Chem 221 W08 Sect 52 Dr. C. Rogers

Answer Key

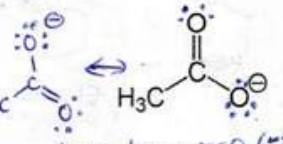
NAME: Rogers

INTRODUCTORY ORGANIC CHEMISTRY I --- PROBLEM SET #3

INSTRUCTIONS: ANSWER ALL QUESTIONS ON THESE PAGES.
HAND IN (stapled, with no extra pages please) ON **Thursday April 11th** (I will hold office hours that day from 6-7pm.)
ALL MATERIAL CAN ALL BE FOUND IN THE CLASS NOTES and/or IN BRUICE CHAPTERS 1-9, 11.

 # 1. Provide one or two key words for explanation, and circle the reagent in each pair that is most..

- Nucleophilic in a polar aprotic solvent: (so it can dissolve well... / does NOT screen Nu...) → more Nu'ic if more basic



lower charge per O (−½ each) or  higher charge on O (−1)

- Nucleophilic in a polar aprotic solvent: → more Nu'ic if can GET where it is going! eg. RCH_2X

$(CH_3)_3CO^-$ ← −1 on O — BULKY, cannot access backside of electrophilic C's... or $CH_3CH_2O^-$ ← −1 on O — NOT BULKY

- Reactive towards S_N2: CONCERTED

rate $_{SN2} = k[RX][Nu]$ (conc. AND reactivities!)

$R\text{-}X + Nu^\ominus \rightarrow Nu\text{-}R + X^\ominus$

→ faster if less steric hindrance at backside of electrophilic C

$CH_3CHBrCH_3$ 2° or $CH_3CH_2CH_2Br$ 1°

- Reactive towards S_N1: VIA C⊕ INTERMEDIATE

rate $_{SN1} = k[RX]$ (conc., RX reactivity)

$R\text{-}X \rightarrow R^\oplus + X^\ominus \rightarrow \ldots$ (RLS)

→ faster if more stable carbocation int.
→ faster if better LG!

CH_3CHICH_3 2° I or $CH_3CHClCH_3$ 2° Cl

- Reactive towards E1: VIA C⊕ INTERMEDIATE

rate $_{E1} = k[RX]$ (RX reactivity!)

$R\text{-}X \rightarrow R^\oplus + X^\ominus \rightarrow \ldots$ (RLS)

→ faster if more stable C⊕
→ faster if better LG.

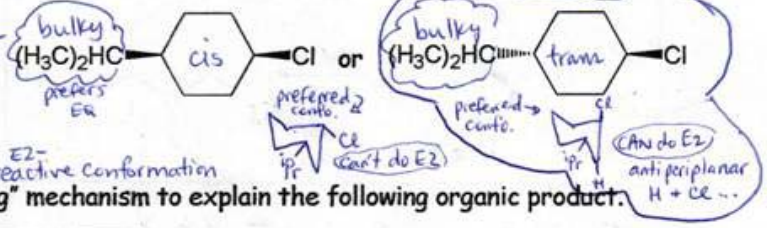
$CH_3CHBrCH_3$ 2° Br or $CH_3CH_2CH_2Br$ 1° Br

- Reactive towards E2: CONCERTED

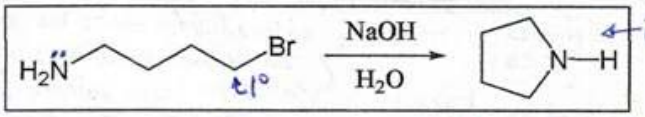
rate $_{E2} = k[RX][B]$ (↑ in reactive conformation...)

$R\text{-}X + B^\ominus \rightarrow$ alkene + $BH^\oplus X^\ominus$

→ faster if stronger base or if better LG or if more of molecule in E2-reactive conformation



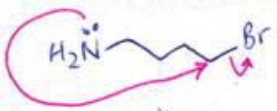
 # 2. Write a step-by-step "arrow-pushing" mechanism to explain the following organic product.



