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Isocyanates, Part 5.[1]

Synthesis of Chiral Oxazolidin-2-ones and Imidazolidin-2-ones *via* DMAP-Catalyzed Isocyanation of Amines with Di-*tert*-butyl Dicarbonate

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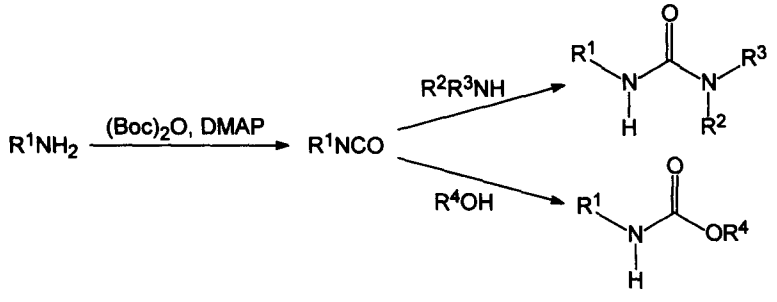
Abstract: Oxazolidin-2-ones and imidazolidin-2-ones are prepared under mild reaction conditions by DMAP-catalyzed isocyanation of 1,2-aminoalcohols and 1,2-diamines with di-*tert*-butyl dicarbonate and subsequent cyclization.

Optically active oxazolidin-2-ones derived from α-amino acid esters are an important class of chiral auxiliaries for asymmetric synthesis.[2] They were applied for example to the total syntheses of the macrolide antibiotic rutamycin B[3] and the immunosupressant (–)-FK-506.[4] More recently, enantiopure imidazolidin-2-ones were used as chiral auxiliaries for dynamic kinetic resolution.[5] The most common method for the preparation of oxazolidin-2-ones and imidazolidin-2-ones is the reaction of 1,2-aminoalcohols and 1,2-diamines with diethyl carbonate,[6] phosgene,[7] triphosgene,[8] or 1,1'-carbonyldiimidazole.[9]

We recently reported a novel procedure for the synthesis of isocyanates under mild conditions (10 min at room temperature) by a DMAP-catalyzed[10] reaction of amines[11] and α-amino acid esters[1] with di-*tert*-butyl dicarbonate, $(Boc)_2O$. *In situ* derivatization of the isocyanates by addition of amines and alcohols affords the corresponding ureas[12] and carbamates[13] (Scheme 1).



Scheme 1

An intramolecular version of the above-mentioned *in situ* addition of amines and alcohols should provide an easy access to a variety of cyclic ureas and cyclic carbamates. Thus, using the standard set of reaction conditions for the isocyanation of amines, $(Boc)_2O$, DMAP, 10 min, 20°C, a broad range of enantiopure 1,2-aminoalcohols were converted into the corresponding oxazolidin-2-ones **1** (Table 1).

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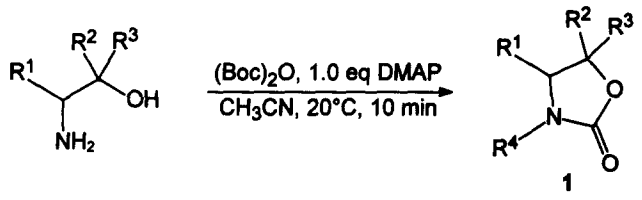


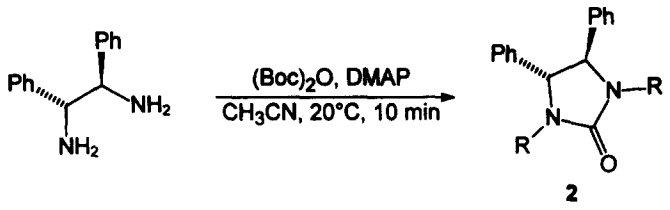
Table 1. Synthesis of enantiomerically pure oxazolidin-2-ones **1**.

