MILD AND CHEMOSELECTIVE CLEAVAGE OF *p*-NITROBENZYL ESTERS AND *p*-NITROBENZYLOXYCARBONYL AMINES WITH ZINC DUST

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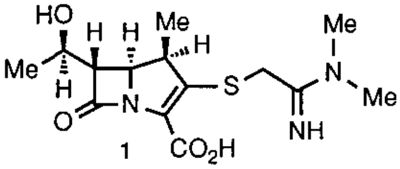
Abstract - *p*-Nitrobenzyl esters and *p*-nitrobenzyloxycarbonyl amines have been efficiently deprotected by treatment with zinc dust in THF - 0.35 M phosphate buffer solution (pH 6) to obtain the parent carboxylic acids and amines. Olefinic bond, S-N bond, and diphenylmethyl- and benzyloxycarbonylamino groups are intact under the deprotection conditions.

Since discovery of non-natural 1β-methylcarbapenem (**1**),[1] there have been many reports on synthetic studies of the related compounds.[2] Recently, we have reported total asymmetric synthesis of a new 1β-methylcarbapenem (**2**) which exhibited strong and wide-ranging antibacterial activities and excellent stability against human renal dehydropeptidase- I.[3] The crucial step in the synthesis of **2** was simultaneous deprotection of C3-carboxylic *p*-nitrobenzyl (PNB) ester and C2-[bis *p*-nitrobenzyloxycarbonyl (PNZ)]pyrazolidine moiety in the compound (**3**).[3] We adopted a conventional hydrogenation procedure[4] by use of 10% Pd-C for these deprotection reactions. However, yield of **2** from **3** involving the hydrogenolytic deprotection was low (44%). Especially, 1β-methylcarbapenems bearing quarternary ammonium groups such as **4** and **5** must be sensitive to the Pd-charcoal procedure.[5] Thus, we focused on the development of a new and mild procedure useful for chemoselective cleavage of PNB and PNZ groups employing Zn dust which can easily reduce nitro group.[6] First, in order to determine the reaction conditions, a mixture of PNB ester (**4**) and Zn dust was stirred at room temperature for 1 h in a mixture of THF and phosphate buffer solution (pH 6). All results are summarized in Table 1.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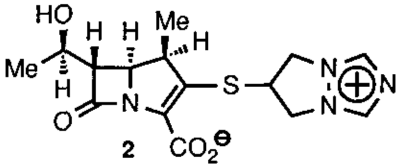
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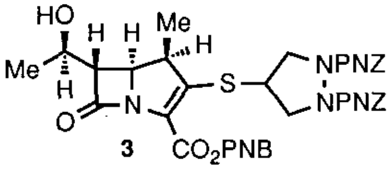
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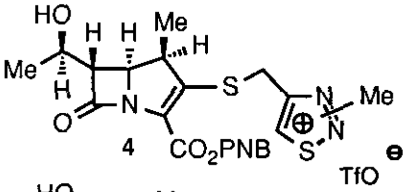
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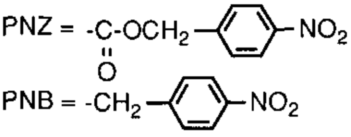

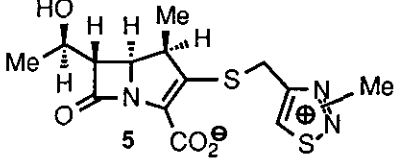
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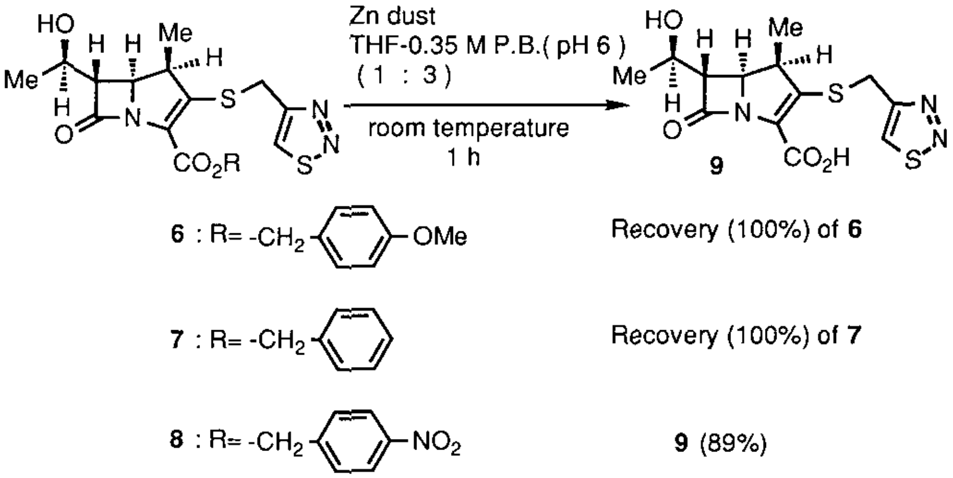
Table 1. Investigation of the reaction conditions for deprotection of PNB ester (**4**) by employing Zn dust

