Pergamon

Tetrahedron Letters 44 (2003) 1465–1467

TETRAHEDRON
LETTERS

# A simple, mild and efficient procedure for selective cleavage of prenyl esters using silica-supported sodium hydrogen sulphate as a heterogenous catalyst☆

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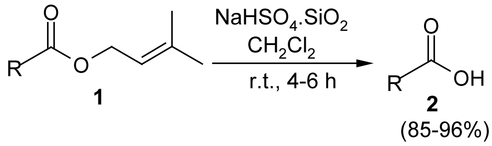
Received 1 November 2002; revised 5 December 2002; accepted 13 December 2002

**Abstract**—Prenyl esters were selectively and efficiently cleaved under slightly acidic reaction conditions using silica-supported sodium hydrogen sulfate as a heterogenous catalyst at room temperature to regenerate the parent carboxylic acids in very high yields. © 2003 Elsevier Science Ltd. All rights reserved.

Protection of carboxylic acids and subsequent deprotection have been used in multi-step transformations and syntheses of several bioactive naturally occurring molecules.[2] Carboxylic acids are frequently protected as esters and unsaturated esters are particularly preferred due to the ease of preparation and their stability.[2] Among these unsaturated esters prenyl (3-methylbut-2-en-1-yl) esters are routinely prepared and utilized for protection of carboxylic acids.[3] A limited number of methods have been developed for cleavage of these prenyl esters. However, most of these methods suffer from certain drawbacks which include the utilization of hazardous ($I_2$)[3a] and expensive [$Pd(OAc)_2$][3b,c] reagents and a requirement for higher temperature or reflux conditions (using $Pd(OAc)_2$,[3b,c] sulfated $SnO_2$,[3d] K-10 clay[3d] and $CeCl_3{\cdot}7H_2O$–NaI[3f]). Recently, TMS triflate catalyzed cleavage of prenyl esters has been reported[4] to occur at room temperature but the catalyst is moisture sensitive and dangerous while wet with $H_2O$. Selectivity has also not properly been studied or narrow selectivity has been observed with some of the reagents used in the reported methods.[3c–e] However, selectivity is very important for protection–deprotection of multifunctional acids, particularly amino acids as they are frequently used as reagents, catalysts and chiral auxiliaries for asymmetric synthesis.[4] Thus there is a need of suitable methods for selective deprotection of prenyl esters of multifunctional acids including amine protected amino acids under mild reaction conditions.

We have developed an efficient procedure for selective cleavage of prenyl esters over a wide range of functional groups using silica-supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$). Several prenyl esters were selectively deprotected to the corresponding acids (Table 1) by applying this catalyst at room temperature.



The deprotection occurred under mild and slightly acidic conditions. The yields of regenerated acids were very high. The catalyst ($NaHSO_4{\cdot}SiO_2$) can easily be prepared[5] and is inexpensive and non-toxic. As the reaction is heterogenous in nature the catalyst can conveniently be removed by simple filtration.[6] The structures of all the products were established from their spectral ($^1H$ NMR and LSIMS) data.[6]

The process is associated with high chemoselectivity—prenyl esters can be deprotected without affecting other functional groups present in the acid molecules. Conjugated and isolated double bonds were unchanged; alkyl, benzyl, allyl and THP ethers remained intact; acetates and allyl esters were also not cleaved. Additionally, an *N*-Cbz group was not affected by the reagent. Thus the method is suitable for deprotection of prenyl esters of *N*-Cbz protected amino acids without interfering with

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*Keywords*: prenyl esters; $NaHSO_4{\cdot}SiO_2$; amino acids.

☆ Part 22 in the series, 'Studies on Novel Synthetic Methodologies'. For Part 21, see Ref. 1. IICT Communication No. 4605.

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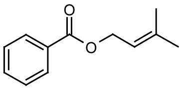
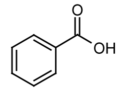
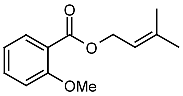
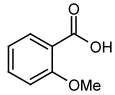
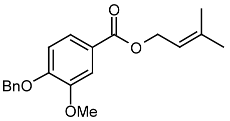
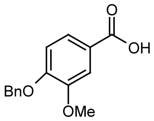
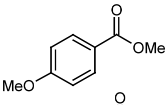
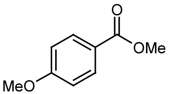
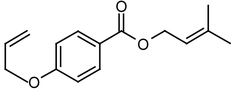
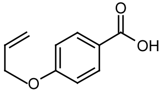
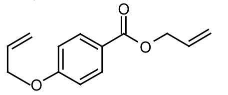
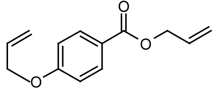
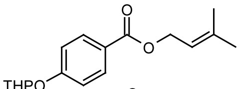
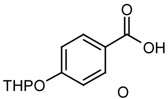
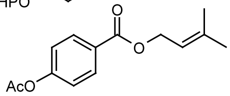
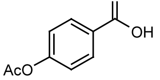
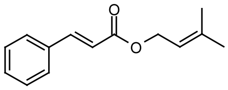
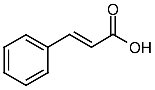
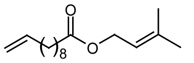
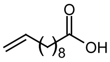
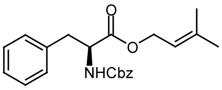
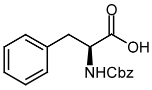
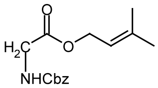
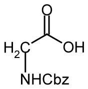
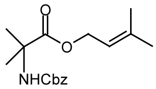
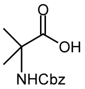
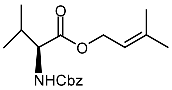
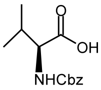
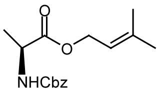
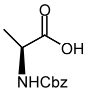
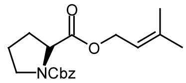
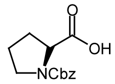
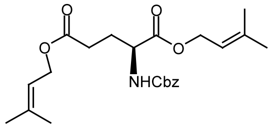
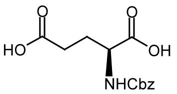
PII: S0040-4039(02)02858-7

