Versatile Methods for Promoting Crystallinity in Small Molecules

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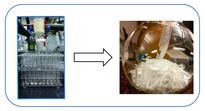
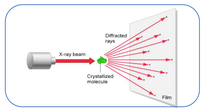
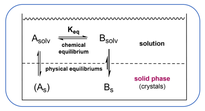
Background Information

Benefits of Crystallinity:

- ❖ Replaces chromatography with recrystallization
- ❖ Enables structural determination by X-ray crystallography
- ❖ Promotes stereoconvergence when paired with asymmetric catalysis





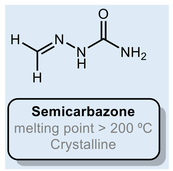


Experimental Goals:

- Explore method to enhance crystallinity in molecules with diverse functionality
- Examine product structures using NMR spectroscopy and melting point analysis

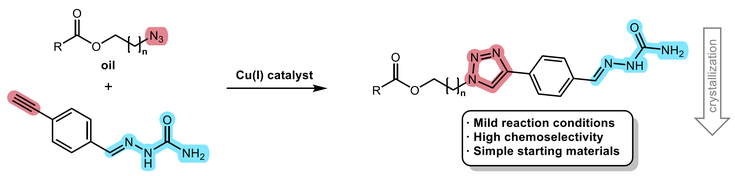
Experimental Design

Method 1: Modification of existing functional groups



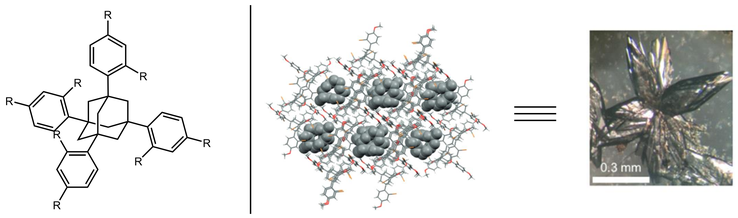
Hypothesis:
Incorporation of semicarbazone subunits into molecules increases their crystallinity.

Incorporation of Semicarbazones *via* Cu-catalyzed cycloaddition:



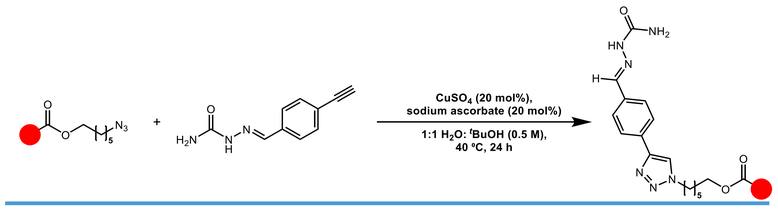
Method 2: Design of co-crystallization chaperones

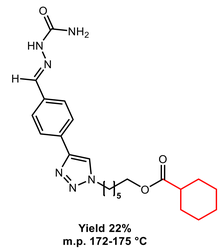
Richert *et al*.: Tetraaryladamantanes form co-crystals with small molecules.



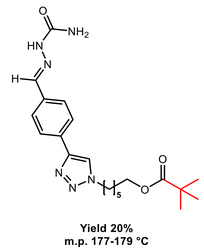
Hypothesis: Altering aryl substituents influences the crystallinity of tetraaryladamantanes.

