Utilization of *N*,*N*,*N*′,*N*′-Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH) in Peptide and Organic Synthesis

Ayman El-Faham,*[a,b] Sherine N. Khattab*[a]

[a] Faculty of Science, Chemistry Department, Alexandria University, P.O. Box 426, Ibrahemia, 21321 Alexandria, Egypt
E-mail: Aymanel_faham@hotmail.com; E-mail: ShKh2@Link.net

[b] College of Science, King Saud University, P.O. Box 2455, Riyadh, Saudi Arabia

Received 20 August 2008

Abstract: *N*,*N*,*N*′,*N*′-Tetramethylfluoroformamidinium hexafluorophosphate (TFFH) has been shown to be an excellent peptide-coupling reagent. It is an easily handled, crystalline compound, it has a long shelf life, and it reacts rapidly with carboxylic acids to give the corresponding acid fluorides or mixed anhydrides depending on the reaction conditions. TFFH has been shown to be useful as a peptide-coupling reagent and for the preparation of various carboxylic acid derivatives. Both aspects will be surveyed in this Account.

SYNLETT 2009, No. 6, pp 0886–0904
Advanced online publication: 16.03.2009
DOI: 10.1055/s-0028-1088211; Art ID: A51208ST

Key words: TFFH, amino acid fluorides, solution-phase peptide synthesis , solid-phase peptide synthesis, carboxylic acid derivatives, heterocycles

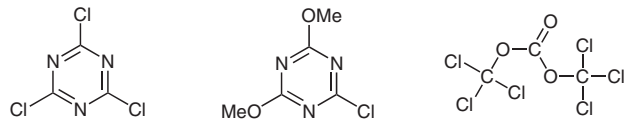
1 Introduction

Recently, the use of new coupling reagents for peptide synthesis has been reviewed.[1] The present Account concentrates on the fluoroformamidinium salts which show some advantages over other commonly used coupling reagents.

2 Formation of Carboxylic Acid Halides

The most obvious method for activating the carboxyl group of an amino acid for amide bond formation at room temperature or below would appear to be via a simple acid chloride.[2] The acid chloride method was first introduced into peptide chemistry by Fischer in 1903.[3] Since then, chlorination of amino acids has been carried out with various chlorinating reagents, such as pivaloyl chloride,[4] phthaloyl dichloride,[5] thionyl chloride,[6] and oxalyl chloride.[7] Thionyl chloride in pyridine was applied to the coupling reactions for this purpose.[7b] Other useful acid halogenating reagents are cyanuric chloride[8] (1) and 2-chloro-4,6-dimethoxy-1,3,5-triazine[9] (CDMT, 2) (Figure 1). Gilon has reported the use of bis(trichloromethyl) carbonate (BTC, 3) as a chlorinating reagent in solid-phase peptide synthesis.[10] There is some question as to the nature of the exact intermediates involved in the Gilon process.[10b]

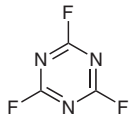
Coupling reactions mediated by BTC gave good results for Fmoc-amino acids containing acid-labile side chains. In some solvents, such as *N*-methyl-2-pyrrolidinone, reaction with BTC gives the chloroiminium ion. Since this leads to racemization, inert solvents such as tetrahydrofuran or dioxane are used in the Gilon reaction. For many



cyanuric chloride, **1** CDMT, **2** BTC, **3**

Figure 1 Structures of chlorinating reagents

years acid chlorides were rarely used and, among peptide practitioners, they long ago gained the reputation of being 'overactivated' and therefore prone to numerous side reactions including loss of configuration.[11] However, because of the stability of the 9-fluorenylmethoxycarbonyl (Fmoc) group to the conditions of preparation, Fmoc-amino acid chlorides were shown to be very useful in peptide coupling. Under appropriate conditions such acid chlorides can be used without loss of configuration. Because of their high reactivity, they can be used for highly hindered substrates. One deficiency of these systems is that acid-sensitive side chains, such as those derived from *tert*-butyl residues, cannot be accommodated.[6c] Acid fluorides, on the other hand, are known to be more stable to hydrolysis than acid chlorides and, in addition, are not subject to the limitation mentioned with regard to *tert*-butyl-based side-chain protection. Thus, Fmoc-based solid-phase peptide synthesis can be easily carried out via Fmoc-amino acid fluorides.[12,13] Cyanuric fluoride (**4**) (Figure 2) is the most commonly used reagent for the conversion of amino acids into the corresponding acid fluorides.[13]



cyanuric fluoride, **4**

Figure 2

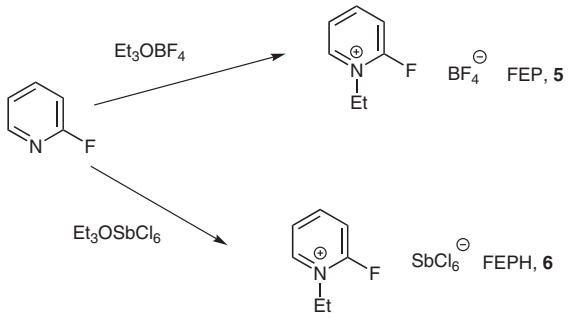
Other reagents which can be used are (diethylamino)sulfur trifluoride (DAST),[14] and the pyridinium salts FEP (2-fluoro-1-ethylpyridinium tetrafluoroborate, **5**) and FEPH (2-fluoro-1-ethylpyridinium hexachloroantimonate, **6**)[15] (Scheme 1), Mukaiyama reagents modified by substitution of the simple halide counterion for the more solubilizing BF_4^- or $SbCl_6^-$ counterion.[15,16]

The conversion of acids into acid fluorides with all of these reagents follows a similar process. For example, with cyanuric fluoride (**4**) the intermediate **7** is involved

Biographical Sketches

Ayman El-Faham received his BSc degree in chemistry in 1980 and his MSc degree in physical organic chemistry in 1985, from the Faculty of Science, Alexandria University, Egypt. In 1991 he received his PhD in organic chemistry in a joint project between Alexandria University and the University of Massachusetts, Amherst, U.S.A., under the supervision of Professor L. A. Carpino, in which he worked on the synthesis of new protecting groups for both solution and solid-phase peptide synthesis. In addition, he was involved in the development of new coupling reagents based on 1-hydroxy-7-azabenzotriazole. He continued working on these new coupling reagents during his postdoctoral work (1992–1999) in Professor Carpino's laboratory at the University of Massachusetts. He holds many patents in this field. He received the Alexandria University Award in Chemistry in 1999. He joined the Barcelona Science Park during the summers of 2006 and 2007, working with Professor Fernando Albericio on the development of a new family of immonium-type coupling reagents. His research interests include the synthesis of peptides under solution and solid-phase conditions, natural products, heterocyclic synthesis, and biologically active synthetic targets. He acted as Head of the Chemistry Department, Beirut Arab University, Lebanon (2000–2004), and as Professor of Organic Chemistry, Faculty of Science, and the Direct Manager of both the NMR Laboratory and the Central Laboratory at the Faculty of Science, Alexandria University, Egypt (2004–2008). Currently, he is Professor of Organic Chemistry at the College of Science, King Saud University, Riyadh, Saudi Arabia.

Sherine N. Khattab received her BSc degree in chemistry in 1987 from the Faculty of Science, Alexandria University, Egypt. In 1990 she received her Diploma in Organic Chemistry from the University of Zurich-Irchel, Switzerland. In 2000 she received her PhD in organic chemistry from the Faculty of Science, Alexandria University, Egypt. The title of her thesis was 'Synthesis of Some Biodegradable Peptides for Possible Use as Sequestering Agents'. She received the Alexandria University Award in Chemistry in 2008. Her research interests include the synthesis of peptides under solution and solid-phase conditions, development of new coupling reagents, heterocyclic synthesis, and biologically active synthetic targets. Currently, she is Associate Professor of Organic Chemistry at the Faculty of Science, Alexandria University, Egypt.



Scheme 1

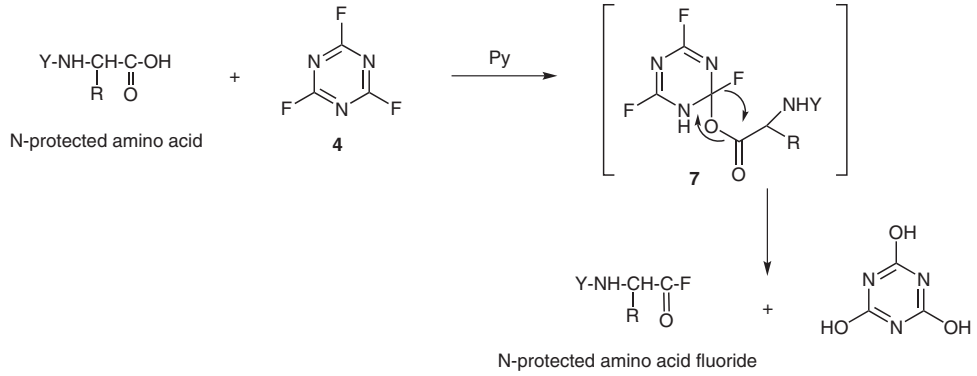
(Scheme 2). The presence of a base was found to be essential for formation of the carboxylic acid fluorides. IR and UV spectroscopic measurements confirm this course of the reaction.[16–18]

Standard methods for the preparation of carboxylic acid fluorides often involve noxious reagents such as various metal fluorides.[19] A notable advance was the development of fluoroformamidinium salts. Carpino and El-Faham reported that the air-stable, non-hygroscopic solid *N*,*N*,*N*′,*N*′-tetramethylfluoroformamidinium hexafluorophosphate (TFFH, **8**) acts as a convenient in situ reagent for the formation of amino acid fluorides during peptide synthesis (Scheme 3).[20] TFFH is especially useful for the two amino acids histidine and arginine since the corresponding amino acid fluorides are themselves not stable toward isolation or storage.

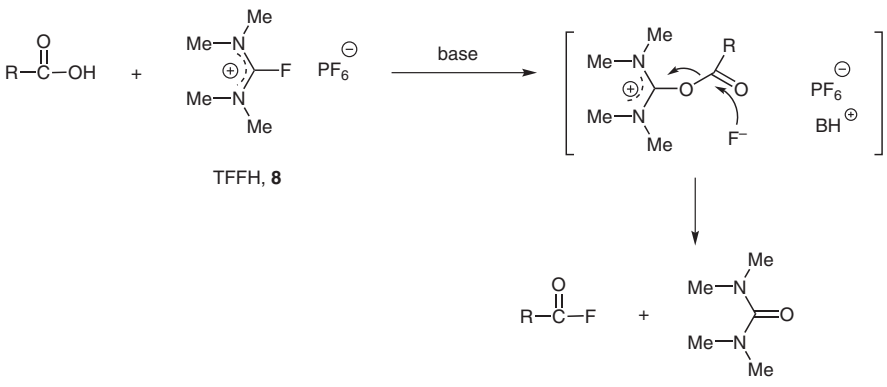
Infrared examination shows that, in the presence of *N*,*N*-diisopropylethylamine (DIPEA), Fmoc-amino acids are converted into the acid fluorides using TFFH.[20] In dichloromethane solution at room temperature, an IR absorption characteristic of the carbonyl fluoride moiety (1842 cm^{-1}) appears after about 3 minutes, with complete conversion into the acid fluoride occurring after 8–15 minutes. For hindered amino acids [e.g., α-aminoisobutyric acid (Aib)], complete conversion may require 1–2 hours.[20,21] If desired, the acid fluorides may be isolated and purified, making TFFH a benign substitute for the corrosive cyanuric fluoride.

Other analogous reagents have also been synthesized (Figure 3). Bis(tetramethylene)fluoroformamidinium hexafluorophosphate (BTFFH, **9**) has the advantage over TFFH in that, upon workup, the reaction mixture does not generate toxic byproducts.[21,22]

Fluorinating reagents **9**, **11**, **12**, and **13** behave in a similar way to **8** in their ability to provide a route to amino acid fluorides for both solution and solid-phase reactions,[20,21] whereas **10**, being more reactive but more sensitive to moisture, never gives complete conversion into the acid fluoride. Except for **10**, all of these reagents can be handled in air in the same way as common onium reagents,[23] such as *N*-[(dimethylamino)(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (N-HATU, **14**)[24] and *N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene]-*N*-methyl-



Scheme 2 Synthesis of amino acid fluorides using cyanuric fluoride



Scheme 3 Synthesis of amino acid fluorides using TFFH

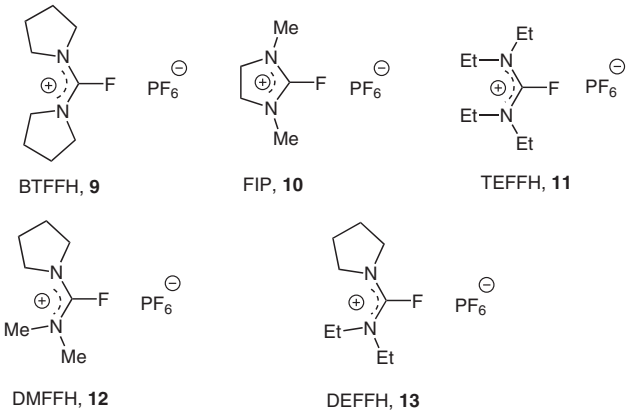


Figure 3 Structures of fluorinating reagents

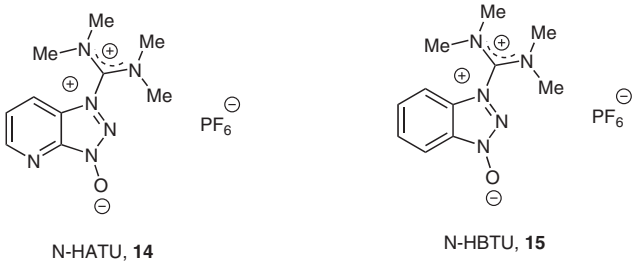


Figure 4

methanaminium hexafluorophosphate *N*-oxide (N-HBTU, **15**)[25] (Figure 4).

