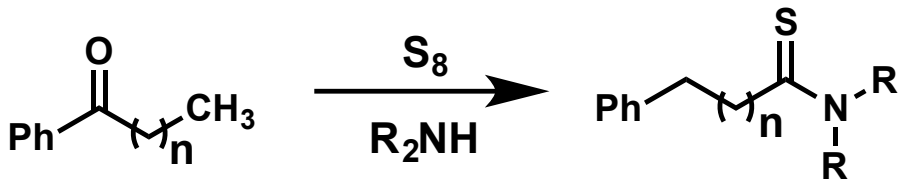
The Willgerodt Reaction



Brad Gilbert

Denmark Group Meeting

November 15, 2016

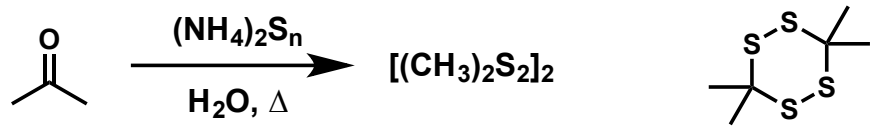
Conrad Willgerodt

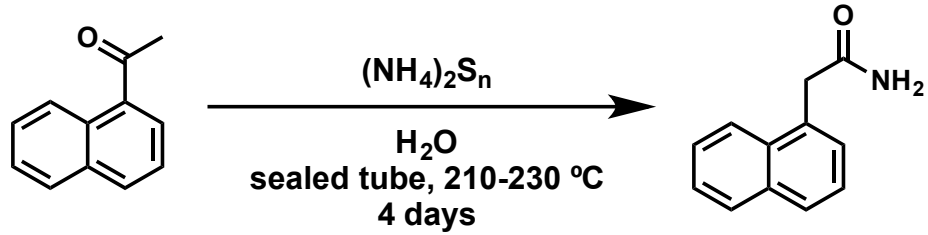
- Born November 2, 1841 in Harlingerode, Duchy of Brunswick (now Germany)
- Ca. 1875: Obtained PhD at University of Freiburg
  - Doctoral Advisor Adolf K. L. Claus
  - Studied alizarin and hydroxyanthraquinone
- 1881: Became associate professor at Freiburg
- 1895: Granted full professorship
- Also credited with describing iodobenzene dichloride and iodosobenzene
- Died December 19, 1930

Willgerodt Reaction. In *Name Reactions in Organic Cehmistry*, 2nd ed.; Surrey, A. R., Ed.; Academic Press: New York, 1961; p. 241-243.

Discovery of the Willgerodt reaction

- First described in 1887
- Acetone was known to react with ammonium polysulfide to form a compound with the formula $[(CH_3)_2S_2]_2$
- Investigation of derivatives for structure elucidation led to the reaction of 1-acetylnaphthalene with ammonium polysulfide





Willgerodt, C. *Ber.*, **1887**, *20*, 2467-2470.
Willgerodt, C. *Ber.* **1881**, *21*, 534-536.

Ammonium polysulfide

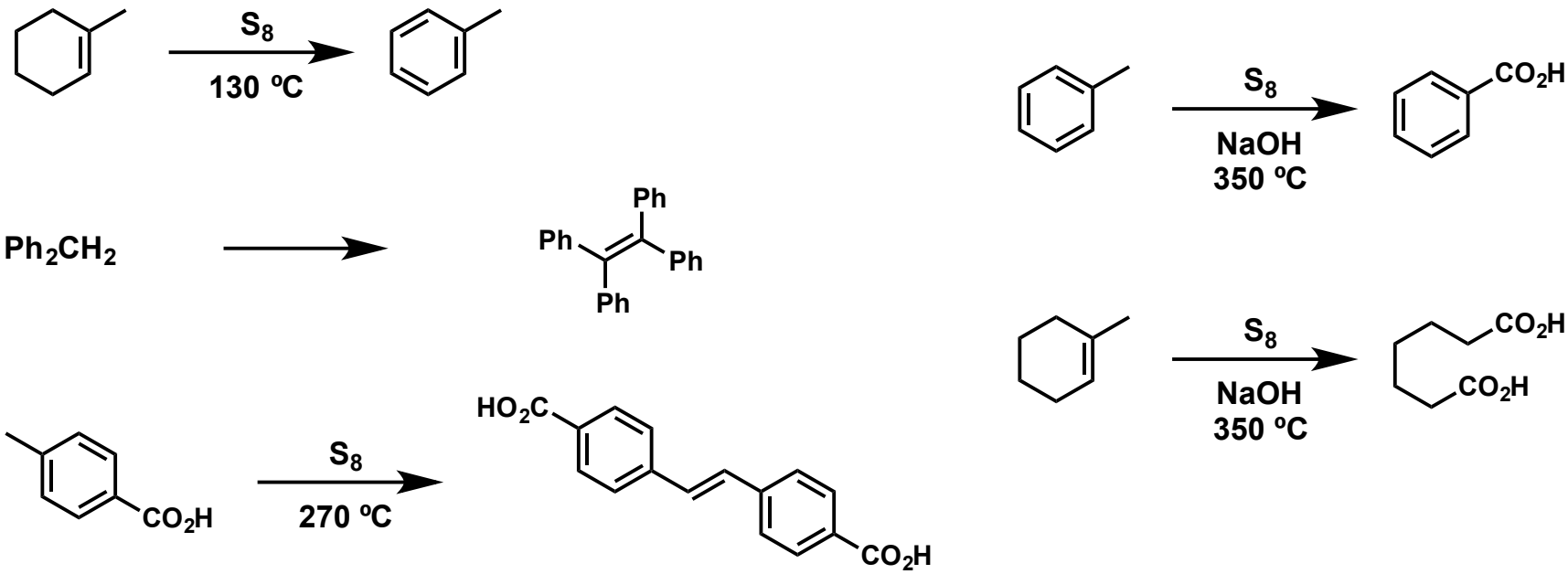
- Sometimes referred to as "yellow ammonium sulfide"
- Generated in three steps:
  - Pass H_2S through aqueous ammonia until saturation is achieved
  - Add 1 equivalent of ammonia
  - Add sulfur (amount can be varied)

$$NH_3\ (aq.) \xrightarrow{H_2S\ (1\ equiv.)} [NH_4]^+[HS]^- \xrightarrow{NH_3\ (aq.)\ (1\ equiv.)} [NH_4]^+_2[S]^{-2}$$

$$\xrightarrow{S_8} [NH_4]^+_2[S_n]^{-2}\ (aq.)$$

Curtman, L. J.; Lehrman, L. *J. Chem. Educ.* **1929**, *6*, 2203-2208

Sulfur as a reagent

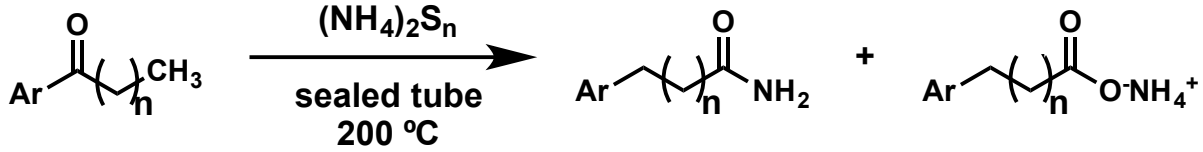


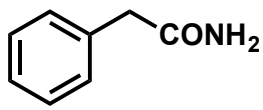
Mayer, R. Elemental Sulfur and its Reactions. In *Organic Chemistry of Sulfur*. Oae, S., Ed.; Plenum Press: New York, 1977. p. 33-69.

Willgerodt reaction conditions

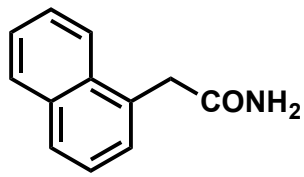
- The reaction typically involves pre-formed ammonium polysulfide
- However, the original procedure called for the addition of substrate to ammonium sulfide solution, followed by sulfur
- Large excess (5-10 equivalents) of sulfur are employed
- Reactions are typically performed "neat" (only in the water remaining from the concentrated aqueous ammonia) or with 1:1 v/v quantities of organic solvent.
- Sealed tubes or autoclaves are required, as reaction temperatures greatly exceed the boiling point of water and especially the substrate in many cases.

Early substrate scope

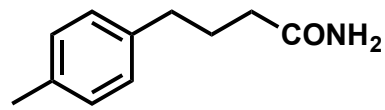




63%
(31% with $(NH_4)_2S$)



34%



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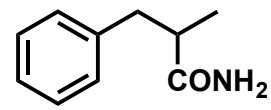

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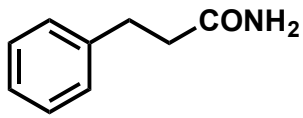
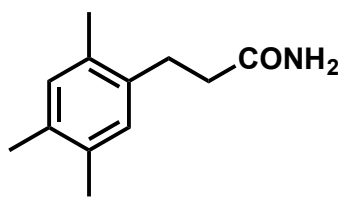


50%



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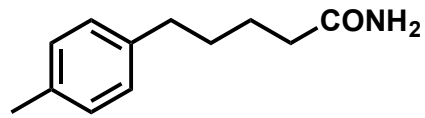

