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A NOVEL SYNTHESIS OF N-CARBOXY-α-AMINO ACID ANHYDRIDE

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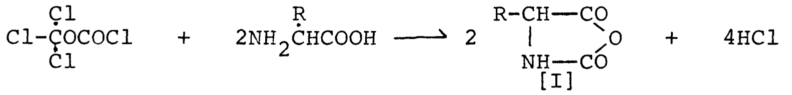
N-Carboxy-α-amino acid anhydrides were prepared by the reaction of α-amino acids with trichloromethyl chloroformate. The yields were good to moderate, and the products obtained were as pure as those obtained by a conventional way using phosgene.

N-Carboxy-α-amino acid anhydrides (NCAs) have most conveniently been prepared by the reaction of α-amino acids with phosgene.1) However, phosgene has become commercially inaccessible these days. Such a situation prompted us to investigate a substitute for phosgene in the synthesis of NCAs.

Trichloromethyl chloroformate (TCF)2,3) has been known as a phosgene dimer and used as a substitute for phosgene in the industries.

We have succeeded in the synthesis of NCAs using TCF instead of phosgene. The operation merely involves the addition of an amino acid to a solution of a specified amount of TCF in dry tetrahydrofunan (THF), and standing the reaction mixture until a clear solution is effected. The NCA of high purity is obtained in a good to moderate yield after recrystallization of the crude product. No racemization was found to take place during the synthesis. A half mole of TCF was sufficient to convert a mole of an amino acid to the NCA (eq. 1). The mechanism of the reaction is now under investigation.



$$\mathrm{Cl{-}\underset{Cl}{\overset{Cl}{C}}OCOCl} + 2\mathrm{NH_2\overset{R}{C}HCOOH} \longrightarrow 2\ \underset{[\mathrm{I}]}{\begin{array}{l}\mathrm{R{-}CH{-}CO}\\ \ \ |\qquad\ \ \rangle \mathrm{O}\\ \mathrm{NH{-}CO}\end{array}} + 4\mathrm{HCl} \qquad \text{(eq. 1)}$$

The following is a typical procedure for the preparation of NCAs: A solution of 5.1 g (0.0252 mol) of TCF in 200 ml of dry THF was kept at 60°C for 4-6 hr, and then cooled to 40°C. Into the solution was added 5.0 g (0.043 mol) of L-valine, and the suspension was stirred at 40°C until a clear solution was obtained. The solution was concentrated to a viscous oil under reduced pressure keeping the temperature below 40°C. n-Hexane (ca. 200 ml) was added to the oil and the mixture was cooled to -10 - -20°C until crystals appeared in a substantial quantity. The crystals were collected by filtration, washed with n-hexane several times to remove the remaining TCF, and dried in a vacuum desiccator over P_2O_5. The crude NCA was dissolved in 100 ml of ether, and the solution was filtered with a glass filter(No.4) to remove any insoluble material. The ethereal filtrate was added to 300 ml of n-hexane, and the mixture was cooled to -10 - -20°C to give colorless crystals. They were collected on a filter and again recrystallized from the same solvents. The crystals obtained were finally recrystallized from a minimum amount of diisopropyl ether by dissolving at 30°C and cooling to -10 - -20°C. After drying, 4.2 g (70%) of L-valine NCA (4-isopropyl-oxazolidine-2,5-dione) was obtained, mp 71°C. Anal. Calcd for $C_6H_9NO_3$; C, 50.27; H, 6.34; N, 9.79%. Found: C, 50.94; H, 6.45; N, 9.92%. $[\alpha]_D^{24} = -42.8°$ (c = 0.02479 g/ml in acetone), [Lit.[4)] $[\alpha]_D^{27} = -44.4°$ (c = 4.476 g/ml in acetone)]. Chlorine content was less than 0.05% (measured by Fr. Mohr's method). The physical properties of the NCA thus obtained agreed well with those of the reported.[5)]

When TCF was added to suspension of L-valine in THF, a longer time was required to give a clear solution.

In the same way, glycine NCA (oxazolidine-2,5-dione), L-alanine NCA (4-methyloxazolidine-2,5-dione), and γ-methyl-L-glutamate NCA [4-(2-methoxycarbonylethyl)-oxazolidine-2,5-dione] were prepared without any trouble. Results are summarized in Table 1.

Table 1. N-Carboxy-α-amino acid Anhydrides [I]

R	Starting amino acid	Yield,%	Mp,°C	$[\alpha]_D^{23}$	Anal Found%/Calcd% C	H	N
H	Glycine	66.9	100[5)]		36.27 35.65	3.08 3.05	14.24 14.87
CH_3	L-Alanine	55.8	92[5)]	47.2[a)]	42.02 41.73	4.35 4.35	12.44 12.17
$CH_3OCOCH_2CH_2$	γ-Methyl-L-glutamate	84.0	100[5)]	-20.2[b)]	45.20 44.80	4.82 4.82	7.28 7.48

a) c = 0.02 g/ml in methylene chloride. b) c = 0.018 g/ml in acetonitrile.

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