For some amino acids, e.g. Fmoc-Aib-OH, it was found that the use of TFFH alone gave results that were less satisfactory than those obtained with isolated amino acid fluorides. The deficiency was traced to inefficient conversion into the acid fluoride which, under the conditions used (DIPEA, 2 equiv), was accompanied by the corresponding symmetric anhydride and oxazolone.[21,26] On the other hand, it has now been shown that if a fluoride additive such as benzyltriphenylphosphonium dihydrogen trifluoride (PTF, **16**) or hydrogen fluoride–pyridine (**17**)[27] (Figure 5) is present during the activation step, the latter two products can be avoided and a maximum yield of acid fluoride is obtained. Assembly of the difficult pentapeptide Tyr-Aib-Aib-Phe-Leu-NH_2 via TFFH coupling in the presence of PTF (**16**) gave a product of similar quality to that obtained via the isolated acid fluorides.

Figure 5

More interestingly, conversion of the acid into the acid fluoride was also observed upon treatment with *N*,*N*′-dicyclohexylcarbodiimide (DCC, **18**), diisopropylcarbodiimide (DIC, **19**) (Figure 6), N-HATU (**14**), or N-HBTU (**15**) in the presence of the additive PTF (**16**).[27,28]

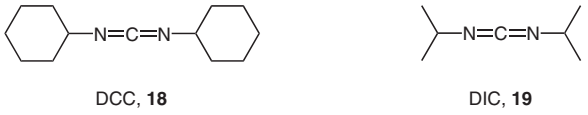


Figure 6

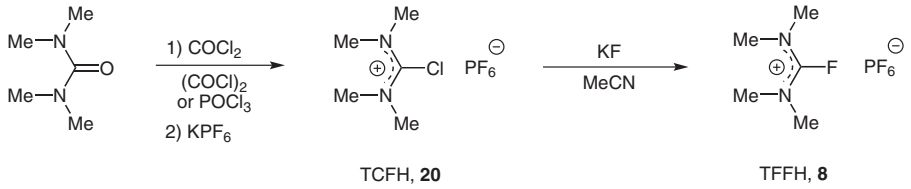
Because the fluoride additive binds excess hydrogen fluoride as part of the complex dihydrogen trifluoride anion, an accompanying acidic buffering effect might prove to be of value in the case of coupling reactions where loss of configuration at the activated carboxylic acid residue might be important. Such a protective effect was in fact observed in the case of the sensitive histidine derivative Fmoc-His(Trt)-OH upon reaction with proline amide, which with TFFH/DIPEA under ordinary conditions gave the desired dipeptide in good yield with 7.4% stereomutation; in the presence of additive **16**, stereomutation dropped to 1.8%.[27]

Generation of the amino acid fluoride using TFFH (**8**) is more efficient if PTF (**16**) is present, as shown by model solid-phase syntheses.[27] Presumably, this technique can also be used to improve conversion into the isolable acid fluorides.[28]

3 General Method for the Synthesis of Fluoroformamidinium Salts

Following is a typical procedure for the preparation of fluoroformamidinium salts;[20] namely, TFFH (**8**) (Scheme 4):

In a two-liter, three-necked round flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser, oxalyl chloride (70 mL, 0.80 mol) was added in one portion to a solution of 1,1,3,3-tetramethylurea (69.7 g, 0.60 mol) in toluene (1 L) with vigorous stirring. The mixture was heated at 60 °C for two hours and then cooled to room temperature. The addition funnel was replaced with a fritted adapter and the supernatant liquid was expelled using a positive pressure of nitrogen. The precipitate was collected and washed with toluene and then with anhydrous diethyl ether. The dichloro salt was collected and dissolved quickly in dichloromethane (1 L) and treated with a saturated solution of potassium hexafluorophosphate (0.6 mol) in water. The reaction mixture was stirred vigorously at room temperature for 10–15 minutes and then the dichloromethane phase was collected and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the chloro salt, TCFH (**20**). To a solution of **20** (0.5 mol) in anhydrous acetonitrile (300 mL) was added oven-dried anhydrous potassium fluoride (1.5 mol) and the mixture was stirred at room temperature for three hours (monitoring by ^1H NMR spectroscopy). Longer times are required for large-scale preparations. Following the removal of potassium chloride by filtration, the filtrate was concentrated and the residue was recrystallized (MeCN–Et_2O) to give TFFH (**8**) as non-hygroscopic, white crystals in 92% yield.



Scheme 4 Synthesis of TFFH

The above method has been modified for a one-pot preparation,[29] as follows:

In a one-liter, three-necked flask equipped with a mechanical stirrer, an addition funnel, and a reflux condenser, oxalyl chloride was added over a period of 10 minutes to a solution of 1,1,3,3-tetramethylurea in anhydrous dichloromethane with vigorous stirring. The reaction mixture was refluxed for three hours and the solvent was removed under reduced pressure. The residue was washed twice with anhydrous diethyl ether and dissolved in anhydrous acetonitrile. Then, a predried mixture of potassium fluoride (3 equiv) and potassium hexafluorophosphate (1 equiv) was added. The resulting mixture was heated at 60 °C for three hours, then the reaction mixture was cooled to room temperature, filtered, and washed with acetonitrile. The combined filtrate was concentrated, the resulting oily residue was taken up in hot dichloromethane, and the cloudy solution was filtered while hot and concentrated under reduced pressure to approximately half the volume. Anhydrous diethyl ether was added with vigorous stirring to promote precipitation of the salt as a white solid, in a yield of 91%.

4 Solution and Solid-Phase Peptide Coupling Using TFFH

Not only does the acid fluoride methodology coexist well with acid-sensitive groups [*tert*-butoxycarbonyl (Boc) and *tert*-butyl side-chain-protecting groups, see Section 2], it is the unique acyl fluoride functionality itself that is likely to assure the widespread applicability of this general class of reagents.[12a,20,30] Due to the nature of the C–F bond, acyl fluorides are of greater stability than the corresponding chlorides toward neutral oxygen nucleophiles such as water or methanol, yet appear to be of equal or nearly equal reactivity toward anionic nucleophiles and amines.[12a,13c,20]

Use of the fluoroformamidinium salts TFFH (**8**) and BTFFH (**9**) was shown to be as effective as the isolated acid fluorides in either solution or solid-phase peptide assembly. Arginine, however, represents a special case. Reaction between Fmoc-Arg(Pbf)-OH (Pbf = 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-ylsulfonyl) and TFFH or BTFFH in the presence of *N*,*N*-diisopropylethylamine (1:1:2) in *N*,*N*-dimethylformamide was monitored by infrared analysis. The acid fluoride (IR: 1845 cm^{-1}) was generated within 2 minutes and, although it slowly cyclized to the corresponding lactam (IR: 1794 cm^{-1}), a significant amount of the acid fluoride remained unreacted even after 60 minutes[20,21a]

TFFH has recently been used as an in situ reagent for solid-phase peptide synthesis. In many ways TFFH is an ideal coupling reagent for solid-phase syntheses, being readily available, inexpensive, and capable of providing crude peptides of high quality.[21] Examples are applications to leucine enkephalin (**21**),[20] the prothrombin amide **22**,[20,21] ACP (65–74) (**23**),[31] bradykinin amide (**24**),[21b] human preproenkephalin (100–111) (**25**),[32] insulin B-chain (19–25)(**26**),[21a] substance P (**27**),[33] the peptaibols alamethicin amide (**28**)[34] and magainin I amide (**29**),[21] and the leucine enkephalin analogue **30** containing adjacent Aib units in place of the Gly units (Table 1).[21,22] The final system is often used as a simple model in order to compare various coupling reagents.[22]

Table 1 Examples of Solid-Phase Peptide Couplings Using TFFH

Entry	Compound	Amino acid sequence
1	**21**	H-Tyr-Gly-Gly-Phe-Leu-OH
2	**22**	H-Ala-Asn-Lys-Gly-Phe-Leu-Glu-Glu-Val-NH_2
3	**23**	H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-NH_2
4	**24**	H-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-NH_2
5	**25**	H-Tyr-Gly-Gly-Phe-Met-Lys-Arg-Tyr-Gly-Gly-Phe-Met-NH_2
6	**26**	H-Cys-Gly-Glu-Arg-Gly-Phe-Phe-NH_2
7	**27**	H-Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2
8	**28**	Ac-Aib-Pro-Aib-Ala-Aib-Ala-Glu-Aib-Val-Aib-Gly-Leu-Aib-Pro-Val-Aib-Aib-Glu-Gln-Phe-NH_2
9	**29**	H-Gly-Ile-Gly-Lys-Phe-Leu-His-Ser-Ala-Gly-Lys-Phe-Gly-Lys-Ala-Gly-Glu-Ile-Met-Lys-Ser-NH_2
10	**30**	H-Tyr-Aib-Aib-Phe-Leu-NH_2

Using *N*,*N*-dimethylformamide as solvent and an instrument programmed for 7 minutes of preactivation, 7 minutes of deblocking, and 30 minutes of coupling [fivefold excess of acid, tenfold excess of base (DIPEA)] for all amino acids, except in the case of Aib-Aib for which a one-hour double coupling was used, pentapeptide **30** was obtained in 88% yield with a purity of crude product of 92% (amount of des-Aib tetrapeptide: 4%).[21] In contrast,

under similar conditions, earlier syntheses[23b] using HATU and HBTU gave the pentapeptide in 94% purity and 43% purity,[20] respectively.

5 Synthesis of Small Phosphotyrosine-Containing Peptides and Peptide Mimetics Incorporating α-Methylated Amino Acids

A series of small phosphotyrosine-containing peptides with the sequence mAZ-pTyr-Xaa-Asn-NH_2 (mAZ = *m*-aminobenzyloxycarbonyl) (Figure 7) were synthesized as highly potent inhibitors of the Grb2-SH2 domain;[35] these systems are important for signal transduction.[35,36] Couplings involving α-methylated amino acids were carried out using TFFH. Other amino acids were introduced via standard coupling techniques. The building block Fmoc-L-(α-Me)Tyr($PO_3Bn)_2$-OH was synthesized following the general methods for preparing protected phosphotyrosine.[37–39]

mAZ-pTyr-pTyr-Asn-NH_2

mAZ-pTyr-(α-Me)Phe(4-CO_2H)-Asn-NH_2

mAZ-pTyr-(α-Me)pTyr-Asn-NH_2

mAZ-pTyr-(α-Me)Phe(4-CH_2CO_2H)-Asn-NH_2

Figure 7 Small phosphotyrosine-containing peptides

6 Synthesis of Lysine Analogues

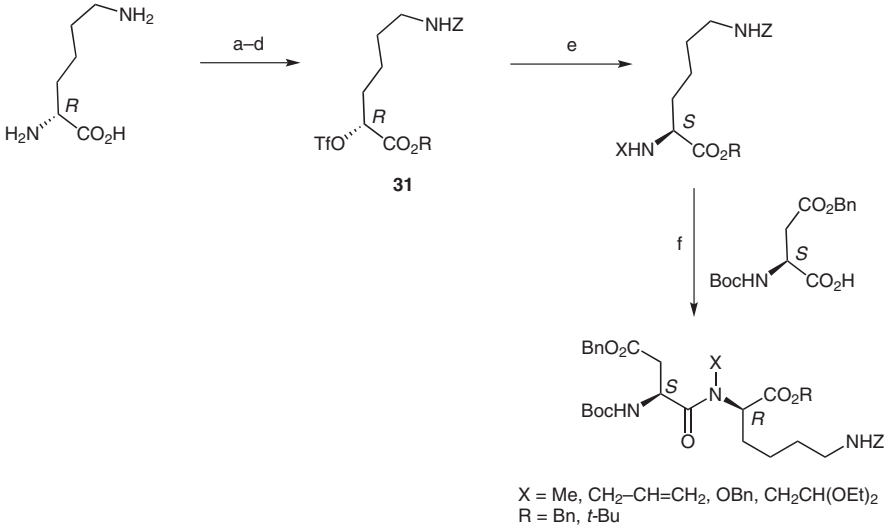
Lysine analogues have been introduced into pseudopeptide sequences by use of the acyl fluoride methodology.[40,41] In order to synthesize such compounds, it is necessary to use a single synthon which would afford a wide range of pseudopeptides. Such a strategy relies upon the unique properties of the triflate derivatives **31** of 6-(benzyloxycarbonylamino)hexanoic acid derivatives. Triflates **31** can easily be obtained through a four-step sequence starting from lysine.[40] Triflates **31** could be treated with various nucleophiles to afford the 2-substituted derivatives (Scheme 5). The coupling step of the secondary amines obtained by reaction of the triflate **32** with primary amines, with an aspartic acid derivative with proper protection of the α-amino and side-chain carboxylic acid groups, was investigated (Scheme 6).[40] From the different activation methods screened (PyBroP, PyBOP, mixed anhydride), only the acyl fluoride method using TFFH gave a consistently good yield (60–80%) whatever the amino component.[40]

