N-Carbamylamino Alcohols as the Precursors of Oxazolidinones via Nitrosation-Deamination Reaction

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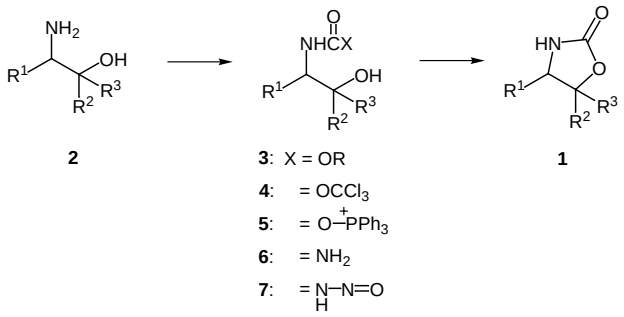
Abstract: Oxazolidinones were effectively prepared from *N*-carbamylamino alcohols by treatment with nitrous acid, via *N*-nitroso compound as the intermediate. A new route to *(R)*-4-benzyloxazolidinone was developed starting from DL-phenylalanine, utilizing D-hydantoinase-catalyzed enantioselective hydrolysis of 5-benzylhydantoin under the dynamic kinetic resolution conditions, and the subsequent reduction to the precursor for the above-mentioned cyclization reaction, by taking advantage of the intermediates bearing an *N*-carbamylamino functionality.

Key words: *N*-carbamylamino alcohols, *N*-nitrosourea, enzymes, hydrolysis, oxazolidinones

The importance of oxazolidinones **1** has been addressed in both pharmaceutical[1] and synthetic organic chemistry,[2] especially in asymmetric syntheses of natural- and non-natural products.[3,4] Needless to say, the starting materials of oxazolidinones are the corresponding amino alcohols **2**. A variety of synthetic intermediates have been elaborated, such as alkyl or aryl carbamates **3** which served for cyclization under either acidic[5] or basic[6] conditions, trichloromethyl carbamates **4** derived from the action of diphosgene[7] or triphosgene,[8] and triphenylphosphonium salts **5**[9] (Scheme 1).



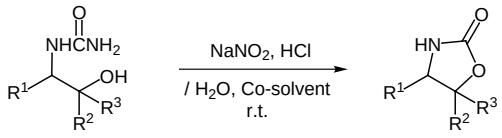
Scheme 1

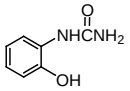
Among them, the use of urea derivatives **6** was developed more than 50 years ago.[1b,10] This is an excellent method, in terms of the cheapness of the derivatizing reagents; the intermediates can be prepared by the reaction of amino alcohols between either urea or potassium cyanate. The cyclization reaction of the urea intermediates **6**, however, requires an elevated temperature. Our plan was the treatment of **6** with nitrous acid to convert the amino group to the corresponding *N*-nitroso compounds **7**,[11] which would eventually eliminate a nitrogen molecule and water under milder conditions.

Toward this end, *N*-carbamylamino alcohol **6a** was treated with sodium nitrite in the presence of hydrochloric acid at room temperature. The initially formed intermediate **7a** immediately cyclized to the corresponding oxazolidinone **1a** in 88% yield. The major byproduct was the further *N*-nitrosated oxazolidinone.[12] To avoid this undesirable reaction, a two-phase method was attempted, by the addition of an organic co-solvent. For this purpose, ethyl acetate was effective and the yield was slightly improved (90%).

The results were summarized in the Table. The efficiency of the reaction was, indeed, affected by both the steric hindrance of the products and the solubility of the starting material. For example, acetic acid was essential for the dissolution of a crystalline substrate **6c**. An *N*-carbamylamino alcohol with a tertiary alcohol moiety **6d**, which was prepared by the addition of Grignard reagent on amino acid ester,[7c,13] was also effective. It was concluded that the elaboration of the reaction conditions, especially the equivalence of the nitrosation reagent as well as the choice of the co-solvent was important.[14] The above

