N-Acylation in combinatorial chemistry

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Abstract

Polymer-supported N-acylation utilizing carbodiimides with additives, direct coupling reagents (phosphonium salts and uronium salts), N-acylazoles, and other reagents have been discussed.

Keywords: N-Acylation, N-acylating reagents, solid-phase, polymer-supported, combinatorial chemistry

Contents

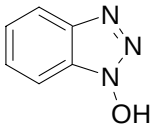
Introduction

N-Acylation is an important reaction in combinatorial peptide synthesis. Small peptides are readily prepared in solution phase and since early 1960s many reagents have been developed to improve the yield and to reduce the racemization.[1] However, solution phase synthesis of oligo- and polypeptides has been largely replaced by solid phase synthesis, introduced by Merrifield and taking advantage of the fact that the insolubility of polymers allows purification by filtration.[2] Another important aspect of solid phase synthesis is the production of a large number of compounds by combinations and permutations of components. This review will discuss N-acylation reactions, particularly as applied to solid phase synthesis using (i) conventional coupling reagents, and (ii) polymer-bound coupling reagents.

1. Reagents for formation of active esters

Active ester methodology has been much applied to form peptide bonds under mild conditions in both liquid-phase and solid-phase synthesis. In liquid-phase synthesis, most frequently the activation of the carboxyl group of amino acids has utilized 1-hydroxysuccinimides (HOSu) followed by esters of pentafluorophenol and nitrophenols; HOBt esters were found to be unstable. In solid-phase synthesis, 1-hydroxybenzotriazole (HOBt) derivatives including its phosphonium and uronium salts have been widely used. Other less common activating reagents are also discussed in this review. The preparation of these active esters requires a coupling reagent such as *N,N'*-dicyclohexylcarbodiimide (DCC) or *N, N'*-diisopropylcarbodiimide (DIC or DIPCDI). The active esters are then treated with amines (including amino acids) to form amides. This method of amide bond formation has been well documented.[1a,c]

1-Hydroxybenzotriazole (HOBt)

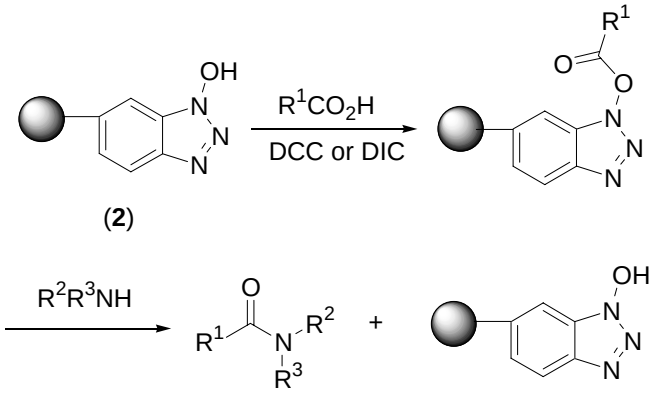


(**1**)

HOBt (**1**) is currently the most frequently used activating agent for the carboxyl group of amino acids.[1a] The procedure is fast and suppresses racemization, but the intermediate esters are moisture sensitive.[1a]

HOBt is used in liquid-phase, and also in solid-phase peptide synthesis. HOBt-DCC or -DIC methodology can be used in all peptide couplings. DIC is often preferred because its urea by-product is more soluble in organic solvents than that formed from DCC. An N-protected amino acid and an amino acid are coupled in liquid-phase for preparation of small peptides such as dipeptides and tripeptides. Solid-phase peptide synthesis with HOBt-DCC is widely used in combinatorial peptide synthesis taking advantage of fast reactions. Large and small peptides can be prepared by this methodology in which polymer-bound peptides with free N-terminus are coupled with N-protected amino acids, and this sequence can be continued by N-terminal deprotection of a polymer-bound peptide, followed by adding another N-protected amino acid or carboxylic acid; all this work follows from the seminal contribution of Merrifield.[3] Polymer-bound HOBt (**2**) has been found to be a useful tool, providing simplified workup and purification procedures (Scheme 1).[4] Moreover, preparation of more reactive polymer-supported HOBt esters, whose reactivity is enhanced by attaching the electron-withdrawing 6-sulfonamide moiety, has been synthesized. According to the acidity data, the reactivity of 1-hydroxybenzotriazole-6-sulfonamide (pKa 3.59) is presumed to be the same as HOAt (pKa 3.47).[5]

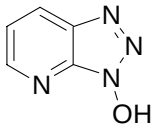
Nowadays the acylating process on polymer-supported HOBt is frequently carried out with HOBt phosphonium, uronium, or onium salts, and these reagents will be discussed later.



R^1CO_2H can be carboxylic acids or *N*-protected amino acids.
R^2R^3NH can be primary and secondary amines.

Scheme 1

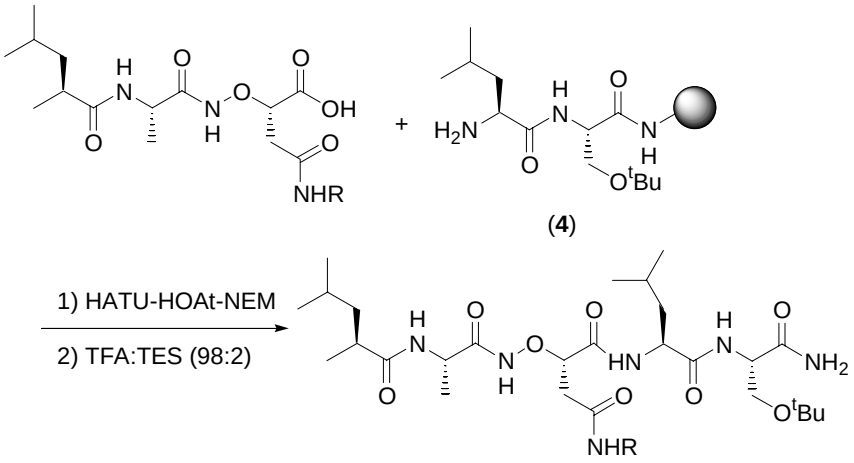
1.1. 1-Hydroxy-7-azabenzotriazole (HOAt)



