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Properties and formation by elimination method of Didehydroamino acids derivatives

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Abstract

The lack of two hydrogen atoms from an α-amino acid is known as the didehydroamino acid. They are found in nature, generally as secondary metabolites of bacteria and fungi or other lower organisms. Didehydroamino acids are pharmaceutically and medicinally important due to their biological activity. There are several methods for the preparation of didehydroamino acids in the laboratory. One of them is the elimination approach. The removal of HCl from α-amino acid derivatives by N-chlorination is useful for preparing didehydroamino acid derivatives. Elimination of water from β-hydroxy-amides is also a good method for preparing simple dehydroamino acid derivatives. A range of dehydrating agents have been utilized for this purpose. The mesylation and dehydration methodology is one of them. Depending on the amino acid structure, the elimination of *O*-oxalyl chloride unit formed from the amino acid and oxalyl chloride gives the corresponding didehydroamino acid. Martin's sulfurane [diphenyl bis-(1,1,1,3,3,3-hexafluoro-2-phenyl-2-prppyl) sulfurane] can also be used to dehydrate a variety of β-hydroxy-α-amino acid derivatives. The production of β-dehydroamino acids from protected β-hydroxy-α-amino acids using diethyl amino sulphur trifluoride (DAST) in pyridine is an efficient process. The nitration and elimination method is a complementary method for preparing didehydroamino acid. The Hofmann type degradation and elimination method are rarely used to synthesize didehydroamino acid. This mini-review aims to synthesize didehydroamino acid by various elimination methods.

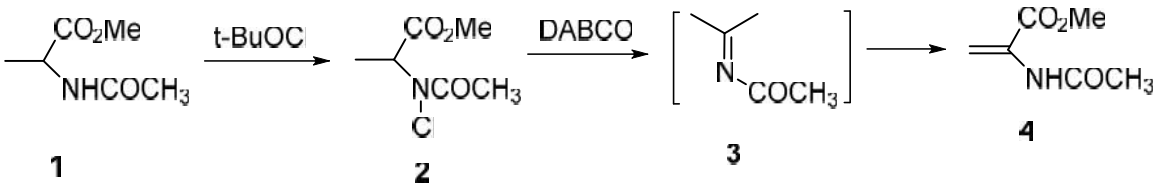
Keywords: α-Amino acid derivatives, elimination, didehydroamino acid.

Introduction

α, β-Didehydroamino acids (DDAA) frequently occur in nature as a component in the structure of various enzymes (Givot et al.,1969 ; Hanson et al., 1970), hormones (Gupta et al.,1990) and phytotoxins (Wakamara et al.,1983). They have been found in a family of polycyclic peptide antibiotics known as lantibiotics (Jung, 1991; Freud et al., 1991). Didehydroamino acid derivatives show interesting biological activities, such as the β-lactam antibiotics of the cephalosporin group, the herbicidal tetrapeptide tentoxin, or the antitumor agent azinomycin A (carzinophilin). Importantly, they have served as the biosynthetic precursors of unusual or D-configured amino acids in several natural peptides (Pearce et al., 1979 ; Banerjee et al., 1988). They are known (Palmer et al., 1992; Gupta et al., 1993) to introduce side-chain and backbone conformational constraints within peptides. They have the potential to bind metal ligands and are used as a β-turn inducer. For these reasons, interest in the synthesis and the reaction of didehydroamino acids (DDDA) and didehydropeptides (DDP) have proved to be an interesting area of research. The following section briefly reviews the synthesis of various didehydroamino acids and didehydropeptides and their reactions.

N-chlorination and elimination method:

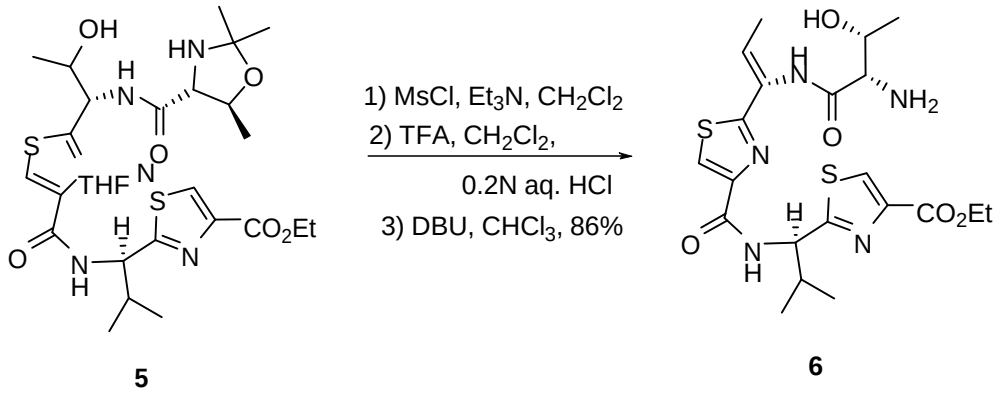
Schmidt et al. (1988) reported N-chlorination of N-acetyl alanine (**1**) with *tert*-butyl-hypochlorite followed by elimination with diazabicyclooctane (DABCO) to give an intermediate imine **3**, that tautomerism to methyl 2-acetamidoacrylate (**4**) under the reaction conditions (Scheme 1).