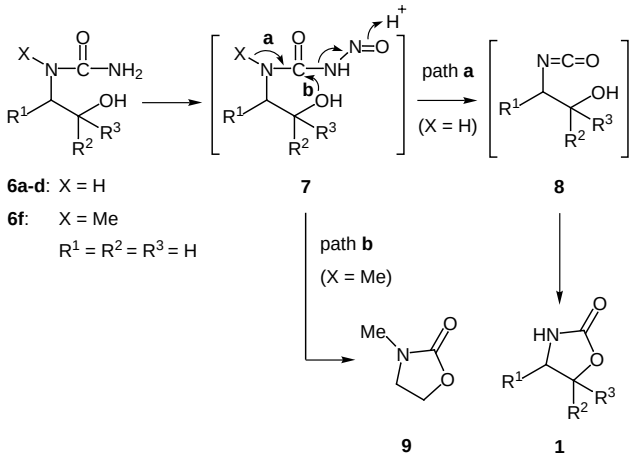
Table



Substrate **6**	R^1	R^2	R^3	Co-solvent	Yield of **1** (%)
a	$PhCH_2$	H	H	——	88
				$(i\text{-Pr})_2O$	74
				AcOEt	90
b	*i*-Pr	H	H	——	92
				AcOEt	91
c	Ph	Ph	H	AcOH	quant.
d	$PhCH_2$	Me	Me	——	87
e				——	30

cyclization of *N*-carbamylamino phenol **6e**, which is susceptible to nitrosation on aromatic ring, proceeded, although the yield of **1e** was as low as 30%. An attempt for the application of this reaction on the related substrate, *N*-thiocarbamylamino alcohol,[15] resulted only in decomposition of the precursor.

The reaction intermediate after the elimination of leaving groups from the precursors **3**-**6** had been supposed to be isocyanates **8** via path **a**.[1b,16] In the present case, however, *N*-methyl derivative **6f** also afforded efficiently (89% yield) the corresponding oxazolidinone **9**.[17] This result suggests another path, **b**, involving the participation of the neighboring hydroxyl group, at the stage of the elimination.

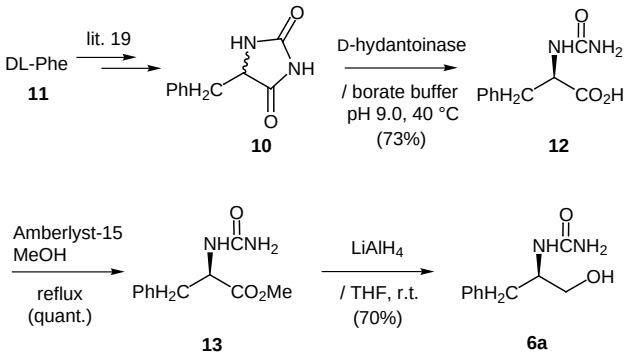


Scheme 2

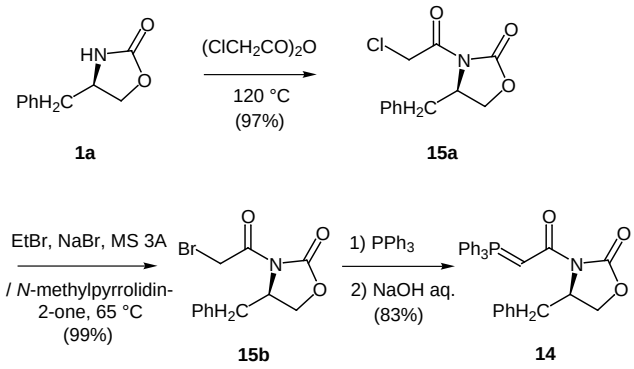
Next, we turned our attention to the *N*-carbamylamino functionality, which plays an important role in the cyclization reaction. The *N*-carbamylamino alcohols would be obtained by the reduction of the corresponding *N*-carbamylamino acids, whose enantiomerically enriched forms have been obtained by the enzyme-catalyzed hydrolysis[18] of the corresponding hydantoins.

