A Simple Preparation of Symmetrical Anhydrides of *N*-Alkyloxycarbonylamino Acids

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The symmetrical anhydride **4** has long been considered a possible intermediate along with the *O*-acylisourea **3** in the dicyclohexylcarbodiimide (**2a**)-mediated couplings of *N*-alkoxycarbonylamino acids (**1**) with amino groups to form peptides (**7**)[1]. The anhydrides are amply reactive[2-5], and their use in solid-phase synthesis, where they are prepared using **2a** but not isolated, is gaining favor[6]. A recent paper shows that for synthesis on a solid support, **4** indeed is the reactive intermediate, and recommends the use of purified anhydrides to eliminate side reactions[7].

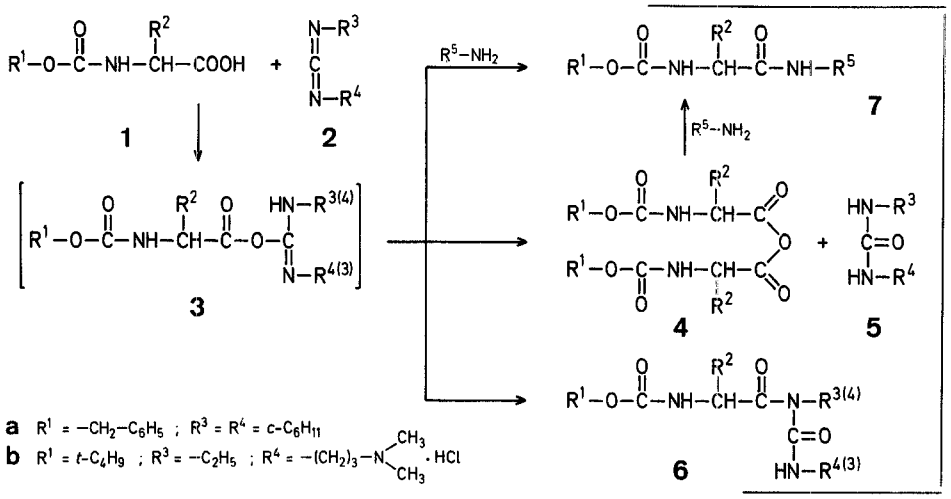

Table. Synthesis of Symmetrical Anhydrides (**4**) of *N*-Alkoxycarbonylamino Acids

		N-Benzyloxycarbonyl derivatives **4a**				*N*-*t*-Butoxycarbonyl derivatives **4b**			
Amino Acid	R^2	Yield [%]	m.p. (dec)	Lit. m.p. or Molecular formula[a]	$[\alpha]_D^{23}$ (2, $CHCl_3$)	Yield [%]	m.p. (dec)	Lit. m.p. and/or Molecular formula[a]	$[\alpha]_D^{23}$ (2, CH(
Gly	H	80	118–119°	108–114°[2] 118°[10]		60	82–83°	70–72°[8] $C_{14}H_{24}N_2O_7$ (332.4)	
L-Ala	CH_3	81	119–121°		−16.4°	75	95–97°	95–96°[8] 103–110°[4]	−16.9°
L-Val	$-CH(CH_3)_2$	80	99–101°	96–99°[2]	+17.3°	51	84–85°[b]	103–104°[8] 79–80°[4]	− 4.0°
L-Leu L-MeLeu	$-CH_2-CH(CH_3)_2$	90	oil[c]	oil[2]	− 3.0°	83	oil[b]	70–72°[8]	−16.6°
L-Ile	$-CH(C_2H_5)CH_3$	86	oil	$C_{30}H_{40}N_2O_7$ (540.6)	−39.0°	55[d]	68–69°[b]	77–79°[8]	−32.8°
L-Phe	$-CH_2-C_6H_5$	77	128–129°	$C_{34}H_{32}N_2O_7$ (580.6)	+27.3°	76	95–97°	80–82°[4] $C_{28}H_{36}N_2O_5$ (512.6)	+19.6°
L-Pro	$[-CH_2-CH_2-CH_2-]$	90	oil	oil[2]	−71.0°	80	oil	oil[8] $C_{20}H_{32}N_2O_7$ (412.5)	−60.8°
L-Met	$H_3C-S-CH_2-CH_2-$					73	76–78°	$C_{20}H_{36}N_2O_7S_2$ (480.6)	− 1.8°
L-Ser(Bzl)	$C_6H_5-CH_2-O-CH_2-$					54	oil		− 3.5°
L-Tyr(Bzl)	$C_6H_5-CH_2-O-C_6H_4-CH_2-$					69	75–77°	76–78°[8]	+ 8.1°
L-Asp(OBzl)	$C_6H_5-CH_2-O-C(=O)-CH_2-$					86	oil	$C_{32}H_{40}N_2O_{11}$ (628.7)	− 4.0°
L-Glu(OBzl)	$C_6H_5-CH_2-O-C(=O)-CH_2-CH_2-$					50	70–72°	70–72°[8]	−27.0°

[a] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.40; H, ±0.22; N, ±0.21. The analyses w performed by Dr. C. Daessle, Montreal. All compounds gave appropriate I.R. and ^{1}H-N.M.R. spectra.
[b] Less stable than the other compounds.
[c] Optical purity established at >99.85 % as in Ref. [11].
[d] Use of dimethylformamide as solvent gave a slightly lower yield.