Entry [a)]	Amount(g) of Zn dust	Concentration of P.B.[b)] and Solvent Ratio	Yield(%) [c)] of **5**
1	12	THF-0.35 M P.B. (1:2)[d)]	60
2	12	THF-0.10 M P.B. (1:2)[d)]	23
3	2	THF-0.35 M P.B. (1:2)[d)]	70
4	2	THF-0.35 M P.B. (1:3)[d)]	75
5	2	THF-H_2O (1:2)[d)]	no reaction
6	1.5	THF-0.35 M P.B. (1:2)[d)]	68
7	1	THF-0.35 M P.B. (1:2)[d)]	45

a) In all reactions, 1.1 g of PNB ester (**4**) was employed. b) P.B.: Phosphate buffer (pH 6.0). c) Isolated yield based on **4.** d) Solvent ratio (v/v)

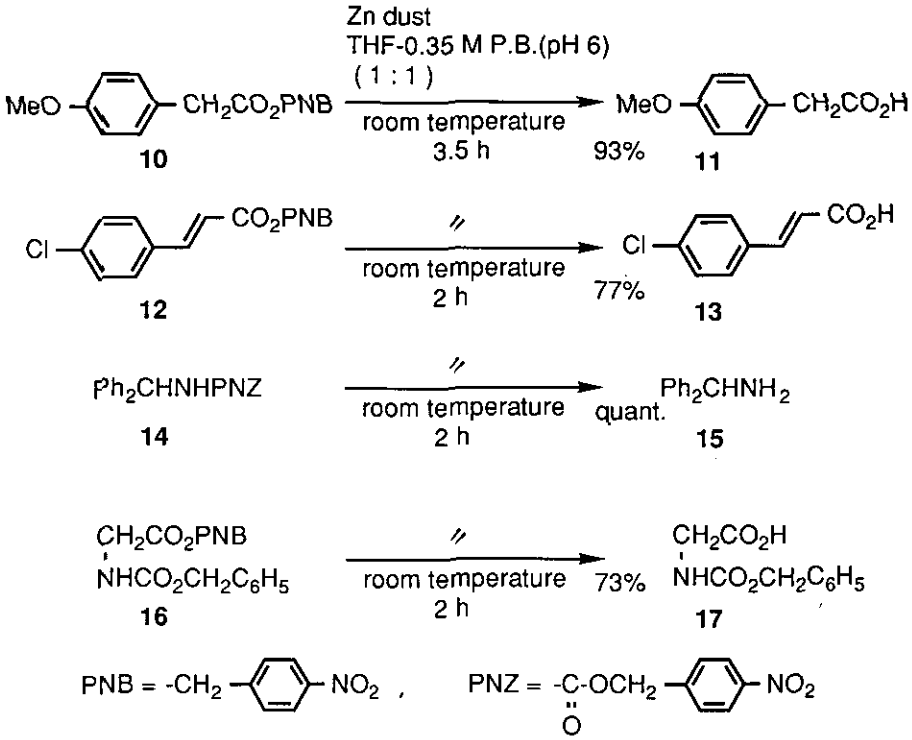
Phosphate buffer solution (pH 6) should be essential (Entry 5 and other entries) and its concentration seems to be effective on the PNB cleavage (Entries 1 and 2). Amount of Zn dust is required more than two times of the weight of **4** (Entries 1, 3, 6, and 7).

Then, we applied this Zn dust procedure to deprotection of the 1β-methylcarbapenem esters such as methoxybenzyl ester (**6**), benzyl ester (**7**), and PNB ester (**8**) (Scheme 1). Although cleavage of **8** smoothly proceeded to afford carboxylic acid (**9**) in 89% yield,[7] the esters (**6**) and (**7**) were quantitatively recovered, respectively (Scheme 1). It is noteworthy that S-N bond of thiadiazole, disubstituted olefinic bond, diphenylmethylamino group, and benzyloxycarbonylamino group are virtually intact in the Zn dust procedure in a solution of THF-0.35M phosphate buffer (pH 6) (Schemes 1 and 2).[8]

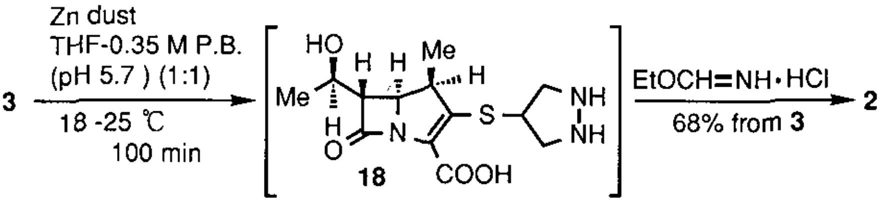


Scheme 1

Finally, this new method was efficiently applied to simultaneous deprotection of the PNB ester and the (bis PNZ)pyrazolidine moiety in the molecule (**3**). Compound (**3**) (2.0 g) was treated with Zn dust (20.0 g) in a solution of THF (45 ml) and 0.35 M phosphate buffer solution (pH 5.7, 45 ml) at 18 - 25 ℃ and then the resultant pyrazolidino carboxylic acid (**18**) was submitted to cyclization reaction with ethyl formimidate hydrochloride to furnish the desired compound (**2**) in 68% yield from **3** (Scheme 3).[8]

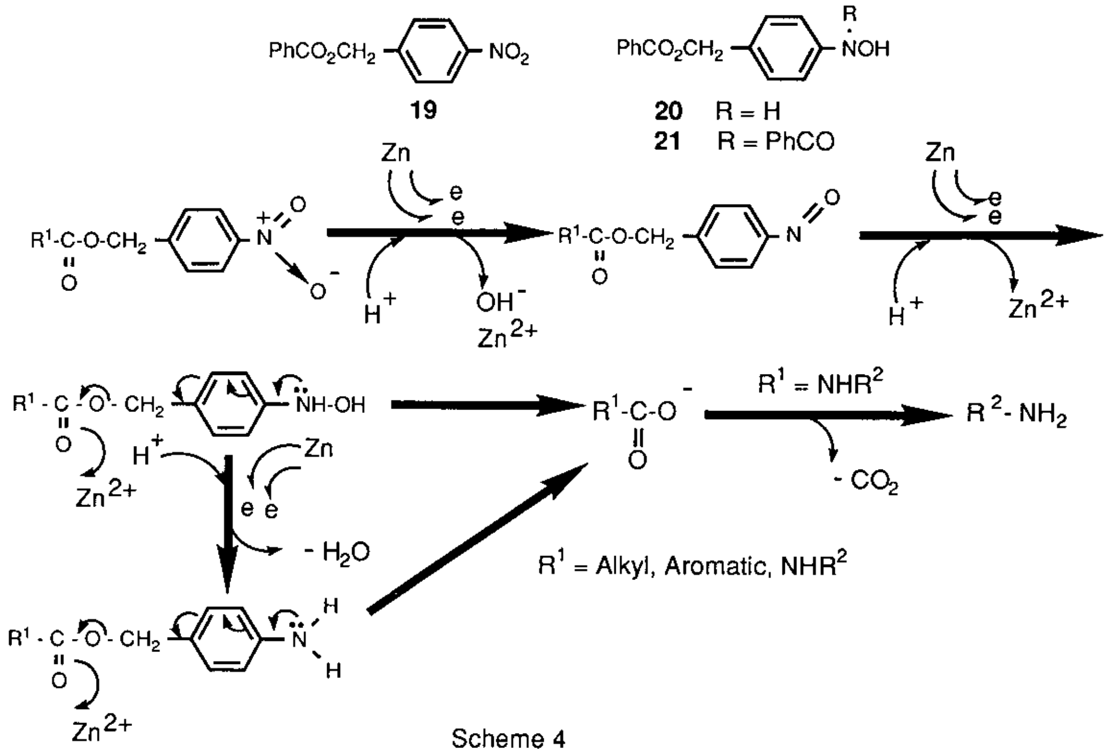


Scheme 2



Scheme 3

Unstable hydroxylamine (**20**), derived from the Zn dust treatment of PNB ester (**19**), could be trapped with benzoyl chloride to give the hydroxamate (**21**) as we expected. Thus, chemoselective cleavage of *p*-nitrobenzyl group may be explained in terms of favorable electron transfer from Zn to the nitro group on the aromatic ring followed by Zn^{2+}-promoted elimination of *p*-hydroxylaminoand/or *p*-aminobenzyl group[9] to give the corresponding carboxylic acid or amine after decarboxylation (Scheme 4).



Scheme 4

In conclusion, we have found a new Zn dust procedure for chemoselective deprotection of PNB esters and PNZ amines. This reported procedure should be practically useful for carbapenem synthesis.

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5. Treatment of the isolated compound (**5**) (178 mg) with 10% Pd-C (356 mg) in a solution of THF (10 ml) and 0.1 M phosphate buffer(pH 6) (10 ml) under H_2 (4 kg/cm^2) for 20 min resulted in decomposition of **5** more than 50% (hplc analysis).
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7. A typical procedure: Freshly activated zinc dust[10] (38 g) was added to a solution of compound (**8**) (4.76 g) in THF (30 ml) and 0.35 M phosphate buffer (pH 6) (90 ml). After being stirred vigorously at room temperature for 1 h, the mixture was filtered and the filtrate was washed with ethyl acetate. The aqueous layer was adjusted to pH 6.5 and concentrated *in vacuo*. The concentrated solution (70 ml) was charged on a SP-207 column and purified (eluent: 6% i-propyl alcohol in water) to give **9** (3.04 g, 89% yield).
8. It has been reported that treatment of imipenem with $ZnCl_2$ in a buffer solution of MOPS - KOH (pH 7.2) at 30 ℃ caused hydrolysis of the β-lactam ring.[11] However, under the conditions (pH 5.7 or 6.0, < 30 ℃) that Zn^{2+} can be gradually formed in our Zn dust procedure, the β-lactam ring must be intact.
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