This pathway is exemplified in Scheme 3. A hydantoin **10**,[19] prepared from DL-phenylalanine (**11**) was hydrolyzed with commercially available Adzuki bean D-hydantoinase (Sigma).[20] The enantioselective hydrolysis proceeded with concomitant racemization of the substrate[18] to give *(R)*-**12**. This was converted to *N*-carbamylamino alcohol **6a** via methyl ester **13**.[21]

The increased availability of *(R)*-**1a** encouraged us to develop an expeditious route to the Wittig phosphorane **14**, whose advantage in natural product synthesis has recently been demonstrated.[22] The intermediate **15a** could effectively be prepared by the reaction of **1a** with excess amount of chloroacetic anhydride[1b] in 97% yield.[23] Chloroacetamide **15a** was readily converted to the corresponding bromide **15b**,[24,25] which is the direct precursor of **14**,[26] and this total path could avoid the use of lachrymator bromoacetyl bromide for the acylation step (Scheme 4).



Scheme 3



Scheme 4

In conclusion, new route to oxazolidinones from amino alcohols and amino acids was developed, and some routes for the derivatization of the products became available.

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(14) Typical cyclization procedure: To a solution of *(R)-N*-carbamyl-valinol (**6b**, 100 mg, 0.68 mmol) in 2 M HCl (5.1 mL) was added a solution of $NaNO_2$ (57 mg, 0.83 mmol) in water (0.3 mL). After stirring at room temperature for 40 min, the reaction mixture was extracted with AcOEt three times. The combined organic layer was washed with brine and dried over Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel column chromatography (14 g). Elution with hexane-AcOEt (1:3) afforded *(R)*-**1b** (92% yield). Recrystallization from hexane-AcOEt afforded colorless needles. Mp 71.0 °C; $[\alpha]_D^{22}$+19.3 (c 1.00, EtOH) [lit.[6e] $[\alpha]_D^{20}$ -20.0 (c 1, EtOH) for *(S)*-**1b**]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (br s, 1H), 4.45 (t, 1H, *J* = 8.8 Hz), 4.10 (dd, 1H, *J* = 6.3, 8.8 Hz), 3.62 (m, 1H), 1.73 (m, 1H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.3 Hz); IR (KBr) 3270, 2961, 1750, 1726, 1472, 1406, 1362, 1247, 1091, 1050, 1010 cm^{-1}.
(S)-**1d** [from *(S)*-**6d**]: Mp 67.4-67.8 °C; $[\alpha]_D^{22}$ −103.9 (c 1.00, $CHCl_3$) [lit.[27] $[\alpha]_D^{23}$ −103.5 (c 0.6, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 5H), 5.02 (br s, 1H), 3.62 (dd, 1H, *J* = 3.9, 10.5 Hz), 2.76 (dd, 1H, *J* = 3.9, 13.4 Hz), 2.61 (dd, 1H, *J* = 10.5, 13.4 Hz), 1.40 (s, 3H), 1.38 (s, 3H); IR (KBr) 3260, 2976, 1748, 1732, 1374, 1307, 1270, 1145, 1089, 997 cm^{-1}.
1e: Mp 106.0-107.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 7.37-7.22 (m, 4H); IR (KBr) 3231, 1775, 1736, 1481, 1343, 1147, 1009 cm^{-1}.
Use of AcOEt as co-solvent. To a solution of *(R)*-**6a** (200 mg, 1.03 mmol) in 2 M HCl (1.5 mL, 3.0 mmol) and AcOEt (4.0 mL) was added a solution of $NaNO_2$ (197 mg, 2.85 mmol) in water (1.0 mL). The reaction mixture was stirred at room temperature for 5 min. The reaction was worked up in the same manner as above. *(R)*-**1a**: Mp 88.2-88.8 ¡C; $[\alpha]_D^{23}$+63.5 (c 1.035, $CHCl_3$) [lit.[7a] $[[\alpha]_D^{25}$+64 (c 1.00, $CHCl_3$)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.12 (br s, 1H), 4.52-4.04 (m, 3H), 2.95-2.81 (m, 2H); IR (KBr) 3282, 2925, 1753, 1709, 1475, 1405, 1245, 1096, 1021 cm^{-1}. This reaction could reproducibly be performed in more than 5 g scale.
Use of AcOH as co-solvent. To a suspension of (1*S*,2*R*)-**6c** (50 mg, 0.20 mmol) in 2 M HCl (2.5 mL, 5.0 mmol) and acetic acid (2.5 mL) was added a solution of $NaNO_2$ (38 mg, 0.55 mmol) in water (0.5 mL). After stirring at room temperature for 5 min, a white solid was deposited. To the reaction was added aqueous KOH until the pH of the mixture reached 10, and worked up in the same manner as above. (4*R*,5*S*)-**1c**: Mp 226.5-226.7 °C; $[\alpha]_D^{19}$+61.3 (c 1.00, MeOH) [lit.[28] $[\alpha]_D^{20}$+60.6 (c 0.858, MeOH)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.03 (m, 5H), 6.89 (m, 5H), 5.88 (d, 1H, *J* = 8.1 Hz), 5.68 (br s, 1H), 5.12 (d, 1H, *J* = 8.1 Hz); IR (KBr) 3271, 1748, 1711, 1455, 1352, 1236, 1095, 1072 cm^{-1}. The spectral data of **1a**-**1e** and **9** were identical with those of commercially available samples.

