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PROTECTION OF AMINES WITH THE 4-AZIDOMETHYLENOXYBENZYLOXYCARBONYL GROUP

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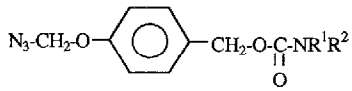
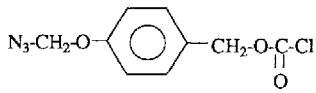
Abstract : A new urethane type protective group for amines, the 4-azidomethylenoxybenzyloxycarbonyl (AZ) group is described. This group is cleaved under very mild reductive conditions.It can be cleaved in the presence of the Z and methyl ester groups. Independent removal of AZ and BOC groups, each in the presence of the other, is possible.

The use of azidomethylenes to block phenolic hydroxyls (1) has enabled us to develop a new protection method for carboxylic acids, useful for peptide synthesis (ABz group) (2). This method, characterized by mild deprotection conditions, makes it possible to obtain interesting selectivities. Following this observation, we used the same azidomethylene derivative for the protection of amines (AZ group).

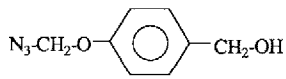


AZ-NR^1R^2

The introduction of the AZ group using chloroformate 1 (3) as an intermediate posed some problems, due to the unstability of the latter. While yields of 50-85 % are convenient for simple amines, they are lower to 40 % with aminoacids. Irrespective of the experimental method used to prepare 1 from 2, followed by condensation of the latter on the amine, a significant amount of 3 is formed by decarboxylation.



1



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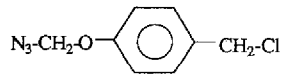
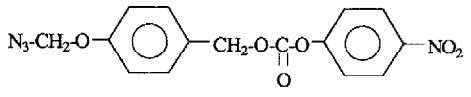


3

It is much easier to use the carbonates 4 and 5 (4). Compound 4 is a crystalline solid (mp 103°C) and could be stored in the dark. A yield of 65-70 % is obtained after recrystallization in ethyl acetate. Compound 5 is an oily liquid whose preparation requires more reaction steps and necessitates purification by chromatography (yield 40-50 %).



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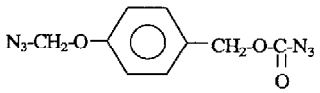
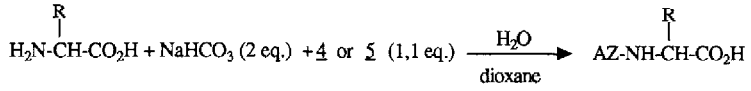


5

Some examples of N-protected amino acids prepared from 4 and 5 are presented in Table 1.

Table 1



Aminoacid	4 or 5	Reaction time (h)	Product Mp (°C)	Yield (%)
Gly	4	24	76	77
	5	18		87
L-Phe	4	22	120	75
	5	18		85
L-Ala	4	16	-	62
	5	16		70
L-Met	4	50	-	70
L-Val	4	78	-	54
L-Ile	4	45	94-96	56
α BOC-L-Lys	4	46	64-8	76
ε Z-L-Lys	4	46	-	34

The stability of the AZ group makes it possible to carry out peptide coupling without problems (Table 2). We confirmed that there was no loss of chirality during the protection period by comparing the 400 MHz ^1H NMR spectra of some dipeptides, for example, AZ-L-Ala-L-Phe-OMe and AZ-D-Ala-L-Phe-OMe or AZ-L-Phe-L-Ala-OMe and AZ-D-Phe-L-Ala-OMe.

Table 2

$$AZ\text{-}R^1\text{-}OH + H_2^{\oplus}\text{-}R^2\text{-}OMe,\ X^{\ominus}\ ^{(a)} \xrightarrow[Et_3N\ (2\ eq.)\ CH_2Cl_2,\ 2\ h,\ 25°C]{BOP\ (1\ eq.)} AZ\text{-}R^1\text{-}R^2\text{-}OMe$$

R1	R2	Product F°C	Yield (%)
L-Ala	L-Phe	63	77
DL-Ala	L-Phe	-	85
L-Phe	L-Ala	97	79
DL-Phe	L-Ala	-	76
L-Pro	L-Phe		79
Gly-L-Phe	L-Met		87
L-Met	L-Ala	-	82
Gly	L-Val	-	89
Gly	L-Met-L-Ala	-	63
L-Ile	Gly	126	85
L-Val	Gly	137	82
α-BOC-ε-AZ-L-Lys	L-Phe	104	79
α-AZ-ε-Z-L-Lys	L-Ala	-	66

(a) $X^{\ominus}$ = $Cl^{\ominus}$ except for L-Met-L-Ala where $X^{\ominus}$ = $TsO^{\ominus}$

