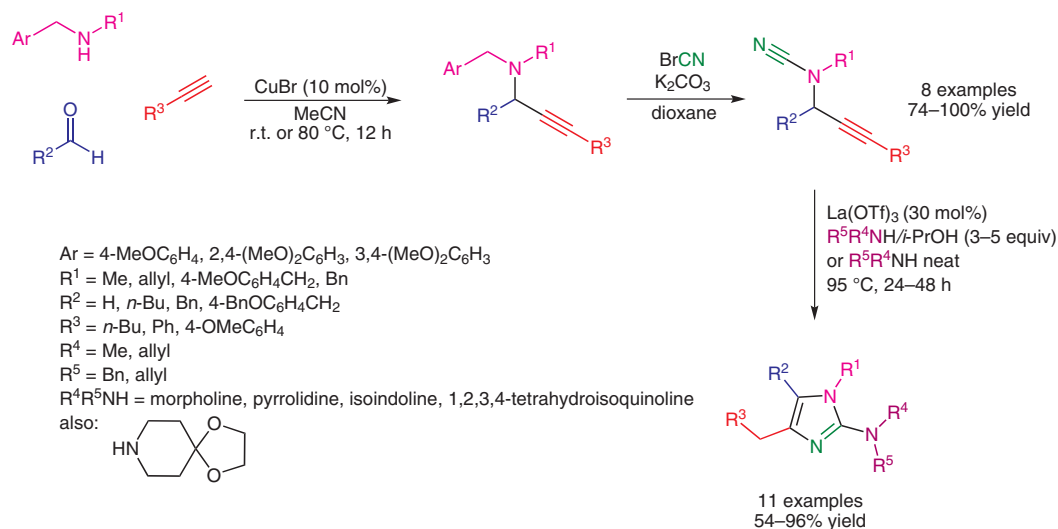


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Addition–Hydroamination Reactions of Propargyl Cyanamides: Rapid Access to Highly Substituted 2-Aminoimidazoles
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Synthesis of Substituted 2-Aminoimidazoles



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 $\text{La}(\text{OTf})_3$ 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 physico-chemical 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 α -amino/ α -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.

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Category

Synthesis of Heterocycles

Key words

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cyanamides
hydroamination
lanthanum(III)

SYNFACTS
of the month