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(17) **9**:^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (t, 2H, *J* = 8.1 Hz), 3.58 (t, 2H, *J* = 8.1 Hz), 2.90 (s, 3H); IR (NaCl) 3504, 2922, 1746, 1498, 1442, 1407, 1271, 1125, 1045 cm^{-1}.

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(21) D-Hydantoinase (Sigma, H4028, 54.0 mg, 25.3 units) was added to a solution of the hydantoin (**10**, 400 mg, 2.10 mmol) in borate buffer (pH 9.0, 105 mL), and the mixture was stirred for 2 days at 40 °C. After adjustment of its pH to 3.0 with diluted H_2SO_4, the reaction mixture was lyophilized. The residue was charged in a glass-made column and eluted with EtOH. The extract was concentrated in vacuo, and the residue was purified by silica gel column chromatography (8 g). Elution with AcOEt afforded **12** (73% yield). Quantitative determination of **12** was carried out colorimetrically according to the reported procedure.[29a] **12**: mp 178.0-178.4 °C; $[\alpha]_D^{20}$ −40.2 (c 0.99, MeOH); ^{1}H NMR (270 MHz, CD_3OD) δ 7.17 (m, 5H), 4.46 (dd, 1H, *J* = 5.0, 7.3 Hz), 3.08 (dd, 1H, *J* = 5.0, 13.9 Hz), 2.91 (dd, 1H, *J* = 7.3, 13.9 Hz); IR (KBr) 3455, 3303, 1696, 1637, 1561, 1303, 1259, 1157 cm^{-1}. Its optical rotation was identical with an authentic sample prepared from D-phenylalanine. Although a microbial D-hydantoinase from *Pseudomonas putida* IFO 12996[29] was also available, the effectiveness of the commercial Adzuki bean enzyme was superior for this substrate, especially in the laboratory-scale preparation.
A stirring solution of *(R)-N*-carbamyl-phenylalanine (**12**, 1.50 g, 7.20 mmol) in MeOH (100 mL) was treated with Amberlyst-15 (1.52 g) and refluxed for 70 min. After cooling to room temperature, the reaction mixture was filtered. The organic layer was concentrated in vacuo and the residue was purified through silica gel (12 g). Elution with AcOEt afforded *(R)-N*-carbamyl-phenylalanine methyl ester **13** (*quant.*). Recrystallization from hexane-AcOEt provided colorless needles. Mp 103.2-103.7 °C; $[\alpha]_D^{21}$ −66.9 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 5H), 5.78 (d, 1H, *J* = 8.3 Hz), 4.76-4.69 (m, 3H), 3.69 (s, 3H), 3.07 (dd, 1H, *J* = 5.6, 13.9 Hz), 2.97 (dd, 1H, *J* = 6.6, 13.9 Hz); IR (KBr) 3413, 3327, 3214, 3026, 2956, 1726, 1650, 1542, 1391, 1255 cm^{-1}. Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.49; H, 6.31; N, 12.54.
To a vigorously stirred suspension of $LiAlH_4$ (23 mg, 0.61 mmol) in dry THF (1.5 mL) was added, a solution of **13** (100 mg, 0.45 mmol) in dry THF (2.5 mL) dropwise. After stirring for 40 min, the reaction was quenched with H_2O, added Na_2SO_4 (5 g) and lyophilized. The residue was charged in a glass-made column and eluted with MeOH. The extract was concentrated in vacuo to give **6a** (70% yield). **6a**:^{1}H NMR (270 MHz, D_2O) δ 7.31 (m, 5H), 3.88 (br s, 1H), 3.63 (dd, 1H, *J* = 4.9, 11.5 Hz), 3.51 (dd, 1H, *J* = 6.6, 11.5 Hz), 2.89 (dd, 1H, *J* = 4.9, 13.7 Hz), 2.64 (dd, 1H, *J* = 9.0, 13.7 Hz). This was further derived to **1a**: mp 88.0-88.5 °C; $[\alpha]_D^{24}$+64.1 (c 1.00, $CHCl_3$).