Scheme-1: Formation of methyl 2-acetamidoacrylate.

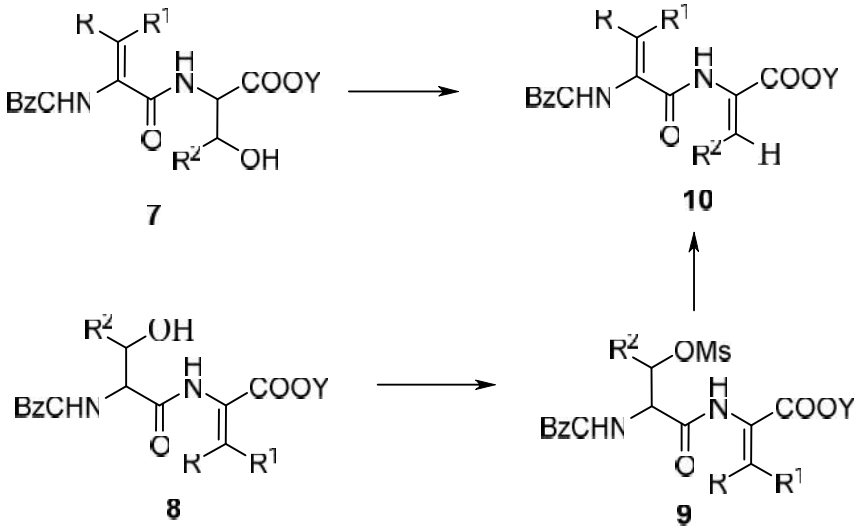
Mesylation and elimination method:

Elimination of water from β-hydroxy-amides is also a suitable method for preparing simple dehydroamino acid, dehydroamino peptide and dehydrodehydro peptide derivatives. A range of dehydrating agents has been utilized for this purpose. Thus, Ciofolini et al. (1999) applied this dehydrative elimination method for the total synthesis of micrococcin P1, a member of the thiostrepton group of antibiotics (Scheme 2).



Scheme-2: Formation of micrococcin P1.

Shin et al. (1982) reported the preparation of dehydropeptides from the corresponding serine and threonine containing dehydrooligopeptides by mesylation and subsequent base catalysed elimination with triethylamine or diazabicyclooctane. Thus, Δ-DHP **10** was obtained directly from an N-terminal DHP 7 and methane-sulfonyl chloride in dichloromethane with excess Et_3N. The same Δ-DHP **10** was obtained from a C-terminal DHP **8** with mesyl chloride followed by elimination with DBU stepwise (Scheme 3).



Scheme-3: Preparation of Δ-DHP.

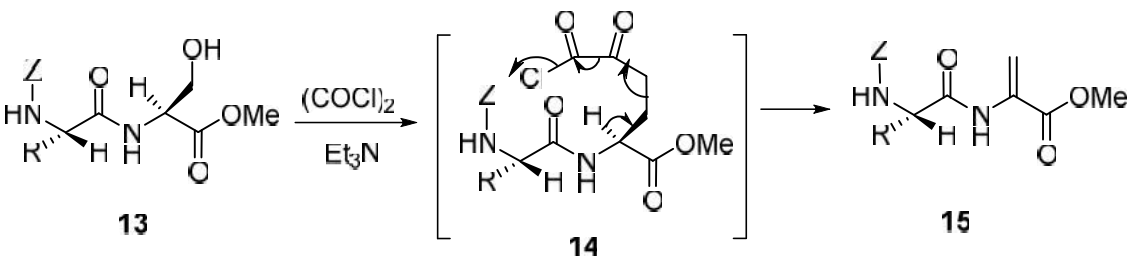
The geometry of the olefin proved to be (Z, Z) from the spectral determination, and the process is less prone to racemization.

