"SAFETY-CATCH" PROTECTING GROUPS IN PEPTIDE SYNTHESIS*

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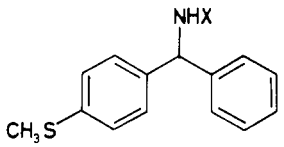
A new benzhydryl-type protective groups for amides based on the concept of converting a stable protecting group into a labile one (safety-catch principle) are described. The *p*-substituted benzhydrylamine derivatives *III*(*a*, *b*), *IV*(*a*, *b*) are shown to be labile toward various acids but in their oxidized state — *V*(*a*, *b*), *VI*(*a*, *b*) exhibit the resistance to conditions commonly used for removal the Boc group. Independent removal of Boc or Fmoc groups, each in the presence of derivative *VIa*, is demonstrated by a synthesis of Pro-Leu-Gly-NH_2. Some mechanistic aspects of deprotection reactions are discussed.

The synthesis of peptide amides by solid-phase method can be performed under either strong acid (anhydrous hydrogen fluoride, trifluoromethanesulfonic acid) or base (e.g., ammonia) conditions for final cleavage from the support. The increasing importance of peptide synthesis stimulated the development of anchor groups which release the peptide amides prepared by Fmoc-solid-phase peptide synthesis (SPPS) upon mild acidic cleavage conditions. Hence, a number of benzylamine and benzhydrylamine derivatives substituted with electron-donating alkoxy groups have appeared[1-10]. Nevertheless, the development of new protecting groups and handles which would extend the currently used orthogonal[11,12] systems (N^{α}-Boc/side-chain Fmoc protection/benzyl ester or *p*-methylbenzhydrylamine (MBHA) resins; N^{α}-Fmoc/ /side-chain tert-butyl/acid labile handles) in SPPS is a challenging problem in peptide chemistry.

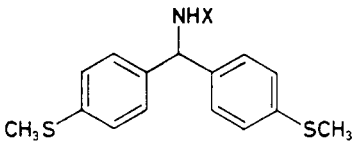
In our preliminary communication we have reported on the "safety-catch" type of amide protecting groups based on the heterolytic benzhydryl–nitrogen cleavage affected by electronic character of a *para* substituent of the aromatic moiety[13]. In this

* Abbreviations used in this paper follow the recommendations of the IUPAC–IUB Commission on Biochemical Nomenclature (Eur. J. Biochem. *138*, 9, 1984). Other abbreviations are as follows: DCC dicyclohexylcarbodiimide, DCM dichloromethane, DIEA N,N-diisopropylethylamine, EDC 1,2-dichloroethane, HOBt N-hydroxybenzotriazole, TFA trifluoroacetic acid, TFMSA trifluoromethanesulfonic acid, TfOTMS trimethylsilyl trifluoromethanesulfonate, TMSBr trimethylsilyl bromide.

paper we report the preparation and use of aforementioned amide protecting groups, i.e., *p*-substituted benzhydrylamine derivatives *III* – *VI*.



III



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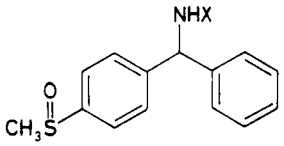

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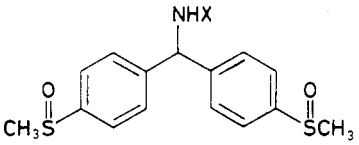


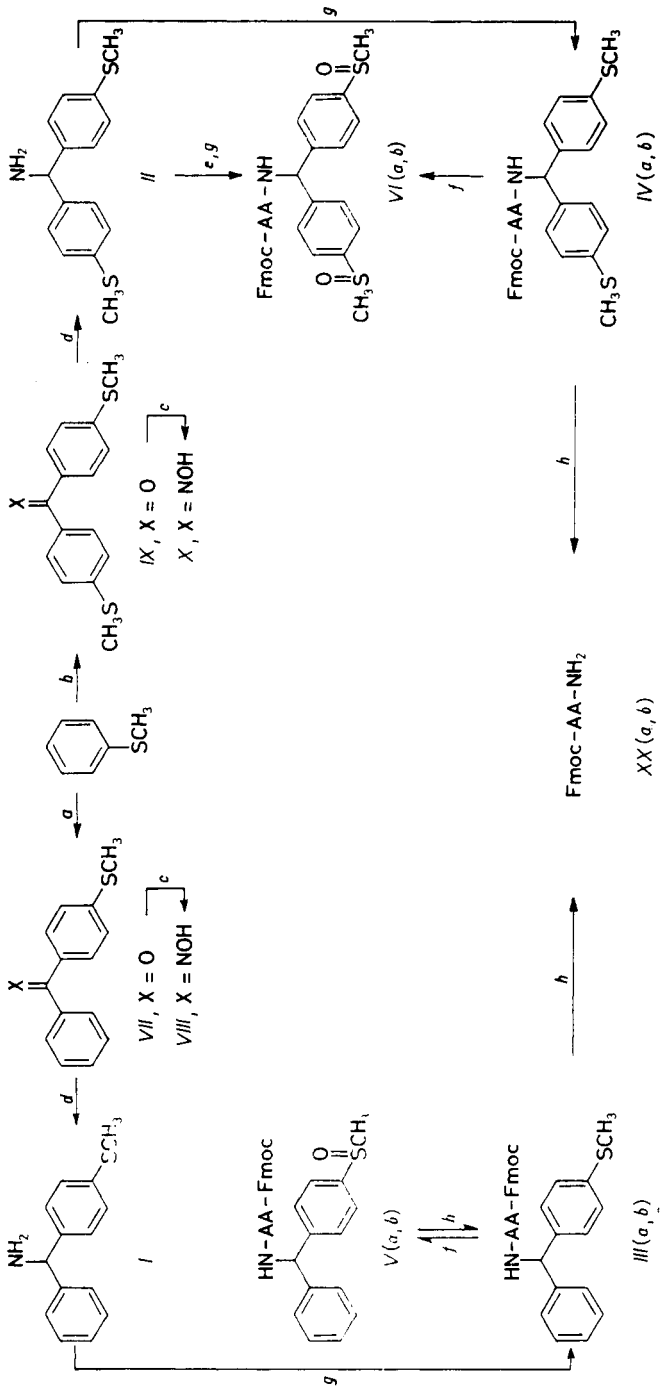
VI

a, X = Fmoc-Gly ; *b*, X = Fmoc-Val ; *c*, X = Z-Phe ; *d*, X = H-Phe

RESULTS AND DISCUSSION

Preparation of Benzhydrylamine Derivatives I, II, *and* III(a–d)–VI(a–d)

4-(Methylthio)benzhydrylamine *I* was prepared by a straightforward three step procedure according to Scheme 1. Friedel–Crafts acylation using thioanisole and benzoyl chloride with $AlCl_3$ as a catalyst afforded the corresponding benzophenone[14] *VII* in 77% yield. The benzophenone was converted to oxime *VIII* which was reduced to benzhydrylamine derivative *I* in 47% overall yield (stored as 4-toluenesulfonate salt). Analogously, Friedel–Crafts acylation using thioanisole and oxalyl chloride afforded 4,4'-bis(methylthio)benzophenone[14] *IX* which was in the same way transformed to *II* (4-toluenesulfonate salt) in 13% overall yield. This low overall yield was affected by low yield of Friedel–Crafts acylation (23%); no attempts were made to its optimization. Regarding N^{α}-Fmoc amino acids used in this work, Fmoc-glycine was chosen as a simple amino acid derivative with small steric demands. On the other hand, Fmoc-valine was chosen as amino acid derivative with bulky side chain which makes this amino acid more difficult to couple and cleave. Both amino acid derivatives were introduced in the usual manner (DCC/HOBt/DMF) to give the desired compounds *III*(*a*, *b*) and *IV*(*a*, *b*) in good yield. To determine stability of 4,4'-bis(methylsulfinyl)benzhydrylamide moiety of Z-phenylalanine derivative *VIc* toward acidic conditions used for removal of *Z*-group, the corresponding derivative *VIc* has also been prepared.

