New Facets of 2-Imidazoline Scaffold for Synthetic and Medicinal Chemistry

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Background

Lead-like chemistry space is scarcely populated. 2-Imidazoline core is privileged and is highly suitable for designing new lead-like libraries. Until 2012, Pd-Catalyzed N-arylation of 2-imidazolines was missing in the toolbox of synthetic methods. It significantly attenuates core’s basicity, permits wider range of appendage diversity. Judicial manipulation of the latter may also lead to novel lead-like scaffolds.

Imidazoline N-arylation\(^1,2\)

\[
\text{R-N} + \text{H}_{2}\text{NCH}_{2}\text{CH}_{2}\text{NH}_{2} \rightarrow \text{R-N-NH}_{2}
\]

NBS (1.1 equiv.)

\[
\text{H}_{2}\text{NCH}_{2}\text{CH}_{2}\text{NH}_{2}
\]

\[
\text{R-N} + \text{H}_{2}\text{NCH}_{2}\text{CH}_{2}\text{NH}_{2} \rightarrow \text{R-N-NH}_{2}
\]

56-96% 

(amine to parallel format under microwave irradiation)\(^3\)

Examples:

Metal-free intramolecular N-arylation\(^5\)

\[
\text{R-N} \rightarrow \text{R}\text{-}\text{N}=\text{N} \rightarrow \text{R-N}
\]

\[
\text{R-N} \rightarrow \text{R}\text{-}\text{N}=\text{N} \rightarrow \text{R-N}
\]

\[
\text{R-N} \rightarrow \text{R}\text{-}\text{N}=\text{N} \rightarrow \text{R-N}
\]

\[
\text{R-N} \rightarrow \text{R}\text{-}\text{N}=\text{N} \rightarrow \text{R-N}
\]

Lead-like space

MW

Polar-core COX-2 inhibitors\(^6\)

Novel kinase-inhibitory chemotype\(^7\)

New antitubercular lead\(^8\)

... all designed with 2-imidazoline N-arylation in mind.

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References


...constructed in 5 simple steps with 3 elements of diversity!