March 2020

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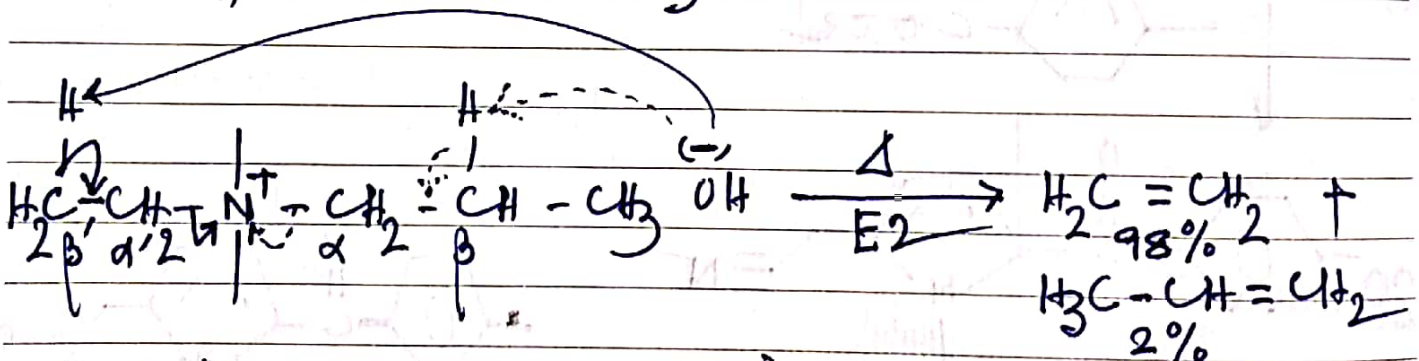
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31					

Elimination reactions in quaternary ammonium ions:

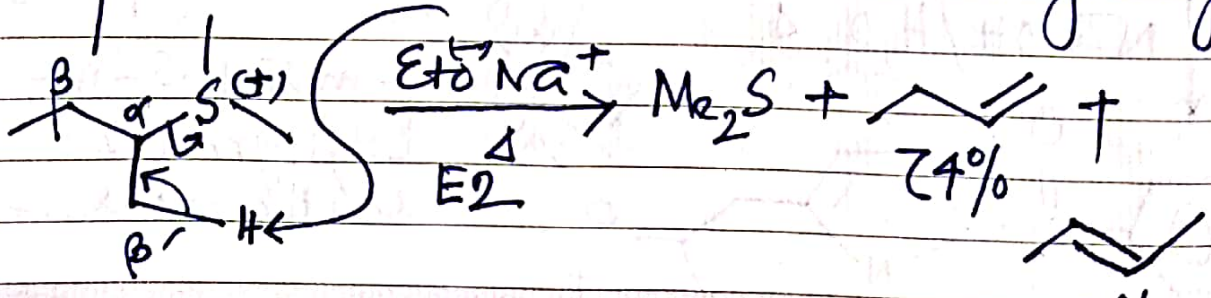
Quaternary ammonium ions undergo thermal dissociation to generate 3° amines & alcohols; in presence of a β-H, they undergo E2 elimination where the more acidic β-H is preferentially stripped off to generate the corresponding alkene. The reaction is popularly known as Hoffmann elimination.

$$2Me_4\overset{+}{N}\bar{O}H \longrightarrow 2Me_3N + Me\text{-}O\text{-}Me + MeOH$$

$$Me_4\overset{+}{N}\bar{O}H \longrightarrow Me_3N + MeOH$$



Sulphonium salts eliminate analogously.



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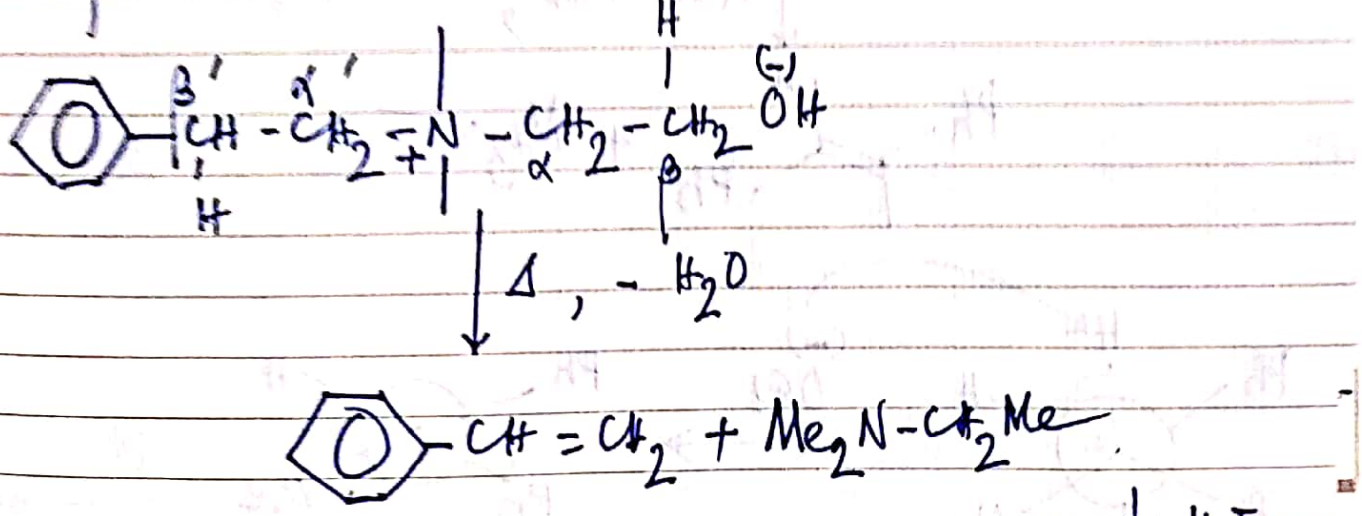
It is evident that the β-H attached to the β-C having maximum no. of H atoms attached is the

most acidic and is eliminated, leading to the formation of the less substituted alkene (Hoffmann alkene) in appreciable predominance.

This is characteristic of eliminations involving the onium ions which exert greater -I effect compared to neutral leaving groups and hence dictate a preference regarding the β-H to be removed. The stability of the alkene so formed does not determine the predominant product in these cases, quite unlike Saytzeff eliminations.