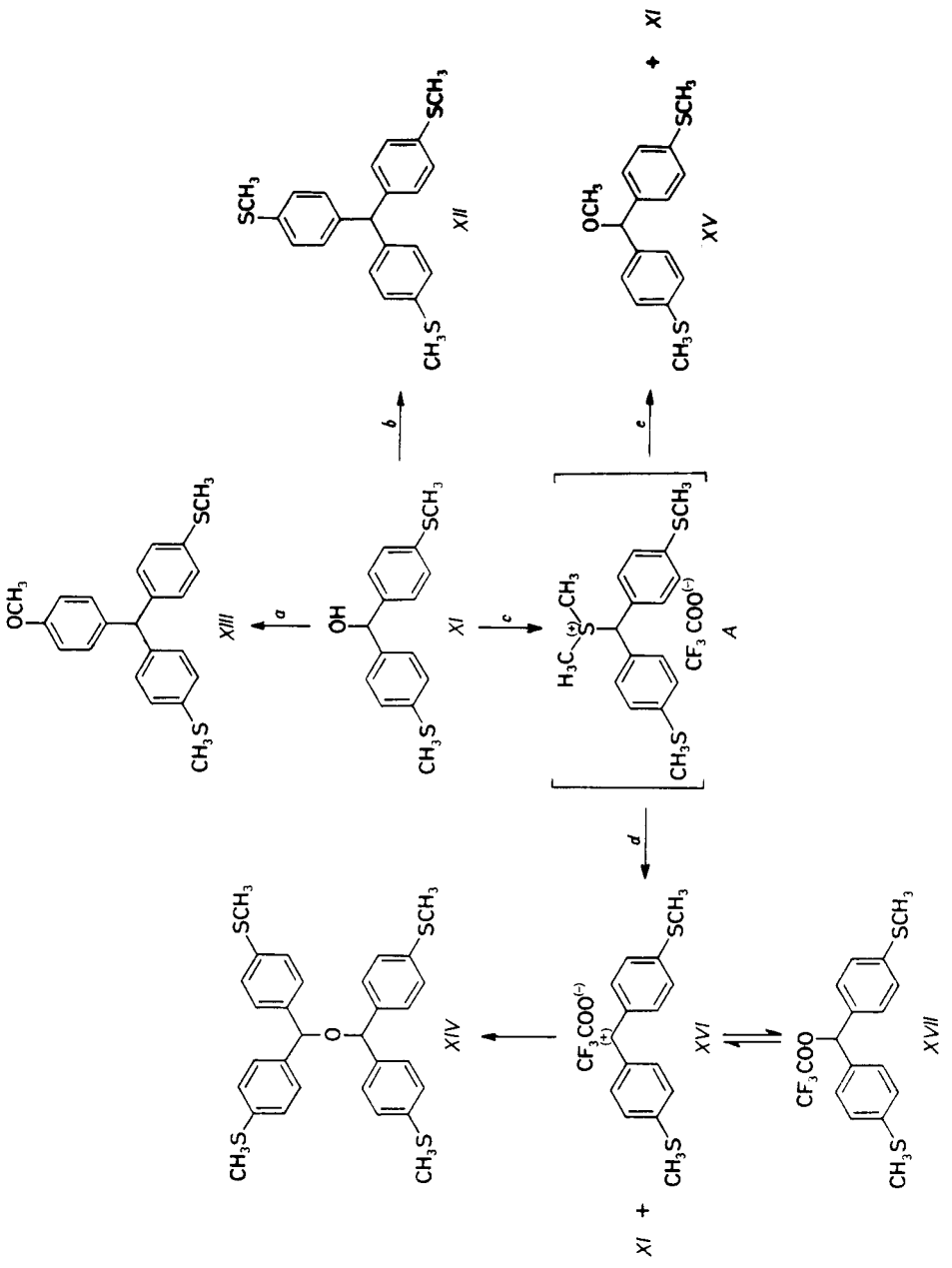

AA = Gly, Val
a, C_6H_5COCl, $AlCl_3$, EDC ; b, $(COCl)_2$, $AlCl_3$, EDC ; c, $NH_2OH.HCl$, NaOH, EtOH ; d, Zn, AcOH ; e, $NaIO_4$, aq. MeOH ,
f, SO_2Cl_2, wet silica gel, K_2HPO_4 ; g, DIEA, Fmoc-AA-OH, DCC, HOBt, DMF ; h, TFA, scavenger

SCHEME 1

Sulfoxides *V*(*a*, *b*) and *VI*(*a*, *b*) were obtained through two synthetic routes as shown in Scheme 1. Sulfides *III*(*a*, *b*) and *IV*(*a*, *b*) were oxidized with SO_2Cl_2 on a wet silica gel[15]. This procedure was described to be convenient and mild for oxidation of sulfides to sulfoxides without detection of sulfones or chlormethylsulfinyl derivatives. In our hands, besides a small amounts of sulfones and chloromethylsulfinyl derivatives, some cleavage products of starting sulfides *III*(*a*, *b*), *IV*(*a*, *b*) were detected. We suppose that this was caused by the presence of liberated hydrogen chloride in dichloromethane solution. Indeed, these cleavage reactions were suppressed by addition of 5 equivalents of potassium hydrogen phosphate to the reaction mixture. Subsequently, the yields of sulfoxides increased by about 20%. By this improved method, the sulfoxide *VIc* was also prepared. Alternatively, the oxidation of benzhydrylamine *II* with sodium periodate followed by coupling with Fmoc amino acid afforded required sulfoxides *VI*(*a*, *b*). The latter method gave better yields because of neutral and very mild conditions for oxidation. As the only side product, the sulfone derivatives of *VI*(*a*, *b*) were detected. All the sulfoxides prepared proved to be very hygroscopic. Unsatisfactorial elemental analysis of these sulfoxides can also be explained by solvatation of sulfoxides with solvents used in isolation steps[37]. Furthermore, there are some very interesting differences in the ^{1}H NMR spectra of sulfoxides *Va*, *VIa* and *V*(*b*, *c*), *VI*(*b*, *c*) prepared by the oxidation of corresponding sulfides. In both *V*(*b*, *c*) and *VI*(*b*, *c*) there are two singlets for $SOCH_3$ groups with the difference $\approx$0·04 ppm. We explain these observations by the presence of a mixture of diastereomers formed in the oxidation step.

