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New Family of Peptidomimetics Based on the Imidazole Motif

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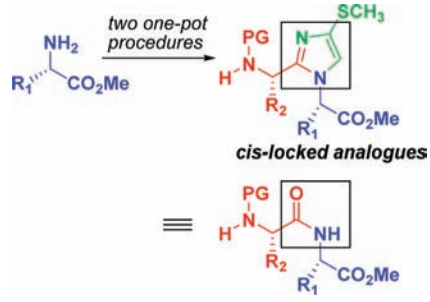
ABSTRACT



Starting from amino acid esters, new peptidomimetics based on the imidazole scaffold were prepared. An efficient and rapid sequence consisting of two subsequent one-pot procedures was developed and applied to various aminoacids. As they provide more substitution patterns, these heterocyclic mimics are promising tools for structural and biological studies.

Peptide−protein or protein−protein interactions play a vital role in biochemistry, and their understanding is often the key to the design of new bioactive compounds. Owing to great advances in molecular modeling, X-ray structural analysis, and NMR techniques, the secondary and/or tertiary structures of peptidic scaffolds increasingly have been elucidated. However, due to the ubiquitous presence of peptidases, most bioactive peptides cannot be administered as drugs, since their rapid degradation or low biodisponibility prevent them from reaching their targets. Over the years, many groups have focused on the synthesis of constrained peptidomimetics for the better understanding of bioactive conformations or enhanced metabolic stabilities. More recently, the efforts have focused on the cis and trans conformations in natural peptides, especially those bearing proline, pipecolic acid, or *N*-methylated amino acids. It is now well established that a wide panel of heterocyclic synthons, such as bicyclic analogues,[1] or the simple replacement of the scissile peptide bond by a five-membered ring heterocycle could lead to interesting mimics.

In particular, aza heterocycles such as tetrazoles,[2] 1,2,4-triazole,s[3] and more often 1,2,3-triazoles were synthesized. Early work in this area had focused on the use of 1,4-substituted triazoles,[4] which were obtained by Cu^{I}-mediated Huisgen reaction,[5] but recent developments of this reaction allowed a reversed regioselectivity owing to the use of ruthenium catalysts.[6] Recently, elegant ligation strategies, in which a cis-peptide bond analogue is replaced by a 1,5-disubstituted triazole, were described.[7]

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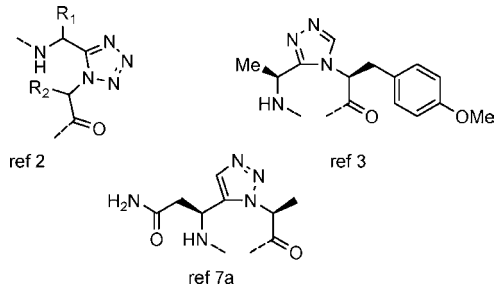


Figure 1. Examples of aza-heterocyclic mimics of the amide bond.

The global aim of this work was the synthesis of 1,5-disubstituted imidazole-based peptidomimetics. The choice of this heterocycle was suggested by a close resemblance with the amide bond, of greater diversity than afforded with triazoles. In addition, as our synthetic route uses mercaptoimidazole intermediates, the presence of the sulfur atom can lead to functionalized side-chains or modulate the basicity of the imidazole by oxidizing a thioether to a sulfone. Furthermore, imidazole being a naturally occurring 5-members heterocycle, its pharmacological implications may be better understood than those of other heterocycles.

In a previous work,[8] we had studied the replacement of the carboxyl group of amino acids by an imidazole, as well as the incorporation of the nitrogen atom of the amino group itself in the heterocycle. The C-terminus replacement by imidazoles[9] or imidazolines[10] has also been studied by other groups who proposed various efficient synthetic pathways, such as palladium cyclization of amidoximes,[9b] thio-Ugi reaction,[9c] or using azavinyl azomethine ylides as precursors.[9d]

Our retrosynthetic approach is summarized in Figure 2, the key intermediate being the dipeptide bearing a thiocarboxamide, which will be condensed with the peptidic bond itself. Contrary to our preliminary observations for synthons incorporating a single amino acid, the very strong deactivating effect of the *N*-cyanomethyl group made the initial coupling step almost impossible for dipeptidic synthons, with classical coupling reagents such as EDCI, HATU, HBTU, BOP.

