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New TFA-Free Cleavage and Final Deprotection in Fmoc Solid-Phase Peptide Synthesis: Dilute HCl in Fluoro Alcohol

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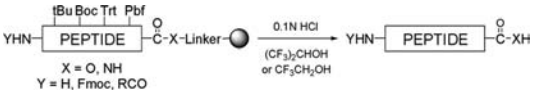
ABSTRACT



A novel method for cleaving from resin and removing acid-labile protecting groups for the Fmoc solid-phase peptide synthesis is described. 0.1 N HCl in hexafluoroisopropanol or trifluoroethanol cleanly and rapidly removes the *tert*-butyl ester and ether, Boc, trityl, and Pbf groups and cleaves the common resin linkers: Wang, HMPA, Rink amide, and PAL. Addition of just 5−10% of a hydrogen-bonding solvent considerably retards or even fully inhibits the reaction. However, a non-hydrogen-bonding solvent is tolerated.

Peptides act as key molecules in diverse biological processes. Their derivatives are used extensively for drug design and drug discovery and as probes for molecular imaging and disease diagnosis. After the advent of solid-phase peptide synthesis (SPPS),[1] peptides have attracted considerable synthetic attention for both industrial manufacturing and small-scale laboratory production. The Fmoc SPPS has been established since the end of the 1970s as a convenient way of making peptides.[2] As the Fmoc group[3] is labile to bases, acid-labile protecting groups for amino acid side chains in the Fmoc SPPS could be removed under less stringent acidic conditions[4] than in the alternative Boc method.[5] The latter commonly requires liquid HF,[6] 1 M trifluoromethanesulfonic acid (TFMSA) in TFA,[7] or neat methanesulfonic acid (MSA)[8] usually in the presence of additives such as anisole,[5] thioanisole,[6] or dimethyl sulfide,[9] for removing protecting groups of benzyl or related types[10] and cleaving from solid supports such as 4-methylbenzhydrylamino resin (MBHA)[11] for peptide amides or phenylacetamido resin (Pam)[12] for peptide acids. In the Fmoc synthesis, trifluoroacetic acid (TFA) is usually employed as a deprotecting agent at high concentration (90−95%). The remaining 5−10% are usually water and various scavengers such as 1,2-ethanedithiol[13] and triisopropylsilane.[14] Scavengers are used to minimize side reactions occurring with sensitive residues, e.g. Trp in the presence of reactive cationic intermediates generated by TFA from protecting groups.

Most acid-labile protecting groups used in the Fmoc method to mask the side chains of amino acids belong to

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the *tert*-butyl family: *tert*-butyl ester for carboxylic acid groups of Asp and Glu, *tert*-butyl ether for hydroxy groups of Tyr, Ser, and Thr, and Boc for the amino group of Lys and indole nitrogen of Trp.[15] Also employed are the triphenylmethyl (trityl, Trt) protecting group for the amides of Asn and Gln, imidazole ring of His, and thiol group of Cys.[15] Third, arenesulfonyl protecting groups such as 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf)[16] or 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc)[17] are used for the guanidino group of Arg. Finally, one should add acid-labile anchor groups that link the C-terminal amino acid to the resin. For the peptide acids, common linkers are *p*-benzyloxybenzyl ester (Wang resin),[18] *p*-hydroxymethylphenoxyacetyl ester (HMPA),[19] and trityl ester.[20] For the peptide amides there are Rink amide[21] and PAL[22] anchors. All the above linkers could be cleaved by TFA at concentrations from as low as 1% in CH_2Cl_2 for the least stable trityl ester to up to 95% TFA for most of the others.

TFA is considered a milder deprotecting agent than liquid HF, TFMSA, or MSA. However, TFA is an aggressive, extremely corrosive chemical capable of inflicting bodily harm through inhalation as well as skin contact leaving hard to heal chemical burns. It readily attacks or infiltrates many common materials and is relatively expensive, both for the initial purchase and for ultimate disposal, especially when large-scale peptide synthesis requires copious quantities of the chemical. Peptides for medicinal use have to be freed from traces of TFA, which is often used as a component of HPLC buffers as well. In the latter case, the trifluoroacetate counterion has to be exchanged with a biologically benign counterpart such as chloride.[23] Therefore, the problem of replacing TFA in peptide synthesis with an equally or more effective equivalent which would be less hazardous, less corrosive, and less environmentally dangerous is worth investigating.