(**3**)

HOAt (**3**) was introduced as a carboxyl group activating reagent by Carpino in 1993, who reported that HOAt completes the coupling reaction faster than HOBt and indicates the completion of the acylation reaction with color change (yellow to colorless). HOAt with *N*-ethyl-*N'*-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC) system gave the most efficient activation with least racemization.[6] The synthesis of HOAt, its coupling reaction, and the preparation of benzo-derivatives for comparison of their reactivities in liquid-phase have been reported by Carpino.[7]

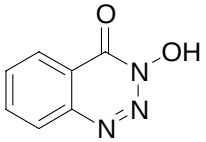
Use of HOAt as additives in DIC–mediated solid-phase peptide synthesis proved to be more effective in suppressing racemization as compared to using HOBt or other 1-hydroxy-1,2,3-tetrazoles.[8] Glycosylated tripeptide mimics have been coupled to the *C*-terminal dipeptides attached to polystyrene-based resins (**4**) under HATU-HOAt-NEM (*N*-ethylmorpholine) conditions (Scheme 2).[9]



(**4**)

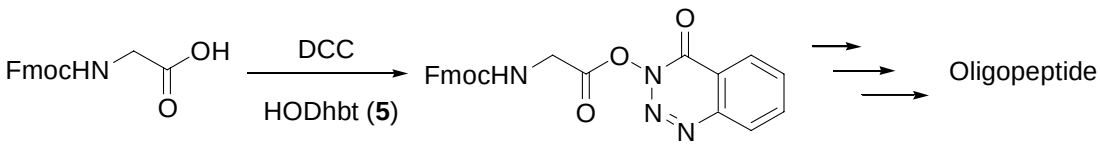
Scheme 2

1.2. 3,4-Dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (HO-Dhbt)



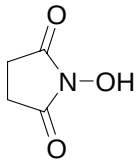
(**5**)

HO-Dhbt (**5**) has been reported as a coupling additive that can indicate the completion of acylation by color change.[10] Unfortunately, HO-Dhbt has been reported to give a relatively higher degree of racemization than other azole derivatives in the presence of DIC when poly(ethylene glycol)-cross-linked polyamide (PEGA)-bound dipeptide was used for peptide synthesis.[8] Fully protected amino acid esters of HO-Dhbt are stable crystalline solids, which can be stored for long periods at low temperature. Fmoc-amino acid esters with **5** are used for N-acylation with polydimethylacrylamide resin in solid-phase synthesis. However, a ring opening side-reaction leading to 2-azidobenzoic acid Dhbt ester was observed in DCC-mediated HO-Dhbt conditions.[11] Fmoc-amino acid esters with HO-Dhbt have been prepared in high yield (Scheme 3).[12]



Scheme 3

1.3. *N*-Hydroxysuccinimide (HOSu)



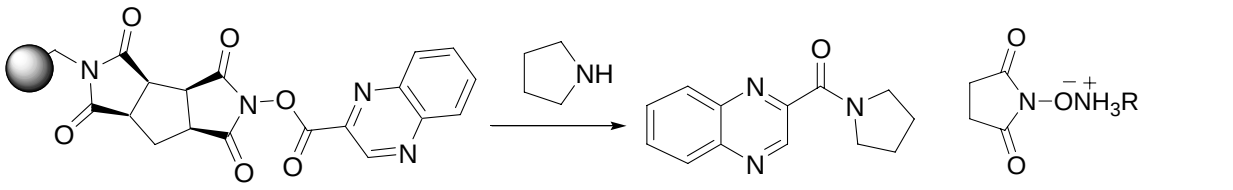
(**6**)

Among *N*-hydroxylamine derivatives, *N*-hydroxysuccinimide (HOSu) derivatives (**6**) are popular as active esters. Advantageously, the by-product *N*-hydroxysuccinimide is water-soluble.[13]

Polymer-supported *N*-hydroxysuccinimide esters (P-HOSu) tend to be more stable against hydrolysis in DMF than polymer-supported 1-hydroxybenzotriazole (P-HOBt) esters,[14] but P-HOSu esters are less reactive to amines compared to P-HOBt esters. Formation of P-HOSu esters is carried out by adding anhydrides, acid chlorides, or carboxylic acids with bases or coupling reagents such as DCC or DIC, while P-HOBt esters require additives such as phosphate salts of HOBt.[5]

Some aliphatic and aromatic cross-linked co-polymer HOSu esters have been developed by polymerization with maleic anhydride or *N*-hydroxymaleimide derivatives.[15] Recently, *N*-hydroxysuccinimide ring-opening metathesis was performed to give polymeric HOSu.[16] Synthesis of polymer-supported HOSu esters on a linker using *N*-hydroxymaleimide with thiol resins has been reported.[17] Comparison of preparation of *C*-terminal protected dipeptides in the DCC-mediated reaction shows that polymer-supported HOSu gives almost the same yields with

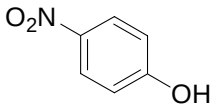
HOSu under similar conditions.[18] Other polymer-supported HOSu derivatives include those prepared using 1,2,3,4-cyclopentanetetracarboxylic dianhydride such as **7**, and ammonium and alkylammonium salts (**8**) (Scheme 4).[14,19]



(**7**)

Scheme 4

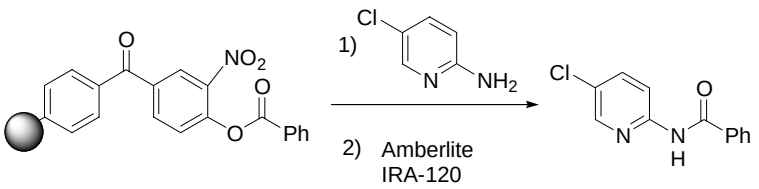
1.4. Nitrophenol



(**9**)

