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A SAFETY-CATCH TYPE OF AMIDE PROTECTING GROUP

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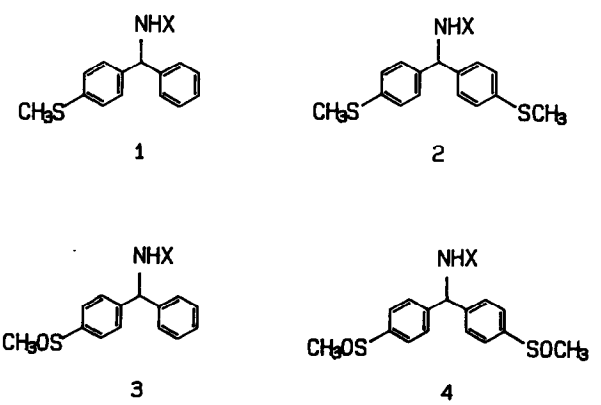
Summary: A p-substituted benzhydrylamine derivatives 1 - 4 were synthesized and evaluated for their lability toward various acids. The pair 2 & 4 seems to be suitable for peptide synthesis using the base labile Fmoc- and/or acid labile Boc- strategy.

Quite recently a safety-catch type of amino and carboxyl sulfur containing protecting groups were reported and used for the peptide synthesis.[1,2] In connection with our studies aimed at developing a safety-catch type of acid labile linkage agents for the synthesis of peptide C-terminal amides, we have examined some benzhydrylamines 1 - 4 containing p-methylsulfinyl or p-methylthio groups as a model amide protecting groups. In this paper we describe the synthesis of p-(methylthio)benzhydrylamines 1 and 2, oxidation of their derivatives to the sulfoxides 3b,c and 4b,c, and results on the lability of the above mentioned protecting groups toward various acids.

Figure 1



a) X = H, b) X = Fmoc-Gly-, c) X = Fmoc-Val-

The structures of the benzhydrylamine derivatives studied[3] are given in Figure 1. 4-(Methylthio)benzhydrylamine was prepared by a straightforward three step procedure. Friedel-Crafts acylation using thioanisole and benzoylchloride with $AlCl_3$ as a catalyst afforded the corresponding benzophenone in 77% yield.[4] The benzophenone product was converted to its oxime ($HCl.NH_2OH/NaOH/EtOH$) which was reduced to its benzhydrylamine derivative (Zn/AcOH) in 45% overall yield and stored as 4-toluenesulfonate salt. Analogously, 4,4'-bis(methylthio)benzhydrylamine was prepared. Friedel-Crafts acylation using thioanisole and oxalylchloride afforded 4,4'-bis-(methylthio)benzophenone[5] which was in the same way transformed to 2a (4-toluenesulfonate salt) in 12% overall yield. No attempts were made to maximize the yields of the synthetic reactions. Fmoc-Gly-OH and Fmoc-Val-OH were introduced in the usual manner (DCC/HOBt/DMF) to give the desired derivatives 1b (89%), 1c (85%) and 2b (98%), 2c (74%), respectively. Fmoc-valine was chosen as the test amino acid because its bulky steric properties would presumably make this a more difficult amino acid to couple and cleave. Sulfoxides 3b,c and 4b,c were obtained from the corresponding sulfides 1b,c and 2b,c by oxidation with SO_2Cl_2/CH_2Cl_2 on a wet silicagel[6] in moderate yield (40-60%).

For determination of acid lability the above described Fmoc-amino acid derivatives a series of deprotection experiments was performed. The results are summarized in Table 1. From a practical point of view, the 24h cleavage period was chosen as an upper limit. Aliquots of reaction mixture were taken at various times and the cleavage reaction was quenched by water. After evaporating and drying of the product in vacuo, the residue was dissolved in DMF and applied to TLC and RP HPLC analysis. Due to the pseudo first order conditions, the half-lives for some cleavage reactions could be evaluated.

