Fluoride-Catalyzed Synthesis of Hydantoins

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Introduction

Hydantoins are chemically interesting molecules because of their five-membered ring structure and versatility to diverse synthetic modifications. In this novel synthesis, basic fluoride salts with the addition of crown ethers were used to catalyze the deprotonation of methyl propiolate, followed by nucleophilic addition to isocyanates to create a urea derivative, which then cyclizes to form the five-membered ring hydantoin. This synthesis method can explore many structural analogs with different mechanisms and physical properties, and can still be further optimized.

* Kalník M, Gabko P, Bella M, Koóš M. The Bucherer-Bergs Multicomponent Synthesis of Hydantoins-Excellence in Simplicity. Molecules. 2021 Jun 30;26(13):4024. doi: 10.3390/molecules26134024. PMID: 34209381; PMCID: PMC8271528.

Background

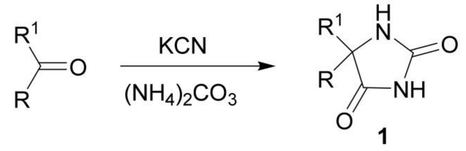


Figure 1. Burcher-Bergs' synthesis of hydantoins

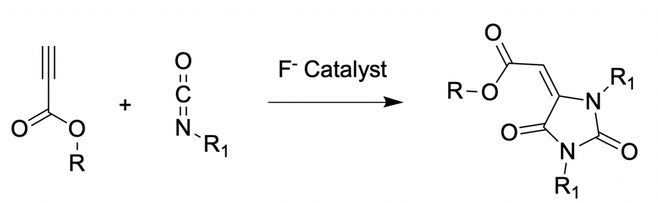


Figure 2. Reaction scheme of fluoride-catalyzed hydantoin synthesis

Methods

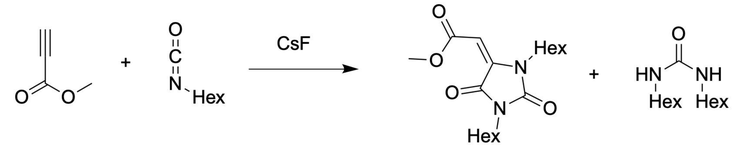


Figure 3. Initial synthesis

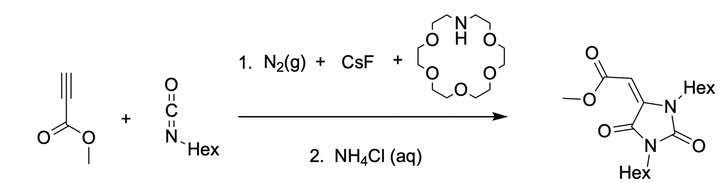


Figure 4. Optimized reaction with inert conditions, addition of 18-crown-6 to help fluoride base catalysis, and an ammonium chloride wash to remove catalyst

Results

Rxn	Eq CsF	Eq Crown	Solvent	Time (hr)	Temp °C	% yield (crude)	% yield (A)	% yield (B)
1	1	1	ACN	1	25°C	~0%	~0%	~0%
2	1	1	ACN	1	25°C	N/A	19.30%	4.94%
3	1	1	ACN	2	25°C	41.24%	N/A	N/A
4	0.5	0.5	ACN	2	25°C	39.00%	N/A	N/A
5	0.1	0.1	ACN	2	25°C	24.64%	N/A	N/A

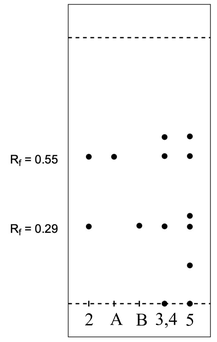


Figure 5. Crude TLC of Rxns

Column conditions for reaction 2 were 10 mL fractions with 9:1 Heptane to Ethyl Acetate

Reactions 3, 4, and 5 contained more than two spots, and require further purification and isolation to determine identity

Reaction 1 refers to figure 3 had a 0% yield because it wasn't under nitrogen, and created urea as a result

