Radical-Based Regioselective C-H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability


\[
\begin{align*}
R_1\text{Het} & \xrightarrow{\text{Zn(SO}_2\text{R})_2, \text{TBHP}} R_1\text{Het} \quad R \\
\text{solvent, 50 }^\circ\text{C} & \\
R = \text{CF}_3, \text{CF}_2\text{H}, i-\text{Pr}
\end{align*}
\]

Evan Carder
Wipf Group Current Literature
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Trifluoromethylation and Pharmaceuticals

- Medicinal chemists face major challenges converting drug candidates into viable pharmaceutics\[1\].

- Pharmacologically active compounds can have poor structural characteristics that adversely influences its metabolism and excretion\[2\].

- Trifluoromethylation is commonly employed to rationally protect labile positions against cytochrome P450 oxidation\[3\].

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Examples Currently Available in the Market

- **Celebrex**
  Arthritis, Pfizer
  
- **Prozac**
  Depression, Eli Lilly
  
- **Monsanto**
  Herbicide
Programmed Trifluoromethylation

Transition metal catalysis

Y = Cl, I, B(OH)₂


Innate Trifluoromethylation

Direct C-H Functionalization


Value in Exploiting Innate Reactivity

- Incorporates electrophilic radicals at potentially metabolically labile positions.

- Reduces the need for pre-functionalization and allows late-stage trifluoromethylation of diverse arenes and heteroarenes.

- Potentially predictable regioselectivity and tunable regiocontrol, which offers divergent synthetic strategies.

- Allows substitution on various π-deficient heteroarenes – pyridines, pyrimidines, pyrazines, and pyrazines.

![Chemical Structure](image)
Objective

- Establish trends that allow for practical predictions in regioselectivity of radical functionalization of heteroarenes

A. Influence of acid additives: e.g. Lynch, 1964 (ref. 10)

B. Influence of solvent: e.g. Minisci, 1974 (ref. 11)

C. Influence of functional groups: e.g. Minisci, 1986 (ref. 13)

D. Influence of nature of radical: e.g. Minisci, 1974 (ref. 11)
Mechanism of Heteroarene Functionalization using Alkylsulfinate-Derived Radicals

Regioselectivity is influenced by three major factors:

i. Innate reactivity of the parent heterocycle

ii. Conjugate activity of \(\pi\)-conjugating electron withdrawing groups

iii. Electron properties of the radical

\[
\begin{align*}
\text{Regiochemistry?} \quad \begin{array}{c}
\text{Zn(SO}_2\text{R})_2, \text{ TBHP} \quad \text{solvent, 50 °C}
\end{array}
\end{align*}
\]

\(\begin{array}{|c|c|}
\hline
\text{solvent} & \text{C-3 : C-2} \\
\hline
\text{DMSO} & 4.3 : 1 \\
\text{DMF} & 2.7 : 1 \\
\text{MeCN} & 1 : 2.3 \\
\text{CHCl}_3/\text{H}_2\text{O} & 1 : 3.0 \\
\text{DMSO/1 eq. H}_2\text{SO}_4 & 1 : 3.9 \\
\text{CHCl}_3/\text{H}_2\text{O/excess TFA} & 1 : 5.0 \\
\text{DMSO/excess H}_2\text{SO}_4 & 1 : 6.6 \\
\hline
\end{array}\]

(A) solvent/pH effect: \((R = i-\text{Pr}, R_1 = \text{CN})\)

- addition of acid reduces influence of conjugate reactivity

(B) nature of substituent \(R_1\): \((R = i-\text{Pr}, \text{solvent} = \text{DMSO})\)

- influence of conjugate reactivity decreases with decreasing electrophilicity of \(\pi\)-conjugating EWG

- no C3 products observed in the absence of a \(\pi\)-conjugating EWG

(C) nature of radical \(R\): \((R_1 = \text{CN}, \text{solvent} = \text{DMSO})\)

- effect of protonation increases with radical nucleophilicity
Innate Reactivity and Tunability

A. Innate reactivity: activated at inherently reactive positions of parent heterocycle

- Innate reactivity at α and γ positions
- Influence dependent on overall electron density
- Reactivity accentuated by H⁺

B. Conjugate reactivity: activated at positions in conjugation with a π-EWG

- Conjugate reactivity ortho-para to π-EWG
- Influence dependent on solvent

C. Radical electrophilicity and nucleophilicity: reactivity at δ⁻ and δ⁺ sites

- α-withdrawing π-donor
- Non-polar at C3
- Unreactive at C3
- Reacts with electrophilic radicals at C3

- π-withdrawing
- Reacts with nucleophilic radicals at C3

A. Influence of acid and solvent on C2:C3 ratio

- CHCl₃/H₂O
- DMSO

- Enhanced δ⁺ at C2
- More δ⁺ at C2
- More δ⁺ at C2
- "Effectively" more δ⁺ at C3

- C2 >> C3
- C2 > C3
- C2 >> C3
- C3 >> C2

B. Reduced sensitivity of C2:C3 ratio to solvent change for CF₃ radical

- (i) i-Pr radical: nucleophilic

- Reactive at most δ⁺ site
- Reacts at most δ⁺ site
- Too electron rich to be reactive at δ⁺ site

- C2 >> C3
- C3 >> C2
- Unreactive
- C2 = C3

- (ii) CF₃ radical: less nucleophilic, can behave as electrophile

- Also reactive at least δ⁻ site
- Most reactive at most δ⁺ site
- Reacts as electrophile at δ⁻ site

- C2 > C3
- C3 > C2
- C3 ≈ C2

- Remains reactive at electron rich δ⁺ site
A. Predictable selectivity in CHCl₃/H₂O or CHCl₃/H₂O/TFA: innate reactivity dominates

B. Predictable selectivity in DMSO: conjugate reactivity dominates

C. Predict poor reactivity or need for forcing conditions
Application in Biologically Available Compounds

11\%  
diflufenican 49\textsuperscript{a}  
herbicide

heterocycle electrophilic  
arenes poorly nucleophilic

CF\textsubscript{3} behaves as nucleophile

35\%  
trimethoprim 50\textsuperscript{b}  
antibiotic

heterocycle poorly electrophilic  
arene nucleophilic

CF\textsubscript{3} behaves as electrophile
Conclusion

- This paper provides an empirical model to predict regioselectivity of radical functionalization in diverse heterocycles.

- Proposes solvent mediated regiochemical control

- Guidelines were shown to have application in biologically relevant compounds, which may influence future efforts on radical-mediated functionalization of pharmaceuticals.