

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

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Recommended texts:

1. Study Guide to Organic Chemistry, Volume 2, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192669588,
2. Study Guide to Organic Chemistry, Volume 4, by Saha, Chakraborty, Saha & Basu, Techno World, ISBN 9788192695259,
3. Organic Chemistry, Second Ed. by Clayden, Greeves & Warren, OUP, ISBN 9780198728719

## Rearrangements in Organic Chemistry

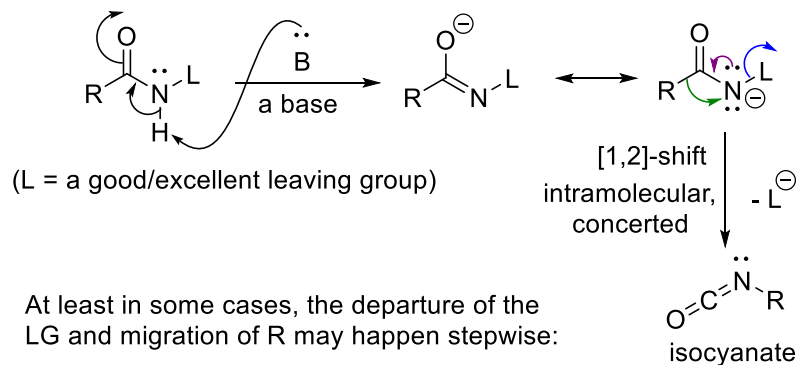
Migration from carbon to electron-deficient nitrogen: Hofmann, Curtius, Lossen and Schmidt rearrangements: Synthesis of amines

These rearrangements share a few common features:

1. These involve migration from a carbon to an adjacent e-deficient nitrogen atom,
2. All of these proceed via the intermediacy of an isocyanate.

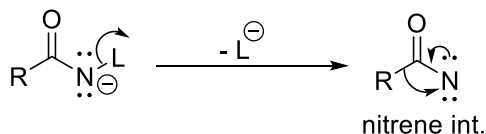
Generalised mechanism:

1) Formation of isocyanate from the respective starting materials:



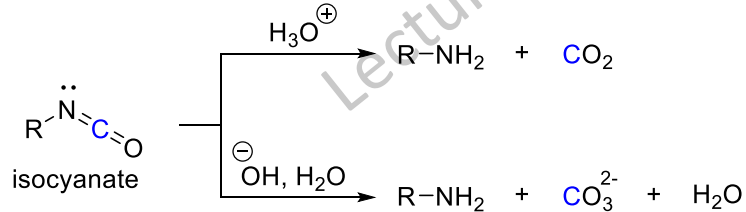
L leaves,  
R migrates,  
nitrogen stabilises  
the incipient cation  
R and L anti

At least in some cases, the departure of the LG and migration of R may happen stepwise:

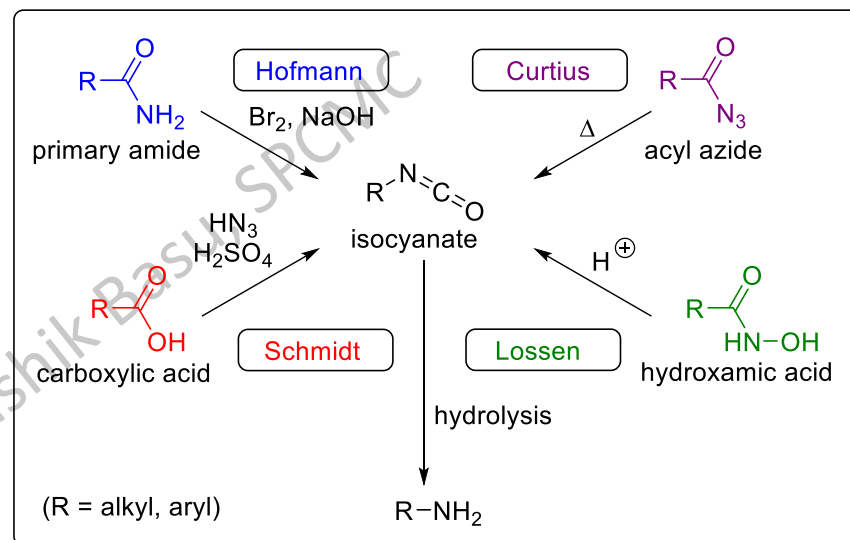
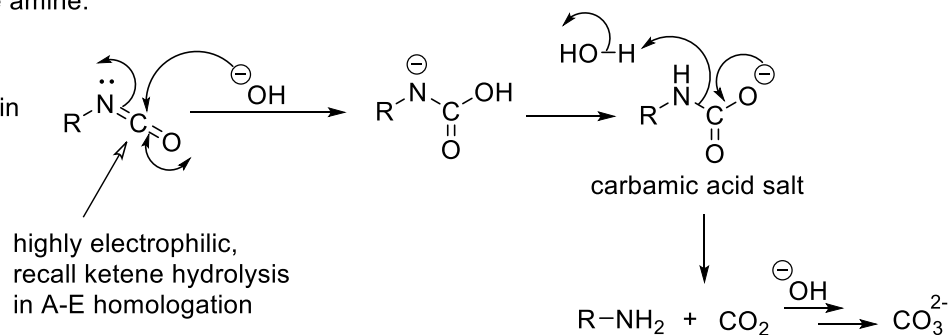


