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ONE POT AMIDE/ PEPTIDE SYNTHESIS *VIA* TWO REDOX REACTIONS

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Abstract: A new and highly efficient one-pot self-regulated approach to amide/ peptide synthesis has been developed based on two redox reactions using azide as a latent amine component. For the first time, selenophenol, generated *in situ* has been found to be an effective reducing agent for the conversion of azides to amines.

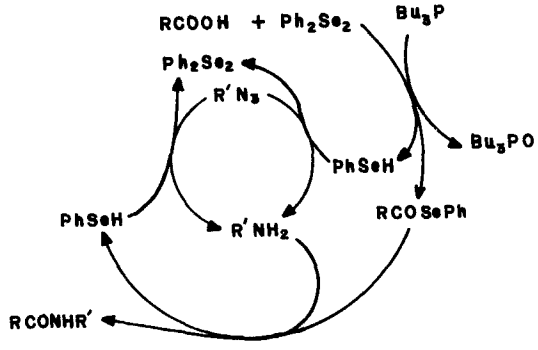
Amino acids have been used in the synthesis of peptides and proteins[1] since the inception of protein chemistry. However, the preparation of peptides containing unnatural amino acids is restricted due to their non-availability. The azido group is known[2] to be a latent functionality for primary amines. The reduction of azido acids has proven to be an extremely attractive approach to the synthesis of proteinogenic as well as non-proteinogenic amino acids which have subsequently been used for the synthesis of biologically active peptides and their analogues[3]. The difficulty associated with this strategy lies in the preparation of amino acids from azides and subsequent condensation, resulting in a two-step process which involves difficulties associated with azide reduction and characteristic side reactions[4] of amino acid/ peptide derivatives. Therefore, it remains a challenge to devise methods that lead to amide bond formation by the direct use of azido compounds.

Roberts[5] and Garcia[6] have independently reported a solution to the above problem by using phosphine during the condensation of carboxylic acids and azides. This reaction proceeds *via* iminophosphorane intermediates which on subsequent condensation with carboxylic acids provide amides as the product. The major drawbacks in their approach are: (i) the use of nonpolar solvent *viz* toluene which works well as a general reaction but is not suitable for peptide synthesis in particular and (ii) loss of chiral integrity of hindered amino acids like valine.

In search for alternative approaches, we envisaged a reduction of azide to the corresponding amine *in situ* and in the presence of a preformed activated carboxyl component. Simple approaches to achieve this goal are not so far known and so also the merits of this strategy have not been explored. It is imperative to develop such a strategy since both the enantiomeric azido acids can be prepared[3,7] readily in high optical purity.

Our recent work[8] on the one-pot self-regulated peptide synthesis via selenophenyl ester has shown that addition of N-methylmorpholine N-oxide oxidised the by-product selenophenol, thus resulting in regeneration of diselenide and reduced itself to N-methylmorpholine. This suggests that selenophenol may be a mild effective reducing agent for the reduction of azides which was hitherto unknown and has not been explored at all in the synthesis of amides/ peptides. We, therefore, felt that addition of azides to the reaction pot containing a selenophenyl ester and selenophenol may fulfill both the purposes viz oxidation of the amine poisoning selenophenol to diselenide with synchronous generation of amine from azide. This communication describes yet another one-pot approach to the synthesis of peptides wherein azides have been reduced in situ to amines by selenophenol was hitherto unknown.

Treatment of a mixture of an N-protected amino acid or peptide carboxylic acid (RCOOH) and Ph_2Se_2 with Bu_3P at room temperature generates the selenophenyl ester (RCOSePh) and selenophenol (PhSeH). Addition of an azide/ azido acid ester ($R'N_3$) oxidises the selenophenol to diphenyl diselenide, which in turn gets reduced to the amine ($R'NH_2$). This on subsequent condensation with active selenophenyl ester gives the desired amide/ peptide and a molecule of selenophenol. Selenophenol, thus generated again reacts with the azide ($R'N_3$) and the above sequence of reactions get repeated (**Scheme 1**) thus constituting a self-regulated one-pot peptide synthesis as a result of two redox reactions.

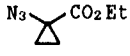
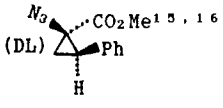


Scheme 1

Several examples of amide/ peptides are shown in **Table 1** that demonstrates the utility of this reaction. Young's peptide[9] (Bz-Leu-Gly-OEt) has been synthesized in different solvent systems and product is >96% optically pure in all cases. Benzoyl and acetyl protected peptides viz Bz-Phe-Ala-OEt, Bz-Val-Ala-OEt and Ac-Phe-Ala-OEt have been

synthesized and no trace of the other diastereomeric product was detected by high field ^{1}H-NMR[10]. Anderson's peptide[11] (Z-Gly-Phe-Gly-OEt) was also synthesized with complete retention of chirality. Peptides, containing uncommon amino acids such as 1-amino-cyclopropanecarboxylic acid (ACC)[12] have been synthesized. A dramatic improvement of yields for this type of hindered amino acids was observed when 1-hydroxy-benzotriazole[13] was used as catalyst. The high optical purity of the products can be explained on the basis that this method is totally free from use of any tertiary amine or formation of any ammonium salts[14] and even the generation of the amine component is controlled by the self-regulated reaction itself.

Table 1: List of Peptides[!]

Entry	Carboxyl component	Azido component	Amide/ Peptide	Solvent	Yield %	m.p. °C	$[\alpha]_D^{25}$ (c)
1.	Z-DL-Phe	$N_3(CH_2)_6-CH_3$	Z-DL-Phe-NH-$(CH_2)_6-CH_3$	CH_2Cl_2	80	118	-
2.	Bz-Leu	$N_3CH_2CO_2Et$	Bz-Leu-Gly-OEt	,,	93	154-5	-33.4 (3.0)
3.	,,	,,	,,	MeCN	85	154	-32.8 (3.0)
4.	,,	,,	,,	DMF	79	154-5	-33.0 (3.0)
5.	Z-Gly-Phe	,,	Z-Gly-Phe-Gly-OEt	CH_2Cl_2	91	118-9	-13.1 (2.0)
6.	Bz-Phe	(L)$N_3CH(CH_3)CO_2Et$[7d]	Bz-Phe-Ala-OEt	,,	82	150-1	-45.5 (1.0)
7.	Bz-Val	,,	Bz-Val-Ala-OEt	,,	84	158	-43.9 (0.9)
8.	Ac-Phe	,,	Ac-Phe-Ala-OEt	,,	80	152-4	-10.8 (1.0)
9.	Z-Val		Z-Val-Acc-OEt	CH_2Cl_2-DMF	24 (65)	185	-14.8 (1.4)
10.	Z-Gly	,,	Z-Gly-Acc-OEt	,,	47 (72)	105	-
11.	,,		Z-Gly-DL-$_V$[2]Phe-OMe	,,	(50)	liq.	-

[!] All amino acids used are of L configuration, otherwise mentioned. Optical rotations are taken in ethanol as solvent. Yields given in parentheses corresponding to use of 1-hydroxybenzotriazole (0.2eq.) as catalyst. All products are characterized by high field ^{1}H & ^{13}C-NMR, IR, MS and C H N analysis.

In conclusion, this approach offers a new, highly efficient method for amide/ peptide synthesis in high optical purity. For the first time, selephenol has been found to be an efffective reducing agent for azides to amines. Amides/ peptides which are otherwise difficult to prepare can be easily synthesized. The other advantages as reprted[8] earlier hold true with this new method also.

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