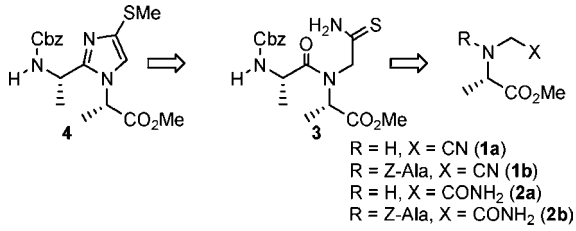
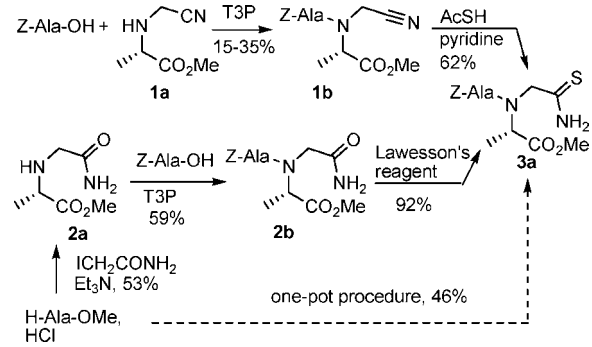


Figure 2. Retrosynthetic pathway.

As shown in Scheme 1, we could overcome this difficulty by using a carboxamide instead of a nitrile as the thioamide precursor. The best results for the coupling step were obtained with propanephosphonic anhydride T3P. Starting from H-Ala-OMe hydrochloride, the amino group was alkylated with iodoacetamide in 53% yield, followed by coupling with Cbz-Ala in 59% yield. Hydrophobic aminoacids such as phenylalanine gave better results, due to their easier extraction. Subsequent treatment of these compounds with Lawesson's reagent cleanly led to selective thionation of the primary amide[10] versus the peptidic bond, for instance a 92% yield was obtained on the Ala-Ala model substrate. To make this synthetic route shorter, we tested a one-pot procedure, in which iodoacetamide and DIEA were added to the aminoester, followed by *N*-protected aminoacid and T3P, and finally Lawesson's reagent. Better yields were obtained using this procedure, and only the final thioamides **3a**−**h** listed in Table 1 required purification to discard the Lawesson's reagent byproduct.

Scheme 1. Aminoacetonitrile/Aminoacetamide Pathways



We also observed that the carboxamide **2b** could also be readily dehydrated via treatment with trifluoroacetic anhydride,[11] affording the nitrile **1b** in 86% yield. Thioamides in this series can also lead to the corresponding nitriles upon treatment with DCC.

The formation of the imidazole ring being a crucial step of the synthesis, we thoroughly optimized it for these substrates. This reaction was first described by Hopkins[12] for the synthesis of mercaptoimidazoles bearing alkyl substituents. Our preliminary findings had shown that trapping the transient thiol with CH_3I or Boc_2O was required to both increase the yields and facilitate the isolation of the products.

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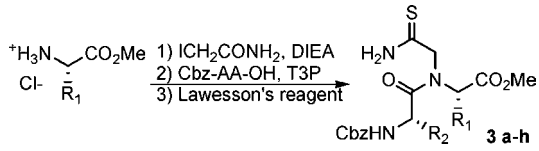
Table 1. One-Pot Procedure for the Preparation of Thioamide-Bearing Dipeptides