**Table 1.** Selective cleavage of prenyl esters using $\text{NaHSO}_4\cdot\text{SiO}_2$†

| Entry | Substrate (**1**) | Product (**2**) | Time (h) | Isolated yield(%) |
|---|---|---|---|---|
| a |  |  | 5 | 95 |
| b |  |  | 5 | 96 |
| c |  |  | 5 | 91 |
| d |  |  | 10 | - |
| e |  |  | 4 | 94 |
| f |  |  | 10 | - |
| g |  |  | 6 | 88 |
| h |  |  | 5.5 | 89 |
| i |  |  | 5 | 92 |
| j |  |  | 5 | 89 |
| k |  |  | 5 | 95 |
| l |  |  | 6 | 86 |
| m |  |  | 6 | 89 |
| n |  |  | 5 | 91 |
| O |  |  | 5 | 85 |
| P |  |  | 6 | 93 |
| q |  |  | 6 | 85 |

†All products were characterized from their spectral ($^1$H-NMR, LSIMS) data.

the protection of the amine group. However, with prenyl esters of *N*-Boc protected amino acids, the rate of deprotection of prenyl esters while keeping the *N*-Boc group intact was slow, and the yields of the corresponding acids were poor. If a large amount of the reagent, $NaHSO_4 \cdot SiO_2$ was used, the rate of deprotection of the esters was increased but both the prenyl ester and *N*-Boc groups were found to be cleaved. The present procedure did not cause epimerization of chiral centers neighboring the prenyl esters, the regenerated parent acids showing no change in the values of their optical rotations, indicating complete retention of configuration.

In conclusion, we have developed a mild and easy process for selective deprotection of prenyl esters of carboxylic acids using $NaHSO_4 \cdot SiO_2$ under slightly acidic conditions. The process is remarkable for high yields of the parent acids and high chemoselectivity without causing epimerization of the neighboring chiral centers and isomerization of double bonds. The operational simplicity of the procedure is also attractive. The catalyst can be prepared easily with readily available inexpensive reagents and is heterogenous and non-hazardous. To our knowledge, this is the first report of an efficient general method for selective deprotection of prenyl esters at room temperature by using a safe, simple catalyst.

## Acknowledgements

The authors thank UGC and CSIR, New Delhi for financial assistance.

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6. **Experimental procedure**: Prenyl ester[7] (1 mmol) and $NaHSO_4 \cdot SiO_2$ (200 mg) were taken in $CH_2Cl_2$ (10 ml). The mixture was stirred at room temperature. After completion of the reaction (TLC) the catalyst was filtered off and washed with EtOAc (2×5 ml). The filtrate and washings were combined and the solvents were removed under vacuum. The residue was purified by column chromatography over silica gel using mixtures of hexane and EtOAc as eluents to yield the parent carboxylic acid. The spectral data of some of the compounds are given below:
   Compound **1e**: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.98 (2H, d, $J=8.0$ Hz), 6.84 (2H, d, $J=8.0$ Hz), 6.02 (1H, m), 5.40 (1H, m), 5.38 (1H, d, $J=15.0$ Hz), 5.26 (1H, d, $J=10.0$ Hz), 4.76 (2H, d, $J=7.0$ Hz), 4.59 (2H, d, $J=5.5$ Hz), 1.78 (3H, s); LSIMS: $m/z$ 247 ($M^{+\bullet}$+1).
   Compound **2e**: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 8.05 (2H, d, $J=8.0$ Hz), 6.92 (2H, d, $J=8.0$ Hz), 6.05 (1H, m), 5.40 (1H, d, $J=15.0$ Hz), 5.31 (1H, d, $J=10.0$ Hz), 4.56 (2H, d, $J=5.5$ Hz): LSIMS: $m/z$ 179 ($M^{+\bullet}$+1).
   Compound **1k**: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.38–6.97 (10H, m), 5.22 (1H, m), 5.12 (1H, d, $J=7.0$ Hz), 5.04 (2H, s), 4.58 (2H, d, $J=7.0$ Hz), 4.45 (1H, m), 3.04 (2H, d, $J=7.0$ Hz), 1.78 (3H, s) 1.72 (3H, s); LSIMS: $m/z$ 368 ($M^{+\bullet}$+1).
   Compound **2k**: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.40–7.02 (10H, m), 5.18 (1H, d, $J=7.0$ Hz), 5.06 (2H, s), 4.64 (1H, m), 3.20–3.01 (2H, m); LSIMS: $m/z$ 300 ($M^{+\bullet}$+1).
   Compound **1m**: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.40–7.18 (5H, m), 5.42 (1H, brs), 5.28 (1H, m), 5.02 (2H, s), 4.59 (2H, d, $J=7.0$ Hz), 1.77 (3H, s), 1.73 (3H, s), 1.54 (6H, s), LSIMS: $m/z$ 306 ($M^{+\bullet}$+1).
   Compound **2m**: $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.38–7.24 (5H, m), 5.41 (1H, brs), 5.04 (2H, s), 1.58 (6H, s); LSIMS: $m/z$ 238 ($M^{+\bullet}$+1).
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