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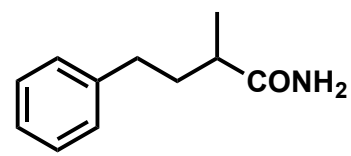
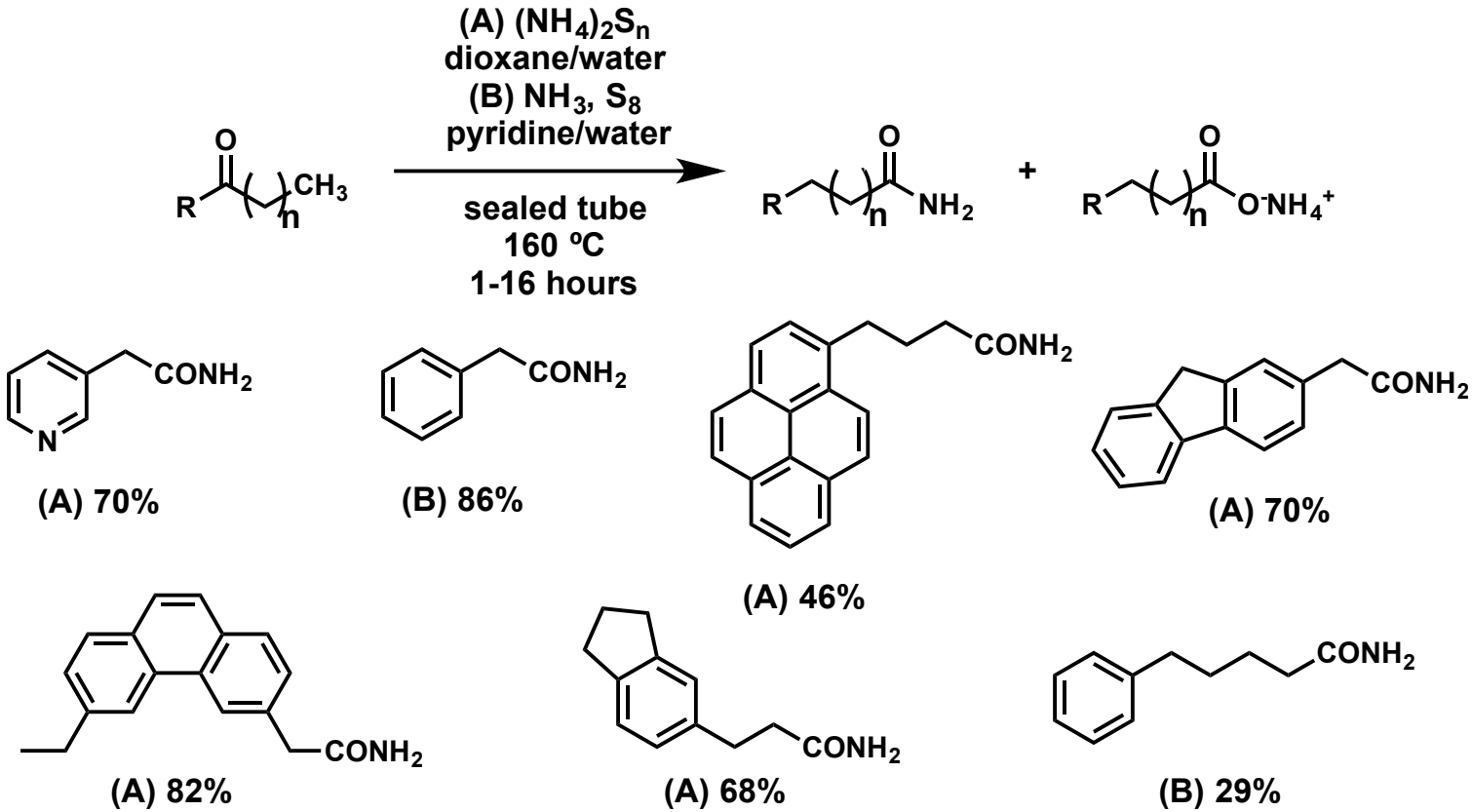


17%

(1) Willgerodt, C. *Ber.*, **1887**, *20*, 2467-2470 (2) Willgerodt, C. *Ber.*, **1888**, *21*, 534-536. (3) Willgerodt, C. *J. Prakt. Chem.*, **1909**, *80*, 183-191. (4) Willgerodt, C.; Merk, F. H. *J. Prakt. Chem.* **1909**, *80*, 192-200. (5) Willgerodt, C.; Hambrecht, W. *J. Prakt. Chem.* **1910**, *81*, 74-85. (6) Willgerodt, C.; Scholtz, T. *J. Prakt. Chem.* **1910**, *81*, 382-402. (7) Willgerodt, C.; Albert, B. *J. Prakt. Chem.* **1911**, *84*, 383-394

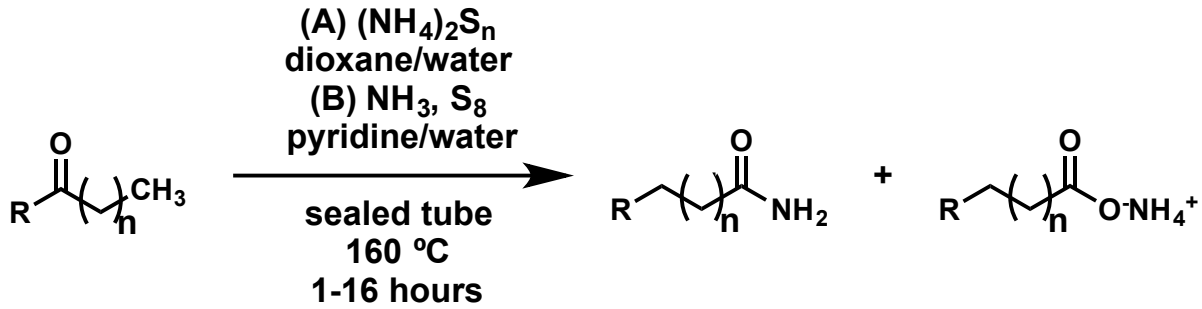
Modification of reaction conditions

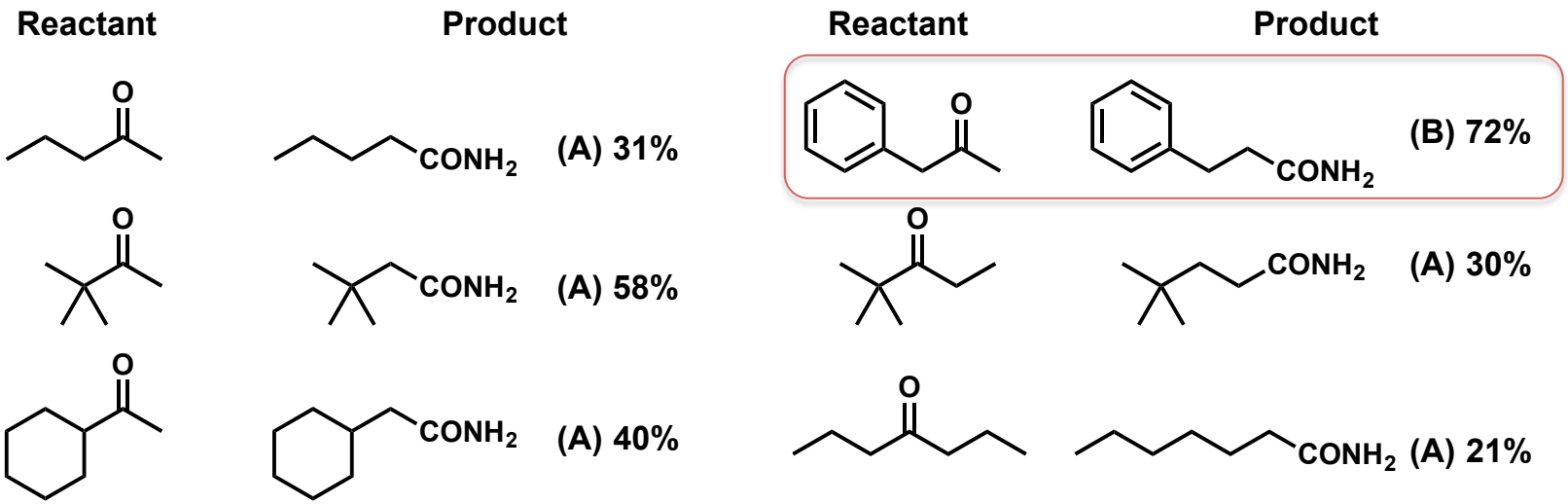
- Dioxane/water and pyridine/water mixtures allow for lower reaction temperatures and give better yields than water alone



(1) Hartmann, M.; Bosshard, W. *Helv. Chim. Acta.* **1941**, *24*, 28E-35E. (2) Bachmann, W. E.; Sheehan, J. C. *J. Am. Chem. Soc.* **1940**, *62*, 2687-2690. (3) Bachmann, W. E.; Carmack, M. *J. Am. Chem. Soc.* **1941**, *63*, 2494-2499. (4) Bachmann, W. E.; Cortes, G. D. *J. Am. Chem. Soc.* **1943**, *65*, 1329-1334. (5) Astle, M. J.; Cropper, W. P. *J. Am. Chem. Soc.* **1943**, *65*, 2395-2399. (6) DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* **1946**, *68*, 2025-2029. (7) Carmack, M.; DeTar, D. F. *J. Am. Chem. Soc.* **1946**, *68*, 2029-2033

Alkyl ketones

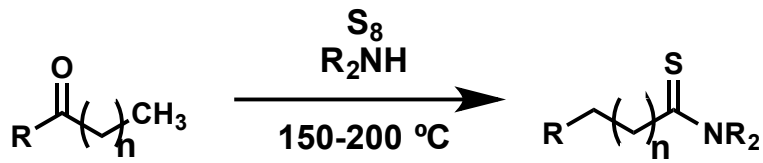




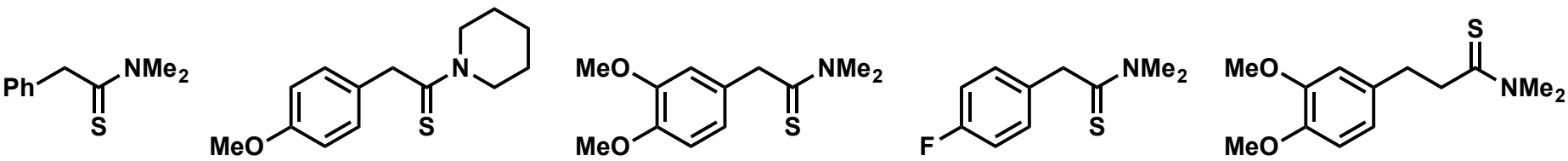
(1) DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* **1946**, *68*, 2025-2029. (2) Carmack, M.; DeTar, D. F. *J. Am. Chem. Soc.* **1946**, *68*, 2029-2033. (3) Cavalieri, L.; Pattison, D. B.; Carmack, M. *J. Am. Chem. Soc.* **1945**, *67*, 1783-1786.