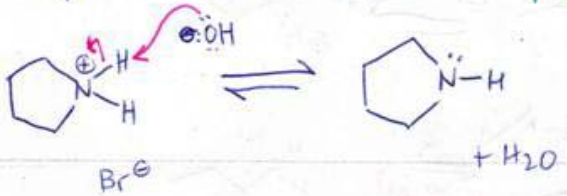
← intramolecular substitution reaction!

- S_N2 attack by neutral $:NR_3$ tail of molecule
- followed by deprotonation by ^-OH
- Note: pKa of protonated amines ≈ 10 so if we didn't have NaOH, the solution pH would likely be near neutral, and the product amine would remain protonated (pH of solution < pKa!)

NOTE: ^-OH is not a strong enough base to quantitatively deprotonate an amine! (pKa ~40!)



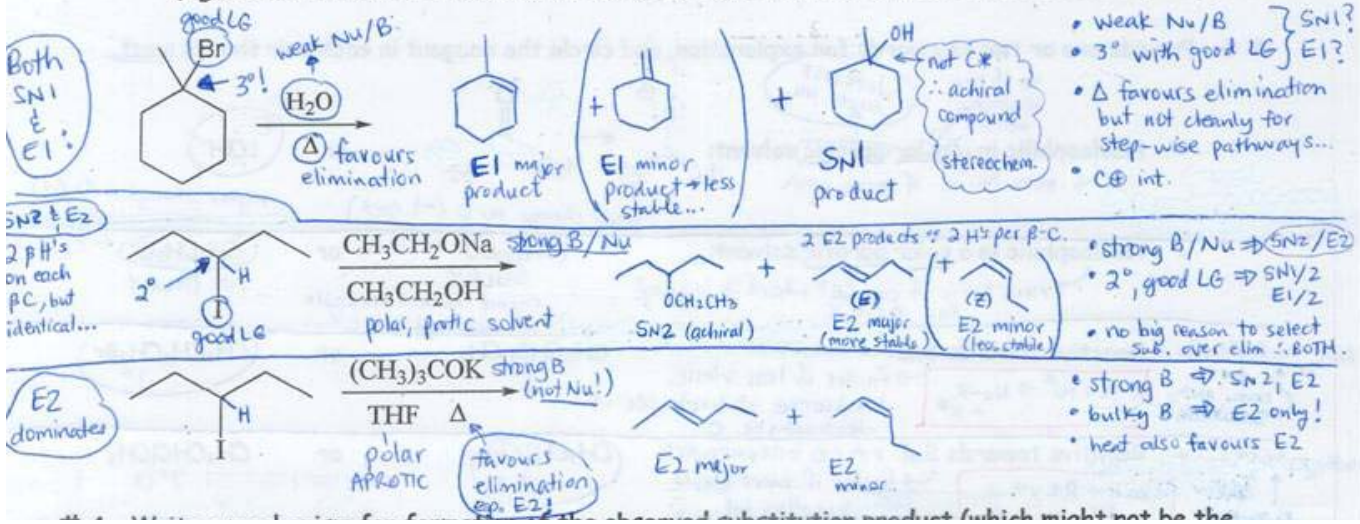
S_N2 ↓



 # 3. Draw line structures of the major product(s) of the reactions below. If more than one product is likely, draw both but indicate which product is preferred and why. For each rxn, also include:

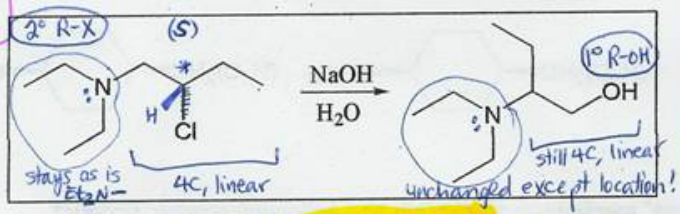
i. the expected stereochemistry

ii. a few keywords about the mechanism that explain the reaction outcome (*e.g.*, substitution/elimination (S_N1, S_N2, E1, E2), C+/radical intermediate, concerted, *etc.*).



