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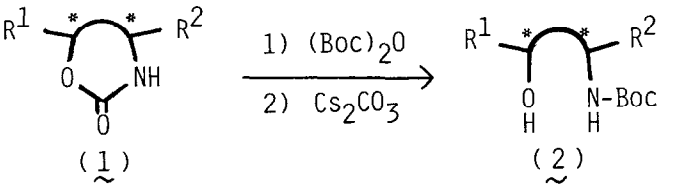
MILD AND SELECTIVE RING-CLEAVAGE OF CYCLIC CARBAMATES TO AMINO ALCOHOLS

Tadao Ishizuka and Takehisa Kunieda*
Faculty of Pharmaceutical Sciences, Kumamoto University
Oe-honmachi, Kumamoto 862 Japan

Summary: N-tert-Butoxycarbonylated 2-oxazolidinones and tetrahydro-2-oxazinones are smoothly cleaved to acyclic N-Boc-amino alcohols on treatment with catalytic amounts of cesium carbonate at room temperature. The versatility of the procedure is demonstrated in a facile cleavage of highly functionalized heterocycles without epimerization and β-elimination.

The vic- amino alcohol functionality is found in a substantial number of bioactive compounds such as enzyme inhibitors, antibiotics and sympathomimetic amines.[1] Cyclic carbamates, readily arising from cyclocarbamation of allylic or homoallylic amines and alcohols[2] and chemical modifications of 2-oxazolidinones and related heterocycles[3], have been utilized as crucial intermediates for highly stereoselective construction of 1,2- and 1,3-amino alcohol structures. Although classical methods are available for the hydrolytic conversion of cyclic carbamates into their corresponding amino alcohols,[4] the conditions are too drastic in most cases and there is still need to develop the procedures mild and selective enough to avoid undesirable reactions such as dehydration and epimerizations.

This paper describes mild and hence versatile ring-opening of five- and six-membered cyclic carbamates (1) into acyclic N-protected 1,2- and 1,3-amino alcohols (2) by the process which consists in N-tert-butoxycarbonyl protection followed by treatment with bases. The N-protection of cyclic carbamates was



(1) (2)

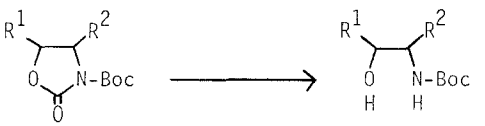
readily achieved with di-tert-butyl dicarbonate [$(Boc)_2O$] and triethylamine in the presence of catalytic amounts of 4-dimethylaminopyridine.[5] N-Boc-cyclic carbamates were found to undergo an extremely smooth ring-opening to acyclic N-Boc-amino alcohols on treatment with catalytic amounts of cesium carbonate in methanol at room temperature.[6] Among the effective bases examined including anion-exchange resins, cesium carbonate was most satisfactory with regard to mildness and selectivity. On the other hand, the similar treatment of N-benzyloxycarbonyl-2-oxazolidinones failed to give the open chain products and

N-deprotection was only observed.

Thus, the solutions of N-Boc-2-oxazolidinone and N-Boc-tetrahydro-2-oxazinone in methanol were kept in the presence of cesium carbonate (0.2 equiv) at room temperature for 3h to give N-Boc-2-aminoethanol (77%) and N-Boc-3-amino-1-propanol (79%), respectively. In the place of cesium carbonate, the use of lithium hydroxide and potassium carbonate in aqueous methanol were also satisfactory for the ring opening, while even a large excess of sodium bicarbonate or sodium acetate was entirely ineffective under the conditions. Further examples are summarized in Table I. The advantage of the cesium carbonate method over other base-hydrolyses was shown in the successful cleavage of methyl 2-oxazolidinone-5-carboxylate and 4-methoxy-2-oxazolidinone into N-Boc-isoserine methyl ester and N-Boc-2-amino-2-methoxyethanol in good yields (entries 4,6). This method leaves the amino and carboxyl functions in protected forms, thus permitting easy isolation and purification as well as further elaboration of the residue.

As shown in Table, methyl trans(4S,5R)- and cis(4S,5S)-5-methyl-2-oxazolidinone-4-carboxylates were smoothly cleaved to N-Boc-L-threonine methyl ester and N-Boc-L-allo-threonine methyl ester, respectively, without any epimerization[7] and with negligible amounts of the β-elimination products (entries 11, 12). On the other hand, treatment of methyl 2-oxazolidinone-4-carboxylate with bases including cesium carbonate gave substantial quantity of N-Boc-2-

Table I. Ring-cleavage of N-Boc-2-oxazolidinones to 1,2-Amino Alcohols[a)]



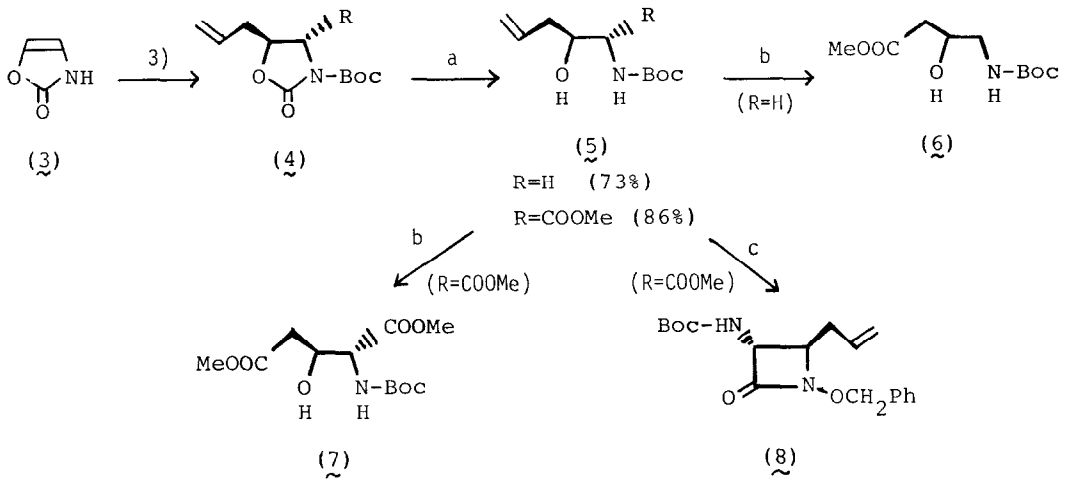
Entry	R^1	R^2	Base (equiv)	Solvent	Time	Isolated Yield
1	H	H	Cs_2CO_3 (0.2)	MeOH	3 (h)	77 (%)
2	H	H	LiOH (5.0)	MeOH-H_2O	0.5	85
3	H	H	K_2CO_3 (2.0)	MeOH-H_2O	1.5	88
4	COOMe	H	Cs_2CO_3 (0.2)	MeOH	2	72
5	C_6H_5	H	Cs_2CO_3 (0.2)	MeOH	1	94
6	H	OMe	Cs_2CO_3 (0.2)	MeOH	2	76
7	H	5-Me-2-furyl	LiOH (5.0)	MeOH-H_2O	1	84
8	allyl (threo)	5-Me-2-furyl	LiOH (5.0)	MeOH-H_2O	1	98
9	H	COOMe	Cs_2CO_3 (0.2)	MeOH	4	56 (16)[b)]
10	H	COOH	Cs_2CO_3 (1.2)	MeOH	18	73[c)] (0)[b)]
11	Me (threo)	COOMe	Cs_2CO_3 (0.2)	MeOH	3	70
12	Me (erythro)	COOMe	Cs_2CO_3 (0.2)	MeOH	3	76

a) All reactions were run at room temperature. b) Yield of methyl N-Boc-2-aminoacrylate. c) Determined as the methyl ester.

aminoacrylate as a by-product (entry 9). This β-elimination reaction was virtually suppressed to aford an exclusive formation of N-Boc-serine when the carboxylic acid (R^2=COOH) instead of the ester was treated with cesium carbonate in methanol (entry 10).

Representative experimental procedure (Table, entry 12) is given as follows: To a stirred solution of methyl (4S,5S)-3-tert-butoxycarbonyl-5-methyl-2-oxazolidinone-4-carboxylate (0.175g, 0.67 mmol) in methanol (10 ml) was added cesium carbonate (0.13 mmol) at room temperature. The reaction mixture was kept for 3h. After neutralization with citric acid, the product was extracted with ethyl acetate. Usual work-up followed by column chromatography on silica gel (CH_2Cl_2-AcOEt/8:2) gave 0.12g (76%) of N-Boc-L-allo-threonine methyl ester as an oil, $[\alpha]_D$ +26.5° (c=1.0, $CHCl_3$). ^{1}H-NMR spectrum (400MHz) showed no contamination with threo-derivatives.[7]

As outlined below, this method was successfully applied to smooth cleavage to the amino alcohols (5), which served well as synthetic intermediates for hydroxy amino acids (6 and 7) of biological interests[8] as well as β-lactam (8).[9]



a: Cs_2CO_3/MeOH, b: TBDMSi-Cl/imidazole; $NaIO_4$-$KMnO_4$; CH_2N_2; Bu_4NF,
c: LiOH; $PhCH_2ONH_2$/DPPOx[10]; $(EtOOCN)_2$/PPh_3

Work is now in progress to explore further aspects of the cesium carbonate catalyzed ring-opening reaction.

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5) High yield N-protection of the cyclic carbamates may be feasible in the presence of stronger bases, if tolerable, such as NaH and BuLi in aprotic solvents. Typical examples are given. a) A solution of 2-oxazolidinone in THF was treated with $(Boc)_2O$ (1.3 equiv) and Et_3N (1.2 equiv) in the presence of dimethylaminopyridine (0.2 equiv) at room temperature for 3h. Chromatographic purification gave 97% yield of N-Boc-2-oxazolidinone, mp 85°. b) Methyl trans-5-methyl-2-oxazolidinone-4-carboxylate was treated with NaH (1.1 equiv) in THF at room temperature for 1h. Then $(Boc)_2O$ (1.3 equiv) was added and the mixture was kept at room temperature to give 89% yield of the corresponding N-Boc methyl ester, mp 67°.

6) Similar type hydrolysis of secondary amides and lactams with large excess LiOH was reported. D. L. Flynn, R. E. Zelle and P. A. Grieco, J. Org. Chem., 48, 2424 (1983).

7) N-Boc-L-allo-Threonine methyl ester: ^{1}H-NMR ($CDCl_3$, 400MHz) δ 1.20(d,J=8.0 Hz,3H), 1.45(s,9H), 3.32(br.s,1H), 3.78(s,3H), 4.13(m,1H), 4.37(m,1H), 5.58 (br.s,1H). N-Boc-L-Threonine methyl ester: δ($CDCl_3$) 1.24(d,J=6.8Hz,3H), 1.46(s,9H), 2.77(Br.s,1H), 3.77(s,3H), 4.24-4.29(m,2H), 5.45(br.s,1H).

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