Kindler modification

- Advance made in 1923 (36 years after initial discovery)
- Reaction with sulfur and a secondary amine provided the thioamide



- Low-boiling amines still required pressure vessels
- Scope was later explored in more depth by other authors

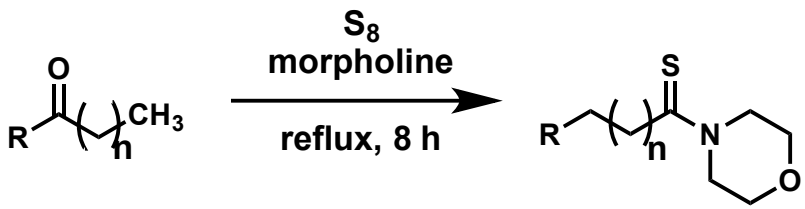


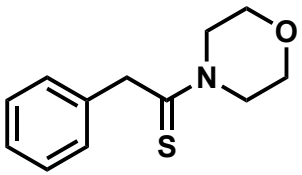
70% 48% 68% 40% 42%

(1) Kindler, K. *Arch. Pharm.* **1927**, *265*, 389-415. (2) Kindler, K.; Peschke, W. *Arch. Pharm.* **1932**, *270*, 340-353. (3) Kindler, K.; Peschke, W. *Arch. Pharm.* **1934**, *272*, 236-241. (4) Kindler, K.; Li, T. *Ber.* **1941**, *74*, 321-327.

Expansion of scope

- Schwenk and Block were the first to use refluxing morpholine instead of pressure vessels





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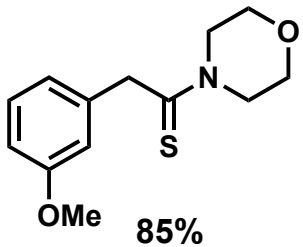

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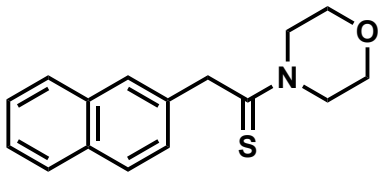

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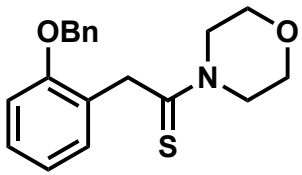
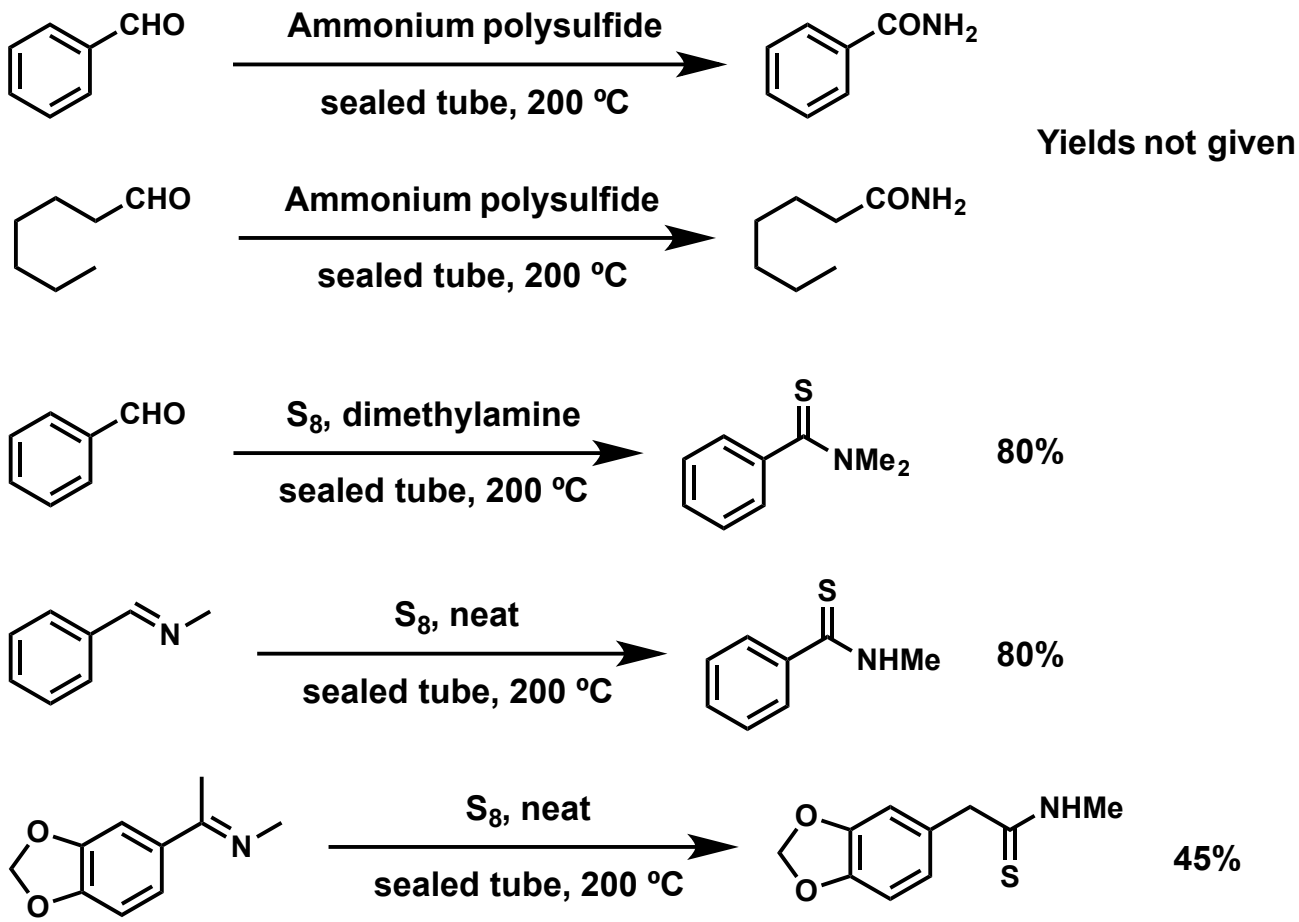


72%

Schwenk, E.; Bloch, E. *J. Am. Chem. Soc.* **1942**, *64*, 3051-3052.

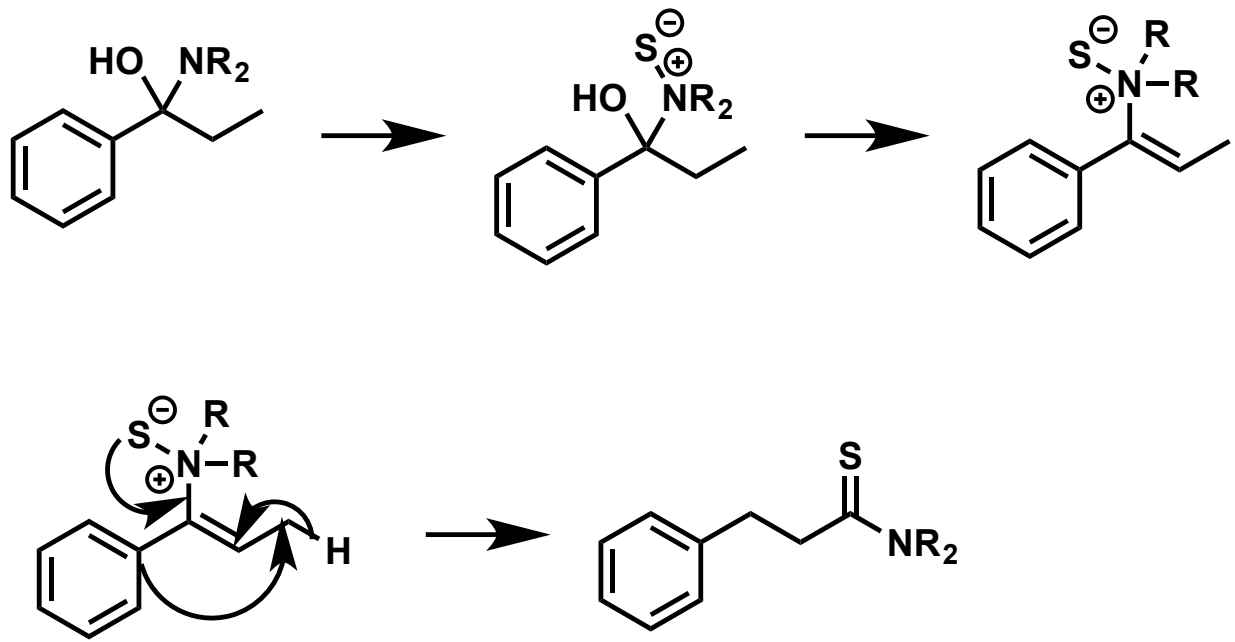
Non-ketone substrates



(1) Willgerodt, C. *Ber.*, **1888**, *21*, 534-536. (2) Kindler, K. *Arch. Pharm.* **1927**, *265*, 389-415.