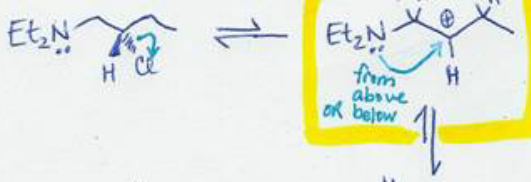
This will not be counted for marks.

 # 4. Write a mechanism for formation of the observed substitution product (which might not be the only product – it is simply the product of interest). If the starting material has the S configuration, what is the configuration of the stereocentre in the product? ⇒ racemic

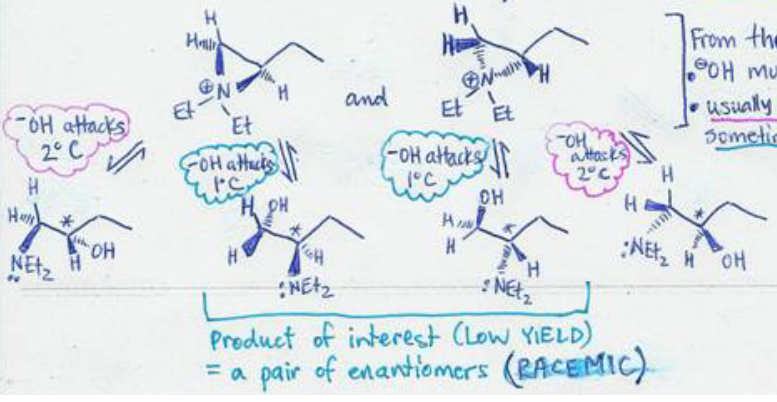


NOTE: this probably is NOT the major product

- major differences between reactant + product is that the
  1. amine group has moved along the carbon chain ⇒ rearrangement?
  2. LG gets replaced by OH, but not at same position ⇒ NOT S_N2.
     ⇒ some sort of S_N1 pathway



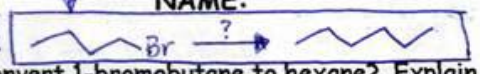
- 2° C⊕ (planar)
- Is there any way to rearrange (via bonds/e⁻) on adjacent atoms) to ↑ its stability?
  - → if 1,2-hydride shift occurs: new 2° C⊕ (no great help)
  - → if N's lone pair "leans over": cyclic intermediate like a halonium ion! now closed valence! ☺ much more stable "masked carbocation"



From these intermediates:
- ⊖OH must attack anti to NR_2
- usually attacks the 2°C, but sometimes might attack 1°C (not major regiochemistry path) only way to imagine the desired product forming!

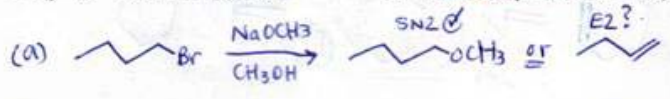
Note: a "masked" 1° C⊕ is more stable than a real 1° C⊕, so the probability of a reaction proceeding via a masked 1°C⊕-like ≠ is higher than via a 1°C⊕...

Note: 1° RX ⇒ SN2, E2 ; SN1 ✗, E1 ✗ (good LG)

i.e., Achieve this synthesis: 

 # 5. Which sequence of reagents would work best to convert 1-bromobutane to hexane? Explain briefly. *Hint: you may need to refer to the alkyne reactions from Ch.6....*

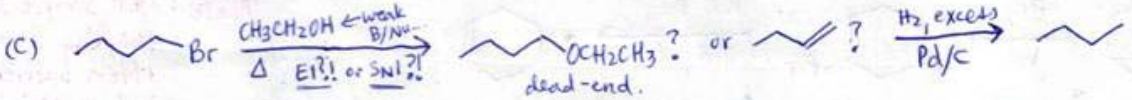
- ✗ a) 1. $NaOCH_3$, CH_3OH ✓ 2. NaCN ✗ 3. $NaNH_2$ (i.e., Na, NH_3) ← i.e., Na, NH_3 ... which reduces alkynes to trans alkenes.
- ✓ b) 1. $NaC{\equiv}CH$ 2. H_2 (excess), Pd/C
- ✗ c) 1. CH_3CH_2OH, Δ ✗ 2. H_2 (excess), Pd/C
- ✗ d) 1. NaCH ?!! 2. BH_3/THF 3. H_2O_2, OH^-, H_2O
- ✗ e) 1. $NaC{\equiv}CCH_2CH_3$ ✓ 2. $NaNH_2$ (i.e., Na, NH_3) ✗