On-Demand Crystallinity in Azido Esters

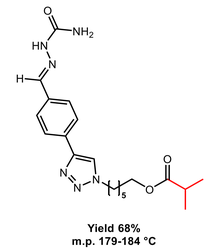




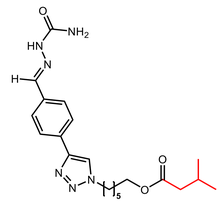
Yield 22%
m.p. 172-175 °C



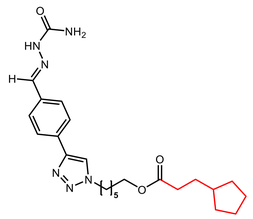
Yield 20%
m.p. 177-179 °C



Yield 68%
m.p. 179-184 °C

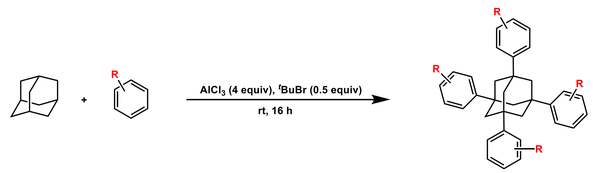


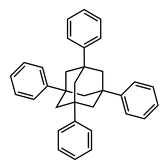
Yield 30%
m.p. 176-178 °C



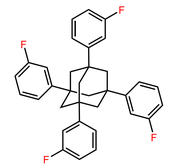
Yield 33%
m.p. 172-176 °C

Synthesis of Tetraaryladamantanes

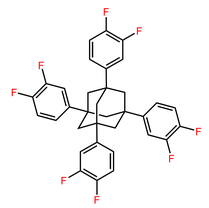




Yield 50%
m.p. > 300 °C



Yield 63%
m.p. > 300 °C



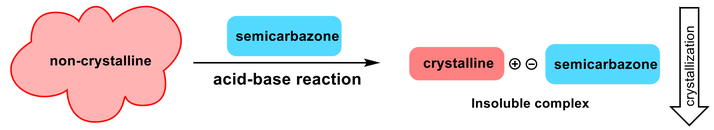
Yield 28%
m.p. > 300 °C

Discussion

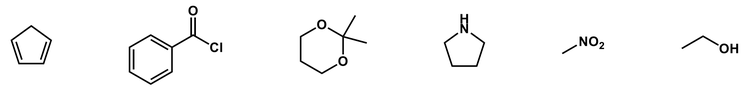
- ❖ Preliminary optimization of click reactions afforded crystalline triazoles from lipophilic azido esters, and a modest substrate scope demonstrated the methods' utility. High atom efficiency and mild conditions of the click reaction is promising for its utility in industrial chemistry.
- ❖ Highly crystalline tetraaryladamantanes were successfully synthesized on gram scale for future co-crystallization attempts.

Future Directions

- ❖ The copper click reactions will be optimized to increase the yield, then the reaction will be run on gram scale.
- ❖ Other methods of incorporating semicarbazones into molecules will be explored, including salt formation *via* a Brønstead acid-base reaction.



- ❖ On-demand crystallinity will be merged with existing asymmetric catalysis methods.
- ❖ The relationship between the aryl substituent identity and the tetraaryladamantane's performance as a chaperone will be studied.
- ❖ The ability of tetraaryladamantanes to co-crystallize with common small molecules will be studied.



- ❖ Tetraaryladamantanes will be tested to help facilitate a crystallization-induced diastereomer transformation (CIDT).

Acknowledgements & References

We thank the UNC Dept. of Chemistry NMR Core and the Johnson Lab for all the helpful discussion and support.

(1) Cassels, W. R.; Johnson, J. S. *Sci. Adv.* **2023**, *9* (27),6765.(2) Anderson, N. G. *Org. Process Res. Dev.* **2004**, *8* (2), 260–265. (3) de Jesús Cruz, P.; Cassels, W. R.; Chen, C.-H.; Johnson, J. S. *Science* **2022**, *376* (6598), 1224–1230. (4) Sherman, E. R.; Cassels, W. R.; Johnson, J. S. *Org. Lett.* **2023**, *25* (36), 6779–6783. (5) Belletire, J. L.; Rauh, R. J.; Huérou, Y. L. John Wiley & Sons, Ltd, 2006. (6) Krupp, F.; Frey, W.; Richert, C. *Angew. Chem. Int. Ed Engl.* **2020**, *59* (37), 15875–15879. (7) Gowrisankar, S.; Bernhardt, B.; Becker, J.; Schreiner, P. R. *Eur. J. Org. Chem.* **2021**, *2021* (48), 6806–6810.