Versatile methods for promoting crystallinity in small molecules

Zhiwei Zhang, Emily R. Sherman, Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, United States

While the contemporary focus of organic research has shifted from synthesis of specific molecules to production of desirable properties, crystallinity of chemicals has attracted much attention, as it replaces solvent-intensive column chromatography with recrystallization, enables characterization via X-ray crystallography, and participates in asymmetric catalysis through diastereocovertrent crystallizations. Therefore, it would be promising to propose versatile methods for effectively promoting crystallinity of small, non-crystalline molecules. Herein we report two separate methods of promoting on-demand crystallinity:

Semicarbazones are a class of chemicals exhibiting crystallinity and stability under most reaction conditions, so a strategy of incorporating semicarbazone subunits to target molecules without affecting original reactivity would be desirable in enhancing product crystallinity. Therefore, by designing a cheap, two-step synthesis of alkynyl semicarbazones and attaching azido groups onto esters, we successfully connected semicarbazone subunits to a wide range of esters via copper-catalyzed azide-alkyne cycloadditions (CuAACs) and greatly enhanced the crystallinity of esters via melting point analysis.

For other small molecules being unable to perform CuAAC, another approach to enhancing crystallinity is to form co-crystallization complexes with large molecules. Therefore, we successfully designed three tetraaryladamantanes (TAAs), a class of compounds that have been reported as co-crystallization chaperones for various common chemical feedstocks.
References


