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CONVENIENT ONE-POT ESTERIFICATION OF N-PROTECTED AMINOACIDS *via* ISOPROPENYL CHLOROFORMATE ACTIVATION.

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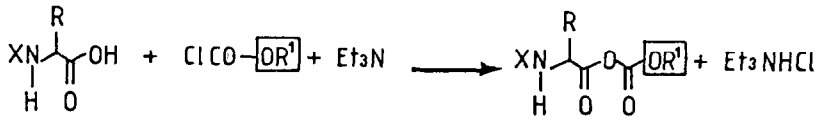
Summary : Activation of N-protected aminoacids by isopropenyl chloroformate leads to esters of primary, secondary and tertiary alcohols with 4-dimethylamino-pyridine as catalyst.

Esters of N-protected α-aminoacids are commonly prepared from alkyl halides.[1] Although numerous methods are available for the activation of N-protected aminoacids,[2] only few simple processes allow esterification of aminoacids from alcohol under mild conditions.[3,4] In the course of our investigation on isopropenyl chloroformate (IPCF) **2b** reactivity, we now report an efficient one-pot esterification of N-protected aminoacids with alcohols, by using IPCF for the acid activation.

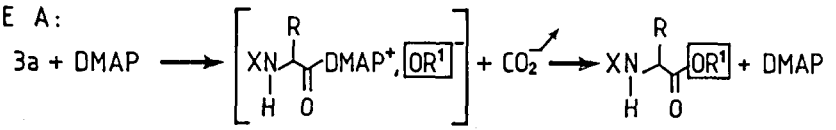
Isopropenyl chlororoformate **2b** has already been used for the aminoacid activation in peptide synthesis.[5] It was reasonably postulated that the reactive species was the mixed anhydride intermediate **3b**, as it has been demonstrated in other respects when utilising the isobutyl or other usual alkyl chloroformates.[6] During the course of the coupling step, the mixed anhydride obtained by alkyl chloroformate **2a** activation, liberates the corresponding alcohol **5** as a by-product.[6] This alcohol could react with the activated acid **3a** to give the corresponding ester **6a**. S. Kim *et al.* recently took advantage of this side reaction for the preparation of esters using 4-dimethylamino-pyridine (DMAP) as catalyst[3] (Scheme, route A) ; the catalytic ability of DMAP to produce esters from activated amino acids was previously noticed in the case of carbodiimide activation.[2] However, the procedure utilising alkyl chloroformates is restricted to available chloroformates, and is often inappropriate to laboratory applications unless common commercial chloroformates are used. In contrast, the mixed anhydride **3b** prepared from isopropenyl chloroformate liberated acetone and did not led to the corresponding isopropenyl ester in similar conditions,[7] but the addition of one equivalent of an alcohol **5** to the reaction mixture led exclusively to the formation of the corresponding ester **6a** in good yields (Scheme, route B).

Scheme : Synthesis of α-aminoesters *via* chloroformate activation.



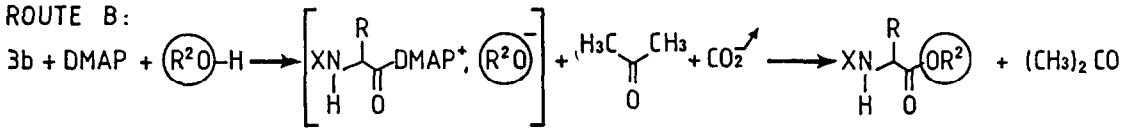
1 2a : R^1 = alkyl 3a : R^1 = alkyl
2b : R^1 = isopropenyl 3b : R^1 = isopropenyl

ROUTE A:



4 6a : R^1 = alkyl
6b : R^1 = isopropenyl

ROUTE B:



5 4 6

Esters of N-protected aminoacids were prepared from IPCF addition (1.1 eq.) to the N-protected aminoacid in the presence of triethylamine (1 eq.) and DMAP (0.1 eq.), and an equivalent of alcohol, in methylene chloride solution at 0° C (method I). The esters formed were easily purified by aqueous acid and basic washings of the organic solution. This one-pot preparation of esters from N-protected aminoacids has been exemplified to a variety of structurally different residues including primary and secondary alcohols whose corresponding chloroformates were not commercially available (Table, entries 4, 6, 8, 9, 10) or not accessible like 2,3-O-isopropylidene glycerol (Table, entries 5, 11) or 4-methoxybenzyl alcohol (Table, entry 7) due to their acidic sensitivity. This strategy was extended to tertiobutanol (Table) ; in this later case, additional quantities of tertiobutanol was needed (method II : Table entries 14, 18, 19) and the use of tertiobutanol as solvent at 35 °C was even necessary to enhance the yield in few giving examples (method III ; Table, entries 15, 16, 17, 20). As expected, this method of esterification failed with aminoacids with non-protected side chain fonctions such as hydroxyl or amine ; thus, the presence of the free hydroxyl group in Ser or Thr did not allowed the preparation of the corresponding esters by this procedure.