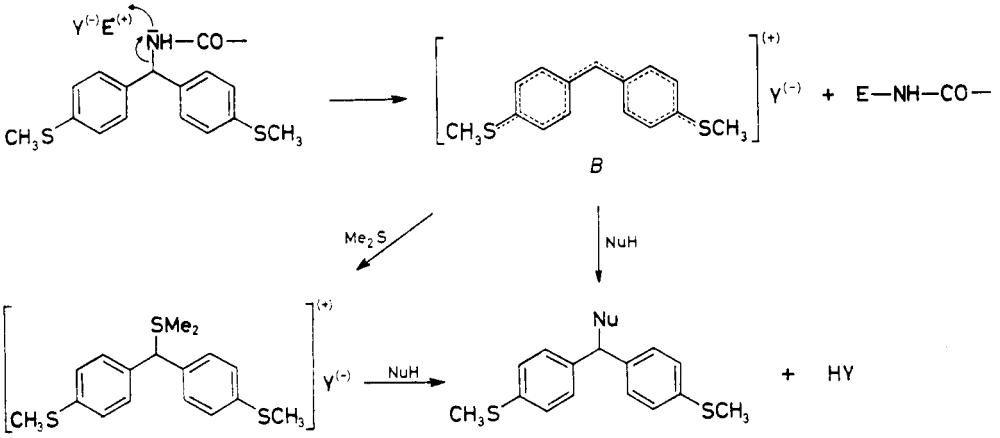
Mechanistic Aspects of Deprotection Reactions

Before description of acid lability of derivatives *III*(*a*–*c*)–*VI*(*a*–*c*) we feel compelled to mention several mechanistic considerations of the electrophile-assisted cleavage of C—N bond in benzhydrylamides. Data on the solvolysis of substituted trityl chlorides[16], benzhydryl chlorides[17–19], and benzyl tosylates[20] can be found in the literature. Of fundamental importance to the understanding of the cleavage process are earlier studies of Okamoto and Brown[21] which utilized the Hammett equation for kinetic and mechanistic description of benzyl derivative solvolysis. It was found that benzyl tosylates containing electron-donating substituents undergo solvolysis via a mechanism involving the benzyl cation. During the last 20 years, an important development in this area has been provided by Yajima and Kiso. In 1976 Yajima and associates[22] for the first time have observed the cleavage of aromatic ethers in terms of the hard and soft acids and bases (HSAB) principle[23–25]. In the next paper[26] they have used this principle for deprotection of Z-Lys-OH. Subsequently, Kiso and co-workers have improved this hard acid deprotecting procedure and called the cleavage mechanism as a "push-pull" mechanism[27]. Generally accepted mechanism involves the initial attack of $E^{(+)}$ (hard acid) on the oxygen atom (hard base)


a, 1M anisole–TFA; b, 1M thioanisole–TFA; c, 1M dimethylsulfide–TFA; d, wet diethyl ether; e, dry methanol

SCHEME 2

of the ether or ester bond, and nucleophilic attack of Nu (thioether as a soft base) on the electron deficient benzyl carbon (soft acid). The role of thioether is to "push" the acidolytic cleavage, and therefore, this reaction involves the coopearative action of a soft nucleophile and hard electrophile on a substrate. The reaction rate depends on the nature of attacking nucleophiles; thioanisole was more effective than dimethylsulfide and anisole, owing to the stabilization of the resulting sulfonium ion by π-electrons of benzene ring[27,28]. The corresponding benzylmethylphenylsulfonium salt was obtained in quantitative yield[29]. There is a large body of experimental data for cleavage reactions of other species (methylthio-substituted benzyl derivatives, alkoxy-substituted benzhydrylamides)[3-10,13,30,31] which probably proceed via analogous carbenium intermediates. We anticipate that the cleavage mechanism of sulfur-containing benzhydrylamides *III*(*a*, *b*), *IV*(*a*, *b*) is roughly analogous to the one for the above mentioned cleavage reactions of O-benzyl and N-benzyloxycarbonyl derivatives. Since carbon–nitrogen bond is formally made up of a soft acid ($CH^{(+)}$) and hard base ($NH^{(-)}$), reagent system consisting of a hard acid and a soft nucleophile should cleave those bonds faster than only hard acid alone. To our knowledge, there are no other reports dealing with cleavage mechanism of substituted benzhydrylamides of the type *III*(*a*, *b*), *IV*(*a*, *b*) in the presence of soft nucleophiles. Thus, we decided to check this hypothesis by performing several experiments intended for trapping of benzhydrylium ion (Scheme 2). In order to do this, we prepared 4,4'-bis-(methylthio)benzhydrole *XI* which represents precursor to benzhydrylium ion *B*



E ≡ $H^{(+)}$, $(CH_3)_3Si^{(+)}$; Y = $CF_3COO^{(-)}$, $CF_3SO_3^{(-)}$, $Br^{(-)}$; NuH = $PhSCH_3$, $PhOCH_3$, H_2O, ROH

SCHEME 3

depicted in Scheme 3. This benzhydrole was readily prepared by reduction of 4,4'-bis(methylthio)benzophenone *IX* with $NaBH_4$ in ethanol in 99% yield.

The TFA solution of *XI* forms deep blue color which did not disappear upon evaporation. Presumably the derivative *XI* solvolyze to the colored benzhydrylium ion *B* (Scheme 3), which during solvent removal does not collapse to the colorless, non-ionic benzhydryl trifluoroacetate. Addition of a scavenger to TFA solution of *XI* is followed by loss of blue color. To trap the benzhydrylium intermediate as the [4,4'-bis(methylthio)benzhydryl]methylphenylsulfonium trifluoroacetate, we performed the cleavage of *XI* with 1M thioanisole–TFA at 20°C for 5 min. Surprisingly, we isolated tris(4-methylthiophenyl) methane *XII* in quantitative yield. It should be noted that the same compound *XII* was isolated from the reaction of *IVa* with 1M thioanisole–TFA at 20°C for 11 h (Table I, entry 3). Analogously, 4-methoxyphenyl[bis(4-methylthiophenyl)]methane *XIII* was isolated from reaction of *XI* with 1M anisole–TFA (20°C, 5 min). Repeating the same experiment with 1M dimethylsulfide–TFA (20°C, 5 min), however, gives a mixture of products which composition depends upon reagent used for quenching of the reaction, but no sulfonium salt *A* is detected. When wet diethyl ether is used, the starting benzhydrole *XI* (50%), di[4,4'-bis(methylthio)benzhydryl] ether *XIV* (27%), and trifluoroacetate *XVI* (15%) were isolated. The constitution of trifluoroacetate *XVI* was supported by ^{19}F NMR spectroscopy. The spectrum of compound *XVI* in hexane–ethyl acetate (65 : 35; sample from flash chromatography) displays two NMR signals in 3 : 1 ratio. Based on chemical shifts, we conclude that the main signal correspond with "ionic" form of ester *XVI* and the second signal with covalent trifluoroacetate ester *XVII*. When dry methanol was used for quenching, 4,4'-bis(methylthio)benzhydrylmethyl ether *XV* (90%) and the starting benzhydrole *XI* (10%) were isolated (Scheme 2). It is possible that sulfonium salt *A* exists only as intermediate which rapidly decomposed upon isolation to give products resulting from attack of benzhydrylium ion *B* (Scheme 3) to nucleophile (H_2O, ROH). The lability of sulfonium ion *A* could be explained by the large steric demands of methyl groups and mainly by the relative stability of benzhydrylium ion. This hypothesis follows from visible differences in reaction mixture coloration. The mixture is light green in the presence of dimethylsulfide, in contrast to deep blue colored when no scavenger is added. In addition, similar mechanism with the loss of dimethylsulfide from dimethyl[4-(methylthiobenzyl)]sulfonium trifluoroacetate upon distillation (41°C/1·1 mm) has been reported by Samanen for related reaction[30]. For comparison, a computer-generated* view of intermediate ion *A* and dimethyl-[4-(methylthiobenzyl)]sulfonium ion are depicted in Fig. 1. As can be seen from this figure, significant steric hindrance exists in the intermediate ion *A*.