7 Synthesis of Proline Conformation in Tripeptide Fragments of Bovine Pancreatic Ribonuclease A Containing the Nonnatural Proline Analogue 5,5-Dimethylproline

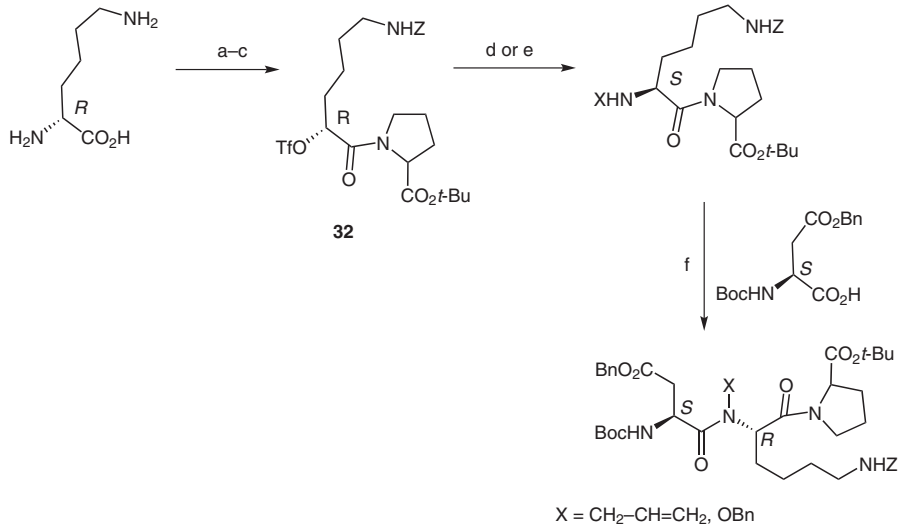
Based on the sequence of residues 92–94 (Tyr-Pro-Asn) and 113–115 (Asn-Pro-Tyr) in bovine pancreatic ribonuclease A, in which the X-Pro peptide groups are in the *cis* conformation, the tripeptides Ac-Tyr-dmP-Asn and Ac-Asn-dmP-Tyr (L-DMP = L-5,5-dimethylproline) were synthesized using the Fmoc-amino acids strategy with TFFH as coupling reagent in the presence of DIPEA as a base. This gave a higher yield (75%) than the TBTU strategy (58%).[42]

8 Synthesis of Different Types of Dipeptide Building Units Containing N- or C-Terminal Arginine for the Assembly of Backbone Cyclic Peptides

Different types of dipeptide building units containing N- or C-terminal arginine were prepared for the synthesis of backbone cyclic analogues of the peptide hormone bradykinin (Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg).[43] In order to avoid lactam formation of the N-terminal arginine to



Scheme 5 Synthesis of L-lysine analogues: (a) ROH/H^+; (b) Z-OSu, Et_3N; (c) BzlBr, Et_3N, acetone; (d) Tf_2O, lutidine, CH_2Cl_2; (e) nucleophile, Et_3N; (f) TFFH (1.2 equiv), DIPEA (2 equiv) CH_2Cl_2.



Scheme 6 Preparation of pseudotripeptides: (a) Z-OSu, Et_3N; (b) WSC (water soluble carbodiimide, 1.5 equiv), DIPEA (3 equiv), HOBt (1 equiv), ProOBut (1.2 equiv); (c) Tf_2O, lutidine, –78 °C; (d) H_2NOBn (5 equiv); (e) $NH_2CH_2CH{=}CH_2$, Et_3N (4 equiv); (f) TFFH (1.2 equiv), DIPEA (2 equiv), CH_2Cl_2.

the alkylated amino acids at position 2 during the condensation, the guanidine function has to be protected. The best results were obtained upon coupling Z-Arg(Z_2)-OH with TFFH/collidine in dichloromethane. Another dipeptide building unit with an acylated reduced peptide bond containing C-terminal arginine was prepared to synthesize bradykinin analogues with backbone cyclization at the C-terminal.

9 Synthesis of Peptidyl Methylcoumarin Esters as Substrates and Active-Site Titrants for Prohormone Processing

Although peptidyl methylcoumarin amides are well established as model substrates for understanding protease specificity, the corresponding methylcoumarin esters have attracted scant attention despite their potential utility in active-site titration mechanistic characterization. Initial attempts to synthesize methylcoumarn esters via a modification of the well-established isobutyl chloroformate coupling procedure used to prepare methylcoumarin amides gave low yields and extensive racemization.[44] Several other coupling reagents gave only trace amounts of product. Transesterification of commercially available protected *p*-nitrophenyl esters proceeded readily, but the resulting products were contaminated with trace amounts of *p*-nitrophenol, which proved incompatible with subsequent manipulations. As described,[44] the best results were obtained via DCC coupling with 1.2–2.0 equivalents of 7-hydroxy-4-methylcoumarin (β-methylumbelliferone, hymecromone) using *N*-methylmorpholine as base and ethyl acetate–*N*-methyl-2-pyrrolidinone as solvent. Poor results were obtained with ethyl acetate as sole solvent because of the low solubility of the alcohol. Attempts to couple the methylcoumarin (α-amino) esters (α-amino MCEs) to tripeptides using standard segment-coupling conditions gave poor yields and unacceptable levels of racemization. After an extensive survey of coupling reagents and protocols, the optimal results were obtained by activating tripeptides with the coupling reagent TFFH at 0 °C. The α-amino ester was then added slowly under argon and allowed to react overnight at 4 °C. Some racemization of the activated residue in the tripeptide occurred with this procedure (<13%), but the epimers were separable by HPLC; however, such purification has proven unnecessary, because interference from minor epimers has not affected the characterization of serine proteases with these compounds. Additionally, in all cases examined, racemization at the MCE-containing C-terminal residue itself has been undetectable. This procedure has been successfully used to prepare a number of tetrapeptidyl methylcoumarin esters **33** (Scheme 7), including Z-Ala-Tyr-Lys-Lys-MCE, Z-Nle-Tyr-(Boc)Lys-Arg(Mtr)-MCE (Mtr = 4-methoxy-2,3,6-trimethylphenylsulfonyl), Z-Nle-Tyr-Lys-(D-Lys)-MCE, and Z-(D-Nle)-Tyr-Lys-Lys-MCE.

10 Synthesis of Boc-(*N*-All)Xaa-(*N*-All)Xaa-OMe

Dipeptides containing a *N*-allyl substituent on both nitrogens have been prepared from the N-alkylated amino acids and N-alkylated amino acid esters in the presence of TFFH as coupling reagent to afford the dipeptides in 35–75% yield.[45] The resulting dipeptides were subjected to ring-closing metathesis (RCM) using Grubbs catalyst to afford the cyclized dipeptides,[46] e.g. **34** (Scheme 8).

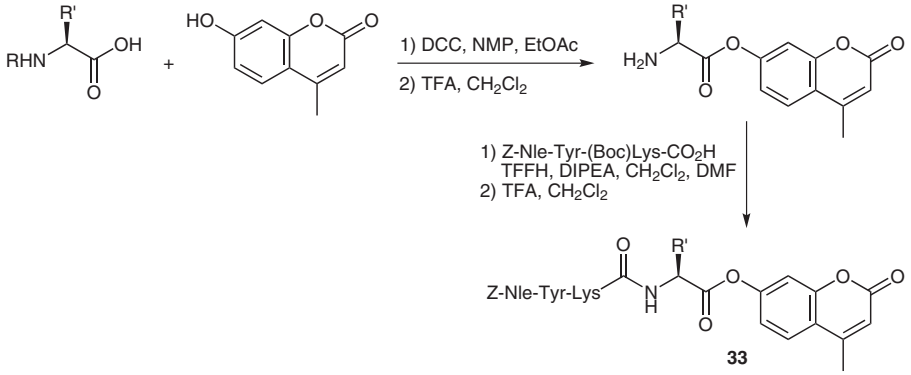
11 Synthesis of Alamethicin F30 and Analogues Using TFFH

The use of Fmoc-amino acid fluorides for the solid-phase synthesis of Aib-containing polypeptides has proved to be

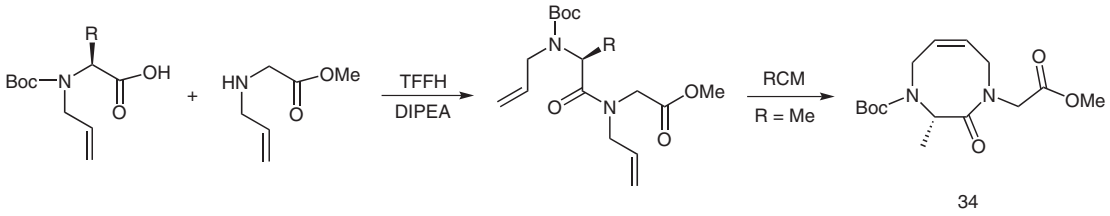
the method of choice for these difficult sequences.[47–49] The synthesis of alamethicin peptides N- and C-terminally modified with fullerene or lipopeptide units were carried out by in situ acid fluoride activation with TFFH- on 2-chlorotrityl chloride polystyrene resin and conjugation with fullerenes C_{60} and C_{70} was carried out in solution.[50] Further improvements were presented for automated solid-phase synthesis via generation of Fmoc-amino acid fluorides in situ using TFFH. Examples for the *in situ* activation with TFFH for the synthesis of difficult peptide sequences without Aib residues have been reported in a short communication.[51]

11.1 C-Terminal Alamethicin F30–Fullerene C_{60} and C_{70} Conjugates

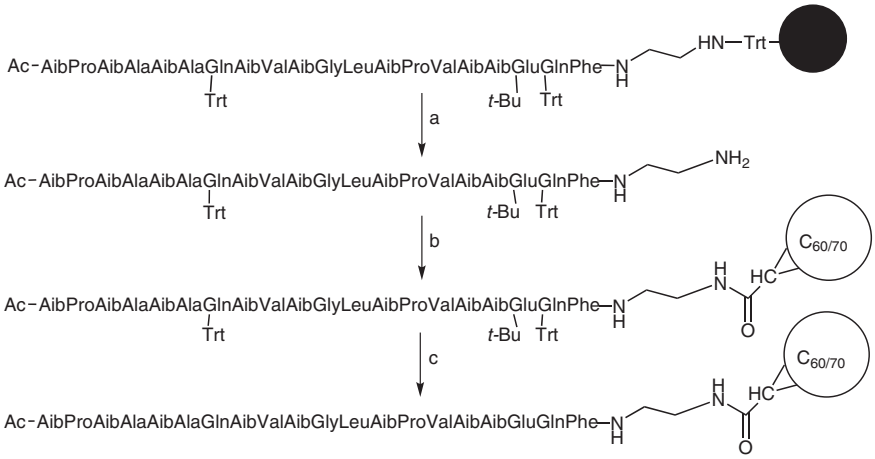
The synthesis of the two conjugates is outlined in Scheme 9.[52] The fully protected alamethicin F30-2-aminoethyl amide was synthesized on a PE Applied Biosystems Synthesizer 433A.[52] The first residue Fmoc-L-phenylalanine (replacing phenylalaninol) was coupled to the resin loaded with ethane-1,2-diamine. All couplings were carried out with Fmoc-amino acid (10 equiv), TFFH (10 equiv), and *N*,*N*-diisopropylethylamine (20 equiv) in pure *N*,*N*-dimethylformamide for 60 minutes. Cleavage from the resin was performed with hexafluoro-2-propanol–dichloromethane (2:3) for one hour and, after partial concentration, the polypeptide was precipitated with



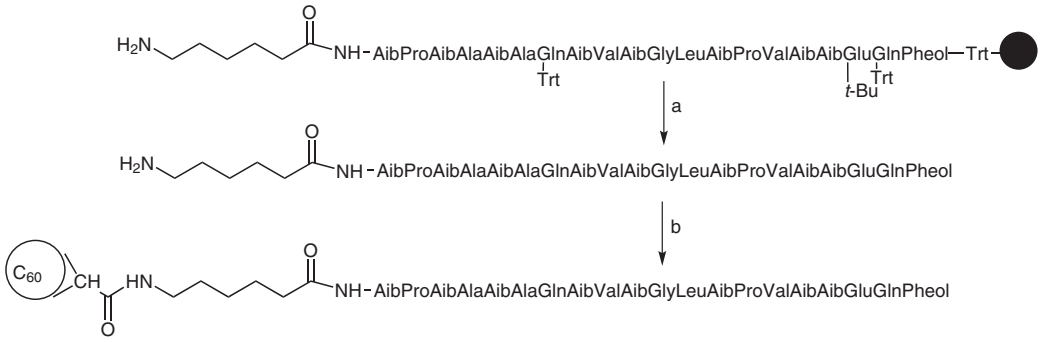
Scheme 7 Synthesis of tetrapeptidyl methylcoumarin esters



Scheme 8 Synthesis of a cyclized dipeptide



Scheme 9 C-Terminal active ester conjugation of fullerene C_{60} or C_{70} in solution to [Phe20]alamethicin F30-2-aminoethyl amide synthesized on 2-chlorotrityl resin using in situ TFFH activation; (a) cleavage (hexafluoro-2-propanol–dichloromethane, 1 h); (b) coupling of the fullerene succinimide ester (CH_2Cl_2, 4 h), precipitation, and flash chromatography on silica gel; (c) deprotection [TFA–CH_2Cl_2 (1:1) containing 5% H_2O and 2% *i*-Pr_3SiH].

