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Catalytic Transfer Hydrogenolysis of 4-Nitrobenzyl Esters of Cephalosporins

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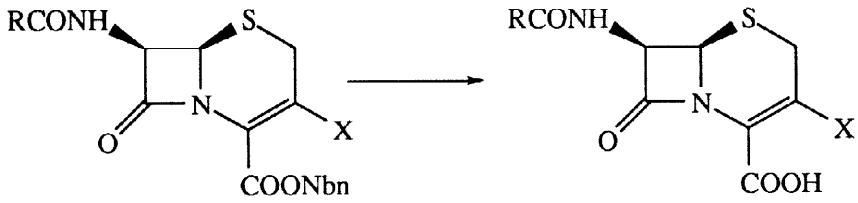
Abstract: Cephalosporins **1a-d** have been selectively hydrogenolysed to their corresponding acids **2a-d** without isomerisation of the cephem double-bond using anhydrous ammonium formate or phosphinic acid as catalytic transfer agents in the presence of 10% Pd/C.

The clinical importance of C-3 functionalised cephalosporins has been known for many years.[1] The synthetic manipulation of the cephalosporin nucleus, however, has to deal with the facile isomerisation of 3-cephems to 2-cephems under mild basic conditions.[2]

In particular, suitable protection of the amino and carboxyl groups is crucial for the successful realisation of the synthetic project. For example, 3-*nor*-cephalosporins are prepared from penicillins G and V through expansion of the thiazolidine to the dihydrothiazine ring and removal of one carbon atom, followed by 3-heterofunctionalisation.[3] Of the various carboxyl protective groups the 4-nitrobenzyl (Nbn) is one of the most frequently used in azetidinone chemistry due to its easy introduction and relative stability to acids and bases.[4]



1a-d **2a-d**

a: R = $PhCH_2$, X = Cl

b: R = $PhCH_2$, X = OMe

c: R = $PhOCH_2$, X = Cl

d: R = $PhOCH_2$, X = OMe

Nbn = 4-nitrobenzyl

Scheme

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Recently we have been involved in the selective deprotection of the Nbn esters of 3-chloro and 3-methoxy cephalosporins **1a-d** (Scheme).[5]

Several methods have been reported for the reductive cleavage of Nbn esters including alkaline hydrolysis with sodium sulfide[6] or sodium dithionite[7] and dealkylation with LiI[8] or tetrabutylammonium fluoride (TBAF).[9] In the case of 3-cephems **1a-d**, however, we obtained only the corresponding 2-cephem acids in variable yields by alkaline hydrolysis or with LiI in THF or CH_3CN, while no conversion of the starting material was observed with TBAF in DMF. Catalytic hydrogenation has also been used, although low yields are occasionally observed due to the poisoning of the catalyst by the divalent sulfur containing cephalosporins.[6]

Catalytic transfer hydrogenolysis (CTH) is a well known procedure for reduction and hydrogenolysis of various functional groups.[10] In particular the removal of benzyl protecting groups from peptides has been reported with different hydrogen donors such as cyclohexene,[11] formic acid[12] and ammonium formate (AF).[13]

We found and here report that the removal of the Nbn protecting group in 3-cephems **1a-d** can be efficiently realised under mild conditions by heterogeneous CTH in the presence of anhydrous AF or 50% aqueous phosphinic acid as hydrogen donors and 10% Pd/C.

The 3-chloro-cephalosporin **1a** was chosen as a model compound for the optimisation of the reaction conditions performing the hydrogenolyses in MeOH at room temperature, in the presence of 50% by weight of the catalyst. Less polar solvents such as CH_2Cl_2 and THF were totally or partially ineffective.

As expected, the rate of hydrogen transfer strongly depends upon the hydrogen donor used (Table). In fact cyclohexene, formic acid, alone or in combination with sodium formate, converted the ester **1a** to the acid **2a** in less than 5% yield after 48 hours, while $H_2NNH_2 \cdot H_2O$ (2 mol equiv) produced a faster reaction, the yield of the expected product being negligible (8%, 2h). The use of AF (5 mol equiv) brought about some improvement and **2a** was isolated in a 35% yield after 6 hours (entry 1).

Table. Catalytic Transfer Hydrogenolysis with 10% Pd/C.[a]

entry	substrate	H donor[b]	time (h)	product	yield[c] (%)
1	**1a**	A	5	**2a**	35
2	**1a**	B	24	**2a**	82
3	**1a**	C	6	**2a**	90
4	**1b**	A	5	**2b**	42
5	**1b**	B	24	**2b**	89
6	**1b**	C	8	**2b**	67
7	**1c**	B	24	**2c**	88
8	**1c**	C	6	**2c**	97
9	**1d**	B	24	**2d**	86
10	**1d**	C	6	**2d**	81

[a] 50% by weight. [b] A = AF 5 mol equiv; B = H_3PO_2 11 mol equiv; C = CH_3COOH+AF 10 mol equiv.
[c] HPLC analysis on Hypersil BDS C18 5 μm, 250 x 4.6 mm.

On the other hand, 90% of **2a** was produced by carrying out the reaction with 10 mol equiv of AF in the presence of an equal amount of CH_3COOH (entry 3).[14] Under the same reaction conditions the 3-cephem acids **2b-d** were obtained in 67-97% yield in 6-8 hours (entries 6, 8, 10). The beneficial effect of the acetic acid can be ascribed to the neutralisation of ammonia, generated from AF after decomposition over the catalyst surface. Nevertheless an effect on the displacement of molecules strongly bound to the catalyst, thus inhibiting its catalytic activity, cannot be ruled out.

Good results, although in a longer reaction time, were obtained by using 50% aqueous phosphinic acid that is overall oxidised to phosphorous acid by water in giving up its hydrogen. Under the same reaction conditions previously described for AF, the hydrogenolysis generated the acids **2a-d** in a 82-89% yield after 24 hours (entries 2, 5, 7, 9).

In conclusion we have demonstrated that heterogeneous CTH can be successfully applied to the selective deprotection of sensitive molecules such as cephalosporins **1a-d**. To the best of our knowledge this is the first application of CTH to the modification of cephalosporins. The methodology is easy to perform and doesn't require any special equipment for high pressure reactions. Moreover, the choice of the appropriate solvent and H donor allows 3-cephems to be generated in good to excellent yields without $\Delta^3 \rightarrow \Delta^2$ isomerisation.

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5. Compounds **1a-d** were prepared in 80-83% yield by reacting the hydrochlorides of 4-nitrobenzyl 7 -amino-3-cephem-3-chloro-4-carboxylate[3b] and 4-nitrobenzyl 7-amino-3-cephem-3-methoxy-4-carboxy late[3b] with an equimolar amount of the appropriate acyl chloride at room temperature in dichlorometha ne, in the presence of a four-fold excess of solid potassium hydrogen carbonate.
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14. A typical procedure follows: 0.5 g of 10% Pd/C, AF (20 mmol) and CH_3COOH (20 mmol) were added to a stirred suspension of ester **1a** (2 mmol) in anhydrous MeOH (25 ml) under a nitrogen atmosphere. After completion of the reaction (TLC or HPLC control), the catalyst was removed by filtration through celite and the filtrate evaporated to dryness. The residue was dissolved in a saturated sodium chloride solution, some insoluble material filtered, and acidified to pH 1 with 10% HCl. The acid **2a** was isolated by filtration as a white crystalline compound. Products **1,2a-d** are known compounds and all spectrosco pical and analytical data match those reported in the literature (see for example U. S. Patent 3,925,372; *Chem. Abstr.*, **84**, 105620q. German. Offen. 2,408,698 *Chem Abstr.*, **82**, 4278n. German. Offen. 2,331,133 *Chem Abstr.*, **80**, 83019).