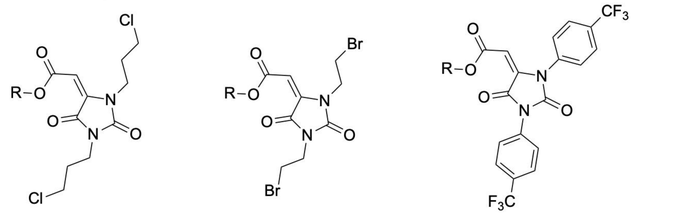
Future Directions

Work Up To-Do:
- GC-MS Data
- ^{13}C NMR
- 2D NMR
- Discover O or N ring closure mechanism

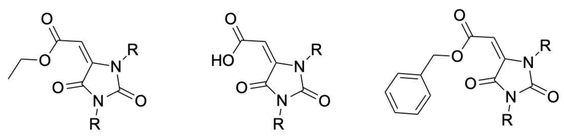
Variables to Experiment:

Temp °C	Solvent	Catalyst	Time
0°C	THF	Cu(1)I	1 hr
40°C	DMSO	KF	3 hr
100°C	DMF	TBAF	5 hr

Substrate Scope:

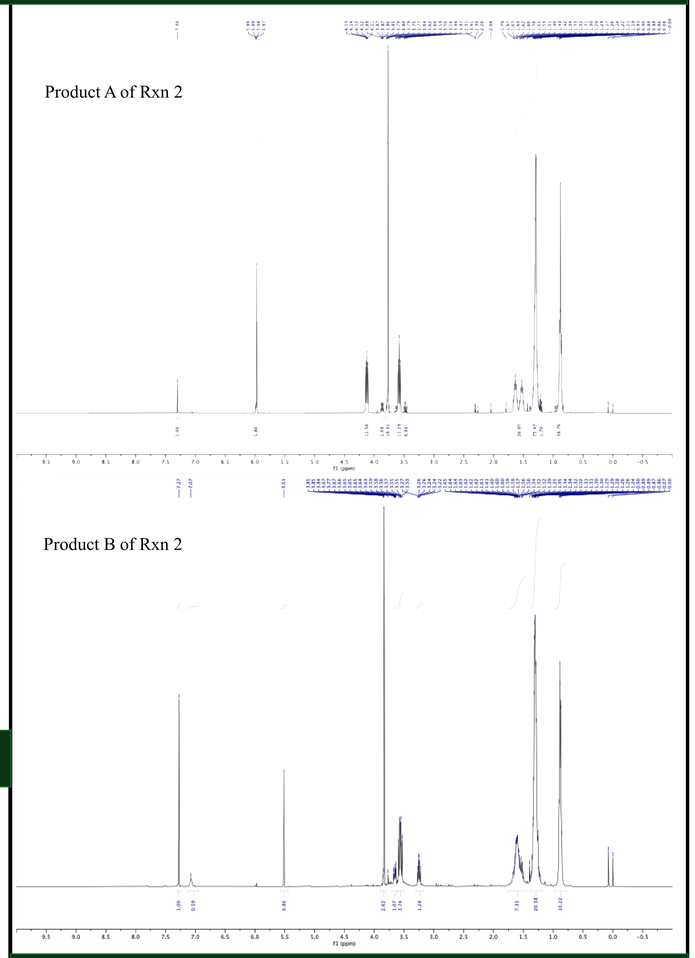


a. 3-Chloropropyl Isocyanate b. 2-Bromoethyl Isocyanate c. 4-(Trifluoromethyl)phenyl isocyanate



d. Ethyl Propiolate e. Propiolic Acid f. Benzyl Propiolate

^{1}H NMR Data



Conclusion

Through our experimentation, we found the yields of the synthesis to be poor to fair under current conditions, but with decent purity and potential E/Z isomers of our product, with A being the major product. Not much changed under the catalyst equivalence changes, but seemingly there is a difference in what is produced from the first and second hour from TLC

References

1. Kalník M, Gabko P, Bella M, Koóš M. The Bucherer-Bergs Multicomponent Synthesis of Hydantoins-Excellence in Simplicity. Molecules. 2021 Jun 30;26(13):4024. doi: 10.3390/molecules26134024. PMID: 34209381; PMCID: PMC8271528.

Acknowledgements

1. William and Linda Frost Fund and Frost Center for Research and Innovation
2. Kevin Dunham, CSM Equip Tech III, electromechanical
3. Joaquin G. Gonzalez and Quinn E. Williams, alumni