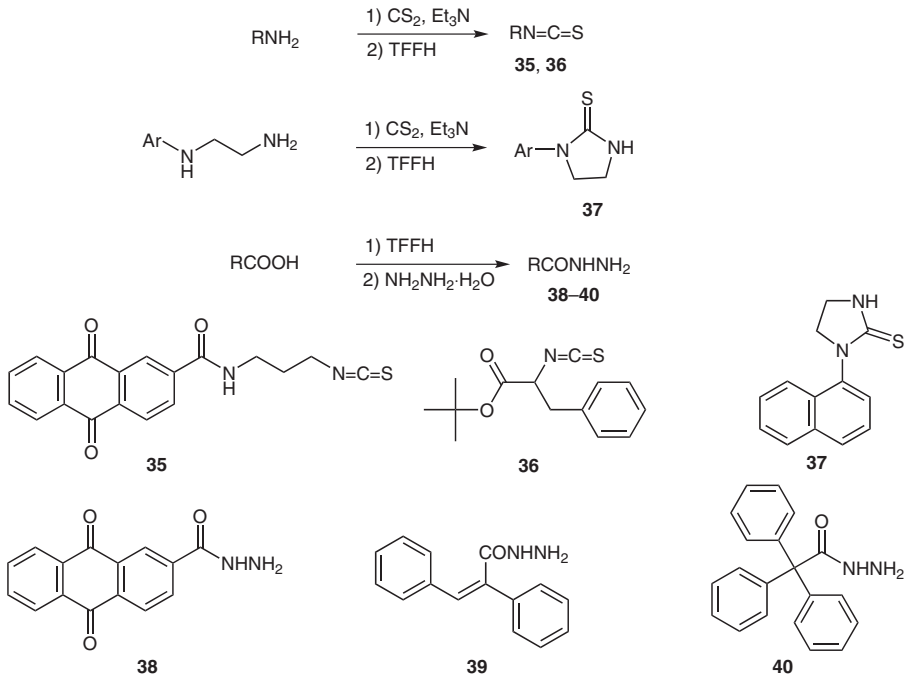


Scheme 10 N-Terminal conjugation of fullerene(60)-carboxylic acid to [Ac21]alamethicin F30 synthesized on 2-chlorotrityl resin using TFFH activation; (a) cleavage and deprotection [TFA–CH_2Cl_2 (1:1) containing 5% H_2O and 2% *i*-Pr_3SiH]; (b) after purification (RP-HPLC), conjugation in solution with fullerene(60)-carboxylic acid (preactivation with HATU, DIPEA, bromobenzene–DMF, 15 h).

n-hexane–diethyl ether (1:1). After lyophilization from *tert*-butyl alcohol–water (4:1) and purification by RP-HPLC, the side-chain-protected alamethicin F30-2-aminoethyl amide was acylated with 1,2-dihydro-1,2-methanofullerene(60)-61-carboxylic acid succinimide ester or 1,2-dihydro-1,2-methanofullerene(70)-71-carboxylic acid succinimide ester in dichloromethane within four hours. After precipitation with *n*-hexane and flash chromatography on silica gel using chloroform–methanol (9:1), the protected conjugate (35% yield) was treated with trifluoroacetic acid–dichloromethane (1:1) containing 5% water and 2% triisopropylsilane. Coordination ion-spray mass spectra (CIS-MS) showed the expected molecular ions of C-terminal [Phe20]alamethicin F30-2-aminoethyl amide–fullerene conjugates as ion adducts.[52]

11.2 N-Terminal Alamethicin F30–Fullerene C_{60} Conjugate

2-Chlorotrityl chloride resin was loaded with Fmoc-L-phenylalaninol and the alamethicin sequence was built up, as outlined in Scheme 10;[53] however, instead of attaching acetyl-α-aminoisobutyric acid as the last residue, Fmoc-Aib-OH followed by Fmoc-6-aminohexanoic acid was introduced. The 21-peptide was deprotected and cleaved from the resin with trifluoroacetic acid–dichloromethane (1:1) containing 5% water and 2% triisopropylsilane. Precipitation with *n*-hexane–diethyl ether, lyophilization from *tert*-butyl alcohol–water (4:1), and purification by HPLC on a C_{18} reversed-phase column yielded the free 21-peptide. N-Terminal acylation was performed with fullerene(60)-carboxylic acid (1 equiv),[52] which was dissolved in bromobenzene–*N*,*N*-dimethylformamide (2:1) and activated with HATU (1 equiv) and *N*,*N*-diisopropylethylamine (10 equiv) for 30 minutes, and then added to



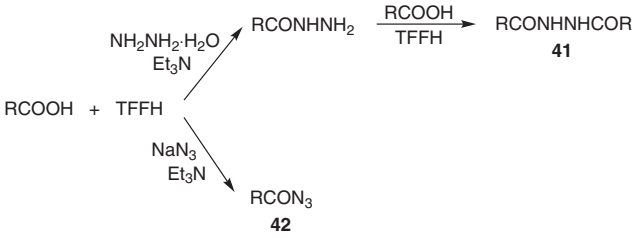
Scheme 11 Synthesis of isothiocyanates, imidazolidine-2-thiones, and hydrazides using TFFH

the solid 21-peptide. After 15 hours, the crude conjugate was purified by flash chromatography on silica gel using chloroform–methanol (7:3) with 1% triethylamine as eluent. The product was characterized by CIS-MS.[52,53]

12 Miscellaneous Examples

12.1 Synthesis of Isothiocyanates and Hydrazides

A mild and quick method has been reported for the synthesis of isothiocyanates from the corresponding amines using TFFH.[54,55] Thus, the reaction between a primary amine, carbon disulfide, and TFFH proceeds rapidly giving the corresponding isothiocyanates **35** and **36** in good yield (Scheme 11). With substituted ethane-1,2-diamines the corresponding substituted imidazolidine-2-thiones **37** are formed, presumably via the isothiocyanates as intermediates. TFFH activation of carboxylic acids followed by reaction with hydrazine allows synthesis of the hydrazides **38–40** (Scheme 11) without contamination by the corresponding *N*,*N*′-diacylhydrazides (see Scheme 12).[55] This is advantageous in the case of compound **38** where the reported synthesis by hydrazinolysis of the ethyl ester gives the hydroquinone as the primary product due to the reducing properties of hydrazine.[56] If the *N*,*N*′-diacylhydrazide **41** is desired, the initially formed hydrazide will react further[57] (Scheme 12).



Scheme 12 Synthesis of *N*,*N*′-diacylhydrazides and acyl azides using TFFH

12.2 Conversion of Carboxylic Acids into Anilides and Azides[57]

Several anilides were prepared by activation of an equimolar solution of a carboxylic acid with TFFH in acetonitrile in the presence of triethylamine. Infrared examination of the reaction mixtures indicates that different active intermediates may be present (Scheme 13). Activation of Z-amino acids [*N*-(benzyloxycarbonyl)amino acids, urethane-type group] by means of TFFH gives initially acid fluoride **43** (IR: 1842 cm^{-1}) as the only detectable species. With a *N*-benzoylamino acid, a mixture of the acid fluoride (IR: 1840 cm^{-1}) and the corresponding oxazolone **44** (IR: 1830 and 1685 cm^{-1}) is formed and, on standing, the oxazolone is converted exclusively into the acid fluoride by attack of fluoride ion.[20,21,57] For phenylacetic acid or cinnamic acid, mixtures of the acid fluoride and anhydride **45** (IR: 1824 and 1780 cm^{-1}) are formed in the ratio 1:1.

Activation of carboxylic acids with TFFH in the presence of sodium azide and triethylamine was carried out similarly (see Scheme 12). Infrared examination of the reaction mixture after five minutes showed the presence of the acyl azide **42** (IR: 2100 cm^{-1}) and traces of the acyl fluoride. Eventually, the acyl fluoride disappeared completely (ca. 1 h).[57]

12.3 Acylation of Alcohols, Thiols, and Dithiocarbamates[58]

Couplings of carboxylic acids with various nucleophiles to produce esters, amides, thioesters, etc. belong to the most widely employed transformations in organic chemistry.[59] Many procedures call for excess alcohol and strong Lewis or Brønsted acid catalysis.[60] Modern coupling reagents utilize only an equimolar amount of acid and nucleophile. Conditions are mild and compatible with a wide variety of functional groups, including the most common protecting groups.[61]

N,*N*′-Dicyclohexylcarbodiimide (DCC, **18**) is one of the most widely used condensation agents in organic chemis-

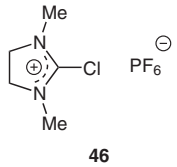
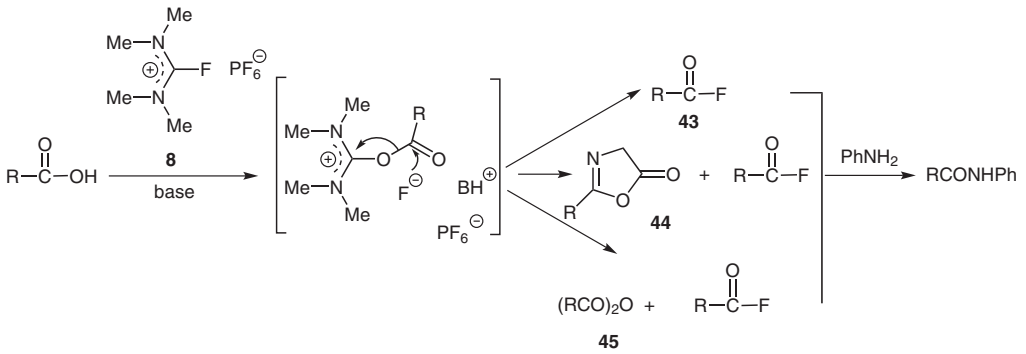


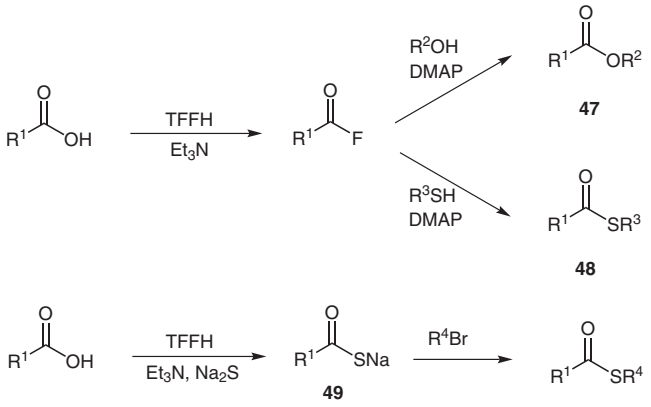
Figure 8



Scheme 13 Activation of carboxylic acids by means of TFFH

try because it is inexpensive and can be used under mild reaction conditions.[62] DCC was introduced by Sheehan and Hess[63] in 1955 and was crucial for completion of the first total synthesis of penicillin V;[64] however, it has the disadvantage of being of low reactivity as well as leading to an insoluble *N*-acylurea byproduct.[65] Halo uronium salts such as the highly reactive 2-chloro-1,3-dimethylimidazolium hexafluorophosphate (CIP, **46**) (Figure 8) and *N*,*N*,*N*′,*N*′-tetramethylchloroformamidinium hexafluorophosphate (TCFH, **20**) (see Scheme 4) have only recently received attention for their use as dehydrating agents in the formation of carboxylic acid derivatives other than amides.[66]

Boas and co-workers[67] reported the use of TFFH in the synthesis of esters **47** and thioesters **48** via in situ acid fluoride formation (Scheme 14). It was also shown that TFFH is effective in giving thioacids **49** upon reaction with a carboxylic acid and sodium sulfide. The thioacids are easily converted into thioesters by reaction with alkyl bromides (Scheme 14).



Scheme 14 Synthesis of esters, thioesters, and thioacids using TFFH

Acylation proceeds smoothly upon addition of triethylamine to a concentrated solution of a carboxylic acid and one equivalent of TFFH in a variety of solvents, such as dichloromethane, chloroform, or *N*,*N*-dimethylformamide. All reactions proceed in high yield with little or no side reactions, and are catalyzed by the addition of DMAP (typically 5–10%). Inert atmosphere is only necessary if the reactants/products are air-sensitive. Figure 9 depicts a number of esters **50**–**58** that were prepared from the acid and the corresponding alcohol via the acid fluoride using TFFH as the fluorinating agent. A wide range of functionalities is compatible with the mild esterification conditions.

Both linear and highly hindered alcohols can be used (Figure 9), and even the extremely acid-sensitive 4,4′-dimethoxytrityl group can be present, which makes the esterification procedure useful in the preparation of protected nucleotides for the automated synthesis of nucleosides. Bromo ester **54** has been prepared conveniently on a 30-gram scale, demonstrating that scaling up of TFFH reactions is feasible. Sensitive esters, such as **55**, and acrylic acid esters, e.g. **56**, were also prepared using TFFH. The acrylic acid does not complicate the esterification procedure which was superior to the coupling reaction between acryloyl chloride and the corresponding alcohol.

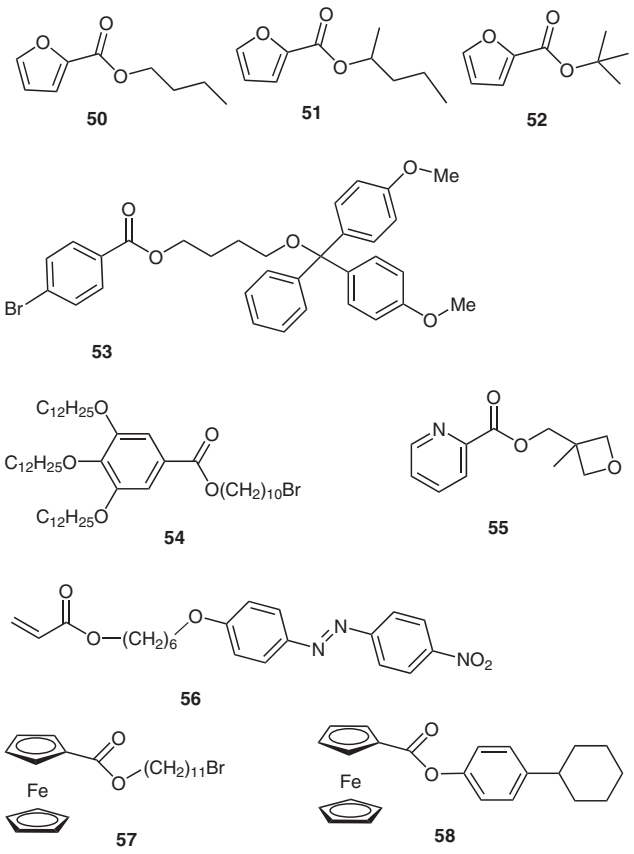
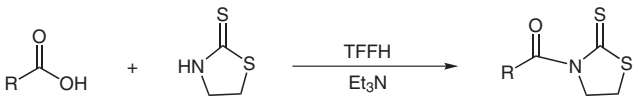


Figure 9 Esters synthesized using TFFH as fluorinating agent

The procedure works well with the difficult ferrocenecarboxylic acid, giving esters **57** and **58**. These ferrocene derivatives are of interest in connection with the development of aromatic building blocks for application in liquid crystal displays and other disciplines within the field of materials science. It has been reported that 4,4′-dihydroxybiphenyl can be monoesterified in moderate yield with TFFH.[67]

Thioesters are also useful compounds in the field of materials science, and their preparation has been demonstrated in two different ways.[58] The first route proceeds via coupling between an acid fluoride, prepared from the corresponding carboxylic acid, and a thiol, as shown in Scheme 14. The second route involves reaction between a carboxylic acid, TFFH, and sodium sulfide to give the sodium salt of the corresponding thioacid, as outlined in Scheme 14. Reaction with an alkyl halide then gives the desired thioester (Figure 10). Chemoselective acylation of dithiocarbamates from in situ generated acid fluorides and thiazolidine-2-thione has been accomplished using TFFH (Scheme 15, Figure 10). These derivatives are useful for the preparation of aldehydes from the corresponding carboxylic acids by reduction with diisobutylaluminum hy-

dride, but preparation of the acylated thiazolidine-2-thione usually proceeds via a thallium(I) salt making the synthetic procedure somewhat unattractive.[67]



Scheme 15 Chemoselective N-acylation of thiazolidine-2-thione using TFFH

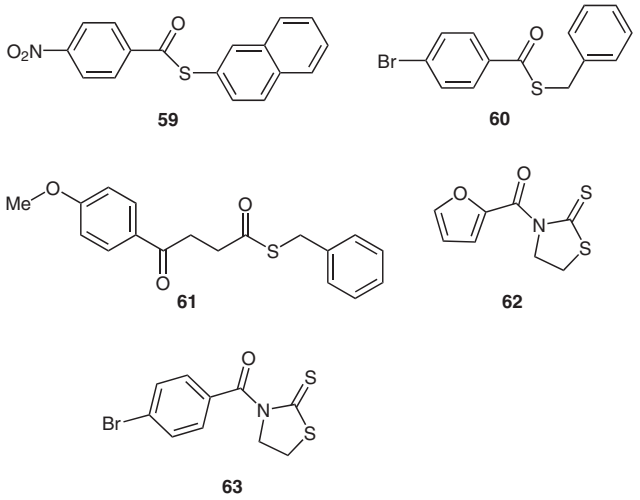
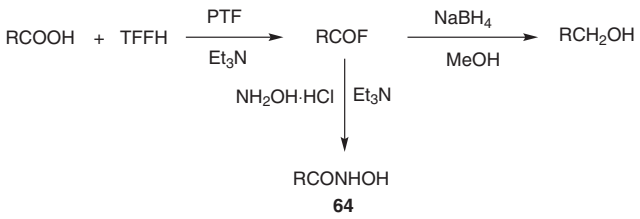


Figure 10 Examples of thioesters and *N*-acylthiazolidine-2-thiones synthesized using TFFH as fluorinating agent



Scheme 16 Synthesis of alcohols and hydroxamic acids using TFFH/PTF

12.4 Conversion of Carboxylic Acids into Alcohols and Hydroxamic Acids Using TFFH/PTF[28]

The poor results obtained with some aryl carboxylic acids in the presence of TFFH (**8**) can be improved by using PTF (**16**) as an additive during the preactivation step. The resulting such fluorides can be reduced to the corresponding primary alcohols or converted into the hydroxamic acids **64** by reaction with sodium borohydride or hydroxylamine, respectively (Scheme 16). Addition of the fluoride additive (PTF) avoids symmetric anhydride formation and allows maximum formation of the acid fluoride.[27,28]

12.5 Preparation of 2-Aminobenzimidazole, 2-Aminobenzoxazole, and 2-Aminobenzothiazole Derivatives[68]

Formamidinium salts have been mainly used as coupling reagents in peptide synthesis by activation of the carboxyl group of the amino acid; however, during the much slower activation of hindered amino acids, protected peptide segments, or carboxylic acids involved in cyclization, the formamidinium salts may undergo reaction with the amino component to give the corresponding guanylated derivatives.[69] Recently, advantage was taken of this side reaction which was used for the synthesis of 1,1,3,3-tetrasubstituted 4-aminoguanidines **65**, as well as the [1,2,4]triazolo derivatives **67** and **69**[70] (Scheme 17).

Interestingly, compounds such as 2-benzyl-3-hydrazinoquinoxaline (**66**) or 1-hydrazinophthalazine hydrochloride (**68**) react with formamidinium salts in a different manner to normal under similar conditions. In these cases, the intermediate guanidine undergoes heterocyclization to give the corresponding [1,2,4]triazolo derivatives **67** and **69**.[71,72]

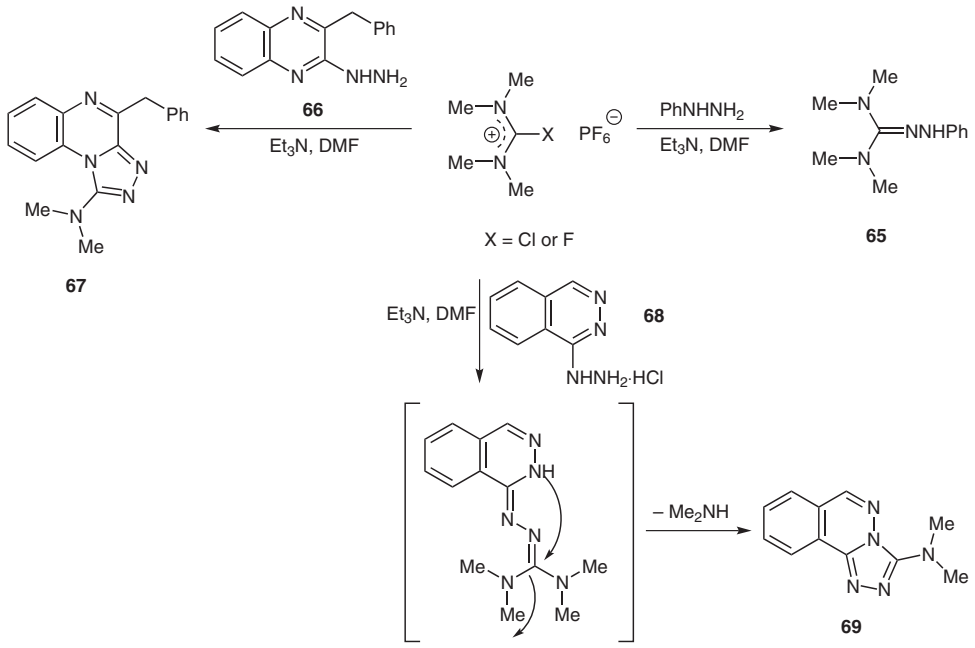
Similar reactions occur in the case of *o*-substituted anilines, such as 2-aminophenol (**70a**), benzene-1,2-diamine (**70b**), and 2-aminothiophenol (**70c**), which give 2-aminobenzoxazole, 2-aminobenzimidazole, and 2-aminobenzothiazole derivatives **73a**, **73b**, and **73c**, respectively (Scheme 18).[68] Compounds **73** could be formed by two alternative routes (A or B), depending on the nucleophilicity of substituent X. For route A, if X = S it is more nucleophilic than the aniline nitrogen atom, and X attacks the central carbon atom of the formamidinium salt to give an intermediate which then undergoes in situ heterocyclization with the loss of dimethylamine from intermediate **71** to give product **73c**. For route B, the aniline nitrogen atom first attacks the central carbon atom of the formamidinium salt to give intermediate **72** which then undergoes in situ intramolecular cyclization to afford the azole derivatives **73a** or **73b** (Scheme 18).

