatives were smoothly deoxygenated in good yields. The 3-pyridyl analogue was also deoxygenated in moderate yield (run 2) while the phenyl analogue (diphenylmethylacetate) was not at all under the reaction conditions.

We then tried to apply the deoxygenation to the complex molecule **1** as shown in Scheme 2. When the reaction was carried out using 4 equiv. of SmI_2–THF in the presence of isopropanol as a proton source at room temperature, the desired product **2** was obtained not only in quantitative yield but in a stereocontrolled manner. The stereochemical course might be due to thermodynamically favored protonation to the enamine intermediate.



Scheme 2.

The catalytic use of expensive SmI_2 is currently under investigation.

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