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


**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-dialkyl(propargyl)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.

**Scheme:**

1. CuBr (10 mol%) in MeCN r.t. or 80 °C, 12 h
2. BrCN in dioxane
   - 8 examples 74–100% yield
3. La(OTf)_3 (30 mol%) in R^5N=H/i-PrOH (3–5 equiv) or R^5NH neat
   - 95 °C, 24–48 h
   - 11 examples 54–96% yield

Ar = 4-MeOC_6H_4, 2,4-(MeO)_2C_6H_3, 3,4-(MeO)_2C_6H_3
R^1 = Me, allyl, 4-MeOC_6H_4CH_2, Bn
R^2 = H, n-Bu, Bn, 4-BnOC_6H_4CH_2
R^3 = n-Bu, Ph, 4-OMeC_6H_4
R^4 = Me, allyl
R^5 = Bn, allyl
R^5N=NH = morpholine, pyrrolidine, isoindoline, 1,2,3,4-tetrahydroisoquinoline

Also:

4-MeOC_6H_4CH_2
n-Bu
4-BnOC_6H_4CH_2
Bn
4-OMeC_6H_4
Me
allyl