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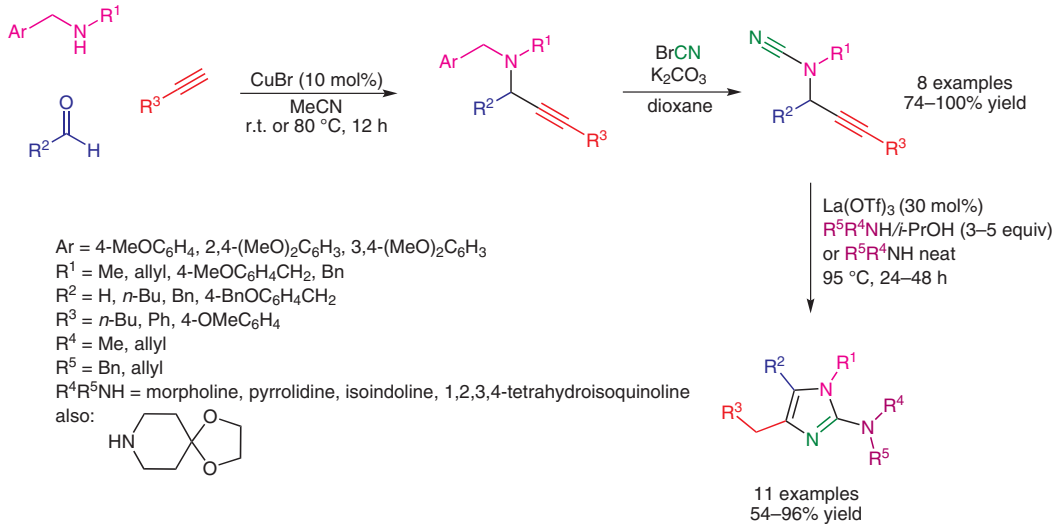
Synthesis of Substituted 2-Aminoimidazoles



Ar = 4-MeOC$_6$H$_4$, 2,4-(MeO)$_2$C$_6$H$_3$, 3,4-(MeO)$_2$C$_6$H$_3$
R^1 = Me, allyl, 4-MeOC$_6$H$_4$CH$_2$, Bn
R^2 = H, *n*-Bu, Bn, 4-BnOC$_6$H$_4$CH$_2$
R^3 = *n*-Bu, Ph, 4-OMeC$_6$H$_4$
R^4 = Me, allyl
R^5 = Bn, allyl
R^{4}R^{5}NH = morpholine, pyrrolidine, isoindoline, 1,2,3,4-tetrahydroisoquinoline
also:

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 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 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)