Exceptions:



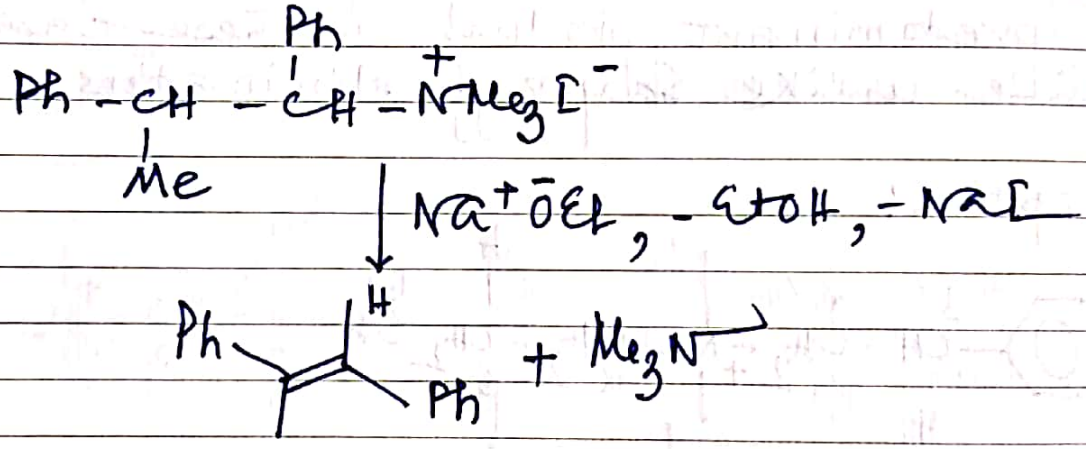
In this case, the phenyl group attached to the benzylic carbon stabilizes the incipient +ve charge on this benzylic carbon in the transition state of the reaction, upon initiation of the removal of β-H by the base. Hence the

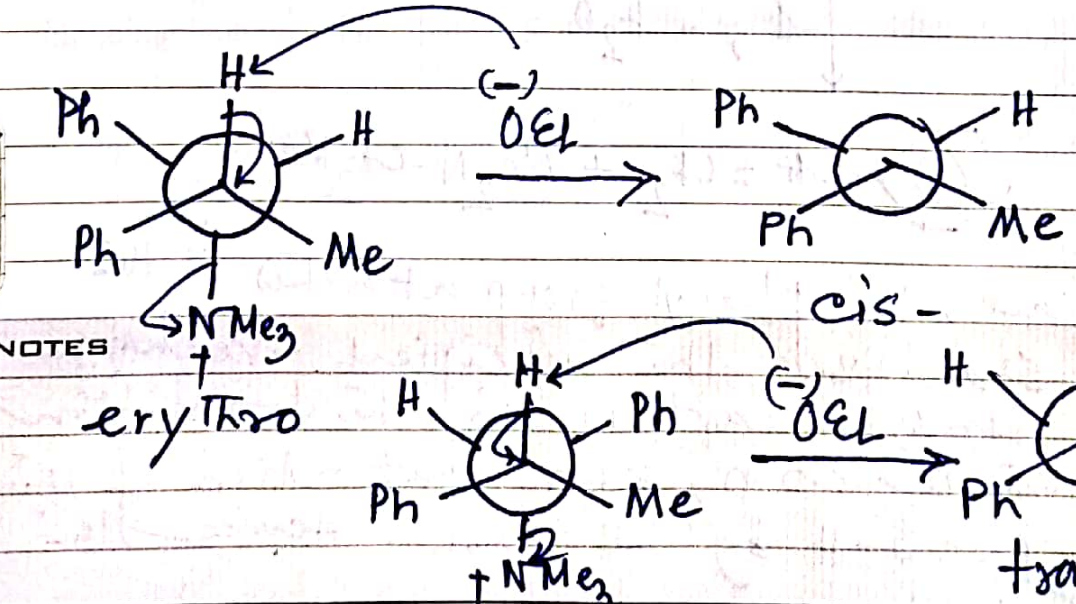
more stable alkene (Saytzeff alkene) is selectively generated.

Stereochemistry:

Following E2 mechanism, the conformation of the reactant having the eliminant moieties in anti periplanar orientation determines the configuration of the product; the reaction, is, hence, stereospecific.