(a) 

dead-end because: ① cannot push off $^{\ominus}OCH_3$ (stronger B!) ② won't react with alkene.

(b) 

✓ target!

(c) 

dead-end. ✗ not target

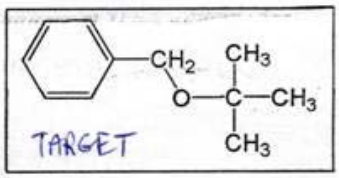
(d) 

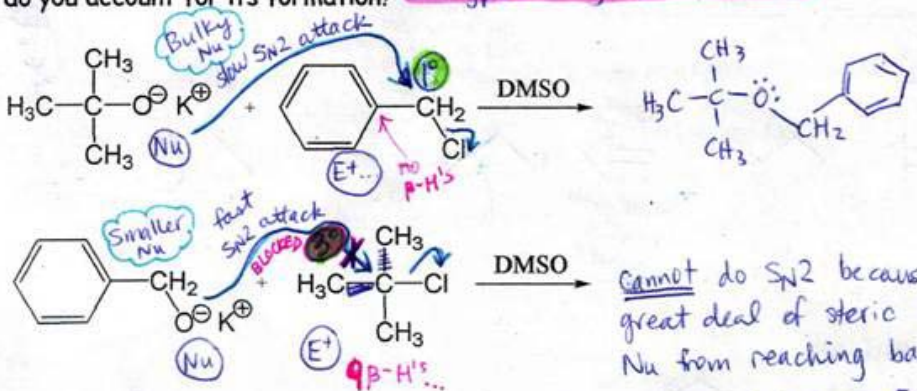
makes no sense... must not be correct answer... a nonsense reagent!

(e) 

✗ not desired target.

 # 6. The Williamson ether synthesis involves treatment of an alkyl halide with a metal alkoxide. Shown below are two reactions intended to give benzyl *tert*-butyl ether (shown in the box). One reaction gives the ether in good yield, the other reaction does not. Which reaction gives the ether? What is the product of the other reaction, and how do you account for its formation? Rxn types: strong Nu/B ⇒ SN2/E2 ...



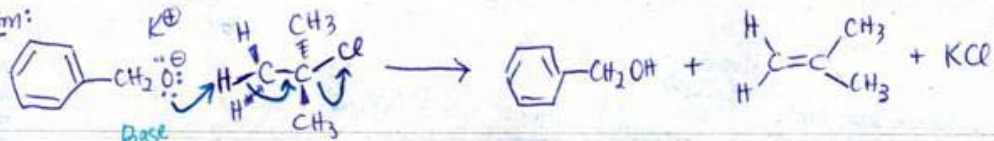


Note: the R-X has NO β-H's, so E2 cannot occur. Substitution must be an option. Nu is bulky (∴ slow at attacking), but at least the electrophilic C is 1° ∴ not blocked there.

Cannot do S_N2 because R-X is 3°, so there is a great deal of steric hindrance that prevents Nu from reaching backside of the C-Cl bond.

Major product here = E2 product = alkene, not ether.

E2 mechanism:



Base attacks β-H that is anti-periplanar to the Cl...

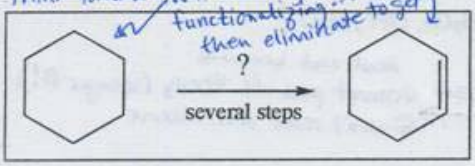
→ NOT MECHANISMS...

