Hoffmann Rearrangement

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May, 1, 2009

MSU

Presentation Outline

- Biography
- Similar reactions
- Recent applications

August Wilhelm von Hofmann

Born 8 April 1818 Giessen, Germany

Alma mater University of Gottingen

Doctoral advisor Justus von Liebig

Doctoral students
 Richard Abegg
 Adolf Pinner
 Fritz Haber
 Karl Friedrich von Auwers
 Rudolf Hugo Nietzki
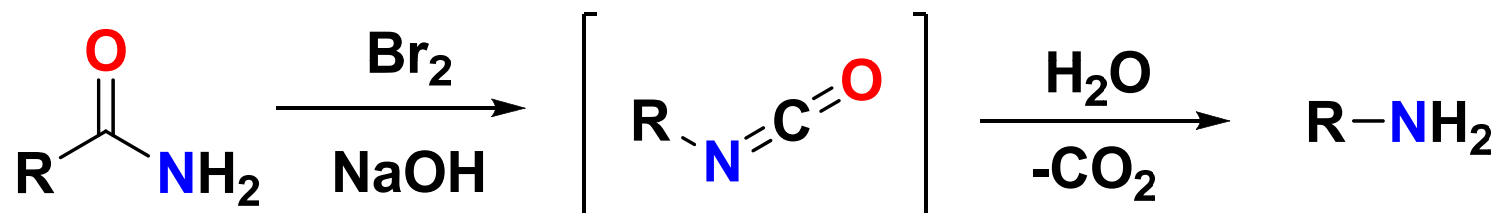 Ferdinand Tiemann
 Eugen Bamberger

Died 5 May 1892 (aged 74) Berlin, Germany

Major Discoveries

- Hofmann was the first to introduce molecular models into his public lectures around 1860
- Hofmann elimination
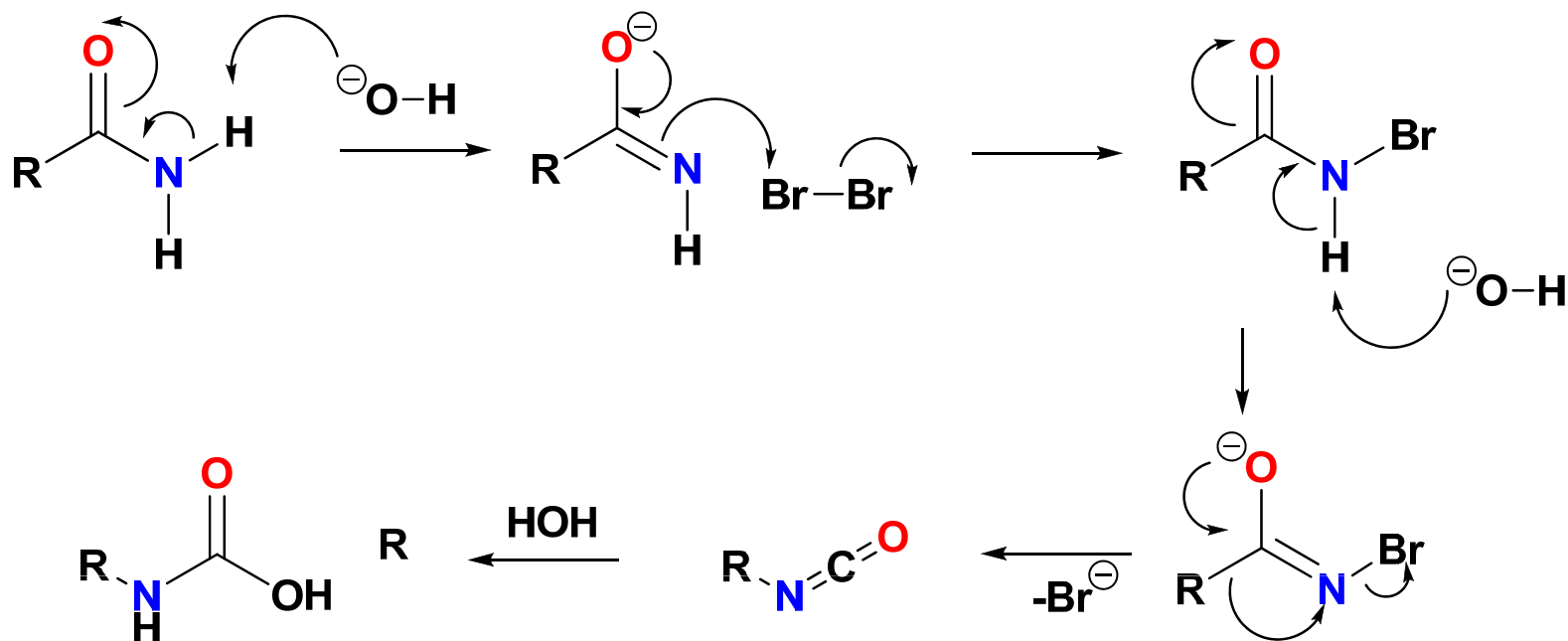- Hofmann's rule
- Hofmann rearrangement