Bodanszky activated carboxylic acids by the formation of *p*-nitrophenyl esters utilizing *p*-nitrophenol (**9**) in 1955.[20] Since then, this method has been developed in both liquid- and solid-phase chemistry. The esterification of carboxylic acids in solution can be achieved via intermediate mixed carboxylic-carbonic anhydrides:[21] *p*-nitrophenyl chloroformate is added to N-protected amino acids in the presence of triethylamine and 10 mol% 4-dimethylaminopyridine (DMAP) for 45 min at room temperature followed by the addition of amino acids to give di- and tripeptides in 15-98% yields with minimal racemization.[22]

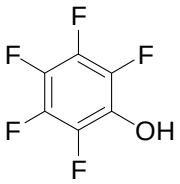
The initial work on solid-supported nitrophenyl esters was by Fridkin,[23] and Panse.[24] In 1974, Kalir *et. al.* reported a one-step synthesis of solid-supported *p*-nitrophenol from polystyrene, but the coupling reaction of its active ester with non-N-protected amino acids required hours for completion.[25] 4-Hydroxy-3-nitrobenzophenone was prepared by the same group as an acylating reagent to increase the rate of the coupling reaction. The relative reactivity of various active esters towards *tert*-butylamine was studied: *o*-nitrophenyl benzoate, 4-(benzoyloxy)-3-nitrobenzophenone, and 1-(benzoyloxy)benzotriazole required 11 days, 7 hours, and 2 min, respectively. Coupling polymeric *o*-nitrophenyl esters with C-terminal protected amino acids gave dipeptides in quantitative yields within 10-15 min.[26] Solid-supported 4-hydroxy-3-nitrobenzophenone ester **10** was used for the N-acylation (12 hours, 60 °C) of weakly nucleophilic heterocyclic amines such as aminothiazoles and aminopyridines (Scheme 5);[27] Acylation of simple amines was complete within 1 hour at 20 °C to give the amides in 33 to 97% isolated yield.



(**10**)

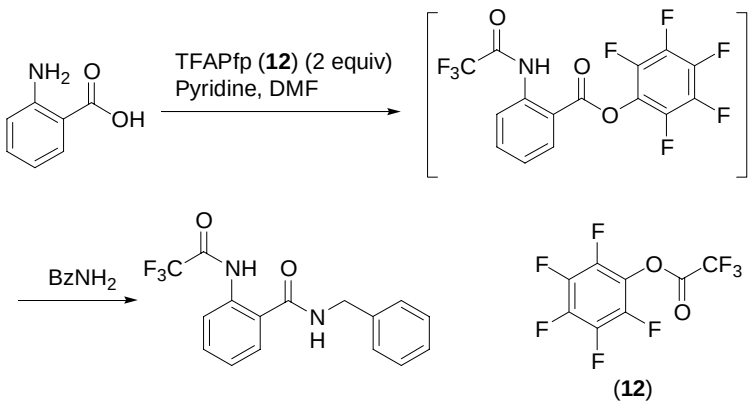
Scheme 5

1.5. Pentafluorophenol (PFP)



(**11**)

Pentafluorophenol (**11**) is known as an auxiliary whose esters couple with amino acids efficiently, although HOBt is often preferable. In liquid-phase, the *N*-carbobenzoxy-*S*-benzyl-*L*-cysteine pentafluorophenyl ester with valine methyl ester gave 90% of the dipeptide in 5 min.[28] The coupling rate constants for other pentahalogenated phenols have also been measured; pentachlorophenyl (PCP) ester took 62 min to obtain 90% of the dipeptide, and it was insoluble in THF.[28] Dipeptide and tripeptide esters can be prepared in high yields with no racemization if pentafluorophenyl esters are initially prepared with DCC and then used for the coupling reaction with amino acids.[29] Oligopeptides have been similarly prepared by a stepwise addition procedure.[30] Various *N*-carbobenzoxyamino acid pentafluorophenyl esters,[31] especially pentafluorophenyl esters of Fmoc-amino acids,[32] have been prepared and fully characterized. A one-pot procedure for the simultaneous N-protection and C-terminal activation of amino acids and thiol carboxylic acids using pentafluorophenyl trifluoroacetate (**12**) has been reported (Scheme 6).[33] In solid-phase synthesis, PFP esters are applied in nonadecapeptide synthesis using an automatic continuous flow synthesizer.[34]



(**12**)

Scheme 6

2. Alternative reagents for direct coupling to replace carbodiimides

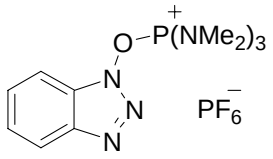
Other condensation or coupling reagents have been developed in search for effective and mild conditions, since carbodiimides frequently lead to much racemization.[1a]

Phosphonium, uronium salts and phosphate reagents are commonly used as coupling reagents, and have intensively been studied. Phosphonium and uronium salts are usually 1-hydroxybenzotriazole-based but 1-hydroxy-7-azabenzotriazole is also utilized. These coupling reagents are often used in combination with the parent HOBt or HOAt derivatives.

2.1. Phosphonium salts

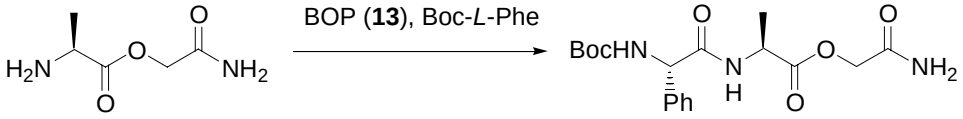
Phosphonium salts have widely been used for stepwise fragment coupling reactions of peptides. This technique has especially been applied to solid-phase peptide synthesis. The major advantage of the method is to offer easy purification of the final product by gel filtration after multiple-steps of condensation reactions. BOP, PyBOP, and PyAOP phosphonium salt coupling reagents are often used.