	R^1	R^2	R^3	R^4	$(Boc)_2O$ [eq]	**1**, Yield [%]	$[\alpha]_D^{20}$, c=1, solvent
a	(*R*)-Et	H	H	H	1.1	85	+5.9°, $CHCl_3$
b	(*S*)-*i*Pr	H	H	H	1.1	71 [a]	–20.0°, EtOH
c	(*S*)-*t*Bu	H	H	H	1.1	90	–19.6°, EtOH
d	(*R*)-Ph	H	H	H	1.1	66	–60.4°, $CHCl_3$
e	(*R*)-CH_2Ph	H	H	H	1.1	63	+64.9°, $CHCl_3$
f	(*R*)-Ph	(*S*)-Ph	H	H	1.1	80	+80.9°, $CHCl_3$
g	(*S*)-Me	Ph	Ph	H	1.1	65	–298.9°, DMF
h	(*R*)-Et	H	H	Boc	2.1	81 [b]	–36.4°, $CHCl_3$
i	(*S*)-*i*Pr	H	H	Boc	2.1	85 [b]	+49.9°, $CHCl_3$
j	(*S*)-*t*Bu	H	H	Boc	2.1	95 (72)[c]	+41.9°, EtOH
k	(*R*)-Ph	H	H	Boc	2.1	85	–68.9°, $CHCl_3$
l	(*R*)-CH_2Ph	H	H	Boc	2.1	84	–19.4°, $CHCl_3$
m	(*R*)-Me	(*R*)-Ph	H	Boc	2.1	82	–70.4°, $CHCl_3$
n	(*R*)-Ph	(*S*)-Ph	H	Boc	2.1	92 (78)[c]	+74.0°, $CHCl_3$
o	(*S*)-Me	Ph	Ph	Boc	2.1	81	–252.3°, $CHCl_3$

[a] Solvent: CH_2Cl_2. [b] Solvent: CH_2Cl_2, reaction time: 60 min. [c] Catalytic reaction with 0.1 eq DMAP.

Dependent on the amount of di-*tert*-butyl dicarbonate (1.1 or 2.1 eq) either the *N*-unsubstituted oxazolidin-2-ones **1a-g** or the *N*-Boc-oxazolidin-2-ones **1h-o** were obtained as products. In the synthesis of the *N*-unsubstituted heterocycles the *N*-Boc- and *N,O*-bis-Boc-1,2-aminoalcohols were formed as by-products due to competing *tert*-butoxycarbonylation of starting material. Again, we noted that high sterical demand of substituents in the α- or β-position of the amino group leads to higher yields of the isocyanates and their consecutive products. Therefore, (*S*)-2-amino-3,3-dimethyl-1-butanol (*tert*-valinol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol gave the best results. The transformation to the oxazolidin-2-ones **1** was also achieved by using catalytic amounts of DMAP. The values for the optical rotation of **1a-e** and **1l** were in agreement with those reported in the literature,[14] indicating that the cyclization to the oxazolidin-2-ones occurred without partial racemization.

The method was also used for the transformation of 1,2-diamines to the imidazolidin-2-ones **2** (Table 2). In this case the intramolecular trapping is much more efficient because of the higher nucleophilicity of the amine. Thus, (1*R*,2*R*)-1,2-diamino-1,2-diphenylethane was quantitatively converted to the *N,N'*-bis-Boc-substituted cyclic urea **2a** with 3.1 eq of di-*tert*-butyl dicarbonate using stoichiometric or catalytic amounts of DMAP. The value for the optical rotation of the *N,N'*-unsubstituted imidazolidin-2-one **2b** was in agreement with that reported in the literature.[15]

