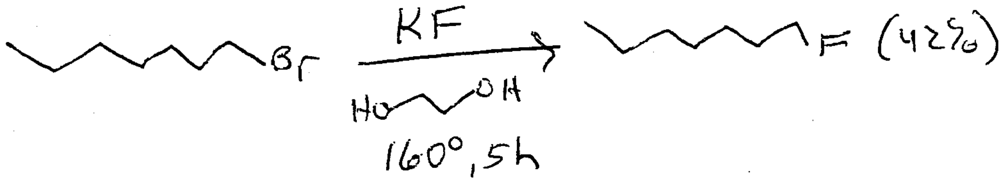
①



Why this solvent instead of H_2O?

What if it had been n-heptyl bromide?

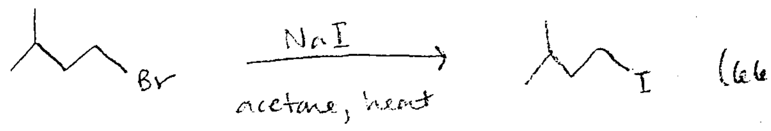
mechanism: S_N2

nucleophile: $F^{\ominus}$

leaving group: $Br^{\ominus}$

Lesson: Classic S_N2 reaction
- stronger base (F^-) replacing weaker base (Br^-)
- Even in a protic solvent you can get S_N2 reaction

②



(66%)

Why does the better leaving group substitute in?

Why is the yield what it is?

What if Cl was in the reaction instead of Br or I?

What if we used a different solvent?

What if heat wasn't added?

What if the Br was on a tertiary or secondary Carbon?

mechanism: S_N2

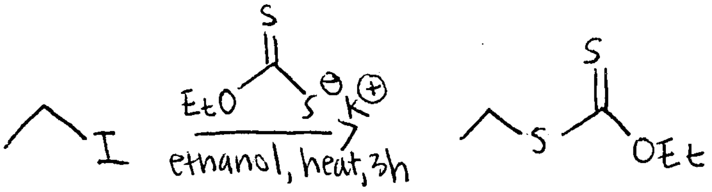
nucleophile: $I^{\ominus}$

leaving group: $Br^{\ominus}$

lesson: the better leaving group (I^-) can be substituted by a worse leaving group (Br^-) under the right conditions

NaI is soluble in acetone, but NaBr is not so NaBr precipitates out of solution and the reaction does reverse

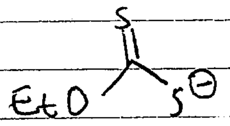
③



(77%)

- why do you heat it?
- why is there such a high yield?
- what if an aprotic solvent had been used instead of ethanol?

mechanism: S_N2

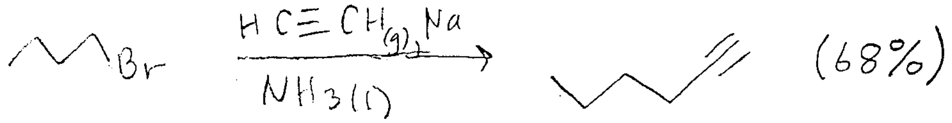
nucleophile / base: 

leaving group: $I^{\ominus}$

lesson: Iodide is a good leaving group because it is a weak base.

In a protic solvent such as ethanol, I^- becomes more nucleophilic and is a worse leaving group, lowever, but this nucleophile becomes even more nucleophilic. (see table on page 355) because of the sulfur.

④



why is NH_3 the solvent?

What happens if Br is attached to a tertiary Carbon instead of being on the end?

Why is the percent yield 68%?

Mechanism: S_N2

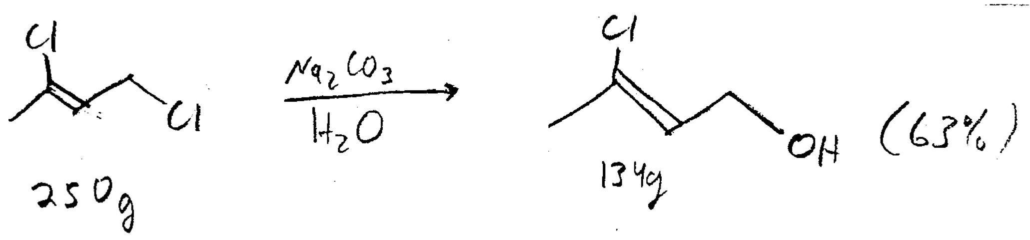
Nu/Base: $HC{\equiv}C^-$

Leaving group: Br^-

Lessons: Standard substitution can occur even if the nucleophile is a ~~Compound~~ multiatomic ion instead of a single atom.

