Late-Stage Deoxyfluorination of Alcohols with PhenoFluor

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Current Literature
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Fluorine in Medicinal Chemistry

- The carbon fluorine bond plays an integral role in agrochemicals, pharmaceuticals, materials, and imaging
- Approximately 20% of all pharmaceuticals contain fluorine
- Strategies for the introduction of fluorine atoms in medicinal chemistry:
  - Metabolic stability by blocking metabolically labile sites
  - Modulate the physicochemical properties such as lipophilicity or basicity
  - Enhance binding affinity to a target protein
- Non-natural $^{18}\text{F}$ is the most commonly used positron-emitting isotope for molecular positron emission tomography (PET) imaging in oncology

Lipitor (Pfizer) $7.7$ billion (2011)
Advair Diskus (GSK) $4.6$ billion
Lexapro (Forest Laboratories) $2.9$ billion (2011)

Carbon-Fluorine Bond Formation

• Despite fluorine’s importance, carbon-fluorine bond formation still represents a formidable synthetic challenge
• Only 21 biosynthesized natural molecules containing fluorine are known and no fluoroperoxidase is known
• Conventional fluorination reactions are generally limited to very simple molecules, with reliable fluorination of more complex molecules at specific positions being difficult
• New methods to incorporate fluorine into complex organic molecules are crucial to the progress of the field

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- Conventional fluorination reactions are generally limited to very simple molecules, with reliable fluorination of more complex molecules at specific positions being difficult.
- New methods to incorporate fluorine into complex organic molecules are crucial to the progress of the field.

Deoxyfluorination Reagents: DAST and Deoxo-Fluor®

- Reported by Middleton in 1975 as the first bench-stable deoxyfluorinating reagent and a useful alternative to SF$_4$
- DAST suffers from poor thermal stability and potentially hazardous scale-up
- Deoxo-Fluor® was introduced in 1999 and is a significant competitor to DAST for deoxyfluorination reactions due to its improved thermal stability

Deoxyfluorination Reagents: XtalFluor-E® and XtalFluor-M®

- In 2009, Courturier and co-workers reported the preparation and use of XtalFluor-E® and XtalFluor-M®
- XtalFluor-E® and XtalFluor-M® are crystalline reagents that are relatively safe and cost-efficient to prepare
- The reactions require the addition of either an HF•amine reagent or DBU for efficient transformation
- The XtalFluor® reagents are typically more selective and reduce the levels of elimination side products often observed with DAST and Deoxo-Fluor®

Deoxyfluorination Reagents: Fluolead™ and TFEDMA, Yarovenko’s and Ishikawa’s reagents

- In 2010, Umemoto and co-workers introduced the second generation PhSF₃, which is marketed as Fluolead™
- More chemically stable than PhSF₃, and more more thermally stable than DAST because of the stronger C-S bond in Fluolead™
- Ishikawa’s, Yarovenko’s, and TFDMA reagents fluorinate a wide range of primary and secondary alcohols to provide alkyl fluorides
- There reagents are generally prepared by the addition of Et₂NH to the corresponding halogenated alkene
- This group of reagents can suffer from formation of ester and amide side products

Deoxyfluorination Reagent: PhenoFluor

- PhenoFluor was first reported by Ritter and co-workers in 2011 for deoxyfluorination of phenols
- PhenoFluor is commercially available from Sigma-Aldrich
- PhenoFluor is a crystalline, nonexplosive solid that can be handled in air, but hydrolyzes upon prolonged storage in a wet atmosphere
- PhenoFluor can be stored in a dry toluene solution for at least 2 months without detectable decomposition

Tang, P.; Wang, W.; Ritter, T. WO 2012/142162
PhenoFluor: Proposed Mechanism

- Ritter and co-workers propose that the mechanism for fluorination proceeds via a 2-phenoxyimidazolium bifluoride salt

\[
\text{PhOH} \quad \text{toluene, 23 }^\circ\text{C} \quad \text{F}^+ \quad \text{F}^- \quad \text{toluene-d}_8, 110^\circ\text{C} \quad \text{67%}
\]

PhenoFluor: Proposed Mechanism

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\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
\xrightarrow{\text{toluene, 23 °C}} & \\
\text{N} & \quad \text{N} & \quad \text{Pr} & \quad \text{Pr} & \quad \text{Pr} & \quad \text{Pr} \\
\text{MeO} & \quad \text{OH} & \quad \text{F} & \quad \text{F} & \quad \text{Pr} & \quad \text{Pr} \\
\end{align*}
\]

PhenoFluor: Hydrogen Bonding

Title Paper: Deoxyfluorination of Aliphatic Alcohols

- Modifications of the initial reaction conditions allowed for the deoxyfluorination of aliphatic alcohols

[FmocHN·CO₂Me] → [FmocHN·CO₂Me]
PhenoFluor

74% in dioxane
80% in toluene

<table>
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<th>Deoxo-Fluor®</th>
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<th>DAST</th>
<th>DFI</th>
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Chiral secondary alcohols could typically be deoxyfluorinated with inversion

Carbonyl functional groups are well tolerated

**Title Paper: Late-Stage Deoxyfluorination of Alcohols**

![Reaction Scheme](image)

**PhenoFluor**

- 2.0 equiv EtNPr$_2$
- 2.0 equiv KF

**Parent Compound**

Yield %

**Solvent, Temperature**

- (2S, 4R)-4-hydroxy-proline: 92% yield, toluene, 80 °C
- D-allofuranose: 83% yield, toluene, 80 °C
- Reserpine: 82% yield, toluene, 80 °C
- Artemisinin: 79% yield, toluene, 80 °C
- Testosterone: 88% yield, toluene, 80 °C
- Epi-androsterone: 84% yield, toluene, 80 °C
- 77% yield, toluene, 80 °C

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Title Paper: Late-Stage Deoxyfluorination of Alcohols

- Secondary allylic alcohols afforded allylic fluorides consistent with an $S_{N}2$ mechanism
- Deoxyfluorination is site-selective and predictable

Deoxyfluorination can be carried out at room temperature, allowing for fluorination of temperature sensitive substrates. KF was not required.
Primary alcohols are selectively deoxyfluorinated
Secondary alcohols react slower or not at all when they are \( \beta,\beta' \)-dibranched, unless it is allylic
Hydroxyl groups engaged in hydrogen bonding are not reactive
Tertiary alcohols do not react, unless they are allylic
Deoxyfluorination with PhenoFluor: Mechanistic Considerations

- The formation of elimination products could be reduced by increasing the reaction temperature from 23 °C to 80 °C
- The addition of DIPEA was beneficial to shorten the reaction time
- KF was found to reduce side products resulting from elimination, but was not generally required for the reaction to proceed

Conclusions and Outlook

- A general method for selective, late-stage deoxyfluorination of complex aliphatic alcohols has been developed

\[
\begin{align*}
\text{PhenoFluor} & \quad R^2 \quad \text{OH} \\
& \quad 2.0 \text{ equiv EtN}^+\text{Pr}_2 \\
& \quad 2.0 \text{ equiv KF} \\
& \quad 2-20 \text{ h}
\end{align*}
\]

- The substrate scope and functional group tolerance of this methodology surpass all others reported to date
- PhenoFluor has a better safety profile and higher chemoselectivity than other deoxyfluorination reagents
- One drawback is the molar mass (427 g/mol), which is convenient for subgram- and gram-scale reactions, but is wasteful for larger-scale reactions
- Extending this method to late-stage \(^{18}\text{F}\) radiolabeling would be useful for positron emission tomography (PET) applications