Fluoro alcohols such as 2,2,2-trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) have been widely used as solvents and reagents in organic synthesis in general and in peptide chemistry in particular. Typical fluoro alcohols are acidic: the pK_a of TFE is 12.4[24] and that of HFIP is 9.3.[25] Fluoro alcohols are known to form strong hydrogen bonds[24] and stabilize acid anions with HFIP notably surpassing TFA in that ability.[26] Noteworthy, addition of TFE to superacids whether protic, Lewis, or polymeric such as Nafion increases their "superacidity".[27] Fluoro alcohols are good solubilizing agents for peptides, especially those forming secondary structures.[28] Addition of 10−20% TFE to CH_2Cl_2 improves yields of solid-phase carbodiimide coupling.[29] No premature Boc deprotection has been noted. However, preformed HFIP esters of N^{α}-Boc- or Z-protected amino acids were found to be about 10^3 times less active acylating agents than the *p*-nitrophenyl esters.[30] Ester formation was thus a major drawback of the use of fluoro alcohols in peptide coupling, which may be alleviated by the addition of an appropriate cosolvent.[31]

More success has been achieved by employing fluoro alcohols for removing acid-labile protecting groups and cleaving from resin. Some very acid-sensitive *N*-protecting groups such as dicyclopropylmethoxycarbonyl are cleaved by HFIP.[32] It has been also observed that the *N*-Trt group could be removed selectively in the presence of other acid-labile groups such as *p*-biphenylylisopropoxycarbonyl (Bpoc) in 90% aq TFE by titration with conc aq HCl at ambient temperature.[33] The Bpoc group could be cleaved off by heating to 60 °C in 90% aq TFE.[34] A mixture of TFE−CH_2Cl_2−AcOH (1:8:1 v/v) has been used for detaching fully protected peptides from very acid-labile Barlos *o*-chlorotrityl resin.[20] Similarly, a 4:1 (v/v) mixture of CH_2Cl_2 and more acidic HFIP was found to cleave the *o*-chlorotrityl resin linkage within 15 min−1 h without any damage to protecting groups of the *tert*-butyl type.[35] The only group affected to any significant extent was Trt on His. However, peptides dissolved in HFIP were observed to lose *tert*-butyl ester over 24 h at ambient temperature.[36] Recently, both HFIP and TFE at elevated temperature or

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MW irradiation (100−150 °C) have been applied to remove *tert*-butyl ester or carbonate[37] or Boc group[38] from a range of compounds within several hours. Cleavage of fully protected peptides from a trityl resin may be effected by dilute HCl in aq DMF with optional TFE (up to 10% v/v).[39] We set out to investigate the applicability of fluoro alcohols such as HFIP or TFE as potential reagents or additives for cleaving acid-labile resin linkers and deprotecting acid-labile protecting groups to produce fully unprotected peptides.

First, we have checked if neat HFIP at elevated temperature would remove the *tert*-butyl ether group from Tyr, Ser, or Thr or the N^{ε}-Boc from Lys, in line with the published procedure.[37,38] We have observed sluggish cleavage of the *tert*-butyl ether from Fmoc-Tyr(*t*Bu)-OH in neat HFIP at 60 °C: 3.4% conversion after 1 h, 7.6% after 3 h, and 48% after 18 h of reaction. Some byproducts were also evident: *ca.* 2% after 18 h at 60 °C and 7% after 4 h at 100 °C. Even slower was the unmasking of other protected amino acids: Lys 4.8%, Thr 2.1%, and Ser 0.7% after 4 h at 60 °C. The use of HFIP at higher temperatures is discouraged by its low boiling point (59 °C) and high volatility, which require special glassware such as tightly capped microwave tubes as screw-cap polypropylene tubes with a rubber O-ring are unsuitable for HFIP. This has prompted us to look for a fluoro alcohol deprotection that could be carried out at ambient temperature in conventional QuickFit glassware readily available in any chemical lab.