Reaction Scheme

$$R-C(=O)-NH_2 \xrightarrow[\text{NaOH}]{\text{Br}_2} \left[R-N=C=O \right] \xrightarrow[\text{-CO}_2]{\text{H}_2\text{O}} R-NH_2$$
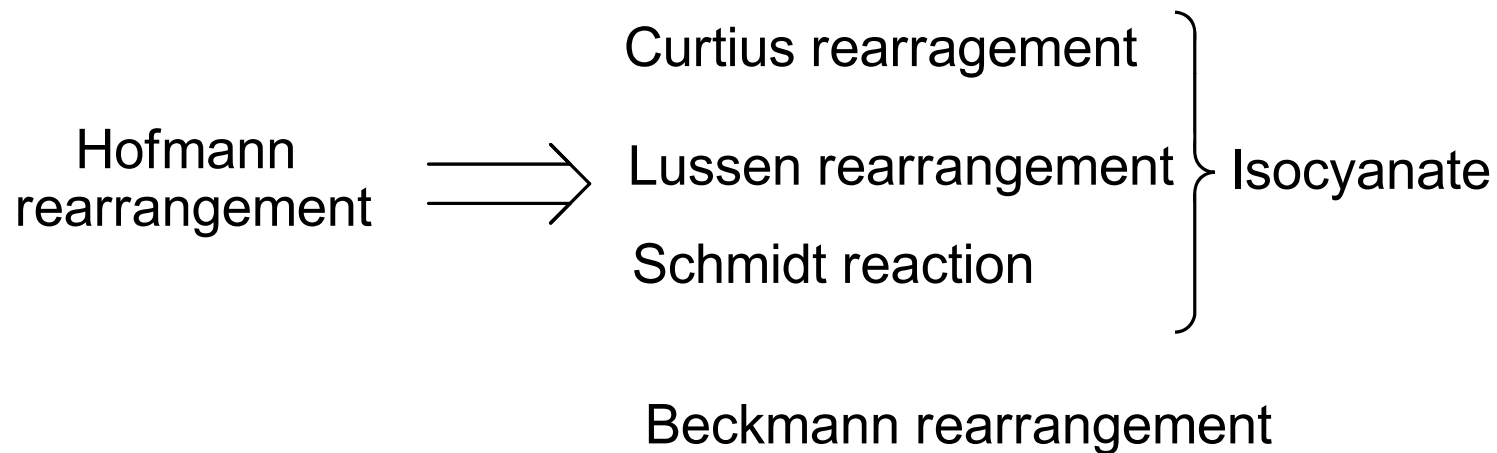
- First published 1881

Hofmann, A. W. *Chem. Ber.* **1881**, *14*, 2725.
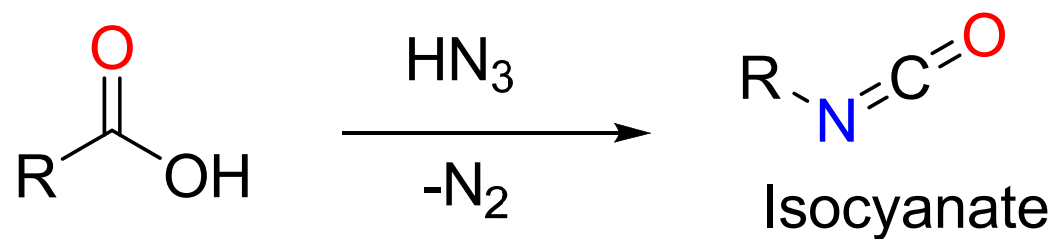Shioiri, T. *Comp. Org. Syn.* **1991**, *6*, 800-806. (Review)