 # 7. Synthesize the following compounds (via a series of sequential reactions) starting from the starting material shown. You can use any other reagents you need. **For each step in your pathway:**

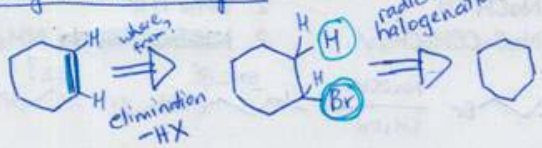
- **above/below the reaction arrow: show the required reagents (+ solvent & conditions if critical)**
- **after the arrow: draw the major product (& if you think the yield will not be good, say so...)**

Hint: Refer to Bruice sections 4.12, 6.12 & 9.11 for synthetic strategies and practice.

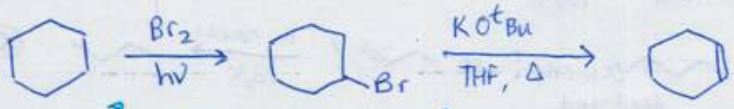
Think forward: will start by functionalizing... then eliminate to target



Think backwards: Retrosynthetic analysis:



SYNTHESIS: 3-step sequence

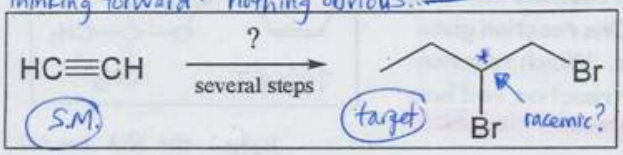


↑ only way we know to functionalize an alkane!

↑ want to eliminate HBr, and not substitute Br by B... ∴ block substitution by using bulky base + warm up a little to encourage elimination

Note: for simple sequences, thinking forwards is often sufficient.... but as things get more complicated, working backwards helps a lot.

Thinking forward: nothing obvious.. ∴ break it down...



Pieces:

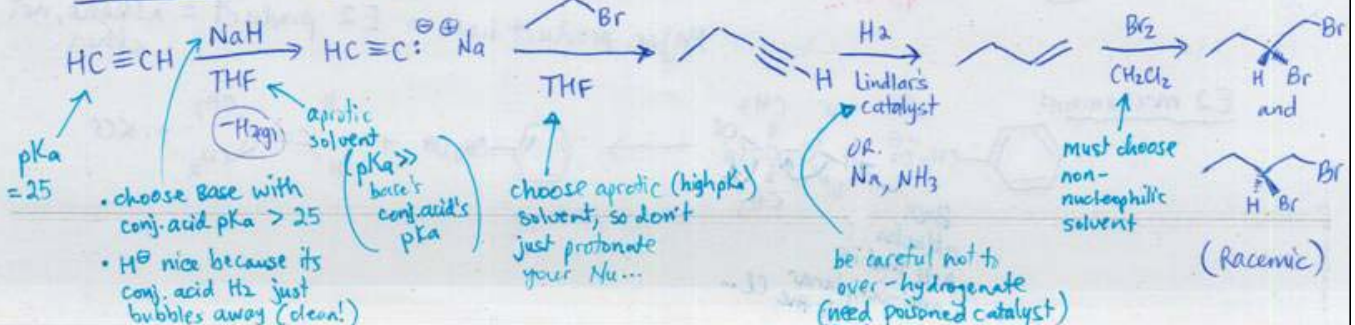
- SM = 2C, alkyne, best used as $^{\ominus}:C\equiv CH$ Nu!
- target = 4C, vicinal dihalide ⇒ precursor ?

need to attach SM's 2C to a 2C chain with attached LG

from alkene! + Br_2

Retrosynthetic analysis:

SYNTHESIS: 4-step sequence



pKa = 25

- choose base with conj. acid pKa > 25
- $H^{\ominus}$ nice because its conj. acid H_2 just bubbles away (clean!)

aprotic solvent (pKa» base's conj. acid's pKa)

choose aprotic (high pKa) solvent, so don't just protonate your Nu...

be careful not to over-hydrogenate (need poisoned catalyst)

must choose non-nucleophilic solvent