CHEM 221 section 01

LECTURE #26 Thurs., Dec.01, 2005

ASSIGNED READINGS:

TODAY'S CLASS: Finish Ch.11

PLAN A PROBLEM SESSION DURING EXAM PERIOD:

Dec.13?
Dec.14?
Dec.15?
Dec.19?

http://artsandscience.concordia.ca/facstaff/P-R/rogers

11.9 Substitution & elimination rxns in synthesis

Classic use of S_N2 reaction: TO PREPARE ETHERS

Williamson ether synthesis

$$\underset{\text{alkyl halide}}{R{-}Br} + \underset{\text{alkoxide ion}}{R{-}O^-} \longrightarrow \underset{\text{ether}}{R{-}O{-}R} + Br^-$$

- **Alkoxides are easily & cleanly made by treating ROH with:**

  sodium metal: $ROH + Na \rightarrow RO^- + Na^+ + \frac{1}{2} H_2$ (redox rxn)

  OR

  sodium hydride: $ROH + NaH \rightarrow RO^- + Na^+ + H_2$ (acid-base rxn)

- **Versatile:** can use either of 2 combinations of alkyl halide & alkoxide whichever favours the desired S_N2 rxn more (over E2…)

$$\underset{\text{propyl bromide}}{CH_3CH_2CH_2Br} + \underset{\text{butoxide ion}}{CH_3CH_2CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_2CH_2CH_3} + Br^-$$

$$\underset{\text{butyl bromide}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{propoxide ion}}{CH_3CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_2CH_2CH_3} + Br^-$$

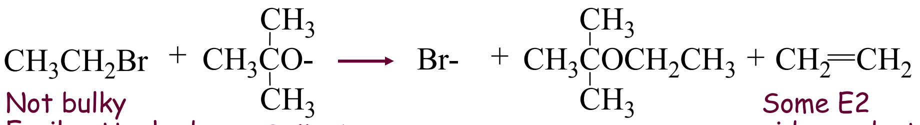
More important if one alkoxide is bulkier… Poorer Nu…

To synthesize an ether:

see best results if…

- **provide the less hindered group via the alkyl halide**

use bulkier one as alkoxide; otherwise δ^+ C's backside is too hindered…



$$CH_3CH_2Br + CH_3\overset{CH_3}{\underset{CH_3}{C}}O^- \longrightarrow Br^- + CH_3\overset{CH_3}{\underset{CH_3}{C}}OCH_2CH_3 + CH_2{=}CH_2$$

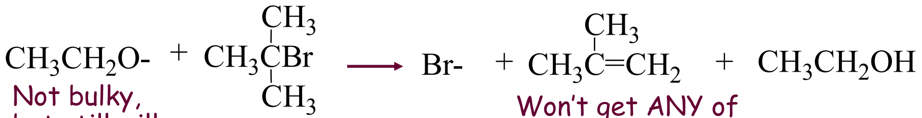
Not bulky
Easily attacked
via backside

Bulky base,
so will still
get some alkene…

Desired ether

Some E2
side product
(*t*-BuOH too)

Compare to results if do rxn the other way around:



$$CH_3CH_2O^- + CH_3\overset{CH_3}{\underset{CH_3}{C}}Br \longrightarrow Br^- + CH_3\overset{CH_3}{C}{=}CH_2 + CH_3CH_2OH$$

Not bulky,
but still will
not be able to
reach backside
of the δ^+ C

Too hindered!
Not reactive
at all via S_N2!

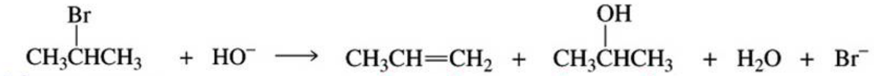
Won't get ANY of
the desired ether!
(a good way to make
this alkene though!)