The lack of rearrangement causes the addition of a triple bond at the end of the molecule. (never rearrangement in S_N2 reactions)

⑤



Why is it only 63% efficient?
What would be different if there was no double bond?
Would change in temperature affect the reaction?

mechanism: S_N2

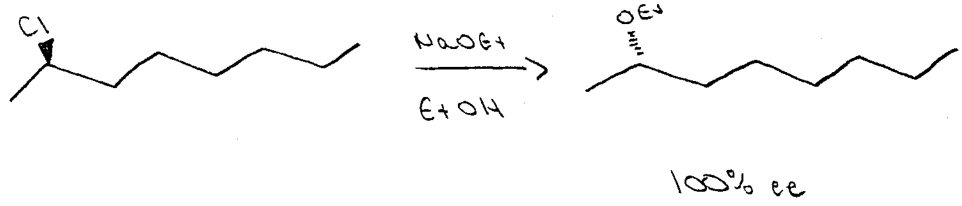
nucleophile: $OH^{\ominus}$

leaving group: $Cl^{\ominus}$

Lessons

→ The nucleophile is not obvious. The base removes the H^+ from the H_2O.
→ A chlorine attached to a double bond cannot be substituted.

⑥



1. Why did OEt add to the opposite side?

2. What would happen to the rate of reaction if the solvent's polarity was increased?

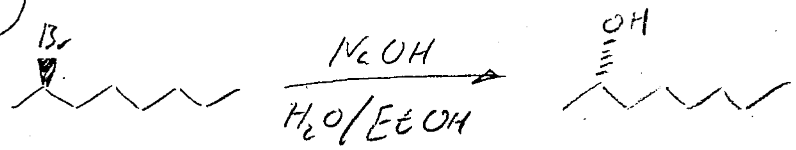
Mechanism: S_N2

nucleophile: $^{\ominus}$O Et

leaving group: Cl$^{\ominus}$

Lesson: inverted configuration relative to reactant?
(not really case specific though)
S_N2 involves direct, stereospecific inversion

⑦



(100% ee)

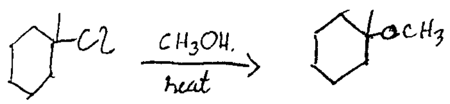
- Why doesn't S_N1 rxn happen here? Why doesn't Br leave of its own accord?
- Why do we only have one product when multiple nucleophiles are present (as solvant) that could do an S_N1 rxn?
- What would happen if you remove NaOH from rxn?

- Mechanism: S_N2
- Nucleophile: OH^-
- Leaving group: Br^-
- Lesson(s)
  - if multiple nucleophiles are present, the strongest one is used; In this case, H_2O is more acidic than ethanol, so we have

$$\underbrace{OH^{\ominus}}_{\text{active nucleophile}} + EtOH \rightleftarrows H_2O + EtO^{\ominus}$$

Also, $EtO^{\ominus}$ has more <u>steric</u> <u>hindrance</u> than $OH^{\ominus}$

8)



Why is heat added?

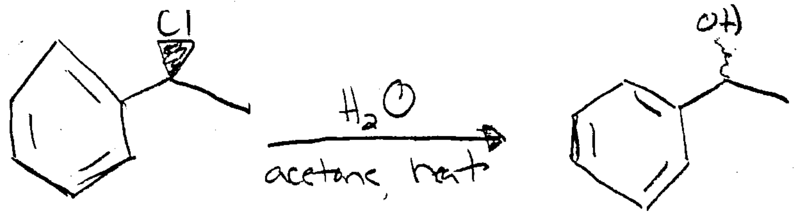
mechanism: S_N1

nucleophile: CH_3OH

Leaving Group: $Cl^{\ominus}$

Reason:
- the more basic group replaces the less basic group ($^{\ominus}OCH_3$ is more basic than $Cl^{\ominus}$)
- CH_3OH is a protic solvent, which will stabilize the carbocation intermediate and the transition state. This conditions favor S_N1 over S_N2 reactions
- The reaction must wait go through the carbocation phase to interact with the solvent.
- Particularly fast with tertiary alkyl halides.

