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Peptide synthesis in room temperature ionic liquids

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Abstract—We demonstrate that chemical peptide coupling using modern coupling agents is efficient in rt ionic liquids. This new approach presents some advantages, especially in the case of hindered amino acids, which are not easy to couple under standard conditions, since high purities for the crude peptides were observed with respect to coupling in classical solvents.

The unique properties of room temperature ionic liquids (RTIL's) present many advantages in the context of green chemistry.[1] As part of our program focusing on chemistry in ionic liquids,[2] including asymmetric synthesis and chirality studies,[3] we describe herein preliminary results on peptide synthesis. As outlined in recent reviews,[1] a number of classical organic reactions have been examined with success in these new media. To the best of our knowledge (and rather curiously with regard to the importance of this topic) no report describes chemical peptide synthesis in ionic liquids; only a study from Erbeldinger et al. was devoted to enzymatic access to (*Z*)-aspartame.[4] We decided to embark on this approach by considering 'modern' coupling agents such as HATU and BOP as reagents of choice for this chemistry in ionic liquids, since they present structural similarities with neoteric solvents, such as [bmim]PF_6 (Fig. 1). Thus we expected these coupling agents to be easily dissolved in ionic liquids, and sufficiently stabilized by the solvent to give slow and selective reactions.

As a first approach, we chose to examine the coupling of nonproteinogenic quaternary α-amino acids, which are known to be more difficult to couple than their tertiary congeners.[5] The coupling reactions were also carried out in the usual solvents, showing the necessity of using charged coupling agents for efficient reaction. The

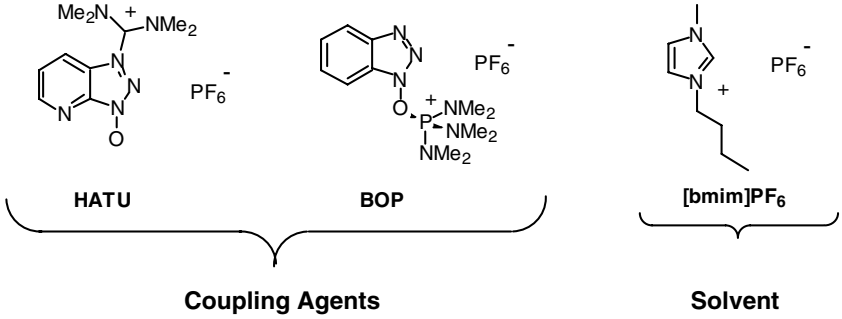

Figure 1. Comparison of the structures of coupling agents and the ionic liquid.

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structures of amino acids studied are presented in Figure 2.

All the amino acids studied are commercially available except for MPG, which was prepared according to a literature procedure.[6] The usual *Z* and Boc protecting groups were used in the first set of experiments. The carboxyl function of the second amino acid was protected as its methyl ester (Scheme 1).

The main results for different coupling reactions are given in Table 1, along with a comparison with analogous reactions carried out in classical solvents (dichloromethane or THF).

Interestingly, fair conversions were observed under both sets of conditions. The reactions in the ionic liquid seem generally more tedious than those in a classical solvent, an observation, which can be explained by the expected stabilization of the charged species in the ionic solvent. On the other hand, a real advantage, which was observed in this set of experiments was the higher purity of the crude product when the reaction was performed in an ionic liquid with respect to reactions in dichloromethane or THF. This could be explained by a more selective chemical pathway due to the stabilization effect of the ionic liquid as the coupling reagents. Indeed, we observed that extraction of the peptide from the ionic solvent was not easy, and thus assumed that the modest yields observed were mostly due to this extraction step. We therefore decided to examine procedures other than 'manual' diethyl ether extraction (Table 2).

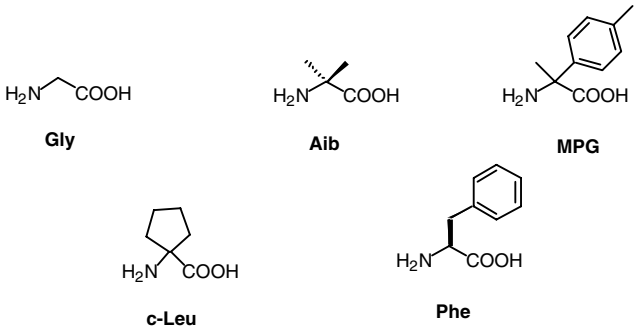
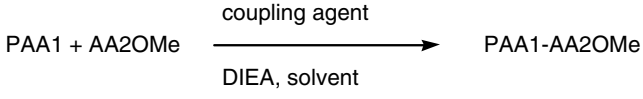


Figure 2. Structures of the amino acids studied (Gly = glycine, Aib = aminoisobutyric acid, MPG = 2-methyl-2-(*p*-tolyl)-glycine, c-Leu = cycloleucine, Phe = phenylalanine).



Scheme 1. Synthesis of dipeptides in ionic liquids.

According to our hypothesis, we were delighted to obtain substantially better results using toluene as the extraction solvent, as well as when using a liquid–liquid extractor for an overnight continuous extraction. These rather good yields, along with the excellent purity of the crude products encouraged us to consider ionic liquids as interesting solvents for peptide coupling. With this procedure in hand, we carried out a second set of couplings, which are summarized in Table 3. Warming the reaction mixture up to 65 °C accelerated the coupling.

In addition, we carried out the synthesis of a tetrapeptide under the same conditions in 83% overall yield (Scheme 2).

In this study, we have demonstrated that 'chemical' peptide coupling using 'modern' coupling agents is efficient in ionic liquids. Even if numerous controls and optimizations remain to be done, this new approach could be powerful, especially for hindered amino acids, which are not easy to couple under standard conditions. Interestingly, the crude peptides were obtained with higher purities than those from coupling in classical solvents. Our ongoing studies focus on the possibility of coupling the salts of the parent amino acids directly, since these salts can be solubilized into ionic liquids. If

Table 1. First set of peptide couplings in ionic liquids (extraction with diethyl ether)

Dipeptide formed	Coupling agent[a]	*T* (°C)	Time (d)	Yield in [bmim]PF_6 (%)	Yield in CH_2Cl_2 (%)
*Z*Gly-MPGOMe	HATU	rt	1.5	66	93
*Z*Gly-MPGOMe	BOP	rt	4	62	67
BocMPG-GlyOMe	HATU	rt	1.5	60	92
BocMPG-GlyOMe	BOP	rt	1.5	82	66
BocMPG-MPGOMe	HATU	50	8	43	43[b]
BocAib-MPGOMe	HATU	rt	4	52	59[b]
BocMPG-AibOMe	HATU	rt	4	49	58

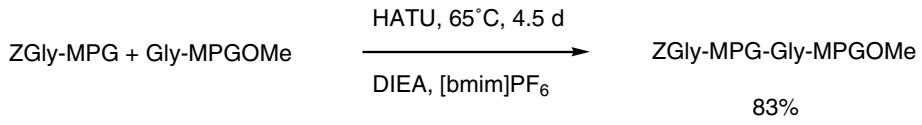
[a] Experiments without any coupling agent, or using DCC led to no conversion.
[b] Experiment carried out in THF.

Table 2. Role of the extraction procedure

Dipeptide formed	Coupling agent	*T* (°C)	Time (d)	Yield in [bmim]PF_6 (%)	Extraction
*Z*Gly-MPGOMe	HATU	rt	4	66	Et_2O manual extraction
*Z*Gly-MPGOMe	HATU	rt	4	77	Toluene manual extraction
*Z*Gly-MPGOMe	HATU	rt	4	87	Et_2O liquid–liquid extraction

Table 3. Peptide synthesis under optimized conditions (Et_2O liquid–liquid continuous extraction)

Dipeptide formed	Coupling agent	*T* (°C)	Time (d)	Yield in [bmim]PF_6 (%)
*Z*Gly-GlyOMe	HATU	65	3	93
*Z*Gly-MPGOMe	HATU	65	3	Quantitative
*Z*Gly-cLeuOMe	HATU	65	3	93
BocAib-cLeuOMe	HATU	65	3	43
BocPhe-PheOMe	HATU	65	3	Quantitative
BocPhe-GlyOMe	HATU	65	3	96
BocPhe-cLeuOMe	HATU	65	3	Quantitative



Scheme 2. Synthesis of a tetrapeptide in an ionic liquid.

successful, this approach will avoid the necessity of the usual protection/deprotection procedures.[7]

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