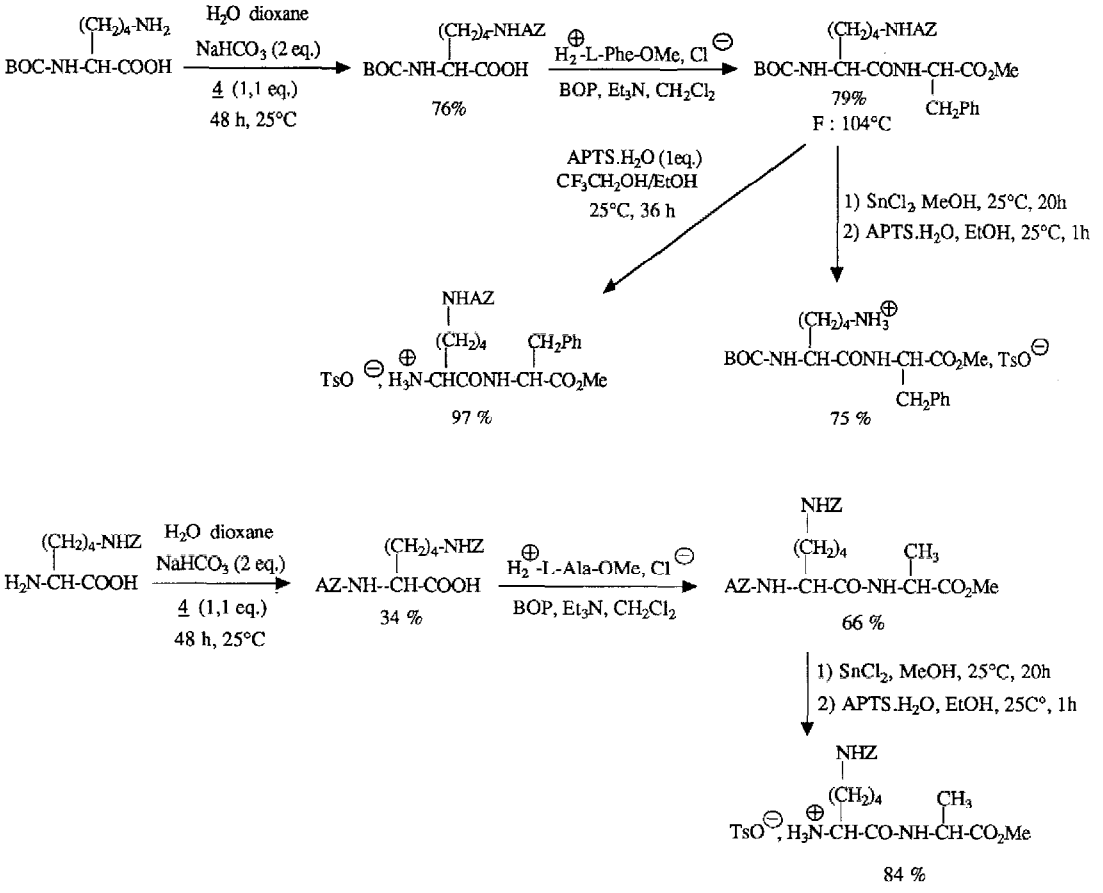
The deprotection to the free aminogroup, was carried out in two stages :

- reduction of the AZ group by $SnCl_2$ to the 4-hydroxybenzyloxycarboxyl group
- acid or base - catalyzed 1,6-elimination and decarboxylation.

The AZ group is stable in basic, nucleophilic, oxidizing and weak acid media. It is possible, for example, to decouple a BOC while the AZ group remains intact (APTS, CF_3CH_2OH/EtOH).

After treating with $SnCl_2$, the liberation of a simple amine could be carried out with excess of dilute NaOH or HCl. In the case of peptides, it is necessary to control the quantity of reactants used. Although NaOH is suitable, its use leads to the hydrolysis of the substrate ester functions (BOC and Z are stable under these conditions). Moreover, it should be noted that for almost all protecting groups which are cleaved in nucleophilic medium, this is often done with an amine, which can also react with ester functions (FMOC (5), DObz (6), BIC (7), Tcroc (8), Z' (9)). When APTS (1 eq.) in CH_3CH_2OH is used, ammonium tosylate is obtained without difficulty. Under these conditions, BOC and Z are unaffected.

A few reaction pathways are shown in the Scheme below.



Notes and references

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3. Compound 1 is prepared at 0°C in toluene from the alcohol 2 in presence of excess of phosgene. The solvent is removed by bubbling nitrogen through the final reaction mixture.
4. The experimental method used to synthesize products 4 and 5 is the same as that described by Weygand for the preparation of the carbonate of p-methoxybenzylalcohol and for the preparation of the azidocarbonate of p-methoxybenzylalcohol. F. Weygand, K. Hunger, Chem. Ber., 1962, 95, 1.
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