Mechanism of Hofmann Rearrangement
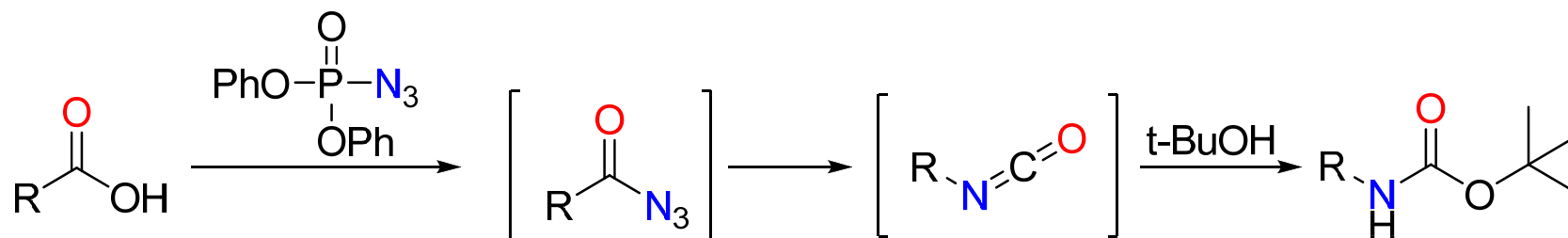
Similar Reactions

Hofmann
rearrangement $\longrightarrow$

Curtius rearragement

Lussen rearrangement

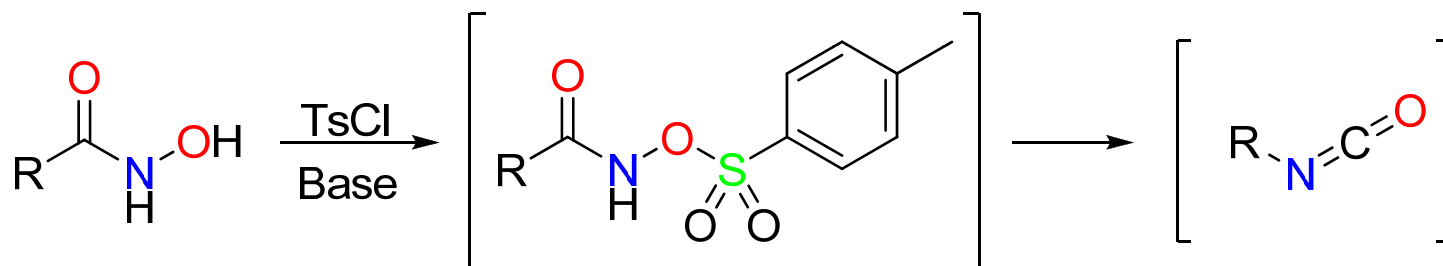Schmidt reaction

Isocyanate

Beckmann rearrangement

Schmidt reaction

Curtius Rearrangement

Lossen Rearrangement

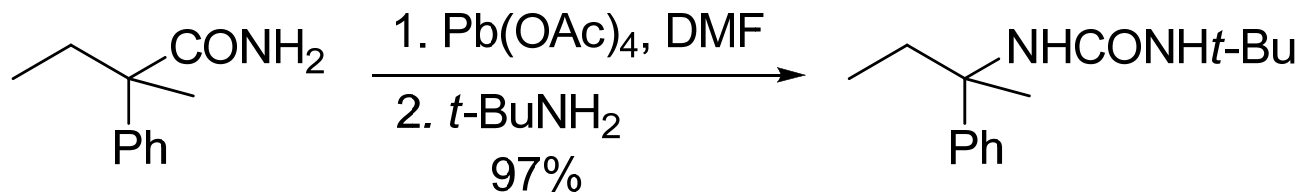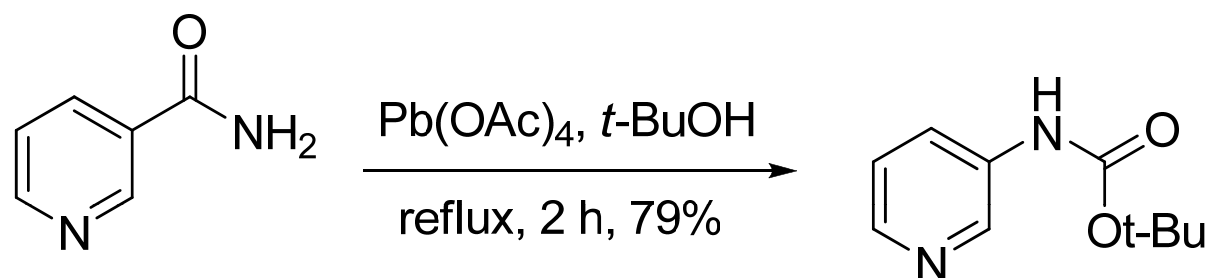# Mild Replacement for Bromine