* The energy minimization procedure is based on the formulae and data given in "Strategic approaches to drug design-I. An integrated software framework for molecular modelling"[38].

Several deductions can be made from these results. First, soft nucleophiles act here only as scavengers for carbenium ion *B* (Scheme 3) which is stabilized by large charge delocalization. Anisole and thioanisole undergo facile electrophilic *para*-alkylation. Observed *para*-regioselectivity can be explained considering both steric and electronic effects. Steric effects are well known to be important in reducing the ratio of *ortho*/*para*-product. Furthermore, for thioanisole and anisole, the total charge is larger on *ortho*-carbons, but the frontier electron population is larger on the *para*-position and therefore, we can expect the softer electrophiles to give more *para*-substitution[32]. Second, the "push-pull" mechanism does not apply to the cleavage of benzhydrylamides with *para*-electron-donating substituents, because the cleavage takes place independently on the presence and type of soft nucleophile. From rate constants estimated from cleavage reactions is evident that reaction rates are almost independent on the softness of nucleophile. This observation is in sharp contrast to cleavage of benzyl group where the promoting effect of nucleophiles used was in the order thioanisole > dimethylsulfide > ethanedithiol ≈ phenol > anisole[29,33].

These findings are important in that they suggest that electrophile-assisted benzhydrylamide cleavage adheres to the same mechanistic category like benzyl derivatives and proceeds via the formation of a carbenium intermediate. But in contrast to "push-pull" mechanism, presence of a soft nucleophile is not necessary (Scheme 3).

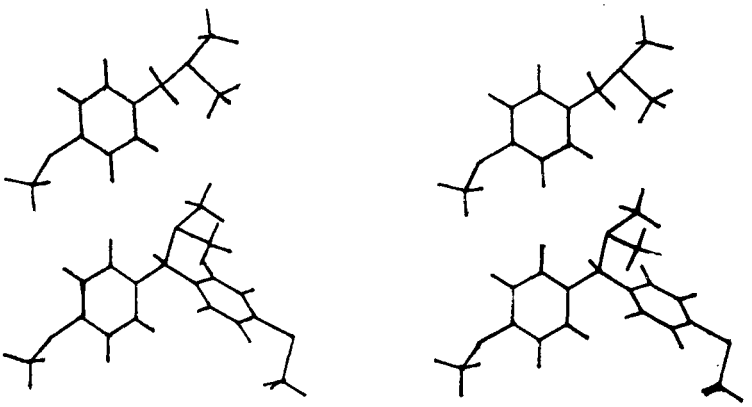


FIG. 1

Computer-generated stereoview of dimethyl[4-(methylthiobenzyl)]sulfonium ion (top) and intermediate ion *A* (bottom)

Acid Lability of Benzhydrylamine Derivatives III(a–c)–VI(a–c)

To determine the Ar_2CH—NH bond acid lability, a series of cleavage experiments was performed. From a practical point of view, the 24 h cleavage period was chosen as an upper limit. Aliquots of reaction mixture were taken at various time intervals and the cleavage reaction was quenched by water. After evaporation and drying of the product in vacuo, the residue was dissolved in DMF and subjected to TLC and RP HPLC analysis. Under conditions where the concentration of hard acid and soft base was high, the rate constants and half-lives for some cleavage reactions could be estimated because of the pseudo first order conditions used. Observed rate constants (k) were calculated according to $kt = \ln(a/a - x)$, where a and $a - x$ are the concentrations of cleaved derivatives at zero time and time t, respectively. These results are summarized in Table I. From Table I it is evident that:

(i) The substitution of glycine for valine enhanced the rate of cleavage by a factor of 3 to 4, depending upon cleavage conditions. This fact is in agreement with steric demands of glycine and valine.

(ii) The dependence of the cleavage rate on the *para*-substitution of benzhydryl

TABLE I

Results of the acidolytic cleavage experiments with some derivatives *III*– *VI*

Entry	Cleavage conditions[b]	Cleavage time, h[a]					
		IIIa	*Va*	*IVa*	*VIa*	*IVb*	*VIb*
1	90% (95% TFA–5% H_2O)–DCM, 20°C	>24	–[c]	7(99)	–[c]	23(320)	–[c]
2	Me_2S–TFA (5 : 95), 20°C	>24	>24[d]	9(126)	–[c]	24(362)	–[c]
3	1M thioanisole–TFA, 20°C	>24	>24[d]	11(160)	–[c]	>24	–[c]
4	1M anisole–TFA, 20°C	n.d.	n.d.	9(130)	–[c]	n.d.	n.d.
5	33% HBr–AcOH, 20°C	n.d.	n.d.	19(260)	>24[e]	n.d.	>24[e,f]
6	1M TMSBr–thioanisole–TFA, 0°C	24	n.d.	2(32)	3[e,f]	7·5(106)	9(126)
7	1M $SiCl_4$–anisole–TFA, 0°C	n.d.	n.d.	n.d.	8[e](110)	n.d.	24(415)
8	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] Fmoc-amino acid derivative *III(a, b)*– *VI(a, b)* (6 μmol) was treated with cleavage reagent (0·6 ml); [c] after 24 h the starting sulfoxides were unchanged; [d] reduction to *IIIa* was observed; [e] within 1 h the sulfoxides were reduced to corresponding sulfides; [f] this reaction has also been performed in preparative scale; [g] first sample was taken at 1 h, complex mixture of products was obtained.

group is considerable. As the number of electron-releasing methylthio groups is increased, the rate of cleavage increases about ten-times (*IIIa*, *IVa*).

(iii) The rate-limiting step is considered to be acid strength (i.e., hardness of the acid used), because the C—N cleavage is almost independent on the presence and type of soft nucleophile.

(iv) The sulfoxides *V*(*a*, *b*), *VI*(*a*, *b*) were found to be extremely stable to conditions commonly used for removal of the Boc group (50% TFA/CH_2Cl_2–anisole). Therefore the system sulfide *IV*–sulfoxide *VI* seems to be suitable for peptide synthesis using the Fmoc- and/or Boc- strategy. Further, the stability of 4,4'-bis(methylsulfinyl)-benzhydrylamide skeleton towards TFA was proved by isolation of *VId* after treatment of *VIc* with 1M thioanisole–TFA (20°C, 5 h) in quantitative yield. The Z group was removed by a "push-pull" method described earlier[33]. We assume that there are several reasons for high sulfoxide acid-stability. First, the benzhydryl carbon behaves as hard electrophile because of the shift of electrons into aromatic rings. Accordingly, the carbon–nitrogen bond becomes far more stable to cleavage by hard acid. Second, the cleavage of sulfoxides is not advantageous because of insufficient delocalization of positive charge formed through aromatic system.

(v) The above mentioned sulfoxides undergo one-pot reductive cleavage when treated with $SiCl_4$–TFA-scavenger[31] or TMSX–TFA-scavenger reagents (X = Br, CF_3SO_3)[34,35] to give corresponding Fmoc-amino acid amides *XX*(*a*, *b*). It is remarkable that the analogous reduction was also observed with HBr-AcOH. The above mentioned silicon-containing agents can be classified as superhard (not Brönsted) acids with ability to reduce sulfoxides to thioethers and subsequently cleave C—N bond of methylthio-substituted benzhydrylamides. Silylated compounds formed are easily decomposed with water or ammonium fluoride to afford free Fmoc-amino acid amides. The system consisting of 1M TMSBr–thioanisole–TFA was found to be most suitable for mild deprotection of derivatives *IV*(*a*, *b*), *VI*(*a*, *b*).

