Fluorinated Synthons

GM Focus: Interesting applications of fluorinated starting materials and reagents therein.

To Be Covered:
1. Rongalite: "The Confused Sulfinate Salt"
2. "The Nitrogen Walk"
3. Perfluoroheteroaromatics and "Mirror Image Logic"
4. N-Fluoropyridinium Salts and "The Fluorine Walk"
5. "The Negative Fluorine Effect" and the "chemical chameleon"

Not Covered:
General/"Traditional" Fluorination Reagents and techniques:
- i.e. Selectfluor,NFSI, DAST, XeF₂, AgF₂ (see Fluorination GM by S. Su (2008))

Rongalite: "The Confused Sulfinate"

**J. of Flourine Chemistry, 64 (1993) 37-46**

\[ \text{R}, \text{R}' = \text{H, CH}_3 \]
\[ \text{R}, \text{R}' = \text{C}_6\text{F}_{13}, \text{C}_7\text{F}_{15}, \text{C}_8\text{F}_{17}, \text{Cl(CF}_2)_6 \]

General Isomer Distribution:
C2:C3:C4 = 1:4:4

Observed byproducts:
R_FH and R_FSO₂Na

*Bicarb. kept rxn slightly basic and prevent dissociation of Rongalite.
*Also works on pyrroles (selective C2 substitution), quinolines and isoquinolines.
*Pyrazine and imidazole were problematic.

Rongalite With Olefins


**General Mechanism:**

\[ \text{HOCH}_2\text{SO}_2^- \rightarrow \text{SO}_2^{2-} + \text{HOCH}_2^+ \]

\[ \text{SO}_2^{2-} + \text{R}_F\text{I} \rightarrow \text{R}_F^+ + \text{I}^- + \text{SO}_2 \]

**The "Nitrogen Walk"**


\[ \text{F} \]

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Perfluorinated Heterocycles as Synthons?

Perfluoroheteroaromatic systems

- Perfluoropyrazine
- Perfluoropyridine
- Perfluoroisoquinoline
- Perfluorquinoline
- Perfluoropyridazine

bp (°C) = 54  bp (°C) = 84  bp (°C) = 212  bp (°C) = 212  bp (°C) = 117

Heteroaromatic systems

- Pyrazine
- Pyridazine
- Quinoline
- Pyridine
- Isoquinoline

bp (°C) = 115  bp (°C) = 208  bp (°C) = 238  bp (°C) = 115.5  bp (°C) = 243

Increasing base strength

*All perfluoroheteroaromatic compounds are weak bases - a fluorine atom placed ortho to the nitrogen atom significantly decreases the basicity of the system.

*Boiling points: Lower bp is attributed to lower intermolecular forces and low basicities of fluorocarbon systems that compensate for the increase in mass upon replacing hydrogen by fluorine.

General synthesis of perfluoroheteroaromatic heterocycles (many other methods available).

Perfluoroheteroaromatics: "Mirror Image" Chemistry

Nucleophilic substitution of perfluorinated heteroaromatic systems occurs at sites that:
1) are para to the ring nitrogen
2) maximize the number of activating ortho and meta F atoms
3) minimize the number of F atoms para to the site of attack

Favored sites of attack for S_NAr

```
F
\|\|
F\|\|N
\|\|F
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Regioselectivity Pattern

```
Nuc_1
\|\|
F\|\|N
\|\|F
\|\|F
```
```
Nuc_2
\|\|
F\|\|N
\|\|F
\|\|F
```
```
Nuc_3
\|\|
F\|\|N
\|\|F
\|\|F
```
```
Nuc_4
\|\|
F\|\|N
\|\|F
\|\|F
```

Position of Nuc_2 is dependent on Nuc_1.
Can get mono, bis, or tri.
Difficult to get mono only (highly activated).

"Mirror Image Logic" Examples

*a reaxys search showed 1134 reactions with (1) as starting material

Reagents and Conditions: i, CH$_3$NHCH$_2$CH$_2$NHCH$_3$, NaHCO$_3$, MeCN, reflux; ii. MeONa, MeOH, reflux, 2d; iii. Et$_2$NLi,THF, reflux; iv. (a) PhC=NNH$_2$, NaHCO$_3$, MeCN, reflux, (b) LDA, THF, rt; v. PHCH$_2$NMe, THF, 150°C; microwave; vi, PHSO$_2$Na, DMF, 140°C

Biologically active compounds using "Mirror Logic" (used by Novartis and others)

Substitution via Radical:

Carbenes from N-Fluoropyridinium Salts: Featuring the "Fluorine Walk"?

The Negative Fluorine Effect (NFE)


\[
\begin{align*}
\text{(R}_1^2 \text{R}_2^2 + F^-) \text{ or (R}_1^2 \text{F} + \text{R}_2^-) & \text{ or elimination reduces concentration of 3 and decreases r}_1
\end{align*}
\]

(decreased nucleophilicity of 3 due to side reaction with \(r_2\))

**Factor 1**

**Negative Fluorine Effect**

**Factor 2**

intrinsic reactivity of 3 toward \(E^+\) (e.g. unmatched hard/soft nature between 3 and \(E^+\) results in higher activation barrier of desired reaction and decreases \(r_1\))

4 Methods for Modulating the NFE

A. Change fluorine atoms
B. Slightly change neighboring groups (\(R_1^1, R_2^2\))
C. Enhance generation of carbene species
D. Change the metal counterion \(\text{M}^+\) or covalent bond to \(\text{M}\)

**Method A: Nucleophilic Difluoromethylation Reactions with 1**

**Method A: Nucleophilic Monofluoromethylation Reactions with 2**

Org. Lett. 2006, 1693-1696
The Negative Fluorine Effect: Changing Neighboring Groups

Method B:

*The sulfone functionality is a "chemical chameleon" that is ideal for various types of reactions.

sulfone  
2-pyridyl sulfone  
sulfoxime

*Slightly changing R groups results in dramatically different chemistry.

Difluoromethylation of S-, N-, and C-Nucleophiles with 1.

Fluorinated alkenes from nitrones.

14 Examples up to >99% yield

Angew. Chem. Int. Ed. 2013, 52, 3949 –3952

Org. Lett. 2010, 1444-1447
The Negative Fluorine Effect: Carbene, Counterion, M-X

C. Enhance Generation of Carbene

D. Changing the Counterion

For Ketimines: Chelation-Controlled


D. Modulation of M-X bond

cross-coupling

Cu⁰, R³-I

intra molecular cyclization

Cu⁰

homocoupling

D. Modulation of M-X bond

For Ketimines: Chelation-Controlled