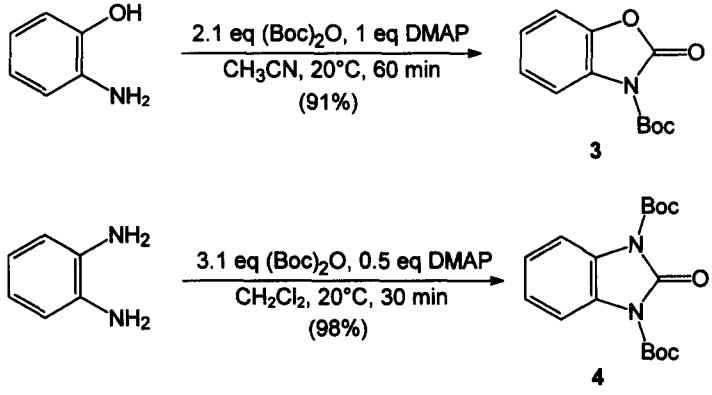


2

Table 2. Synthesis of (4*R*,5*R*)-4,5-diphenylimidazolidin-2-ones **2**.

	R	$(Boc)_2O$ [eq]	DMAP [eq]	**2**, Yield [%]	$[\alpha]_D^{20}$, c=1, solvent
a	Boc	3.1	1.0	94	+30.1°, $CHCl_3$
a	Boc	3.1	0.1	96	+30.1°, $CHCl_3$
b	H	1.1	1.0	81	+53.3°, $CHCl_3$

For **1a** and **2b** the formation of an intermediate β-hydroxy and β-amino isocyanate was confirmed by following the reaction using FT-IR spectroscopy. A band for the intermediate isocyanate occurred at 2273 and 2274 cm^{-1} respectively, increased to a maximum (after a reaction time of 29 s in case of **1a**), and decreased again due to cyclization to the heterocycles. Subsequent to the cyclization an additional *N*-*tert*-butoxycarbonylation of the cyclic carbamates and ureas occurred if an excess of di-*tert*-butyl dicarbonate was applied. The efficiency of the DMAP/$(Boc)_2O$ reagent for the *N*-Boc protection of amides and carbamates is well-known.[16]



3 **4**

Scheme 2

The corresponding benzo-annulated heterocycles are also available by the present method. Using 2.1 eq di-*tert*-butyl dicarbonate and stoichiometric amounts of DMAP *o*-aminophenol afforded the *N*-Boc-protected benzoxazolin-2-one **3** in 91% yield.[17] Reaction of *o*-phenylenediamine with 3.1 eq $(Boc)_2O$ and substoichiometric amounts of DMAP provided quantitatively the *N*,*N*'-bis-Boc-benzimidazolin-2-one **4** (Scheme 2).[17]

In conclusion, a novel method for the synthesis of oxazolidin-2-ones and imidazolidin-2-ones under mild reaction conditions was developed using the DMAP/$(Boc)_2O$ reagent system. Either the *N*-unsubstituted or the *N*-Boc-protected heterocycles were obtained dependent on the amount of $(Boc)_2O$. The present one-pot procedure provides an improved route to Boc-protected chiral oxazolidin-2-one auxiliaries.[18]

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17. **3**: colorless crystals, mp 78°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.65 (s, 9 H), 7.13-7.19 (m, 3 H), 7.65 (m, 1 H); ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 27.87 (3 CH_3), 86.03 (C), 109.82 (CH), 114.50 (CH), 124.25 (CH), 124.62 (CH), 127.35 (C), 141.56 (C), 147.43 (C=O), 149.26 (C=O). Analysis calcd. for $C_{12}H_{13}NO_4$: C 61.27, H 5.57, N 5.95; found: C 61.51, H 5.71, N 5.92.
4: colorless crystals, mp 144°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 18 H), 7.20 (m, 2 H), 7.85 (m, 2 H); ^{13}C NMR and DEPT (100 MHz, $CDCl_3$): δ = 28.02 (6 CH_3), 85.30 (2 C), 113.99 (2 CH), 124.29 (2 CH), 126.10 (2 C), 147.32 (C=O), 148.44 (2 C=O). Analysis calcd. for $C_{17}H_{22}N_2O_5$: C 61.07, H 6.63, N 8.38; found: C 61.07, H 6.70, N 8.29.
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