12.6 Formation of Interchain Carboxylic Anhydrides on Self-Assembled Monolayers[72]

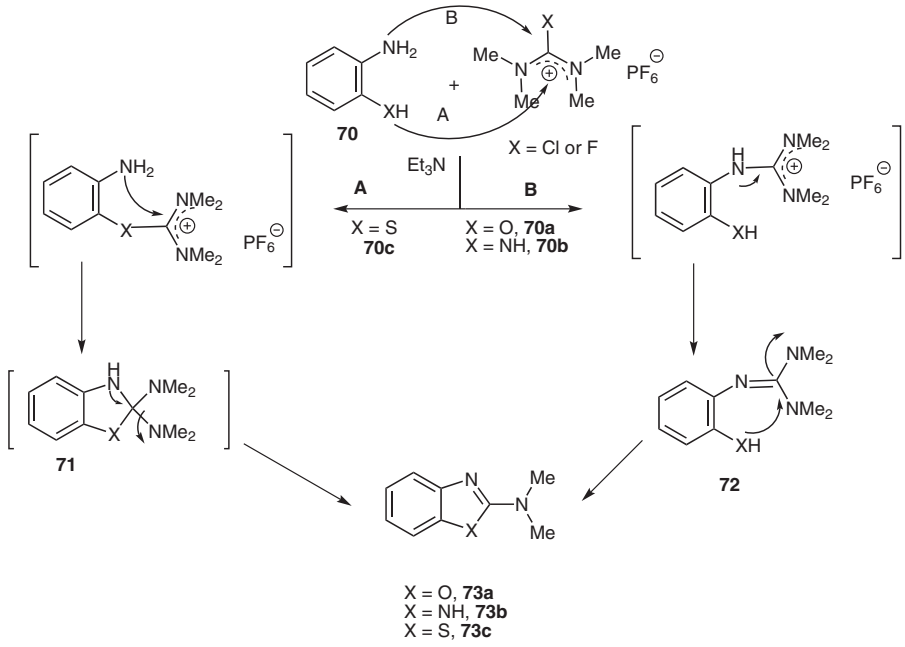
Recently, self-assembled monolayers (SAMs) were introduced as an ideal platform for studying the rules that govern 'reactions in two dimensions'. SAMs are highly ordered molecular assemblies which are formed spontaneously by chemisorption of functionalized surfactants onto solid surfaces.[73] The well-defined, highly controllable structures of SAMs provide great advantages for the design of two-dimensional systems for investigating interfacial phenomena or reaction behavior.[74,75] Reactions on SAMs are also crucial for the design of surfaces for further applications, such as the construction of biochips via the tethering of biologically active molecules.[75] Therefore, it is of practical importance for efficient surface-tailoring to understand the characteristic behavior of SAM-based reactions. Such phenomena often have no analogies in solution-based reactions.[76] For example, be-

cause of their being densely packed and highly ordered, SAM-based reactions often show pronounced steric effects.[77–80] SAMs of 16-mercaptohexadecanoic acid were formed on gold and treated with cyanuric fluoride and pyridine to generate the acid fluoride.[81] Two different products, acid fluoride and interchain carboxylic anhydride (ICA),[80] were controllably obtained under different reaction conditions with the same reagents. With TFFH, the reaction pathway is very similar to that with cyanuric fluoride, and IR peaks for the carboxylic acid group (1742 and 1719 cm^{-1}) disappeared and two new peaks appeared at 1821 and 1754 cm^{-1}. No peak appeared at 1840 cm^{-1}, as would be expected for the acid fluoride. The two new peaks are characteristic for the anhydride (Scheme 19).

When the amount of pyridine was fixed and the concentration of TFFH was increased along with an increase in the reaction time, predominantly ICA formed at the surface with acid fluoride as a minor product. When the amount of TFFH was fixed and the amount of pyridine was varied, ICA was still formed at the surface as the major product and no change in the product distribution was observed. Addition of tetrabutylammonium fluoride dramatically changed the surface product to that of the acid



Scheme 17 Synthesis of 1,1,3,3-tetrasubstituted 4-aminoguanidines and [1,2,4]triazolo derivatives using TFFH



Scheme 18 Synthesis of azole derivatives using TFFH

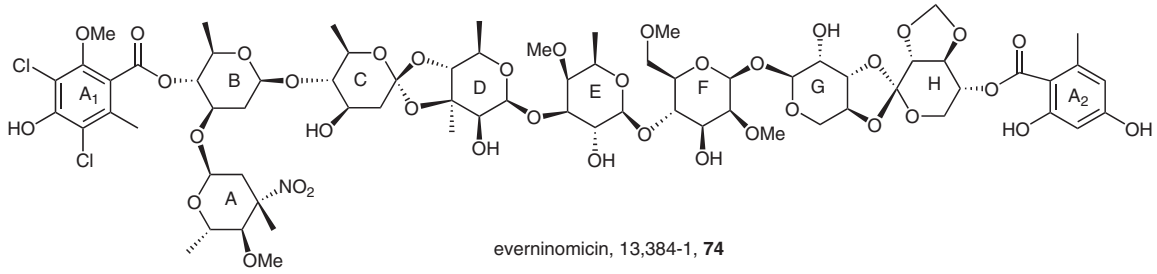
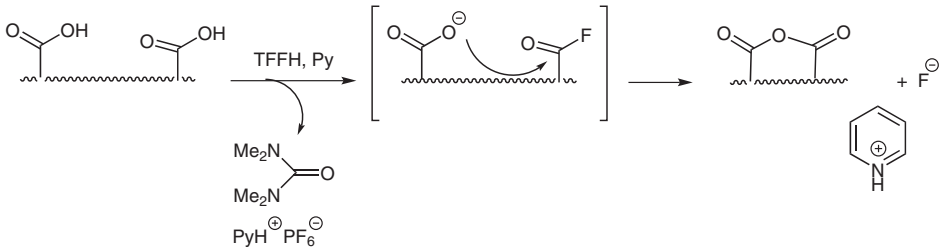


Figure 11 Everninomicin 13,384-1 (**74**)

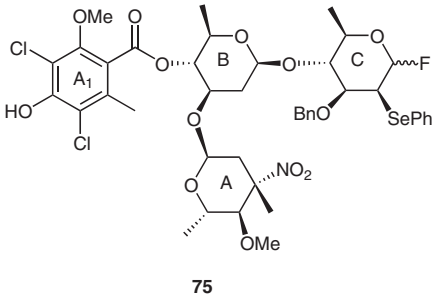


Scheme 19 Proposed mechanism for the formation of interchain carboxylic anhydride

fluoride. The surface was fully covered with acid fluoride via decomposition of the ICA.[82,83]

12.7 Synthesis of the $A_1B(A)C$ Fragment of Everninomicin 13,384-1[84,85]

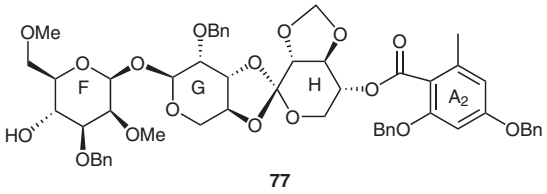
Everninomicin 13,384-1 (Ziracin™, **74**) (Figure 11), a member of the orthosomicin class of antibiotics.[86,87] The total synthesis of everninomicin 13,384-1 (**74**) using a number of novel synthetic strategies and methods has been reported.[84] The $A_1B(A)C$ fragment **75** (Figure 12), which is the phenylseleno fluoride fragment, consists of four building blocks. A more efficient synthesis than the one previously reported[88] for the aromatic fluoride fragment **76** was developed and is summarized in Scheme 20. TFFH was used and afforded the acyl fluoride derivative in 97% yield.



75

Figure 12 Structure of the $A_1B(A)C$ fragment **75**

The same method was employed for preparation of the acyl fluoride derivative used in the synthesis of the $FGHA_2$ fragment **77** (Figure 13) of everninomicin 13,348-1, in an overall yield of 80%.[89]



77

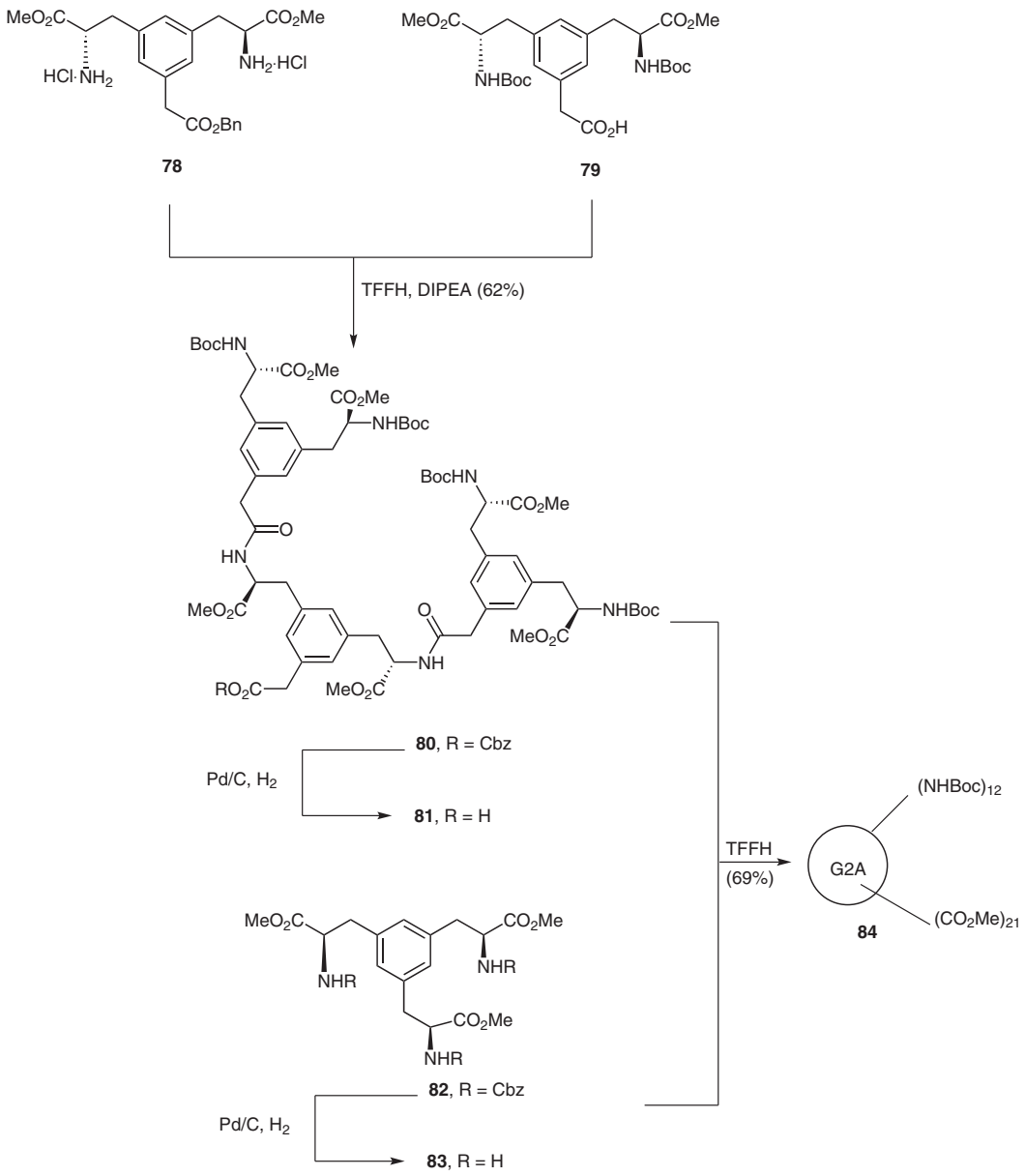
Figure 13 Structure of the $FGHA_2$ fragment **77**

12.8 Synthesis of Chiral Polyionic Dendrimers with Complementary Charges[90]

Dendrimers, regularly branched polymers of well-defined size, have been very actively studied in recent years.[90] As synthetic techniques are now well developed, the interest has shifted towards taking advantage of the properties of these unique macromolecules in various applications such as catalysis and molecular recognition.[91,92] The dendrimer is assembled in a convergent, or outside-in, fashion (Scheme 21). Deprotection of the appropriate groups of monomer A yielded **78** and **79**. These derivatives were not isolated, but were subjected to coupling by means of TFFH. To ensure complete coupling, a double acylation of **78** with TFFH-activated **79** (2 + 2 equiv) was carried out. This provided the dendritic wedge **80** in 62% yield. Hydrogenolytic removal of the focal-point protecting group yielded carboxylic acid **81**, while deprotection of the core phenyltrisalanine derivative **82** gave triamine **83**.