Introduction of a new protecting group would be incomplete without demonstration of its utility through successful peptide synthesis. Therefore, starting from sulfoxide *VIa*, H-Pro-Leu-Gly-NH_2, a simple peptide, was prepared. As expected, treatment of *VIa* with piperidine–DMF (1 : 1) gave N^{α}-deprotected *VIa*. In the next step *VIa* was coupled with Boc-Leu-OH. Exposure of this protected dipeptide *XVIII* to mixture of TFA–CH_2Cl_2–anisole (50 : 50 : 5) afforded N^{α}-deprotected dipeptide without any damage to the benzhydryl–sulfoxide moiety. To the preceding dipeptide Boc-Pro-OH was coupled to give protected tripeptide *XIX*. Final cleavage step was accomplished with 1M TMSBr–thioanisole–TFA at 0°C for 4 h. After HPLC purification; the target peptide identical with the standard (HPLC, FAB MS) was obtained in 43% yield.

In conclusion, these investigations indicate that the concept of converting a stable protecting group into a labile one (safety-catch principle) can also be applied to

benzhydrylamine skeleton, albeit with several limitations. Nevertheless, these protecting groups are amenable to improvement in both the possibility of addition the next electron-withdrawing/donating groups and the attachment of carboxyl terminal chain to give a new type of safety-catch handle[36]; as such, it may provide a next step to the design of a completely general scheme for the convenient peptide synthesis by use of the solid-phase method.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. ^{1}H NMR spectra were recorded on a Tesla BS 497 instrument (100 MHz) with tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded on a Varian UNITY 500 (FT mode, 470·27 MHz) with CF_3COOH as external standard. Chemical shifts are given in ppm. Mass spectra were measured on a ZAB–EQ spectrometer (VG Analytical Ltd., Manchester). Thin-layer chromatography was performed on silica gel (Silufol UV 254 Kavalier, Czechoslovakia), and the spots were detected by fluorescence quenching or by spraying with a dilute ethanolic ninhydrin solution. Development was with: A, chloroform–methanol (20 : 1); B, 1-butanol–acetic acid–water (4 : 1 : 1); C, hexane–ethyl acetate (65 : 35). Both analytical and preparative HPLC were carried out on an Spectra Physics instrument using Vydac 218TP5 column with a linear gradient over 40 min, starting from 25% eleuent B (eluent B: 80% acetonitrile in water containing 0·1% TFA) and 75% eluent A (eluent A: 0·1% TFA in water), flow rate 1 ml/min, UV absorbance setting 280 nm.

4-(Methylthio)benzophenone (*VII*)

The compound was prepared from thioanisole and benzoyl chloride (EDC as a solvent) according to described method, yield 77%, m.p. 78—78·5°C (ref.[14], m.p. 79°C); R_F(A) 0·78.

4-(Methylthio)benzophenone Oxime (*VIII*)

By the exactly analogous procedure to *X*. Reaction time 17 h, yield 87%, m.p. 111—125°C (mixture of isomers); R_F(A) 0·60. EI MS (*m/z*, rel. int. %): 243 (M^+, 100), 226 (40), 211 (15), 124 (30), 108 (12). For $C_{14}H_{13}NOS$ (243·3) calculated: 69·10% C, 5·39% H, 5·76% N, 13·15% S; found: 68·89% C, 5·35% H, 6·03% N, 12·99% S.

4-(Methylthio)benzhydrylammonium 4-Toluenesulfonate (*I*)

Compound *I* was prepared analogously to *II*. Reaction time 3 h, yield 71%, m.p. 217—219°C; R_F(B) 0·55. EI MS (*m/z*, rel. int. %): 229 (M^+, 50), 214 (68), 152 (100), 105 (52), 60 (67). For $C_{21}H_{23}NO_3S_2$ (401·1) calculated: 62·82% C, 5·77% H, 3·49% N, 15·97% S; found: 62·47% C, 5·71% H, 3·35% N, 16·10% S.

4,4′-Bis(methylthio)benzophenone (*IX*)

The compound was prepared from thioanisole and oxalyl chloride (EDC as a solvent) according to described method, yield 23%, m.p. 126·5—127°C (ref.[14], m.p. 125·5°C); R_F(A) 0·77. ^{1}H NMR ($CDCl_3$): 2·50 s, 6 H (2 × SCH_3); 7·20—7·75 m, 8 H (arom.). EI MS (*m/z*, rel. int. %): 274 (M^+, 71), 256 (6), 227 (14), 151 (100), 123 (11), 108 (13), 45 (19), 28 (40). For $C_{15}H_{14}OS_2$ (274·4) calculated: 65·65% C, 5·14% H, 23·37% S; found: 65·81% C, 5·02% H, 23·17% S.

4,4'-Bis(methylthio)benzophenone Oxime (*X*)

A suspension of *IX* (7·00 g, 26 mmol), hydroxylamine hydrochloride (19·52 g, 281 mmol), and potassium hydroxide (15·77 g, 281 mmol) in ethanol–water (5 : 1, v/v, 200 ml) was refluxed until completion of the reaction (7 h). The mixture was filtered and concentrated to dryness. The residue was suspended in water (50 ml), the pH adjusted to 2 by addition of 2M-HCl, extracted with chloroform (3 × 50 ml) and dried over $MgSO_4$. After removal of the solvent, the residue was crystallized from ethanol to give the title product (6·25 g, 85%), m.p. 172–174°C; R_F(A) 0·53. ^{1}H NMR ($CDCl_3$): 2·53 s, 6 H (2 M SCH_3); 7·24–7·75 m, 8 H, (arom.). For $C_{15}H_{15}NOS_2$ (289·4) calculated: 62·25% C, 5·22% H, 4·84% N, 22·15% S; found: 62·44% C, 5·57% H, 4·74% N, 22·09% S.

4,4'-Bis(methylthio)benzhydrylammonium 4-Toluenesulfonate (*II*)

Compound *X* (6·25 g, 22 mmol) was dissolved in acetic acid (200 ml) at 50°C. Then zinc-dust (14·12 g, 220 mmol) was added over a period of 1 h and mixture was stirred at room temperature for 6 h. After filtration, the solvent was evaporated, the residue dissolved in methanol (50 ml) and solution of 4-toluenesulfonic acid (4·11 g, 22 mmol) in methanol (20 ml) was added. The mixture was stirred for 2 h to give white solid and then poured into cold water (200 ml) to precipitate all product. Filtration and drying in vacuo over P_2O_5 provided an off-white solid (6·76 g, 70%), m.p. 231–234°C; R_F(B) 0·52. EI MS (*m/z*, rel. int. %): 275 (M^+, 40), 260 (40), 151 (100), 105 (22). For $C_{22}H_{25}NO_3S_3$ (447·1) calculated: 59·03% C, 5·63% H, 3·13% N,!21·48% S; found: 59·14% C, 5·43% H, 2·92% N, 21·26% S.