Recently, Shin et al. (2004) applied the mesylation and dehydration methodology on substrate **11,** from which product **12** was used to synthesise natural products. They have combined both triethylamine and DBU as a base to afford the expected (Z)-Δ^2-dehydropeptide (**12**) (Scheme 4).

Scheme-4: Formation of (Z)- Δ^2-dehydropeptide.

Oxalyl Chloride method:

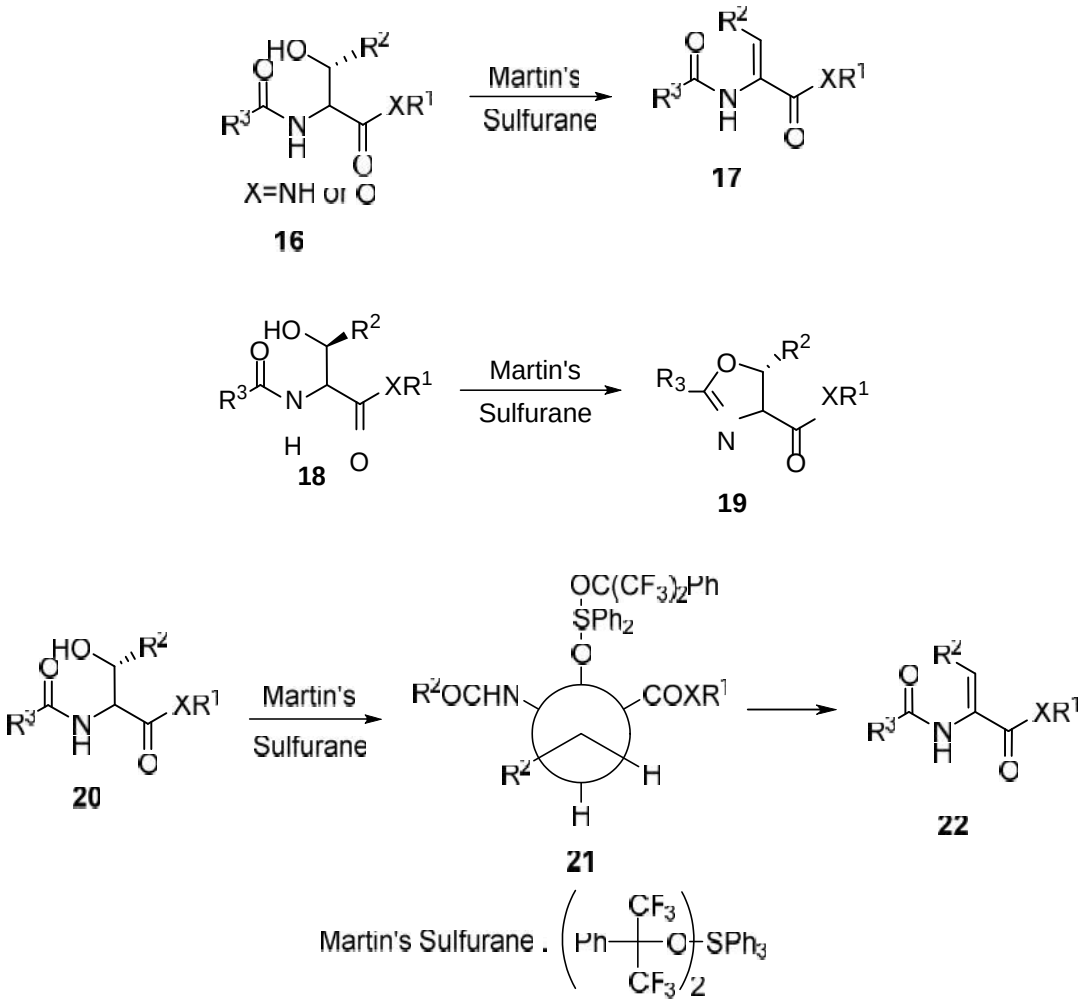
Δ-Ala peptides were also formed from the corresponding serine precursors with oxalyl chloride and triethylamine by the intermediate formation of Ser-O-oxalyl chloride unit. Rangathan et al. (1992) reported a facile generation of Δ-Ala units in peptides. The most exciting feature of this study was that peptide containing disulfide bridges was unaffected and the lack of reactivity of the serine residue when located at the N-terminal position in Ser-peptides (Scheme 5).



