RUHR-UNIVERSITÄT BOCHUM

A TRIFLUOROACETATE DERIVED, BENCH-STABLE TRIFLUOROMETHYLATION REAGENT FOR PHOTOCATALYTIC C–H FUNCTIONALIZATION OF (HETERO)ARENES

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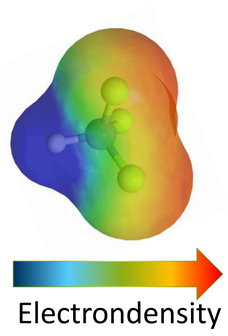
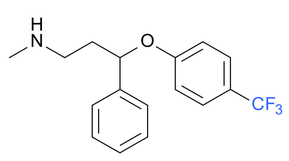
We report a bench-stable trifluoromethylation reagent derived from trifluoroacetic acid anhydride as a terminal CF_3-source via decarboxylative Barton ester rearrangement and S-oxidation. Shifting the decarboxylation step from the trifluoromethylation process to reagent synthesis enables efficient radical trifluoromethylation under mild conditions, as demonstrated in the photocatalytic trifluoromethylation of (hetero)arenes and thiols.

Background

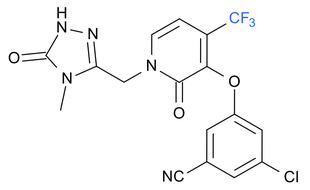
The incorporation of fluorinated groups, especially CF_3, is a powerful strategy to modulate the biological and physicochemical properties of organic molecules[2][3]. Consequently, the development of practical, sustainable and efficient trifluoromethylation reagents remains an important objective in synthetic chemistry[4][5].

- Hansch π value of +0.88
- Enhanced target binding affinity: improve hydrogen bonding and electrostatic interactions with biological targets compared to CH_3
- Enhanced hydrophobic interactions compared to CH_3
- Higher metabolic stability: prolonging the drug's half-life

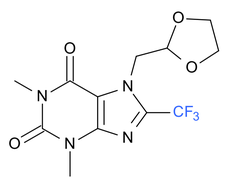




Fluoxetine (Prozac)



Doravirine (Pifeltro)

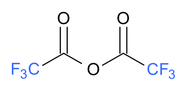


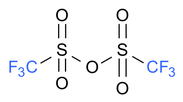
Doxofylline

Introduction

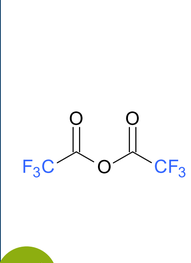
Current challenges:

- Practical access to CF_3-transfer reagents often relies on specialized syntheses or expensive fluorinated feedstocks[1].
- Readily available fluorinated building blocks such as trifluoroacetic anhydride remain underexploited for the preparation of photocatalytic CF_3 reagent

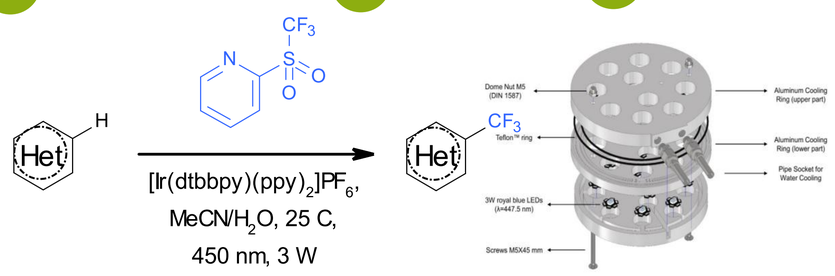




- ✓ **Low production cost (~€ 50 per 100 ml)**
- ✓ **Low moisture sensitive**
- ✓ **Easier handling chemical**
- × **Higher production cost (~€ 375 per 100 g)**
- × **Highly moisture-sensitive**
- × **Extremely reactive chemical**