2.1.1. *O*-Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP)



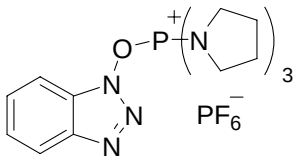
(**13**)

BOP (**13**) was prepared by Castro in 1975 by mixing tris(dimethylamino)phosphine with 1-hydroxybenzotriazole in CCl_4 at -30 °C followed by treatment with KPF_6.[35] In this paper, protected amino acids were coupled with amino acid esters at ambient temperature in 81 to 98% yield. Another peptide synthesis using **13** at room temperature in the presence of DIEA uses carboxyamidomethyl ester as a carboxyl protecting group (Scheme 7).[36] Among most other works, a stepwise solid-phase peptide synthesis using BOP has been described for the preparation of 7–10 amino acid residue peptides using *p*-hydroxyphenyl propionic resin.[37]



Scheme 7

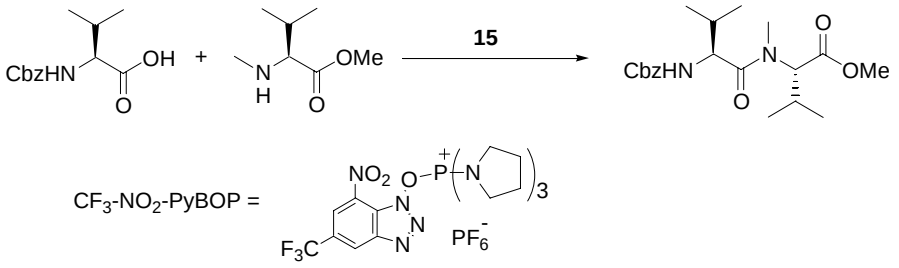
2.1.2. *O*-Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP)



(**14**)

PyBOP (**14**) and BOP (**13**) were commonly used coupling reagents in N-acylation, especially in peptide synthesis.[38] PyBOP enables the preparation of phthalimides from the corresponding primary amines, including amino acids, in two steps.[39]

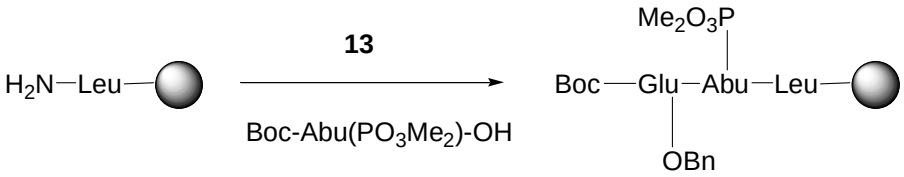
1-Hydroxy-4-nitro-6-(trifluoromethyl)benzotriazole phosphonium salt (CF_3-NO_2-PyBOP or PyFNOP) (**15**), a modified PyBOP reagent, has been described as highly reactive and efficient for the N-acylation of *N*-methyl amino acids (Scheme 8);[40] earlier work has indicated that DCC/HOBt and BOP show less efficiency in octapeptide synthesis.[41] 1-Hydroxybenzotriazole derivatives including PyBOP are comparable in reactivity and yield for the N-acylation of *N*-methyl amino acids.



(**15**)

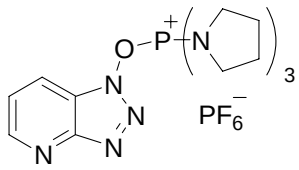
Scheme 8

In an advantageous solid-phase synthesis of peptides,[42] 4-phosphano-2-aminobutanoyl (Abu(PO_3Me_2))-containing peptides, which can be used for biochemical studies as Ser(PO_3R_2)-containing peptides (R = alkyl), were assembled by the coupling reaction using polymer-bound Boc-Leu resin with PyBOP and *N*-methylmorpholine for 20 min (Scheme 9).[43]



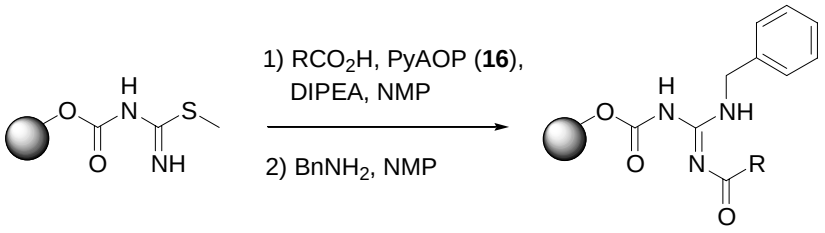
Scheme 9

2.1.3. 7-Azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP)



(**16**)

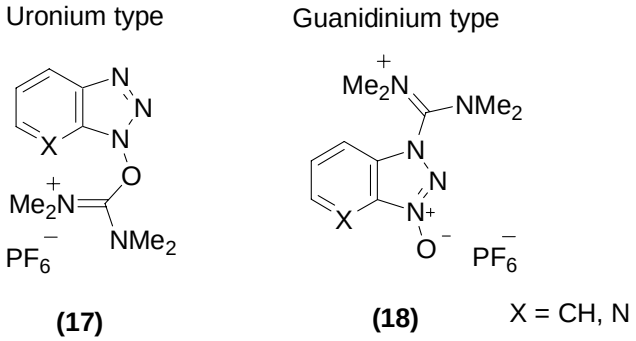
PyAOP (**16**) has been studied as an extension of phosphonium salt coupling reagents such as the commonly used BOP (**13**) and PyBOP (**14**). The reaction intermediates of **16** are less stable but more reactive than those of **14**. In a comparison of different reagents for cyclization of a polymer-bound heptapeptide, PyAOP/HOAt/DIEA in DMF for 2 min at 25 °C gave the best result, 74% of the cyclized product in 61% purity.[44] N-Acylation of resin-immobilized *S*-methylisothiourea with carboxylic acids using PyAOP in the presence of HOAt has been reported in the synthesis of N,N'-substituted acylguanidines (Scheme 10).[45]



Scheme 10

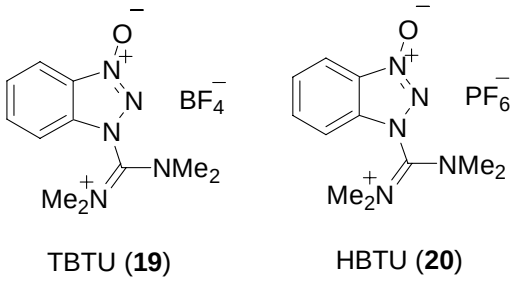
2.2. Uronium salts

The coupling reaction with uronium salts is a popular methodology for solid-phase N-acylation.[46,47] Their structures were assigned as uronium salts **17** until Carpino recognized the presence of another guanidinium salt structure **18**, which was characterized by ^{1}H NMR in both solid state and in solution.[48] By IR analysis, uronium salts **17** are formed in the early activation process of an acid, and are gradually isomerized to guanidinium salts **18**.