0039–7881/78/1232–0928 $ 03.00

Two pure *N*-benzyloxycarbonylamino acid anhydrides (**4a**) were obtained using **2a**, after crystallization from benzene[2], but removal of the final traces of the contaminating urea **5a** and *N*-acylurea **6a** is generally difficult or impossible. *N*-Butoxycarbonylamino acid anhydrides (**4b**) can be obtained by the action of phosgene on the sodium salt of acid **1b**[8], purification being effected by washing them with water, but this method has not been adopted by others. And in addition, the anhydrides **4b** are reported to be unstable[8]. We have found that anhydrides **4a** and **4b** are stable to washing with cold dilute aqueous acid and sodium hydrogen carbonate solution. As a consequence, if a water-soluble reagent such as *N*-(3-dimethylaminopropyl)-*N'*-ethyl-carbodiimide hydrochloride (**2b**)[9] is used to prepare them, and they are washed with acid and base, the urea by-products **5b** and **6b** and unreacted starting materials are removed, and the chemically pure anhydrides are obtained readily in good yields.

The compounds **4a** and **4b** prepared using 2 mol of acid **1** and 1 mol of carbodiimide **2b** in dichloromethane are described in the table. Yields were higher for **4a** than **4b**. All work-up was done at 0° because the anhydrides **4b**, except that of proline, partially decompose during evaporation of the solvent at 23°. All the compounds described were stable at −5°. Anhydrides **4a** were stable at least 2 months at 23°, and at least 5 h in chloroform at 50° in the absence of moisture. Anhydrides **4b** were completely decomposed after 5 h at 23°, and ~5% decomposed (loss of *t*-butyl group, N.M.R.) after 1 h in chloroform at 23°. The anhydrides **4b** of leucine, valine, and isoleucine are the least stable. The anhydride **4b** of *N*-methylvaline was too unstable to be prepared by this method.

N-Alkoxycarbonylamino Acid Anhydrides (4); General Procedure: A solution of amino acid derivative **1** (2 mmol) and soluble carbodiimide **2b** (1 mmol) in dichloromethane (20 ml) is stirred at room temperature for 1 h for **1a** and 0° for 2 h for **1b**. The solvent is evaporated in vacuo at 0° using a rotary evaporator, ethyl acetate (25 ml) is added, and the solution is washed successively with cold (containing ice) aqueous solutions (2 × 10 ml) of citric acid (10%), sodium chloride (saturated), sodium hydrogen carbonate, and sodium chloride (saturated). The organic phase is dried with magnesium sulfate, filtered, and evaporated in vacuo at 0°. Crystals appear immediately, or after storing at −5°. The crystals are washed with light petroleum (b.p. 40–70°)/ether (20:1).

The anhydrides **4** all show characteristic I.R. absorptions (KBr or liquid film) at $\nu \approx 1830$ and 1750 cm^{-1} [8]. Their ^1H-N.M.R. spectra ($CDCl_3$) are almost identical with those of the starting materials except for the absence of the acidic proton at $\delta \approx 10$ ppm.

Received: June 5, 1978

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B. Hemmasi, E. Bayer, *Hoppe-Seyler's Z. Physiol. Chem.* **355**, 481 (1974).
D. Yamashiro, C. H. Li, *Proc. Nat. Acad. Sci. USA* **71**, 4945 (1974).
S. Lemaire, D. Yamashiro, C. Behrens, C. H. Li, *J. Am. Chem. Soc.* **99**, 1577 (1977).

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[8] T. Wieland, F. Flor, C. Birr, *Justus Liebigs Ann. Chem.* **1973**, 1595.

[9] J. C. Sheehan, P. A. Cruickshank, G. L. Boshart, *J. Org. Chem.* **26**, 2525 (1961).

[10] T. Wieland, W. Kern, R. Sehring, *Justus Liebigs Ann. Chem.* **569**, 117 (1950).

[11] S. T. Cheung, N. L. Benoiton, *Can. J. Chem.* **55**, 911 (1977).

