

Organic Chemistry-4
Semester-4, CBCS
Course: CEMA CC-4-8-TH

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata
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Recommended texts:

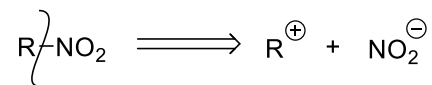
1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

Organonitrogen Chemistry

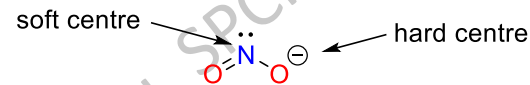
Chemistry of aliphatic nitro compounds:

Synthesis of nitroalkanes:

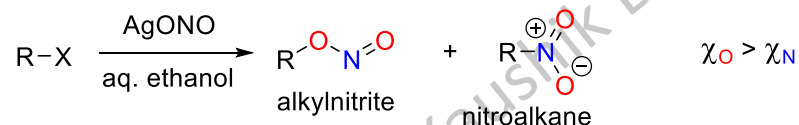
A] Formation of C-N bond is easier, therefore, we may consider the following disconnection in order to plan for a synthesis of an aliphatic nitro compound:



This will require a nucleophilic substitution on R-X with an ambident nucleophile nitrite ion:



Thus we have the following observation:



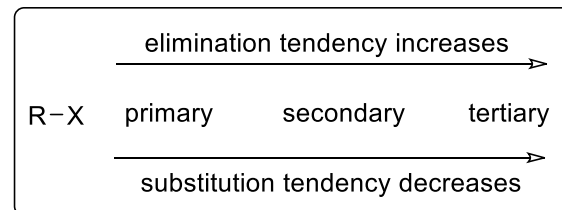
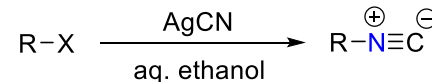
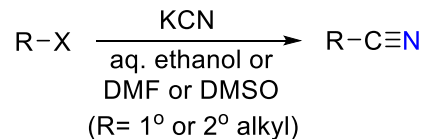
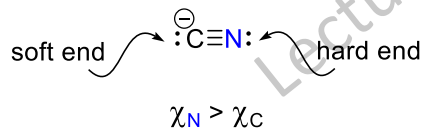
The yield of nitroalkane can be improved

i) by taking R as a primary alkyl, as secondary and tertiary alkyls are prone to elimination.

ii) X has to be either bromide or iodide. For chloride, yield is really poor.

iii) preferred solvent is DMSO or DMF, promoting S_N2 .

iv) preferred source of nitrite is $NaNO_2$, yield can be as high as 55-60% (recall the synthesis of alkyl cyanides with sodium cyanide and formation of isocyanides with silver cyanide; cyanide, like nitrite, is an ambident nucleophile).



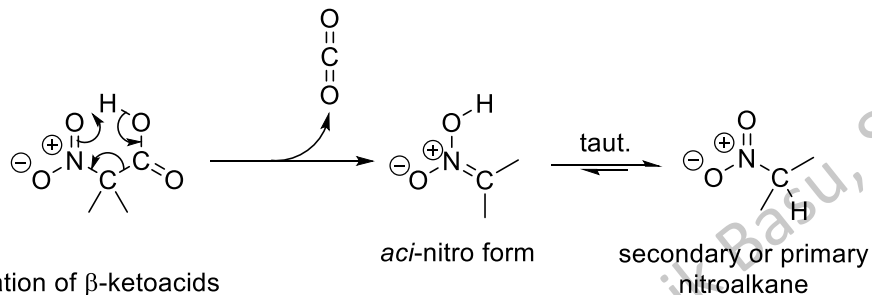
For $NaNO_2$ in DMF, urea has to be added to improve the nitrite salts solubility. No such additive is required if one uses DMSO.

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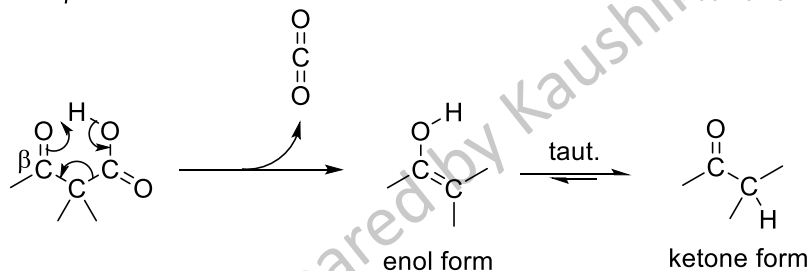
Chemistry of aliphatic nitro compounds:

Synthesis of nitroalkanes:

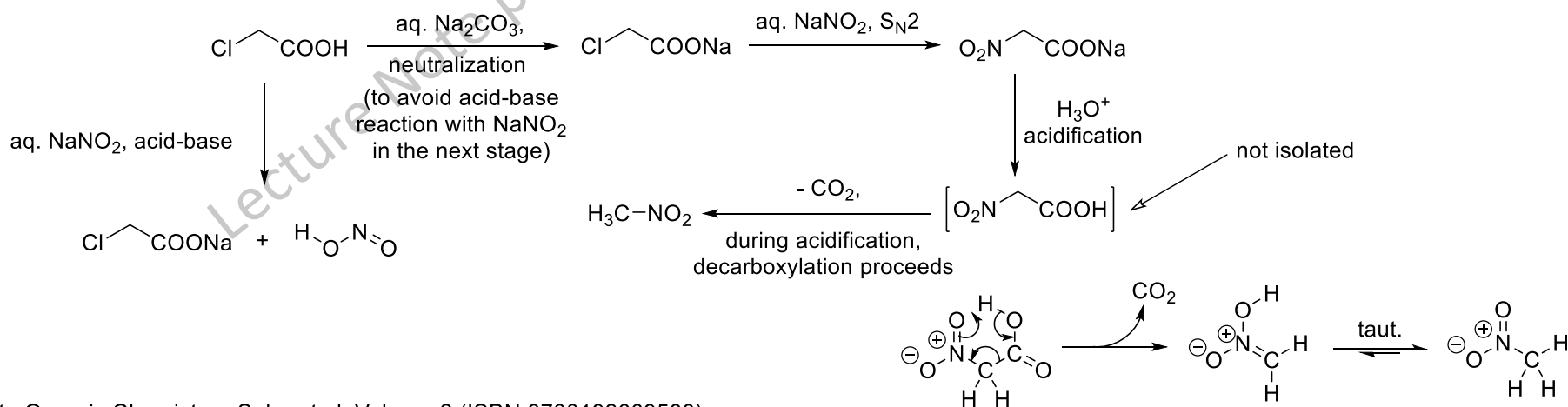
B] α -Nitrocarboxylic acids have a tendency to decarboxylate, eventually leading to a nitroalkane:



This is closely similar to decarboxylation of β -ketoacids



Following this concept, we have the preparative technique for nitromethane:

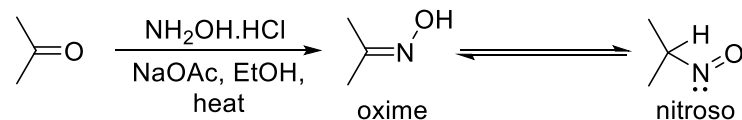


Organonitrogen Chemistry

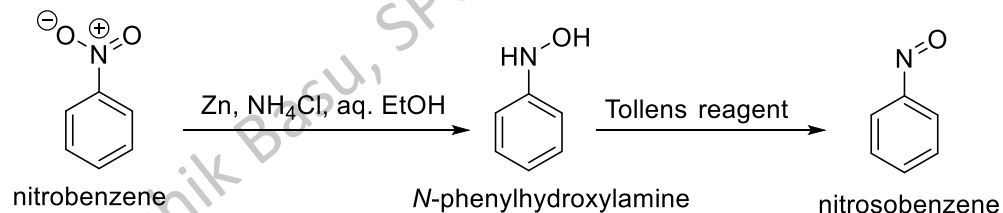
Chemistry of aliphatic nitro compounds:

Synthesis of nitroalkanes:

C] Oximes exist in an equilibrium with the corresponding nitroso which are somewhere between amino to nitro redox spectrum.



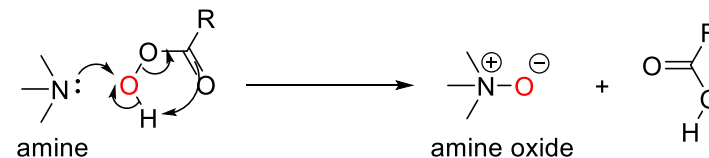
We have seen previously that aromatic nitro compounds can be reduced to the respective ArNHOH, which, on oxidation with Tollens reagent goes over to ArNO.



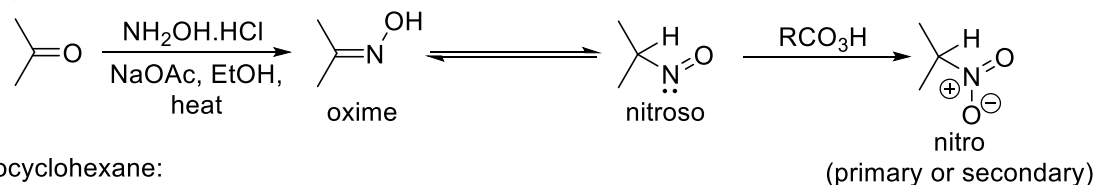
So it is reasonable to assume that the nitroso compounds can be oxidized to nitro.

But how to do it?

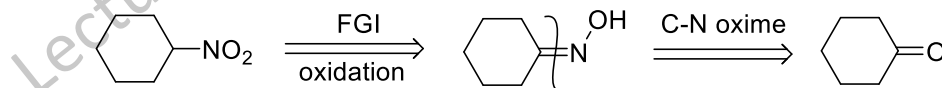
Recall that tertiary amines are oxidized to the corresponding amine oxides when treated with peracids. These amine oxides are substrates for the pyrolytic Cope elimination.



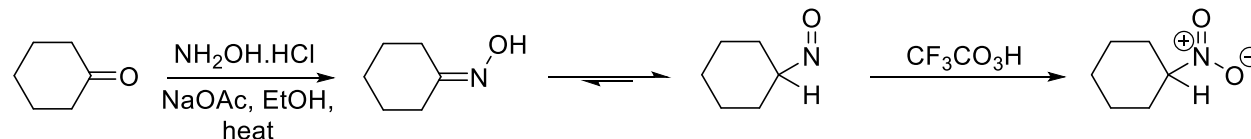
So it is reasonable to assume that the nitroso compounds can be oxidized to nitro when treated with such a suitable oxidizing agent (e.g. $\text{CF}_3\text{CO}_3\text{H}$).



Following this method, we have the retrosynthetic plan for nitrocyclohexane:



Thus,

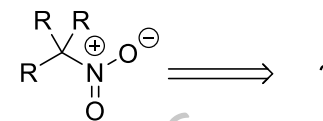


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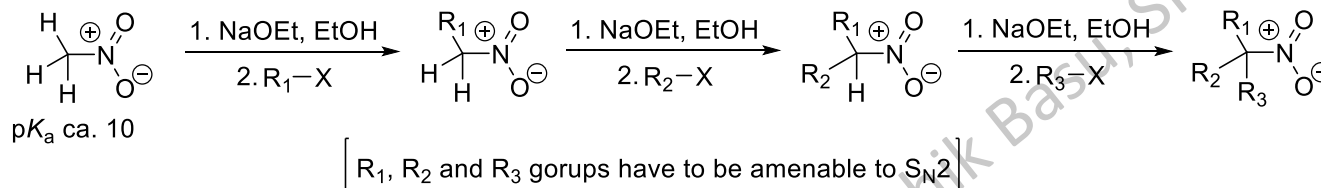
Chemistry of aliphatic nitro compounds:

Synthesis of nitroalkanes:

D] Synthesis of tertiary nitroalkanes poses a problem because none of the above methods will work.

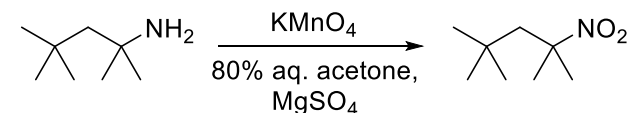


Way out? Fortunately, we can "load-up" alkyl groups of our choice on the α -carbon of a nitroalkane by exploiting the acidity of the protons at that site:

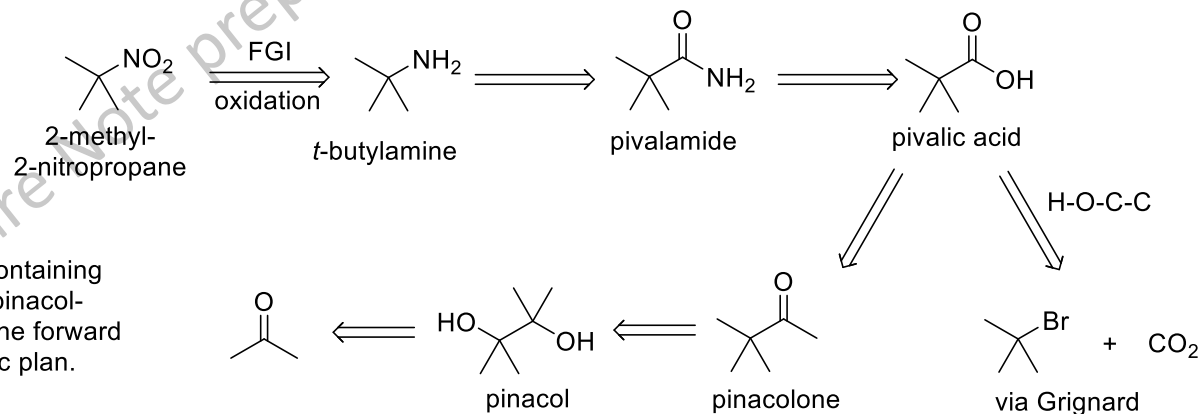


You might want to brush up your acid-base concepts here and think why the protons of nitromethane are so unusually acidic. Of course, when all the alkyl groups are methyl, we get Me_3CNO_2 .

Another way of accessing the tertiary nitro compound is to oxidize the corresponding amine, i.e.



Using the last technique, we can propose the following retrosynthetic scheme for 2-methyl-2-nitropropane:



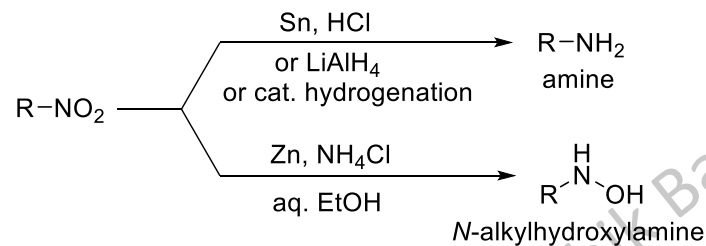
Recall in this regard that compounds containing *t*-butyl group can be accessed via the pinacol-pinacolone rearrangement. Complete the forward synthesis for the adjacent retrosynthetic plan.

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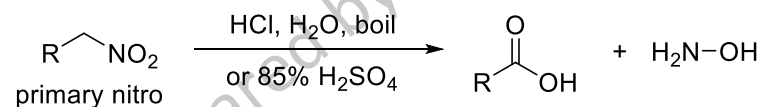
Chemistry of aliphatic nitro compounds:

Reactions of nitroalkanes:

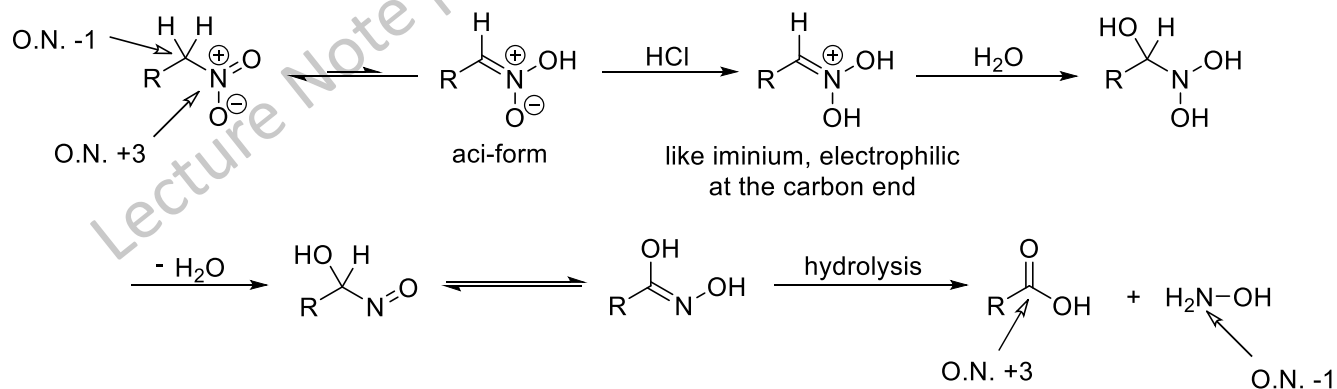
A] Reduction: The product depends upon the reaction condition, as we have seen for the aromatic counterpart:



B] Reaction with hydrochloric acid: The C-N bond is cleaved, the N of nitro is reduced to hydroxylamine while the methylene carbon is oxidized. This is a way of hydroxylamine synthesis.



Mechanism:

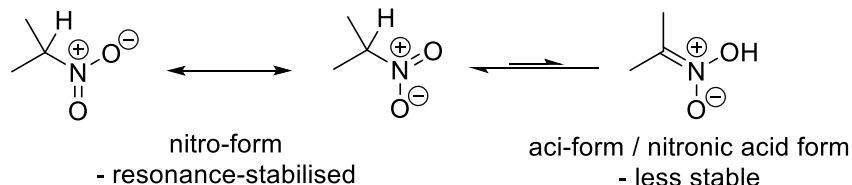


Organonitrogen Chemistry

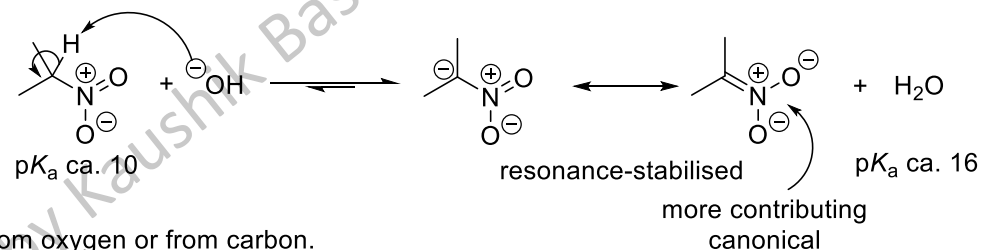
Chemistry of aliphatic nitro compounds:

Reactions of nitroalkanes:

C] Nitro-*aci*-nitro tautomerism: primary and secondary nitro compounds exhibit tautomerism:



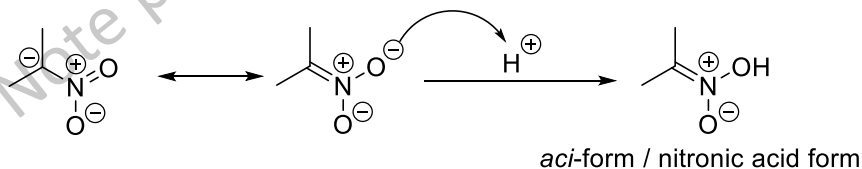
When treated with a base, nitroalkanes (except tertiary ones!) lose a proton from the α -carbon. The conjugate base, nitronate anion, is resonance-stabilised and places most of the extra electron density on the more electronegative O-atom.



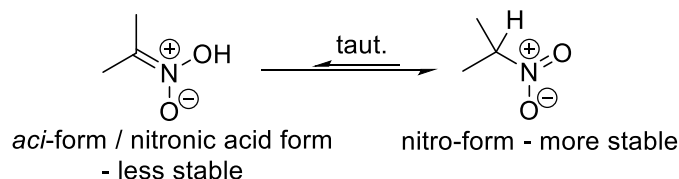
The nitronate anion, when reprotonated, can capture the proton either from oxygen or from carbon.

Protonation on oxygen is more likely as the nitronate is more structurally more like the second canonical (the more contributing one) and PNLM dictates that those elementary reactions that involves least structural change are associated with lower activation energies and are subsequently, favoured.

Therefore, the sodium salt of nitroalkane, upon acidification, first forms the *aci*-nitro form which is a colourless solid, soluble in aqueous medium:



However, recall that the nitro form is thermodynamically more stable, and so, this *aci*-nitro form slowly tautomerises to the corresponding nitro, which is a yellow liquid, insoluble in alkali and separates as droplets.



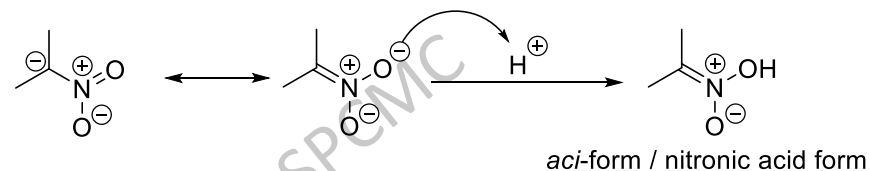
Organonitrogen Chemistry

Chemistry of aliphatic nitro compounds:

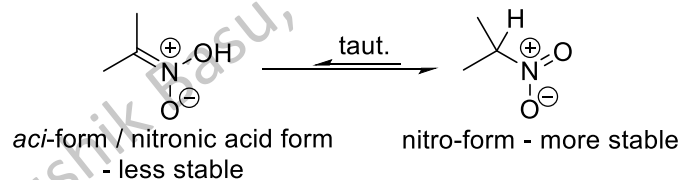
Reactions of nitroalkanes:

C] Nitro-*aci*-nitro tautomerism: reprotonating the nitronate

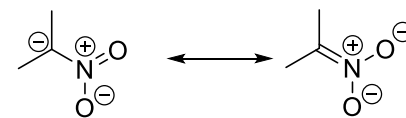
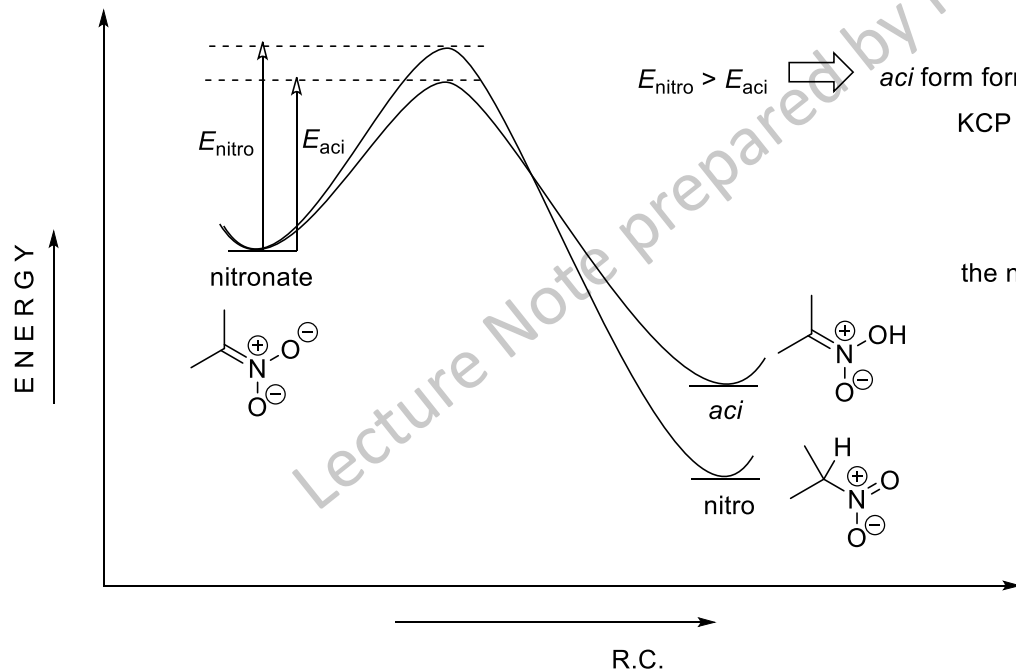
The sodium salt of nitroalkane, upon acidification, first forms the *aci*-nitro form which is a colourless solid, soluble in aqueous medium:



This *aci*-nitro form slowly tautomerises to the corresponding nitro, which is a yellow liquid, insoluble in alkali and separates as droplets.



This is, thus, a clear case of kinetic versus thermodynamic control.