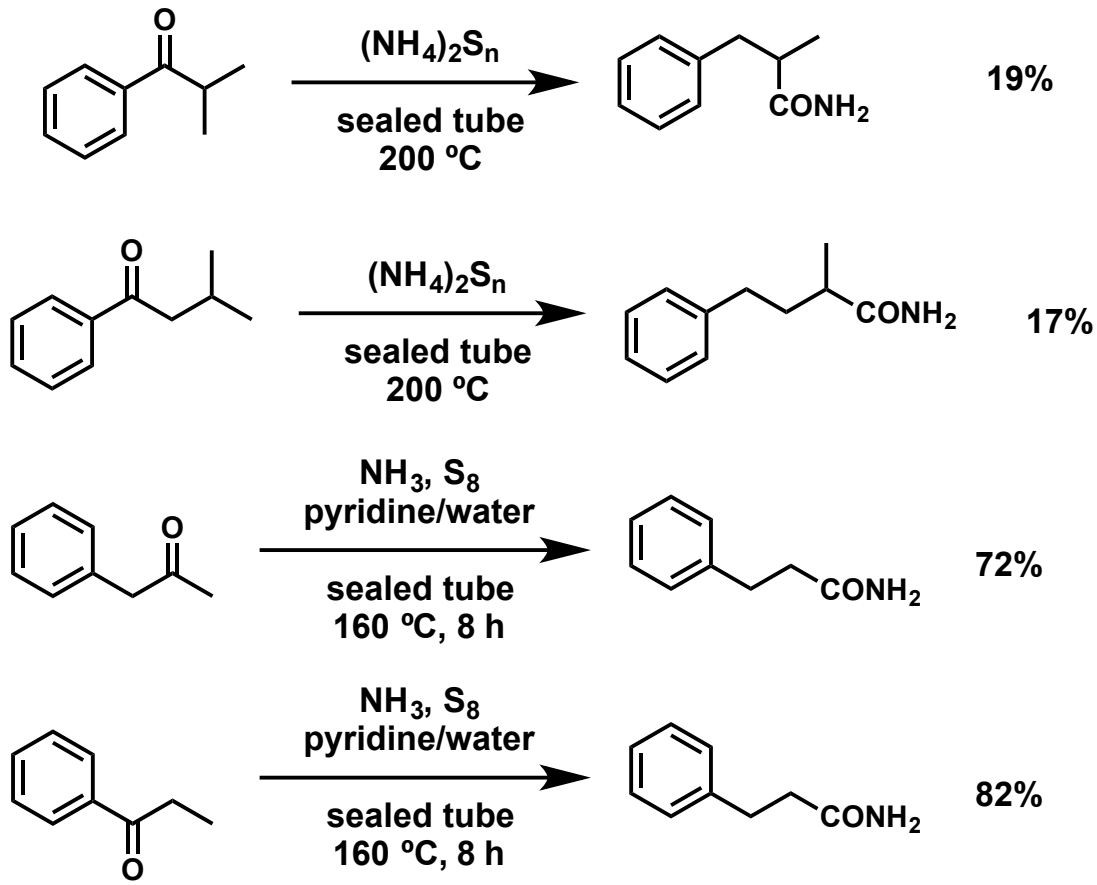
Propose a Mechanism

Kindler's original proposal



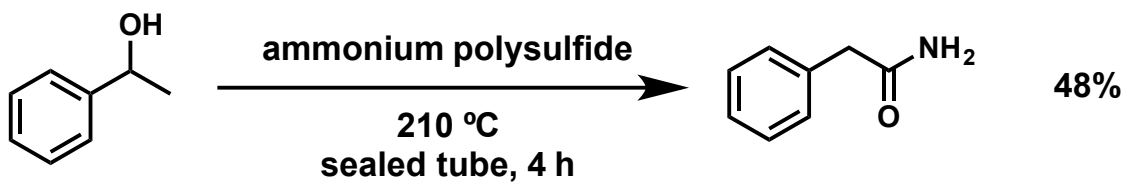
Kindler, K.; Li, T. *Ber.* **1941**, *74*, 321-327.

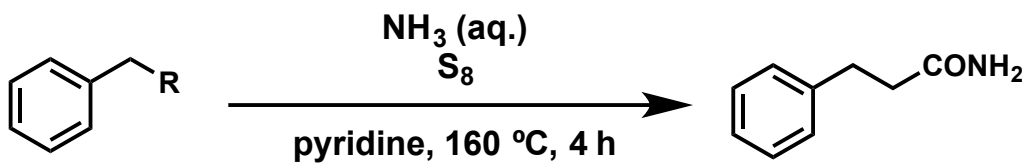
Early mechanistic evidence



(1) Willgerodt, C.; Merk, F. H. *J. Prakt. Chem.* **1909**, *80*, 192-200. (2) King, J. A.; McMillan, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 632-636. (3) DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* **1946**, *68*, 2025-2029.

Multiple entries into productive pathway

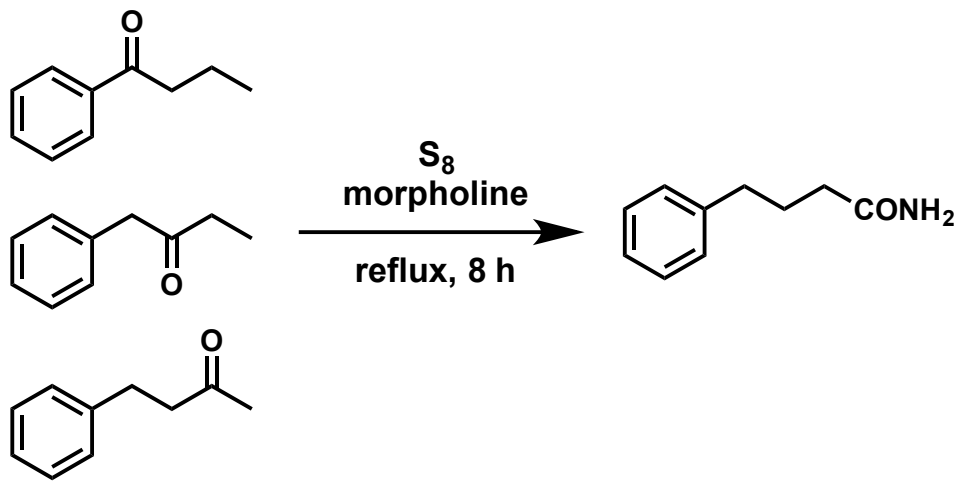




R = $-CH_2CHO$	48%
R = $-(C{=}O)CH_3$	72%
R = $-C{\equiv}CH$	90%
R = $-C{=}CH_2$	74%

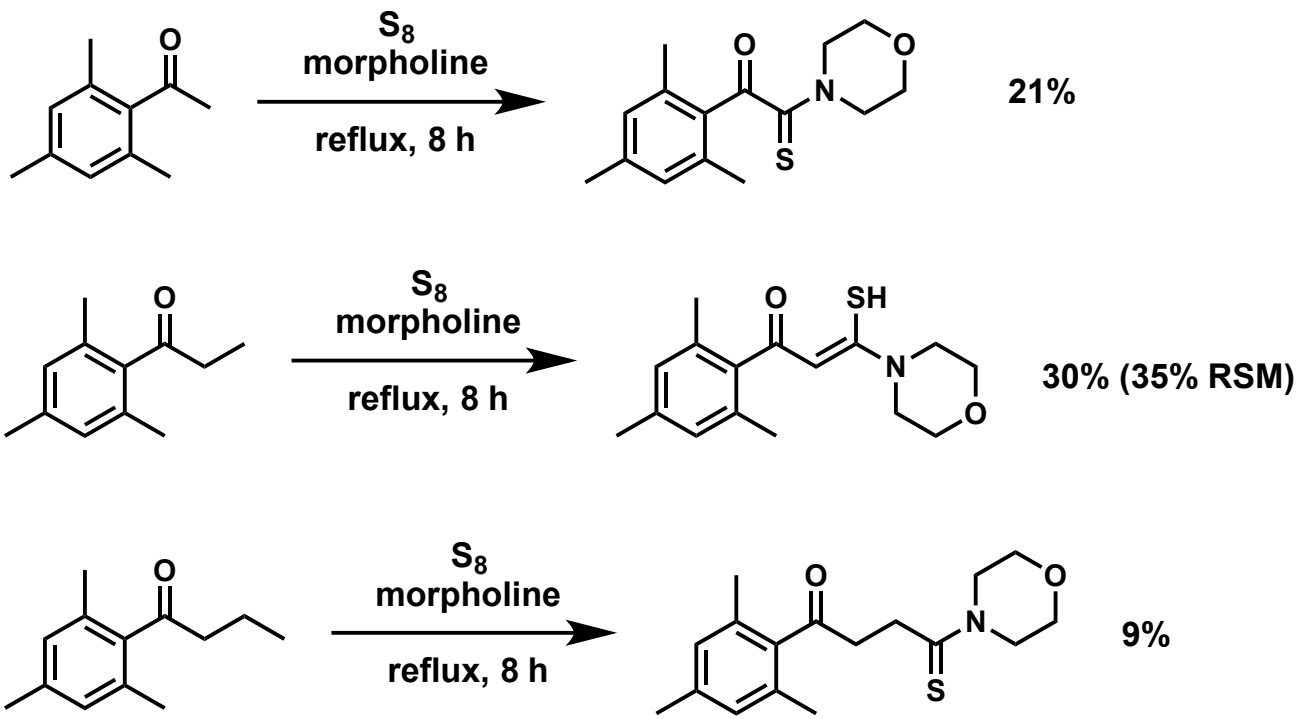
(1) King, J. A.; McMillan, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 525-526. (2) Carmack, M.; DeTar, D. F. *J. Am. Chem. Soc.* **1946**, *68*, 2029-2033.

