Iodine in Dichloromethane – A Simple Method for Selective Cleavage of Prenyl Ethers

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Abstract: Treatment of prenyl (Pre) ethers of simple alcohols, carbohydrates, steroids, with I_2 in CH_2Cl_2 in the presence of 3\AA molecular sieves, constitutes an effective method for their deprotection. This method tolerates other etheral functionalities such as acetals, allyl, *t*-butyldiphenylsilyl or benzyl groups as well as base labile groups such as acetates. This method applied to a prenyl aryl ether gave rise to a 2,2-dimethylchroman derivative in an acceptable yield.

Key words: chromans, iodine, prenyl ethers, protecting groups

Selective protection and, more importantly, deprotection of functional groups play a central role in organic synthesis as shown by the number of monographs and reviews dedicated to this topic.^{1,2} Because hydroxyl groups are present in a large number of compounds of biological and synthetic interest (carbohydrates, macrolides, polyethers, prostaglandins, etc.), a plethora of hydroxyl protecting groups has been developed. However, because only very few of them have found wide applications, the development of new protecting groups and the improvement of existing methods of deprotection continue to be the subject of intensive research.

In connection with an ongoing program directed to the development of a new generation of safety-catch protecting groups,³ we needed a hydroxyl protecting group stable under both acidic and basic conditions and cleaved under neutral conditions.

The allyl group, one of the most frequently used protective group in carbohydrate chemistry, ^{1b,2b} does fulfill acid-base requirements but none of the numerous methods of deprotection reported for this protecting group was satisfactory for our purpose.^{1b,4} Indeed, most of them use drastic conditions, are capricious⁵ or not suitable for large scale preparations. The allyl group being dismissed, we focussed our attention to a related allyl group: the prenyl (3-methylbut-2-enyl) group. Only, three methods of cleavage of prenyl ethers have been described⁶ but still none of them meet our requirements.

In 1994, Cossy and coworkers, published a simple and mild method for the deprotection of prenyl esters using iodine in cyclohexane as a reagent.⁷ We decided to study the applicability of this protocol to the removal of prenyl protecting groups. We first examined the reactivity of iodine towards 3-*O*-prenyl diacetone glucose **1a** under various experimental conditions.⁸ As seen in the Scheme, the products obtained are very dependent on the solvent used.



Scheme

The cleavage of the prenyl ether of diacetone glucose proceeded best by using 1.5 equivalent of iodine in dichloromethane, at room temperature, in the presence of powdered 3Å molecular sieves. Without sieves, at room temperature, only polar compounds were observed. In methanol, in the presence of 20 mol% of I_2 , selective cleavage of the 5,6-*O*-isopropylidene ketal of **1a** occurred.⁹ In aqueous THF, the iodohydrin **4** was obtained in good yield. This new protocol for cleavage of prenyl ethers was successfully applied to various substrates and the results are listed in the Table.¹⁰

With substrates containing acid-labile protecting groups (entries 1–3, 9, 10), 3Å molecular sieves were added to the reaction mixture in order to trap HI, which is presumably formed during the reaction. Interestingly, treatment with 1.2 equivalent of I_2 of compound **1c**, containing a primary and a secondary prenyl ether, cleaved only the prenyl group attached to the secondary group functionality in an acceptable yield. The applicability of this method was successfully tested in the presence of acetonides (entries 1)

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Entry	Substrate	I ₂ (equiv)	Time (h)	Product	Isolated yield (%)
1	OPre O O O O O	1.5	8	OH COH	72
	1b			2b	
2	PreO-	1.2	2	R 2c1	54
3	Preo O O O O O O O O O O O O O O O O O O O	3	3	HOODBROOD 2c2 R=H	50
4	IC OPre	1.5ª	1	с он 2d	92
5	OPre 1e	3ª	3 ^b	PH OH 2e	79
6	OPre	1.5ª	1 ^b	С 2f	75
7	PreO OAll 1g	3 ^{a,c}	1.5 ^b	HO OAII	80
8	PreO OAc 1h	1.5ª	1	HO OAc 2h	77
9	PreO OTBS	1.5	4	HO OTBS 2i	22
10	PreO OTBDPS 1j	2	3	HO OTBDPS 2j	70
11	Preo OPre	1.5ª	1	2к	56

Table Selective Cleavage of Prenyl Ethers with Iodine in CH₂Cl₂

^a No molecular sieves was added.

 $^{\rm b}$ Reaction carried out at 10 °C for entries 5 and 7 and at 0 °C for entry 6.

^c The mixture of the two products obtained (**2g** and the corresponding *vic*-diiodo compound) was treated by zinc in ethanol at 60 °C.

and 2), benzyl (entry 2), acetate (entry 8), *t*-butyldiphenylsilyl (entry 10) groups and a conjugated ketone (entry 5).

Unfortunately, even in the presence of sieves, the *O*-prenyl group could not be removed selectively in the presence of a *t*-butyldimethlysilyl group (entry 9). In the case of compound **1g**, containing an allyl group, the desired compound **2g** was obtained along with the product of addition of iodine to the double bond of the allyl group (ratio 1/3 in favor of the *vic*-diiodo compound). Anyhow, treatment of a mixture of these two compounds with zinc in hot ethanol gave exclusively **2g** in good yield (entry 7).

Another interesting feature of this method is that reaction of iodine to the aryl prenyl ether **1k** led to the 3-iodo chroman derivative **2k** in moderate yield. Mechanistic aspects of this transformation have not been investigated yet but a plausible pathway may start by a [1,3]-sigmatropic rearrangement with formation of an *o*-prenyl phenol¹¹ followed by an electrophilic cyclization. 3-Iodo-2,2dimethylchroman derivatives are precursor of 2,2-dimethylchromenes, a very common structural motif in flavanoids.¹²

In conclusion, the use of iodine in dichloromethane provides a mild and efficient means of removing prenyl ethers in the presence of a number of other functionalities. Studies of the mechanism of this cleavage of prenyl ethers as well as of other cleavage techniques are currently underway.

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