Scheme-5: Preparation of Δ-Ala peptides.

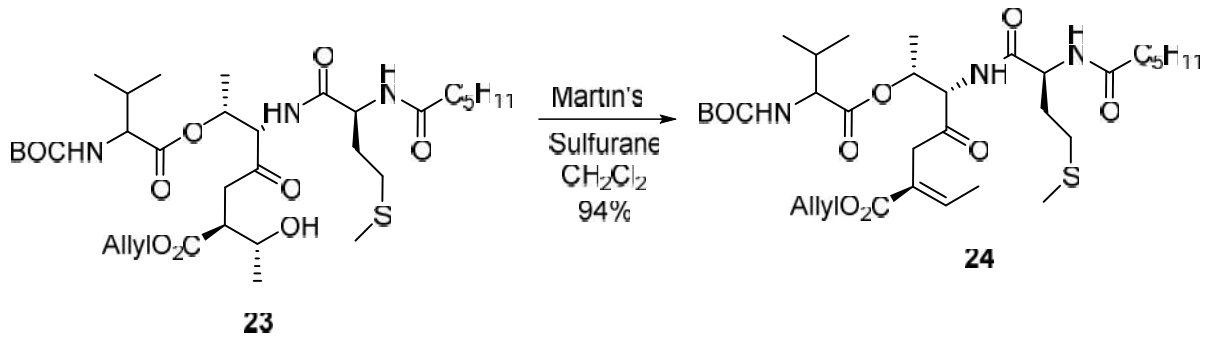
Martins Sulfurane method:

Martin's sulfurane [diphenyl bis-(1,1,1,3,3,3-hexafluoro-2-phenyl-2-propyl) sulfurane] is a helpful reagent for dehydrating a variety of -hydroxy-amino acids. Yokokawa et al. (2002) reported the stereospecific dehydration of threo-N-acyl-hydroxy-amino acid derivatives 16 using Martin's sulfurane to give (Z)- α,β-dehydroamino acids **17**, while erythro-N-acyl-hydroxy-amino acid amides 18 were converted to 4,5-trans-oxazolines **19** using similar reaction conditions (Scheme 6). Martin's sulfurane intermediate production followed by trans E2 elimination from the antiperiplanar conformation **21** explained the stereospecific formation of (Z) dehydroamino acid **17** from the threo hydroxy amino acid 16. Because Martin's sulfurane is a mild and neutral dehydrator, this approach should work with many functional groups.



Scheme-6: Dehydrative elimination of several β-hydroxy-α-amino acid derivatives.

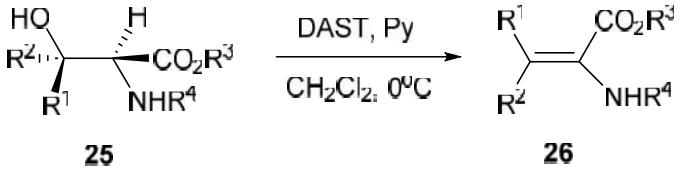
In the entire synthesis of the biologically active natural chemical Sodamide A, Yokokawa et al. (2002) used Martin's sulfurane mediated elimination technique. Thus, employing Martin's sulfurane to dehydrate N-acyl threonine ester **23**, the depsipeptide fragment **24** of Sodamide A was formed 94% of the time (Scheme 7).



Scheme-7: Formation of biologically active natural product Sodamide A.

Elimination involving DAST:

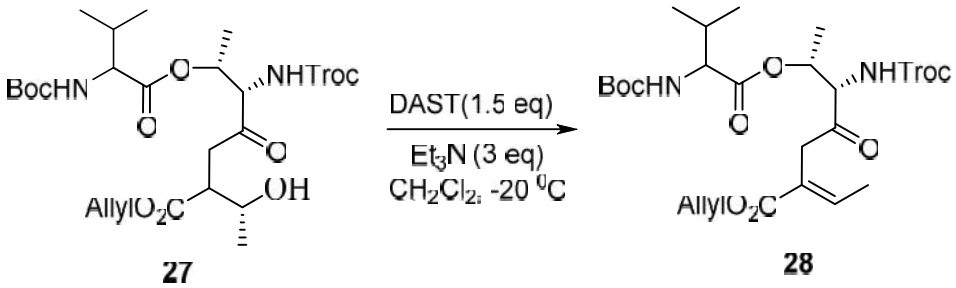
In the presence of pyridine, diethylamino sulphur trifluoride (DAST) is an effective technique for preparing-dehydroamino acids from protected α-hydroxy-amino acids. Somekh et al. (1983) reported the stereospecific one-pot synthesis of multiple (Z)-N-(benzyloxycarbonyl)-2,3-dehydro-2-aminobutyric acid ester derivatives **26** from various N-(benzyloxycarbonyl)threonine benzyl ester derivatives **25** (Scheme 8).



