N-Protected *N*-Carboxyanhydrides IX**. Synthesis of *N*-Aralkyl α-Amino Acid *N*-Carboxyanhydrides by Carbonyl Insertion with Bis(*N*-Succinimidyl)Carbonate

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Cyclization of *N*-aralkyl α-amino acids to *N*-carboxyanhydrides without using phosgene is reported. The weakly acidic reaction conditions allow a safe preparation of new acid-labile derivatives for peptide synthesis.

The standard procedure[2] for preparing *N*-carboxyanhydrides (NCAs) of α-amino acids by means of phosgene, in addition to requiring special safety precautions, proceeds with the formation of two equivalents of hydrogen chloride. Thus, preservation of acid-sensitive groups in the amino acid calls for extra measures in order to reduce the extent of cleavage. Kricheldorf[3] avoided hydrogen chloride formation by first converting the amino acid to the trimethylsilyl derivative. Hirschmann *et al.*[4] were able to prepare N^{ε}-t-butyloxycarbonyl (Boc) lysine NCA in 55 % yield via the silver salt of N^{ε}-Boc lysine. Undesired reactions of phosgene itself with amino acid side chain functions have also been described, such as dehydration of asparagine and glutamine to β- and γ-cyano derivatives[5].

Results and discussion

The amino-protecting group 9-xanthyl (X)[6] is even more susceptible to acid than Boc, and phosgene treatment of N^{α} X amino acids, even in the presence of acid scavengers, is therefore associated with low yields (5–30 %) of X-NCAs. However, we found that high yields (50–90 %) are obtained when another carbonyl insertion reagent, bis(*N*-succinimidyl) carbonate (DSC) is used instead of phosgene for cyclization of *N*-aralkyl amino acids to the corresponding NCAs (Fig. 1).

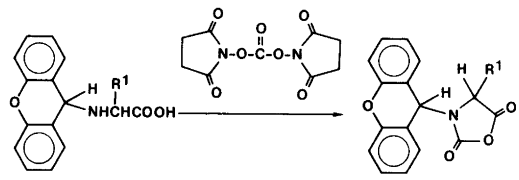

Fig. 1. Cyclization of X amino acid to X–NCA.

In contrast to hydrogen chloride, the by-product *N*-hydroxysuccinimide is only weakly acidic, and therefore not harmful to Boc or X groups. An additional advantage is the substitution of the safe, commercially available[7] solid DSC for the toxic gas phosgene. DSC is used in peptide chemistry for conversion of *N*-acyl amino acids, such as benzyloxycarbonyl and Boc amino acids to succinimidyl (Su) esters[8]. In this reaction, the central carbonyl group of DSC is relased as carbon dioxide. *N*-Aralkyl amino acids, for example 2,4-dimethoxybenzyl (DMB), 4,4′-dimethoxybenzhydryl (Mbh) and X amino acids[9], contain a secondary α-amino function, which is a better nucleophile than the carboxylate. Accordingly, a different reaction occurs, resulting in the formation of *N*-aralkyl NCA, incorporating the carbonyl group donated by DSC. The mechanism

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**See Ref. 1.

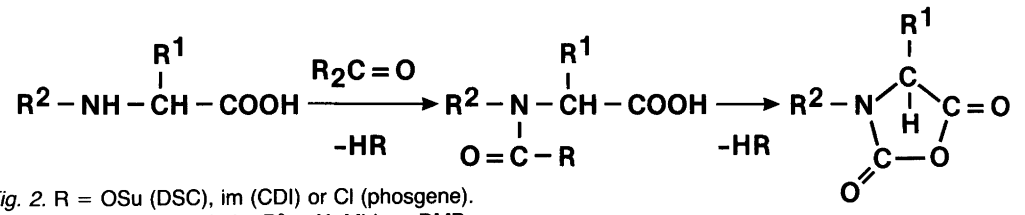

Fig. 2. R = OSu (DSC), im (CDI) or Cl (phosgene).
R^1 = Amino acid side chain, R^2 = X, Mbh or DMB.

presumably involves *N*-substitution by R–CO–, followed by intramolecular anhydride formation catalyzed by tertiary amine (Fig. 2). Thus, the outcome is carbonyl insertion, by analogy to the reported reaction of DSC with aromatic diamines and aminophenols producing 2-hydroxybenzimidazoles and 2-hydroxybenzoxazoles[10]. 1,1′-Carbonyldiimidazole (CDI) also has been used to synthesize five-membered heterocycles by carbonyl insertion, i.e. ureas[11], urethanes[11], and carbonates[12] from diamines, aminoalcohols and *cis*-1,2-diols. However, in the present case, the use of CDI is accompanied by racemization (Table 2).

