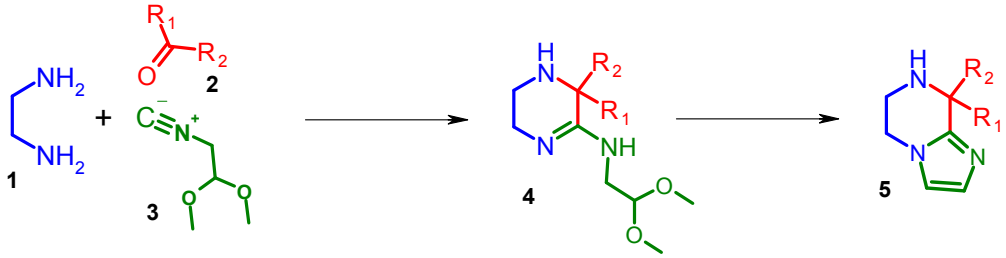
An Efficient Synthesis of Tetrahydroimidazo[1,2-a]pyrazines via Tandem Multicomponent Reaction

Volodymyr Kysil[1], Haiji Xia[1], Vasiliy Stolyarenko[2], Alan Tsavloev[2], Alexandre Ivachtchenko[1]

[1]ChemDiv, Inc., San Diego, CA, USA, [2]Chemical Diversity Research Institute, Khimki, Moscow Reg., Russia

Isocyanide based multicomponent reactions (IMCRs) followed by cyclization have become a valuable tools of drug discovery oriented synthetic heterocyclic chemistry since they allow synthesizing diverse nature-like heterocyclic small molecules in simple one-pot procedures. Recently we have developed IMCR of various primary diamines and carbonyl compounds that leads to a wide variety of heterocyclic scaffolds with pyrazine, quinaxoline, hetarenopyrazine, 1,4-diazepine, 1,4-benzodiazepine, and other pharmaceutically relevant cores [1].

Here we report post-condensation modification of the discovered IMCR by involving of dimethyl isocyanoacetal as a bifunctional isocyanide component. This enables further cyclization of intermediate pyrazine-2-amines **4** into target imidazopyrazines **5** under acidic conditions. Since no purification is required for intermediates 4, the entire synthesis can be performed in one-pot mode.



Notably, imidazopyrazine core of general formula **5** is a key structural feature of orexin receptor antagonists (2012), kappa receptor agonists, mGluR5 modulators, and TrkA inhibitors.

Scope of the developed tandem reaction including its expansion for the synthesis of spiro-imidazopyrazines and tetrahydroimidazo[1,2-a][1,4]diazepines as well as its application for small molecule libraries synthesis will be discussed.

[1] Kysil, V. et al. *Eur. J. Org. Chem.* **2010**, 1525–1543.