Multiple entries into productive pathway



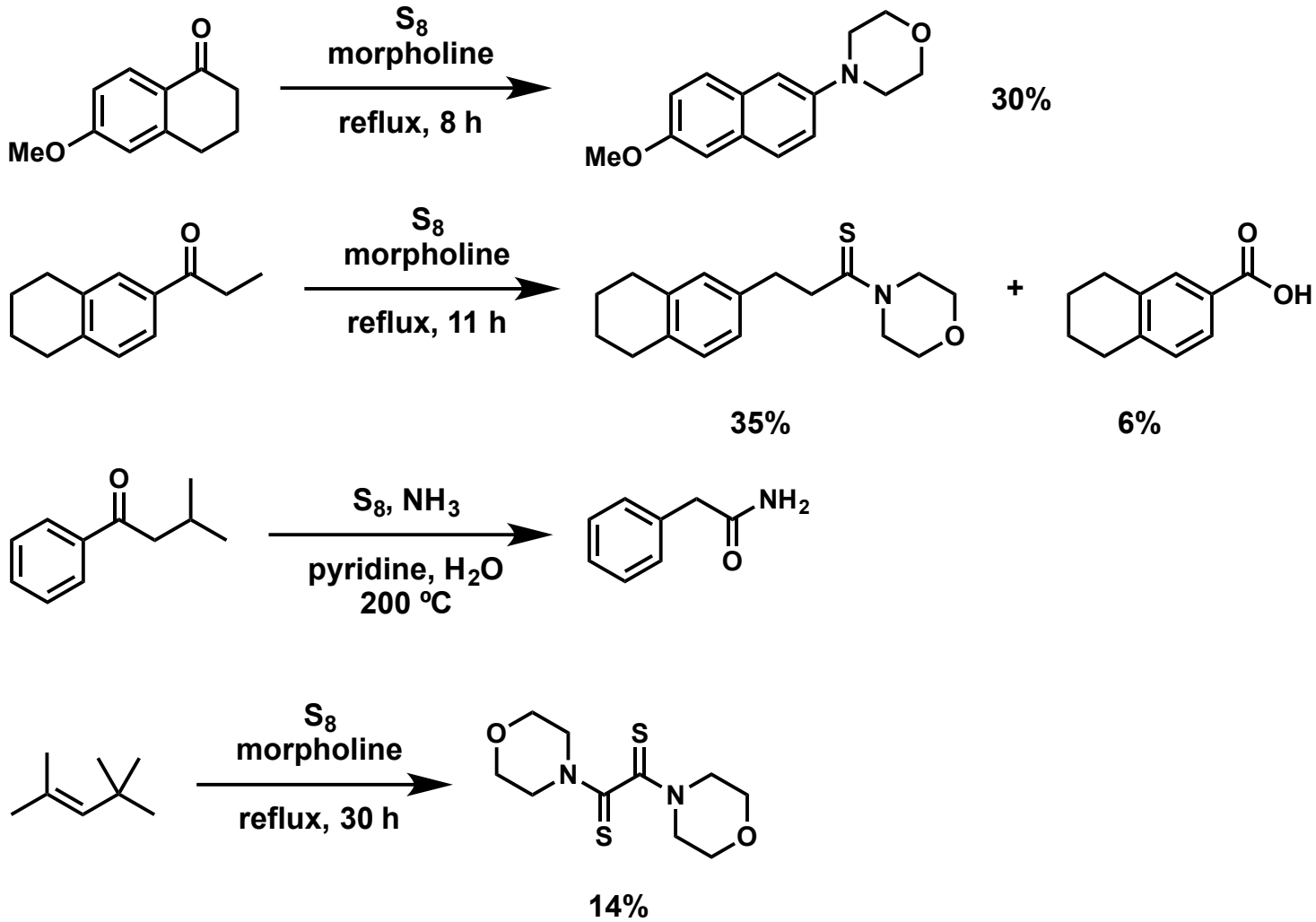
Asinger, F.; Saus, A.; Mayer, A. *Mh. Chem., Bd.* **1967**, *98*, 825-835.

Irregular reaction pathways



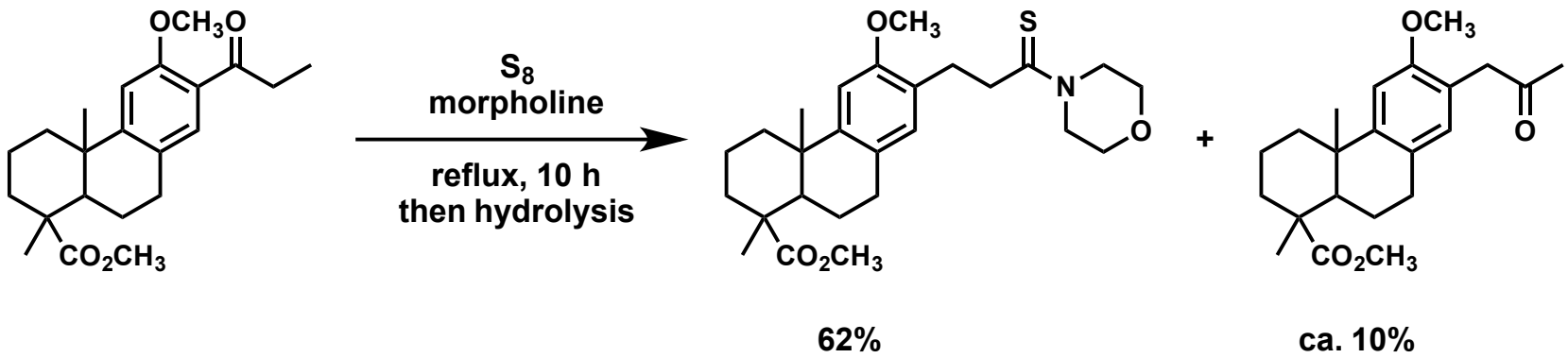
Dauben, W. G.; Rogan, J. B. *J. Am. Chem. Soc.* **1956**, *78*, 4135-4139.

Irregular reaction pathways



(1) Daubin, W. G.; Ciula, R. P.; Rogan, J. B. *J. Am. Chem. Soc.* **1956**, *22*, 362-365. (2) Arnold, R. T.; Schultz, E.; Klug, H. *J. Am. Chem. Soc.* **1944**, *66*, 1606-1607. (3) McMillan, F. H.; King, J. A. *J. Am. Chem. Soc.* **1947**, *69*, 1207-1208. (3) Carmack, M.; DeTar, D. F. *J. Am. Chem. Soc.* **1946**, *68*, 2029-2033.

Interrupted rearrangement

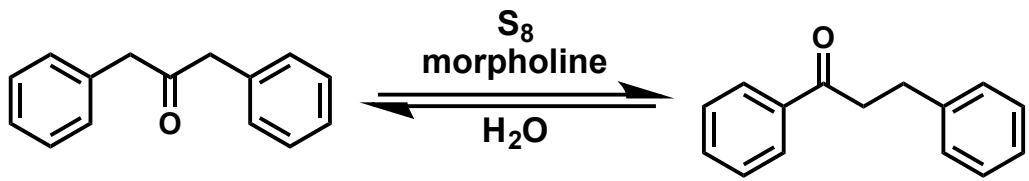


Bible, R. H. Jr. *J. Am. Chem. Soc.* **1957**, *79*, 3924-3925

Refine your Mechanism

Elucidation of the Mechanism

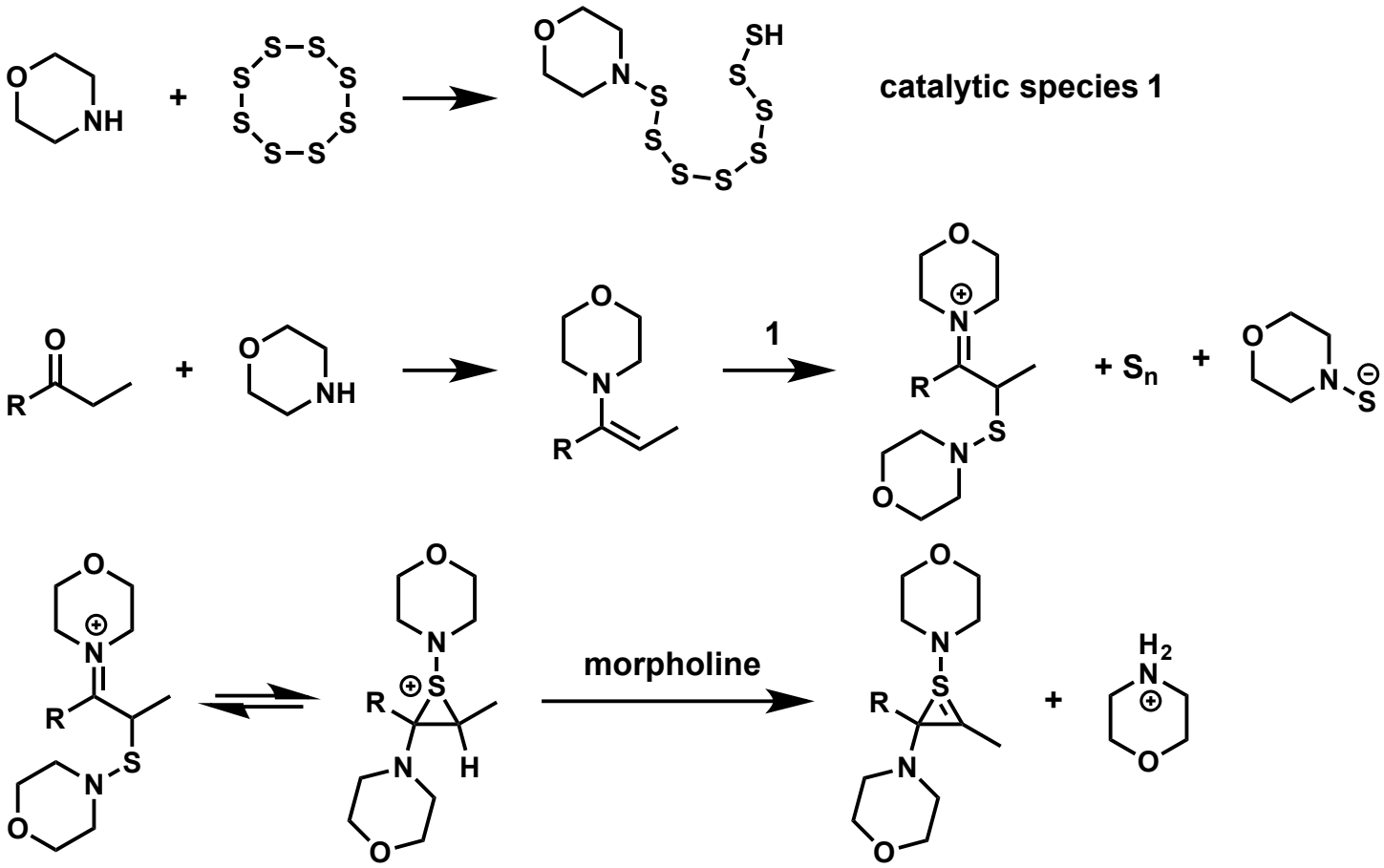
- Carmack et al used *in-situ* IR to observe the migration of the carbonyl in presence of substoichiometric water
  - No carbonyl compounds were observed in the absence of water