} not especially that there is no strong base present.

⑨ 

(2% ee)

- If water was the solvent, how would this reaction be changed?

- Why is there 2% ee?

Mechanism: Sn1 Reaction

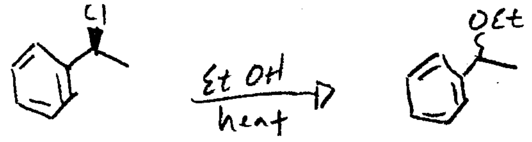
Nucleophile: H_2O

Leaving Group: Cl^-

Lessons: - When heat is applied to a reaction mixture, bonds are more likely to dissociate. -

- ~~when~~ In an $S_{N}1$ reaction you may obtain a racemic mixture. -
(or nearly so)

⑩



("low" % ee)

- Why heat the reaction?
- what changes with different solvents?

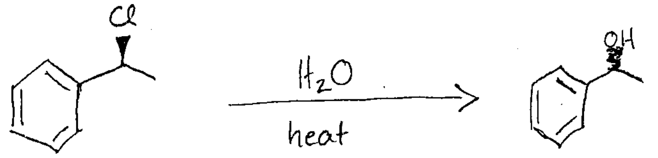
Mechanism: S_N1

Nucleophile: ~~⊖OEt~~ EtOH

Leaving Group: $Cl^{\ominus}$

Lesson: Since the reaction forms a racemic mixture the nucleophile must only attach to the cation after it is completely (or nearly completely) dissociated, allowing it to add to either side

(11)



(17% ee)

* Why is heat required?

* What would happen if a different solvent was used?

* If the C attached to the leaving group was tertiary, how would that affect the enantiomeric excess?

Mechanism: S_N1

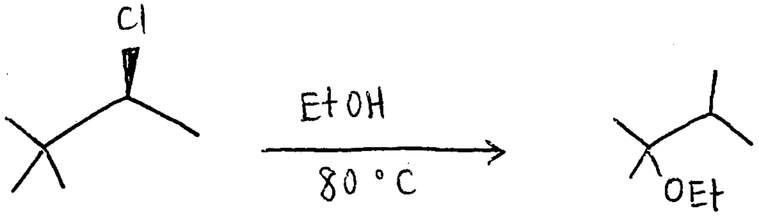
Nucleophile: H_2O

Leaving group: $Cl^{\ominus}$

Lesson: We can see from the 17% ee that when water is the solvent and base ~~the inverted conformation is more probable~~. Squiggle here indicates "unspecified" configuration

- Even with S_N1 conditions we may Not see complete dissociation
- Solvent can have an effect on EE (See #9 & 10)

(12)



Why is EtOH used as solvent?

What if we carried this rxn out at a lower temp.?

mechanism: S_N1

nucleophile: $\mathrm{EtO}^{\ominus}$ (EtOH)

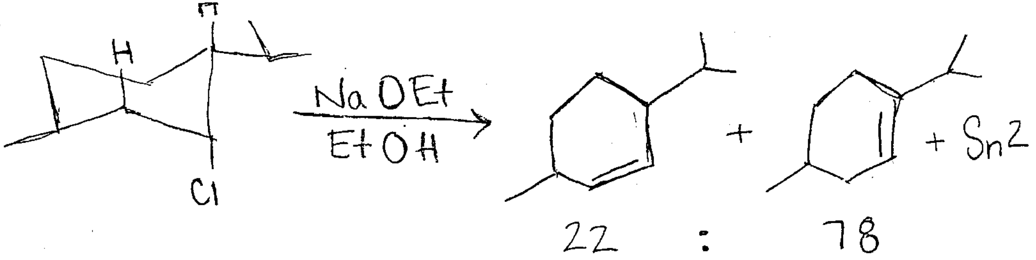
leaving group: $\mathrm{Cl}^{\ominus}$

lesson: carbocation rearrangement
(1,2-methyl shift)

pg. 365

- solvolysis: rxn with a solvent

(13)



- Does Na (making NaCl) react w/ Cl during first stage making $^{\ominus}OCH_3$ to attack H, or is it a byproduct?