76

Scheme 20 Synthesis of acyl fluoride **76** using TFFH



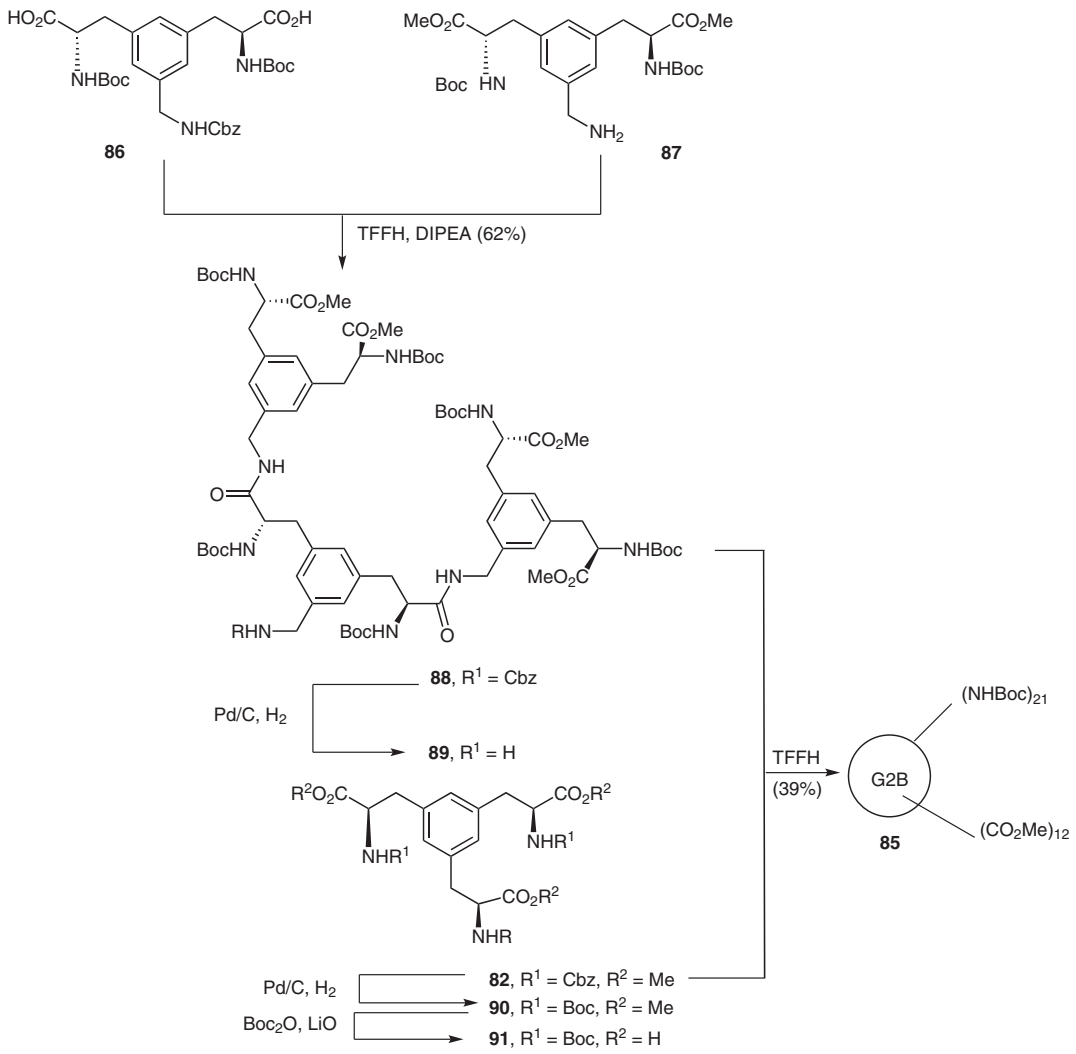
Scheme 21 Synthesis of chiral polyionic G2A dendrimer **84**

Coupling of **81** and **83**, without prior isolation of these fragments, finally furnished G2A dendrimer **84** in 69% yield.

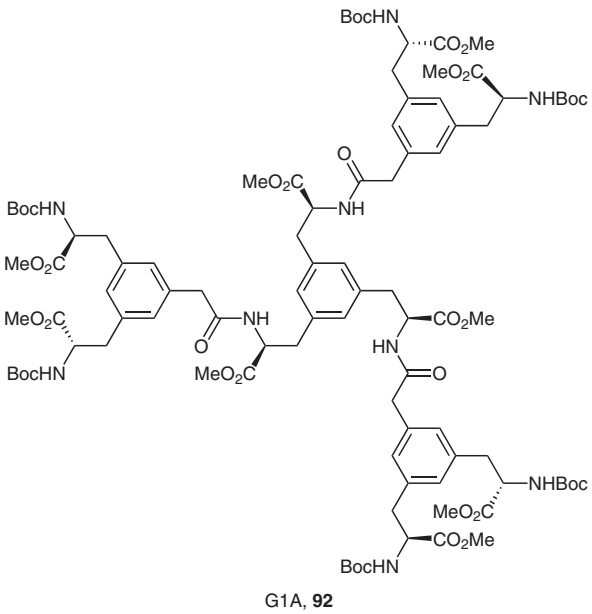
G2B dendrimer **85** was assembled analogously (Scheme 22). Deprotection of monomer B yielded derivatives **86** and **87** which could be coupled in a 1:2 ratio to give dendritic wedge **88** in 62% yield. Deprotection of the focal-point amine gave wedge **89**, which was coupled in a 4:1 ratio with phenyltrisalanine derivative **91**, obtained from **82** by protecting group manipulations via **90**. The coupling furnished G2B dendrimer **85** in 39% yield. Also, the corresponding dendrimers of the first generation, G1A **92** (Figure 14), obtained from **79** and **83** in a 4:1 ratio, and G1B **93** and dendrimer **94** (Figure 15), were synthesized using TFFH and the same methodology as for the G2 dendrimers.

13 Conclusion

Tetramethylfluoroformamidinium hexafluorophosphate (TFFH), a nonhygroscopic salt stable to handling under ordinary conditions, is obtained via reaction of tetramethylchloroformamidinium hexafluorophosphate (TCFH) with excess anhydrous potassium fluoride. TFFH appears to be an ideal coupling reagent for peptide synthesis in solid- and solution-phase synthesis as well as organic synthesis. TFFH is readily available, inexpensive, and capable of providing crude peptides as well as organic compounds such as carboxylic acid derivatives and heterocycles of high quality.

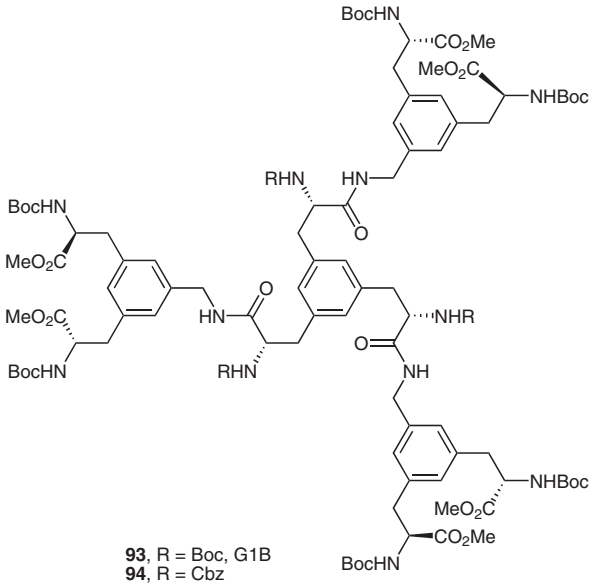


Scheme 22 Synthesis of chiral polyionic G2B dendrimer **85**



G1A, **92**

Figure 14



93, R = Boc, G1B
94, R = Cbz

Figure 15

Acknowledgment

Professor L. A. Carpino, Professor of Organic Chemistry, University of Massachusetts, Amherst, U.S.A., is thanked for his support and advice during preparation of this Account. Professor Fernando Albericio, Professor of Organic Chemistry and the Director of Barcelona Science Park, Spain, is thanked for his support and advice.

References

(1) (a) Elmore, D. T. In *Amino Acids, Peptides, and Proteins*, Vol. 33; Barrett, G. C.; Davies, J. S., Eds.; The Royal Society of Chemistry: Cambridge, **2002**, 83. (b) Li, P.; Xu, J. C. *J. Pept. Res.* **2001**, *58*, 129. (c) *Peptide Chemistry: Design and Synthesis of Peptides, Conformational Analysis and Biological Functions*; Hruby, V. J.; Schwyzer, R., Eds.; Pergamon: Oxford, **1998**. (d) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (e) Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268. (f) Bailey, P. D. *An Introduction to Peptide Chemistry*; Wiley: Chichester, **1990**. (g) Bodanszky, M. *Principles of Peptide Synthesis*; Springer: Berlin, **1984**. (h) Klausner, Y. S.; Bodanszky, M. *Synthesis* **1972**, 453.

(2) For a review of the work on the use of protected amino acid chlorides, see: Schröder, E.; Lübke, K. *The Peptides, Methods of Peptide Synthesis*, Vol. 1; Academic Press: New York, **1965**, 77.

(3) Fischer, E.; Otto, E. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2106.

(4) Weisz, I.; Roboz, J.; Bekesi, G. *Tetrahedron Lett.* **1996**, *37*, 563.

(5) Rozov, L. A.; Rafalko, P. W.; Evans, S. M.; Brockunier, L.; Ramig, K. *J. Org. Chem.* **1995**, *60*, 1319.

(6) (a) Zhang, L.-H.; Chung, J. C.; Costello, T. D.; Valvis, I.; Ma, P.; Kauffman, S.; Ward, R. *J. Org. Chem.* **1997**, *62*, 2466. (b) Lenman, M. M.; Lewis, A.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2297. (c) Carpino, L. A.; Cohen, B. J.; Stephens, K. E. Jr.; Sadat-Aalaee, Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732.

(7) (a) Senokuchi, K.; Nakai, H.; Nagao, Y.; Sakai, Y.; Katsube, N.; Kawamura, M. *Bioorg. Med. Chem.* **1998**, *6*, 441. (b) Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972.

(8) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1979**, 3037.

(9) Kaminski, Z. J. *Synthesis* **1987**, 917.

(10) (a) Thern, B.; Rudolph, J.; Jung, G. *Tetrahedron Lett.* **2002**, *43*, 5013. (b) Falb, E.; Yechezkel, T.; Salitra, Y.; Gilon, C. *J. Pept. Res.* **1999**, *53*, 507. (c) Zouikri, M.; Vicherat, A.; Aubry, A.; Marraud, M.; Boussard, G. *J. Pept. Res.* **1998**, *52*, 19.

(11) Bodanszky, M. *Principles of Peptides Synthesis*, 2nd ed.; Springer-Verlag: Berlin, **1993**, 11.

(12) (a) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651. (b) Bertho, J.-N.; Loffet, A.; Pinel, C.; Reuther, F.; Sennyey, G. *Tetrahedron Lett.* **1992**, *33*, 1303. (c) Carpino, L. A.; Mansour, E. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611.

(13) (a) Kim, Y.-A.; Han, S.-Y. *Bull. Korean Chem. Soc.* **2000**, *21*, 943. (b) Šavrda, J.; Chertanova, L.; Wakselman, M. *Tetrahedron* **1994**, *50*, 5309. (c) Carpino, L. A.; Mansour, E. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162(14).

(14) (a) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048. (b) Badu, S. V. V.; Gopi, H. N.; Ananda, K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2000**, *39*, 384.

(15) (a) Li, P.; Xu, J.-C. *Tetrahedron* **2000**, *56*, 8119. (b) Li, P.; Xu, J. C. *Chem. Lett.* **2000**, 204.

(16) Mukaiyama, T.; Tanaka, T. *Chem. Lett.* **1976**, 303.

(17) Wittmann, R. *Chem. Ber.* **1963**, *96*, 771.

(18) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487; and references cited therein.

(19) (a) Yarovenko, N. N.; Radsha, M. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1959**, *29*, 2125. (b) Olah, G. A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* **1974**, *96*, 925.

(20) Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 4101.

(21) (a) El-Faham, A. *Chem. Lett.* **1998**, 671. (b) El-Faham, A. *Org. Prep. Proced. Int.* **1998**, *30*, 47. (c) Akaji, K.; Kuriyama, N.; Kiso, Y. *Tetrahedron Lett.* **1994**, *35*, 3315.

(22) El-Faham, A.; Khattab, S. N.; Abdul-Ghani, M.; Albericio, F. *Eur. J. Org. Chem.* **2006**, 1563.

(23) (a) Carpino, L. A.; Imazumi, H.; El-Faham, A.; Ferrer, F. J.; Zhang, C.; Lee, Y.; Foxman, B. M.; Henklein, P.; Hanay, C.; Mugge, C.; Wenschuh, H.; Klose, J.; Beyermann, M.; Bienert, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 441. (b) Carpino, L. A.; El-Faham, A.; Minor, C. A.; Albericio, F. *J. Chem. Soc., Chem. Commun.* **1994**, 201.

(24) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

(25) (a) Dourtoglu, V.; Gross, B.; Lambropoulou, V.; Zioudrou, C. *Synthesis* **1984**, 572. (b) Knorr, R.; Terciak, A.; Bannworth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.

(26) Fiammengo, R.; Licini, G.; Nicotra, A.; Modena, G.; Pasquato, L.; Scrimin, P.; Broxterman, Q. B.; Kaptein, B. *J. Org. Chem.* **2001**, *66*, 5905.

(27) Carpino, L. A.; Ionescu, D.; El-Faham, A.; Beyermann, M.; Henklein, P.; Hanay, C.; Wenschuh, H.; Bienert, M. *Org. Lett.* **2003**, *5*, 975.

(28) El-Faham, A.; Kattab, S. N.; Abdul-Ghani, M. *ARKIVOC* **2006**, *(xiii)*, 57.

(29) Vojkovsky, T.; Drake, B. *Org. Prep. Proced. Int.* **1997**, *29*, 497.

(30) Bertho, J.-N.; Loffet, A.; Pinel, C.; Reuther, F.; Sennyey, G. *Tetrahedron Lett.* **1991**, *32*, 1303.

(31) Hudson, D. *J. Org. Chem.* **1988**, *53*, 617.