2) Hydrolysis of isocyanate:

Under the reaction condition the isocyanate may get hydrolysed and afford the amine. The hydrolysis, however, may also be carried out separately:



hydrolysis in alkali via:



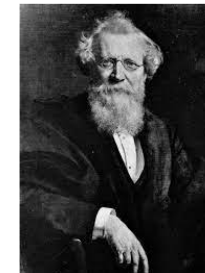
Essential structural features:  $R-C(=O)-N(H)-L$  ← a good-ish LG

must contain a H on N

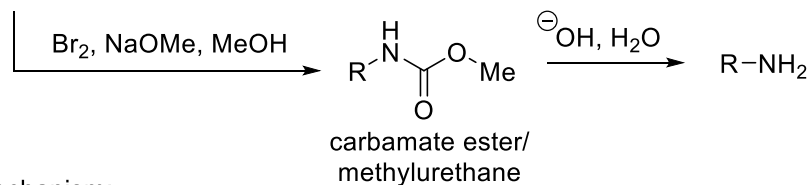
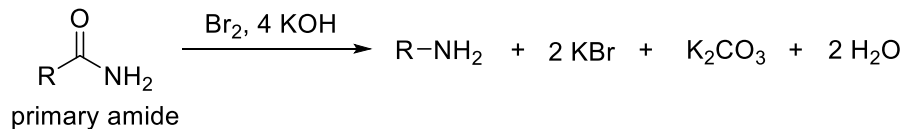
## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Hofmann rearrangement aka Hofmann degradation aka Hofmann hypobromite reaction

The conversion of primary carboxamides to the corresponding one-carbon shorter primary amines.

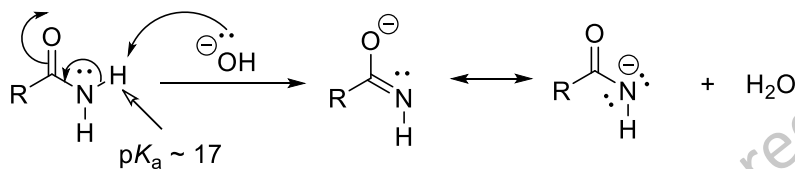


A. W. von Hofmann  
(1818-1892)

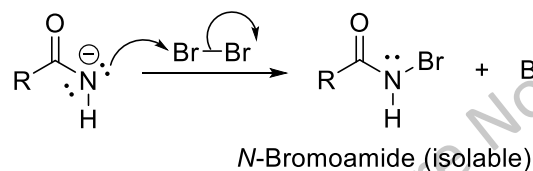


Mechanism:

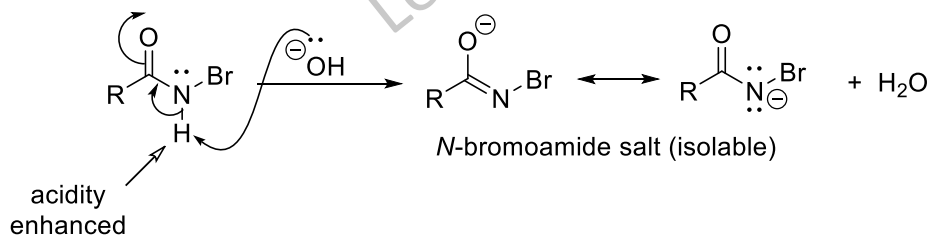
step-1) Formation of resonance-stabilised anion from carboxamide:



step-2) Formation of *N*-bromoamide:

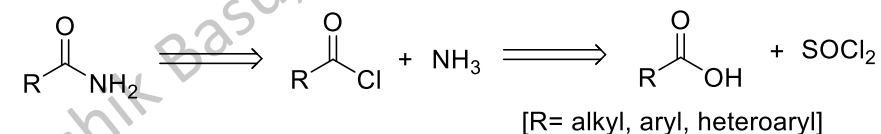


step-3) Formation of *N*-bromoamide salt:

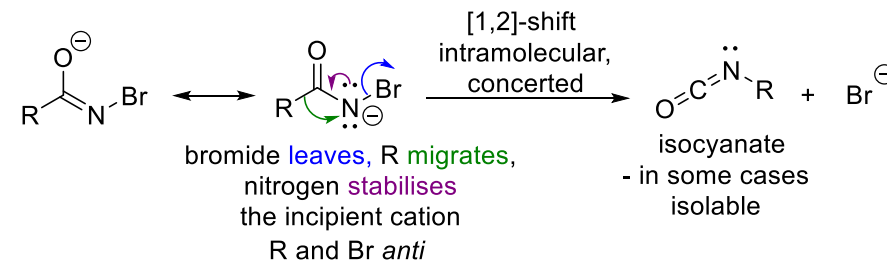


According to the standard procedure, the amide is dissolved in a cold solution of an alkali hypobromite or hypochlorite and the resulting solution is heated to  $\sim 70-80^\circ\text{C}$  to bring about the rearrangement.