To efficiently synthesize an alkene via loss of HX:

- **use the most hindered alkyl halide possible**

EXAMPLE: If we want to prepare propene in the lab: $CH_3CH{=}CH_2$
- Dehydrohalogenate 2-bromopropane ***or*** 1-bromopropane?

A good route to the alkene: (hindered halide, plus strong base
even better if use strong BULKY base)



$$CH_3\overset{Br}{C}HCH_3 + HO^- \longrightarrow CH_3CH{=}CH_2 + CH_3\overset{OH}{C}HCH_3 + H_2O + Br^-$$

2-bromopropane **major product** **minor product**

A good route to an alcohol: (less hindered halide, OH^- as Nu):

$$CH_3CH_2CH_2Br + HO^- \longrightarrow CH_3CH{=}CH_2 + CH_3CH_2CH_2OH + H_2O + Br^-$$

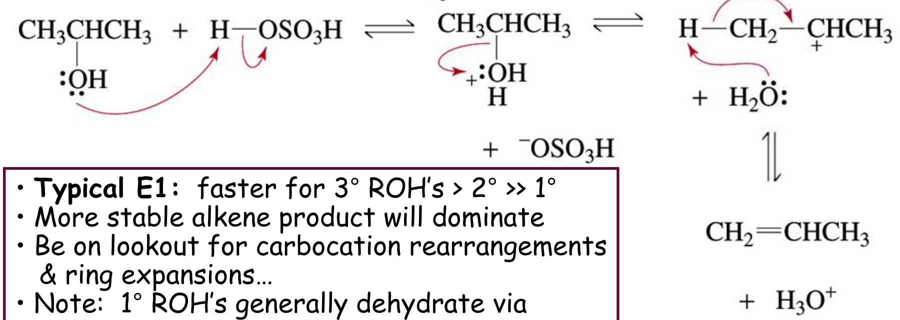
1-bromopropane **minor product** **major product**

Another route to alkenes: E1/E2 loss of H_2O…
Acid-catalyzed dehydration of alcohols (see Ch.12.5)

An E1 rxn following protonation of OH to create a good LG (water!)
"acid-catalyzed dehydration" ***(reverse of hydration of alkenes…)***

$$\underset{\text{a 2° or 3° alcohol}}{RCHH\text{-}CH(OH)\text{-}R'} \xrightarrow[\Delta]{H_2SO_4 \text{ or } H_3PO_4} RHC{=}CH\text{-}R' + H_2O$$

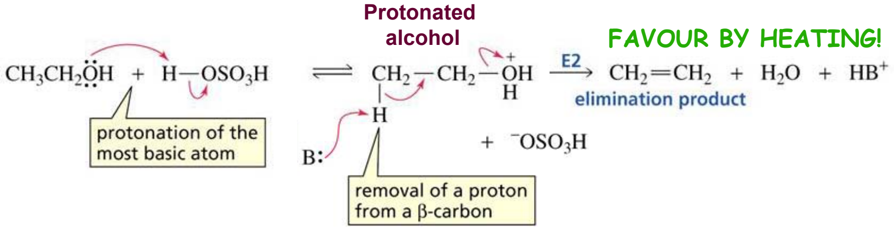
mechanism of dehydration (E1)



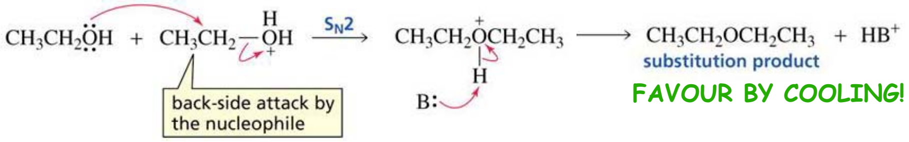
- **Typical E1:** faster for 3° ROH's > 2° >> 1°
- More stable alkene product will dominate
- Be on lookout for carbocation rearrangements & ring expansions…
- Note: 1° ROH's generally dehydrate via an acid-catalyzed E2 mechanism

