PHOTOLYTIC REMOVAL OF A 4-PYRIDYL-(T-BUTYL-AMINO-CARBONYL)METHYL AUXILIARY GROUP FROM THE AMIDE NITROGEN OF A FOUR COMPONENT CONDENSATION PRODUCT

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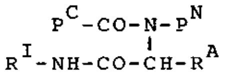
As a model for peptide syntheses the cleavability of the C-N bond in the four-component condensation (4 CC) product (V) of 4-pyridinecarboxaldehyde with t-butyl isocyanide, phenylacetic acid and benzylamine was studied; it was found that (V) yields N-(benzyl)-phenylacetamide on photolysis.

The development of methods for the combination of peptide fragments (I and II) by 4 CC and subsequent replacement of the N-substituent of the new amide group by hydrogen (see Scheme 1) has been the objective of some recent investigations.[1,2]

$$\underset{(\text{ I })}{P^C\text{-}CO_2H} + \underset{(\text{ II })}{H_2N\text{-}P^N} + \underset{(\text{ III })}{R^I\text{-}NC} + \underset{(\text{ IV })}{OHC\text{-}R^A} \xrightarrow{4\ CC}$$



$$\begin{matrix} P^C\text{-}CO\text{-}N\text{-}P^N \\ | \\ R^I\text{-}NH\text{-}CO\text{-}CH\text{-}R^A \end{matrix} \longrightarrow \begin{matrix} P^C\text{-}CO\text{-}NH\text{-}P^N & (\text{ VI }) \\ +\ \text{COPRODUCT} & (\text{ VII }) \end{matrix}$$

(V)

Scheme 1

Waki and Meienhofer[2] synthetised N^{α}-benzyloxycarbonylglycyl-alanyl-N^{α}-(α-cyclohexylcarbamoyl-4-pyridylmethyl)leucylglycine t-butylester (VIII) by 4 CC according to Scheme 1 with 4-pyridine carboxaldehyde. They replaced by hydrogen the N^{α}-(α-cyclohexylcarbamoyl-4-pyridylmethyl) group in (VIII) through electrolytic reduction in analogy to the reductive removal of the isonicotinyloxycarbonyl (iNoc) amino protecting group by Veber et al.[3].

Our previous experience[1] with the photolysis of the 4 CC products from o-nitrobenzaldehyde, and the use of the photolysis of o-nitrobenzylurethanes[4], in a protective group technique as well as the redox behaviour of pyridine derivatives[5] led us to investigate whether the 4 CC products of the type (V) with R^A = 4-pyridyl are photocleavable in the sense (V) → (VI) + (VII).

The 4 CC product (Va) from phenylacetic acid (Ia), benzylamine (IIa), t-butyl isocyanide (IIIa) and 4-pyridinecarboxaldehyde (IVa) was photolyzed (see table of conditions and yields of N-(benzyl)phenylacetamide (VIa)[6].

Table. The photolytic cleavage of (Va) (1.00g in all experiments) at 25° in nitrogen atmosphere by 24^h of irradiation.[a]

ml of solvent	ml of additive	yield of isolated (VIa) in %[e]
350 MeOH	---	23
350 MeOH	3.0 conc. HCl	35[b,c]
350 $CHCl_3$	3.0 conc. HCl	20
350 C_6H_6	5.0 98% HCO_2H	< 10[d]
350 98% HCO_2H	---	< 10[d]
200 i-PrOH +150 MeOH	25 20% H_2SO_4	29

a) Hg-immersion-lamp TQ 150 ("Original Hanau") with a Duran 50 cooling jacket.

b) External irradiation for 24^h with TQ 150 through a 2 mm WG 360 filter[7] (transmission $<10^{-3}$ at 320 nm) yields 15% (VIa). When this filter is used tryptophane is not photolyzed. With an additional 4 mm KG 1 filter[7], transmission ≥ 0.85 between 375 nm and 550 nm, no photolysis of (Va) was observed.

c) 2.0 ml TFA instead of 3.0 ml conc. HCl led to 11% (VIa).

d) not isolated, determined by TLC

e) Column chromatography on silica gel 60 (70-230 mesh) in dichloromethane / ethylacetate / methanol (10:1.5:0.8).

The photochemical formation of methoxy-dihydropyridine derivatives from 3-cyanopyridine and methanol[8] and the reactions in this paper may be mechanistically related.

It is noteworthy that the 4 CC product of 3-pyridinecarboxaldehyde with (Ia), (IIa) and (IIIa) as well as the product of the Passerini reaction[9] between (Ia), (IIIa) and (IVa) are photochemically stable under conditions which lead to the photolysis of (Va).

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