We have found that addition of as low as 0.1 N hydrochloric acid to neat HFIP (equiv to 1 cm^3 of *ca.* 37% aq HCl per 99 cm^3 HFIP) improves the removal of acid-labile protecting groups quite dramatically. For example, Fmoc-Ser(*t*Bu)-OH, which is nearly resistant to neat HFIP at 60 °C, gave 76.6% of Fmoc-Ser-OH after just 5 min of the reaction and, after 1 h 30 min, produced 95.7% conversion. Similarly, all the protecting groups of the *tert*-butyl and trityl families could be cleanly and rapidly removed from all the protected amino acid derivatives commonly used in Fmoc SPPS (Table 1). TFE is also effective but *ca.* 2−3 times slower than HFIP: 0.1 N HCl in TFE with Fmoc-Ser(tBu)-OH gave 86.4% conversion after 2 h of reaction. TFE is also less efficient for solubilizing Fmoc-amino acids.

The rate-enhancing effect of fluoro alcohols on the removal of acid-labile protecting groups is highly specific to fluoro alcohols. In hydrogen-bonding solvents whether protic, e.g. water, MeOH or Pr^{i}OH, or aprotic, e.g. acetone, MeCN, 1,4-dioxane, THF, DMF, or 1-methylpyrrolidin-2-one, 0.1 N HCl is nearly ineffective for the *tert*-butyl removal. For Fmoc-Ser(*t*Bu)-OH, 0.1 N HCl in MeCN gave just 3.3% conversion after 1 h of reaction, in 1,4-dioxane $<0.2\%$ after 25 min, in acetone $<0.1\%$ in 25 min, and in Pr^{i}OH less than 0.1% conversion was observed after 1 h 30 min of reaction. Interestingly, addition of just 5−10% (v/v) of such a solvent to HFIP produced a considerable negative effect on the rate of deprotection. However, addition of a non-hydrogen-bonding solvent such as CH_2Cl_2 showed no appreciable slowdown. Similarly, small quantities (1−2% v/v) of common scavengers such as triisopropylsilane (TIS), thioanisole, or dimethylsulfide were tolerated as well.

Next, we set out to elucidate if even the most robust of all the TFA-cleavable protecting groups Pbf[16] could be removed as well. With 0.1 N HCl/HFIP we have observed 60.6% Pbf removal after 30 min and 84% after 1 h 40 min of reaction, whereas 1 N HCl gave 92.4% conversion after 30 min and 95.3% after 2 h of reaction. Peptides with multiple Arg residues may require prolonged treatment (18−24 h) with dilute HCl in HFIP or a higher percentage of HCl, e.g. 1 N to remove all guanidino protecting groups quantitatively.

Table 1. Deprotection of Amino Acid Derivatives by HCl in Fluoro Alcohol[a]

Fmoc amino acid	product[b]	conditions[c]	time, min	yield, %[d]
Asn(Trt)	Asn	A	10	quant
Asp(OtBu)	Asp	A	240	>99
Arg(Pbf)	Arg	A	30	60.6
		A	100	84.0
		A	240	>99
		B	30	92.4
		B	120	95.3
		C	70	0.8
		D	90	98.5
		E	15	12.3
Cys(Trt)	Cys	A	5	>99
		F	35	quant
Gln(Trt)	Gln	A	15	>99
Glu(OtBu)	Glu	A	240	quant
His(Trt)[e]	His[f]	G	30	quant
Lys(Boc)	Lys	A	240	quant
		H	240	4.8
Ser(tBu)	Ser	A	5	76.6
		A	90	95.7
		I	120	86.4
		H	240	0.7
		J	60	3.3
Thr(tBu)	Thr	A	240	quant
		H	240	2.1
Trp(Boc)	Trp	A	30	>99
		A	100	quant
Tyr(tBu)	Tyr	A	240	quant
		H	60	3.4
		H	180	7.6
		H	1080	48.0

[a] For full experimental conditions, see Supporting Information. [b] An N^{α}-Fmoc amino acid unless indicated otherwise. [c] Conditions: (A) 0.1 N HCl/HFIP, rt; (B) 1 N HCl/HFIP, rt; (C) 0.1 N HCl/HFIP−DMF (9:1 v/v); (D) 0.1 N HCl/HFIP−CH_2Cl_2 (4:1 v/v); (E) 0.1 N HCl/HFIP−Pr^{i}OH (95:5 v/v); (F) 0.1 N HCl/HFIP−TIS (99:1 v/v), rt; (G) 0.01 N HCl/HFIP, rt; (H) neat HFIP, 60 °C; (I) 0.1 N HCl/TFE, rt; (J) 0.1 N HCl/MeCN, rt. [d] Calculated as peak area. [e] H-His(Trt)-OH. [f] H-His-OH.