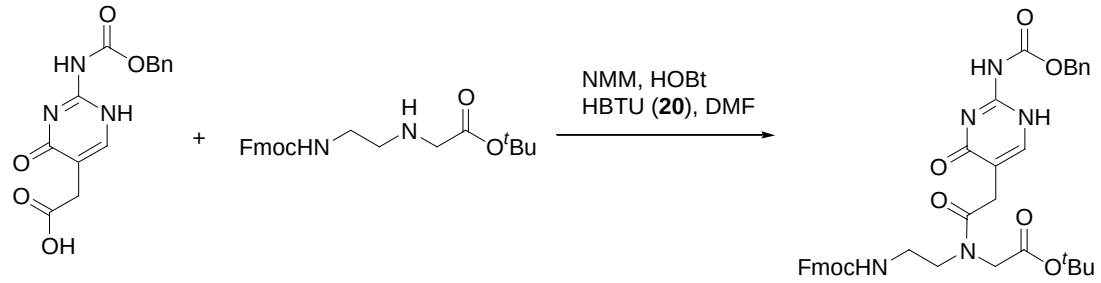
(17) **(18)**

2.2.1. *O*-Benzotriazol-1-yloxytris-1,1,3,3-tetramethyluronium salts



TBTU (**19**) HBTU (**20**)

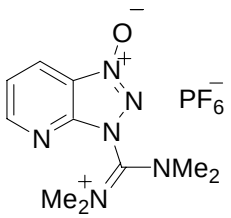
O-Benzotriazol-1-yloxytris-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) (**19**)[47,49] and hexafluorophosphate (HBTU) (**20**)[48] are widely used coupling reagents,[50] and particularly for Peptide Nucleic Acid (PNA) synthesis (Scheme 11).[3d,51]



Scheme 11

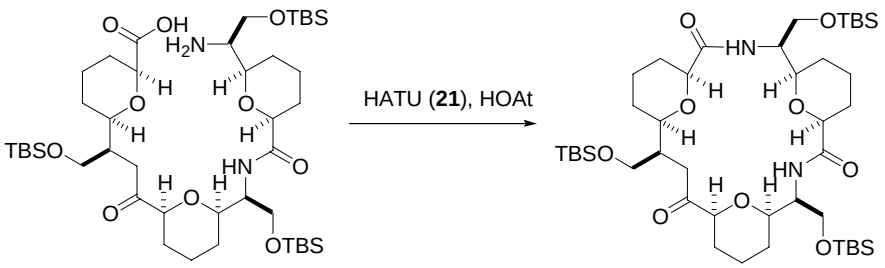
These reagents have been described as good reagents for solid-phase peptide synthesis: HBTU completed 90% of the reaction in 2 min while BOP underwent 80% in 2 min and 90% in 6 min. The counter-ions of HBTU and TBTU have shown no influence in comparative experiments.[47] Polymer-supported TBTU has been reported for preparation of N-protected dipeptide esters in acetonitrile with pyridine as a base.[52] During the reactions, no difference in isolated yield was observed from the reaction in liquid-phase synthesis when the N-terminal was protected by Boc or Cbz group.

2.2.2. *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)



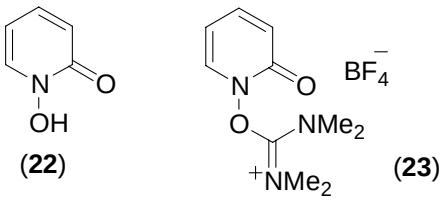
(**21**)

HATU (**21**)[6,53] is a very effective reagent for *N*-methyl and α,α–disubstituted amino acids, for which HOBt-based reagents do not give satisfactory results.[54] The reactions with HATU are generally faster and proceed with less racemization than reactions with HOBt-based coupling reagents.[55] HATU has been successful for sterically hindered peptide and amide bond formation in solid-phase synthesis;[56] for instance, preparation of cyclosporins on solid-phase was achieved by a combination of HATU and HOAt/DIC, and coupling yields were in the range of 50 to 99% for 6 hours reaction time. The macrolactamization was employed with HATU in high-dilution (Scheme 12),[57] and gave higher yields and faster reactions over HOBt-based reagents.[55]



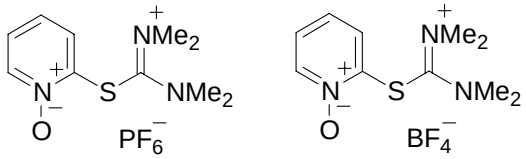
Scheme 12

2.2.3. 2-Oxo- and 2-mercapto-pyridone 1-oxide-based uronium salts

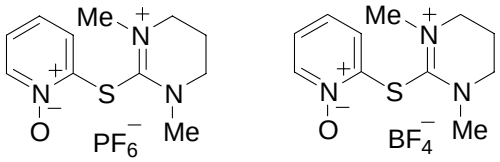


(**22**) (**23**)

As the starting material of *O*-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (TPTU) (**23**), *N*-hydroxy-1,2-dihydro-2-oxopyridine (HOPy) (**22**) was prepared as one of many activating reagents for the preparation of active esters.[58] Use of TPTU (**23**) with HOBt resulted in virtually no racemization (<0.1%) for the coupling of Cbz-Gly-*L*-Phe-OH with Val-OMe while other reagents with HOBt gave 0.1-2.4% of the other diastereomer;[47] however, a reaction with Val-OMe and *N*-benzyl-phenylalanine (Bz-*L*-Phe-OH) in the presence of TPTU/HOBt gave 21% of the *D*-isomer Phe segment.