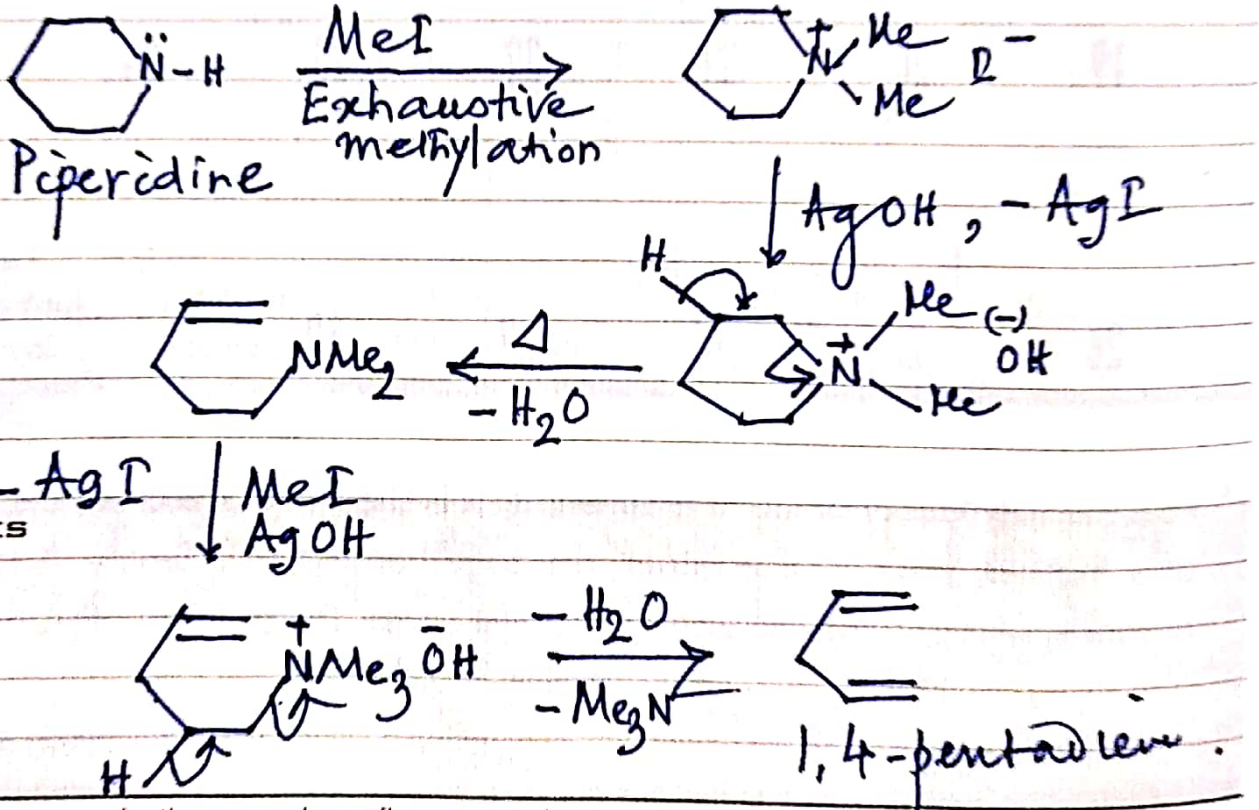
Let us consider the reaction



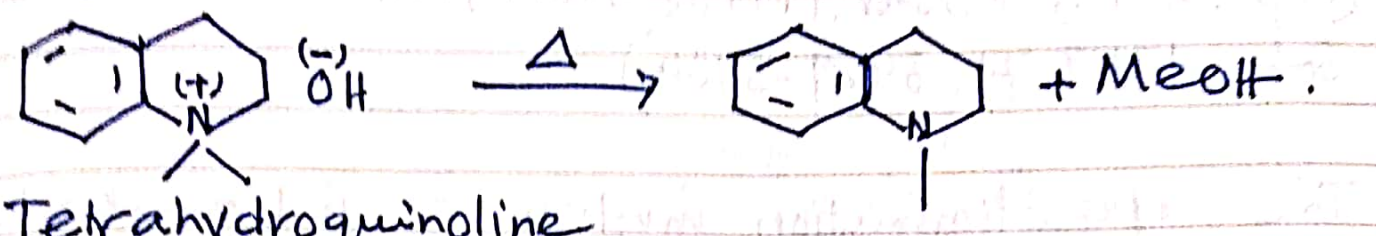


The kinetics of this reaction is naturally governed by the energy of the transition state and hence the energy of activation. For the erythro isomer eliminating to the cis-product, the transition state suffers from steric interaction between the two phenyl groups; this raises the energy of activation and consequently slows down the reaction. Hence, the threo-isomer is observed to react more than 50 times faster compared to the erythro diastereomer.

The Hoffmann exhaustive methylation followed by elimination reaction of the quaternary ammonium hydroxide can, apart from alkene synthesis, be efficiently utilized in understanding the nature of carbon skeleton in N-containing heterocycles.

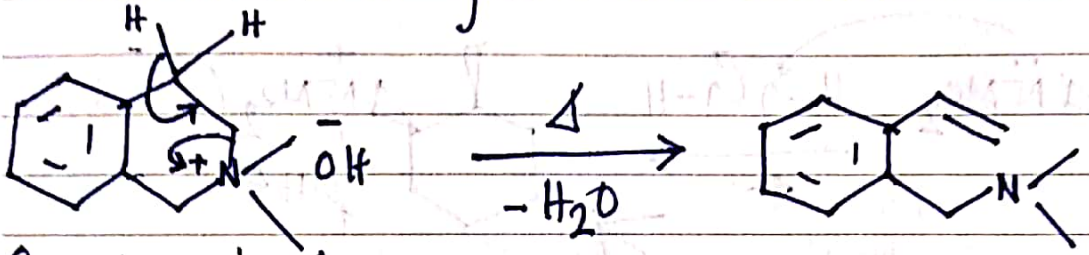


An excellent method for opening heterocyclic rings containing N/S, it however fails in case fused aromatic rings are present, eg.



Tetrahydroquinoline quaternised

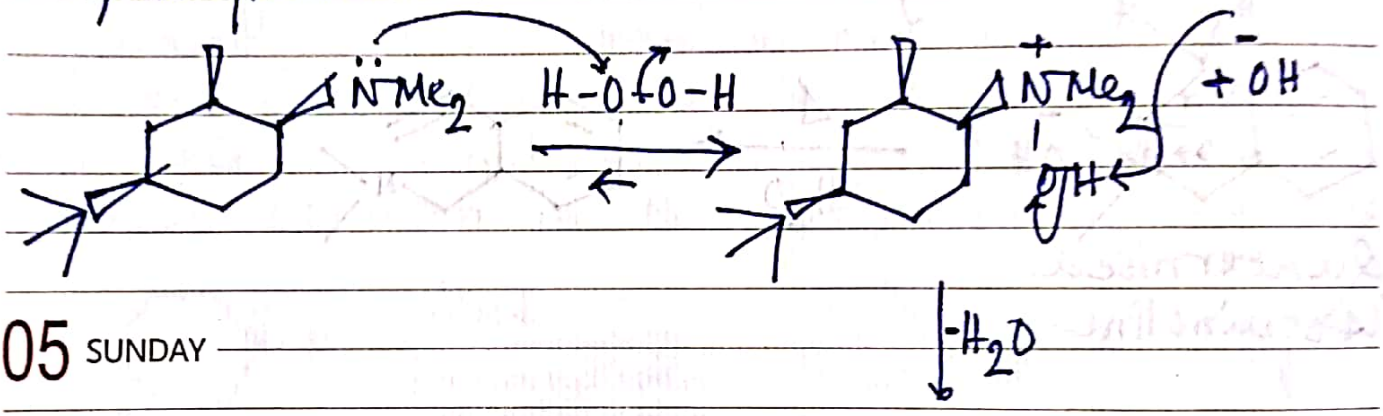
This is likely due to reduction of the positive charge on the 'onium N by electron donor from the aromatic ring.



Quaternised isoquinoline

An alternative to the Hoffmann elimination for the amine → alkene transformation is the Cope Elimination.
(Cope, A. C., Foster, T. T. & Towle, P. H. J. Am. Chem. Soc. 1949, 71, 3929-3934)

The Cope Elimination involves the intramolecular syn elimination of a tertiary amine oxide (formed by oxidation of a 3° amine with peroxide/peracid) having a syn β-H. The products are an alkene and a substituted hydroxylamine.