Typical situation for a primary alcohol: E2 & S_N2

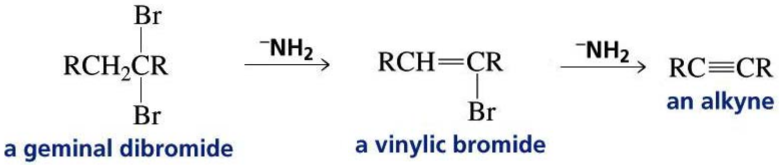
dehydration (E2) and competing substitution (S_N2)



Side reaction = competing substitution, a route to ethers…
"Self-attack" of alcohol (solvent) on protonated alcohol molecule:



11.10 Consecutive E2 elimination reactions

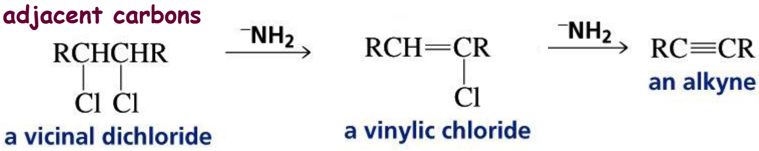


$$RCH_2\overset{Br}{\underset{Br}{C}}R \xrightarrow{^-NH_2} RCH{=}\underset{Br}{C}R \xrightarrow{^-NH_2} RC{\equiv}CR$$

"geminal" = substituents on same carbon

A 2nd elimination can occur under same conditions!
⇨ the sp^{2}C's H in the vinylic halide would be more acidic than any sp^{3}C's H's in molecule, due to:
1) EWG effect of LG &
2) higher electronegativity!

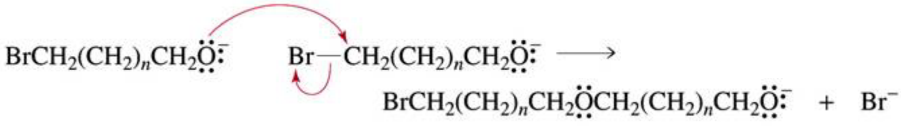
"vicinal" = substituents on adjacent carbons



$$R\underset{Cl}{C}H\underset{Cl}{C}HR \xrightarrow{^-NH_2} RCH{=}\underset{Cl}{C}R \xrightarrow{^-NH_2} RC{\equiv}CR$$

11.11 Intermolecular *vs.* intramolecular reactions

Intermolecular reactions: typical rxn between 2 molecules



$$BrCH_2(CH_2)_nCH_2\ddot{\underset{..}{O}}{:}^- \quad Br{-}CH_2(CH_2)_nCH_2\ddot{\underset{..}{O}}{:}^- \longrightarrow BrCH_2(CH_2)_nCH_2\ddot{\underset{..}{O}}CH_2(CH_2)_nCH_2\ddot{\underset{..}{O}}{:}^- + Br^-$$

Intramolecular reactions: Nu & LG within same molecule
lead to "ring closure"
→ USEFUL ROUTES TO CYCLIC CMPDS

Intramolecular rxns favoured by:
- **low concentration of reactant** → so only Nu it sees is inside itself!
- **formation of a 5- or 6-membered ring**
  →smaller rings very strained, so don't form easily
  (3-memb. rings form faster due to better orientation wrt backside…)
  →larger rings: so much conformational freedom (so many bonds to rotate) that Nu & LG ends are very unlikely to meet up

11.12: Designing a synthesis
(& 4.12) synthetic planning & retrosynthetic analysis

Syn·the·sis \ ˈsin(t)-thə-səs \ noun [Gk, fr. *Syntithenai* to put together]

1.a the composition or combination of parts or elements so as to form a whole
  b **the production of a substance by the union of chemical elements, groups or simpler compounds or by the degradation of a complex compound**
  c the combining of often diverse conceptions into a coherent whole
2.a **deductive reasoning…**

"Starting material" = what you start with "*SM*"
"Target molecule" = desired compound

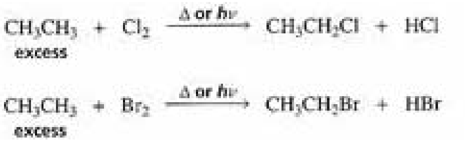
Is there an obvious sequence of rxns that could lead to this product?

