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Highly selective cleavage of prenyl ethers by means of a $TiCl_4$-*n*-Bu_4NI mixed reagent

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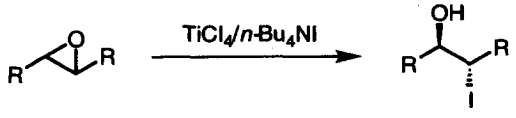
Abstract

Treatment of the prenyl ether of ethyl salicylate with a $TiCl_4$-*n*-Bu_4NI mixed reagent resulted in cleavage of the C–O bond to provide ethyl salicylate in quantitative yield. On the other hand, no cleavage reaction was observed when ethyl *p*-prenyloxybenzoate was used as a substrate. In this system, the cleavage reaction of ethers proved to be accelerated by the chelating effect of a neighboring group in the substrate. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: deprotection; ethers; titanium; titanium compounds; ammonium salts.

Selective removal of a protecting group has been important for organosynthetic methodology.[1] Among numerous deprotection methods, cleavage of the ether linkage is usually performed under basic conditions or by using Lewis acids (BBr_3[2] or Me_3SiI[3]). We have already reported the C–O bond cleavage reaction of epoxides using a titanium tetrachloride–tetrabutylammonium iodide mixed reagent to provide iodohydrin (Scheme 1).[4] This reagent is readily prepared by mixing $TiCl_4$ and *n*-Bu_4NI at 0°C. Here we wish to report that the $TiCl_4$-*n*-Bu_4NI[5] system cleaves prenyl ethers selectively in the presence of allyl or crotyl ethers.[6]



Scheme 1.

Treatment of tetrabutylammonium iodide (1.1 mmol) with $TiCl_4$ (1.1 mmol) in dichloromethane at 0°C provided a dark-red solution. After being stirred for 10 min, an addition of the prenyl ether of 1-octanol (**1a**, 1.0 mmol) afforded deprotected 1-octanol (**2a**) quantitatively (Scheme 2). No trace amount of 1-octanol was obtained when the corresponding allyl or methyl ether was used as a substrate under the

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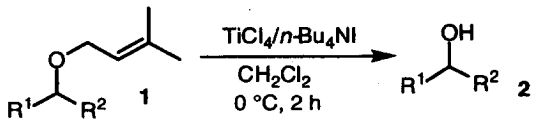
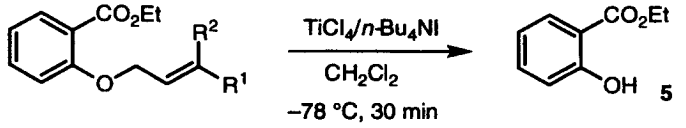
same reaction conditions. The reaction of secondary alcohol prenyl ether **1b** instead of **1a** provided 2-decanol in moderate yield. We then examined cleavage of aryl ethers by means of a $TiCl_4$-*n*-Bu_4NI mixed reagent (Scheme 3). The prenyl and crotyl ethers of ethyl salicylates **3a** and **4** were cleanly converted into phenol **5** at −78°C, while the corresponding allyl ether was much less reactive to provide **5** in only 18% yield under the same reaction conditions. No reaction took place in the case of the corresponding methallyl ether. Selective cleavage of prenyl ether **3a** was achieved in the co-existence of crotyl ether **4**. In this case, crotyl ether **4** was recovered quantitatively.

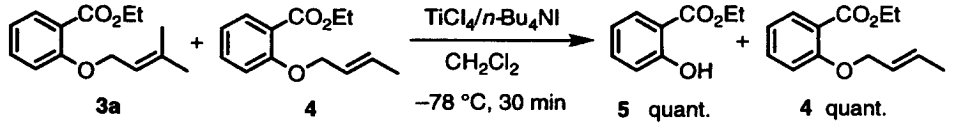


a: R^1 = *n*-C_7H_{15}, R^2 = H: quant
b: R^1 = *n*-C_9H_{19}, R^2 = CH_3: 64%

Scheme 2.



3a: R^1 = R^2 = Me quant. **4**: R^1 = Me R^2 = H 94%



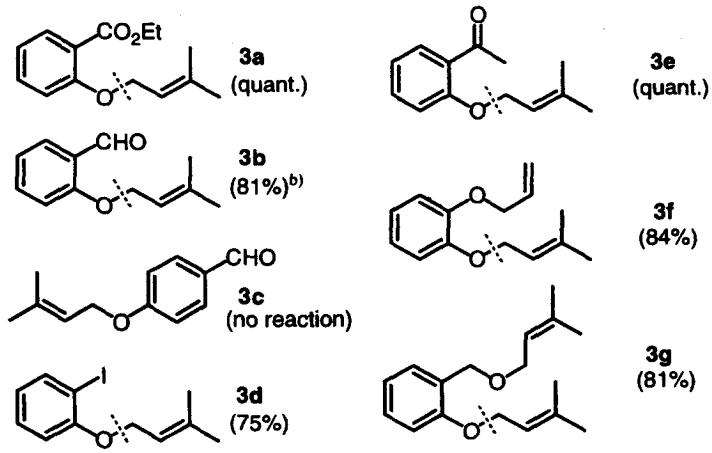
Scheme 3.

