Synthesis of Substituted 2-Aminoimidazoles

Significance: Looper and co-workers described a three-step synthesis of highly substituted 2-aminoimidazoles. The first step consists of the preparation of propargyl cyanamides by copper(I)-catalyzed addition of an iminium generated from condensation of aldehydes ($R^2 = $ alkyl or aryl) with secondary amines. Without further purification, the resulting tertiary amines are subjected to a von Braun reaction. The use of 4-methoxybenzyl-, 2,4- and 3,4-dimethoxybenzyl-substituted propargyl amines lead to the propargyl cyanamides in good yields whereas symmetric $N,N$-dialkylpropargyl amines give exclusively propargyl bromide. Screening of catalysts led to the use of $\text{La(OTf)}_3$ for the final addition–hydroamination step. Both acyclic and cyclic secondary amines generated guanidine intermediates which underwent cyclization to the alkyne to afford 2-aminoimidazoles in good yields.

Comment: Several alkaloids containing the 2-aminoimidazole ring with interesting structures and biological properties have been isolated from marine sponges (S. M. Weinreb *Nat. Prod. Rep.* 2007, 24, 931). This scaffold improves physicochemical properties like lipophilicity, blood-brain barrier passage, cell permeability and bioavailability. Polysubstituted 2-aminoimidazole synthesis remains challenging as the current methods present some disadvantages: i) use of unstable precursors for the condensation of $\alpha$-amino/$\alpha$-haloketone with a cyanamide or a guanidine derivative respectively; ii) multi-step synthesis for the decoration of the imidazole scaffold. This three-step sequence represents a useful tool for the efficient synthesis of diversely substituted 2-aminoimidazoles from readily available starting materials.