(32) Izdebski, J.; Bondaruk, J.; Gumulka, S. W.; Krzascik, P. *Int. J. Pept. Protein Res.* **1989**, *33*, 77.

(33) Carey, R. I.; Bordas, L. W.; Slaughter, R. A.; Meadows, B. C.; Wadsworth, J. L.; Huang, H.; Smith, J. J.; Furusjo, E. *J. Pept. Res.* **1997**, *49*, 570.

(34) For the first solid-phase synthesis of these hindered sequences via isolated amino acid fluorides, see: Wenschuh, H.; Beyermann, M.; Krause, E.; Brudel, M.; Winter, R.; Schumann, M.; Carpino, L. A.; Bienert, M. *J. Org. Chem.* **1994**, *59*, 3275.

(35) Liu, W. Q.; Vidal, M.; Gresh, N.; Roques, P. B.; Garbay, C. *J. Med. Chem.* **1999**, *42*, 3737.

(36) Chardin, P.; Cussac, D.; Maignan, S.; Ducruix, A. *FEBS Lett.* **1995**, *369*, 47.

(37) Perich, J. W.; Ruzzene, M.; Pinna, L. A.; Reynolds, E. C. *Int. J. Pept. Protein Res.* **1994**, *43*, 39.

(38) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276.

(39) Furet, P.; Gay, B.; García-Echeverría, C.; Rahuel, J.; Fretz, H.; Schoepfer, J.; Caravatti, G. *J. Med. Chem.* **1997**, *40*, 3551.

(40) Weber, I.; Potier, P.; Thierry, J. *Tetrahedron Lett.* **1999**, *40*, 7083.

(41) Lenfant, M.; Wdzieczak-Bakala, J.; Guittet, E.; Prome, J.-C.; Sotty, D.; Frindel, E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 779.

(42) An, S. S. A.; Lester, C. C.; Peng, J.-L.; Li, Y.-J.; Rothwarf, D. M.; Welker, E.; Thannhauser, T. W.; Zhang, L. S.; Tam, J. P.; Scheraga, H. A. *J. Am. Chem. Soc.* **1999**, *121*, 11558.

(43) Schumann, C.; Seyfarth, L.; Geriner, G.; Reissmann, S. *J. Pept. Res.* **2000**, *55*, 428.
(44) Müller, B.; Besser, D.; Kleinwächer, P.; Arad, O.; Reissmann, S. *J. Pept. Res.* **1999**, *54*, 383.
(45) Rockwell, N. C.; Krysan, D. J.; Fuller, R. S. *Anal. Biochem.* **2000**, *280*, 201.
(46) Reichwein, J. F.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 2335.
(47) Triolo, S. A.; Ionescu, D.; Wenschuh, H.; Sole, N. A.; El-Faham, A.; Carpino, L. A.; Kates, S. A. In *Peptides 1996, Proceedings of the 24th European Peptide Symposium*; Ramage, R.; Epton, R., Eds.; Mayflower Scientific: Kingswinford U.K., **1998**, 839–840.
(48) Wenschuh, H.; Beyermann, M.; Haber, H.; Seydel, J. K.; Krause, E.; Bienert, M. *J. Org. Chem.* **1995**, *60*, 405.
(49) Schmitt, H.; Jung, G. *Liebigs Ann. Chem.* **1985**, 321.
(50) Jung, G.; Redemann, T.; Kroll, K.; Meder, S.; Hirsch, A.; Boheim, G. *J. Pept. Sci.* **2003**, *9*, 784.
(51) Redemann, T.; Jung, G. *In Situ Fluoride Activation Allows the Preparation of Peptides Not Accessible by Routine Synthesis Protocols, In Peptides 1996, Proceedings of the 24th European Peptide Symposium*; Ramage, R.; Epton, R., Eds.; Mayflower Scientific: Kingswinford U.K., **1998**, 749.
(52) Skiebe, A.; Hirsch, A. *J. Chem. Soc., Chem. Commun.* **1994**, 335.
(53) Bayer, E.; Gfrörer, P.; Rentel, C. *Angew. Chem. Int. Ed.* **1999**, *38*, 992.
(54) Boas, U.; Pedersen, B.; Christensen, J. B. *Synth. Commun.* **1998**, *28*, 1223.
(55) Boas, U.; Gertz, H.; Christensen, J. B.; Heegaard, P. M. H. *Tetrahedron Lett.* **2004**, *45*, 269.
(56) Klingsberg, E. *J. Am. Chem. Soc.* **1958**, *80*, 5786.
(57) El-Faham, A.; Abdul-Ghani, M. *Org. Prep. Proced. Int.* **2003**, *35*, 369.
(58) Pittelkow, M.; Kamounah, F. S.; Boas, U.; Pedersen, B.; Christensen, J. B. *Synthesis* **2004**, 2485.
(59) (a) Albericio, F.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *Org. Prep. Proced. Int.* **2001**, *33*, 203. (b) Han, S. Y.; Kim, Y. A. *Tetrahedron* **2004**, *60*, 2447. (c) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, **1992**, 904.
(60) *Comprehensive Organic Functional Group Transformations*, Vol. 5; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Elsevier: Oxford, **1995**, 121.
(61) Greene, T.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**.
(62) (a) Fiesser, L. F.; Fiesser, M. *Reagents for Organic Synthesis*, Vol. 1; Wiley & Sons: New York, **1967**, 231. (b) *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3; Paquette, L. A., Ed.; Wiley & Sons: West Sussex, **1995**, 1751.
(63) Sheehan, L. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.
(64) (a) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957**, *79*, 1262. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, Vol. 1; Corey, E. J., Ed.; VCH Publishers: New York, **1996**.
(65) Holmberg, K.; Hansen, B. *Acta Chem. Scand., Ser. B* **1979**, *33*, 410.
(66) (a) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6984. (b) Fujisawa, T.; Tajima, K.; Sato, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3529. (c) Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, 1891. (d) Isobe, T.; Ishikawa, T. *J. Org. Chem.* **1999**, *64*, 6989.
(67) (a) Fujita, E.; Nagao, Y.; Seno, K.; Takao, S.; Miyasaka, T.; Kimura, M.; Watson, W. H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 914. (b) Nagao, Y.; Kawabata, K.; Seno, K.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2470.
(68) El-Faham, A.; Chebbo, M.; Abdul-Ghani, M.; Younes, G. *J. Heterocycl. Chem.* **2006**, *43*, 1.
(69) (a) del Frenso, M.; El-Faham, A.; Carpino, L. A.; Royo, M.; Albericio, F. *Org. Lett.* **2000**, *2*, 3539. (b) Albericio, F.; Bofill, J. M.; El-Faham, A.; Kates, S. A. *J. Org. Chem.* **1998**, *63*, 9678. (c) Gausepohl, H.; Pieles, U.; Frank, R. W. In *Peptides: Chemistry and Biology, Proceedings of the 12th American Peptide Symposium*; Smith, J. A.; Rivier, J. E., Eds.; ESCOM: Leiden / The Netherlands, **1992**, 523.
(70) Abdul-Ghani, M.; Khattab, S. N.; El-Massry, A. M.; El-Faham, A.; Amer, A. *Org. Prep. Proced. Int.* **2004**, *36*, 121.
(71) Douglas, E. W.; Hamilton, S. *J. Org. Chem.* **2002**, *67*, 7553.
(72) Shik, Y.; Choi, I. S. *Langmuir* **2006**, *22*, 6956.
(73) Ulman, A. *Chem. Rev.* **1996**, *96*, 1533.
(74) (a) Love, J. C.; Estroff, L. A.; Kriebel, J. K.; Nuzzo, R. G.; Whitesides, G. M. *Chem. Rev.* **2005**, *105*, 361. (b) Chi, Y. S.; Lee, J. K.; Lee, K. B.; Kim, D. J.; Choi, I. S. *Bull. Korean Chem. Soc.* **2005**, *26*, 361.
(75) Sullivan, T. P.; Huck, W. T. S. *Eur. J. Org. Chem.* **2003**, 17.
(76) Chechik, V.; Crooks, R. M.; Stirling, C. J. M. *Adv. Mater.* **2000**, *12*, 1161.
(77) (a) Houseman, B. T.; Mrksich, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 782. (b) Templeton, A. C.; Hosteler, M. J.; Kraft, C. T.; Murray, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 1906. (c) Van Ryswyk, H.; Turtle, E. D.; Watson-Clark, R.; Tanzer, T. A.; Herman, T. K.; Chong, P. Y.; Waller, P. J.; Taurog, A. L.; Wagner, C. E. *Langmuir* **1996**, *12*, 6143.
(78) (a) Shimazu, K.; Teranishi, T.; Sugihara, K.; Uosaki, K. *Chem. Lett.* **1998**, 669. (b) Lee, T. R.; Carey, R. I.; Biebuyck, H. A.; Whitesides, G. M. *Langmuir* **1994**, *10*, 741. (c) Bryant, M. A.; Crooks, R. M. *Langmuir* **1993**, *9*, 385.
(79) (a) Yousaf, M. N.; Chan, E. W. L.; Mrksich, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 1943. (b) Gawalt, E. S.; Choi, I. S.; Mrksich, M. *J. Am. Chem. Soc.* **2004**, *126*, 15613.
(80) Chi, Y. S.; Choi, I. S. *Langmuir* **2005**, *21*, 11765.
(81) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 487.
(82) Yan, L.; Marzolin, C.; Terfort, A.; Whitesides, G. M. *Langmuir* **1997**, *13*, 6704.
(83) (a) Chapman, R. G.; Ostuni, E.; Yan, L.; Whitesides, G. M. *Langmuir* **2000**, *16*, 6927. (b) Yan, L.; Huck, W. T. S.; Zhao, X. M.; Whitesides, G. M. *Langmuir* **1999**, *15*, 1208. (c) Chapman, R. G.; Ostuni, E.; Liang, M. N.; Meluleni, G.; Kim, E.; Yan, L.; Pier, G.; Warren, S.; Whitesides, G. M. *Langmuir* **2001**, *17*, 1225. (d) Lee, K. B.; Kim, D. J.; Yoon, K. R.; Kim, Y.; Choi, I. S. *Korean J. Chem. Eng.* **2003**, *20*, 956. (e) Chi, Y. S.; Choi, I. S. *Adv. Funct. Mater.* **2006**, *16*, 1031.
(84) (a) Nicolaou, K. C.; Mitchell, H. J.; Suzuki, H.; Rodríguez, R. M.; Baudoin, O.; Fylaktakidou, K. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 3334. (b) Nicolaou, K. C.; Mitchell, H. J.; Fylaktakidou, K. C.; Rodríguez, R. M.; Suzuki, H. *Chem. Eur. J.* **2000**, *6*, 3116.
(85) (a) Ganguly, A. K.; Pramanik, B.; Chan, T. C.; Sarre, O.; Liu, Y. T.; Morton, J.; Girijavallabhan, V. M. *Heterocycles* **1989**, *28*, 83. (b) Ganguly, A. K. In *Topics in Antibiotic Chemistry*, Vol. 2, Part B; Sammes, P. G., Ed.; Wiley: New York, **1979**, 61–96. (c) Ganguly, A. K.; Girijavallabhan, V. M.; Sarre, O.; (Schering Plough) WO 87/02366, **1987**. (d) Mahesh, P.; Gullo, V. P.; Roberta, H.; Loebenberg, D.; Morton, J. B.; Miller, G. H.; Kwon, H. Y.; (Schering Plough) EP 0538011A1, **1992**. (e) Ganguly, A. K.; McCormick, J. L.; Jinping, L. A.; Saksena, K.; Das,

P. R.; Pradip, R.; Chan, T. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1209.
(86) Wright, D. E. *Tetrahedron* **1979**, *35*, 1207.
(87) (a) Ganguly, A. K.; McCormick, J. L.; Chan, T. M.; Saksena, A. K.; Das, P. R. *Tetrahedron Lett.* **1997**, *38*, 7989. (b) Chan, T. M.; Osterman, R. M.; Morton, J. B.; Ganguly, A. K. *Magn. Reson. Chem.* **1997**, *35*, 529.
(88) Nicolaou, K. C.; Rodríguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 1874; *Angew. Chem.* **1998**, *110*, 1975.
(89) Ritzén, A.; Frejd, T. *Eur. J. Org. Chem.* **2000**, 3771.
(90) Nicolaou, K. C.; Rodríguez, R. M.; Fylaktakidou, K. C.; Suzuki, H.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 3340.
(91) (a) Newkome, G. R.; Moorefield, C. N.; Dendric, V. F. *Molecules, Concepts, Synthesis, Perspectives*; VCH Publishers: Weinheim, **1996**. (b) Engel, R. In *Advances in Dendritic Macromolecules*, Vol. 2; Newkome, G. R., Ed.; JAI Press: Stamford, **1995**, 73.
(92) Fischer, M.; Vogtle, F. *Angew. Chem. Int. Ed.* **1999**, *38*, 884.