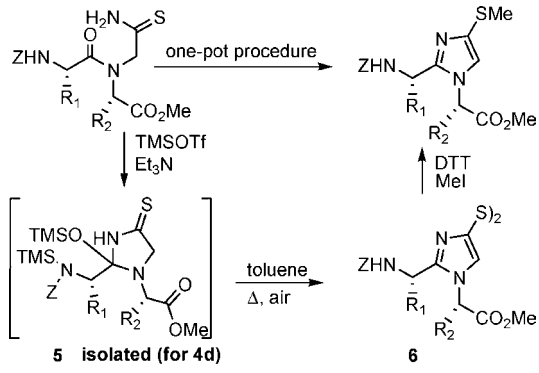


entry	dipeptide	compd nr	yield %
1	Z-Ala-Ala-OMe	**3a**	46
2	Z-Tyr(OBzl)-Ala-OMe	**3b**	77
3	Z-Asp(OBzl)-Phe-OEt	**3c**	42
4	Z-Ala-Lys(Z)-OBn	**3d**	36
5	Z-Pro-Phe-OMe	**3e**	47
6	Z-Phg-Phe-OMe	**3f**	63
7	Z-Pro-Leu-OMe	**3g**	41
8	Fmoc-Ile-Ala-OMe	**3h**	33

However, the presence of the second aminoacid significantly reduced the reactivity and therefore we had to modify the procedure. We used compound **3a** (Ala-Ala derivative) as a model for this study. First attempts with *N*-Boc and *t*-butyl ester protecting groups leading to TMSOTf-promoted deprotection, *N*-Cbz and *N*-Fmoc amino acid methyl esters, were employed. Mechanistic considerations initially suggested that a *S*-TMS intermediate could be first obtained once the cyclization achieved, requiring a *S*-desilylation step before trapping with the electrophile. Thus, following the reaction with TMSOTf, desilylation could be achieved by treatment with methanol; however, TBAF gave lower yields.

This reaction was even less efficient with more hindered dipeptides, leading to a product of very low polarity. Identification of this compound by means of various NMR experiments revealed a structure corresponding to the bis-TMS intermediate **5**, (Scheme 2) obtained in 47% yield after

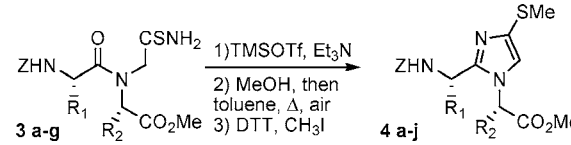
Scheme 2. One-Pot Procedure via a Silylated Intermediate



chromatography through silica gel. The latter could be expected according to the mechanism, that is, selective *O*-silylation with TMSOTf then addition of the nitrogen atom of the thioamide. Monitoring the reaction led us to observe that this first step occurs in a few minutes at −78 °C, with a nearly quantitative conversion. However, the subsequent elimination of TMSOH appears to be a very slow step, especially with aminoacids bearing bulky side-chains. This process does not necessarily require a base, since it can be accomplished either by heating in toluene for 1 h, or by simply keeping the neat compound at room temperature over a 24 h period of time. In both cases, the disulfide was recovered. This implies a final air-induced oxidation step which necessitates a stoichiometric amount of oxygen.

All of these observations led us to propose an experimental one-pot procedure that consisted of a rapid silylation by TMSOTf, followed by methanolysis of excess reagent, then heating in toluene under an air atmosphere, reduction of the disulfide **6** with DTT, and alkylation with CH_3I. Under those conditions, good yields were obtained, even for more hindered aminoacids. The results are listed in Table 2.

Table 2. Formation of the Imidazole Peptidomimetics



entry	compd nr	dipeptide analogue	yield %
1	**4a**	Z-Ala-Ala-OMe	62
2	**4b**	Z-Ala-Ala-OMe[a]	75
3	**4c**	Z-Ala-Ala-OMe[b]	68
4	**4d**	Z-Tyr(OBzl)-Ala-OMe	61
5	**4e**	Z-Asp(OBzl)-Phe-OMe	65
6	**4f**	Z-Ala-Lys(Z)-OMe	72
7	**4g**	Z-Pro-Phe-OMe	47
8	**4h**	Z-Phg-Phe-OMe	61
9	**4i**	Z-Pro-Leu-OMe	41
10	**4j**	Fmoc-Ile-Ala-OMe	28

[a] Trapping the thiol with Boc_2O. [b] Trapping the thiol with t-butyl acrylate.

Several dipeptides were tested for this reaction. Amino acids bearing unfunctionalized side-chains such as Ala, Phe, and Ile gave good yields of imidazoles. Other amino acids having functional groups on the side-chain, such as Asp or Lys, also gave good yields.

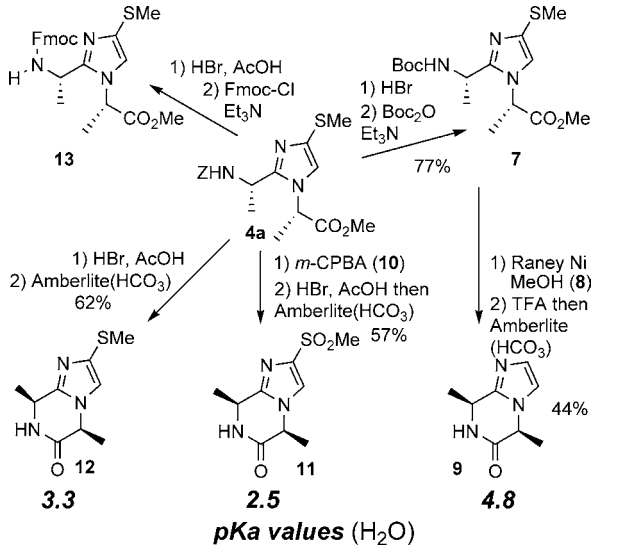
Interestingly, the aspartic derivative, rather prone to racemization, showed a good retention of the chiral center. However, the much more sensitive amino acid phenylglycine led to complete epimerization, and the same mixture of diastereomers was obtained, whatever the configuration of the starting phenylglycine. Therefore, our method appears suitable for classical amino acids but, not surprisingly, phenylglycine derivatives epimerized under heating in toluene.

As shown in entries 2 and 3, trapping the thiol with different electrophiles such as *t*-butyl acrylate or Boc_2O gave the resulting *S*-Boc and $S(CH_2)_2COOtBu$ imidazoles in good yields. This can be of particular interest, since compound **4c** could be further deprotected to afford the *S*-carboxyethyl

group that can be used either as an anchoring moiety, or as a water-soluble substituent.

Another significant feature concerning those peptidomimetics relies on their low basicity, compared to *N*-alkyl imidazoles. In fact, these new mimics of the amide bond should not be protonated at neutral pH. To confirm this hypothesis, we prepared water-soluble diketopiperazines[13] derived from Ala-Ala analogue, following the synthesis described in Scheme 3.

Scheme 3. Protective Group Modifications and Diketopiperazine Formation



As the *N*-Cbz group was likely to react with Raney nickel, we first replaced this protecting group before carrying out the desulfurization. We also oxidized the *S*-Me group to the corresponding sulfone. Upon *N*-deprotection and treatment with hydrogenocarbonate-loaded Amberlite resin, the cyclization was almost instantaneous and afforded clean diketopiperazines.

The pKas of the three diketopiperazines bearing the imidazole ring were measured by titration with NaOH from their hydrochloride salts. *N*-methyl imidazole was used as a reference, a pK_a of 6.90 was found (lit. 6.95).[14] As expected, the unsubstituted imidazole **9** was the most basic, exhibiting a 4.8 value. Interestingly, the electron-withdrawing effect of the amide group accounts for a loss of basicity by 2 orders of magnitude. The presence of the *S*-methyl group in **12** further lowered the pK_a to 3.3 and, as expected, the sulfone **11** gave the lowest basicity with a pK_a value of 2.5.

In conclusion, we developed an efficient protocol for the preparation of peptidomimetics mimicking the cis-locked rotamers of peptides in good and reproducible yields, in very few steps. Those analogues show promising further developments due to their possibility of bearing various substituents, especially the methylsulfonyl group which accounts for a dramatic decrease of the basicity. Further biological evaluations of these compounds are currently in progress.

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Supporting Information Available: Analytical data, copies of NMR spectra, and experimental preparations of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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