- Why is the S_N2 a product?

mechanism → E2 (elimination)

base → $^{\ominus}$OEt

leaving group → $Cl^{\ominus}$

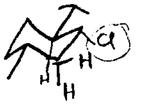
lesson →

— "Zaitsev's rule" the proton is removed from carbon bonded to the fewest H's - thus why we get more of the second product

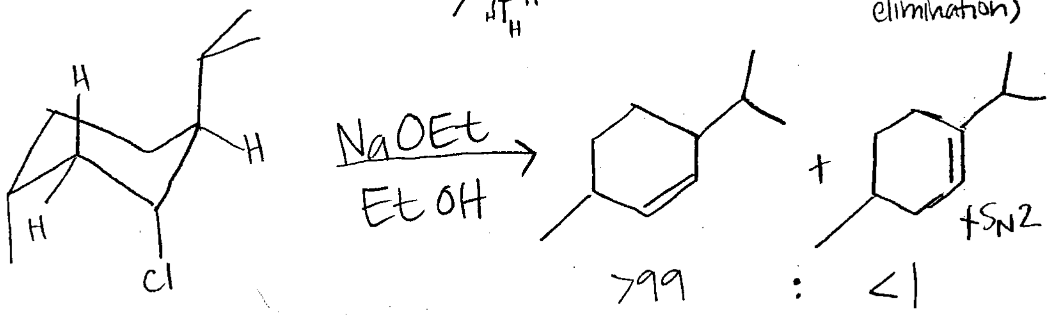
- more substituted (more stable) alkene is major elimination product

-Note: No indication here ratio of E/S

⑭

Note: 

(Equatorial Cl cannot undergo E2 elimination)



1. Is the reason the double bond isn't on the tertiary carbon because the H is in an equatorial position?
2. What if the H and the isopropyl group switched positions?
3. Why is "Zaitsev's" Rule not followed in this rxn?

Mechanism: E2

Nucleophile: $OEt^{\ominus}$

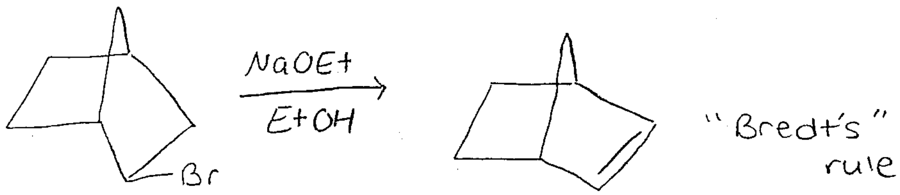
Leaving group: Cl^{-}

LESSON: There is priority when it comes to which H is going to participate in the elimination. The Halide also cannot be in an equatorial position to undergo E2 elimination ✓

} trans-anti elimination best

Note: Almost certainly lots of substitution here.

(15)



-What conditions are necessary for this reaction to take place?

- why this H?

Mechanism: E2

Base: $^{\ominus}OCH_2CH_3$

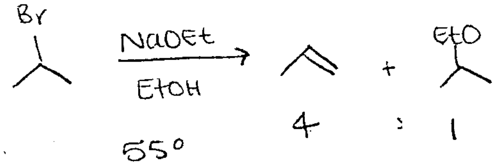
Leaving group: $Br^{\ominus}$

Lesson: In an E2 reaction of a substituted cyclohexane, the groups being eliminated must both be in the axial position (pg 408).

But here we have boat conformation, so instead we have syn-cis elimination from eclipsed H and Br

- "Bredt's" rule - a double bond won't form where it can't fit

⑯



Why does the EtO replace the Br in one of the products?

What if we used NaOH instead of NaOEt?

What if this reaction was done at -80° C?

What if EtOH were replaced with something else?