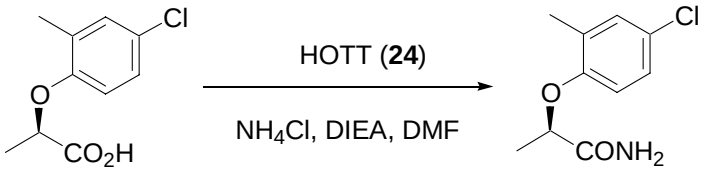
(**24**) (**25**)



(**26**) (**27**)

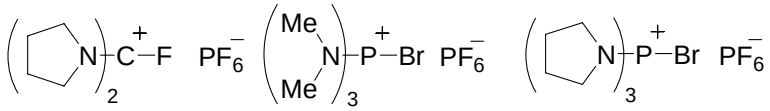
(S)-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT) (**24**) and tetrafluoroborate (TOTT) (**25**) were developed by Nájera[1b] as peptide coupling reagents and were shown to give high yields for preparation of amides (Scheme 13)[59] and 35-97% for the

tripeptide coupling reactions of N-protected amino acids with dipeptide ester hydrogen chloride salts.[60] A study of the racemization levels using TBTU (**19**) and thiouronium salts HOTT (**24**), TOTT (**25**), HODT (**26**), TODT (**27**) in the preparation of Gly-*L*-His-Phe-NH_2 has been reported.[61]

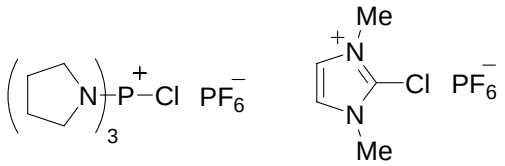


Scheme 13

2.3. Halouronium and halophosphonium salts

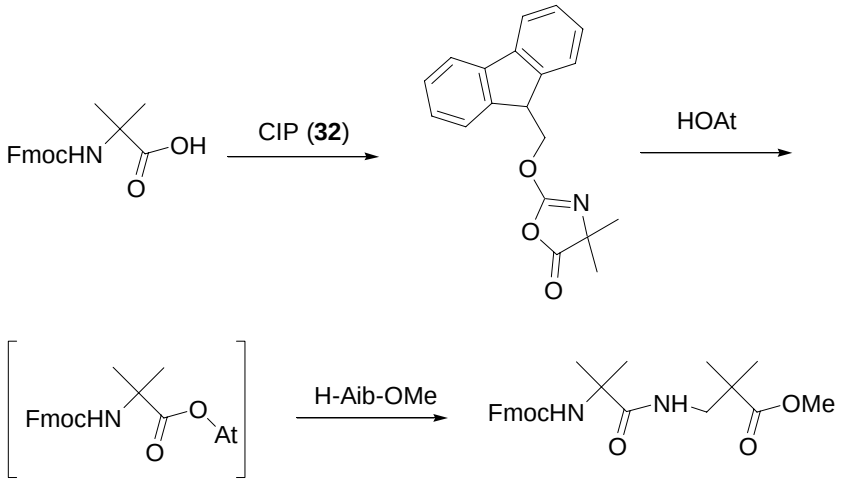


(**28**) (**29**) (**30**)



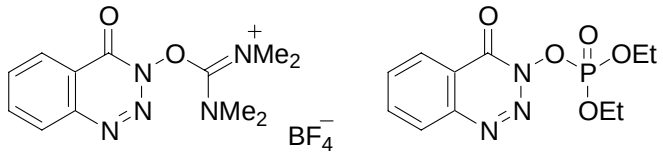
(**31**) (**32**)

Halouronium and halophosphonium salts are frequently described as good reagents especially for coupling of sterically hindered N^{α}-substituted or α,α-disubstituted amino acids, which are not easily carried out under standard conditions.[62] One of the halouronium salts, bis(tetramethylene)fluoroformamidinium hexafluorophosphate (BTFFH) (**28**), was introduced for the formation of acid fluorides in liquid- and solid-phase peptide synthesis,[63] since Fmoc-amino acid fluorides have been recognized as good intermediates for peptide coupling reactions.[64] Reactions with bromotris(dimethylamino) phosphonium hexafluoro-phosphate (BroP) (**29**), bromotripyrrolidino phosphonium hexafluorophosphate (PyBroP) (**30**) and chloro tripyrrolidino phosphonium hexafluorophosphate (PyClop) (**31**) have been compared; in reactions of N-protected amino acids and *N*-methylated amino acids, peptides were obtained in high yields in 60 min with 0-0.3% racemization, but longer reaction time caused 13-18% epimerization.[65] The reaction of 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP) (**32**) was employed with α-aminoisobutyric acid (Aib) (Scheme 14).[66] The efficiency of the reaction with **32** was highly enhanced by adding HOAt as an additive.

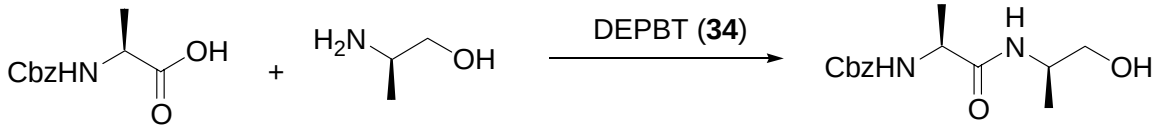


Scheme 14

2.4. Benzotriazine derivatives



O-(3,4-Dihydro-4-oxo-1,2,3-benzotriazine-3-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TDBTU) (**33**) and 3-(diethyloxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT) (**34**) have been reported as coupling reagents for the preparation of fully protected dipeptides[67] and N-protected amino alcohols (Scheme 15).[68] The uronium salt TDBTU (**33**) reduces racemization efficiently and often gives better yields than other reagents (HBTU and HATU *etc*.) as reported for liquid-[69] and solid-phase studies of the racemization of chiral PNAs.[3d] DEPBT (**34**) as a phosphate of HO-Dhbt was described as slightly better reagent than TDBTU (**33**) for increasing the enantiomeric purity. Peptide synthesis using **34** showed higher yields of products and good suppression of racemization.[70] Reagent **34** was applied to coupling with sterically hindered structures using a resin to build cyclic peptidomimetics with potent and selective biological activity.[71] The presence of **34** inhibited racemization and provided high yields in the solid-phase peptide synthesis for cyclic peptides.[72]

