

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 1 β -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 1 β -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 procedure⁴ by use of 10% Pd-C for these deprotection reactions. However, yield of **2** from **3** involving the hydrogenolytic deprotection was low (44%). Especially, 1 β -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.

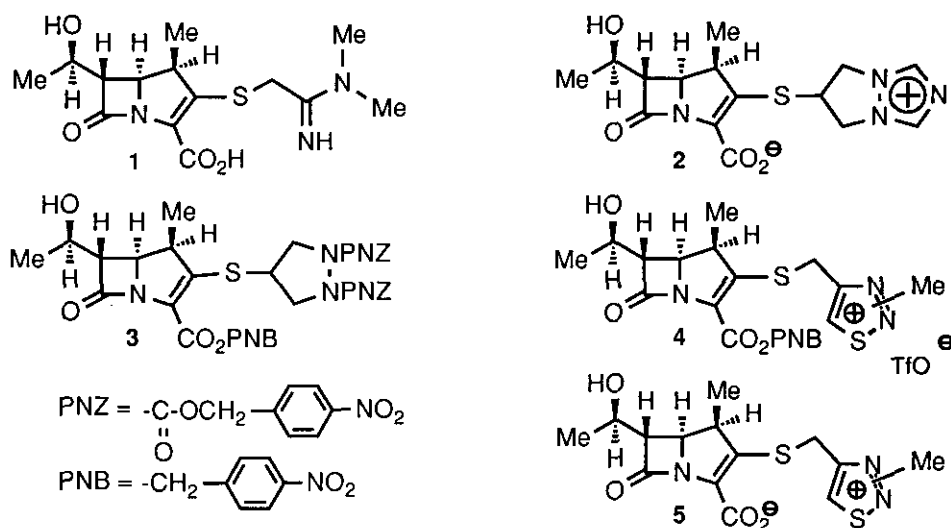


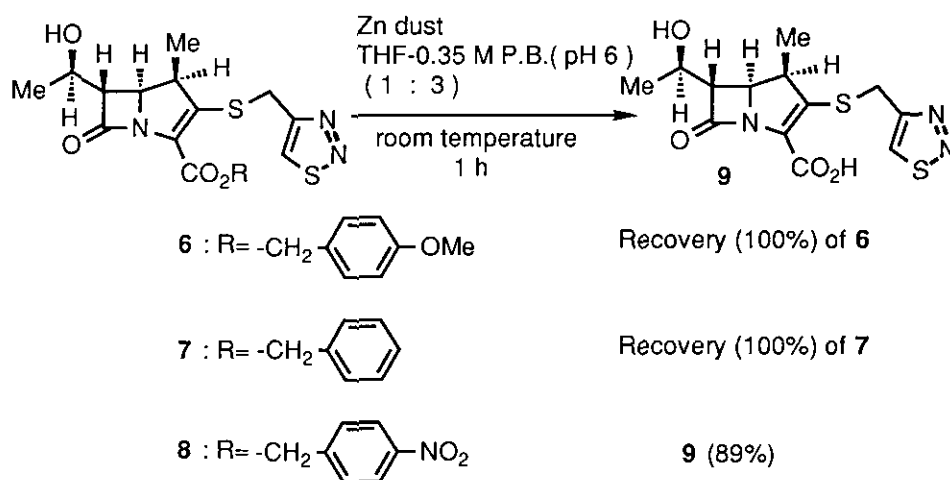
Table 1. Investigation of the reaction conditions for deprotection of PNB ester (**4**) by employing Zn dust

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 ₂ O (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).

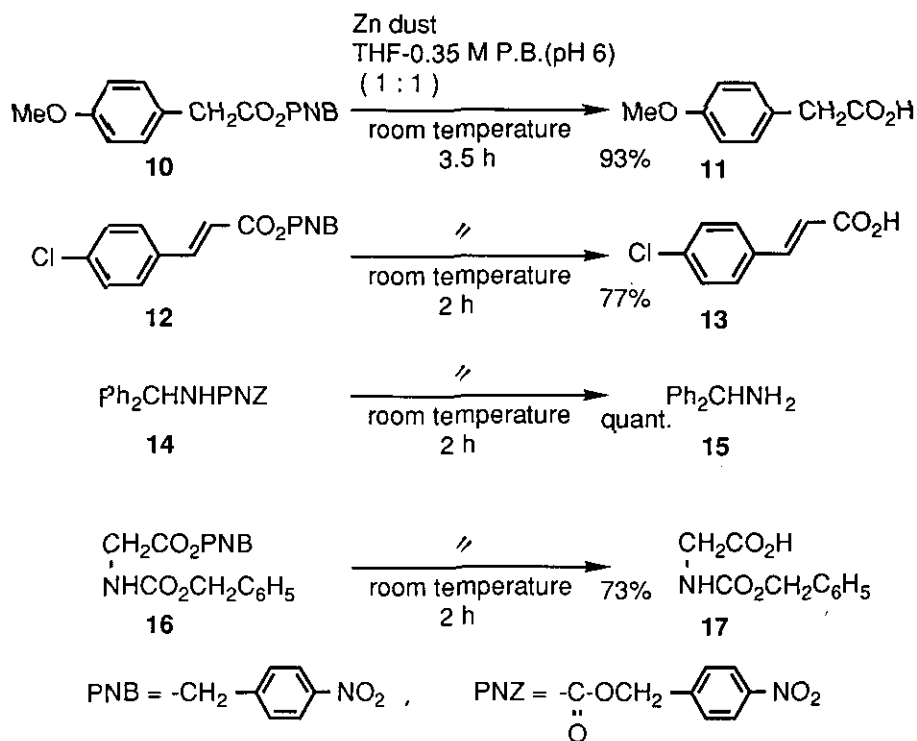
Then, we applied this Zn dust procedure to deprotection of the 1 β -methylcarbapenem esters such as methoxybenzyl ester (**6**), benzyl ester (**7**), and PNB ester (**8**) (Scheme 1). Although cleavage of **8** smoothly proceeded to afford carboxylic acid (**9**) in 89% yield,⁷ the esters (**6**) and (**7**) were quantitatively recovered, respectively (Scheme 1). It is noteworthy that S-N bond of thiadiazole,



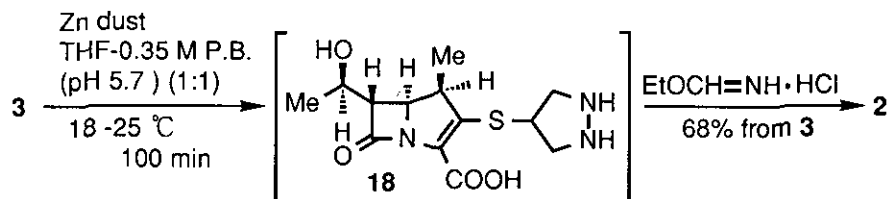
Scheme 1

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

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 °C 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



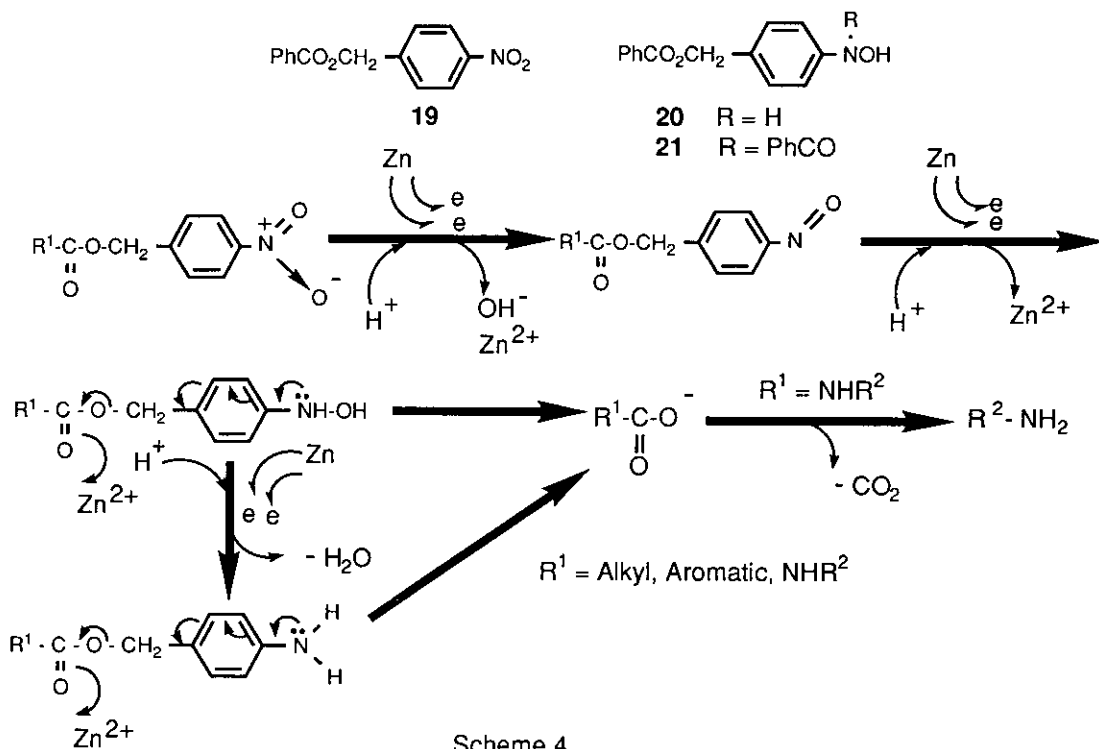
Scheme 2



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 Zn²⁺-promoted elimination of *p*-hydroxylamino-

and/or *p*-aminobenzyl group⁹ to give the corresponding carboxylic acid or amine after decarboxylation (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/cm²) for 20 min resulted in decomposition of **5** more than 50% (hplc analysis).
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7. A typical procedure: Freshly activated zinc dust¹⁰ (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 °C caused hydrolysis of the β -lactam ring.¹¹ However, under the conditions (pH 5.7 or 6.0, < 30 °C) that Zn^{2+} can be gradually formed in our Zn dust procedure, the β -lactam ring must be intact.
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