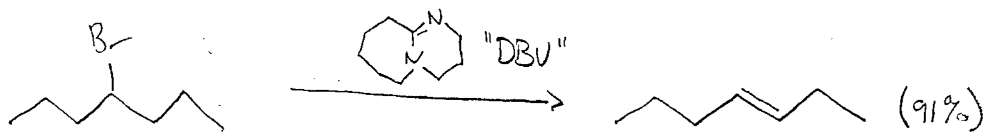
Mechanism: E_2 / S_N2

Base: ~~[illegible]~~ ~~[illegible]~~ $^{\ominus}OCH_2CH_3$

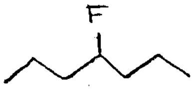
Leaving Group: $Br^{\ominus}$

Lesson: With elimination reactions you can have another product formed along with the main product.

⑰



▷ Why was only 91% of the product shown produced? (Why not 100%?)

▷ What if the structure of the reactant was  instead?

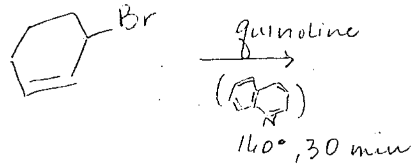
▷ Mechanism: E2

▷ Base: DBU (weak nitrogen base)

▷ Leaving Group: Br^-

▷ Lesson: Substitution does not occur here because DBU is a bulky molecule — it will encounter a large amount of steric hindrance, and is therefore a poor nucleophile.

⑱



(68%)

Questions:

Why doesn't an S_N1 reaction take place?
Why use quinaline instead of NH_3?
What would happen if the reaction were allowed to continue indefinitely?

Mechanism: E2

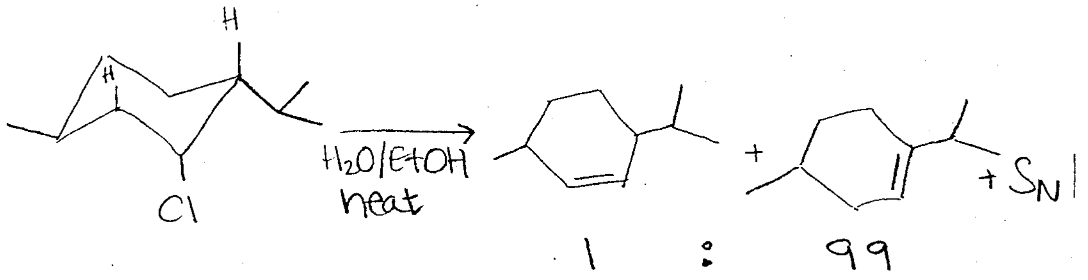
Base: 

Leaving group: Br^-

Lesson:

- weak base → high temp necessary, E2 even with weak base
- nucleophile too big for S_N2
- product unstable (Diels-Alder)

(17)



Questions

- Why do we use EtOH and H_2O instead of just EtOH?
- Why does a S_N1 reaction occur along with the E1 reactions?

- What if we didn't add heat - the reaction was at a lower temp?
- What if a chiral base was used instead OH^-?
- What if a disubstituted halide was used instead of the reactant?

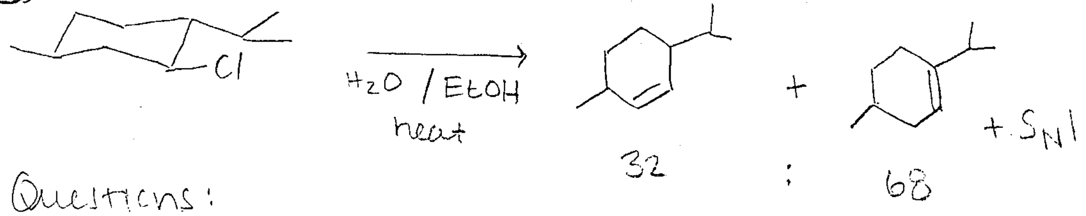
Mechanism: E1

Base: H_2O and/or CH_3CH_2OH

Leaving Group: Cl^-

Lesson: Zaitsev's rule leads to the most substituted alkene, which is usually the most stable alkene so it is the major product. [The E stereoisomer is formed in a greater amount.] (not relevant here)

(20)



Questions:

- Why are there S_N1 products included in this reaction?