- if starting material can only undergo 1 type of rxn: start there!
- remember the tools at your disposal (rxn types, & regio/stereochem)
- often convenient to:
  - use substitution to switch functional groups
  - use alkene intermediate to switch locations of groups

Summary of basic organic reactions (see end-of-chapter summaries)

STARTING WITH AN ALKANE

- **Can add a functional group**
  Route to: alkyl halides



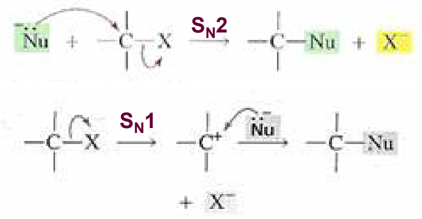
$\underset{\text{excess}}{CH_3CH_3} + Cl_2 \xrightarrow{\Delta \text{ or } h\nu} CH_3CH_2Cl + HCl$

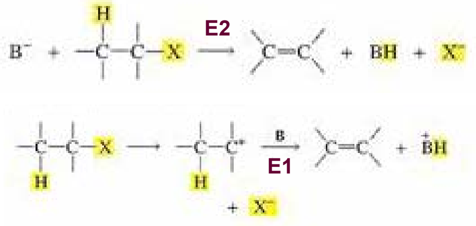
$\underset{\text{excess}}{CH_3CH_3} + Br_2 \xrightarrow{\Delta \text{ or } h\nu} CH_3CH_2Br + HBr$

STARTING WITH AN ALKYL HALIDE

- **Can replace halide (substitution)**

OR **eliminate small molecule HX**





Route to: different halides
alcohols, ethers,
amines, thiols,
nitriles, acetylenes,
ETC!

Route to: alkenes

STARTING WITH AN ALKENE

- **Can add electrophiles**

$RCH{=}CH_2 + H_2 \xrightarrow[\text{or Ni}]{\text{Pd/C, Pt/C}} RCH_2CH_3$ **ALKANES**

MARKOVNIKOV ADDITIONS **ANTI-MARKOVNIKOV ADDITIONS**

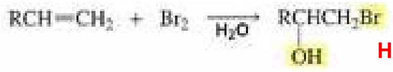

$RCH{=}CH_2 + HX \longrightarrow RCH(X)CH_3$

ALKYL HALIDES

$RCH{=}CH_2 + HBr \xrightarrow{\text{peroxide}} RCH_2CH_2Br$


$RCH{=}CH_2 + Br_2 \xrightarrow[CH_2Cl_2]{} RCH(Br)CH_2Br$

VICINAL DIHALIDES


$RCH{=}CH_2 + Br_2 \xrightarrow[H_2O]{} RCH(OH)CH_2Br$

HALOHYDRINS


$RCH{=}CH_2 + H_2O \overset{H^+}{\rightleftharpoons} RCH(OH)CH_3$

$RCH{=}CH_2 \xrightarrow[\text{2. } HO^-,\ H_2O_2,\ H_2O]{\text{1. } BH_3/THF} RCH_2CH_2OH$

ALCOHOLS


$RCH{=}CH_2 + CH_3OH \overset{H^+}{\rightleftharpoons} RCH(OCH_3)CH_3$

ETHERS

Designing a synthesis: synthetic planning & retrosynthetic analysis

(4.12, 6.11, 11.12)

OUR GOAL (ideally): **SYNTHESIZE THE TARGET MOLECULE USING…**

- fewest # steps possible
- highest yield of desired product possible (intermediate steps too)
- simplest / safest / cheapest / fastest rxns possible

OUR GOALS FOR NOW (we are beginners…):