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(23) A mixture of **1a** (1.00 g, 5.64 mmol) and chloroacetic anhydride (4.82 g, 28.2 mmol) was heated at 120 °C and stirred overnight. After cooling to room temperature, the reaction mixture was poured into a mixture of pyridine (4.11 mL, 50.8 mmol) and catalytic amounts of DMAP in ice, and stirred for the decomposition of excess chloroacetic anhydride. Conventional workup and chromatographic separation [hexane-AcOEt (4:1)] afforded **15a** (97% yield). Recrystallization from Et_2O-$CHCl_3$ provided colorless prisms. Mp 75.0-75.3 °C; $[\alpha]_D^{24}$ −72.8 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.73 (s, 2H), 4.69 (m, 1H), 4.30-4.22 (m, 2H), 3.32 (dd, 1H, *J* = 3.4, 13.7 Hz), 2.82 (dd, 1H, *J* = 9.3, 13.7 Hz); IR (KBr) 3527, 3427, 3060, 3023, 2938, 1768, 1721, 1392, 1356 1238, 1212 cm^{-1}. Anal. Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.82; H, 4.77; N, 5.52. Found: C, 57.10; H, 4.64; N, 5.47.

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(25) A mixture of **15a** (500 mg, 1.97 mmol), ethyl bromide (1.49 mL, 19.7 mmol), NaBr (41mg, 0.39 mmol), *N*-methyl-pyrrolidin-2-one (1.96 mL) and MS 3A (1.20 g) was stirred and heated at 65 °C for 20 hours. Conventional workup and chromatographic separation [hexane-AcOEt (1:1)] afforded **15b** (99% yield). Recrystallization from Et_2O provided colorless needles. Mp 36.2-36.8 °C [lit.[30] mp 41-42 °C]; $[\alpha]_D^{21}$ −79.3 (c 1.01, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 4.71 (m, 1H), 4.56 (d, 1H, *J* = 12.9 Hz), 4.52 (d, 1H, *J* = 12.9 Hz), 4.30-4.21 (m, 2H), 3.33 (dd, 1H, *J* = 3.2, 13.4 Hz), 2.81 (dd, 1H, *J* = 9.5, 13.4 Hz); IR (KBr) 3530, 3381, 3063, 3030, 2986, 1781, 1698, 1386, 1359, 1328, 1200 cm^{-1}. Anal. Calcd. for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N,4.70. Found: C, 48.40; H, 4.15; N, 4.53. Its NMR spectrum was identical with that reported previously.[30]

(26) PPh_3 (97 mg, 0.37 mmol) was added to a solution of the bromoacetamide (**15b**, 109 mg, 0.37 mmol) in CH_2Cl_2 (4.0 mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in hot-water (150 mL). After the addition of 4M NaOH (120 μL), the mixture was immediately extracted with AcOEt and the organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo afforded **14** (83% yield in 2 steps) as colorless solid. Mp 168.2-170.2 °C; $[\alpha]_D^{20}$ −41.3 (c 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 6H), 7.52 (m, 9H), 7.25 (m, 5H), 4.80-4.74 (m, 2H), 4.10 (m, 1H), 4.02 (dd, 1H, *J* = 2.7, 8.8 Hz), 3.28 (dd, 1H, *J* = 3.3, 13.2 Hz), 2.83 (dd, 1H, *J* = 9.3, 13.2 Hz); IR (KBr) 3059, 1753, 1595, 1438, 1362, 1343, 1192, 1106 cm^{-1}.

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