Attempts to convert *N*-triphenylmethyl (Trt) alanine to Trt–Ala NCA by reaction with DSC were unsuccessful, and resulted in the isolation of Trt–Ala–OSu instead. Apparently the bulky Trt-group prohibits *N*-substitution by R–CO– (cf. Fig. 2). This effect was observed also with CDI.

The possibility of using carbonyl insertion reagents like DSC for NCA synthesis probably has not been realized previously because of the poor solubility of free amino acids in organic solvents, and because free NCAs tend to polymerize during work-up. Both of these difficulties are overcome by *N*-aralkyl substitution[9]. X-NCAs have been shown to be useful derivatives in peptide synthesis[6,9,13]. The 9-xanthyl substituent, of proven utility in the classic derivation of amides, contributes to the inherent tendency of NCAs to crystallize, thereby providing well defined, activated amino acid derivatives. The present procedure, due to the mild reaction conditions, opens a route to novel X–NCAs with acid-labile side chain substituents suitable for the synthesis of larger peptides.

Experimental

General procedure: *N*-Aralkyl amino acid (5 mmol) was dissolved/suspended in dry, peroxide-free tetrahydrofuran (75 ml), and DSC (6 mmol) added, followed by triethylamine (0.5 mmol). The progress of the reaction and the purity of the NCA were monitored by thin layer chromato-

Table 1. ^{1}H NMR spectroscopic data of the NCAs synthesized. δ/ppm, 400 MHz, 295 K, solvent: $CDCl_3$, reference: TMS.

Mbh–Arg (NO_2) NCA	1.40–1.85 (m, 4H, $2CH_2$); 3.07 (m, 2H, δ–CH_2; 3.80 (s, 6H, $2CH_3O$); 4.20 (m, 1H, α–CH); 6.06 (s, 1H, CH); 6.89 (t, 4H, *J*=8.5Hz, ArH); 7.17 (t, 4H, *J*=9.5Hz, ArH).
Mbh–Val NCA	0.90 (d, 3H, *J*=6.5Hz, CH_3); 1.05 (d, 3H, *J*=6.5Hz, CH_3); 1.92 (m, 1H, CH); 3.80 (d, 6H, *J*=6.6Hz, $2CH_3O$); 4.00 (d, 1H, *J*=3.2Hz, α–CH); 6.00 (s, 1H, CH); 6.90 (m, 4H, ArH); 7.20 (m, 4H, ArH).
DMB–Leu NCA	0.90 (d, 3H, *J*=6.5Hz, CH_3); 0.98 (d, 3H, *J*=6.5Hz, CH_3); 1.78 (m, 2H, CH_2); 1.94 (m, 1H, CH); 3.84 (d, 6H, *J*=1.5Hz, $2CH_3O$); 4.02 (t, 1H, *J*=6.0Hz, α–CH); 4.18 (d, 1H, *J*=14.5Hz, benzyl H); 4.81 (d, 1H, *J*=14.5Hz, benzyl H); 6.49 (m, 2H, 3–ArH); 7.25 (d, 1H, *J*=8.5Hz, 2–ArH).
X–Val NCA	0.40 (d, 3H, *J*=6.5Hz, CH_3); 0.83 (d, 3H, *J*=6.5Hz, CH_3); 1.45 (m, 1H, CH); 3.60 (d, 1H, *J*=3.5Hz, α–CH); 6.74 (s, 1H, 9–ArH); 7.10–7.75 (m, 8H, ArH).
X–Leu NCA	0.46 (d, 3H, *J*=6.5Hz, CH_3); 0.52 (d, 3H, *J*=6.5Hz, CH_3); 1.06 (m, 1H, CH_2); 1.20 (m, 1H, CH_2); 1.36 (m, 1H, CH); 3.71 (m, 1H, α–CH); 6.70 (s, 1H, 9–ArH); 7.13–7.65 (m, 8H, ArH).
X–Phe NCA	2.41 (m, 1H, benzyl H); 2.75 (m, 1H, benzyl H); 3.96 (m, 1H, α–CH); 6.45 (d, 2H, *J*=7.5Hz, ArH); 6.70 (s, 1H, 9–ArH); 7.05–7.66 (m, 11H, ArH).
X–Lys (Boc) NCA	0.55–1.63 (m, 6H, $3CH_2$); 1.45 (s, 9H, $3CH_3$ (Boc)); 2.78 (m, 2H, ε–CH_2); 3.79 (m, 1H, α–CH); 4.25 (m, 1H, NH); 6.72 (s, 1H, 9–ArH); 7.15–7.70 (m, 8H, ArH).