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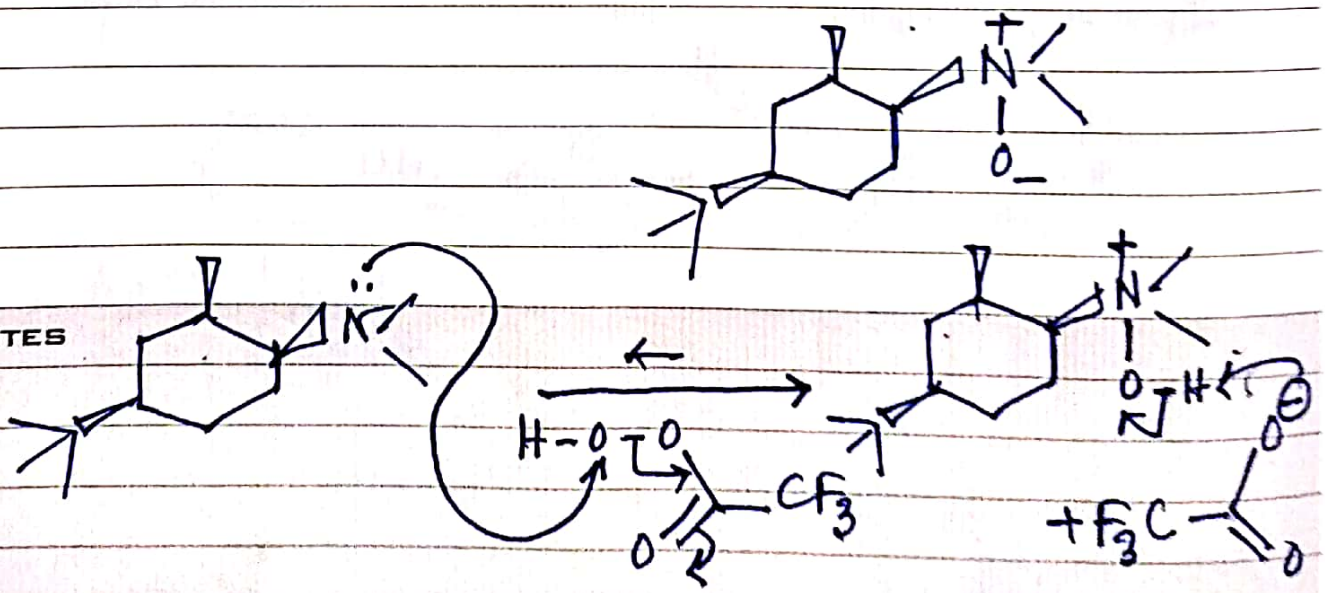
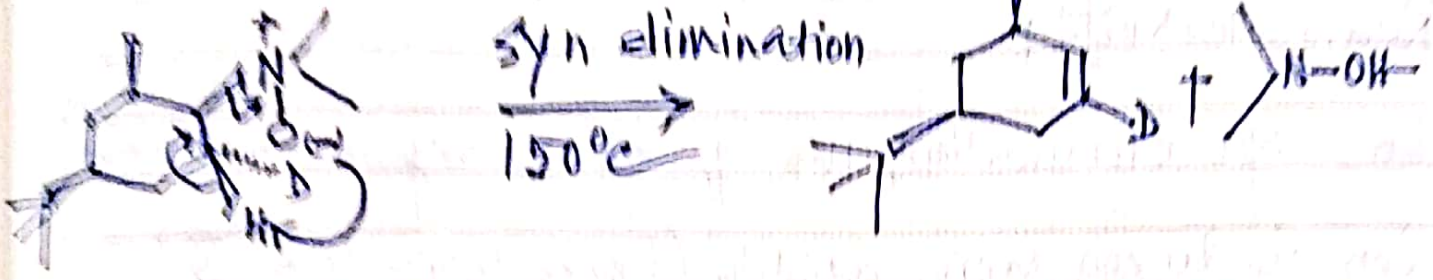
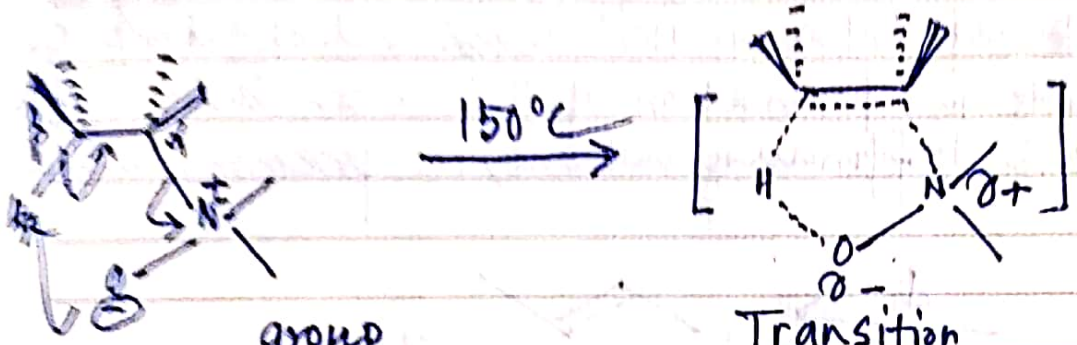


Mechanism & Stereochemistry:

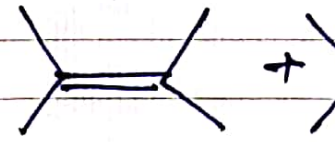
Concerted
syn elimination

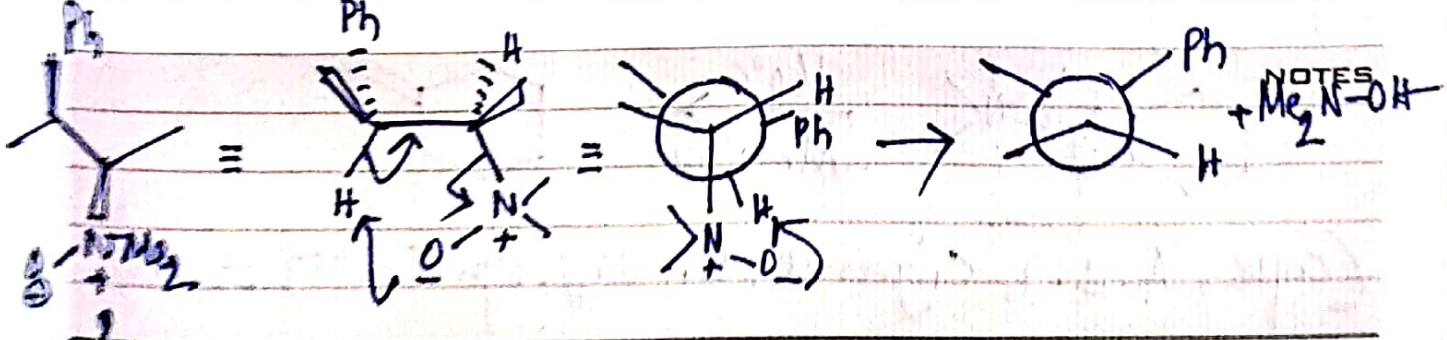


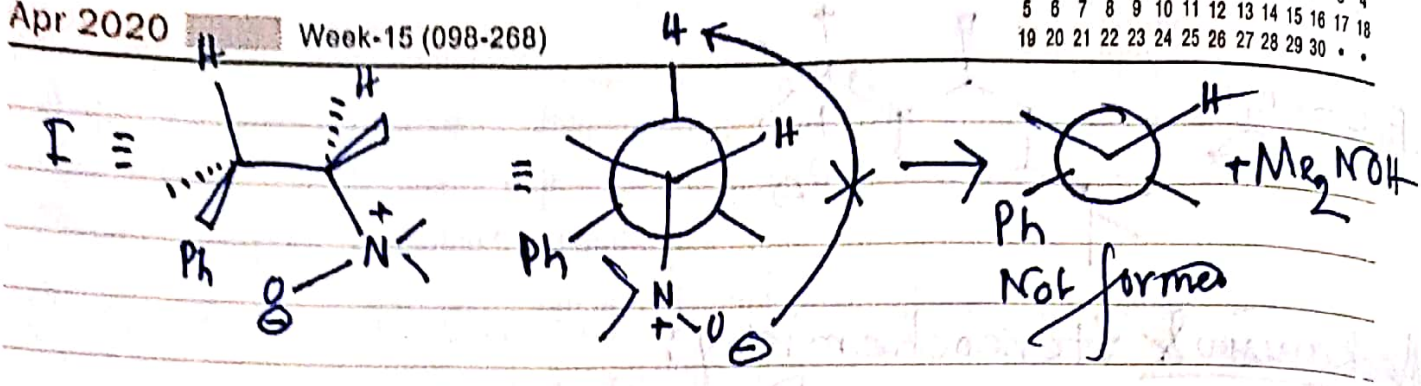


group
The leaving & the βH are syn periplanar in the conformation from which this intramolecular elimination occurs. This reaction may also be termed as a pericyclic reaction.

Transition State

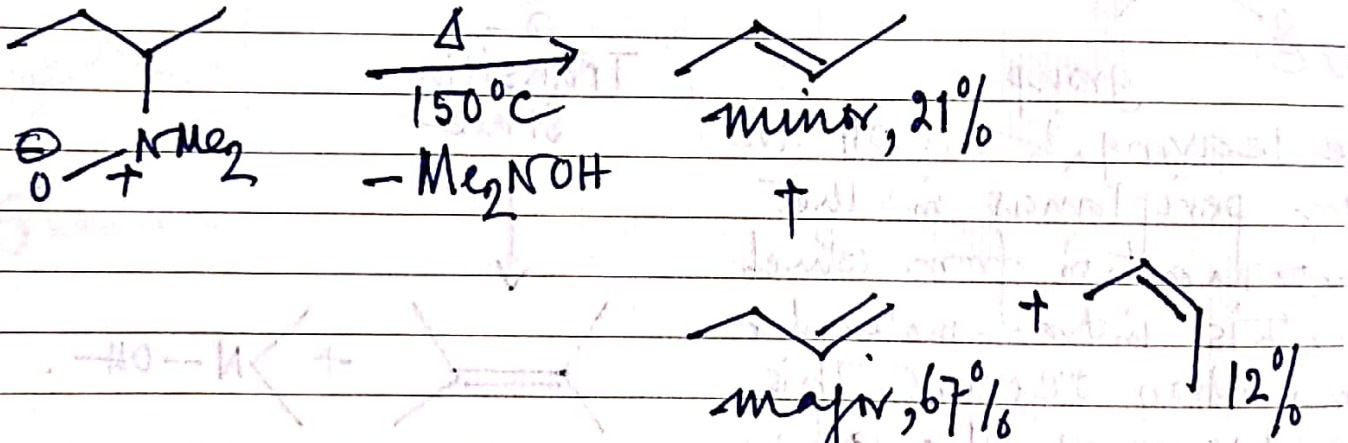






Regioselectivity:

In Cope Elimination, the quaternary ammonium ion induces more acidity (hence more lability) on the β-H attached to the least substituted β-C. This results in formation of the least substituted alkene (the Hoffmann alkene) in predominance



This elimination allows for preferential formation of exocyclic double bonds

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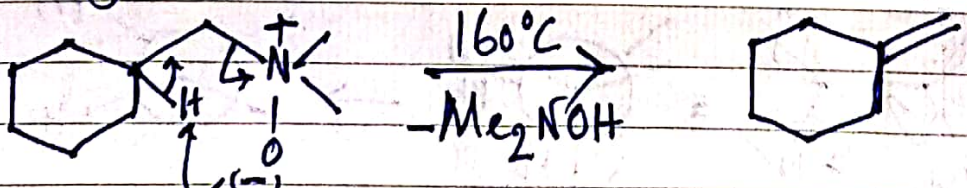
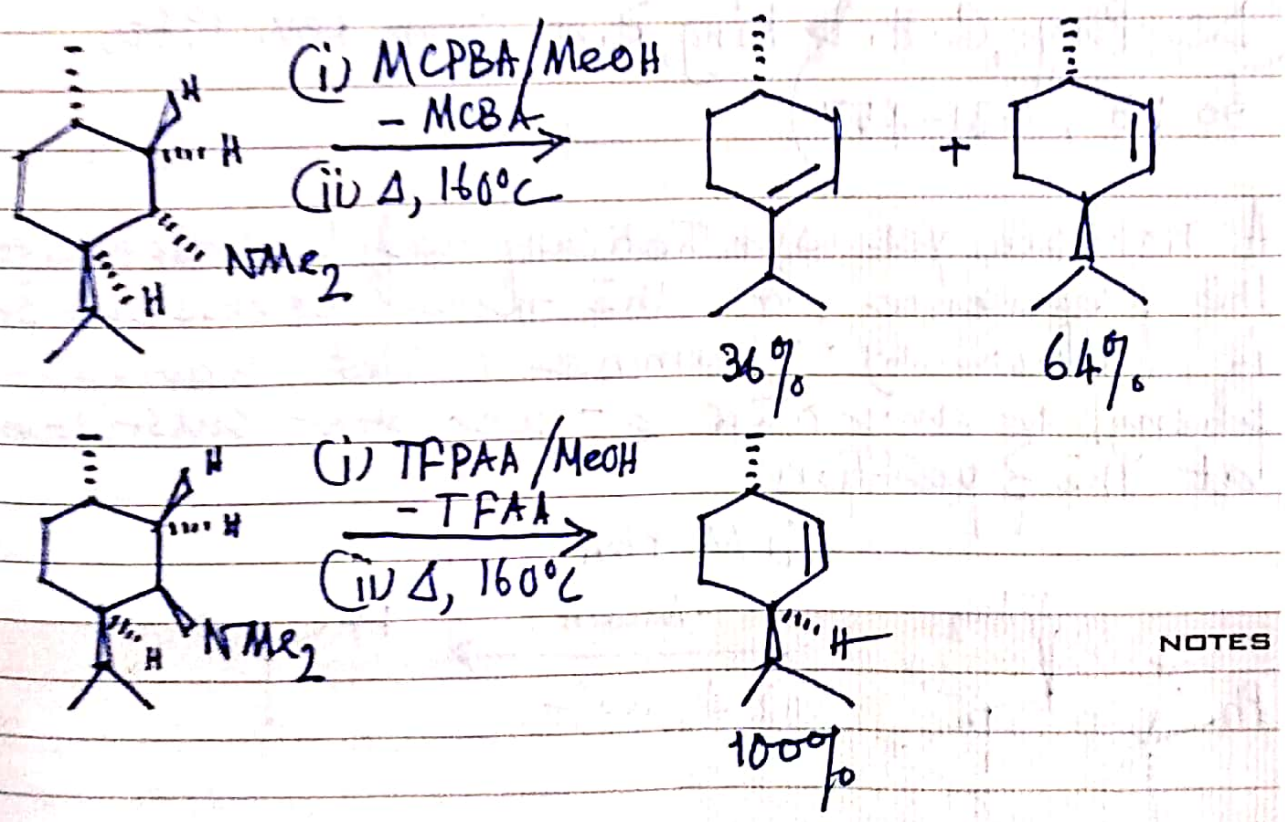


(Cope, A.C. & Ciganek, E. Org. Synth. 1959, 39, 40)

It is to be noted that the Cope elimination is given by 3° amine oxides only; 1° & 2° amine oxides will transform to substituted hydroxylamine prior to elimination and may give rise to other rearrangement routes.

Sterically demanding amine oxides present further cases of selectivity favouring the less substituted alkene. The oxide moiety chooses to absorb the most accessible proton. In cases where two more conformations are eligible for cope elimination, the more sterically relaxed one is chosen, resulting in diastereomeric selectivity.



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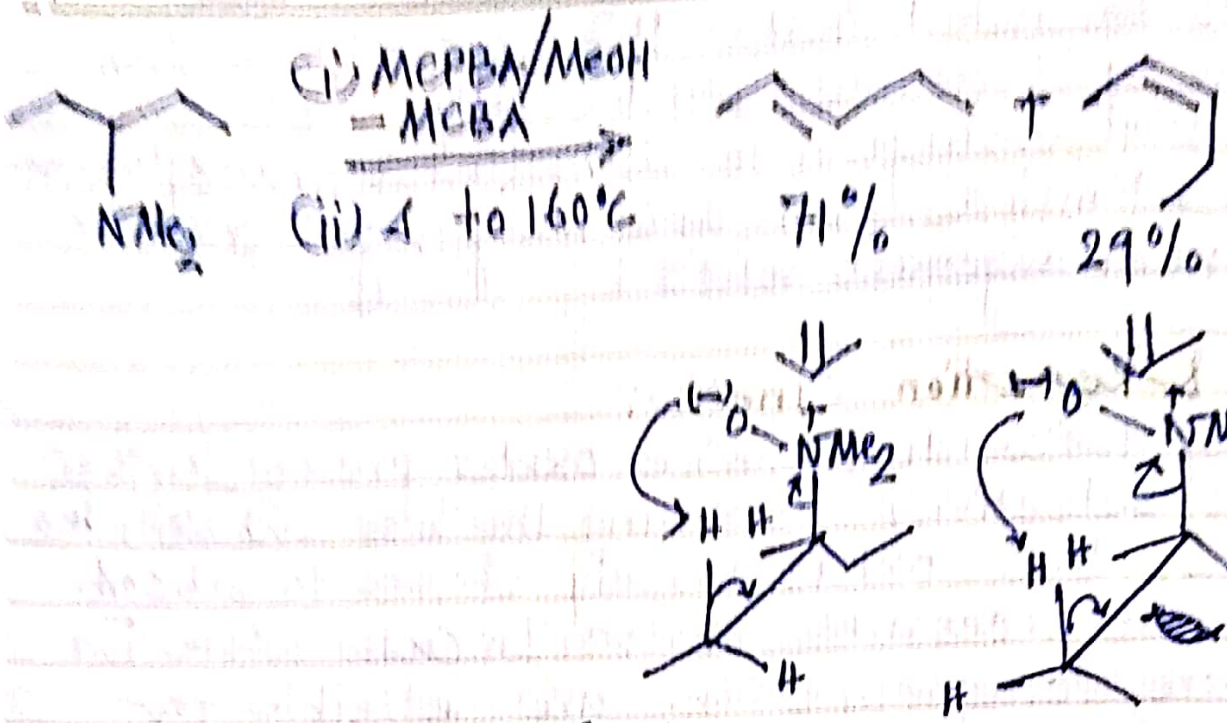
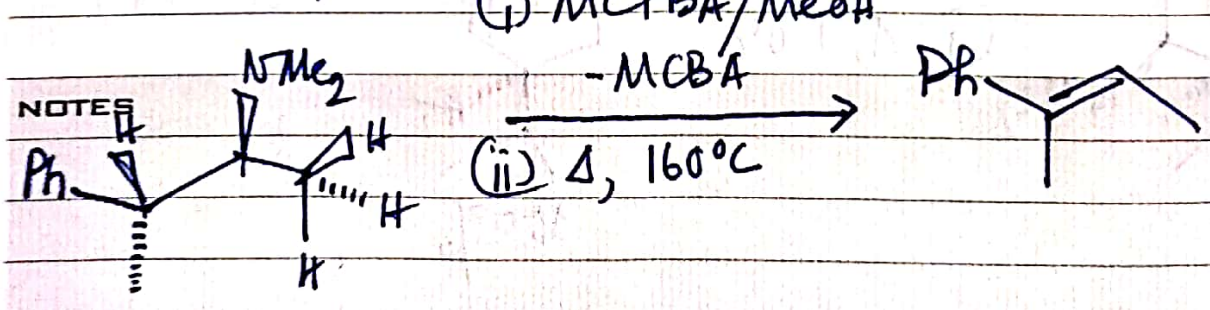
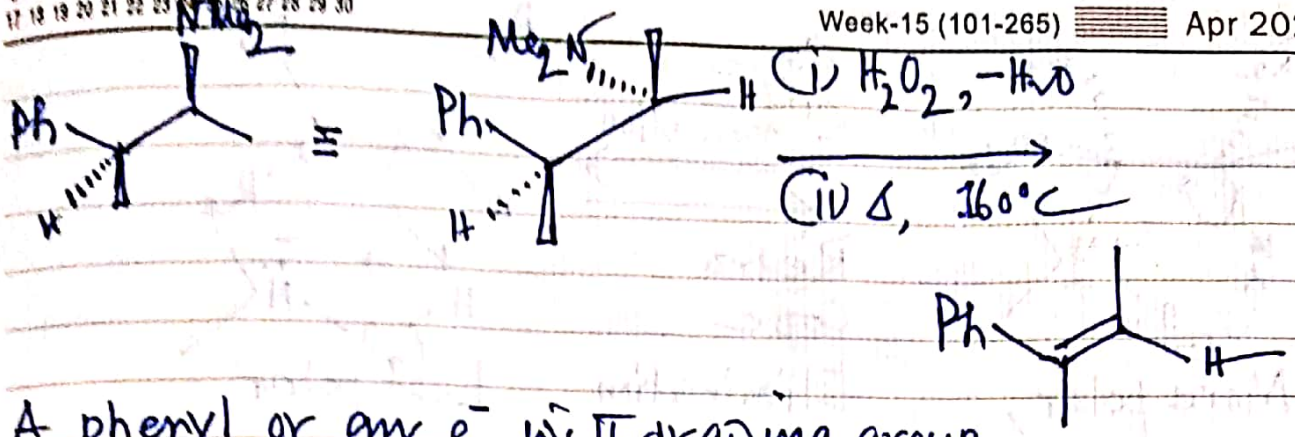


(De Puy, C.H. & King, R.W. Chem. Rev. 1960, 60:5, 431-457)

A notable, yet synthetically useful exception to the preference for the more accessible βH is shown by 3° amine oxides having phenyl or any other e⁻ acceptor substituent at the β position.