The cleavage reaction of various aryl prenyl ethers is summarized in Table 1.[7] Several comments are worth noting: (1) various aryl prenyl ethers possessing a directing group such as a carbonyl group, iodine atom, or ether in the *ortho*-position proved to be easily cleaved by means of $TiCl_4$-*n*-Bu_4NI combination; (2) on the contrary, no reaction occurred in the case of 4-prenyloxybenzaldehyde (**3b**) (based on these results, this cleavage reaction is obviously assisted by the coordination of the hetero atom to titanium);[8] (3) the prenyl ether was selectively removed in the case of catechol allyl prenyl ether (**3f**) (catechol, which would be produced from the cleavage of both ether linkages, could not be detected in the reaction mixture); and (4) benzylic prenyl ether was not reactive at −78°C and selective cleavage of aryl prenyl ether in preference to benzyl prenyl ether was achieved in the reaction of **3g** with the $TiCl_4$-*n*-Bu_4NI system.

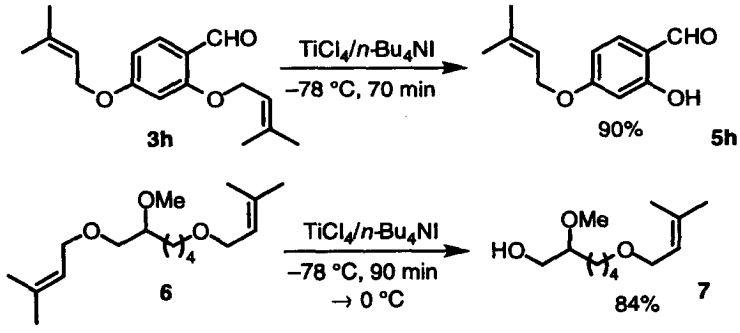
In the case of diprenyl ether **3h**, regioselective cleavage of the nearer prenyl group to the carbonyl group was observed (Scheme 4).[9] No trace amount of dihydroxybenzaldehyde was obtained.[10] Similar regioselectivity was observed in the reaction of diprenyloxyalkane **6**. These selectivities could be attributed to the chelating effect of the neighboring group which coordinates to the titanium species.

We are tempted to assume the following reaction pathway for this chelation-mediated cleavage of prenyl ethers (Scheme 5). The reaction of *n*-Bu_4NI with $TiCl_4$ might provide an ate-complex type iodotitanium species. Coordination of a heteroatom such as carbonyl oxygen onto the titanium center could increase the nucleophilicity of the iodide which could attack the carbon of the C–O bond to remove the prenyl group.

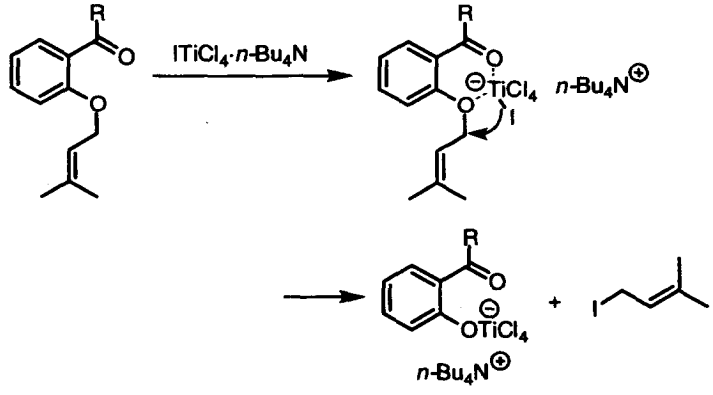
Table 1
Cleavage reaction of aryl prenyl ethers by means of the $TiCl_4$-*n*-Bu_4NI system[a]



a) All reactions were performed at –78 °C. Substrate (1.0 mmol), $TiCl_4$ (1.1 mmol), and *n*-Bu_4NI (1.0 mmol) were employed. The reaction mixtures were stirred for 10 - 60 min. b) The product was isolated as 2-acetoxybenzaldehyde because of the volatility of 2-hydroxybenzaldehyde.



Scheme 4.



Scheme 5.

Typical procedure for the selective cleavage of aryl prenyl ether is as follows: To a solution of $TiCl_4$ (2.0 mmol) in CH_2Cl_2 was added *n*-Bu_4NI (2.0 mmol) in CH_2Cl_2 at 0°C. After being stirred for 10 min, to the resulting dark-red solution was added 2,4-diprenyloxybenzaldehyde (1.0 mmol) at –78°C and the mixture was stirred for 70 min. The whole mixture was poured into saturated ammonium chloride and extracted with hexane (20 ml×3). The combined organic extract was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica-gel column chromatography gave 2-hydroxy-4-prenyloxybenzaldeyde (**5h**, 0.17 g, 0.9 mmol) in 90% yield.

Acknowledgements

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7. Treatment of phenyl prenyl ether at –78°C for 90 min afforded phenol in 74% yield.
8. Kajiro, H.; Mitamura, S.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1999**, *40*, 1689.
9. The use of a decreased amount of the mixed reagent (1.1 equiv.) afforded **5h** in 80% yield.
10. At the higher temperature (0°C), dihydroxybenzaldehyde was formed in 80% yield.