- What if the solvent was mostly EtOH?
- Would minimal heat vs. excessive heat produce different ratios of the products?

mechanism: E1

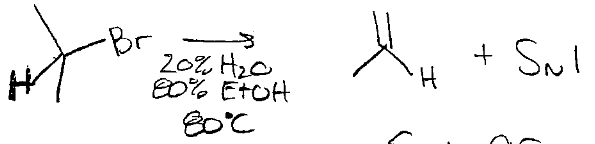
base: H_2O or CH_3CH_2OH

leaving group: $Cl^{\ominus}$

esson: The compound that follows Zaitsev's rule is more probable. (Base takes off H from β-carbon with fewest hydrogens).

- Reason for why an equatorial Cl influences the ratios is unknown.
- Compare with #19 - Something odd in that reaction

㉑



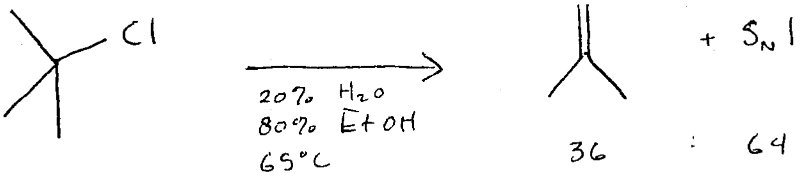
5 : 95

Why so much substitution?
What if it had been t-butyl bromide?

Mechanism: $E1/S_N1$
base: H_2O & EtOH
leaving group: $Br^\ominus$
lesson: It is a secondary carbon, so it requires more heat to form cation than tertiary carbon.

- ~~Eliminati~~
- Elimination from 2° bromide (E1) can be minor product of S_N1 reaction
- No significant base here, so primarily substitution

㉒



Questions:

- Why is the S_N1 product produced majorly?
- What is the S_N1 product in this reaction?
- Why the ratio?
- What if there was a stronger base present?

Mechanism: E1 (S_N1)

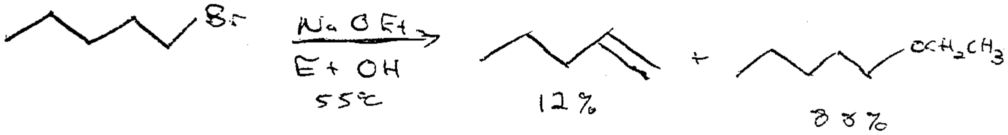
Base: EtOH or H_2O

Leaving Group: $Cl^{\ominus}$

Lesson: Since EtOH is a weak base, the ~~product~~ elimination product is less prevalent in comparison to the S_N1 product. Also, Cl is less reactive than Br, forcing greater elimination than reaction 21, a similar situation.

(See reaction 21)

23



Increasing the polarity of the solvent will do what to the rate of the S_N2 reaction?

Why does the S_N2 <u>and</u> E2 reaction occur?

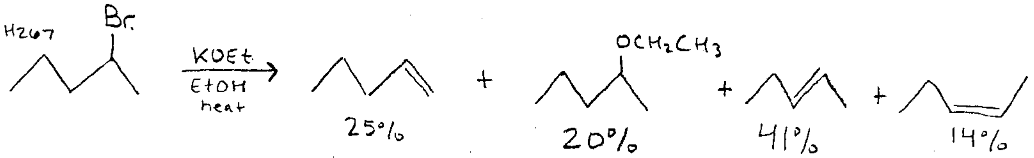
Mechanism: E2/S_N2

Nucleophile: OEt^- (S_N2) same for E2

leaving group: Br^- (S_N2) same for E2

lesson: OEt^- is a stronger nucleophile making it a stronger base, because of this it will replace Br on the pentane chain forcing Br^- to replace OEt^- in the EtOH solvent as a more stable, weaker base. OEt^- combining to pentane increase stability making whole system more stable. This regards the S_N2 which is 88%. For the E2, the nucleophile and leaving group are the same, but the nucleophile will be accepting a proton, neutralizing the strong base, while the leaving group Br^- is a more stable base, causing a d.b. to be formed. The solvent favors an S_N2 rxn, causing the S_{N_2} product to be 88%.

(24)



) Why does elimination produce a higher yield than substition?

2) why are cis and trans products both created?

3) why are some elimination products better than others?