- Rates were slower with more water added, and only about 2% of the material existed as other intermediates at any point
- Nonlinear relationship between sulfur concentration and initial rate was observed
- Role of sulfur in isomerization was proposed to be catalytic

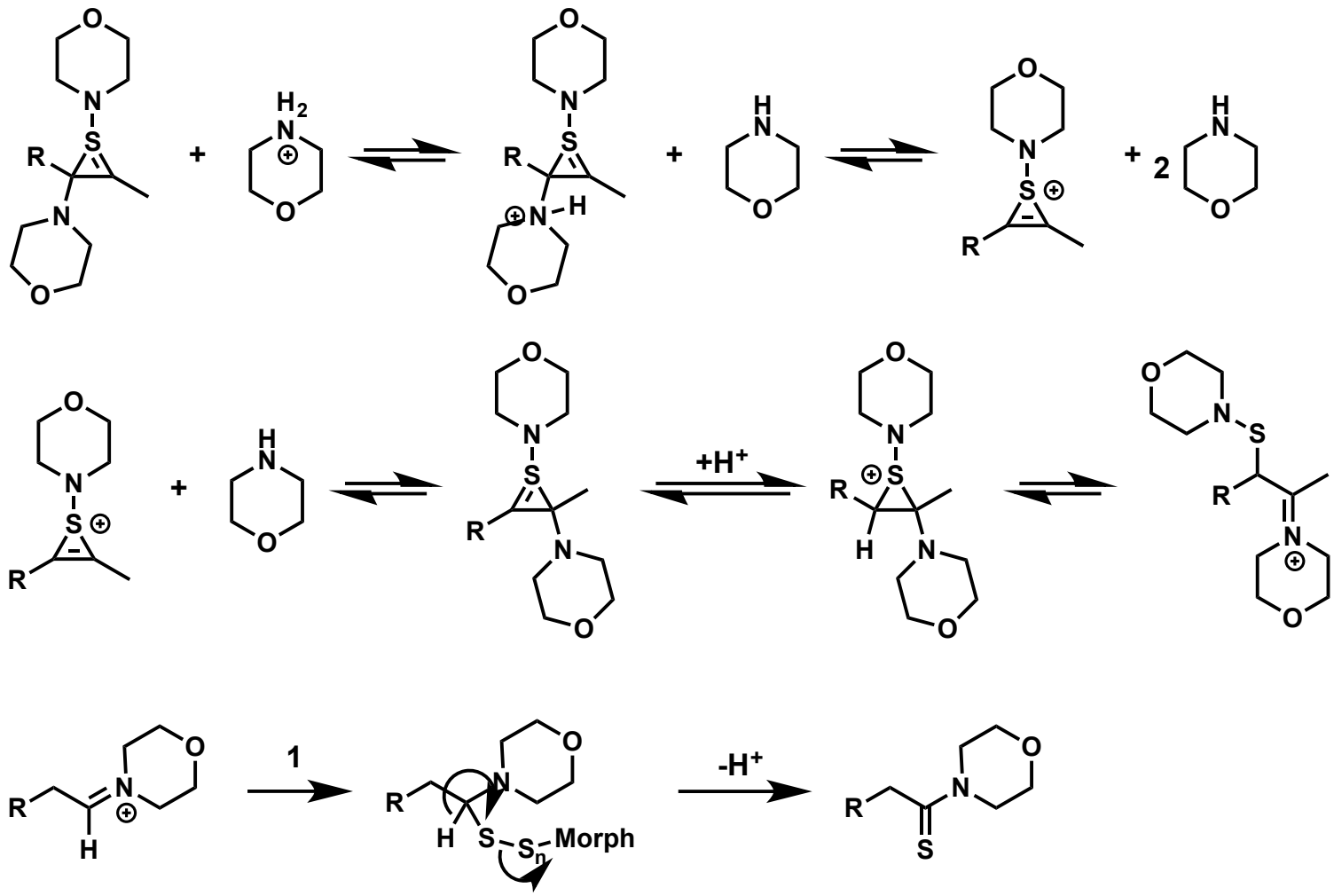
(1) Carmack, M.; Behforouz, M.; Berchtold, G. A.; Berkowitz, S. M. *J. Heterocyclic Chem.* **1989**, *26*, 1305-1318. (2) Carmack, M. *J. Heterocyclic Chem.* **1989**, *26*, 1319-1323.

Proposed Mechanism



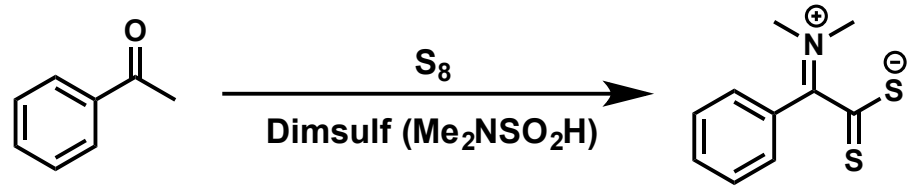
Carmack, M. *J. Heterocyclic Chem.* **1989**, *26*, 1319-1323.

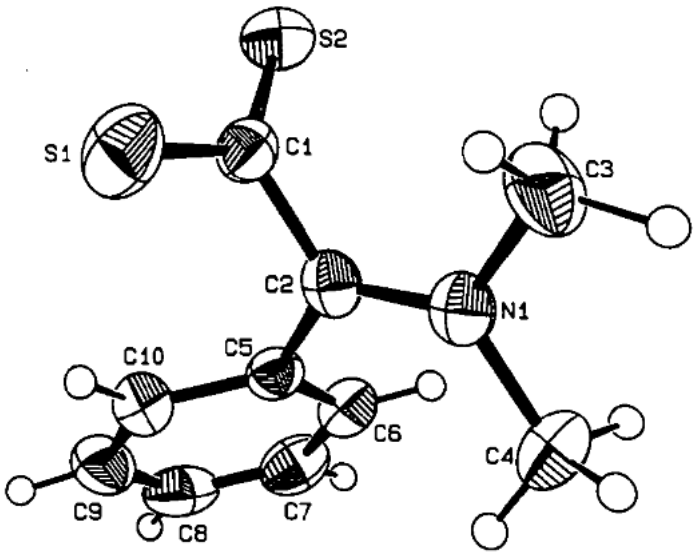
Proposed Mechanism

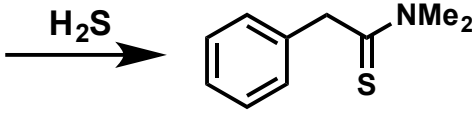


Carmack, M. *J. Heterocyclic Chem.* **1989**, *26*, 1319-1323.

Crystallographic study

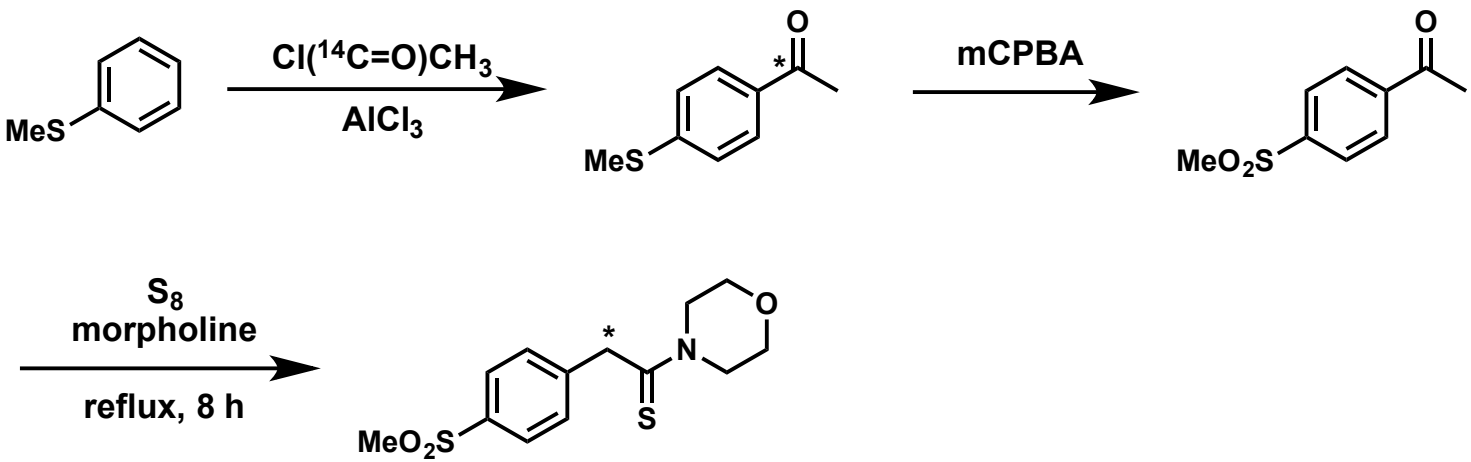






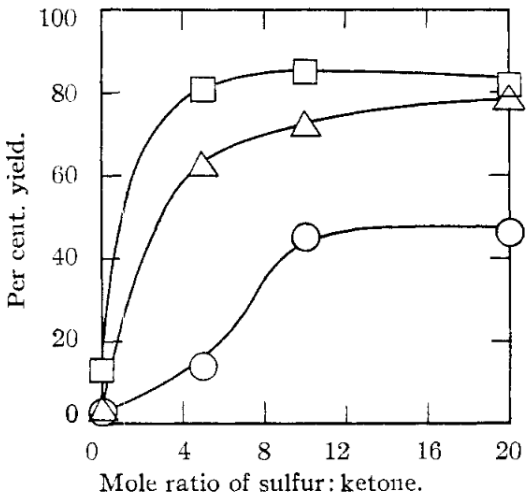
Heinemann, F.; Hartung, H.; Hansen, J.; Maschmeier, C.-P.; Matschiner, H. *Acta. Cryst.* **1992**, *C48*, 2161-2163.

