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Toward waste-free peptide synthesis using ionic reagents and ionic liquids as solvents

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ABSTRACT

CBEIT **1**, an ionic coupling reagent, gives access to amino acid carbamates, and allows waste-free peptide coupling. The only by-products are carbon dioxide and ethylimidazolium triflate that is an ionic liquid playing the role of the solvent.

Owing to their unique properties, ionic liquids (ILs) nowadays are widely examined as eco-compatible solvents for organic chemistry.[1] In recent years, many modern applications have been reported, such as enantioselective,[2] catalytic,[3] or multicomponent reactions.[4]

Peptide synthesis remains a challenging area in organic synthesis, both for the wide applications of peptides in bioorganic and pharmaceutical fields, and for the rather sophisticated methods needed for the control of chain elongation, good efficiency, limitation of racemization, and applicability to unnatural aminoacids.[5] A shining series of excellent reviews has been published in recent years, disclosing the various issues in this area.[6]

Some years ago, we disclosed our first approach about peptide synthesis in ionic liquids, in which we described that these unconventional solvents were quite convenient for this process. Indeed, we observed high conversions even for the coupling of hindered amino acids, as well as purification simplified thanks to the rather pure crude material obtained.[7] Most of these results, along with other aspects of ionic liquids related to peptide chemistry, have recently been reviewed.[8] However our previous findings did not afford significant changes in the fundamental paradigm of peptide synthesis, and we remained convinced that ionic liquid chemistry may afford fundamentally new insights into the field.

Herein we wish to disclose our recent research, which deeply improves the previous results and opens the route for new developments in peptide coupling reactions: we are now combining the use of ionic coupling reagent with ionic solvents in a method in which the only by-products are carbon dioxide and ethylimidazolium triflate *that is an ionic liquid playing the role of the solvent!* In other words, this process, belonging to our current studies about synthesis in ionic liquid only (*SILO*),[9] can be considered as a *waste-free* peptide synthesis. Indeed, such an approach is of real interest in the context of sustainable chemistry, since classical peptide couplings require highly expensive protecting groups and coupling reagents.[5,6]

The basic idea of this new approach was inspired by results published by Rapoport group some years ago.[10] The authors described 1,1′-carbonylbis(3-methylimidazolium) triflate (CBMIT, Fig. 1) as an efficient reagent for aminoacylations, including

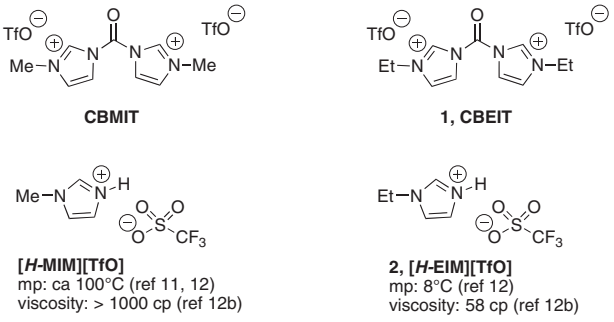

Figure 1. Ionic coupling reagents and their corresponding by-products.

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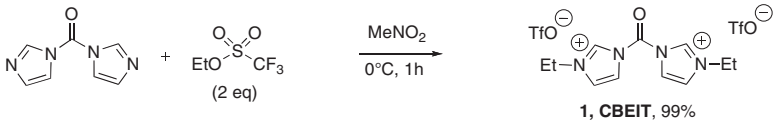
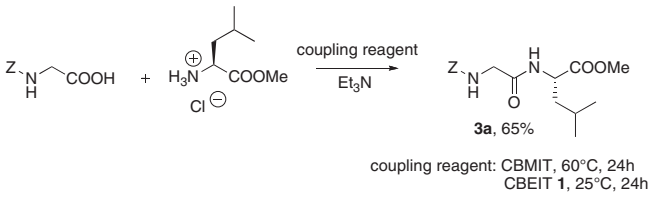


Scheme 1. Synthesis of CBEIT **1**.



Scheme 2. Model peptide couplings and comparison of CBMIT and CBEIT **1**.

peptide couplings. The resulting by-products were only carbon dioxide and methylimidazolium triflate ([*H*-MIM][TfO]).

Because of its high melting point and viscosity (see Fig. 1), [*H*-MIM][TfO] could not easily be considered as an ionic liquid acting as a potential solvent.[11] Thus, we searched for a congener that could be both liquid and fluid enough at low temperature. Literature data gave us access to numerous options,[12] among which we chose to examine the ethyl homolog. Indeed, the corresponding CBEIT **1** appeared easy to synthesize from commercially available materials; also, the resulting salt ([*H*-EIM][TfO]) **2** was reported to behave as a true ionic liquid with low melting point and acceptable viscosity (Fig. 1).

As expected, the synthesis of CBEIT **1** was realized by direct reaction of CDI with ethyl triflate, in quantitative yield and no need for further purification before its use as the coupling reagent (Scheme 1).

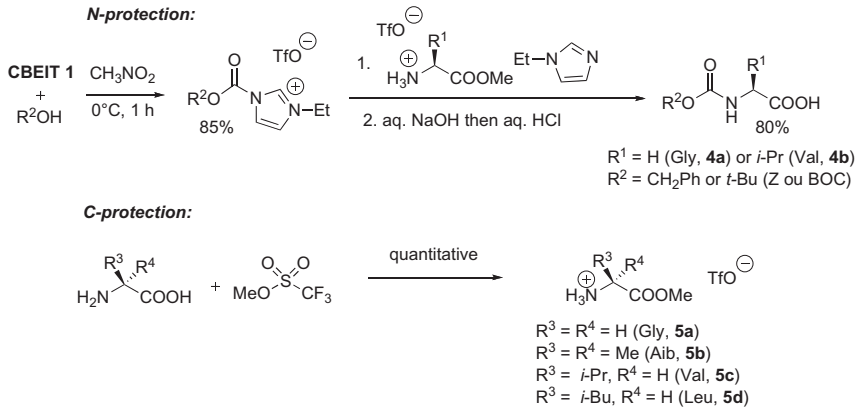
We then engaged both CBMIT and CBEIT **1** in the same model peptide coupling, *without any added solvent*, in order to compare their reactivity and to ensure that both could be efficient under solvent-free conditions (Scheme 2).

Although obtained in moderate yield,[13] the model peptide **3a** could be synthesized under these conditions using both coupling reagents. As anticipated, CBEIT **1** appeared to be of more friendly use since the liberated ionic liquid [*H*-EIM][TfO] **2** fluxed the reaction mixture, thus allowing working at rt.

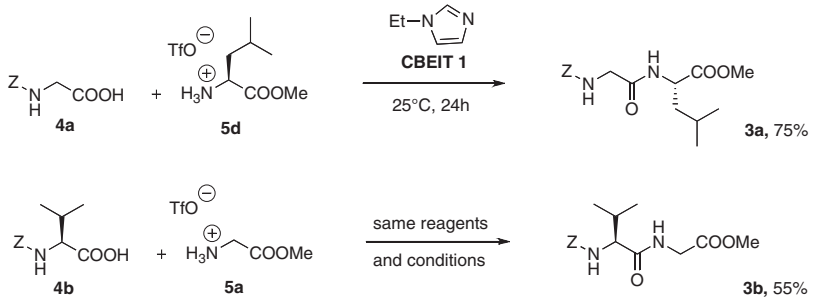
Encouraged by this first result, we decided to focus on a more general method in which all the partners (i.e. protected amino acids) would be prepared in a way that gives access to a full step peptide synthesis with only carbon dioxide and [*H*-EIM][TfO] **2** as by-products. As depicted in Scheme 3, a series of unprecedented methyl amino ester triflates **5** was directly obtained by alkylation of the starting amino acid with methyl triflate. As shown later (Scheme 4), we expected these salts to be liberated by means of ethyl imidazole acting as the base, thus liberating [*H*-EIM][TfO] **2** as well as the subsequent peptide coupling. CBEIT **1** was also reacted with benzyl alcohol and *t*-butanol, then with amino ester salts **5** to give the corresponding carbamates **4** in good yields (Scheme 3).

The last and most exciting step consisted in the coupling of both partners using CBEIT **1** as the coupling agent and ethyl imidazole as the base able to liberate the amino ester salt **5** (Scheme 4).

After optimization of experimental procedure (see Ref. 13), peptides **3** were obtained in yields as high as 75%. We engaged



Scheme 3. N- and C-protection of starting amino acids.



Scheme 4. 'Waste-free' peptide couplings.

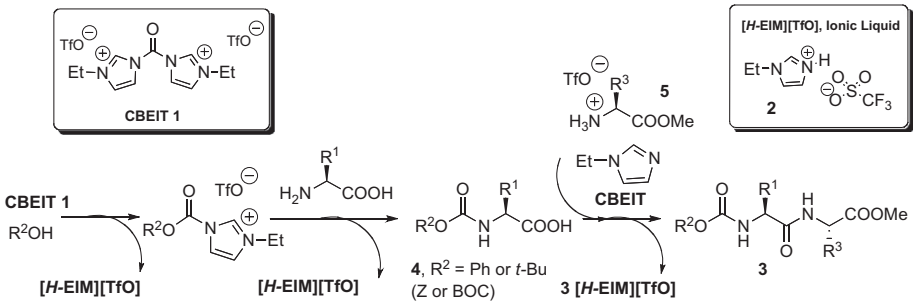


Figure 2. 'Waste-free' peptide synthesis.

enantiopure amino acids both in C- and N-terminal positions, and checked that no racemization occurred (as controlled by optical rotation and chiral HPLC, see Supplementary data). Of course, [*H*-EIM][TfO] **2** was recovered and purified by standard procedure (60–70% unoptimized yield): it can be used either as an ionic solvent for further applications or recycled as starting material for recovery of ethyl imidazole or CBEIT **1**.

In the following Figure 2 is summarized the full strategy for waste-free peptide coupling.

Finally, we show that ionic coupling reagents such as CBEIT **1** could be perfect tools for efficient and 'waste-free' peptide synthesis, since the only by-products are carbon dioxide and an ionic liquid that acts as the solvent. Not only the peptide coupling reaction itself is realized under such conditions, but also the required protections of the starting amino acids. Our current studies focus on the direct coupling of unprotected amino acids, which we expect to be possible thanks to the liberated ionic liquid able to dissolve amino acids.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.072.

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13. The moderate yield observed in the first set of experiments was due to the in situ formation of glycine anhydride. Although this intermediate was also coupled with leucine ester, yield was hampered because of the loss of one glycine unit during this process.