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-NH_2 \xrightarrow[\substack{MeOH, \\ reflux\ 45\ min}]{NBS,\ DBU} R-\overset{H}{N}-\overset{\overset{\displaystyle O}{\|}}{C}-O-CH_3$$
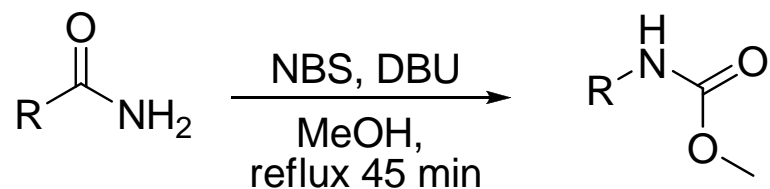
R	Yield, %
$3,4\text{-}(MeO)_2C_6H_3\text{-}$	89
$p\text{-}MeC_6H_4\text{-}$	84
$C_6H_5^-$	95
$p\text{-}ClC_6H_4\text{-}$	94
$p\text{-}NO_2\text{-}C_6H_4\text{-}$	70
$C_6H_5CH_2^-$	95
$CH_3(CH_2)_8^-$	90

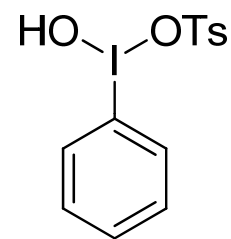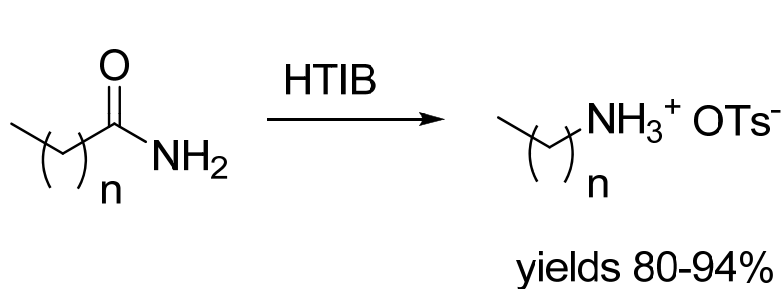- Keillor, J. W.; Huang, X. *Org. Syntheses,* **2004**, Coll. Vol. 10, 549

LTA as Alternative to Basic Conditions

Baumgarten, H. E.; Stalkis, A. *J. Am. Chem. Soc.* **1965**, *87*, 1141

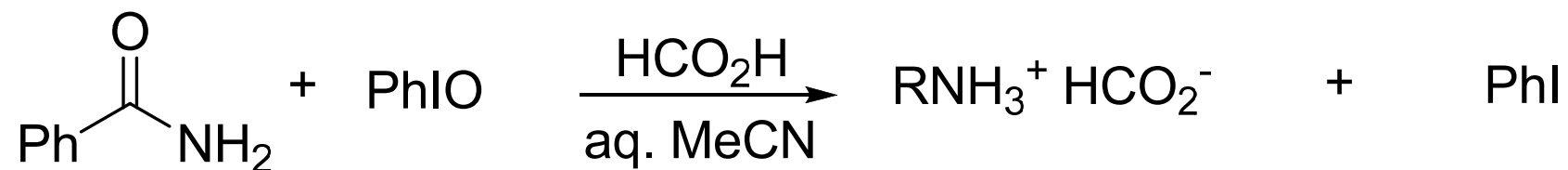Baumgarten, H. E.; Smith, H. L.; Stalkis, A. *J. Org. Chem.* **1975**, *40*, 3554