Scheme-8: Formation of α,β-dehydroamino acid derivatives using DAST.

Inspection of the NMR spectra revealed the exclusive formation of (Z) isomer from the *threo*-β-hydroxy α-amino acid derivative and of the corresponding (E) isomer from the *erythro*-hydroxy precursor.

Yokokawa et al. (2002) reported the stereo-specific dehydrative elimination of the N-acyl threonine ester **27** to the corresponding olefin **28** using DAST and Et_3N as a base in 51% yield (Scheme 9).

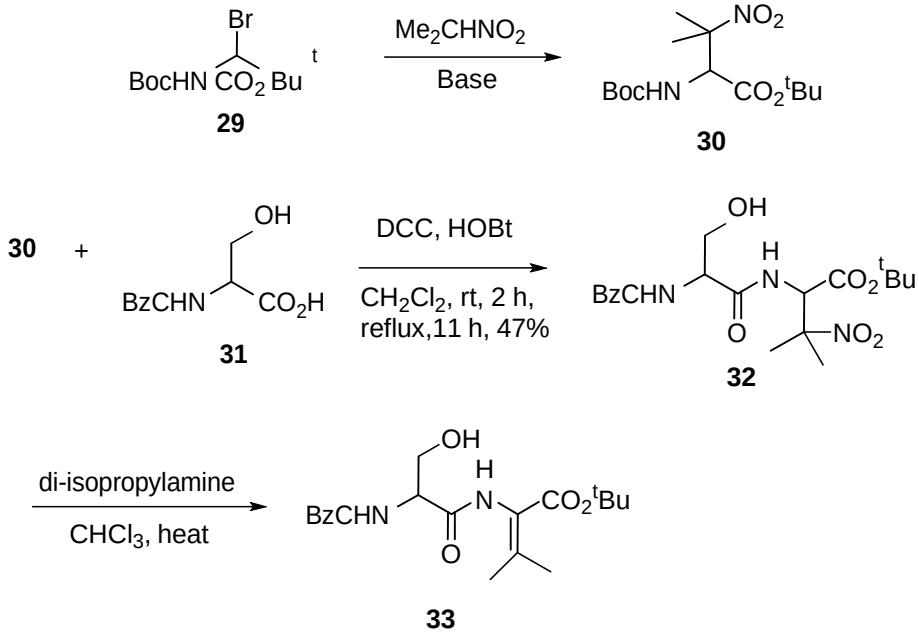


Scheme-9: Stereospecific dehydrative elimination of N-acyl threonine ester

Although some of these -hydroxy -amino acids can be acquired by synthesis, this method's applicability is limited because of the inaccessibility of β-hydroxy- α-amino acids other than serine and threonine that are readily available.

Nitration and elimination method:

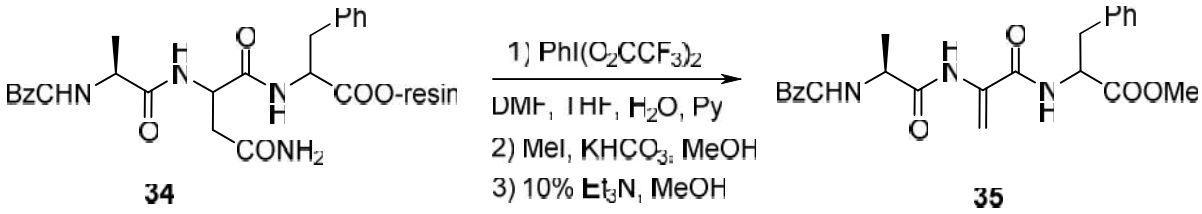
This is a complementary method for the synthesis of α, β dehydroamino acid derivatives containing peptides from β-nitro amino acid and peptide derivatives, which is readily accessible through the reaction of α-bromo glycine derivative with alkyl nitronates. Base treatment of the corresponding β-nitro amino acid and peptides derivatives afforded the desired α, β dehydropeptide. Coghlan et al. (1994) reported the seryl-α,β-dehydrovaline derivative **33** starting from α-bromo glycine derivative **29** following this methodology (Scheme 10).



