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Titanium Tetrachloride Promoted Hydrolysis of Cephalosporin *tert*-Butyl Esters

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Abstract: Titanium tetrachloride was used as a mild and effective deprotective reagent for the hydrolysis of cephalosporin *tert*-butyl esters. Yields up to 91% were obtained.

Protection and deprotection of carboxylic acid functionalities are essential steps in the multistep synthesis of β-lactam antibiotics. Semisynthetic cephalosporins, derivatized congeners of the fermentation product Cephalosporin C, require during their synthesis an efficient carboxylic acid protection strategy since the unprotected carboxyl function can readily undergo decarboxylation under a variety of reaction conditions.[1] Industrial examples of carboxyl protecting groups are allyl, benzhydryl, *tert*-butyl, 4-methoxybenzyl, 4-nitrobenzyl and 2,2,2-trichloroethyl.

As a consequence of the labile nature of the cephalosporin β-lactam ring system, protective groups have to be introduced and deblocked under mild conditions. In the case of 4-methoxybenzyl-, diphenylmethyl- and *tert*-butyl esters, deblocking can be realized using various acids such as trifluoroacetic acid, hydrochloric acid, sulphuric acid or 4-toluenesulphonic acid. In most cases however, an excessive amount of acid is required to complete the reaction which is frequently limited in yield because of the acid lability of many of the β-lactams. The use of phenolic media substantially reduces the amount of acid from 4 to only 0.5 or even 0.1 equivalents. The phenol-assisted cleavage of esters involves an acid-catalyzed process which presumably proceeds via a proton relay mechanism through a hydrogen-bonded phenol matrix.[2] Trimethylsilyl iodide is a convenient reagent for the cleavage of esters under neutral conditions, and even some chemoselectivity may be introduced since benzyl and *tert*-butyl esters react at a much faster rate than methyl or ethyl esters.[3,4] For *tert*-butyl ester deprotection in peptide chemistry, the combination of phenol and trimethylsilyl iodide is advocated.[5] A Me_3SiI-phenol complex, which provides an acidic phenolic proton due to the strong Si-O bond, is thought to be responsible for the hydrolytic activity.

Lewis acid promoted deprotection of carboxylic functionalities is also commonly applied. The best studied example is aluminium trichloride, preferably in the presence of anisole. The proposed mechanism is based on Lewis acid coordination with the carbonyl oxygen to assist generation of a benzyl cation (in case of benzyl esters) which in turn is trapped by anisole.[6] In the absence of anisole, cleavage of benzyl groups gives the acid in similar yields but with lower purity. Aluminium trichloride in combination with anisole was also used for

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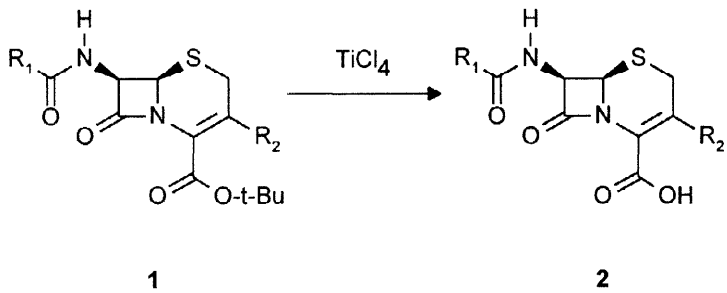
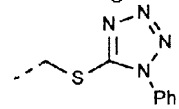
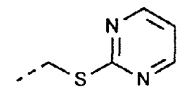
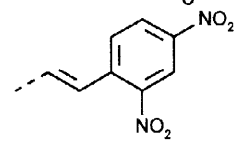
Scheme



1 2

	R_1	R_2
a	$PhCH_2$-	$-CH_3$
b	$PhOCH_2$-	$-CH_3$
c	$PhCH_2$-	
d	$PhCH_2$-	
e	$PhCH_2$-	$-CH=CH-CH_3$
f	$PhCH_2$-	

deprotection of benzhydryl and 4-methoxybenzyl esters of carbapenem derivatives which are very unstable under acidic conditions.[7]

The *tert*-butyl protective group is very attractive for application on an industrial scale due to the fact that it is relatively inexpensive and easy to introduce. For deprotection on a laboratory scale, trifluoroacetic acid is often successfully used. Since trifluoracetic acid is a costly material, large scale application is almost inconceivable in β-lactam chemistry. Since other methods, including the ones mentioned above, gave low to moderate yields in our hands, we set out to identify a high yielding, low cost procedure for the hydrolysis of cephalosporin *tert*-butyl esters.

In a first set of experiments, several Lewis acids were tested for their ability to hydrolyse the ester in *tert*-butyl (6*R*,7*R*)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylate (**1e**, see Scheme), intermediate in the synthesis of the antibiotic Cefprozil. Of the Lewis acids tested, both tin tetrachloride and titanium tetrachloride look very promising with yields of 88% and 91%, as outlined in Table 1. For environmental reasons we decided to further elaborate on the use of titanium tetrachloride. Tin residues are difficult to remove during work-up procedures and are a threat for the environment. On the other hand, titanium dioxide, formed as a co-product during the reaction, is a generally accepted and harmless colouring substance.

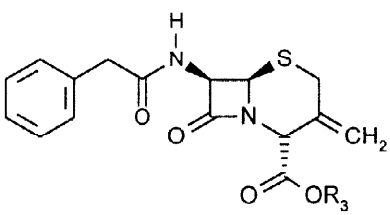
Next, we explored the substrate range of titanium tetrachloride. Different cephalosporin structures were used as substrate (Table 2). Reactions with titanium tetrachloride were performed in dichloromethane at subzero temperatures.[8] In some experiments (entries 4 and 5), anisole was added before the addition of titanium tetrachloride. The reactions were monitored either by HPLC or TLC. No degradation of the β-lactam ring was observed. The yields together with IR spectral data are summarized in the table. Most of the deprotected compounds were obtained in good yields and recovery of titanium waste was facile[9]. In the case of compound **2e** (entry 6), a mixture of E and Z isomers (5/85) was isolated while compound **2f** (entry 7) was isolated following a modified procedure as a single E-isomer.[10]

Table 1 Comparative study of Lewis acid promoted hydrolysis of *tert*-butyl (6*R*,7*R*)-7-phenylacetamido-3-(1-propenyl)-ceph-3-em-4-carboxylate (**1e**)

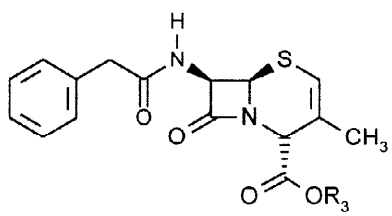
Entry	Lewis acid	T (°C)	Time (h)	Yield (%)	Remarks
1	$AlCl_3$	25	28	50 [a]	Some degradation observed
2	BCl_3	-10	4.0	20 [a]	Extensive degradation observed
3	BF_3	25	18	0 [a]	Extensive degradation observed
4	$FeCl_3$	5	2.5	34 [b]	
5	$SiCl_4$	25	72	0 [a]	No reaction observed
6	$SnCl_4$	-10	2.5	88 [b]	
7	$TiCl_4$	5	3.0	91 [b]	

[a] According to TLC in EtOAc/toluene/HOAc/water, 4/3/2/1, v/v/v/v

[b] According to HPLC (C18 column, mobile phase 30% acetonitrile and 1% THF in 7 mM KH_2PO_4)



3a R_3 = t-Bu
3b R_3 = H



4a R_3 = t-Bu
4b R_3 = H

Table 2 Titanium tetrachloride promoted hydrolysis of cephalosporin *tert*-butyl esters

Entry	Substrate[a]	Product[b]	Time (h)	Yield[c] (%)	IR (cm^{-1})
1	**1a**	**2a**	2.0	69	3270, 1770, 1655
2	**1b**	**2b**	2.0	54	3375, 1755, 1655
3	**1c**	**2c**	4.0	59	3260, 1770, 1650
4	**1c**	**2c**	2.5[d]	50	3260, 1770, 1650
5	**1d**	**2d**	3.5[d]	51	3240, 1760, 1640
6	**1e**	**2e**	2.5	91	3260, 1770, 1650
7	**1f**	**2f**	2.0	63	3300, 1780, 1625
8	**3a**	**3b**	4.0	45	3280, 1745, 1635
9	**4a**	**4b**	2.5	83	3280, 1755, 1640

[a] Starting compounds **1a, 1b, 3a** and **4a** are prepared from penicillin G and penicillin V,[11] **1c-1f** are synthesized from *tert*-butyl 7β-phenylacetamido-3-bromomethyl-3-cephem-4-carboxylate 1β-oxide (3-BMC)[12,13]

[b] See note 14 for NMR data

[c] Yields are based on purity-corrected products and are not optimized

[d] Reactions were carried out in the presence of 6 equivalents anisole

To our knowledge, this is the first use of titanium tetrachloride for the efficient hydrolysis of *tert*-butyl esters in β-lactam chemistry.[15] Yields exceed those previously reported using HCl (65%)[2] and trimethylsilyl iodide (45%).[4] Furthermore, hydrolysis of *tert*-butyl esters was performed at lower temperatures compared to previously reported work where the range between room temperature and 45°C was used. This may be a significant contribution to the suppression of degradation. Finally, work-up yields titanium dioxide, a relatively harmless side-product. Preliminary experiments have indicated that titanium tetrachloride is also a very convenient reagent for the deprotection of cephalosporin 4-methoxybenzyl esters.[16]

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8. A stirred solution of starting ester (2 mmol) in dichloromethane (50ml) was cooled to -10°C. Titanium tetrachloride (8 mmol) was slowly added and the temperature was brought to 0°C. After stirring for an appropriate time (see Table), a chilled 2M solution of HCl (80 ml) was added. The organic phase was separated, washed with 2M HCl (3 x 25 ml), brine (2 x 25 ml) and concentrated under reduced pressure to yield compounds **2a-2e**, **3b** and **4b**.
9. Upon addition of 8M NaOH to the aqueous washings[8] which presumably contain a titanium chlorine complex, precipitation of titanium dioxide starts at pH 0-0.2. At pH 4, precipitation is complete and titanium dioxide is obtained by filtration.
10. The crude product (**2f**) obtained by the same procedure as before was crystallized by dissolving in acetone at 65°C and adding water. Crystallization was allowed to proceed for 16 hr at 0°C and the crystals were collecting by filtration. Recrystalization of the product was performed by dissolving the material in acetone/acetic acid (2/1) at 50°C and removing part of the solvent by evaporation under reduced pressure. Crystals were collected and washed with acetic acid and ether.
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14. The ^{1}H NMR spectra of the synthesized compounds were recorded on a Bruker AM 360 MHz instrument, using DMSO-d_6 as solvent. Chemical shifts are in ppm relative from TMS.
    2a 2.03 (s, 3H, H_3), 3.35/3.50 (ABq, 2H, J=16.7 Hz, H_2), 3.60 (s, 2H, $ArCH_2$), 5.00 (d, 1H, J=5.0 Hz, H_6), 5.60 (dd, 1H, J=8 Hz, H_7), 7.30 (m, 5H, Ar-H), 9.05 (d, 1H, J=7Hz, NH).
    2b 2.05 (s, 3H, H_3), 3.35 (s, 2H, Ar-CH_2), 3.25/3.60 (ABq, 2H, J=12 Hz, H_2), 5.10 (d, 1H, J=6 Hz, H_6), 5.65 (dd, 1H, J=8 Hz, H_7), 7.05 (m, 5H, Ar-H), 9.05 (d,1H, J=8 Hz, NH).
    2c 3.50/3.65 (ABq, 1H, J=18 Hz, H_2), 4.25/4.55 (ABq, 1H, J=13 Hz, H_3), 3.75 (s, 2H, Ar-CH_2), 5.05 (d, 1H, J=5 Hz, H_6), 5.65 (dd, 1H, J=8 Hz, H_7), 7.20-7.45 (m, 5H, Ar-H), 7.65 (s, 5H, Ar-H), 9.10 (d, 1H, J=8 Hz, NH).
    2d 3.60 (s, 2H, Ar-CH_2), 3.50/3.75 (ABq, 1H, J=18 Hz, H_2), 3.95/4.65 (ABq, 1H, J=13 Hz, H_3), 3.65 (t, 1H, J=6 Hz, pyrimidine-H), 5.05 (d, 1H, J=5 Hz, H_6), 5.65 (dd, 1H, J=8 Hz, H_7), 7.20-7.40 (m, 5H, Ar-H), 8.60 (d, 2H, J=5Hz, pyrimidine-H), 9.15 (d, 1H, J=8 Hz, NH).
    2e 1.64 (d, 3H, J=8 Hz, -CH_3), 3.54 (m, 4H, Ar-CH_2 and H_2), 5.11 (d, 1H, J=5 Hz, H_6), 5.63 (m, 2H, H_7 and CH=CH), 6.14 (d, 1H, J=8 Hz, CH=CH), 7.30 (m, 5H, Ar-H), 9.07 (d, 1H, J=8 Hz, NH).
    2f 2.87/3.26 (ABq, 2H, J=17.5Hz, H_2), 3.60 (s, 2H, Ar-CH_2), 4.92 (d, 1H, J=5.0 Hz H_6), 5.76 (dd, 1H, J_1=4.9 Hz, J_2=8.3 Hz,H_7), 6.82 (s, 2H, CH=CH), 6.87 (d, 1H, J=8 Hz, NH), 7.30 (m, 5H, Ar-H), 7.55 (d, 1H, J=8.8 Hz, Ar-H), 8.29 (dd, 1H, J_1=2.1 Hz, J_2=8.8 Hz, Ar-H), 8.84 (d, 1H, J=2.1 Hz, Ar-H).
    3b 3.65 (s, 2H, Ar-CH_2), 3.15/3.75 (ABq, 2H, J=18 Hz, H_2), 5.05 (s, 1H, C=CH_2), 5.25 (s, 1H, C=CH_2), 5.35 (s, 1H, H_4), 5.40 (d, 1H, J=5 Hz, H_6), 5.15 (dd, 1H, J=18 Hz, H_7), 6.35 (d, 1H, J=8Hz, NH), 7.25-7.45 (m, 5H, Ar-H).
    4b 1.75 (s, 3H, CH_3), 3.55 (s, 2H, Ar-CH_2), 4.41 (s, 1H, H_4), 4.95 (d, 1H, J=5.0 Hz, H_6), 5.31 (dd, 1H, J=8 Hz, H_7), 6.29 (s, 1H, CH_2), 7.30 (m, 5H, Ar-H), 9.14 (d, 1H, J=8 Hz, NH).
15. Titanium tetrabromide promoted hydrolysis of *tert*-butyl glycosides was first demonstrated by Lacombe *et al.*: Lacombe, J.M.; Rakotomanomana, N.; Pavia, A.A. *Carbohydrate Res.* **1988**, *181*, 246-252.
16. **2e** could be obtained in 95% yield from the corresponding 4-methoxybenzyl ester after 5 min at 2°C.