Degradation of Long Chain Amides through HTIB
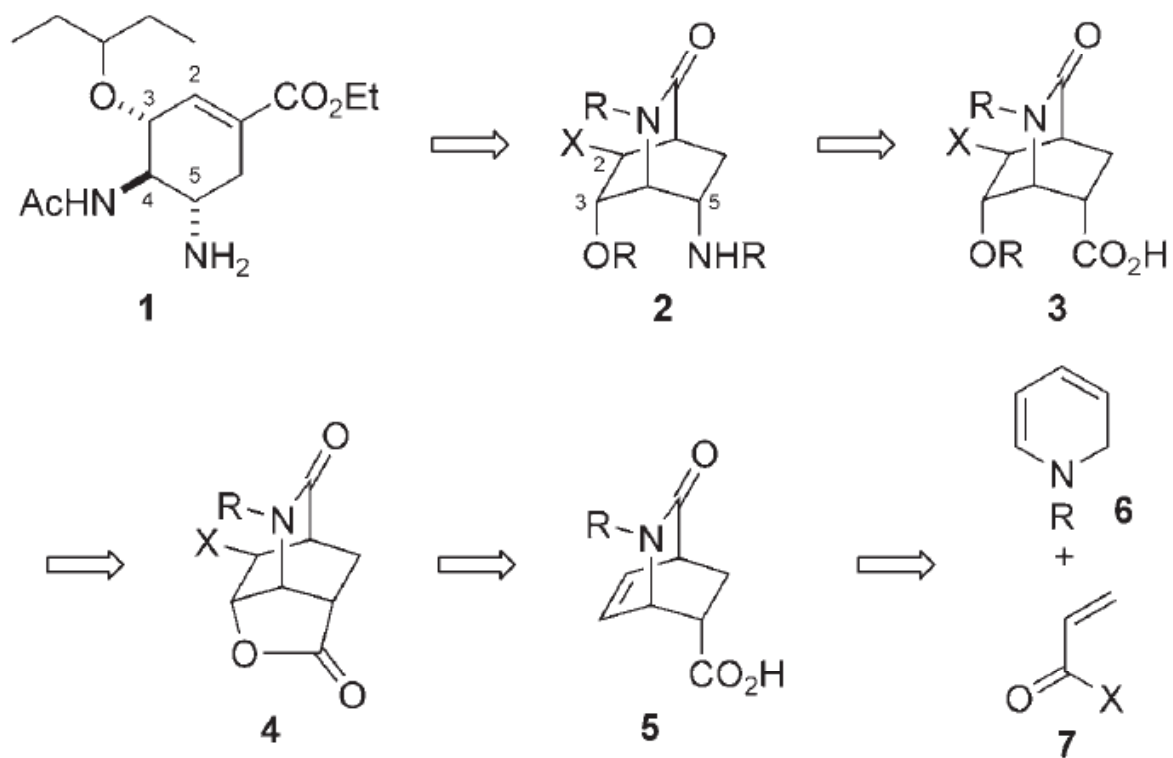

HTIB

yields 80-94%

Hydroxy(tosyloxy)iodobenzane HTIB

Lazbin I. M.; Koser, G.F. *J. Org. Chem.* **1986**, *51*, 2669

Room Temperature Conditions to Replace PIFA

$$\text{Ph}\overset{\displaystyle O}{\underset{\displaystyle NH_2}{\big|}} \quad + \quad \text{PhIO} \quad \xrightarrow[\text{aq. MeCN}]{\text{HCO}_2\text{H}} \quad \text{RNH}_3^+\ \text{HCO}_2^- \quad + \quad \text{PhI}$$

- Radhakrishna, A. S.; Rao, C.G.; Varma, B. B. Bhatnagar, S. P. *Synthesis*, **1983**, 538

A Practical Synthesis of (-)-Oseltamivir with PIFA

Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5734

Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron*, **2009**, *65*, 3239