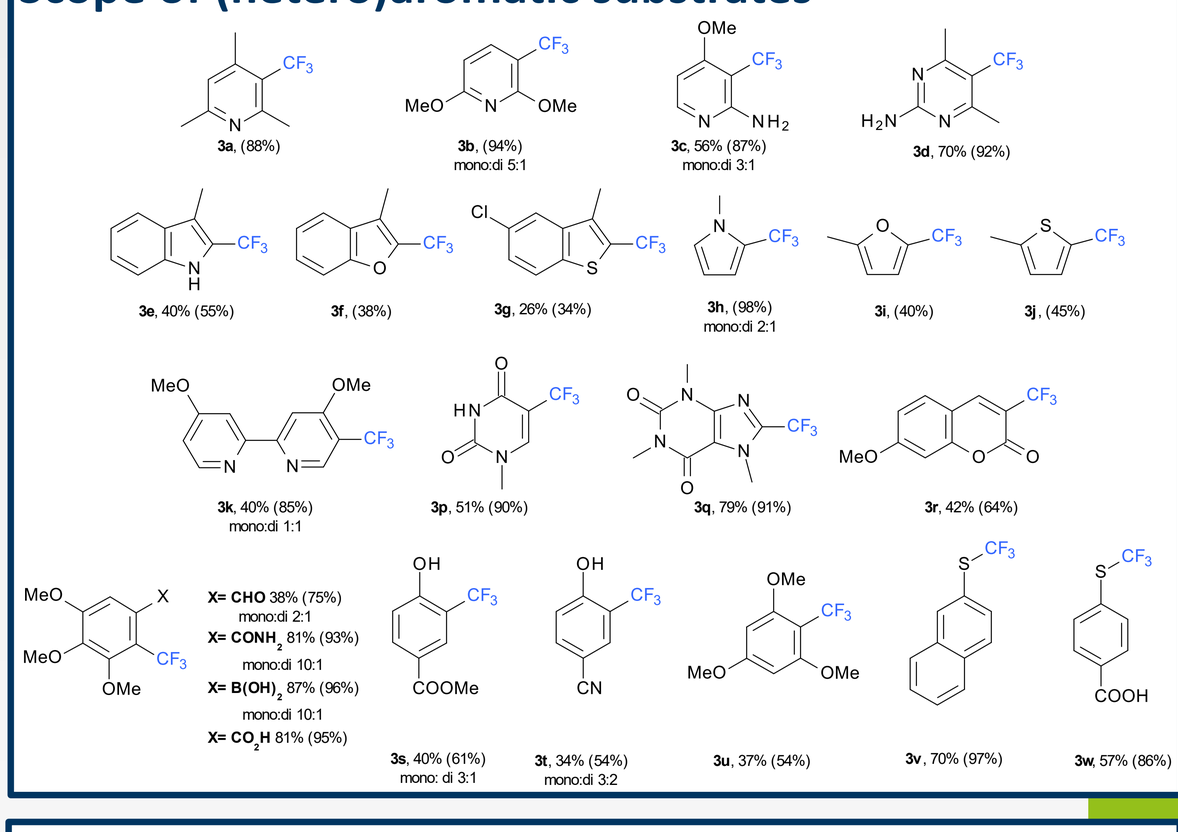


Bench stable **Easy synthesis** **High yield** **Upscalable**



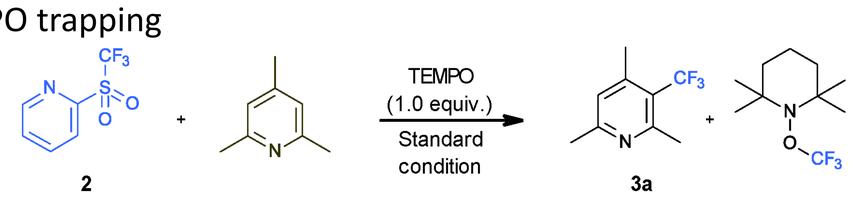
♦ **N, O, S -heteroarenes** ♦ **Up to 98%**

Scope of (hetero)aromatic substrates

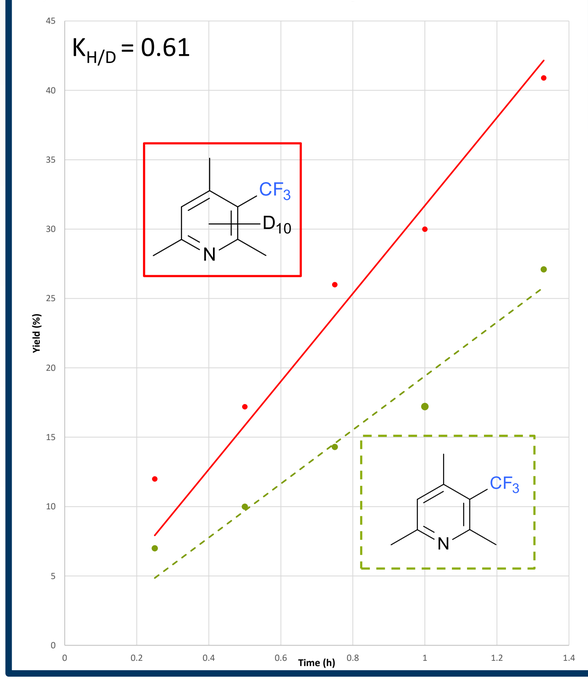


Mechanistic investigations

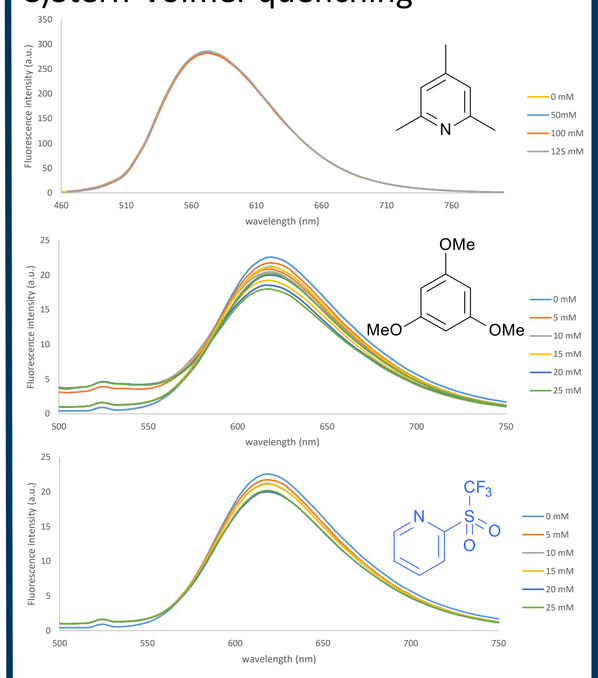
A)TEMPO trapping



B)Parallel kinetic isotopic effect



C)Stern-Volmer quenching



Conclusion and Outlook

It was developed an efficient synthesis of 2-(trifluoromethylsulfonyl)pyridine via decarboxylation of a trifluoroacetic acid Barton ester establishes it as a practical and attractive trifluoromethylating reagent. Its utility was demonstrated through the synthesis of CF_3-substituted arenes and trifluoromethyl thioesters, highlighting its versatility in radical-mediated transformations. Given its ease of preparation, stability, and broad synthetic applicability, we expect this reagent to find widespread use in radical trifluoromethylation chemistry.

References

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