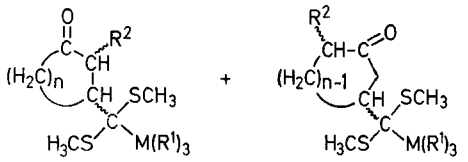
Erratum

F. M. F. Chen, K. Kuroda, N. L. Benoiton, *Synthesis* **1978** (12), 928–929

The 4th, 5th, and 6th entries in the Table (p. 928) should be:

Amino Acid	R^2	*N*-Benzyloxycarbonyl derivatives **4a**				*N*-*t*-Butoxycarbonyl derivatives **4b**			
		Yield [%]	m.p. (dec)	Lit. m.p. or Molecular formula[a]	$[\alpha]_D^{23}$ (2, $CHCl_3$)	Yield [%]	m.p. (dec)	Lit. m.p. and/or Molecular formula[a]	$[\alpha]_D^{23}$ (2, $CHCl_3$)
L-Leu	$-CH_2-CH(CH_3)_2$	90	oil[c]	oil[2]	− 3.0°	83	76–77°	70–72°[8]	−16.6°
L-MeLeu		86	oil	$C_{30}H_{40}N_2O_7$ (540.6)	−39.0°				
L-Ile	$-CH(C_2H_5)CH_3$					55[d]	68–69°[b]	77–79°[8]	−32.8°

Abstract no 5213, *Synthesis* **1978** (6), 483;
The structures for products **8** and **9** should be:



8 **9**

Abstract no. 5254, *Synthesis* **1978** (7), 556;
The title should be:
Reaction of 1-Ethoxy-1-trimethylsiloxycyclopropane with Carbonyl Compounds

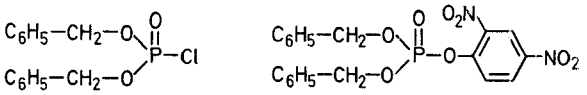
J.-P. Majoral, *Synthesis* **1978** (8), 557–576;
Sub-heading 4.2.1. (p. 565) should read:
4.2.1. 3,4-Dihydro-2*H*-1,2,3-diazaphospholes
The products **83** (p. 569) should be named:
3,4-Dihydro-2*H*-1,2,4,5,3-tetraazaphosphepin derivatives
The products **84** (p. 569) should be named:
2,3,5,6,4-benzotetraazaphosphonin derivatives

J. D. Finlay, D. J. H. Smith, T. Durst, *Synthesis* **1978** (8), 579–580;
The compounds **1** should be named:
5-phenyl-1,2-oxathiolane 2-oxides.

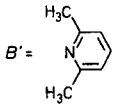
G. Sosnovsky, M. Konieczny, *Synthesis* **1978** (8), 583–585;
The heading for the first experimental procedure (p. 584) should read:
1-Oxyl-2,2,6,6-tetramethyl-4-piperidyl *N,N*-(1,2-Ethanediyl)-benzenephosphonoamidite (7a):

F. Hordziejewicz, Z. Skrowaczewska, *Synthesis* **1978** (8), 585–586;
The heading for the first experimental procedure (p. 586) should read:
Purification of Commercial 2,6-Lutidine:

F. Ramirez, J. F. Marecek, *Synthesis* **1978** (8), p. 601–603;
In Scheme **A** (p. 602) the structures of compounds **5**, **6**, and *B'* should be:

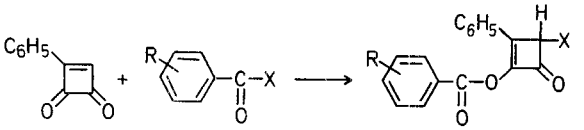


5 **6**



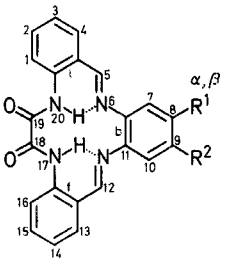
A. R. Katritzky, S. B. Brown, *Synthesis* **1978** (8), 619–620;
The heading for the first experimental procedure (p. 619) should read:
2'-Methoxycarbonylbenzanilide:

H. Knorr, W. Ried, *Synthesis* **1978** (9), 649–666;
The formula for the formation of product **86** (p. 661) should be:



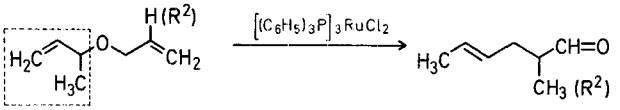
86

C. Skötsch, E. Breitmaier, *Synthesis* **1978** (8), 680–681.
The numbering for compounds **3a–c** (see Scheme p. 680) should be as shown below:



3a $R^1 = R^2 = H$
b $R^1 = H, R^2 = t\text{-}C_4H_9$
c $R^1 = R^2 = CH_3$

Abstract no. 5309, *Synthesis* **1978** (10), 789;
The title and formula **1**→**2** should be as follows:
Ruthenium(II) Catalysed Synthesis of γ,δ-Unsaturated Aldehydes



1 **2**

S. Sharma, *Synthesis* **1978** (11), 803–820;
Product **24** (p. 807) should be named:
12-Oxo-12*H*-benzimidazo[2,1-*b*][1,3]-benzoxazine
and product **28** (p. 807) should be named:
2-thioxo-2,5-dihydroimidazole 3-oxide

F. M. F. Chen, K. Kuroda, N. L. Benoiton, *Synthesis* **1978** (12), 928–929;
The 4th, 5th, and 6th entries in the Table (p. 928) should be:

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