Table : Synthesis of α-aminoesters[i] by IPCF activation of N-protected α-aminoacids

entry	α-aminoester	method	yield %	mp °C (lit)	$[\alpha]_D$ c1 MeOH (lit)
from primary alcohol					
1	Z-Ala-OCH_2-p$NO_2C_6H_4$	1	78	99-100 (98-99)	-16.3 (-16.8 c1 MeOH)[a]
2	Boc-Asp-(OBzl)-OMe		74	61-62	-7 (-7.1 c1 acetone)[z]
3	Boc-Phe-OBzl	1	92	64-65	-6.3 (-12.8 c2 MeOH)[z]
4	Boc-Phe-O-$(CH_2)_{15}$-CH_3	1	96	38-39	-2.6
5	Boc-Phe-OIpG[ii]	1	80	85-86	-2
6	Boc-Val-OCH_2-o,p$Cl_2C_6H_3$	1	85	110-111	-10.5
7	Boc-Val-OCH_2-p$OMeC_6H_4$	1	91	oil	-48
8	Boc-Val-OCH_2-3-pyridyl	1	72	oil	-30.7
9	Boc-Val-OCH_2-Ant[iii]	1	68	98-99	-27.8
10	Boc-Val-O-$(CH_2)_{15}$-CH_3	1	96	oil	-13.9
11	Fmoc-Trp-OIpG[ii]	1	65	61-62	-12
from secondary alcohol					
12	Boc-Val-O(+)Bornyl	1	60	56-57	-75
13	Boc-Val-OCholesteryl	1	80	133-134	-40
from tertiobutanol					
14	Z-Ala-OtBu	11	60	oil	-19.5 (-15.8 c2.1 MeOH)[z]
15	Z-Cys-(Bzl)-OtBu	111	75	oil	-30
16	Z-Lys-(εBoc)-OtBu	111	70	oil	-90
17	Z-Met-OtBu	111	68	oil	-22.9 (-27 c5.7 EtOH)[a]
18	Z-Phe-OtBu	11	88	81-82 (80.5-81.5)	-9.9 (-4.6 c2 EtOH)[a]
19	Z-Pro-OtBu	11	90	- (44-45)	-51 (-52.5 c2.2 EtOH)[a]
20	Z-Trp-OtBu	111	60	70-71	-5.2

i All new compounds gave satisfactory analytical data.

ii IpG : 2,3-O-(isopropylidene)glyceryl ; iii Ant : 9-(methylene)anthracyl.

It was necessary to establish that the use of IPCF for aminoacid activation did not induced unacceptable racemization within the experimental conditions[z,a]. Due to the rather low optical rotations generally observed, these data were inaccurate to estimate the racemization of the process ; we choosed to detect by n.m.r. study, the amount of racemization produced in the more drastic conditions used for the *tert*-butylation reaction. The *tert*-butyl ester from Z-L-Phe-OH and Z-D-Phe-OH were prepared according to method C, and the aminoesters H-L-Phe-OtBu and H-D-Phe-OtBu, obtained after hydrogenolysis, were respectively coupled to Z-L-Ala-OH using standard active ester methodology ; n.m.r. study showed the absence of signals due to the non-expected enantiomer in the spectrum of each dipeptide, thus indicating

the absence of evaluable racemization during the esterification step. However, when this method of esterification was applied to non-carbamate N-protected aminoacid (e.g. N-acyl aminoacid), a dramatic enhancement in the racemization was observed. This was tested for dipeptide esterification. When the dipeptide Z-Ala-Phe-OH was submitted to standard conditions utilizing IPCF and methanol, n.m.r. measurements showed the presence of at least 25% of the wrong enantiomer Z-Ala-D-Phe-OMe with the isolated Z-Ala-L-Phe-OMe.

Isopropenyl chloroformate appeared to be the most versatil chloroformate for acid activation, which was able in any case to replace other chloroformates and to provide additionnal applications. For this purpose, in addition with peptide synthesis and esterifications of N-protected amino acids, numerous IPCF promoted coupling reactions between N-protected amino acids and nucleophiles are in progress.

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[6] See ref. [4] Chapter 6.

[7] We noticed the formation of an appreciable amount of isopropenyl-ester **6b** when N-protected aminoacid reacts with IPCF in absence of alcohol if the reaction is conducted in THF instead of methylene chloride, but addition of one equivalent of alcohol to the THF solution led also predominently to the corresponding ester **6a**.

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