Table 2. Physical data of the NCAs synthesized.

	Lit.[6,9] or C, H, N (upper calc, lower fd)			DSC/NEt_3		
NCA	*a* Yield /% (C	M.p./°C H	*b* $[\alpha]^{20}_{578}$ N)	*a* Yield /%	M.p./°C	*b* $[\alpha]^{20}_{578}$ *c*
Mbh–L–Arg	(56.04	5.34	14.86)	49	85–90	
(NO_2)	(56.37	5.60	14.22)			
Mbh–L–Val	30[9]	78–80	+69.0	51	77–78	+74.1
DMB–L–Leu	40[9]	41–42	−23.3	65	42–43	−24.8
X–L–Val	58[6]	115–116	+81.5	81	113–114	+78.2
X–L–Leu	60[6]	131–132	+62.5	89	129–130	+60.1
X–L–Phe	30[6]	121–122	+112.3	54	118–119	+112.9
X–L–Lys	(66.36	6.24	6.19)	62	103–105	+90.8
(Boc)	(66.78	6.27	6.09)			

[a]Based on *N*-arakyl amino acid. [b](c = 1, benzene). [c]+39.6° (c = 1, ethyl acetate). Use of CDI instead of DSC/NEt_3 affords racemic X–Phe NCA (52 %, m.p. 148–149°) and X–Lys(Boc) NCA (65 %, m.p. 123–125°).

graphy on commercial silica plates (Merck 60 F-254) using mixtures of ethyl acetate and cyclohexane as solvent. UV (254 nm) and ninhydrin spray (Merck) were used for visualization. The plates were heated to 110 °C for 5–10 min, during which time, a blue-red spot developed at R_F 0.5–0.8 with a faint streak from the site of application. (DMB-Leu NCA initially gives a yellow colour). After 1 h of reflux, the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate, and, as necessary, purified by chromatography on a short column of silica (10 g Merck Kieselgel 60) using a mixture of ethyl acetate and cyclohexane as eluent. Aralkyl NCA eluted first. It was concentrated to dryness *in vacuo,* and crystallized from ethyl acetate/cyclohexane. The *N*-aralkyl NCAs so obtained yielded the expected ^{1}H NMR spectra (Table 1). ^{1}H NMR and IR spectra of X-Leu NCA were consistent with the published reference spectra[14,15]. All IR spectra (5 % solutions in $CHCl_3$) showed strong absorptions at 1770 and 1845 cm^{-1} characteristic of anhydride carbonyls. In contrast, the reaction product (m.p. 62–63 °C) obtained from Trt–alanine[16] had a maximum absorption at 1735 cm^{-1}. The C,H,N analysis was in agreement with that calculated for Trt–Ala–OSu. That Su ester formation also took place to a small extent with Mbh and X amino acids was indicated by the occasional presence of a slower migrating ninhydrin-positive by-product on thin layer chromatograms of the crude cyclization mixtures. It was, however, removed by recrystallization.

Yields, melting points and specific optical rotations are given in Table 2, together with the literature values[6,9] or C,H,N analyses. From the specific optical rotations, it is evident that racemization did not occur under the conditions used in the general procedure. The yield of each individual compound remains yet to be optimized.

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