Coupling of N^{α}-Protected Amino Acids to Benzhydrylamine Derivatives *I* and *II* (General Procedure)

To a solution of *I* or *II* (1 mmol) in dry DMF (5 ml), DIEA (188 μl, 1·1 mmol), HOBt (148·6 mg, 1·1 mmol), and N^{α}-protected amino acid derivative (1·1 mmol) were added all at once and the mixture was stirred for 15 min. Then solution of DCC (227 mg, 1·1 mmol) in DMF–DCM (5 : 3, 8 ml) was added, the mixture was stirred at 0°C for 1 h and an additional 5 h at room temperature. The mixture was filtered and the solution evaporated in vacuo to dryness. Then the residue was dissolved in ethyl acetate (700 ml), washed with 1M-$NaHCO_3$ (50 ml), 20% citric acid (50 ml), and brine (50 ml). After drying over $MgSO_4$, the solvent was removed to give a white solid which was crystallized from ethyl acetate–hexane.

Fmoc-Gly-[4-(*methylthio*)*benzhydrylamide*] (IIIa): Yield 89%, m.p. 183–186°C, R_F(A) 0·76. ^{1}H NMR (CD_3SOCD_3): 2·45 s, 3 H (SCH_3); 3·70 d, 2 H (J = 6 Hz); 4·25 bs, 2 H; 5·52 d, 1 H (NH, J = 9 Hz): 6·08 d, 1 H (Ar_2CH, J = 9 Hz); 7·21–7·94 m, 18 H (arom.); 8·70 d, 1 H (NH, J = 9 Hz). FAB MS (*m/z*): 508 (M + 1), 453, 437, 228, 213, 191, 179, 165, 152. For $C_{31}H_{28}N_2O_3S$ (508·6) calculated: 73·20% C, 5·55% H, 5·51% N, 6·30% S; found: 72·87% C, 5·54% H, 5·85% N, 6·34% S.

Fmoc-Val-[4-(*methylthio*)*benzhydrylamide*] (IIIb): Yield 85%; m.p. 174–176°C; R_F(A) 0·87. EI MS (*m/z*, rel. int.): 550 (M^+, 2), 354 (2), 328 (3), 311 (5), 228 (15), 213 (15), 178 (100), 165 (20), 72 (80), 55 (15). FAB MS (*m/z*): 213 (M^+-Fmoc-Val-NH). For $C_{34}H_{34}N_2O_3S$ (550·7) calculated: 74·15% C, 6·22% H, 5·09% N, 5·82% S; found: 74·62% C, 6·18% H, 5·05% N, 5·95% S.

Fmoc-Gly-[4,4'-*bis*(*methylthio*)*benzhydrylamide*] (IVa): Yield 98%; m.p. 193–196°C; R_F(A) 0·75. ^{1}H NMR (CD_3SOCD_3): 2·45 s, 6 H (SCH_3); 3·72 d, 2 H (J = 6 Hz); 4·25 bs, 2 H; 5·54 d, 1 H (NH, J = 9 Hz); 6·04 d, 1 H (Ar_2CH, J = 9 Hz); 7·20–7·96 m, 17 H (arom.); 8·69 d,1 H

(NH, $J = 9$ Hz). FAB MS (m/z): 555 (M + 1), 274, 259, 235, 214. For $C_{32}H_{30}N_2O_3S_2$ (554·7) calculated: 69·29% C, 5·45% H, 5·05% N, 11·56% S; found: 68·78% C, 5·83% H, 5·29% N, 11·50% S.

Fmoc-Val-[4,4′-*bis*(*methylthio*)*benzhydrylamide*] (IVb): Yield 74%; m.p. 204–206°C; R_F(A) 0·89. FAB MS (m/z): 597 (M + 1), 450, 303, 259, 235, 225. For $C_{35}H_{36}N_2O_3S_2$ (596·8) calculated: 70·44% C, 6·08% H, 4·69% N, 10·74% S; found: 70·05% C, 6·22% H, 4·56% N, 10·18% S.

Z-Phe-[4-(*methylthio*)*benzhydrylamide*] (IIIc): Yield 93%; m.p. 166–168°C; R_F(A) 0·77. FAB MS (m/z): 511 (M + 1), 228, 213, 181, 91. For $C_{31}H_{30}N_2O_3S$ (510·7) calculated: 72·90% C, 5·92% H, 5·49% N, 6·27% S; found: 72·36% C, 5·87% H, 5·66% N, 6·05% S.

Z-Phe-[4,4′-*bis*(*methylthio*)*benzhydrylamide*] (IVc): Yield 60%; m.p. 197–198°C; R_F(A) 0·69. FAB MS (m/z): 558 (M + 2), 274, 259, 213, 165. $C_{32}H_{32}N_2O_3S_2$ (556·8) calculated: 69·04% C, 5·79% H, 5·03% N, 11·51% S; found: 69·37% C, 5·82% H, 5·04% N, 11·39% S.

4-(Methylsulfinyl) and 4,4′-Bis(methylsulfinyl) benzhydrylamides (*V*(*a*–*c*), *VI*(*a*–*c*)) (General Procedure *A*)

The solution of 0·55M sulfuryl chloride in DCM (1 ml) for derivatives *III* or 1·9 ml for derivatives *IV*) was added dropwise, during 30 min, to a cooled (0°C) suspension of N^{α}-protected amino acid (0·5 mmol), wet silica gel (100 mg of silica gel, 100 µl of water), and potassium hydrogen phosphate (87 mg, 0·5 mmol) in DCM (4 ml). The stirring was continued for 15 min. The suspension was filtered and diluted with DCM (20 ml). The organic phase was washed with 10% $NaHCO_3$ (10 ml) and water (10 ml). Drying ($MgSO_4$) followed by evaporation in vacuo yielded a white powder which was purified by flash chromatography on silica gel ($CHCl_3$–MeOH 10 : 1) to give a pure sulfoxide.

Fmoc-Gly-[4-(*methylsulfinyl*)*benzhydrylamide*] (Va): Yield 80%; m.p. 108–110°C; R_F(A) 0·19. ^{1}H NMR ($CDCl_3$): 2·68 s, 3 H ($SOCH_3$); 3·94 d, 2 H ($J = 5$ Hz); 4·19–4·42 m, 3 H; 5·56 bs, 1 H (NH); 6·29 d, 1 H (Ar_2CH, $J = 9$ Hz); 7·37–7·89 m, 18 H (arom.). FAB MS (m/z): 525 (M + 1), 229, 213, 179. EI MS (m/z, rel. int. %): 285 (100), 268 (12), 256 (5), 228 (40), 213 (61), 178 (52), 165 (37), 149 (22), 97 (12), 43 (22).

Fmoc-Gly-[4,4′-*bis*(*methylsulfinyl*)*benzhydrylamide*] (VIa): Yield 68%; m.p. 127–130°C; R_F(A) 0·05. ^{1}H NMR ($CDCl_3$): 2·65 s, 6 H ($SOCH_3$); 3·96 d, 2 H ($J = 5$ Hz); 4·18–4·40 m, 3 H; 6·84 bs, 1 H (NH); 6·29 d, 1 H (Ar_2CH, $J = 8$ Hz); 7·24–8·06 m, 17 H (arom.). FAB MS (m/z): 587 (M + 1), 549, 533, 432, 291, 275, 259, 225, 179, 165, 125.

Fmoc-Val-[4-(*methylsulfinyl*)*benzhydrylamide*] (Vb): Yield 77%; m.p. 129–131°C; R_F(A) 0·35. ^{1}H NMR ($CDCl_3$): 0·8–1·0 m, 6 H ($(CH_3)_2CH$); 2·10–2·15 m, 1 H ($(CH_3)_2CH$); 2·64 s and 2·69 s, 3 H ($SOCH_3$); 4·00–4·15 m, 2 H (CH_2, Fmoc-CH); 4·35 d, 2 H (CH_2O, $J = 6$ Hz); 5·4 m, 1 H (NH); 6·25 d, 1 H (Ar_2CH, $J = 8$ Hz); 6·9 m, 1 H (NH); 7·1–7·8 m, 17 H (arom). FAB MS (m/z): 567 (M + 1), 229, 213, 191, 179, 165, 152.