Finally, we have investigated the cleavage of common acid-labile resin linkers for the Fmoc SPPS. Cleavage of the

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trityl ester linkage of TentaGel S Trt resin[40] by 0.1 N HCl in HFIP is almost instantaneous and could be monitored visually by the immediate appearance of the orange-brown color of the resin-bound trityl cation upon contact with the deprotection mixture. In practice, a 15 min period was sufficient for the quantitative cleavage of a peptide from the resin. In the case of TFE no color was observed due to a scavenging effect of TFE. However, the cleavage was complete within the same 15 min period as for HFIP. The *p*-benzyloxybenzyl ester of Fmoc-Leu-Wang resin was cleaved by 0.1 N HCl in HFIP–CH_2Cl_2 (1:4 v/v) more slowly: 91.6% release was seen after 3 h. Notably, the ratio of HCl to the resin-bound ester was nearly equimolar: 0.1 mmol (10 μL of concentrated *ca.* 37% aqueous HCl per 1 cm^3 of the mixture) per 0.095 mmol of the resin-bound amino acid (0.1 g of the resin with the loading of 0.95 mmol g^{-1}). In contrast, substitution of Pr^{i}OH for HFIP in the mixture produced no release of Fmoc-Leu-OH within 72 h. Addition of CH_2Cl_2 was necessary for better swelling of Wang resin as HFIP alone is a poor swelling agent for polystyrene supports such as Wang or MBHA resins. However, other types of resins such as PEG-PS, TentaGel, or NovaPEG have shown good swelling in neat HFIP or TFE.

The Fmoc-Gly-HMPA-PEG-PS resin had slightly lower susceptibility to 0.1 N HCl in HFIP with 84.2% release after 3 h. Addition of 1% (v/v) dimethylsulfide had no appreciable accelerating effect on the cleavage. The two common resins for peptide amides were also cleaved successfully. Rink amide NovaPEG resin released 82% Fmoc-glycinamide after 2 h, and PAL-PEG-PS lost 91% of the same after 1 h of reaction. The type of resin had no clear-cut influence on the rate of deprotection.

To test the general applicability of the new method in a standard Fmoc SPPS, a collagen-stimulating peptide Fmoc-KTTKS-OH[41] was prepared as described[42] on a TentaGel S Trt resin. After the completion of the assembly, a sample of the resin was treated with 0.1 N HCl/HFIP to cleave the peptide from the resin for 15 min and then deprotect for 12 h at ambient temperature. The crude peptide Fmoc-KTTKS-OH was obtained in high yield and purity, and its integrity was confirmed by ESI HRMS. The Fmoc group as expected was stable under the deprotection conditions. Other peptide derivatives were prepared as well (see Supporting Information). Notably, similar results were obtained after treatment with 0.1 N HCl/TFE for 12 h or even 4 h at ambient temperature.

An important side reaction in the new method would be the TFE or HFIP ester formation with the free carboxyl group of e.g. Asp or Glu. To date we have not observed any such ester formation in our experiments (Table 1).

To conclude, we have found that a low concentration of aq HCl in HFIP, e.g. 0.1 N, removes common acid-labile protecting groups of the *tert*-butyl, trityl, and arenesulfonyl (Pbf) type from amino acid side chains and cleaves common acid-labile resin linkers used in the Fmoc SPPS such as Trt ester, Wang, HMPA, Rink amide, or PAL. We believe that the proposed composition of 0.1 N HCl in HFIP may serve as a less hazardous substitute for TFA for the Fmoc SPPS. Further studies on the general utility of the described deprotection method for the synthesis of longer and more complex peptides incorporating sensitive amino acids are underway.

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Supporting Information Available. Experimental procedures and HPLC and MS data for amino acid and peptide derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.