The O atom has a larger share of the negative charge than C atom; protonation at the O atom is more favourable

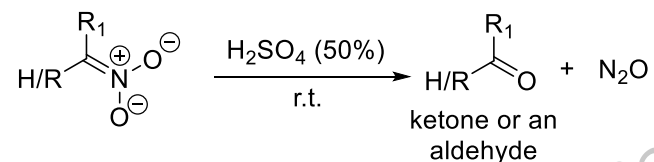
Organonitrogen Chemistry

Chemistry of aliphatic nitro compounds:

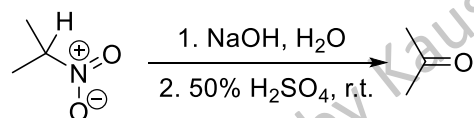
Reactions of nitroalkanes:

C] Nitro-*aci*-nitro tautomerism: reprotonating the nitronate

When the nitronate anion is protonated with 50% H₂SO₄ at room temperature, neither the *aci* nor the nitro form is the final product. What we get is a carbonyl compound. This is Nef carbonyl synthesis.



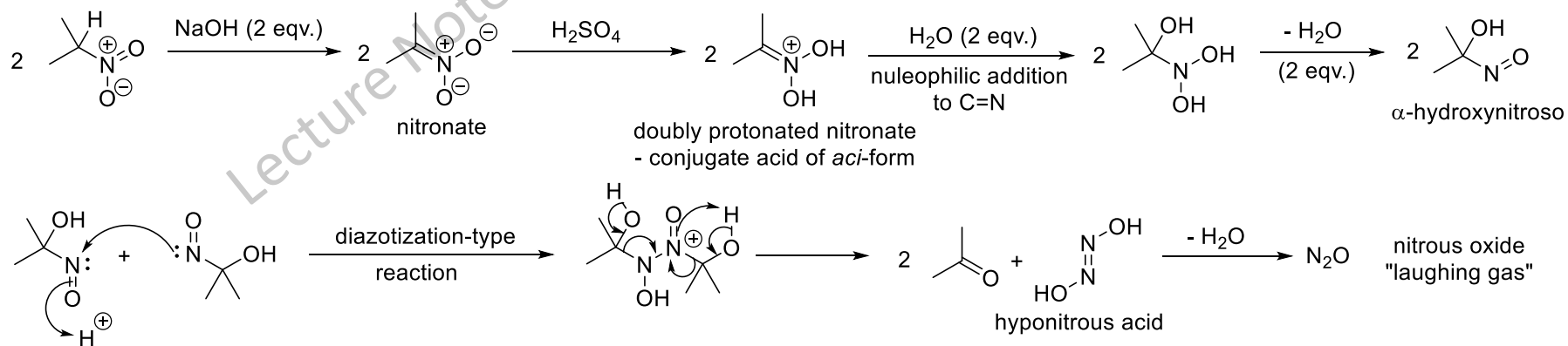
The nature of the final product depends upon the starting material. Nitronates derived from secondary nitro compounds afford ketone, while primary nitroalkanes lead to formation of aldehydes. Nef carbonyl synthesis was once an important technique for the following conversion:



Example,



A plausible mechanism is outlined below:



J. U. Nef
(1862-1915)

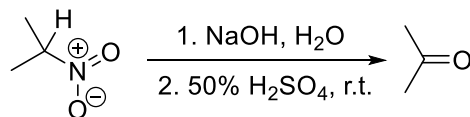
Organonitrogen Chemistry

Chemistry of aliphatic nitro compounds:

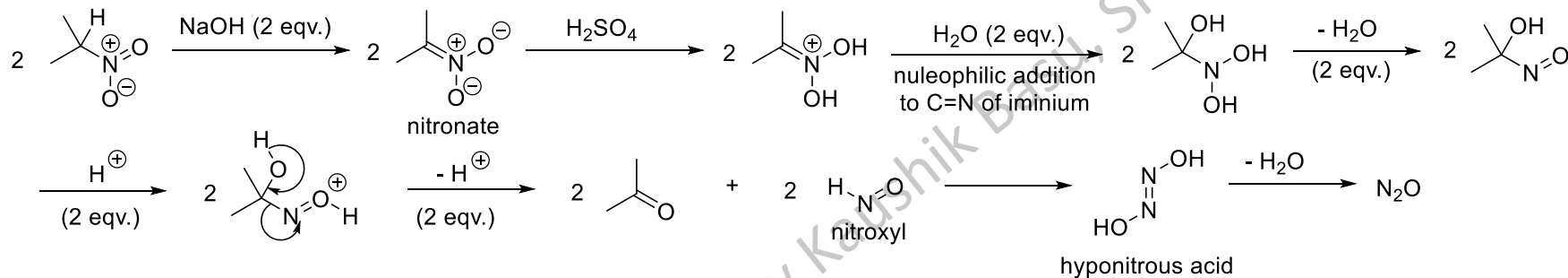
Reactions of nitroalkanes:

C] Nitro-*aci*-nitro tautomerism: reprotonating the nitronate

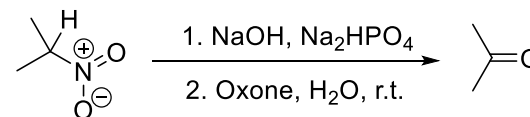
Alternative mechanism of Nef carbonyl synthesis:



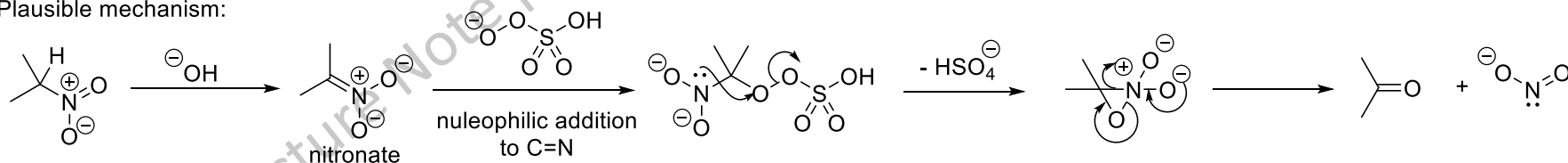
Mechanism involving nitroxyl:



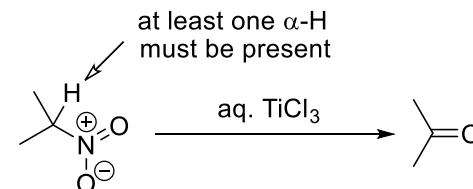
Nef synthesis can be effected by Oxone as well. Oxone is an oxidizing agent with composition: 2KHSO₅·KHSO₄·K₂SO₄, the active ingredient being potassium monopersulfate (KHSO₅, potassium peroxomonosulfate) is a salt from the Caro's acid H₂SO₅.