Fmoc-Val-[4,4′-*bis*(*methylsulfinyl*)*benzhydrylamide*] (VIb): Yield 30%; m.p. 134–137°C; R_F(A) 0·10. ^{1}H NMR ($CDCl_3$): 0·8–1·0 m, 6 H ($(CH_3)_2CH$); 2·10–2·15 m, 1 H ($(CH_3)_2CH$); 2·65 s and 2·69 s, 6 H ($SOCH_3$); 4·19 d, 2 H (CH_2O, $J = 6$ Hz); 4·25–4·45 m, 2 H (CH_2, Fmoc-CH); 5·6 m, 1 H (NH); 6·27 d, 1 H (Ar_2CH, $J = 8$ Hz); 7·2–7·8 m, 17 H (arom, NH). FAB MS (m/z): 629 (M + 1), 613, 291, 275, 259, 225, 179, 152, 93.

Z-Phe-[4-(*methylsulfinyl*)*benzhydrylamide*] (Vc): Yield 78%; m.p. 123–125°C; R_F(A) 0·37. ^{1}H NMR ($CDCl_3$): 2·66 s and 2·69 s, 3 H ($SOCH_3$); 3·06 d, 2 H ($PhCH_2$, $J = 8$ Hz); 4·51 q,

1 H (CH^{α}, J = 8 Hz); 5·03 s, 2 H ($PhCH_2O$); 5·43 d, 1 H (NH, J = 8 Hz); 6·11 d, 1 H (Ar_2CH, J = 8 Hz); 6·74 d, 1 H (NH, J = 8 Hz); 7·00–7·55 m, 19 H (arom.). FAB MS (m/z): 527 (M + 1), 229, 213.

Z-Phe-[4,4′-*bis(methylsulfinyl)benzhydrylamide*] (VIc): Yield 66%; m.p. 93–95°C; R_F(A) 0·27. ^{1}H NMR ($CDCl_3$): 2·65 s and 2·68 s, 6 H ($SOCH_3$); 3·06 d, 2 H (J = 7 Hz); 4·55 q, 1 H (CH, J = 7 Hz); 5·06 s, 2 H ($PhCH_2O$); 5·51 d, 1 H (Ar_2CH, J = 8 Hz); 6·22 d, 1 H (NH, J = 8 Hz); 7·00–7·45 m, 19 H (arom. + NH). FAB MS (m/z): 589 (M + 1), 365, 291, 275, 259, 245, 229, 213. EI MS (m/z, rel. int. %): 588 (M^+, 1), 463 (5), 447 (8), 382 (2), 368 (2), 108 (95), 91 (25), 79 (100), 77 (50), 43 (46), 28 (70).

4,4′-Bis(methylsulfinyl)benzhydrylamides (*VIa, b*) (General Procedure *B*)

The aqueous solution of sodium periodate (10 ml, 5 mmol) was added to a cooled (0°C) suspension of *II* (2·3 mmol) in methanol (30 ml). The mixture was stirred at 0°C for 1 h and then at room temperature until complete reaction (2–3 h). After filtration, the solution was evaporated in vacuo to dryness. The residue was dissolved in mixture of DMF (10 ml) and DIEA (400 µl, 230 mmol) and to this solution, the mixture of a Fmoc-amino acid (2·3 mmol), HOBt (314 mg, 2·3 mmol), and DCC (516 mg, 2·5 mmol) in DMF–DCM (5 : 3, 8 ml) was added. The suspension was stirred at 0°C for 1 h and then at room temperature for 4 h. After filtration, the solution was evaporated in vacuo to dryness, the residue was dissolved in DCM (20 ml) and washed with 10% $NaHCO_3$ (5 ml), 20% citric acid (5 ml), and brine (5 ml). Drying ($MgSO_4$) followed by evaporation in vacuo yielded an off-white solid which was purified by flash-chromatography on silica gel ($CHCl_3$–MeOH 10 : 1) to give a pure sulfoxides *VI(a, b)* both in 81% yield.

4,4′-Bis(methylthio)benzhydrole (*XI*)

Compound *IX* (3·00 g, 11 mmol) was dissolved at 50°C in ethanol (80 ml). Sodium borohydride (0·50 g, 13·2 mmol) was added in small portions during 2 h and the reduction was continued an additional 2 h at 50°C. The reaction mixture was chilled and pH was adjusted to 2 by the addition of 1M-HCl. Ethanol was evaporated, product was extracted by DCM (50 ml), washed with brine (20 ml) and dried over $MgSO_4$. After removal of solvent, the residue was crystallized from ethyl acetate–hexane to give benzhydrole *XI* (2·71 g, 99%), m.p. 102–104°C, R_F(C) 0·34. ^{1}H NMR ($CDCl_3$): 2·46 s, 6 H (SCH_3); 5·75 s, 1 H (Ar_2CH); 7·15–7·30 m, 8 H (arom.). EI MS (m/z, rel. int. %): 276 (M^+, 50), 259 (20), 229 (10), 197 (5), 165 (10), 151 (100), 125 (20), 109 (15), 77 (10), 28 (30). For $C_{15}H_{16}OS_2$ (276.4) calculated: 65·18% C, 5·83% H, 23·19% S; found: 64·55% C, 5·92% H, 23·05% S.

Tris[4-(methylthio)phenyl]methane (*XII*)

Thioanisole solution in TFA (3·6 ml, 3·6 mmol) was added to *XI* (20 mg, 72 µmol) at room temperature. After 5 min, the colorless solution was rotary evaporated to an oil which was triturated by methanol. Separated crystals were collected and washed with cold methanol to give pure *XII* (27 mg, 98%), m.p. 92–94°C, R_F(C) 0·58. ^{1}H NMR ($CDCl_3$): 2·45 s, 9 H (SCH_3); 5·40 s, 1 H (Ar_3CH), 6·90–7·20 m, 12 H (arom.). EI MS (m/z, rel. int. %): 382 (M^+, 98), 335 (100), 287 (20), 259 (50), 211 (28), 165 (45), 108 (15), 77 (12), 45 (19), 28 (82). For $C_{22}H_{22}S_3$ (382·6) calculated: 69·06% C, 5·08% H, 25·14% S; found: 68·75% C, 5·12% H, 25·50% S.

4-(Methoxyphenyl)-di-[4-(methylthio)phenyl]methane (*XIII*)

By the same procedure and on the same scale as for *XII*, with 1M anisole in TFA. Yield 98%,

m.p. 79–82°C, R_F(C) 0·55. ^{1}H NMR ($CDCl_3$): 2·44 s, 6 H (SCH_3); 3·77 s, 3 H (OCH_3); 5·39 s, 1 H (Ar_3CH); 6·75–7·65 m, 12 H (arom.). EI MS (*m/z*, rel. int. %): 366 (M^+, 100), 351 (5), 335 (15), 319 (60), 259 (20), 243 (40), 165 (20), 152 (20). For $C_{22}H_{22}OS_2$ (366·6) calculated: 72·09% C, 6·05% H, 17·5% S; found: 71·92% C, 5·85% H, 17·90% S.

Reaction of *XI* with 1M dimethylsulfide–TFA

A) *Quenching with wet diethyl ether.* Dimethylsulfide solution in TFA (18·1 ml, 18·1 mmol) was added to *XI* (100 mg, 0·362 mmol) at room temperature. After 5 min, the light green solution was rotary evaporated to a light blue oil which was dissolved in wet diethyl ether (20 ml). Concentration in vacuo yielded an oil which was purified by flash chromatography on silica gel (eluent C) to give starting benzhydrole *XI* (50 mg, 50%) and di-[4,4′-bis(methylthio)benzhydryl] ether *XIV* (26 mg, 27%), m.p. 165–166°C (EtOH), R_F(C) 0·51. ^{1}H NMR ($CDCl_3$): 2·46 s, 6 H (SCH_3); 5·29 s, 1 H (Ar_2CH); 7·20–7·25 m, 8 H (arom.) EI MS (*m/z*, rel. int. %): 534 (M^+, 12), 523 (1), 410 (2), 275 (30), 259 (100), 244 (10), 213 (20), 197 (10), 165 (15), 151 (20). For $C_{30}H_{30}OS_4$ (534·8) calculated: 67·37% C, 5·65% H, 23·98% S; found: 67·50% C, 5·75% H, 23·80% S. Furthermore, 4,4′-bis(methylthio)benzhydryl trifluoroacetate *XVII* was isolated in 15% yield (20 mg). A sample of this compound was stored in eluent C due to its lability in solid state. R_F(C) 0·59. ^{19}F NMR (eluent C, chemical shifts were recalculated on $CFCl_3$ standard): 76·26 s (CF_3COO^-), 77·17 s (CF_3COOR). The ratio of signals was 3 : 1.

B) *Quenching with dry methanol.* By the same procedure and on the same scale as for *A*. Starting benzhydrole *XI* was recovered in 10% yield (10 mg) and 4,4′-bis(methylthio)benzhydrylmethyl ether *XV* was isolated in 90% yield (95 mg), m.p. 47–49°C (EtOH), R_F(C) 0·51. ^{1}H NMR ($CDCl_3$): 2·46 s, 6 H (SCH_3); 3·35 s, 3 H (OCH_3); 5·18 s, 1 H (Ar_2CH); 7·22–7·27 m, 8 H (arom). EI MS (*m/z*, rel. int. %): 290 (M^+, 70), 259 (100), 197 (10), 167 (40), 149 (50). For $C_{16}H_{18}OS_2$ (290·5) calculated: 66·17% C, 6·25% H, 22·08% S; found: 65·95% C, 6·18% H, 22·20% S.

Determination of Acid Lability of Derivatives *III*(*a*, *b*)–*VI*(*a*, *b*) (General Procedure)

Fmoc amino acid derivative (6 μmol) was treated with cleavage reagent (600 μl) at temperature given in Table I. Aliquots of reaction mixture (50–100 μl) were taken at various time intervals and the cleavage reaction was quenched by water (100 μl). After evaporation, the product was dried in vacuo, the residue was dissolved in DMF and applied to TLC and RP HPLC analysis (integration at 280 nm). The rate constants were calculated from 6–8 samples at various times for each derivative.

Fmoc-Gly-NH_2 (*XXa*) from the Preparative Reaction of *VIa* with 1M TMSBr–Thioanisole–TFA

Solution of 1M TMSBr in TFA (5 ml) was added to a suspension of *VIa* (56 mg, 0·1 mmol) in thioanisole (621 mg, 5 mmol) at 0°C. After 2 h, water was added and the solution stirred for 5 min. The reaction mixture was evaporated to dryness, diluted to 1 ml with DMF and loaded on a semipreparative RP HPLC column. Fmoc-Gly-NH_2 was isolated in 90% yield (27 mg): R_F(A) 0·09. FAB MS (*m/z*): 593 (2M + 1), 297 (M + 1). For $C_{17}H_{16}N_2O_3$ (296·3) calculated: 68·91% C, 5·44% H, 9·45% N; found: 68·41% C, 5·64% H, 9·12% N.

H-Phe-[4,4′-bis(methylsulfinyl)benzhydrylamide] (*VId*) from Preparative Reaction of *VIc* with 1M Thioanisole–TFA

Compound *VIc* (30 mg, 51 μmol) was treated with 1M thioanisole–TFA (2·5 ml) at 25°C for 5 h. Then the mixture was concentrated in vacuo to dryness and the residue was triturated with solution of 4-toluenesulfonic acid (29 mg, 153 μmol) in diethyl ether (0·5 ml). The precipitate was washed three times with diethyl ether. After drying, *VId* was obtained in 91% yield (21 mg), m.p. 93–96°C; R_F(B) 0·21. FAB MS (*m/z*): 455 (M + 1), 439, 291, 275, 215, 91.

Boc-Leu-Gly-[4,4′-bis(methylsulfinyl)benzhydrylamide] (*XVIII*)

A solution of *VIa* (200 mg, 0·34 mmol) in piperidine–DMF (1 : 1) was stirred for 30 min. The mixture was rotary evaporated and triturated three times with diethyl ether to give yellowish, hygroscopic powder which was employed in the next step without purification.

The solution of above prepared N^{α}-deprotected *VIa* in DMF (5 ml) was added all at once to a solution of Boc-Leu-OH (82·5 mg, 0·36 mmol), DCC (74·3 mg, 0·36 mmol), and HOBt (48·6 mg, 0·36 mmol) in DMF–DCM (5 : 3, 5 ml) chilled to 0°C. The mixture was allowed to warm to room temperature with stirring overnight. After filtration, the solution was concentrated in vacuo, dissolved in ethyl acetate (20 ml) and washed with 10% $NaHCO_3$ (5 ml), 20% citric acid (5 ml), and brine (5 ml). Drying ($MgSO_4$) followed by concentration in vacuo yielded an oil which was used in the next step.

Boc-Pro-Leu-Gly-[4,4′-bis(methylsulfinyl)benzhydrylamide] (*XIX*)

A solution of *XVIII* in TFA–DCM–anisole (50 : 50 : 5, 2 ml) was stirred for 30 min and then rotary evaporated to a colorless oil. To the solution of above N^{α}-deprotected derivative in DMF (5 ml), DIEA (68 μl, 0·4 mmol) was added and this mixture was added all at once to a solution of Boc-Pro-OH (77·5 mg, 0·36 mmol), DCC (74·3 mg, 0·36 mmol), and HOBt (48·6 mg, 0·36 mmol) in DMF–DCM (5 : 3, 5 ml) chilled to 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. After filtration, the solution was concentrated in vacuo, dissolved in ethyl acetate (30 ml) and washed with 10% $NaHCO_3$ (5 ml), 20% citric acid (5 ml), and brine (5 ml). Drying ($MgSO_4$) followed by concentration in vacuo yielded an oil which after trituration by diethyl ether afforded *XIX* as a yellowish powder (118·3 mg, 52%), R_F(A) 0·13. FAB MS (*m/z*): 575 (M + 1 − Boc), 559, 396, 340, 296, 255, 225.

H-Pro-Leu-Gly-NH_2

To a suspension of *XIX* (50 mg, 74 μmol) in thioanisole (434 μl, 3·7 mmol) 1M solution of TMSBr in TFA (3·3 ml) was added at 0°C. After 4 h, the mixture was concentrated in vacuo, diluted with diethyl ether (10 ml) and extracted three times with water. The aqueous solutions were combined and lyophilized to an oily product which was purified by a semipreparative RP HPLC. H-Pro-Leu-Gly-NH_2 was isolated in 43% yield (9 mg) and was identical with standard (HPLC, FAB MS).

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