As can be seen from Table 1, the substitution of glycine for valine enhanced the rate of cleavage by a factor of 3-4, depending upon cleavage conditions. Further, the change in rate of cleavage with alteration of para substitution is considerable. As the number of electron-releasing methylthio groups is increased, the rate of cleavage increase ten-times(1b & 2b). Interestingly, 2b is cleaved faster when dimethylsulfide is used as a soft nucleophile in lieu of thioanisole which was found to be most effective to accelerate the cleavage reaction, compared with other scavengers examined.[8] An explanation of small, but real difference in cleavage rate does not appear obvious at this stage. As regards the electron-withdrawing methylsulfinyl groups, the sulfoxides 3,4(b,c) were found to be extremely high stable to conditions commonly used for removing of the Boc group (50%TFA/CH_2Cl_2-anisole). Therefore the pair 2 & 4 seems to be suitable for

peptide synthesis using the Fmoc- and/or Boc- strategy. Fortunately, the above mentioned sulfoxides undergo one-pot reductive acidolysis when treated with $SiCl_4$/TFA/scavenger[1] or Me_3SiX/TFA/scavenger[9,10] reagents(X=Br, CF_3SO_3) to give corresponding Fmoc-amino acid amides. In accordance with the literature data[9] the 1M-Me_3SiBr/thioanisole/TFA (0^0C, 3h) system was found to be most suitable for mild deprotection of derivatives 2,4(b,c).

Table 1
Results of the acidolytic cleavage experiments with derivatives 1-4(b,c)

Cleavage conditions[b]	Cleavage time (h)[a]					
	Fmoc-Gly-NH_2				Fmoc-Val-NH_2	
	1b	3b	2b	4b	2c	4c
90%(95%TFA/H_2O)/CH_2Cl_2, 20°C	>24	–[c]	7(99)	–[c]	23(320)	–[c]
Me_2S/TFA(95:5), 20°C	>24	>24[d]	9(126)	–[c]	24(362)	–[c]
1M-thioanisole/TFA, 20°C	>24	>24[d]	11(160)	–[c]	>24	–[c]
1M-Me_3SiBr/thioanisole/TFA, 0 °C	24	n.d.	2(32)	3[e,f]	7.5(106)	9(126)
1M-$SiCl_4$/anisole/TFA, 0°C	n.d.	n.d.	n.d.	7.5[e](104)	n.d.	24(415)
1M-TMSOTf/thioanisole/TFA, 0°C	2	n.d.	<1[g]	<1[g]	n.d.	<1[g]

[a] amount of starting material was <5%, values in parentheses are half-lives(min); [b] a mixture of an Fmoc-amino acid derivative 1 - 4b,c(6μmol) was treated with cleavage reagent(0.6ml); [c] after 24h the starting sulfoxides were unchanged; [d] reduction to 1b was observed; [e] within 1h the sulfoxides were reduced to corresponding sulfides; [f] reaction has also been performed on preparative scale[7]; [g] first sample was taken at 1h.

Utility of a new protecting group is presented by a successful peptide synthesis. Starting from sulfoxide 4b, we have prepared H-Pro-Leu-Gly-NH_2 (Boc-strategy). Final cleavage step was accomplished with 1M- Me_3SiBr/ thioanisole/TFA (0°C, 4h) and after HPLC purification the peptide was obtained in 43% yield. In addition, the LHRH (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2) was prepared by a condensation of N^{α}-deprotected 4b with the corresponding peptide fragment followed by deprotection with the mixture described above (0°C, 4h). This experiment was performed with very low amount of peptide precursor and due to the methods used for the purification of final product (precipitation by diethyl ether, gel filtration and reversed phase HPLC), the obtained yield (11%) should not be considered representative. Both prepared peptides were chosen as

substances which could be compared with authentic samples; Both products were found to be identical with the standards(HPLC, FAB-MS).

In conclusion, we have proved that the concept of converting a stable protecting group into a labile one (safety-catch principle) can also be applied to benzhydrylamine skeleton. Further study of this protecting groups as well as the corresponding linkage agents are currently under investigation.

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7) 1M-Me_3SiBr/TFA (5ml) was added to a suspension of **4b** (56mg, 0.1mmol) in thioanisole (621mg, 5mmol) at 0°C. After 2h, water (0.5ml) was added and the solution stirred for 5min. The reaction mixture was evaporated to dryness, diluted to 1ml with DMF and loaded on a semipreparative RP HPLC column. Fmoc-Gly-NH_2 was isolated in 90% yield (27mg).
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