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A NOVEL ACTIVE ESTER SYNTHESIS REAGENT (N,N'-DISUCCINIMIDYL CARBONATE)

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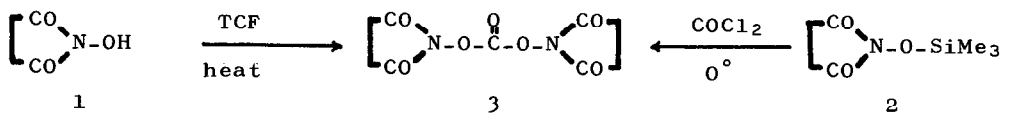
A convenient reagent for active ester synthesis --N,N'-disucinimidyl carbonate-- was prepared. This reagent was useful for the preparation of active esters and peptides in stead of dicyclohexylcarbodiimide.

Recently, we reported halosulfonium chloride as a carboxamide synthesis reagent.[1] Active esters of N-hydroxysuccinimide have been prepared by the dicyclohexylcarbodiimide (DCC) method or the mixed anhydride method.[2] However, mechanistic studies of the reaction of carboxylic acids with amines mediated by DCC show some trouble in the peptide synthesis.[3,4] In this paper, we described a more convenient method of active ester synthesis than DCC method, that is preparation of peptide using N,N'-disuccinimidyl carbonate (DSC).

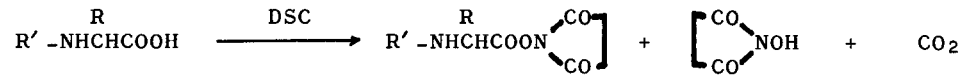
DSC (3) was prepared by two methods (Scheme 1); (i) reaction of N-hydroxysuccinimide (1; HOSu) and trichloromethyl chloroformate (TCF) under reflux in xylene (yield: 62%) or without xylene (yield: 50%) and (ii) reaction of trimethylsillated HOSu (2) and phosgene in tetrahydrofuran at 0° (yield: 80%). DSC (3) was colorless prisms having mp 211-5° (decomp.) and could be kept for years upon storage in a refrigerator.



1 3 2

Scheme 1

In a typical experiment, a mixture of a molar equivalent of Z- or Boc-amino acid (4), DSC (3), and pyridine in acetonitrile was stirred at room temperature (Scheme 2). There were obtained active esters (5) in good yields as shown in Table I.



4 5 1

R′: $COOCH_2C_6H_5$ (Z) or $COOC(CH_3)_3$ (Boc)

Scheme 2

Table I. N-Hydroxysuccinimide Esters of N-Substituted Amino Acids and Peptides

Starting material	Product	Yield (%) (Reported)	$[\alpha]_D$ (Dioxan: °C) Observed	Reported
Z-Ala	Z-Ala-OSu	97 (65)[a]	-37.3 (c 2.1; 25)	-37.2 (c 2; 25)[a]
Z-Val	Z-Val-OSu	100 (53)[a]	-26.8 (c 2.1; 22)	-25.1 (c 2; 25)[a]
Z-Leu	Z-Leu-OSu	98 (51)[a]	-32.8 (c 2.1; 23)	-33.6 (c 2; 25)[a]
Z-Phe	Z-Phe-OSu	100 (76)[a]	-55.6 (c 1; 25)[b]	-54.2 (c 1; 25)[b,c]
Boc-Ala	Boc-Ala-OSu	81 (71)[a]	-51.0 (c 2; 23)	-49 (c 2; 25)[a]
Boc-Val	Boc-Val-OSu	89 (74)[a]	-37.1 (c 2; 24)	-37 (c 2; 25)[a]
Boc-Leu	Boc-Leu-OSu	83 (48)[a]	-40.8 (c 2.1; 21)	-41.8 (c 2; 25)[a]
Boc-Phe	Boc-Phe-OSu	100 (81)[a]	-19.1 (c 2.1; 21)	-19.0 (c 2; 25)[a]
Z-Ala-Ala	Z-Ala-Ala-OSu	99 (-)	-62.5 (c 4.1; 23)	-46.4 (c 3.8; 24)[d]
Z-Ala-Phe	Z-Ala-Phe-OSu	100 (-)	-25.5 (c 3.4; 23)	-24.6 (c 3.8; 24)[d]

a: G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, J. Am. Chem. Soc., 86, 1839 (1964).

b: DMF.

c: T. Mukaiyama, K. Goto, R. Matsuda, and M. Ueki, Tetrahedron Lett., 1901 (1970).

d: H. R. Bosshard, I. Schechter, and A. Beger, Helv. Chim. Acta, 56, 717 (1973).

In paticular, the reaction proceeded at room temperature, the end of reaction could be clarified with generation of gas (CO_2), and optically pure active esters (5) were obtained in high yield without detectable racemization. DSC (3) was not a disagreeable skin irritant such as DCC, and 3 was decomposed easily to water soluble N-hydroxysuccinimide (1) and CO_2 after the reaction. In conclusion, DSC method is more convenient than DCC method for active ester and peptide syntheses.

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