Scheme-10: **Elimination of β-nitro amino acid derivatives.**

Hoffmann type degradation and elimination method:

There are few reports of dehydroamino acid and peptide derivative synthesis on the solid support. Hoffmann type degradation reaction using TIB [bis(trifluoroacetoxy)iodobenzene] followed by Hoffmann type elimination reaction is a versatile technique. Blettner et al. (1994) reported the synthesis of dehydroalanine containing tripeptides and pentapeptides following this method (Scheme 11).



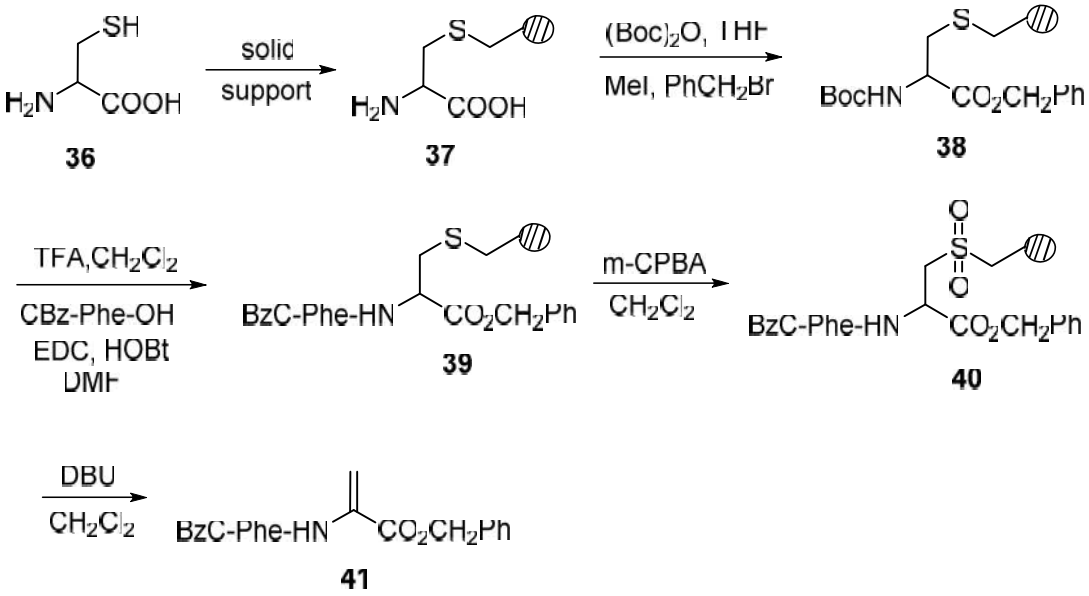
Scheme-11: Formation of dehydroalanine containing tripeptides and pentapeptides.

The precursor peptides were prepared to begin on Merrifield resin, and the application of TIB on a resin-linked peptide created side-chain primary amine from either aspergine or glutamine. This allowed for a single pathway into the synthesis of branched peptides.

Sulfone method:

Conversion of sulphur-containing amino acid into sulphone, which is the desired leaving group for β-elimination, is also an excellent method for synthesising dehydroamino acid and dehydropeptide derivatives on the solid support.

Yamada et al. (1998) reported the solid-phase synthesis of dehydroalanine derivatives starting from commercially available cysteine. Thus, cysteine (**36**) was attached to the Merrifield resin to afford the polymer-bound cysteine **37**. After Boc-protection of the amine functionality, followed by esterification provided, the double protected cysteine derivative **38** is attached to the resin. Subsequent cleavage of the Boc-group and coupling with desired amino acid residue produced the peptide precursor **39**. Oxidation of the sulphide **39** to sulphone **40** and β-elimination in the presence of DBU afforded the desired dehydropeptide **41**(Scheme 12).



Scheme-12: Solid phase synthesis of dehydroalanine derivatives.

Conclusion

In conclusion, most didehydroamino acid derivatives are found in nature, generally as secondary metabolites of bacteria and fungi or other lower organisms. These didehydroamino acid derivatives are biologically active and show important pharmaceutical and medicinal properties, such as the β-lactam antibiotics of the cephalosporin group, the herbicidal tetrapeptide tentoxin, or the antitumor agent azinomycin A (carzinophilin). These natural products may also be prepared in the laboratory by different elimination methods for easy availability in the market.

Acknowledgments

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