A Single Step Selective Polyfluoroarylation of Amides

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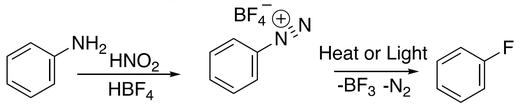
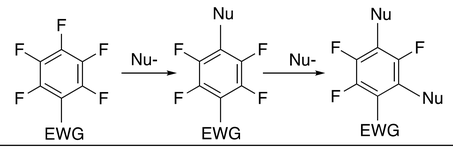
Overview

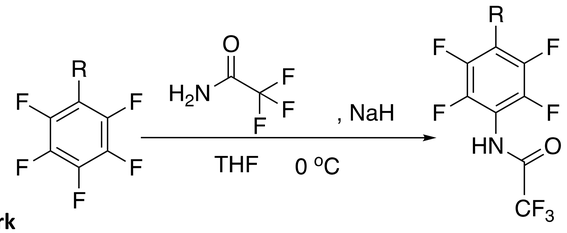
- Polyfluoroarenes important synthetic chemistry targets
  - Bioactive pharmaceutical components
  - Dolutegravir, Januvia, Rufinamide, Dabrafenib, Diflunisal, etc.
- Current synthesis methods involve selectively adding fluorines individually
  - Harsh conditions
  - Poor yields
- Nucleophillic aromatic substitution (S_NAr) enables selective removal of fluorines
- Directed hydrodefluorination allows for easily synthesized, readily available starting material
- Purpose is to optimize reaction conditions for single-step addition of amide functional groups to polyfluoroarenes

Traditional Method of Fluorine addition

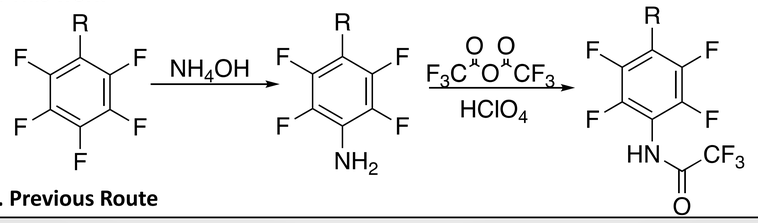


This Work i.e. Fluorine Sculpting:



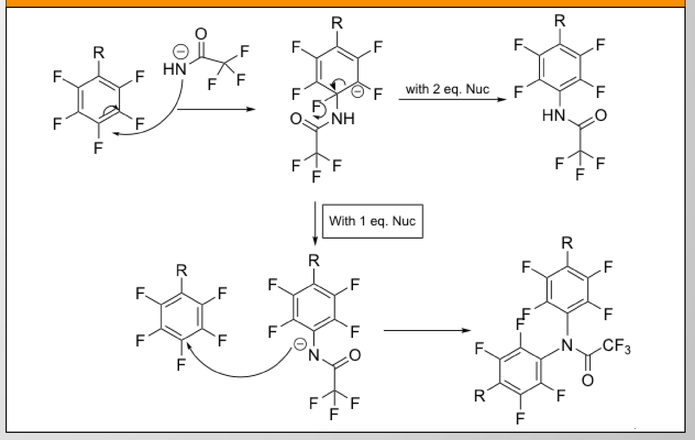


Scheme 1. This work



Scheme 2. Previous Route

Mechanism



Isolation

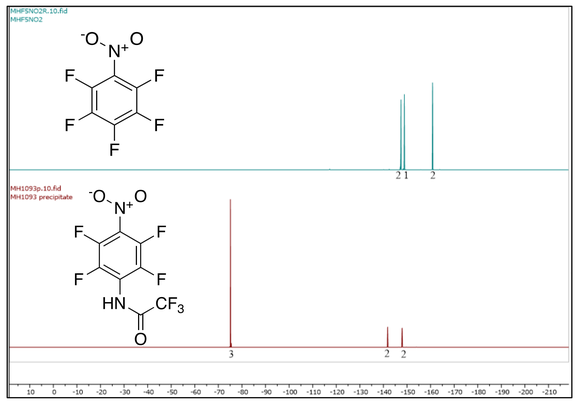


Figure 2. F_{19} NMR of Substrate and Product

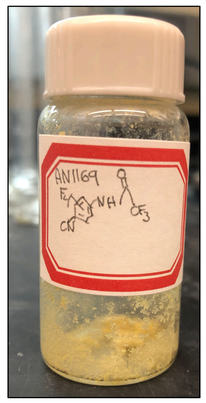


Figure 3. Crystallized Product

Future Plans

- Further investigate scalability for industrial application
- Refine workup conditions
- Other reaction conditions
  - Substrate scope
  - Relative equivalence
  - Solvent

Applications

- Enables selective polyfluoroarylation of amides in a single step
  - Good yields
  - Mild reaction conditions
- Facilitates access
- Streamlines research efforts into bioactivity

Methods

- Schlenk technique
- Base and amide deprotonated and cooled to 0 °C
- Polyfluoroarene substrate added dropwise
- Monitored by F_{19} NMR
- Chromatography free isolation

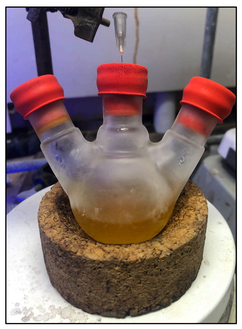


Figure 1. Reaction Mixture

Optimization

Substrate	Temp °C	Eq. of Base	Eq. of F3 Acetamide	% Conversion
Pentafluoronitrobenzoate	0	2.15	2.1	100
Pentafluorobenzonitrile	-20	2.15	2.1	66
Pentafluorobenzonitrile	-10	2.15	2.1	73
Pentafluorobenzonitrile	-5	2.15	2.1	92
Pentafluorobenzonitrile	0	2.15	2.1	98
3,4,5-Trifluoronitrobenzene	25	2.15	2.1	89
3,4,5-Trifluoronitrobenzene	0	2.15	2.1	33
Pentafluoromethylbenzoate	25	2.15	2.1	48
Pentafluoromethylbenzoate	-10	2.15	2.1	65

Acknowledgements and References

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