) what if a weaker base were to be used in the reaction?

) what would happen if water was present?

) what would happen if a different solvent were used?

Mechanism - 2nd product is S_N2
1st, 3rd, 4th is E2

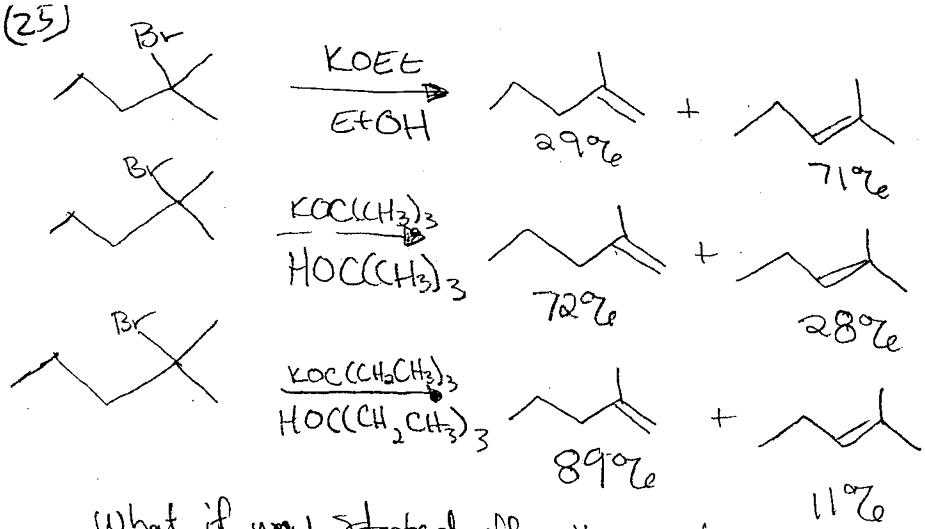
Nucleophile/Base - $^{\ominus}OEt$

Leaving group - $Br^{\ominus}$

Lesson - *In elimination reactions, the base can pull off a hydrogen from either side of substituent, creating cis or trans products.*
(one of which is more stable than the other)

When base is $^{\ominus}OEt$ → E2 or S_N2, but mostly E2

(25)



What if you started off with a less substituted carbon bonded to the leaving group?

Mechanism: E2

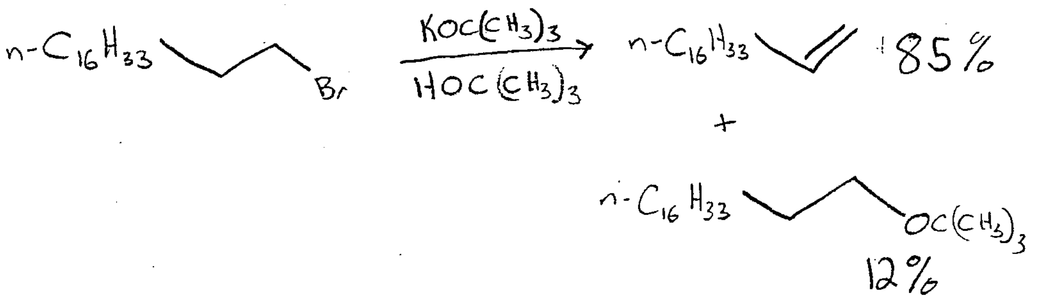
base: $OEt^{\ominus}$ / $OC(CH_3)_3^{\ominus}$ / $OC(CH_2CH_3)_3^{\ominus}$

Leaving group: $Br^{\ominus}$

Lesson: The bulkier bases remove the more terminal hydrogen, leading to the formation of a less substituted alkene because of steric hindrance.