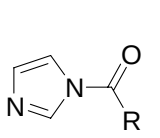


Scheme 15

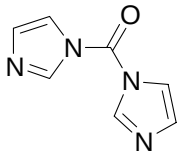
3. *N*-Acylazoles

As documented by Bauer, Staab and Schneider,[73] acyl azolides and *N*-acylimidazoles (**35**) are recognized as efficient acylating regents. 1,1'-Carbonylbis(1*H*-imidazole) (**36**) is a classical reagent much used for the formation of amide bonds and to obtain amides and ureas although little applied in peptide synthesis. *N*-Acylbenzotriazoles (**37**) and their utilities have recently been reported. There are a variety of *N*-acylazoles, but we will limit discussion to the relatively popular acylating reagents; *N*-acylimidazoles and *N*-acylbenzotriazoles.

3.1. *N*-Acylimidazoles

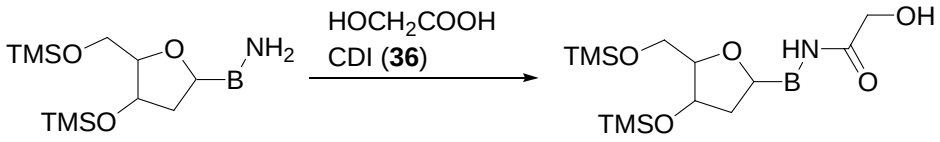


(**35**) R = alkyl, aryl



(**36**)

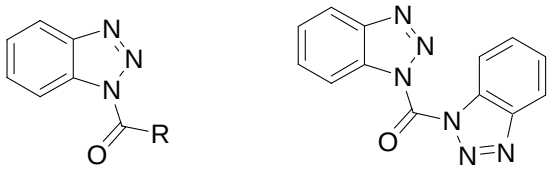
Imidazole groups are found in peptides or proteins. *N*-Acylimidazoles (**35**) are not only used as acylating reagents, but also are related to imidazole building blocks of biomolecules.[74] Imidazole was intensively studied for the catalysis of ester aminolysis, and *N*-acylimidazole (**35**) was found to be an intermediate formed by reaction of alkyl esters.[1a] The reactivity of **35** was well investigated. The presence of bulky groups and electron-donating groups with the acylating reagents may decrease the reactivity. *N*-Acylimidazoles were found to be very stable in 3% TFA in chloroform, but not stable in basic conditions.[75] This methodology has conveniently been used for the formation of amide bonds, and 1,1'-carbonylbis(1*H*-imidazole) (CDI) (**36**) has become an especially popular reagent used in the preparation of peptides from simple amides.[76] N-acylation of adenosine and cytidine nucleosides is an important step in the synthesis of oligonucleotides and is carried out by treatment of carboxylic acids with **36** to obtain *N*-acylimidazoles, which are subsequently treated with adenine or cytosine derivatives (Scheme 16).[77]



B = Adenine, Cytosine

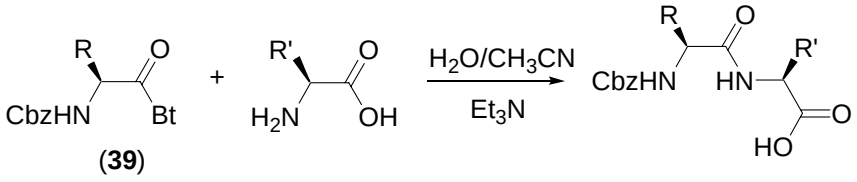
Scheme 16

3.2. *N*-Acylbenzotriazoles



(**37**) R = alkyl, aryl (**38**)

N-Acylbenzotriazoles (**37**)[78] are efficient reagents in liquid-phase and have been used under mild conditions for the preparation of primary, secondary and tertiary amides.[79] 1,1′-Carbonylbis(1*H*-benzotriazole) (**38**) has been used for the preparation of unsymmetrical ureas in liquid-phase[80] and for the acylation of amino acids in both liquid- and solid-phases.[81] Recently, N-acylation of 1-(α-Boc-aminoacyl)benzotriazoles (**39**) with amines was carried out to give single products in high yields without any detectable racemization.[82] In further work, peptides have been prepared in high yields without detectable racemization from Boc- and Cbz-protected benzotriazolyl-amino acids. Activation of C-terminal of Cbz-protected amino acids and dipeptides was carried out at 0 to 25 °C in a solution of 1*H*-benzotriazole with thionyl chloride. On the other hand, 15 to 50% of racemization in Cbz-protected benzotriazolyl-amino acids was observed when methylsulfonyl-benzotriazole was used in THF refluxing for 5 hours in the presence of triethylamine, while Boc-protected amino acids showed no racemization under these conditions. These activated amino acids and peptides underwent coupling reactions with amino acids in acetonitrile/water solution at ambient temperature, and the completion of these reactions was observed by the disappearance of **39** after 10-40 minutes. No racemization was observed in this process by ^{1}H NMR analysis of the crude reaction mixture (Scheme 17).[83] In comparison, HOBt active esters are very sensitive to moisture and their preparation requires another coupling reagent such as DCC or DIC.[1a]



(**39**)