- use chemically reasonable sequence of rxns *(desired product = major)*
- if will get a mixture of products at any step, say so!
  - ⇨ would have to purify the product before using in next step

PLANNING OUR SYNTHESIS:

1. **Compare the SM & target molecule**
   C skeleton: How do SM & target compare? Any clear "subunits"?
   Functional groups: Any new groups? Any groups present in both?
   Choose conditions that won't react with groups that remain unchanged.
2. **Is there an obvious set of reactions to get from SM to target?**
   - Try to add very reactive functional groups near the end.
3. **If there is no obvious forward plan: try to work backwards!**
   "RETROSYNTHETIC ANALYSIS"

“Retrosynthetic analysis” (E.J.Corey, organic chemist – Nobel Laureate 1990)

Work backwards from the target molecule: *(see 6.10 – ignore alkyne rxns)*
→ **do you know any reactions that product that type of compound?**

e.g., a particular functional group:

an alcohol?	*Substitution, or hydration of alkene*
a nitrile?	*Substitution with Nu = CN^-*
a terminal alkyne?	*Substitution with Nu = $HC\equiv C^-$*

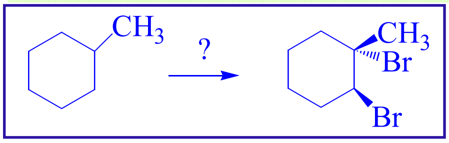
e.g., a particular regiochemistry or stereochemistry:

a primary alcohol adjacent to a 2° C?	*Alkene hydration – anti-Markov.*
vicinal dihalide with anti orientation?	*Alkene halogenation*
vicinal OH & X (= halohydrin)?	*Alkene halogenation in water*
a cyclic alkane with trans substituents (∴ cis H's!)?	*Alkene hydrogenation*

CONVENTIONAL WAY TO SHOW RETROSYNTHETIC ANALYSES:
- → **start with target molecule & work backwards, 1 rxn at a time**
- → **use open arrows “⇒” to denote backwards steps**
- → **once you have a plan: write reactions in forward order & only THEN write in the reagents**

(NOTE: rxns don't need to balance, & don't include mechanistic details)

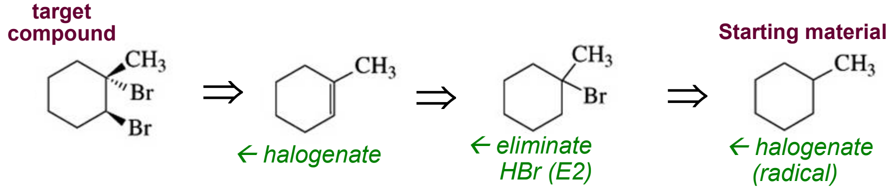
Now we can design a synthesis…



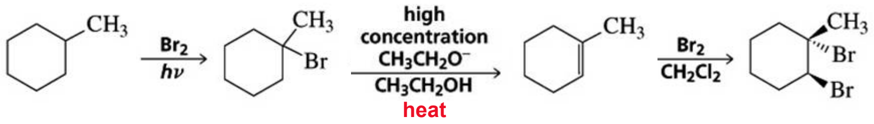
Can't do this in one step!
- SM = alkane (only rxn: halogenation)
- target = vicinal dihalide…

ANY IDEAS?

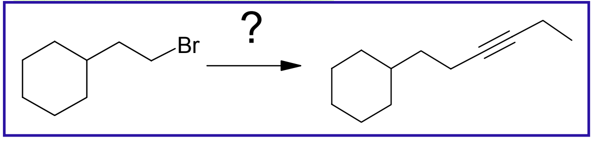
Retrosynthetic analysis: *(don't show reagents; helpful to note rxn types here, since you're thinking about regio & stereochem now!)*



Proposed synthetic route: *(show all reagents & conditions here)*



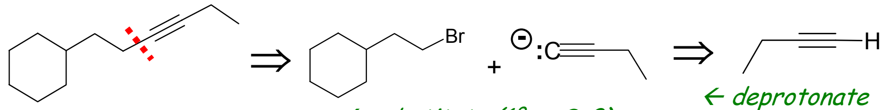
Another synthesis…



- SM = an alkyl halide
- target = an alkyne!