Plausible mechanism:



However, Nef synthesis has lost much of its prominence due to the emergence of newer methods that convert the nitro functional group to carbonyls under a milder reaction condition. One important development is the McMurry reaction:



Organonitrogen Chemistry

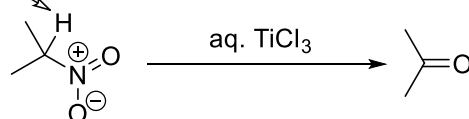
Chemistry of aliphatic nitro compounds:

Reactions of nitroalkanes:

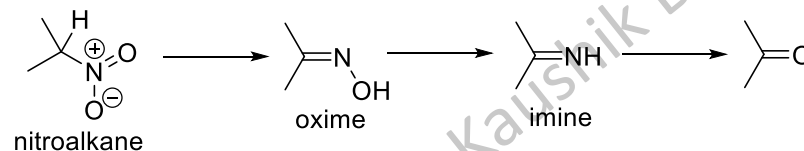
C] Nitro-*aci*-nitro tautomerism: Exploiting the conversion of nitro to carbonyl

One of the general methods for transforming the nitro functional group to carbonyls under a milder reaction condition is the McMurry reaction:

at least one α -H must be present

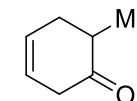


The mechanism is decidedly complicated but it is believed that the reaction proceeds through the following sequence:



J. E. McMurry
(1943-)

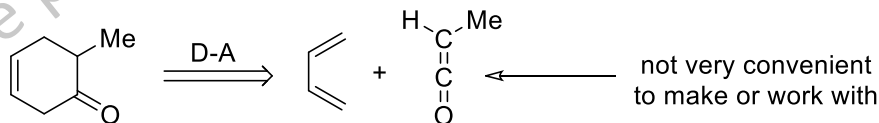
Consider the following target molecule to appreciate the power of converting a nitro to the corresponding carbonyl:



This is a β,γ -unsaturated cyclic ketone. Cannot think of aldol here, or any sort of elimination as the $\text{C}=\text{C}$ is not conjugated to the $\text{C}=\text{O}$.

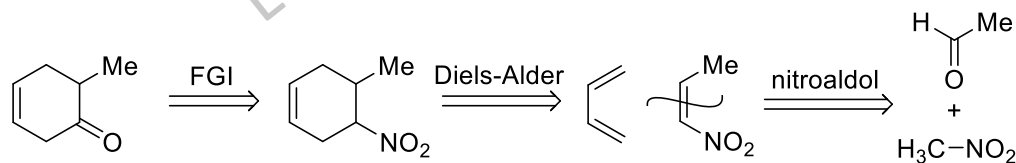
However, there is a six-membered ring with a double bond inside, so we can go for Diels-Alder to construct that.

Only one problem, the carbonyl present would imply that the dienophile has to be a ketene, not exactly a good thing to work with.



So?

So we revise the TM by doing an FGI. If we put an CH-NO_2 in place of the $\text{C}=\text{O}$, things become simplified:

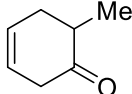


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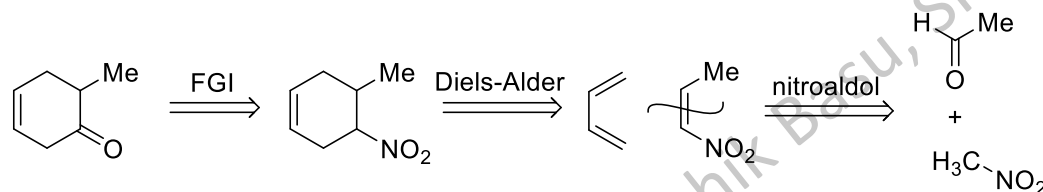
Chemistry of aliphatic nitro compounds:

Reactions of nitroalkanes:

C] Nitro-*aci*-nitro tautomerism: Exploiting the conversion of nitro to carbonyl

Synthesis of 

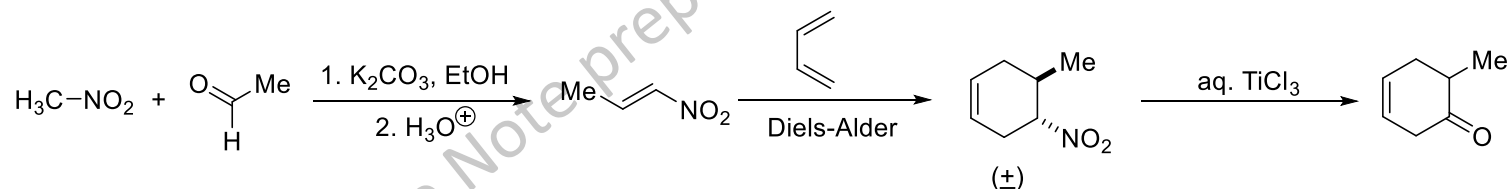
Retrosynthetic analysis:



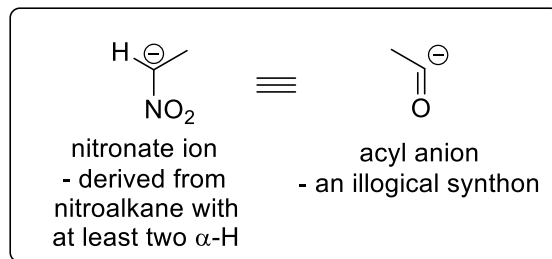
We would need to carry out a Henry reaction between nitromethane and benzaldehyde and then dehydrate the resulting aldol-like product to generate the dienophile.

The stereochemistry of the double bond is not important as the nitro would be eventually converted to C=O, but, probably a *trans*-diastereomer would form here. The Diels-Alder is expected to be favourable as the dienophile contains an electron-withdrawing group (recall normal electron demand).