A phenyl or an e⁻ withdrawing group at the βC reduces the e⁻ density of the relevant C-H bond, making the reaction 100 times more rapid compared to alkyl substituted N-oxides. Computational studies of minimal energy paths indicate that the Cope Elimination is slightly dissymmetric and non-synchronous i.e. removal of β-H occur slightly in advance of other bond reorganizations. (Komaromi, I. & Tronchet, J.M.J. J. Phys Chem. A. 1997, 101:19, 3554-3560)

Solvent effects on Kinetics & Equilibrium:
eg. H_2O, MeOH, etc

A polar solvent, stabilizes the amine oxide by H-bonding & solvation. In aqueous or alcoholic solvents, therefore the charged quaternary amine oxide is far more energetically favourable than the less polar hydroxylamine derivative and this may sometimes displace the equilibrium in favour of the retro-Cope elimination.

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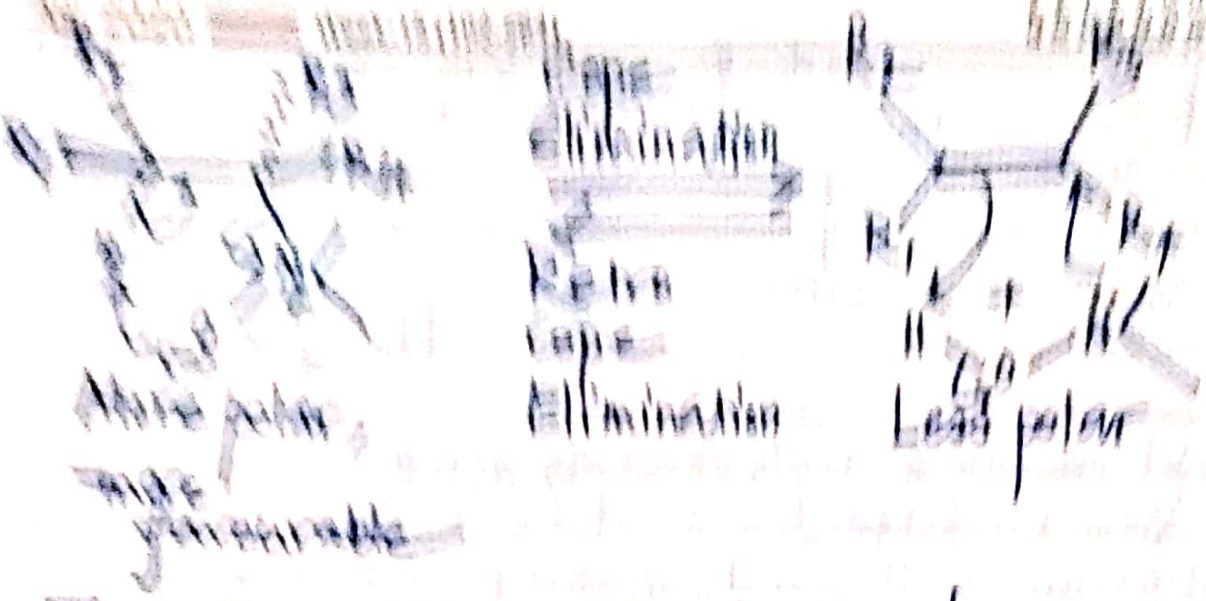
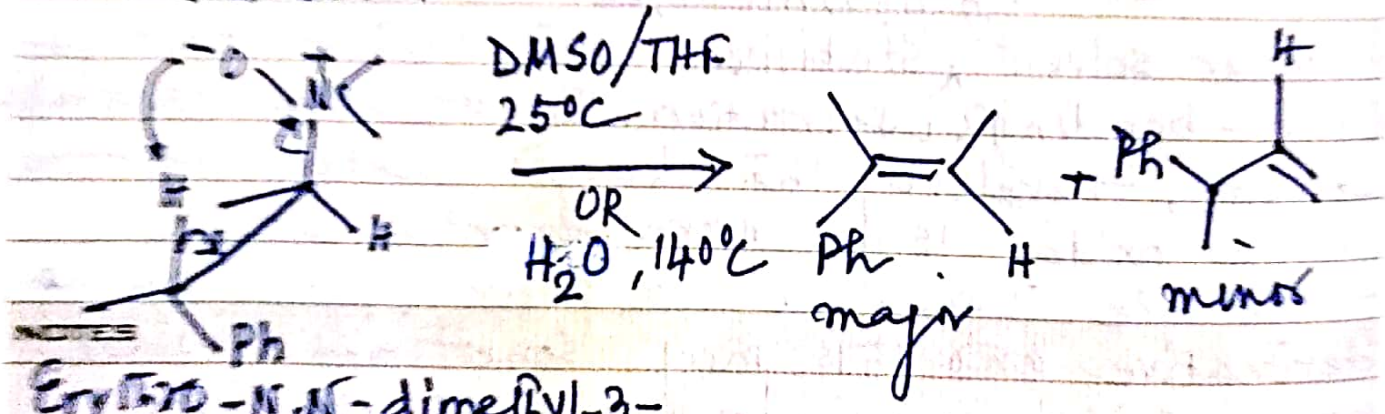