- This is not consistent with Zeitsev's Rule because Zeitsev used $NaOH/H_2O$ for all studies,

㉖



- Is it the structure of $KOC(CH_3)_3$ that makes it a stronger base?
- Why is elimination the favored reaction?

mechanisms: E2 (dominating) and S_N2

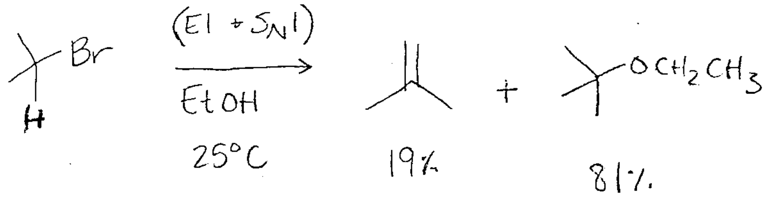
nucleophile: $OC(CH_3)_3^{\ominus}$

leaving group: $Br^{\ominus}$

Lesson: $KOC(CH_3)_3$ is a stronger base than it is a nucleophile, so the elimination is the favored reaction.

Use a hindered base to suppress S_N2 in the elimination of a primary alkyl bromide

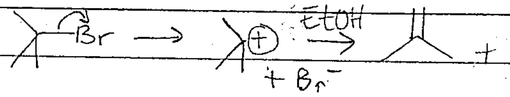
㉗



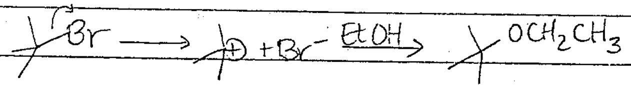
Why do a low temperature and a weak base favor the substitution rxn?

What if the solvent was nonpolar or aprotic?

mechanism: E1



S_N1



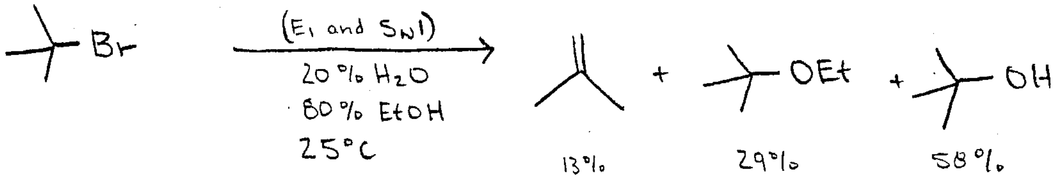
base: EtOH

nucleophile: EtOH

leaving group: Br^-

lesson: We get more of the S_N1 product because EtOH is a weak base and the reaction is carried out at room temperature

(28)



→ Would changing temperature change the products / ratios?

Mechanism: [1st product] E₁ , [2nd product] S$_N$1 , [3rd product] S$_N$1

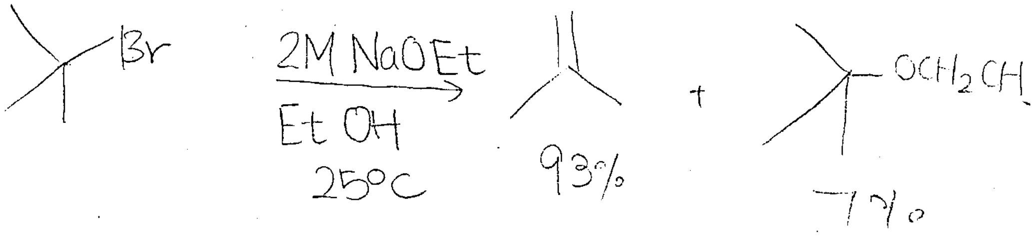
Base / Nucleophile: [1st] weak base = H_2O or EtOH , [2nd] Nu = EtOH , [3rd] Nu = H_2O

Leaving Group: [1st, 2nd, 3rd] Br^-

Lesson:

1) Tertiary alkyl halide CANNOT undergo SN2 ; polar protic solvent, weak base favor E1/S$_N$1 over E2
2) Lack of strong base = E₁ product formation is MINOR
3) Solvent is mixture of 2 nucleophiles. Note the uneven ratio of solvent nucleophiles to their respective products. H_2O, as the smaller and more mobile nucleophile forms the predominant product.

(29) - What if the solvent had been MeOH instead of EtOH?



~2% minor from E1; most coming from E2.

Mechanism: E2 w/ some E1 & SN1

Nucleophile: $OCH_2CH_3^-$
Base: EtO^-

Leaving group: Br^-

Lesson: increasing the concentration of a strong base accelerates the E2 react'n. (E1 & SN1 reactions become minor pathways to product)

- Minor amount of substitution cannot come from SN2 reaction — must be some E1/SN1 here.