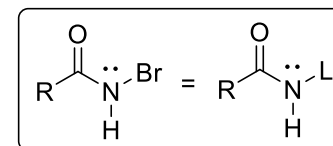
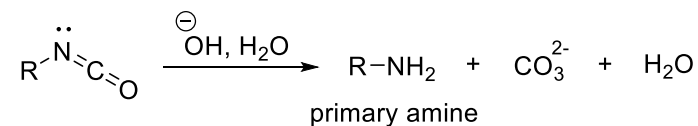
Source of SM - the primary amide:



step-4) Formation of isocyanate:



step-5) Hydrolysis of isocyanate in alkaline medium:

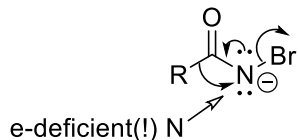


## Rearrangements in Organic Chemistry

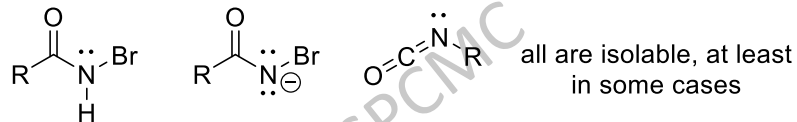
Migration from carbon to electron-deficient nitrogen: Hofmann rearrangement aka Hofmann degradation aka Hofmann hypobromite reaction

Salient features of Hofmann rearrangement:

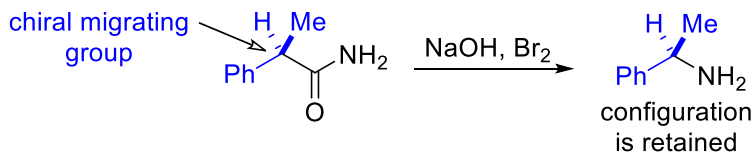
1. It involves migration to an e-deficient N



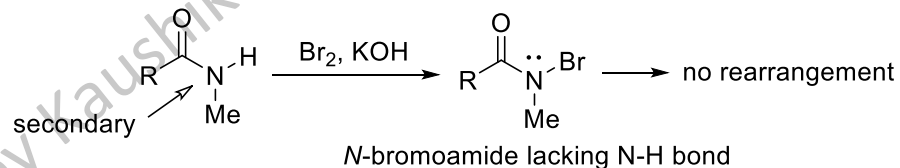
2. The intermediates are isolable, which supports the mechanism outlined.



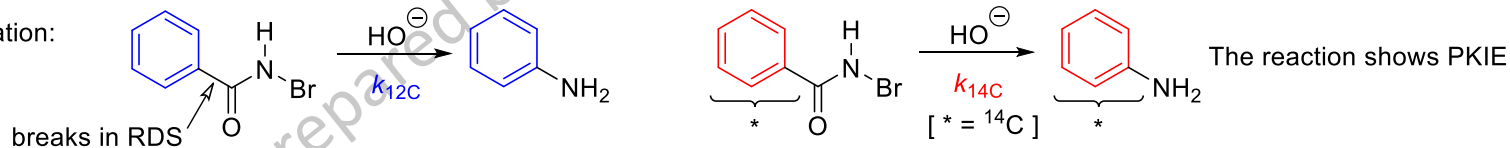
3. If R is chiral, it migrates with retention of configuration, indicating intramolecular nature of the migration:



4. Secondary carboxamides like the following do not undergo the rearrangement, the *lack of the second hydrogen* stops the reaction in its track at the *N*-bromoamide stage:

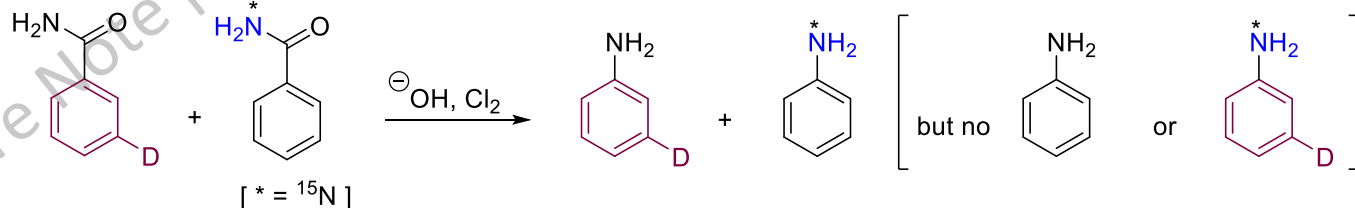


5. RDS is the isocyanate formation:

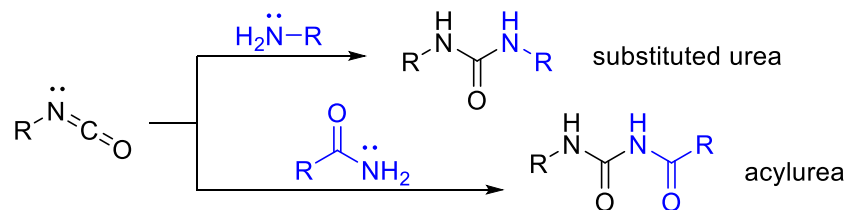


6. No cross-products are found in crossover experiment:

Proves that the reaction is strictly intramolecular.



