N-Alkoxycarbonyl Amino Acid *N*-Carboxyanhydrides and *N,N*-Dialkoxycarbonyl Amino Acid Fluorides from *N,N*-Diprotected Amino Acids†

J. Savrda and M. Wakselman*

CNRS-CERCOA, 2 rue Henri Dunant, F-94320 Thiais, France

Activation of *N,N*-bis-Boc or *N*-Boc *N*-Z amino acids with $SOCl_2$–DMF leads to *N*-protected *N*-carboxy amino acid anhydrides, whereas treatment with cyanuric fluoride at low temperature gives mainly *N,N*-bis-protected amino acid fluorides, which are efficient acylating agents.

The renewed interest in the preparation of *N*-protected amino acid halides[1] and amino acid *N*-carboxyanhydrides (NCA)[2] has recently led to the synthesis of interesting new coupling reagents, the stable *N*-alkoxycarbonyl amino acid fluorides (UAAF; Fmoc, Z or Boc derivatives)[3] and *N*-alkoxycarbonyl *N*-carboxy amino acid anhydrides (UNCA)[4], and their use in peptide synthesis has been exemplified.[3,4] We report here a new route to UNCA **4** and the synthesis of the unknown bis(alkoxycarbonyl) amino acid fluorides (U_2AAF; **3**). Both reagents, which possess easily cleavable *N*-protecting groups, could be useful for acylation of anionic nucleophiles since they are devoid of an exchangeable NH hydrogen.

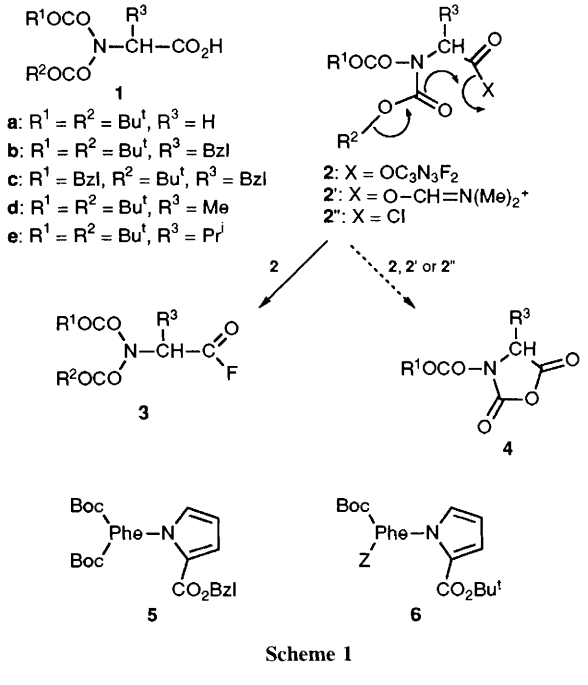
Depending on the activating agent and experimental conditions, reaction of *N,N*-bis(alkoxycarbonyl) amino acid **1**[5]

† *Abbreviations*: Boc: *tert*-butoxycarbonyl; Z = benzyloxycarbonyl; Fmoc = 9-fluorenylmethyloxycarbonyl; Bzl = benzyl; NCA = amino acid *N*-carboxy anhydride; UNCA = urethane-protected amino acid *N*-carboxy anhydride; UAAF = urethane-protected amino acid fluoride; U_2AAF = *N,N*-bis(urethane) amino acid fluoride; DMF = dimethylformamide.

Table 1

Starting compound	Method[a]	Product	M.p./°C	Product[b] yield (%)	$[\alpha]_D$[c]	Lit[4] M.p./°C	Lit[4] $[\alpha]_D$[c]
1a	A	**3a**[d]	50–52	76	—	—	—
1a	B	**4a**	147–149	72	—	—	—
1b	A	**3b**[d]	43–45	82	−112.8 *c* 0.9, EtOAc	—	—
1b	B	**4b**	102–104	92	+120.1 *c* 1.8, THF	—	—
1c	A	**3c**[d]	oil	79	−123.0 *c* 1.2 EtOAc	—	—
1c	B	**4c**	105–106	75	+138.8 *c* 1.8, THF	105–106	+127.6 *c* 1.78, THF
1d	B	**4d**	101–103	80	+56.9 *c* 1.8, THF	103–104	+21.6 *c* 1.78, THF
1e	B	**4e**	117–119	86	+59.7 *c* 1.8, THF	—	—

[a] Method A: (i) **1** + 1 mol equiv. pyridine + 1 mol equiv. cyanuryl fluoride/CH_2Cl_2/−30 °C/90 min; (ii) H_2O; (iii) $MgSO_4$. Method B: (i) **1** + 1 mol equiv. pyridine + 1 mol equiv. [$SOCl_2$/DMF]/CH_3CN/20 °C/120 min; (ii) H_2O/EtOAc; (iii) $MgSO_4$. [b] Satisfactory elemental analyses were obtained for all compounds. [c] $[\alpha]_D^{22}$ for compounds **3** and $[\alpha]_D^{25}$ for compounds **4**. [d] ^1H NMR analysis of crude product shows the presence of small amounts of protected NCA **4**.



Scheme 1

gave either the new *N,N*-bis-protected amino acid fluorides **3**, when treated with cyanuric fluoride[6] (method A), or the urethane protected amino acid *N*-carboxyanhydride **4**, when the $SOCl_2$/DMF Vilsmeier reagent[7] (method B) was used instead (Scheme 1 and Table 1). In method A, a trace amount of *N*-protected NCA **4** is formed beside **3** when working at −30 °C.[8]

N,N-Bis-protected amino acid fluorides **3** are efficient acylating agents. They allowed us to prepare the first examples of fully protected *N*-acyl derivatives of pyrrole-2-carboxylic acid[9] (amino acid pyrrolides), namely the *N*-(*N'*,*N'*-bis-Boc-phenylalanyl)-2-pyrrolecarboxylic acid benzyl ester **5** and the *N*(*N'*-Boc *N'*-Z phenylalanyl)-2-pyrrolecarboxylic acid *tert*-butyl ester **6** by treatment with the sodium salts of pyrrole-2-carboxylic acid esters. They can also be used for peptide bond formation. For instance Boc_2-Phe-Leu-OBzl[5b] was obtained from benzyl leucinate in 80% yield. The *N*-Boc *N*-carboxy amino acid anhydrides **4** are unreactive towards anions of pyrrole-2-carboxylic acid esters.

N,N-Bis-protected amino acid fluorides **3** are stable compounds. They are easily characterized by ^{19}F NMR (δ 28–32 relative to $CFCl_3$; coupled to CH_α) and by ^1H NMR (CH_α coupled to F and at a lower field than the corresponding H_α in **1** and **4**). They do not spontaneously cyclize to give the corresponding protected amino acid *N*-carboxyanhydrides.

Compounds **4** are probably formed from another activated bis-protected amino acid derivative such as the triazinyl ester **2**,[10] the imidoyl ester **2'** or the chloride **2''**. Participation of a neighbouring *tert*-butyl carbamate is preferred to that of a benzyl carbamate[11] probably because of the higher stability of a tertiary carbonium ion: an *N*-Z NCA is obtained from a *N*-Boc *N*-Z amino acid (**1c** → **4c**; Table 1).

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