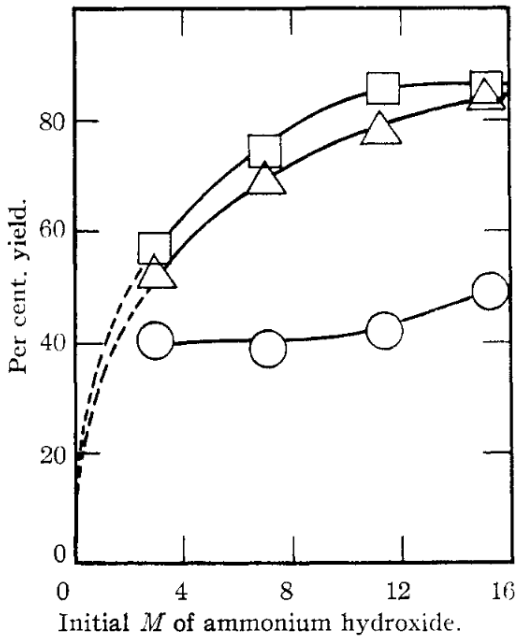
Radiolabeling experiment

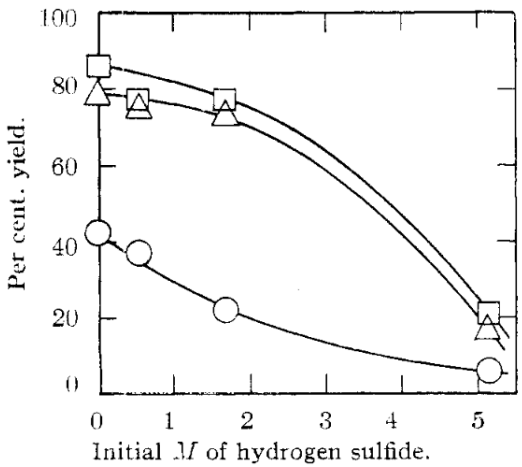


Brewitt, T. J.; Filer, C. N.; Lacy, J. M.; Peng, C. T. *J. Labelled Cpd. Radiopharm.* **2001**, *44*, 413-416.

Improvements to scope: Effects of reagent concentration on yield







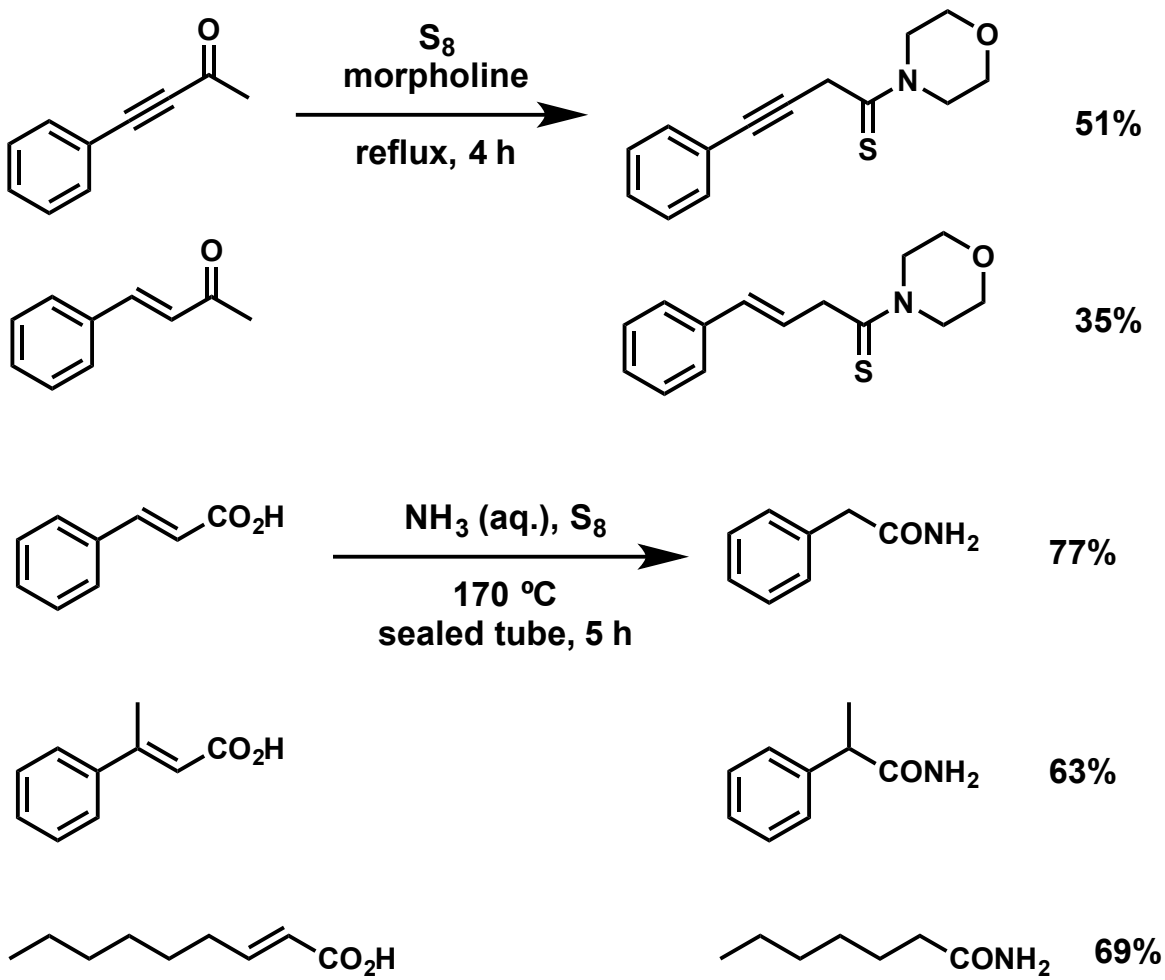
O: 130 ºC
Δ:150 ºC
☐: 190 ºC

O: Sulfur:Acetophenone 2:1
Δ: S:A 5:1
☐: S:A 10:1

O: S:A 2:1
Δ: S:A 5:1
☐: S:A 10:1

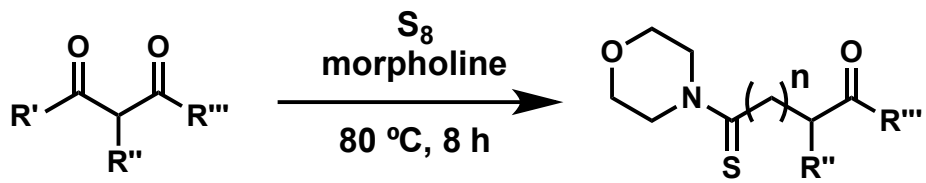
DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* **1946**, *68*, 2025-2029.

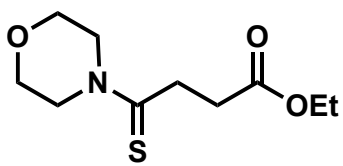
Scope of the Willgerodt reaction



(1) Nightingale, D.; Carpenter, R. A. *J. Am. Chem. Soc.* **1949**, *71*, 3560-3561. (2) Davis, C. H.; Carmack, M. *J. Org. Chem.* **1947**, *12*, 76-78.

Scope of the Willgerodt reaction





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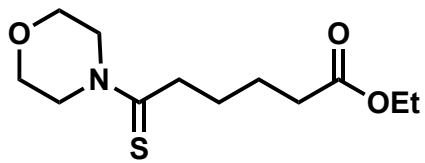

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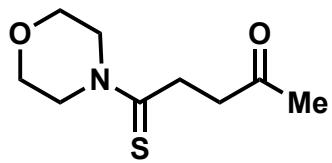

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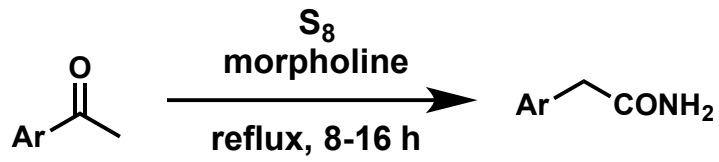
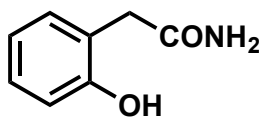
Darabi, H. R.; Aghapoor, K.; Balavar, Y.; Mobedi, E.; Farhangian, H.; Mohsenzadeh, F. *Naturforsch.* **2008**, 993-997.

Scope: aromatic substituents





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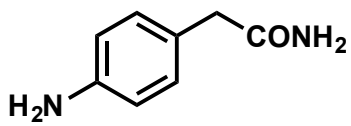

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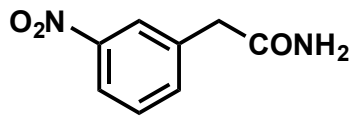

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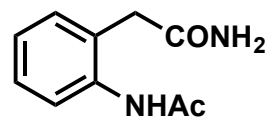

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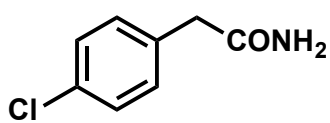

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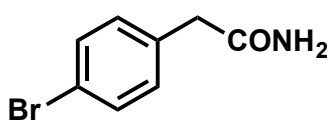

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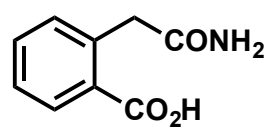
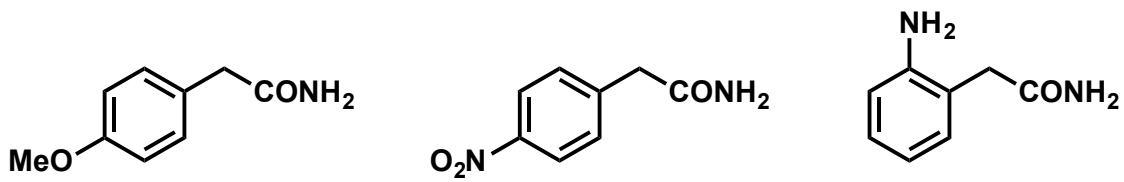


16%

King, J. A.; McMillan, F. H. *J. Am. Chem. Soc.* **1946**, *68*, 2335.