R = $PhCH_2$, Me, Isopropyl
R' = $HOCH_2$, $PhCH_2$, Me, isopropyl, Indoylmethyl

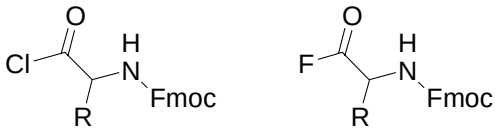
Scheme 17

N-Acylbenzotriazoles (**37**) have also been applied to solid-phase synthesis. Wang-resin-linked amines were converted into the amides using **37** and gave aryl amides followed by the cleavage from the resin (Scheme 18).[84] Acylbenzotriazole-grafted polyurethane has been reported in which the polymer-bound *N*-acylbenzotriazole was subsequently replaced by amine or hydroxyl group.[85]

Scheme 18

4. Other acylating reagents

4.1. Amino acid halides



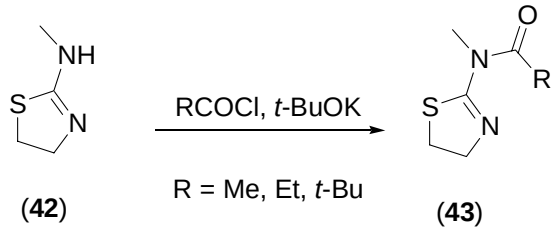
(**40**) (**41**)

Peptide coupling reactions using amino acid chlorides were not recommended initially due to their instability.[1a] Later, Carpino reported that Fmoc-amino acid chlorides (**40**) were highly reactive but stable enough to synthesize short peptide segments,[86] and gave less than 0.1% overall racemization.[87] Peptide synthesis via **40** was introduced as a rapid continuous coupling method using the sequence of (i) activation of carboxylic acid, (ii) the coupling reaction, and (iii) removing Fmoc protecting group.[86,88] However, this method is limited to substances with non acid-sensitive groups (Boc protecting group can not be used.),[89] and long-term storage of the amino acid chlorides is not practical.

Fmoc-amino acid fluorides (**41**) are, on the other hand, highly reactive, but more stable than the corresponding chlorides towards hydrolysis and degradation. Compounds **41** can be advantageously prepared from Fmoc-, Boc-, or Cbz-amino acids via cyanuric fluoride, and are often in crystalline form.[90] Fmoc-amino acid fluorides were also applied to solid-phase peptide synthesis using sterically hindered amino acids,[91] and for the acylation of sulfonamide type linkers (Scheme 19).[92]

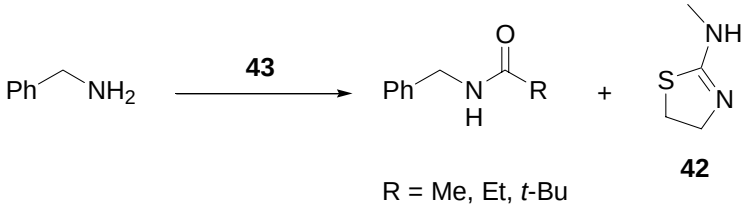
Scheme 19

4.2. *N*-Acyl-2-methylamino-2-thiazolines



(**42**) (**43**)

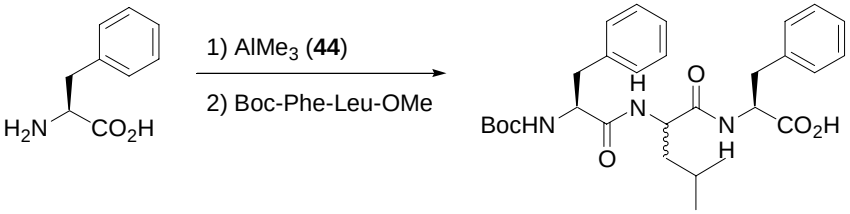
Kim reported on 2-methyl-2-thiazoline (**42**),[93] designed to be a good leaving group for N-acylation; in competitive acylation of a primary and secondary amine, *N*-acyl-2-methylamino-2-thiazolines (**43**) gave higher yields of the products with primary amines, in high chemoselectivity as compared to using acid chlorides and anhydrides (Scheme 20).[94]



Scheme 20

4.3. Lewis acid mediated N-acylation

Since the introduction of Lewis acid mediated N-acylation developed by Weinreb,[95] this methodology has been applied to construct a variety of peptides. In the original method, a dimethylaluminum amide reacts with an ester in dichloromethane at 25-41 °C to give an amide in more than 80% yield. A synthesis of oligopeptides in solution employing the modified Weinreb's method involved the treatment of N-protected amino acids with trimethylaluminum (**44**) followed by the addition of N-protected amino acid esters or peptide esters (Scheme 21).[96] The epimerization in the preparation of dipeptides by this method was observed to be less than 1% by reverse phase HPLC analysis, but in the preparation of tripeptides, 10-20% of epimerization was detected.



Scheme 21

Conclusions

Although DIC or DCC-mediated coupling reactions in the presence of HOBt have been the most commonly used systems in liquid- and solid-phase, new coupling reagents and combinations of coupling reagents and additives are being actively investigated. Structures and conditions affect the yield, enantioselectivity, and reaction rate observed. In the liquid-phase, additives such as HOBt and HOAt were mainly used due to the high reactivity and the good suppression of racemization. When these methods are applied to solid-phase syntheses, the solubility of the reagents and the by-products from DDC become problems. Reactions using a coupling reagent DIC or relatively soluble additives such as HOSu can simplify the workup process. Recently, many combinations of uronium salts with additives were reported especially for applications to solid-phase syntheses. As alternative coupling reagents, phosphonium salts and uronium salts from the additives such as HOBt and HOAt were developed, and were applied to liquid- and solid-phase. However, while polymer-bound uronium salts with the corresponding additives have been utilized, polymer-bound uronium salts have not been developed. Acid fluorides, halonium salts, and halophosphonium salts are effective reagents for sterically hindered substances. Acid fluorides have been reported in solid-phase syntheses, but not halonium and halophosphonium salts. Moreover, many coupling reactions are carried out in organic solutions, and many of the reagents discussed in this review are moisture sensitive. A one-pot reaction using *p*-nitrophenol for small peptide synthesis was conducted in a partially aqueous solution. *N*-Acylbenzotriazoles are also proved to be useful coupling reagents for simple amides as well as peptides in organic/aqueous solution.

Acknowledgements

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