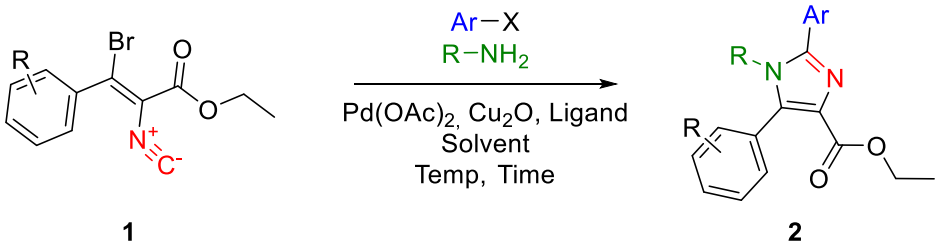
SYNTHESIS OF 1,2,4,5 TETRASUBSTITUTED 1*H-IMIDAZOLE VIA ARYLATIVE CYCLIZATION OF ISOCYANIDES*

<u>Briquet Antoine,</u> Laurent Bischoff, Christophe Hoarau.

Bât IRCOF N°40, rue Lucien Tesnière - 76130 MONT-SAINT-AIGNAN

Over decades, 1,2,4,5 tetrasubstituted 1*H*-imidazoles have been thoroughly studied. These molecules exhibit various biological activities[1] and were mostly prepared by means of condensation reactions[2]. Products of these reactions are limited in term of functionalization. In this work, we developed an original synthesis (figure 1) of a series of unprecedented tetrasubstituted imidazole **2** by means of arylative cyclization of isocyanides (figure 1). Bromo acrylate **1** was the key starting material, it could be prepared at the gram-scale in 3 high-yielding steps, from commercially available reagents.



1 **2**

Figure 1: Synthesis of 1,2,4,5 tetrasubstituted 1H-imidazole *via* arylative cyclization of isocyanides.

Following careful optimization of this synthesis, we are now able to build a wide range of new tetrasubstituted imidazole, *via* simultaneous functionalization at N1 and C2. In addition, our method is applicable to other substrates, encompassing different groups at the β-position of the starting acrylate. **To the best of our knowledge, this is the first reaction affording, in one step, a tetrasubstituted imidazole from ethyl 3-bromo-2-isocyano-3-arylacrylates**. Further explorations of these bromo acrylates for the synthesis of heterocycles having a high functional density is currently under progress in our laboratory.

<u>References</u>

1) (a) S. A. Laufer, W. Zimmermann, K. J. Ruff, *J. Med. Chem*. **2004**, 47, 6311–6325. (b) H. J. Seo, E.-J. Park, M. J. Kim, S. Y. Kang, S. H. Lee, H. J. Kim, K. N. Lee, M. E. Jung, M. W. Lee, M.-S. Kim, E.-J. Son, W.-K. Park, J. Kim, J. Lee, *J. Med.Chem.* **2011**, 54, 6305–6318.
2) (a) S. Kamijo, Y. Yamamoto, *Chem. Asian J.* **2007**, 2, 568–578 (b) M. M. Heravi, M. Daraic, V. Zadsirjan, *Mol. Diversity* **2015**, 19, 577–623