Catalysis of the W-K reaction

- Bronsted bases, acids and ionic liquids have been shown to catalyze the Willgerodt-Kindler reaction
- Microwave heating has also proven effective.



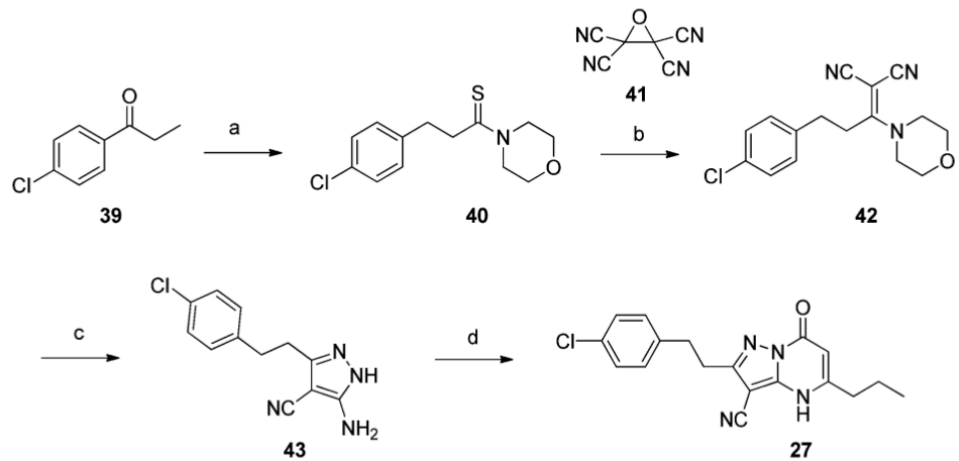
uncatalyzed	**50% @ 130 ºC**	**0%**	**0%**
Et_3N	**67% @ 100 ºC**		
HBF_4/SiO_2	**87% @ 80 ºC**	**87%**	**93%**
[bmim][BF_4]	**80% @ 110 ºC**	**81%**	**81%**
microwave	**85% @ 650 W, 4 min**		**90%**

(1) Yadav, J. S.; Reddy, B. V. S.; Kodaji, G.; Reddy, J. S. S.; Nagaiah, K. *J. Mol. Catal. A: Chem.* **2007**, *266*, 249-253. (2) Bandgar, B. P.; Gawande, S. S.; Warangkar, S. C.; Totre, J. V. *Bioorg. Med. Chem.* **2010**, *18*, 3618-3624. (3) Poupaert, J. H.; Bouinidane, K.; Renard, M.; Lambert, D. M.; Isa, M. *Org. Prep. Proc. Int.* **2001**, *33*, 335-340. (4) Nooshabaid, M.; Aghapoor, K.; Darabi, H. R.; Mojtahedi, M. M. *Tetrahedron Lett.* **1999**, *40*, 7549-7552.

Applications: medicinal chemistry

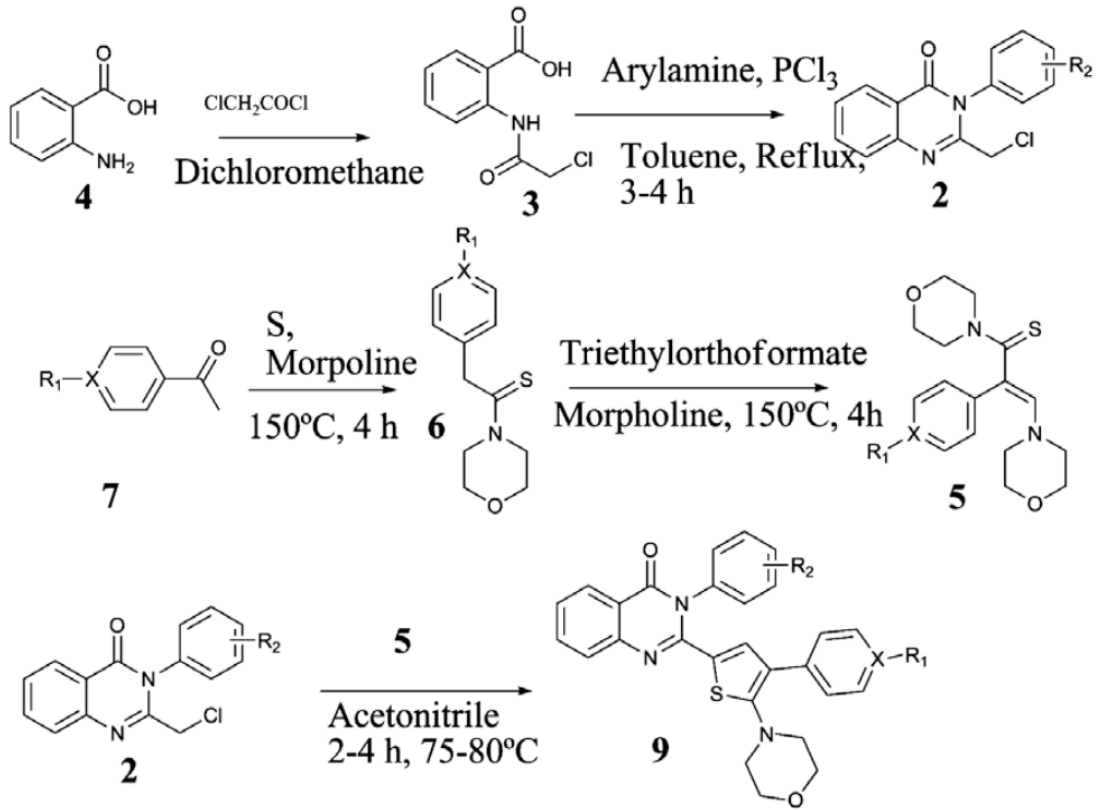
- Allows for the rapid generation of large libraries of arylalkanamides and arylalkanoic acids from readily available arenones.

Scheme 5. Preparation of C-Linked Analogue 27[a]



[a]Reagents and conditions: (a) morpholine, sulfur powder, 130 °C, 24 h, 62%; (b) toluene, rt, 14 h, 90%; (c) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 5 h, 73%; (d) ethyl 3-oxohexanoate, AcOH, reflux, 20 h, 59%.

Applications: medicinal chemistry

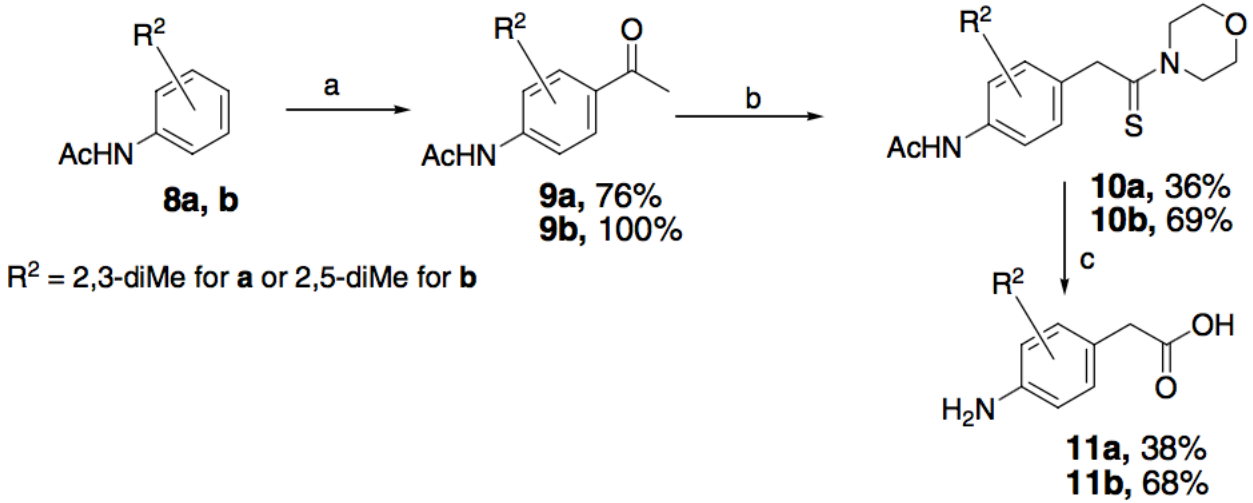


Scheme 2. Synthesis of designed compounds.

Assembled a library of 37 compounds with 6 different groups at X

Giri, R. S.; Thaker, H. M.; Giordano, T.; Williams, J.; Rogers, D.; Vasu, K. K.; Sudarsanam, V. *Bioorg. Med. Chem.* **2010**, *18*, 2796-2808.

Applications: medicinal chemistry



Scheme 2. Reagents: (a) AcCl, $AlCl_3$; (b) S/morpholine; (c) 6 N HCl.

Hu, B.; Quinet, E.; Unwalla, R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 54-59.

Conclusions

- The Willgerodt-Kindler reaction still has synthetic utility for the modern chemist
  - Large libraries of compounds can be assembled by Friedel-Crafts acylation and rearrangement to terminal acids and amides
- Its underutilization can be attributed to the misconception that yields are typically low or irreproducible, or that most functional groups are not tolerated
- Better mechanistic understanding can lead to fine-tuning of reaction conditions to be milder and have broader scope