(so far: know RC≡C$^-$ as Nu)
ANY IDEAS?

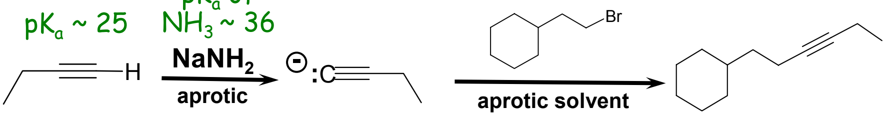
Retrosynthetic analysis: *(helpful to note rxn types – but not required)*



*← substitute (1° ∴ S_N2)
(avoid E2 competition?
ok … S_N2 > E2 for 1°)*

*← deprotonate
(need a base
whose conjugate
acid's pK_a > this)*
pK_a ~ 25

Synthetic route: *(show all reagents & conditions)*



pK_a ~ 25

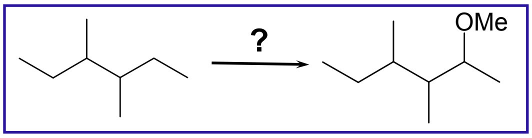
pK_a of NH_3 ~ 36

$NaNH_2$
aprotic solvent

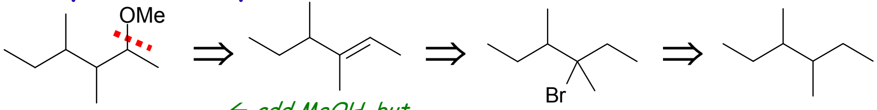
aprotic solvent

One last synthesis…

- SM = an alkane
- target = an ether
- same backbone…



Retrosynthetic analysis:

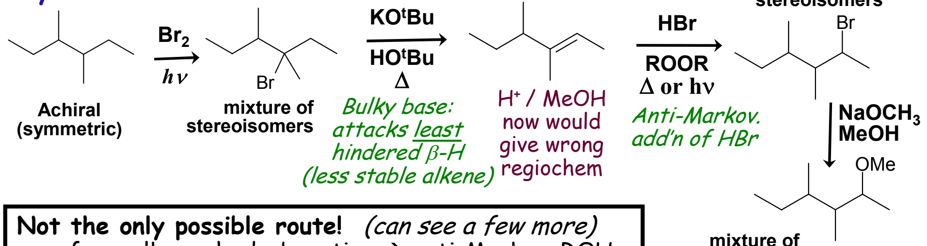


*← add MeOH, but
anti-Markovnikov???
Can't do this directly!*

*← eliminate HX,
non-Zaitsev!*

← brominate

Synthetic route:



Achiral (symmetric)

Br_2
$h\nu$

mixture of stereoisomers

KO^{t}Bu
HO^{t}Bu
Δ

*Bulky base:
attacks least
hindered β-H
(less stable alkene)*

H$^+$ / MeOH
now would
give wrong
regiochem

HBr
ROOR
Δ or hν

*Anti-Markov.
add'n of HBr*

mixture of stereoisomers

$NaOCH_3$
MeOH

**mixture of stereoisomers
(due to Br precursor)**

Not the only possible route! *(can see a few more)*
e.g., from alkene: hydroboration → anti-Markov. ROH
→ deprotonate & react with CH_3I

HERE ENDETH ORGANIC I

FINAL EXAM: Tues. Dec. 20th, 2-5pm
Loyola GYM

Allowed:
calculator
model kit
(pre-build a cyclohexane & 2 chiral C's ⇨ quieter)

Not allowed:
programmable calculators
cell phones
electronic dictionaries
(word-to-word translation dictionaries are ok)