Monofluoromethylation of Acyl Chlorides: Direct Synthesis of Monofluoromethylketones (MFMK) with Fluorobis(phenylsulfonyl)methane (FBSM)

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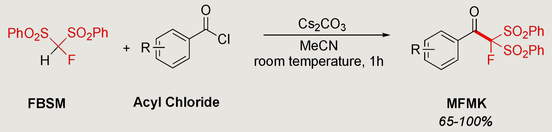
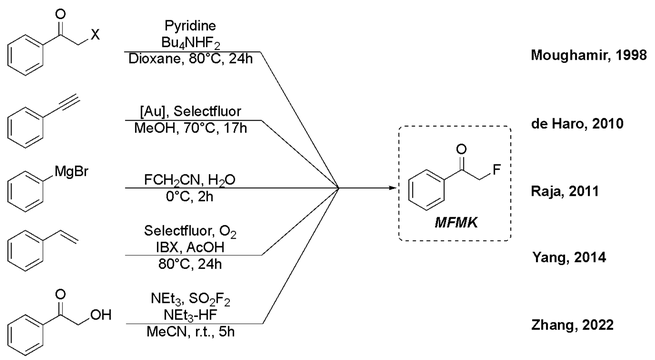
Abstract

The development of new drugs with improved pharmacological properties is a continuous challenge in drug discovery. Recently, however, the incorporation of fluorine into drug molecules has emerged as a promising strategy to improve their metabolic stability, lipophilicity, bioavailability, and binding affinity to target proteins. This project focused on the development of a new metal-free approach for the synthesis of monofluoromethylketones (**MFMKs**) utilizing various substituted acyl chlorides and fluorobis(phenylsulfonyl)methane (**FBSM**) as a monofluoromethyl (**–CH_2F**) precursor. The MFMKs were synthesized in high yields ranging from 65% to 100% in short reaction times, under mild reaction conditions in acetonitrile. Our investigations showed that this transformation tolerates electron-donating, as well as electron-withdrawing functional groups. Further applications include the late stage monofluoromethylation of bioactive compounds (e.g. Aspirin)



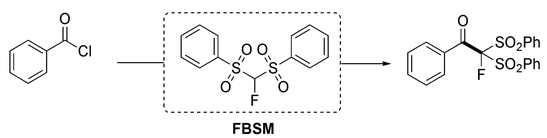
FBSM **Acyl Chloride** **MFMK** *65-100%*

Prior Work



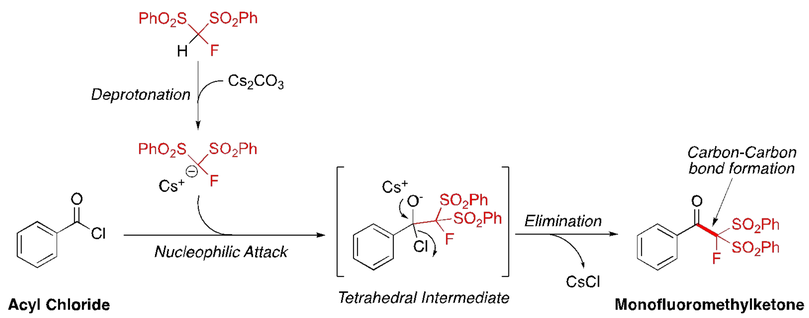
- Long reaction times
- High temperatures
- Utilization of harmful chemicals (e.g. HF)

This Work



- Short reaction times
- High yielding transformation
- High functional group tolerance
  - Electron-donating groups (EDG)
  - Electron-withdrawing groups (EWG)
- Mild reaction conditions

Proposed Mechanism



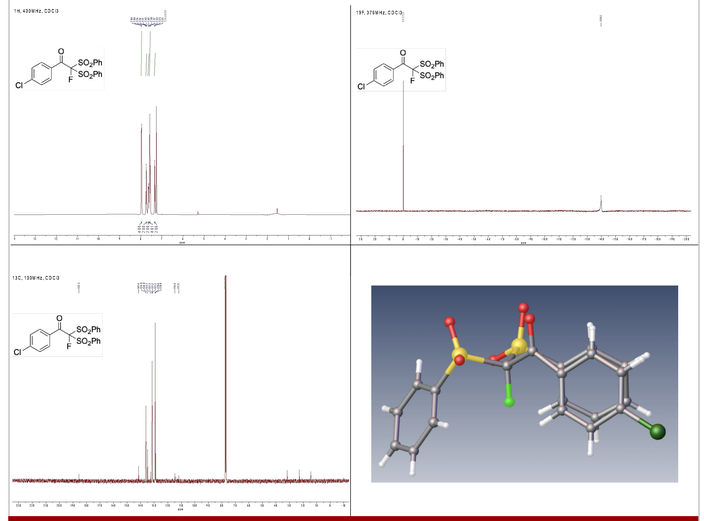
Monofluoromethylketone Scope

Reaction Optimization

Entry	FBSM (eq.)	Base (eq.)	Acyl Chloride (eq.)	Solvent [M]	Temp. (°C)	Yield (%)[a]
1	1.0	Cs_2CO_3 (1.2)	2.0	MeCN [1M]	r.t.	10%
2	1.0	Pyridine (1.2)	2.0	MeCN [1M]	60°C	0%
3	1.0	LiHMDS (1.2)	2.0	MeCN [1M]	r.t.	13%
4	1.0	K_2CO_3 (1.2)	2.0	MeCN [1M]	r.t. and 60°C	0%
5	1.0	Cs_2CO_3 (1.2)	2.0	MeCN [1M]	r.t.	38%[b]
6	1.0	Cs_2CO_3 (1.2)	2.0	THF [1M]	r.t.	0%[b]
7	1.0	Cs_2CO_3 (1.2)	2.0	DCM [1M]	r.t.	0%[b]
8	1.0	Cs_2CO_3 (2.4)	2.0	MeCN [1M]	r.t.	80%[b]
9	**1.0**	**Cs_2CO_3 (3.6)**	**2.0**	**MeCN [1M]**	**r.t.**	**90%[b]**

[a]Yields were determined by ^{19}F-NMR using fluorobenzene as an internal standard.
[b]Pre-stirring of FBSM and Cs_2CO_3 for 15 minutes at room temperature, followed by the addition of the acyl chloride.

Characterization of MFMKs



Conclusion

- Synthesis of 14 monofluoromethylketones in good to excellent yields, under mild conditions in 1 hour at room temperature
- 4 crystal structures were obtained (**2b**, **2f**, **2k**, and **2i**)
- Developed approach tolerates EDG (**2d**, **2e**, **2g**, and **2l**) and EWG (**2b**, **2c**, and **2j**)
- Method can be applied to synthesize bioactive molecules (Aspirin Analogue)
- Future Application can include the medicinally relevant testing of the unique properties of the synthesized fluorinated compounds (e.g. bioavailability, stability, etc.)

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References

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