The forward synthesis is as follows:



Nitroalkane anions are therefore good acyl anion equivalents:



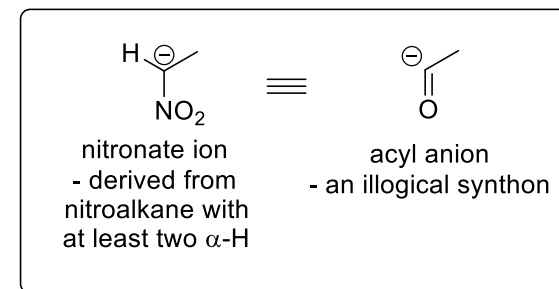
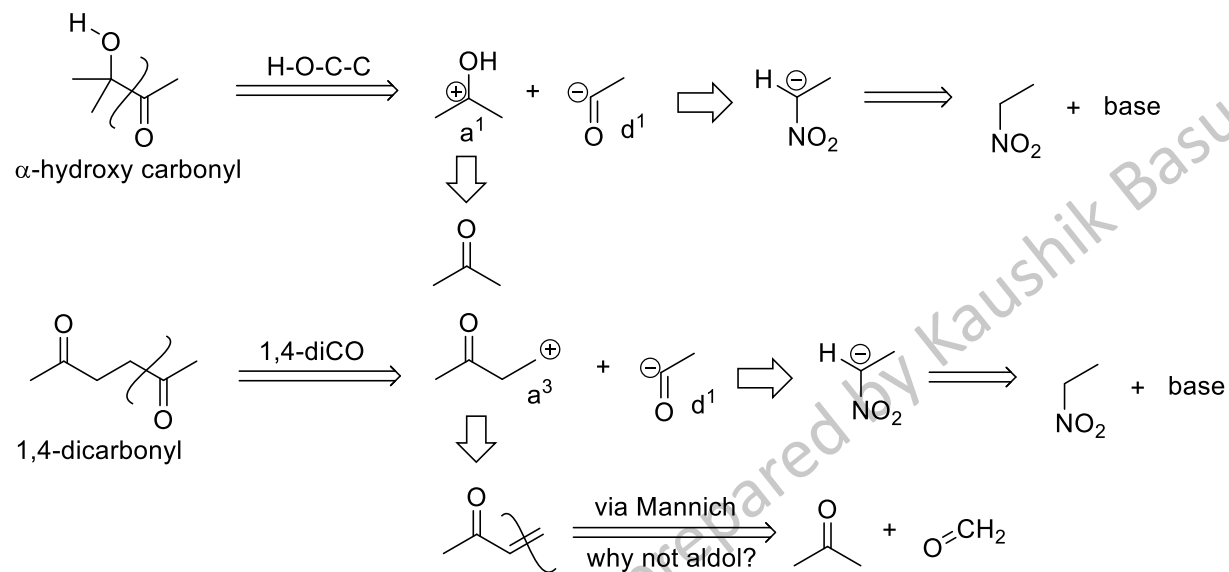
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Chemistry of aliphatic nitro compounds:

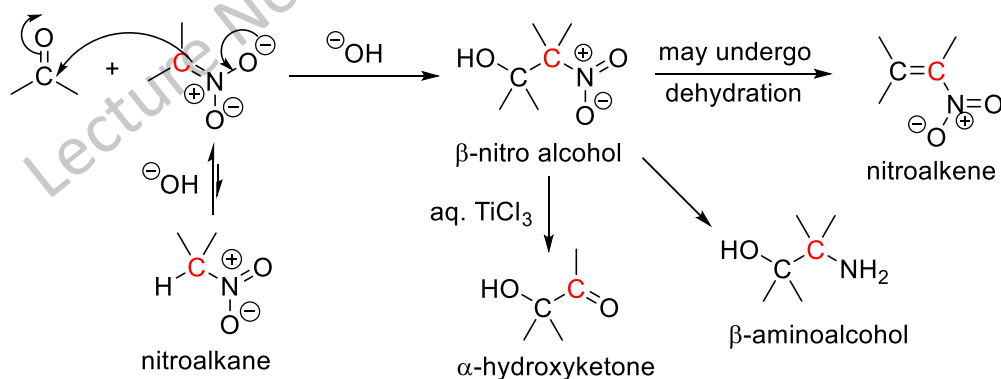
Reactions of nitroalkanes:

D] Nitronate ion as nucleophile: Henry reaction and conjugate addition:

Nitronate ion serves as a nucleophile and acts as an acyl anion equivalent, facilitating the following disconnections and access to several important class of compounds:



The aldol-like reaction between the carbanion derived from nitroalkane and carbonyl compounds is known as Henry reaction:



L. Henry
(1834-1913)

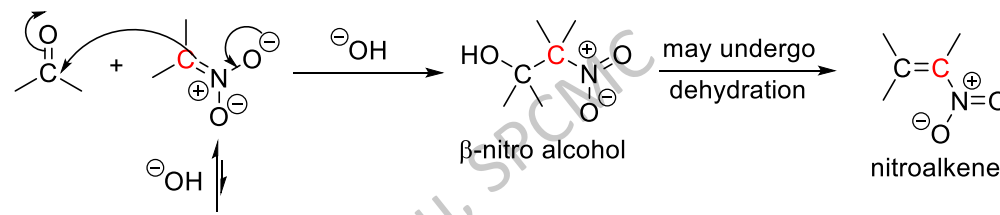
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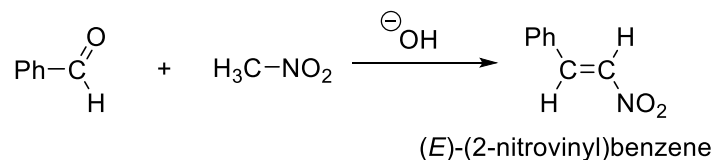
Reactions of nitroalkanes:

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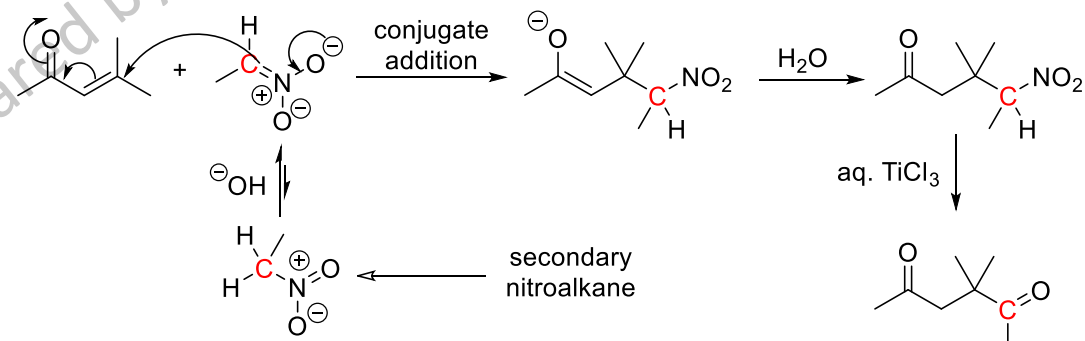
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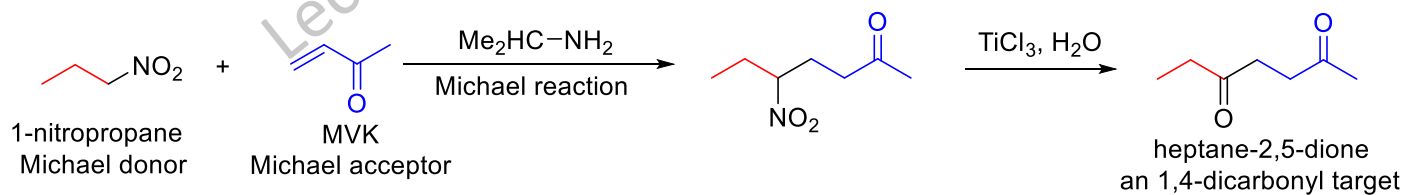
Thus we have the following example:



Carbanions derived from nitroalkanes are soft in nature. They have excellent reactivity towards α,β -unsaturated carbonyl compounds where they add preferentially to the soft electrophilic β -end, thus giving rise to conjugate addition (Michael addition) product:



For example, we have the following synthesis of heptane-2,5-dione:

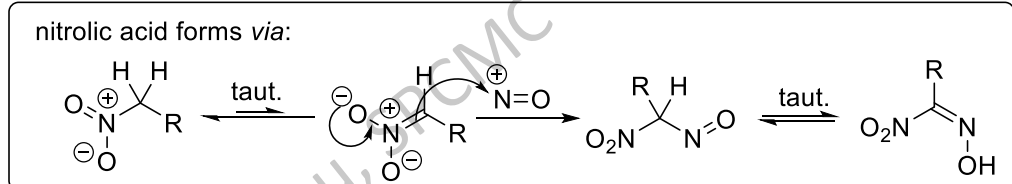
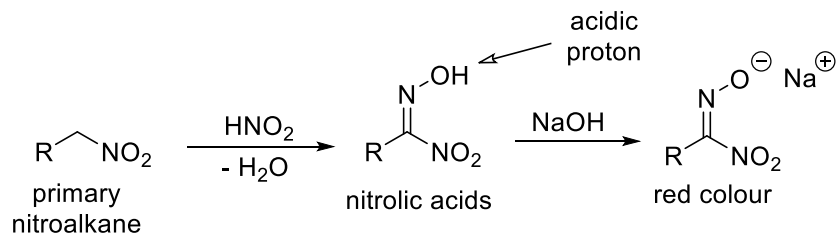


Organonitrogen Chemistry

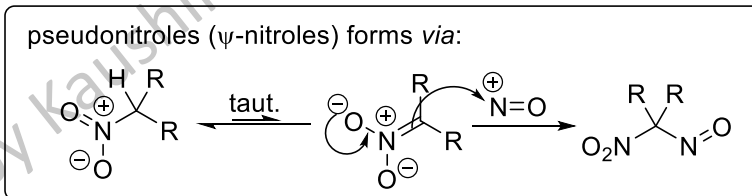
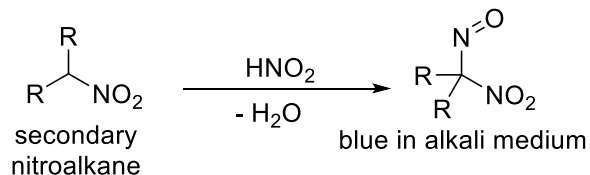
Chemistry of aliphatic nitro compounds:

Distinction between three different classes of aliphatic nitro compounds:

When reacted with nitrous acid, primary nitro compounds form nitrolic acids which dissolve in NaOH to give red solution:

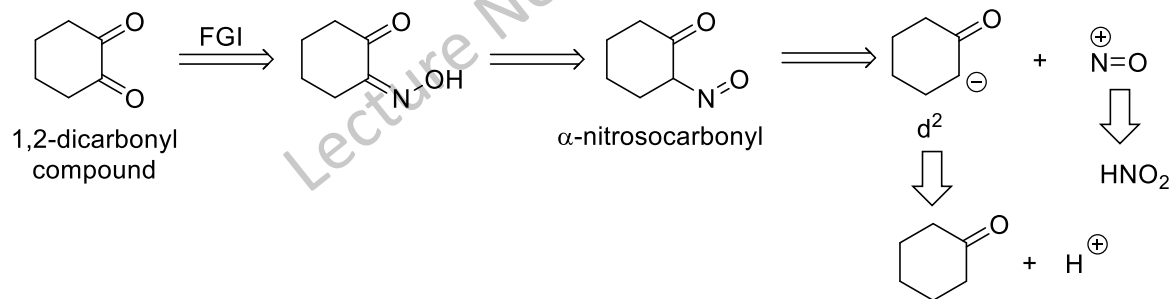


Secondary nitro compounds give pseudonitroles (ψ -nitroles) which dissolve in alkali to give blue solution:



Tertiary nitro compounds do not possess any α -hydrogen and so they do not react with nitrous acid at all.

The reaction of primary and secondary nitroalkanes with nitrous acid is reminiscent of reactions of carbonyl compounds possessing α -hydrogens with the same reagent. In this connection, the following retrosynthetic analysis for a 1,2-dicarbonyl compound such as cyclohexane 1,2-dione is instructive:



α -nitrosation proceeds in the following way:

