DAY 14-4

RX RARE IN NATURE

\{\text{EXCEPTION: RCI in MARINE ORGS}\}

\text{S}_1 \text{ REACTIVE} \rightarrow \text{DESTROYED BY H}_2\text{O}

\[
\begin{align*}
\text{SN}_1 \quad &\rightarrow \quad \text{OH} \\
&\quad \uparrow \text{Cl} \quad \rightarrow \\
&\quad \rightarrow \\
&\quad \rightarrow
\end{align*}
\]

\text{SN}_2 \text{ REACTIVE} \rightarrow \text{TOXIC}

\text{CYTIDINE}

\text{ONLY SOME ATOMS ARE Nu}

\text{REACTS w/ CH}_3\text{I}

\rightarrow \text{MODIFIES DNA}

\text{NO REPLICATION}

\downarrow \text{FATAL}

\text{MISREAD}

\downarrow \text{MUTANT OFFSPRING}

\text{BOTTOM-LINE: SN}_2 \text{ REACTIVE RX NOT PRODUCED BIOCHEMICALLY}
DAY 14-5

"NATURAL" RX ARE RARE, BUT
NOT "NATURAL" $S_{N,X}$
1) COMMON
2) OH Lg

DEOXYRIBOSE → CYTIDINE

GLUCOSE → FRUCTOSE

SUCCROSE
CH$_3$OH + NaCl $\not\rightarrow$ CH$_3$Cl + NaOH

reverse OK

Rcts $[\neq]$ Pdts $\rightarrow$ OK

Analogy $R \rightarrow H$

HOH + NaCl $\rightarrow$ HCl + NaOH

very unfavorable

R-o-T strong BASE

but $\rightarrow$ OH + HCl $\rightarrow$ $\rightarrow$ Cl$- \rightarrow$ H$_2$O

check: analogy HOH + HCl $\rightarrow$ HCl + HOH

Rot HOH weak base ($H_3O^+ - 2$)

mechanism: $S_N^1$

PRINC. MICROSCOPIC REVERSIBILITY

if we know BEST PATH $A \rightarrow B$

then also " " " $B \rightarrow A$

$\rightarrow$ OH $\rightarrow$ H-Cl $\rightarrow$ [ + $\rightarrow$ Cl$^-$ ] $\rightarrow$ [ + H$^+$ ] + $\rightarrow$ OH$^-$

$\rightarrow$ Cl$^-$ $\rightarrow$ [ $\rightarrow$ Cl$^-$ ] $\rightarrow$ H$_2$O$^-$
DAY 14-7

1. Rxn w/ HCl too slow 1° & 2° ROH
2. ROH $\xrightarrow{HBr}$ RBr faster for 3°/2° ROH
   b/c HBr stronger acid

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WHICH RXNS WILL NOT WORK?

1. \[ \text{OH} \xrightarrow{HBr} \text{Br} \]
2. \[ \text{OH} \xrightarrow{HCl} \text{Cl} \]
3. \[ \text{OH} \xrightarrow{NaBr} \text{Br} \]

A. 1 & 2
B. 1 & 3
C. 2 & 3
D. ONLY ONE RXN FAILS
E. THEY ALL FAIL
DAY 14-8

\[
\text{OH} \xrightarrow{\text{HBr, } \Delta} \text{Br} \\
\text{NaBr, } \Delta \\
\]

\[1^\circ \text{ROH} \rightarrow 1^\circ \text{ROH}_2 \rightarrow S_{N2}\]

\[\text{CH}_2\]

\[1^\circ \text{C}^+\]

\[\text{Br}^- + \text{H}_2\text{O}\]

IN YOUR GROUPS, DESIGN A SYNTHESIS

\[\text{OH} \xrightarrow{?} \text{C≡N}\]

Can't do

\[\text{OH} \xrightarrow{\text{NaCN, } \Delta} \text{OR} \xrightarrow{\text{HCN}}\]

\[\text{C≡N} = \text{Nu}\]

\[\text{H-C≡N} \neq \text{Nu}\]

only Nu that "tolerate" low pH Cl^–/Br^–/I^–
DAY 14-9

SPECIAL REAGENTS FOR

ROH $\rightarrow$ [RL₉] $\xrightarrow{\text{Nu}}$ RNu \text{ W/O STRONG ACID}

1. ROH $\xrightarrow{\text{SOCl₂ \text{pyridine}}} RCl$

\[
\begin{align*}
\text{Cl-S-O-R} & \xrightarrow{\text{Nu}} \text{Cl-S-O-R} \\
\text{Cl-S-O-R} & \xrightarrow{\text{SN₂ (or SN₁)}} \text{Cl-S-O-R} \\
\text{Cl-S-O-R} & \xrightarrow{\text{SN₂ (or SN₁)}} \text{Cl-S-O-R}
\end{align*}
\]

analogy:

\[
\begin{align*}
\text{HO-S-O} & \xrightarrow{\text{1+2}} \\
\text{HO-S-O} & \xrightarrow{\text{SN₂ (or SN₁)}} \\
\text{Cl-S-O} & \xrightarrow{\text{SN₂ (or SN₁)}}
\end{align*}
\]

\[
\begin{align*}
\text{Cl-SO₂} & \xleftarrow{\text{+ R-Cl}} \\
\text{Cl-SO₂} & \xleftarrow{\text{+ R-Cl}}
\end{align*}
\]

2. ROH $\xrightarrow{\text{PBr₃}} RBr$

\[
\begin{align*}
P-Br & \text{ very weak} \\
\text{ROH does SN₂ attack @ P making P-O} \\
P-O^- & \text{ Lg analogous to HO-P-O^- weak base}
\end{align*}
\]

similarities to SOCl₂
DAY 14-10

3. $\text{ROH} \xrightarrow{\text{R'SO}_2\text{Cl}} \text{RO-SO}_2\text{R'} \xrightarrow{\text{Nu}} \text{RNu}$

$\text{R'SO}_2\text{Cl} = \text{R}'\overset{+2}{\text{S}}\text{-Cl}$ — very weak

$\text{S_N}_2$ by ROH @ S

$\overset{0^-}{\text{O}}\overset{0^-}{\text{S}}\overset{+2}{\text{R}}' \quad \text{Lg analogous to} \quad \overset{0^-}{\text{O}}\overset{0^-}{\text{S}}\text{-OH}$

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Points of confusion:

1. Must learn to draw $\text{R-O-SO}_2\text{R'}$ “alkyl sulfonate”

2. Must learn abbreviations

- $\text{-Ts (tosyl)} - \overset{0^-}{\text{S}}\overset{+2}{\text{Cl}}\text{-CH}_3$

\[
\begin{align*}
\text{TscI} & \quad \text{tosyl chloride} \\
\text{ROTs} & \quad \text{tosylate} \\
\Theta\text{OTs} & \quad \Theta\text{Lg}
\end{align*}
\]

- $\text{-Ms (mesyl)} - \overset{0^-}{\text{S}}\overset{+2}{\text{CH}}_3$

similar
DAY 14-11

IN YOUR GROUP, IDENTIFY THE ERRORS IN

\[ \text{OH} \xrightarrow{\text{TSCI, pyridine}} \text{Ts} \]

\[ \text{NaN}_3 \downarrow \text{DMSO} \]

\[ \text{N}_3 \]