7. In absence of sufficient alkali, the RNH<sub>2</sub> produced or the unreacted RCONH<sub>2</sub> may attack the isocyanate electrophile to afford the following:

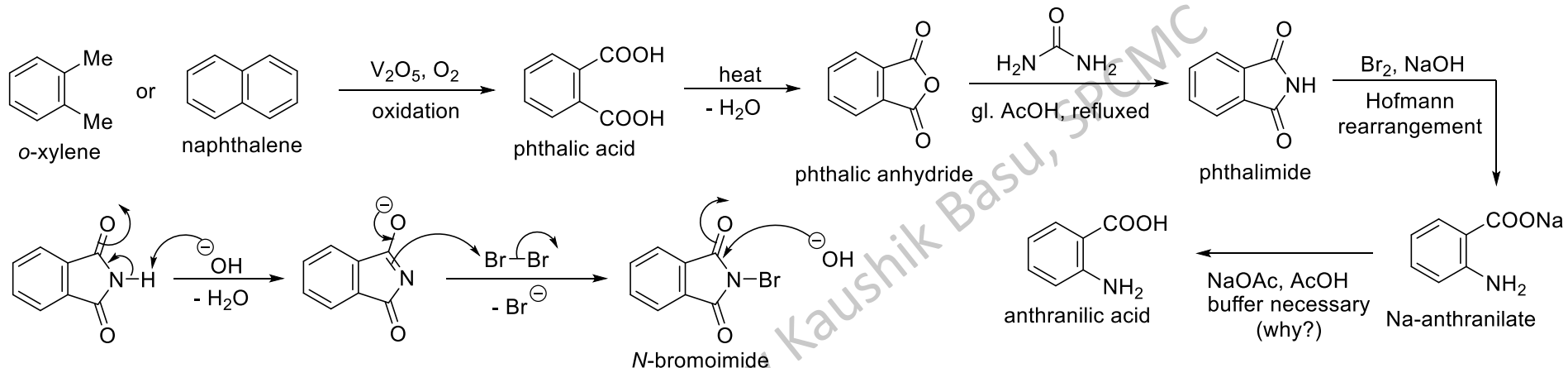


## Rearrangements in Organic Chemistry

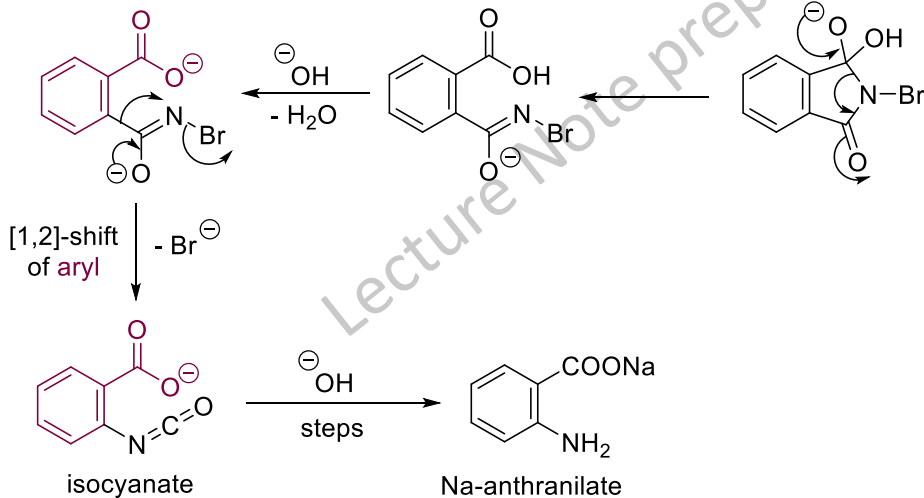
Migration from carbon to electron-deficient nitrogen: Hofmann rearrangement

Synthetic utility:

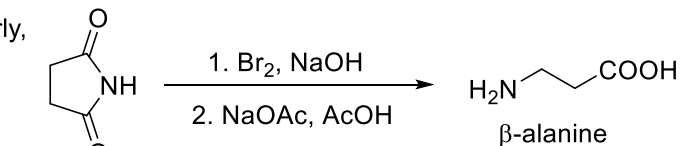
1. Conversion of *o*-xylene or naphthalene to anthranilic acid:



$pK_a$  8.3, unusually acidic N-H, due to EW effect of two C=O that stabilizes the cB



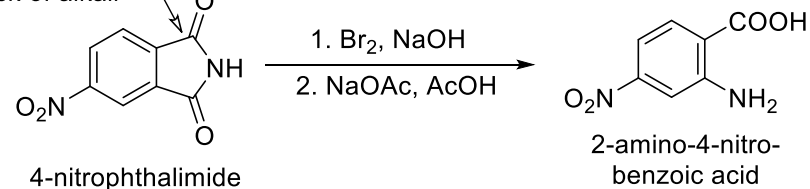
Similarly,



[Recall the synthesis of *N*-bromosuccinimide (NBS) - which is made by treating succinimide with NaOH and Br<sub>2</sub> under ice-cold condition to avoid potential Hofmann rearrangement]

and

regioselective attack of alkali



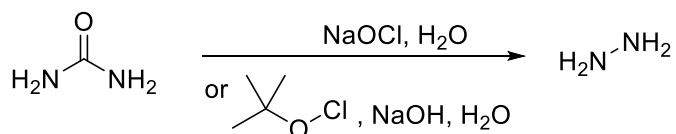
(try the mechanism yourself)

## Rearrangements in Organic Chemistry

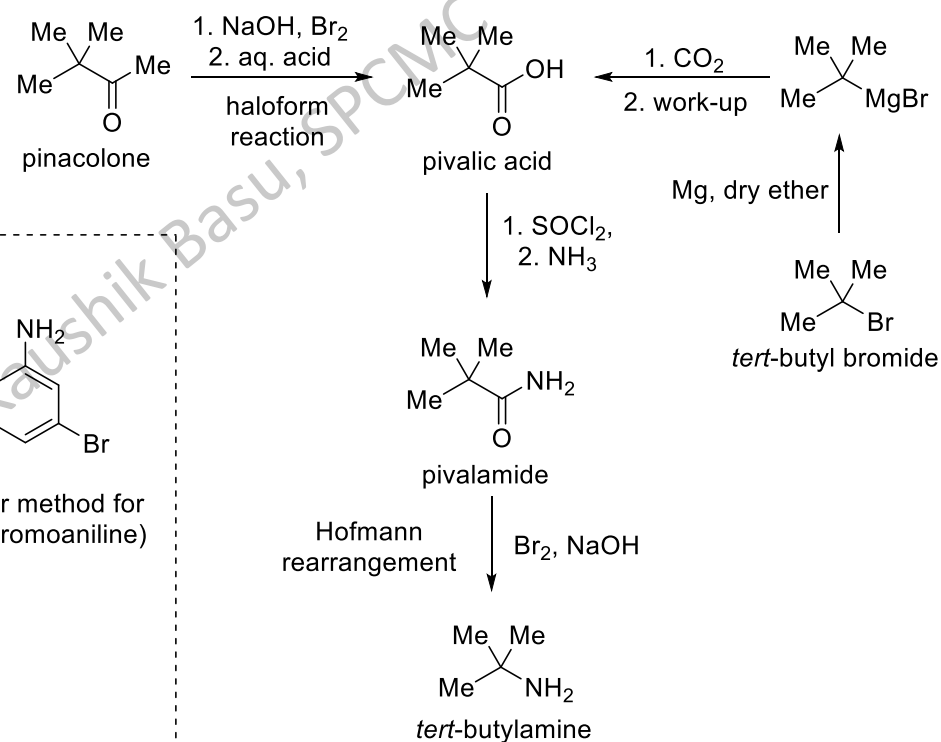
Migration from carbon to electron-deficient nitrogen: Hofmann rearrangement

Synthetic utility:

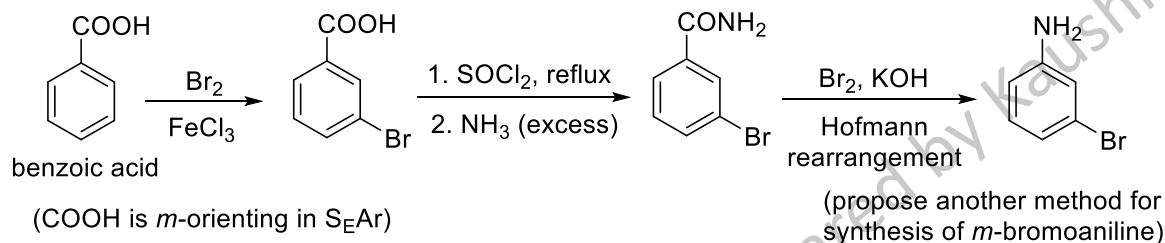
2. Conversion of urea to hydrazine:



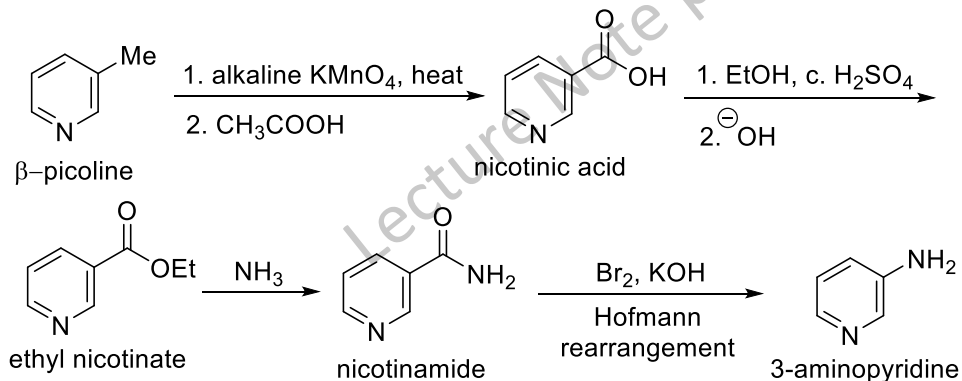
3. Synthesis of *t*-butylamine:



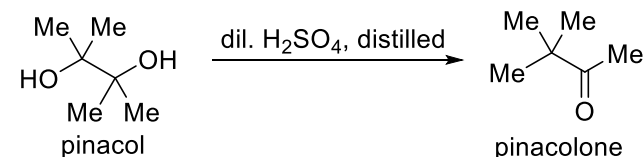
4. Synthesis of *m*-bromoaniline:



5. Conversion of β-picoline (3-methylpyridine) to 3-aminopyridine:



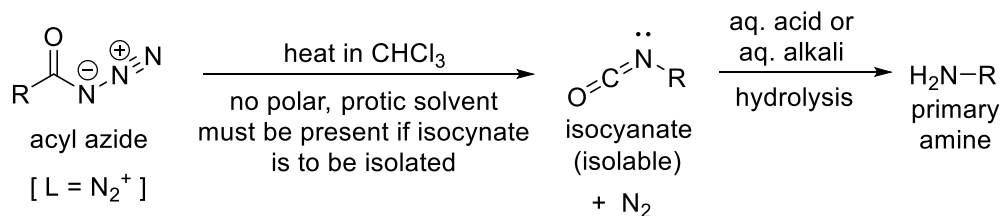
Recall: compounds containing *tert*-butyl groups can be synthesised using the pinacol rearrangement



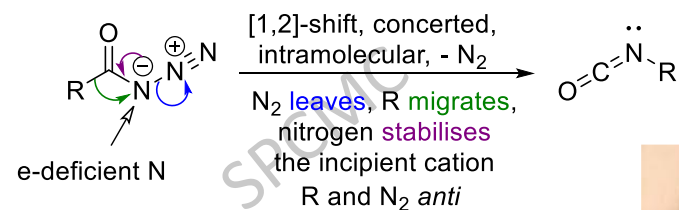
## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Curtius rearrangement

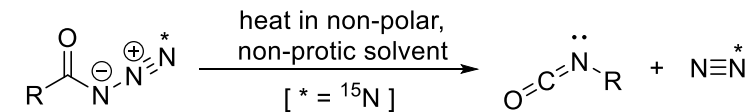
The thermal decomposition (pyrolysis) of acyl azides to the corresponding isocyanates.



Mechanism of isocyanate formation:

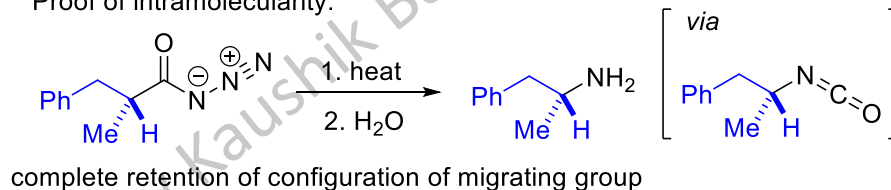


Which N is lost from acyl azide?



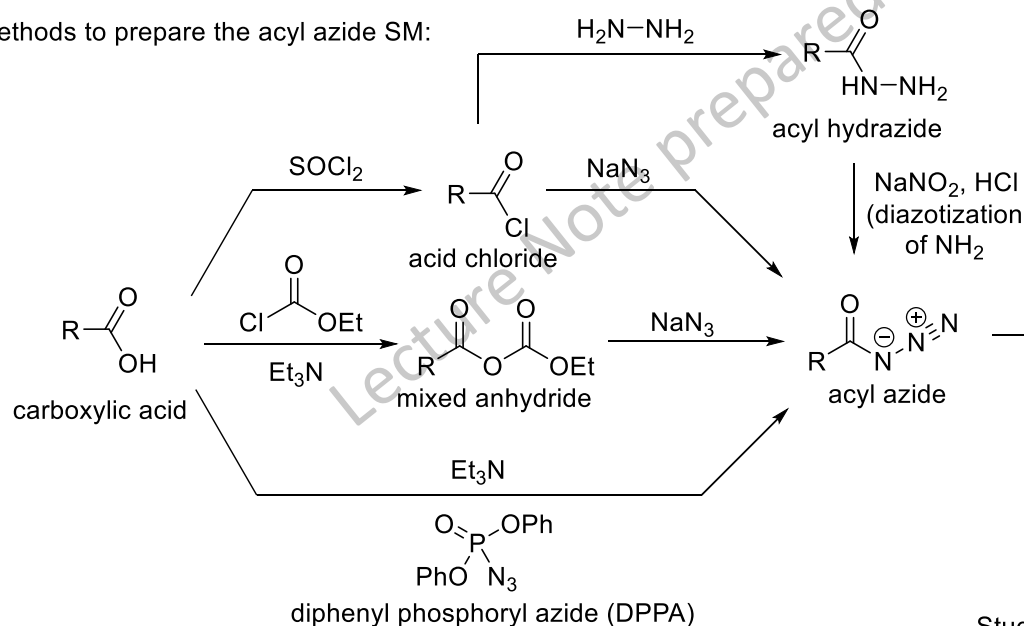
(how might you access this SM?)

Proof of intramolecularity:

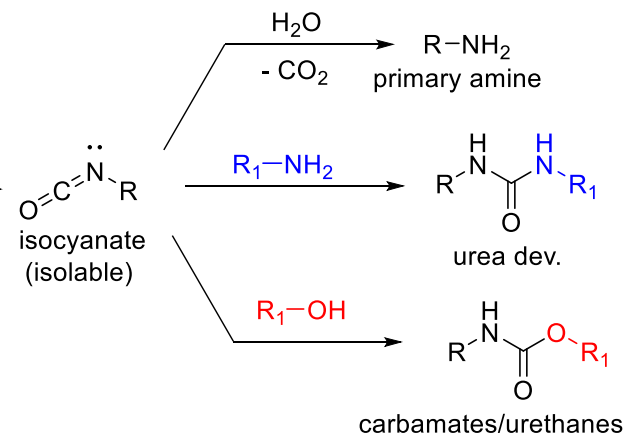


J. W. T. Curtius (1857-1928)

Methods to prepare the acyl azide SM:



Synthetic manipulation of isocyanate:

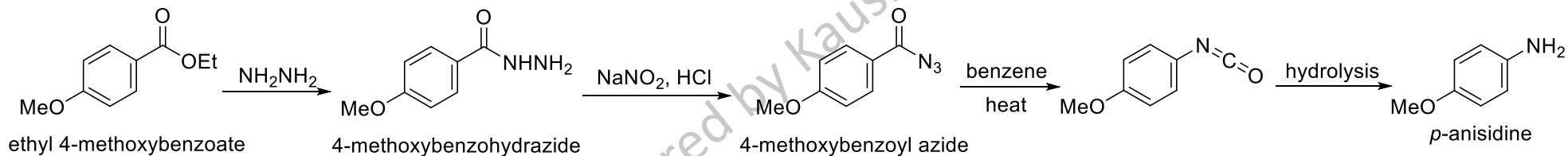
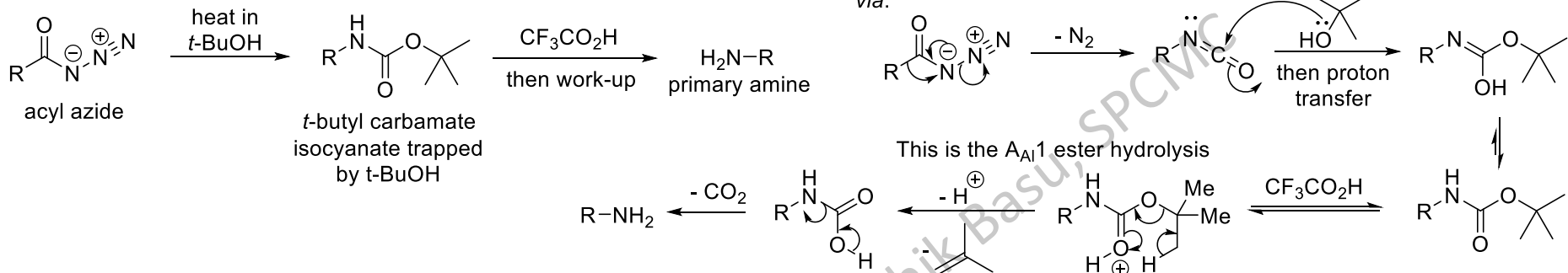


## Rearrangements in Organic Chemistry

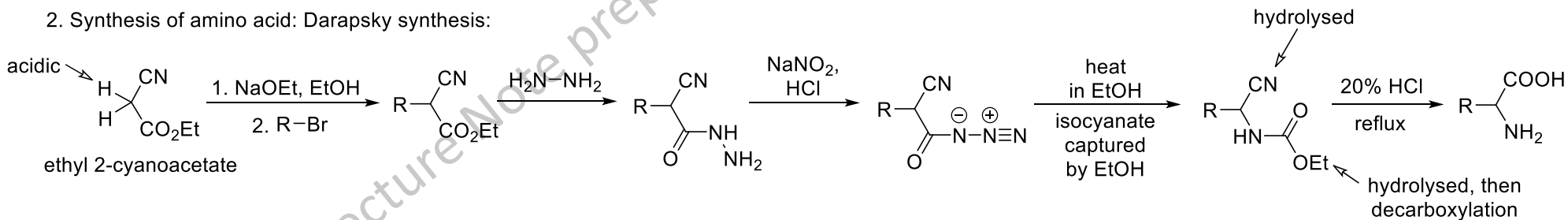
Migration from carbon to electron-deficient nitrogen: Curtius rearrangement

Synthetic utility:

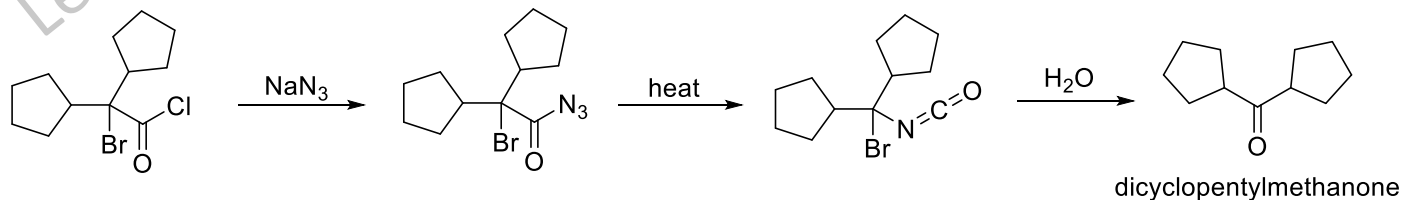
1. Synthesis of amines:



2. Synthesis of amino acid: Darapsky synthesis:



3. Synthesis of ketones from  $\alpha$ -haloazides:

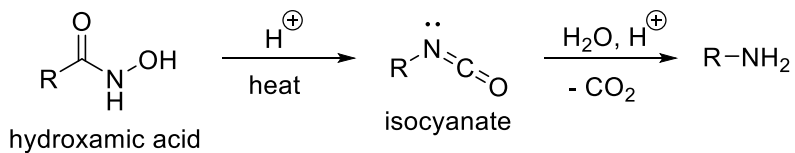




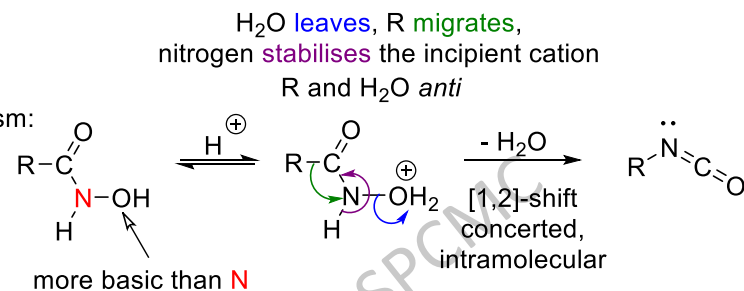
## Rearrangements in Organic Chemistry

Migration from carbon to electron-deficient nitrogen: Lossen rearrangement

The conversion of O-acyl hydroxamic acids to the corresponding isocyanates

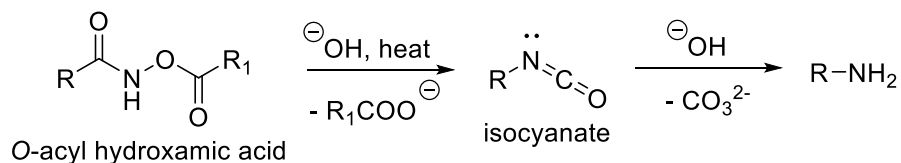


Mechanism:

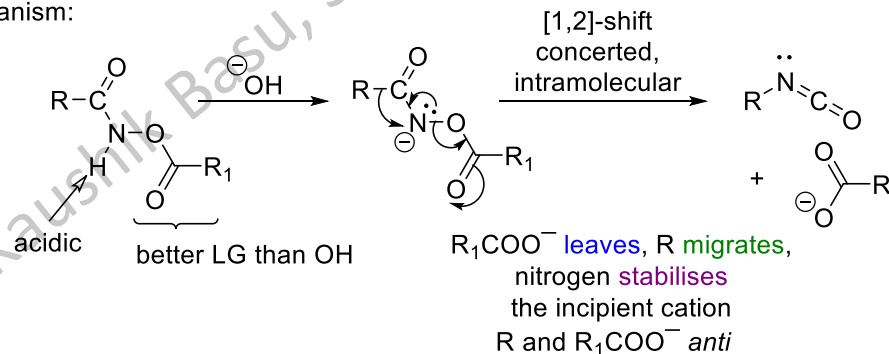


W. C. Lossen (1838-1906)

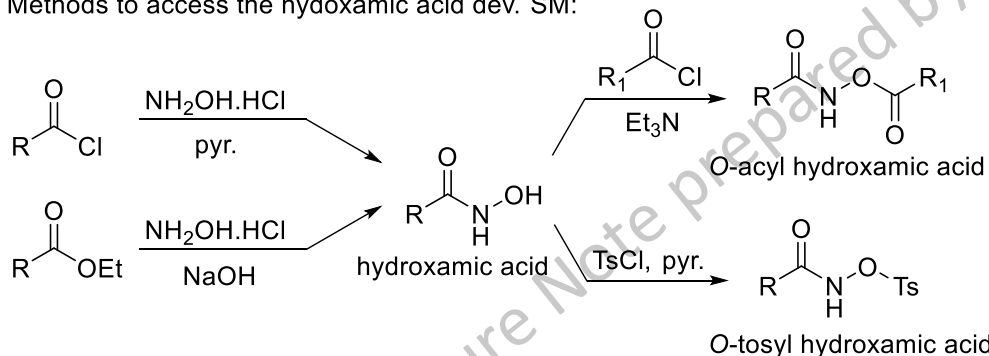
Better yields are found with O-activated hydroxamic acids:



Mechanism:

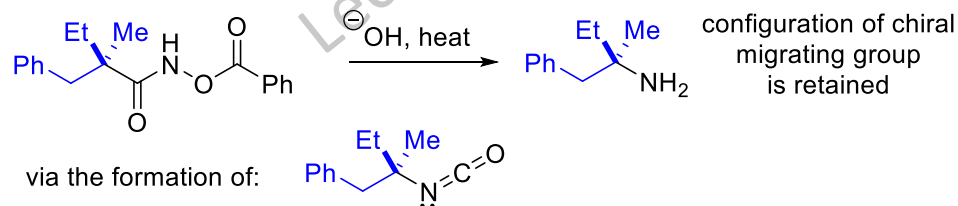


Methods to access the hydroxamic acid dev. SM:



Formation of isocyanate is the RDS which involves migration of R to an e-deficient N centre, thus presence of ERG at R facilitates the reaction.

Proof of intramolecularity:



An interesting problem:

