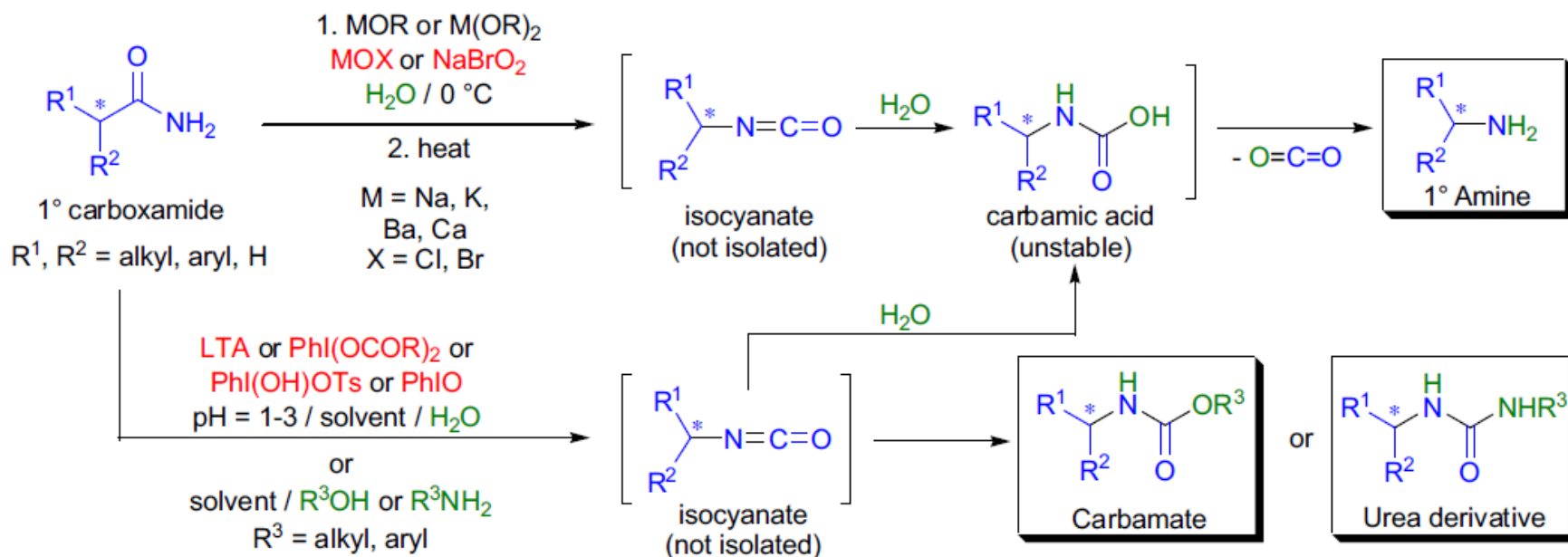


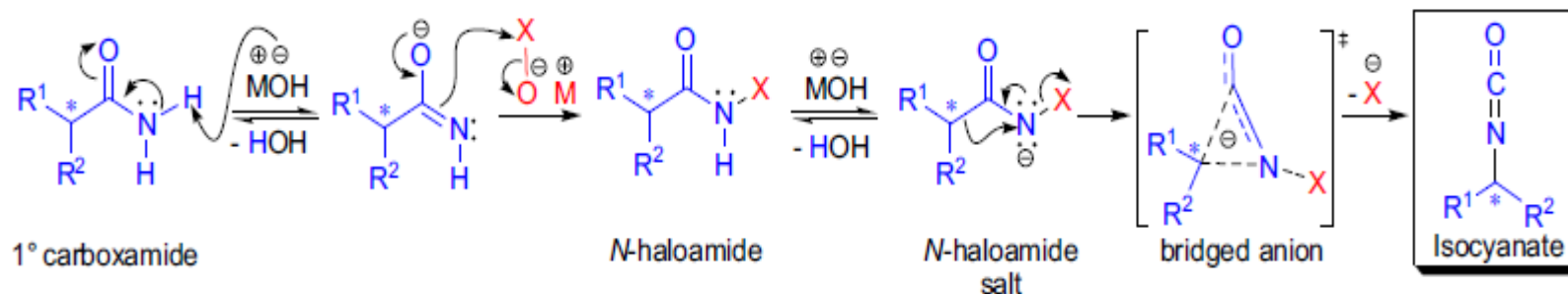
Hofmann rearrangement



Origin

- In 1881, A.W Hofmann found that by treating acetamide with one equivalent of bromine (Br_2) and sodium or potassium hydroxide it afforded *N*-bromoacetamide. Upon further deprotonation and heating, *N*-bromoacetamide gave an unstable salt that in the absence of water readily rearranged to methyl isocyanate.¹ However, in the presence of water and excess base the product was methylamine. The conversion of primary carboxamides to the corresponding one-carbon shorter amines is known as the *Hofmann rearrangement*

Mechanism



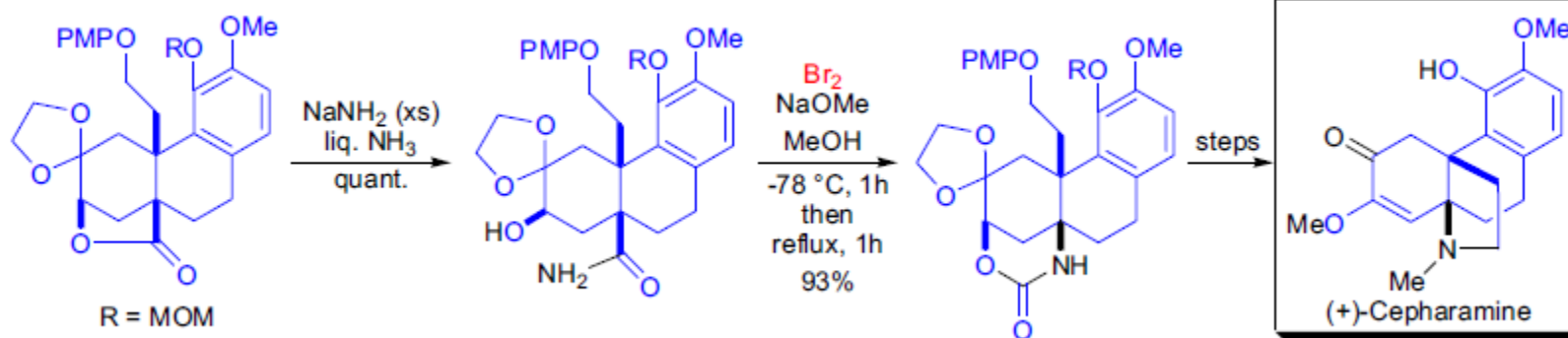
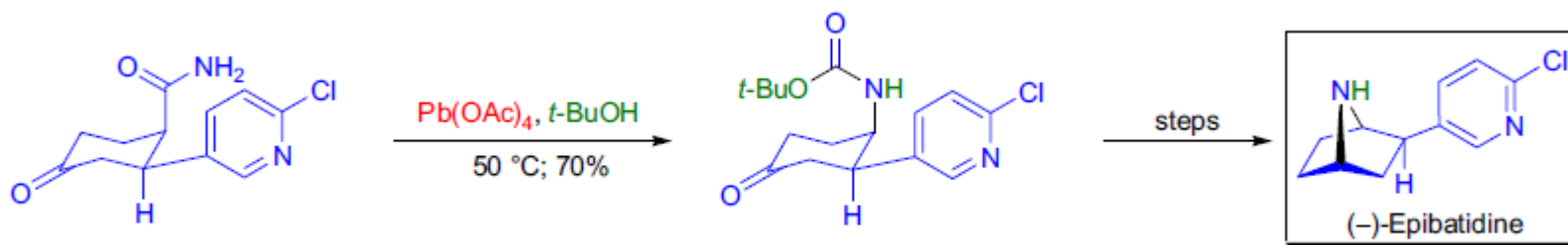
The mechanism of the *Hofmann rearrangement* is closely related to the *Curtius*, *Lossen* and *Schmidt rearrangements*. The first step is the formation of an *N*-halogen substituted amide. Next, the *N*-haloamide is deprotonated by the base to the corresponding alkali salt that is quite unstable and quickly undergoes a concerted rearrangement to the isocyanate *via* a bridged anion. This mechanistic picture is strongly supported by kinetic evidence.³⁶⁻³⁹ As a result, the *Hofmann rearrangement* proceeds with complete retention of configuration.

Features

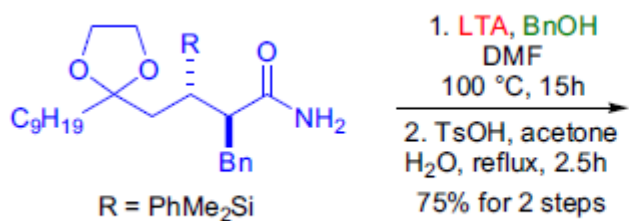
1) the hypohalite reagents are freshly prepared by the addition of chlorine gas or bromine to an aqueous solution of KOH or NaOH; 2) the amides cannot contain base-sensitive functional groups under the traditional basic reaction conditions, but acid-sensitive groups (e.g., acetals) remain unchanged; 3) the isocyanate intermediate is not isolated, since under the reaction conditions it is readily hydrolyzed (or solvolyzed) to the corresponding one-carbon shorter amine *via* the unstable carbamic acid; 4) when the reaction is conducted under phase-transfer catalysis conditions, the isocyanates may be isolated

- 5) if the starting amide is enantiopure (the carbonyl group is directly attached to the stereocenter), there is a *complete retention of configuration* in the product amine; 6) the *Hofmann rearrangement* gives high yields for a wide variety of aliphatic and aromatic amides but the best yields for aliphatic amides are obtained if the substrate has no more than 8 carbons (hydrophilic amides); and 7) α,β -unsaturated amides and amides of α -hydroxyacids rearrange to give aldehydes or ketones. Since the discovery of the *Hofmann rearrangement*, several modifications were introduced: 1) for hydrophobic amides, the use of methanolic sodium hypobromite (bromine added to sodium methoxide in methanol) results in high yields of the corresponding methylurethanes; 2) for acid- and base-sensitive substrates the use of neutral *electrochemically induced Hofmann rearrangement* was developed; 3) in order to extend the scope of the reaction for basesensitive substrates, the *oxidative Hofmann rearrangement* may be carried out with LTA or hypervalent iodine reagents (PIDA, PIFA, PhI(OH)OTs, etc.) under mildly acidic conditions; and 4) when hypervalent iodine reagents or LTA are used in the presence of an amine or an alcohol, the generated isocyanate is *in situ* converted to the corresponding carbamate or urea derivative

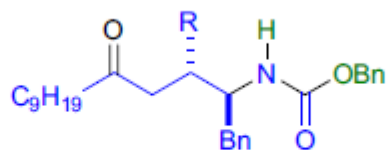
Synthetic Applications



Suárez modification

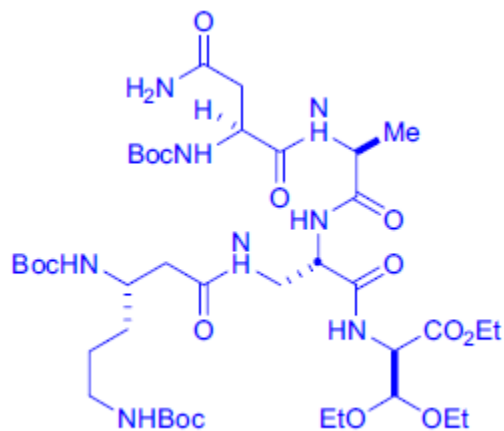
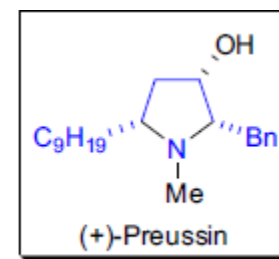


1. LTA, BnOH
DMF
 100°C , 15h
2. TsOH, acetone
 H_2O , reflux, 2.5h
75% for 2 steps

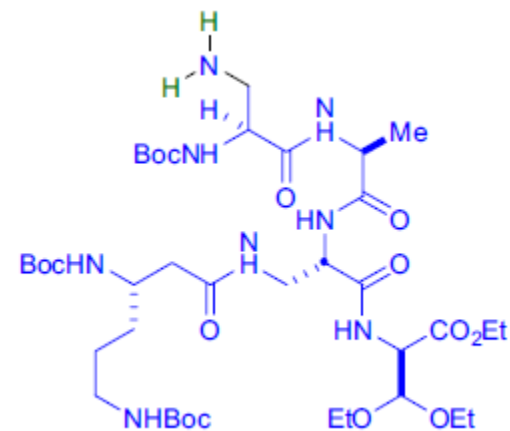


Cbz-protected primary amine

steps



$\text{PhI}(\text{O}_2\text{CCF}_3)_2$
pyridine
DMF, H_2O ; 87%





Thanks