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Research project description

Ionic Liquid Coupling for Access to Macrocyclic Molecules of Biological Interest 2014-2016

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Brief summary of the project:

Many natural peptides have a macrocyclic structure comprising a diaryl isodityrosyne bond (two or three amino acids), and / or a Type biaryl bond of o,o'-biphenol involving tyrosine residues and / or hydroxyphenylglycine. Further interesting biological activities, these molecules also present synthetic difficulties due to the presence of these macrocycles tensioned cyclophane type, which makes them ideal synthetic target for DC coupling method of study (for obtaining the biaryl pattern), C-O (for obtaining the biarylether pattern) and peptide coupling, each of these three methods can be considered for the macrocyclization. If the strategy involving peptide coupling can give satisfactory results in the cyclophanes training to diaryl connection comprising three amino acids (cycles to 17-membered ring), it no longer works once the macrocycles are more tense, as in binding compounds biaryl (cycle 14 or 15-membered) or biarylether comprising two amino acids (15 membered ring). The closure of the macrocycle can then not be achieved only by a coupling reaction between the two aromatic rings of the linear peptide from preformed.
We will study the formation of these macrocycles in ionic liquid medium, both by peptide coupling (macrolactamisation) by coupling C-C or C-O. Indeed, ionic liquids are excellent solvents for both reactions metallocatalysed for peptide coupling reactions, especially in difficult cases such as for example with hindered amino acids. The high viscosity of the ionic liquid also can reduce the diffusivity of solutes, which should favor macrocyclization reactions. Moreover, in the context of the development of sustainable methods in chemistry, ionic liquids can facilitate the recycling of expensive catalysts and limit the use of volatile organic compounds. coupling reactions of C-H activation will be studied, which will prevent a pre-functionalization of the coupling partners.
Conditions developed on macrocycles models will then be applied to the synthesis of compound K-13, an inhibitor of angiotensin I converting enzyme inhibitor which contains a macrocycle isodityrosine tripeptide, and the synthesis of PR-66453, an isolated secondary metabolite of Actinomycetes a line 9738 which contains both a macrocycle and isodityrosine a macrocycle o,o'-biphenol.

Keywords: ionic liquid, Mukaiyama coupling, peptide coupling, coupling diaryl ether, Ullmann, Chan-Lam, catalysis with copper, Cyclopeptides, Tyrosine , C-H activation.

Results:

1) Jebri, K.; Mazières, M.-R., Ballereau, S., Ben Ayed, T., Plaquevent, J.-C., Baltas, M., Guillen, F**.,** ***Synthesis in Ionic Liquids Only: Access to α-Oxo-γ-Thio-Esters via Mukaiyama Coupling*** *Tetrahedron Letters, 2014, 55, 1353.*

2) Khouloud Jebri, Nicolas Galy, Viacheslav Zgonnik, Marie-Rose Mazières, Yves Génisson, Frédéric Guillen, Taïcir Ben Ayed, Michel Baltas, Jean-Christophe Plaquevent, ***Peptide Synthesis in Ionic Liquids (PEPSIL):*** *FRENCH-UKRAINIAN JOURNAL OF CHEMISTRY (2016, VOLUME 04, ISSUE 01)*