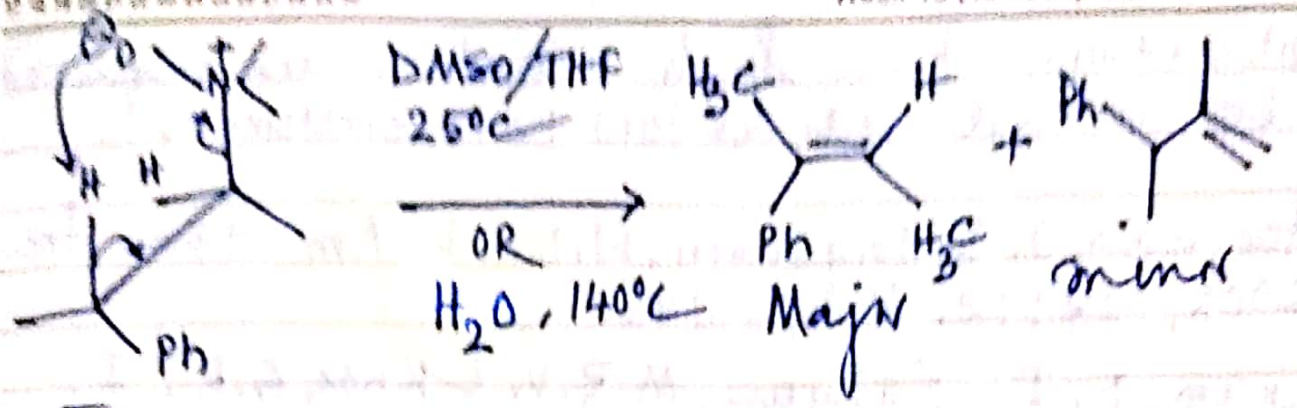
The Cope Elimination is, therefore extremely sensitive to solvent effects; even million fold rate increase may be observed, moving from protic to aprotic solvents. Even for protic solvents, decrease in polarity appreciably enhances the reaction rate.

Hence, in dry DMSO or THF, the Cope elimination is seen to proceed even at room temperature with 80–90% yield.

12 The reaction rates were found to be significantly higher compared to those in H_2O or methanol.



Erythro-N,N-dimethyl-3-phenyl-2-butylamine oxide



erythro -

The following relative reaction rates were observed. at 25°C, the rate for H_2O at this temperature was evaluated by extrapolation from higher temperatures.

Threo: $k_{DMSO}/k_{WATER} \sim 10^5$, $k_{THF}/k_{WATER} \sim 10^6$.

Erythro: $k_{DMSO}/k_{WATER} \sim 10^4$, $k_{THF}/k_{WATER} \sim 10^5$.

For each isomer, addition of 10 mole% water to THF decrease the rate 200 fold, whereas same treatment on DMSO decreased the rate 5-10 fold only.

Thus, the rate is higher in dry THF than in dry DMSO because solvation is less in the former, the rate is lower in wet THF than in wet DMSO because unlike THF, DMSO can compete with the amine oxide for H-bonding to water and thus act as internal drying agent.

The above observations are useful in Synthetic

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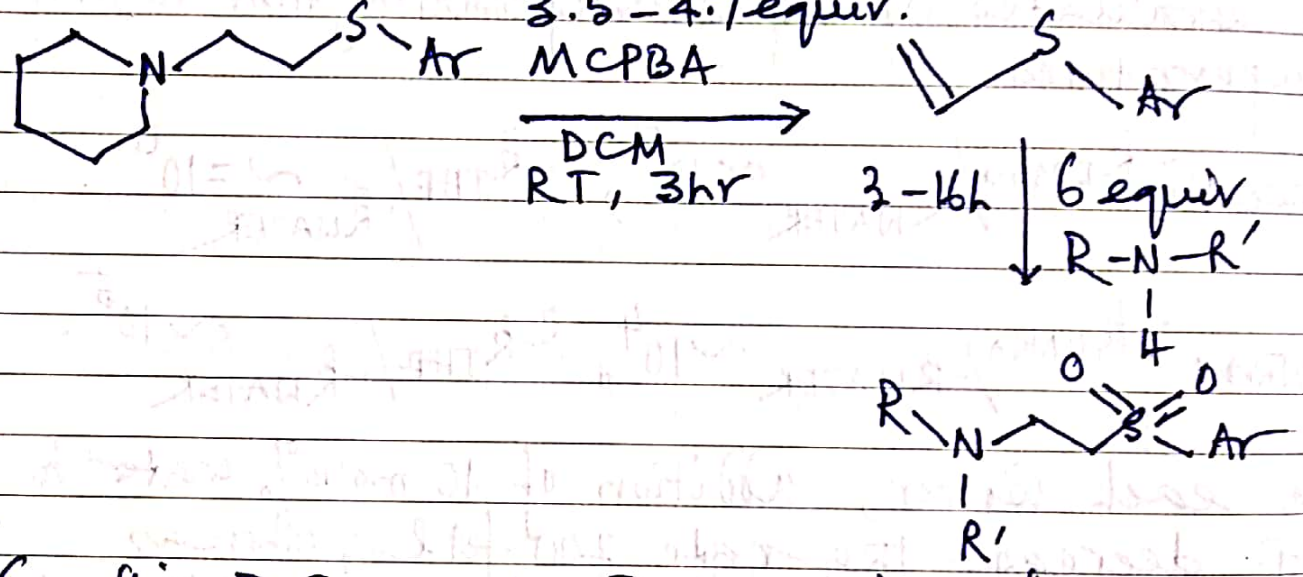
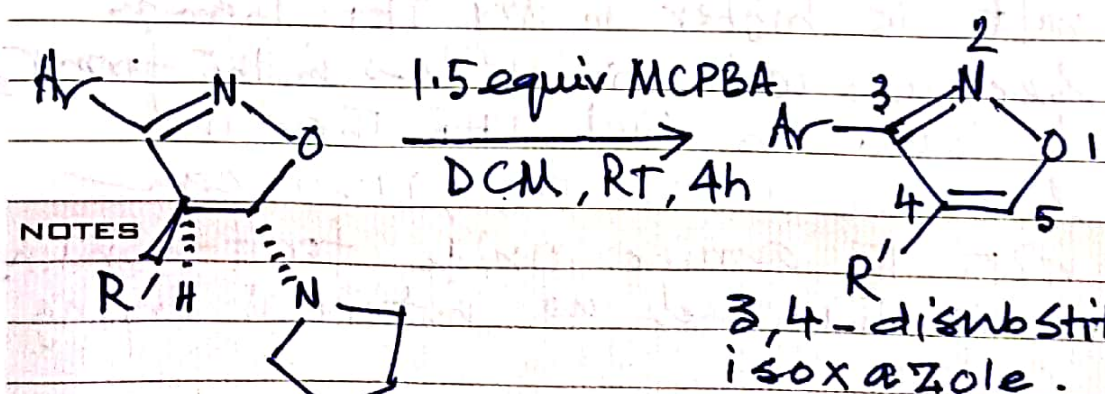
applications where such reactions are required to be carried out at low temperatures.

(Acevedo, O. & Jorgensen, W.L. J. Am. Chem. Soc. 2006, 128:18, 6141-6146.
Cram, D.J., Sahyun, M.R.V. & Knox, G.R. J. Am. Chem. Soc. 1962, 84:9, 1734-1735).

Recent Literature:



(Griffin, R.J. et. al. J. Am. Chem. Soc. 2006, 128:18, 6012-6013).



(Jia, Q.F. et. al. Synlett. 2013, 24, 79-84.