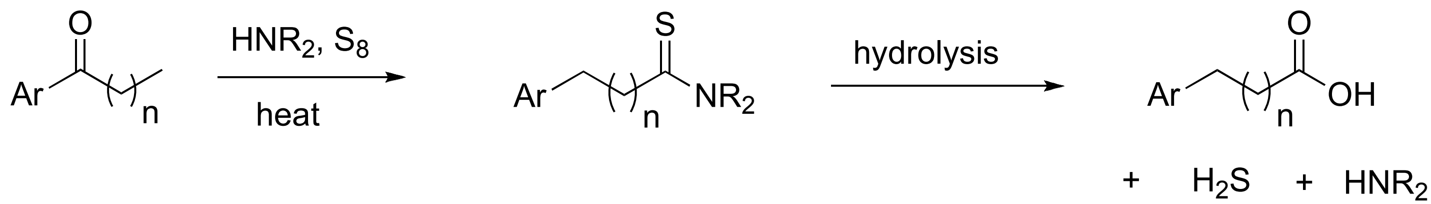
# Willgerodt-Kindler Reaction

Yong Guan

Jan. 30, 2009

# Introduction

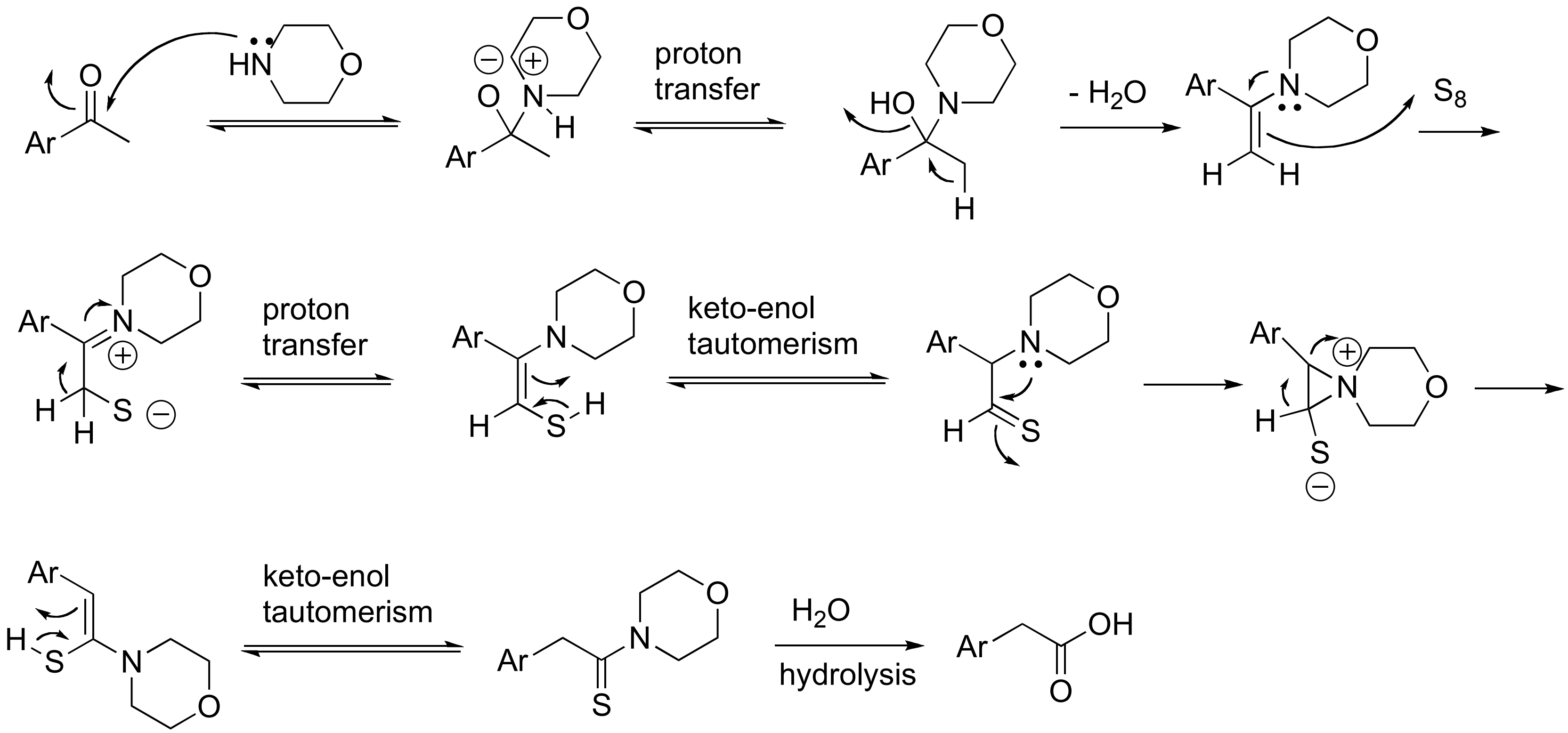



- The Willgerodt rearrangement or Willgerodt reaction is an organic reaction converting an aryl alky ketone to the corresponding amide by reaction with ammonium polysulfide, named after Conrad Willgerodt.

- The related Willgerodt-Kindler reaction takes place with elemental sulfur and an amine like morpholine. The reaction is named after Karl Kindler.

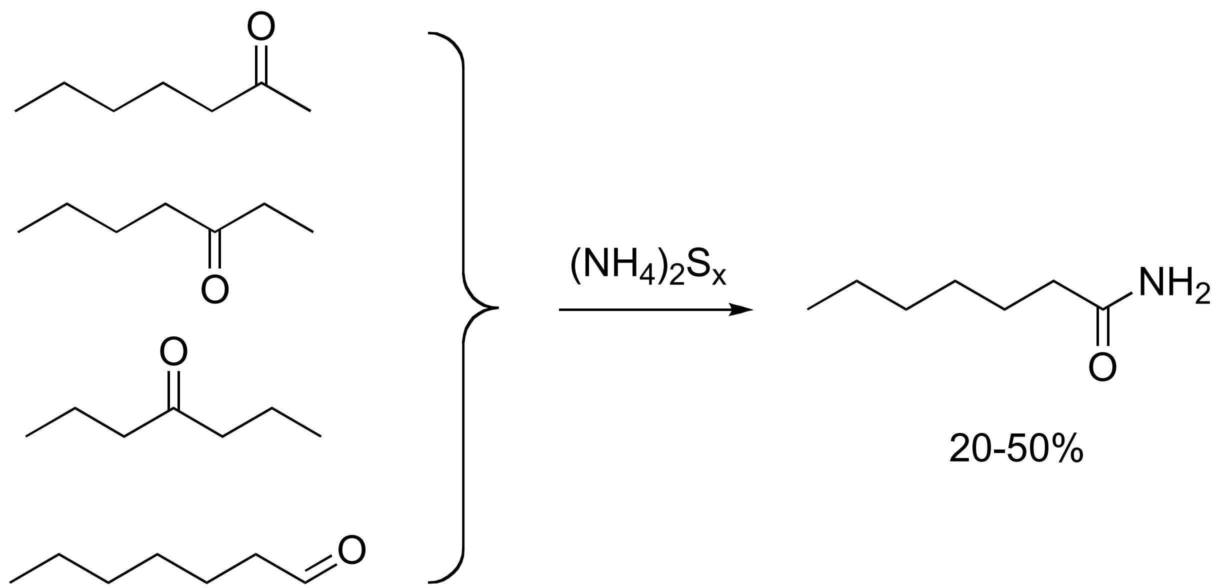

(a) Willgerodt, C. *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 534–536.
(b) Kindler, K. *Liebigs Ann. Chem* **1923**, *431*, 187–207.

# Mechanism



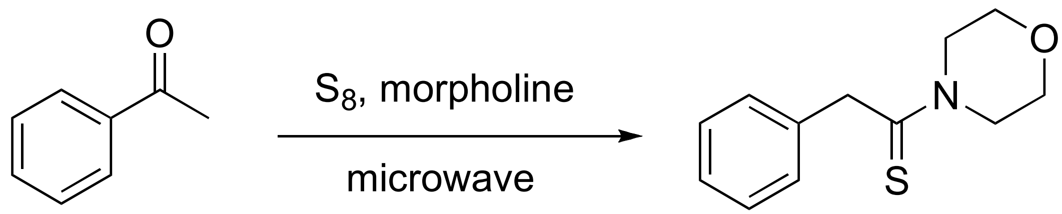

*Name Reactions and  Reagents in Organic Synthesis, 2nd ed;*
Bradford P. Mundy, Michael G. Ellerd, Frank G., Jr. Favaloro; Wiley-Interscience, pp 690.

# Aliphatic Substrates

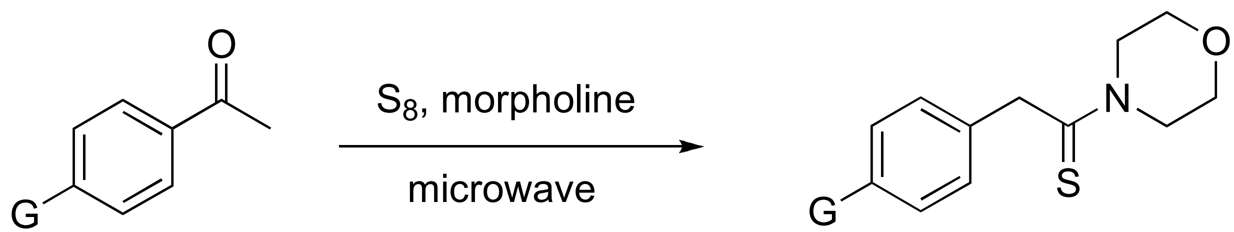



Cavalieri, L; Pattison, D. B.; Carmack, M. *J. Am. Chem. Soc.,* **1945**, *67*,1783.

# Aromatic Substrates



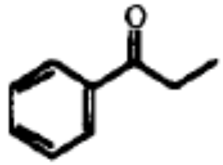
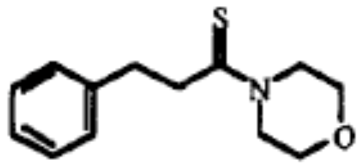
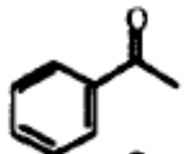
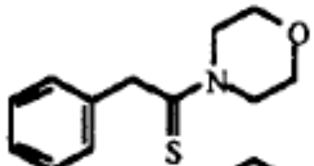
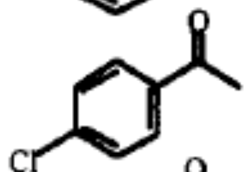
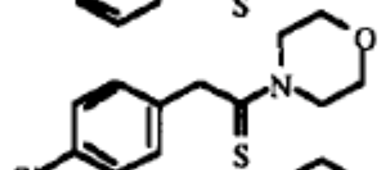
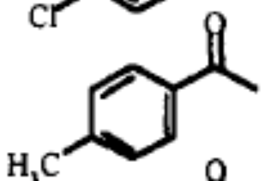
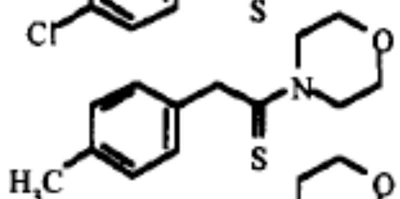
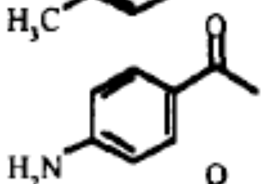
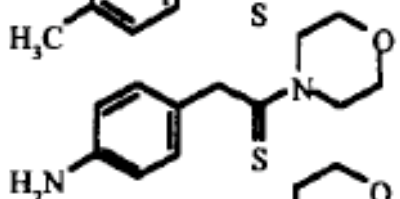
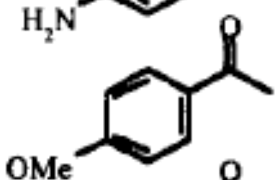
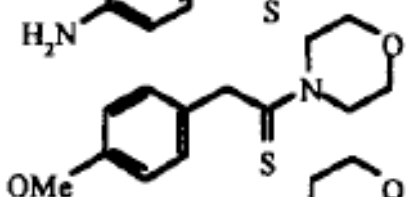
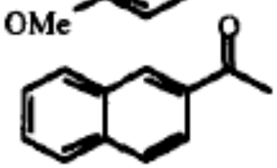
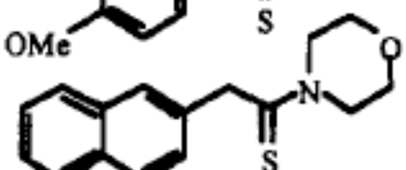

81%




G=Cl, Me, $NH_2$, OMe

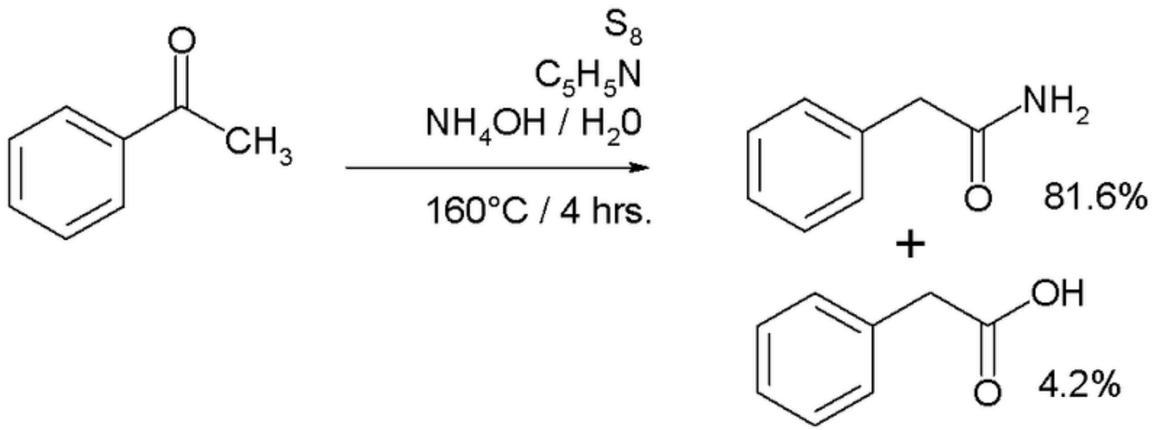
55-74%

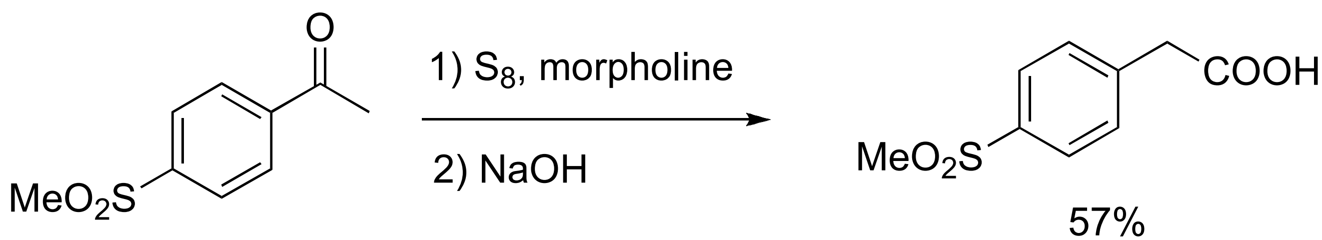
Darabi, H., *et al*. *Tetrahedron Lett.,* **1999**, *40*, 7549.

| Entry | Substrates 1 | *Products* 2[a] | Time (min) | Isolated Yield (%) Series A[b] | Series B[c] | Series C[d] |
|---|---|---|---|---|---|---|
| a |  |  | 4 | 10 | 16 | 40 |
| b |  |  | 4 | 50 | 56 | 81 |
| c |  |  | 6 | 40 | 45 | 55 |
| d |  |  | 4 | 44 | 53 | 74 |
| e |  |  | 3.5 | 42 | 47 | 65 |
| f |  |  | 5 | 49 | 56 | 72 |
| g |  |  | 4.5 | 56 | 61 | 75 |

Darabi, H., *et al*. *Tetrahedron Lett.,* **1999**, *40*, 7549.

# Preparation of Amides and Acids



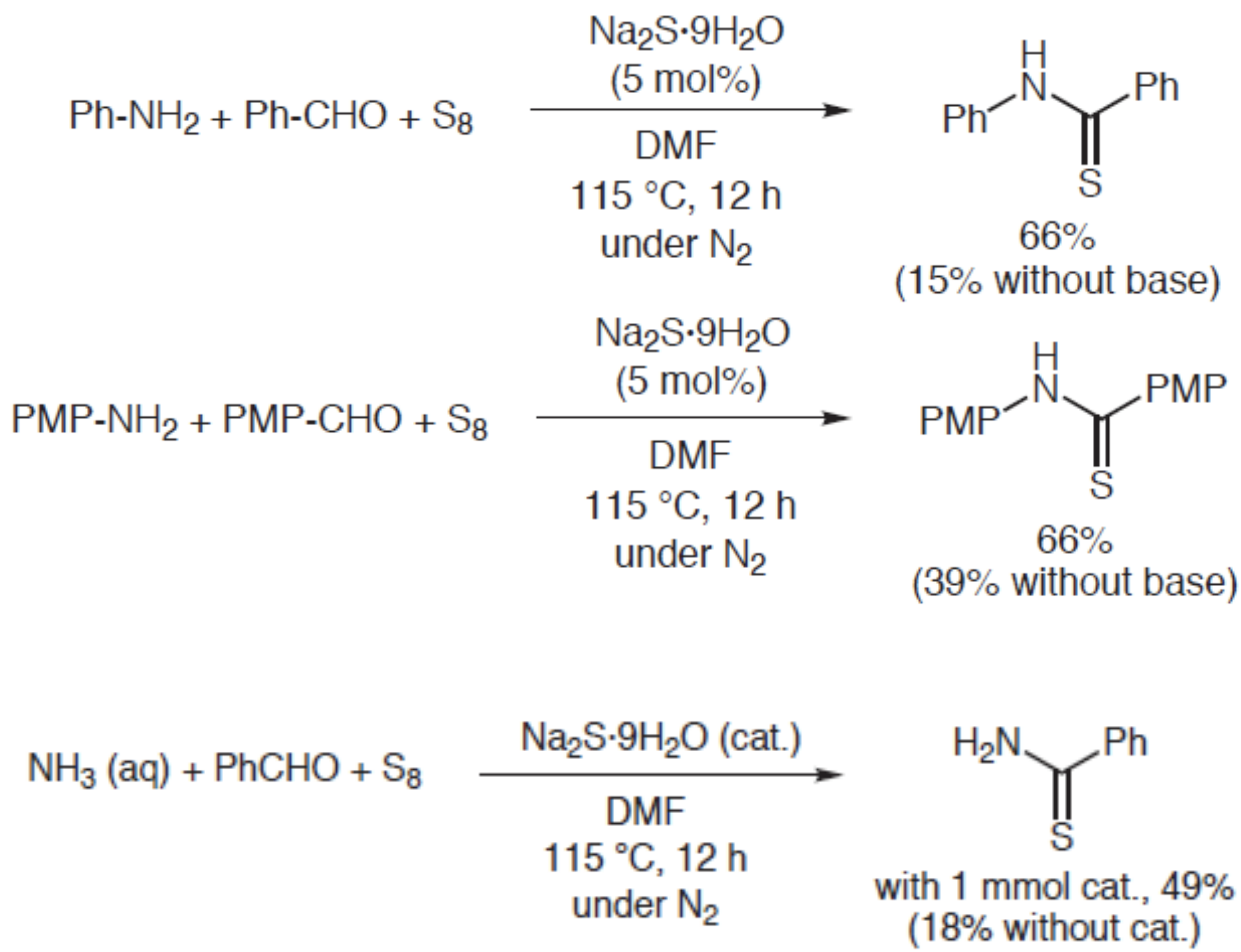





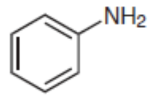
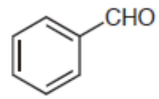
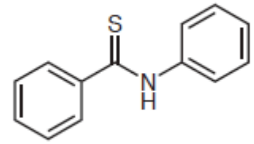
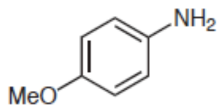
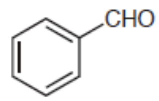
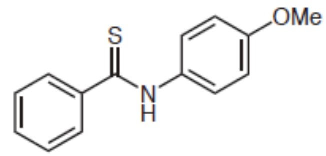
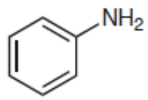
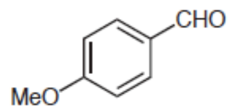
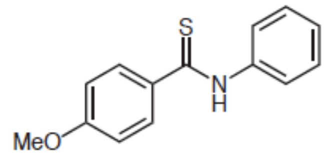
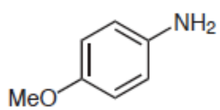
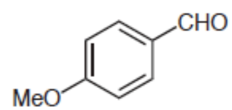
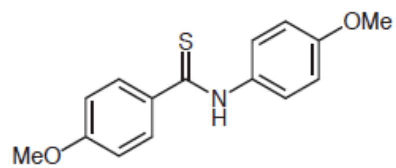
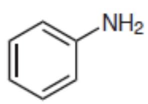
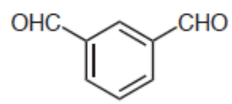
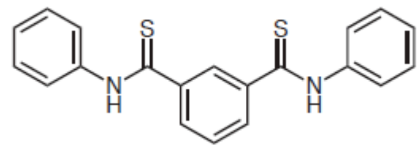
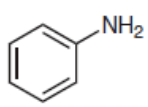
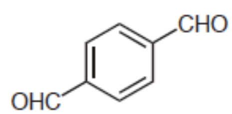
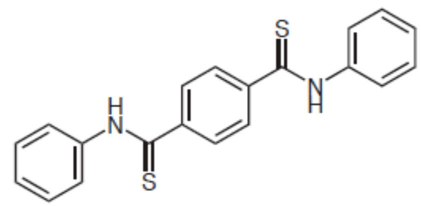
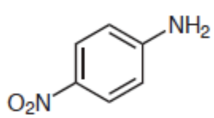
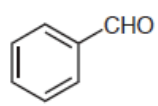
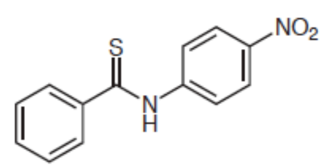
DeTar, D. F.; Carmack, M. *J. Am. Chem. Soc.* ***1946,*** *68,* 2025*.*

Davies, I. W., *et al*. *J. Org. Chem.,* **2000**, *65*, 8415.

# Three Components Reactions

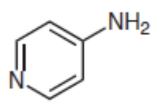
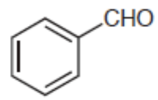
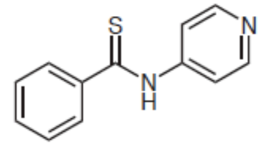
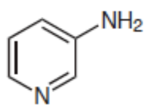
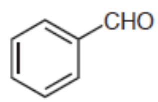
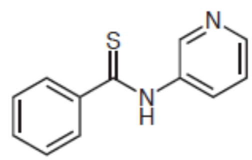
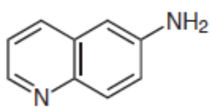
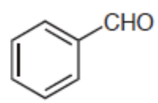
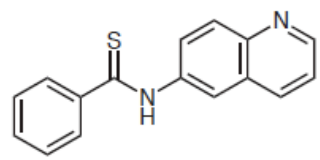
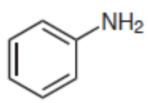
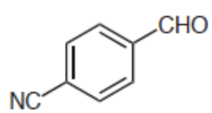
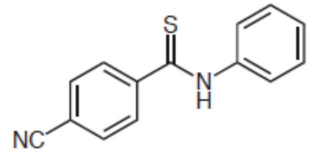
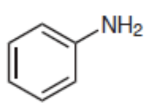
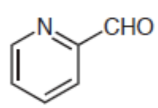
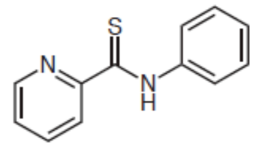



Kanbara, T., *et al*. *Synlett,* **2007**, *17*, 2687.

| Entry | Amine | Aldehyde | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 91 (15) |
| 2 |  |  |  | 92 (40[c]) |
| 3 |  |  |  | 78 (7) |
| 4 |  |  |  | 88 (39) |
| 5[d] |  |  |  | 48 (0[e]) |
| 6[d] |  |  |  | 40 (0[e]) |
| 7[f] |  |  |  | 40 (0[e]) |

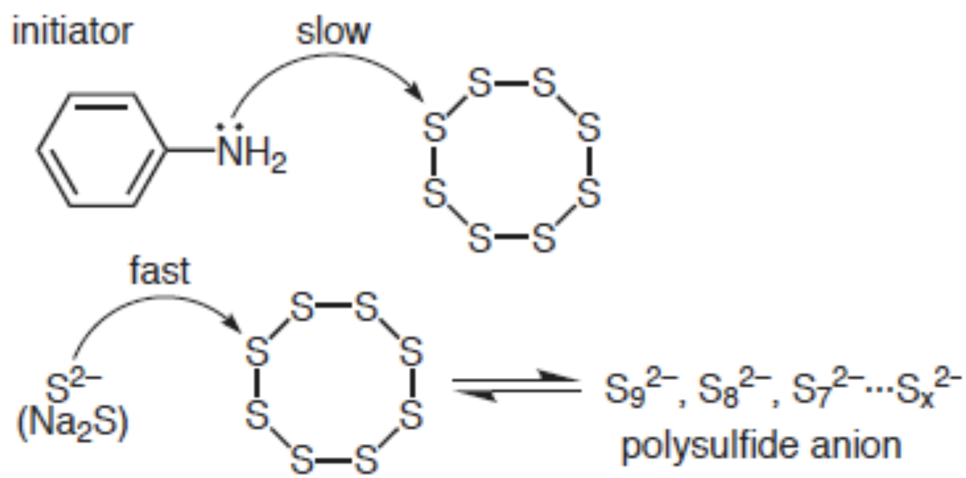
Kanbara, T., *et al*. *Synlett*, **2007**, *17*, 2687.

# Three Components Reactions

| Entry | Amine | Aldehyde | Product | Yield (%)[b] |
|---|---|---|---|---|
| 8 |  |  |  | 70 (51) |
| 9 |  |  |  | 65 (15) |
| 10 |  |  |  | 45 (6) |
| 11[f] |  |  |  | 51 (0[e]) |
| 12 |  |  |  | 88 (71) |

Kanbara, T., *et al*. *Synlett,* **2007**, *17*, 2687.

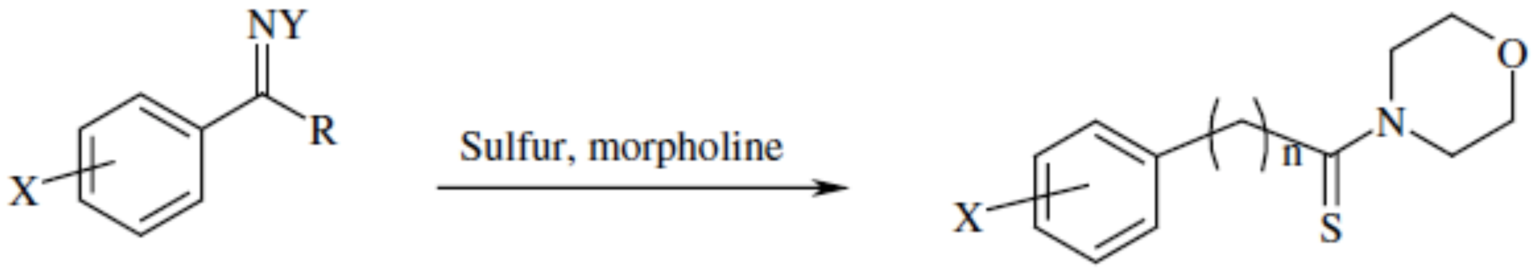
# Three Components Reactions




The addition of a small amount of $Na_2S{\cdot}9H_2O$ into the reaction mixture of sulfur with aniline caused a color change of the reaction system, from pale yellow to deep blue

Kanbara, T., *et al*. *Synlett,* **2007**, *17*, 2687.

# Protected Carbonyl Compounds




**1**

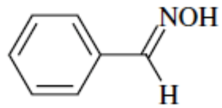
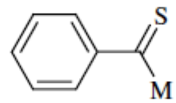
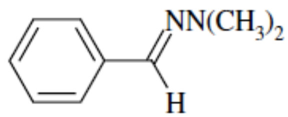
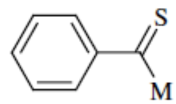
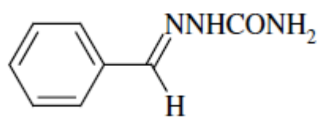
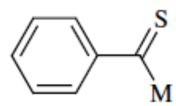
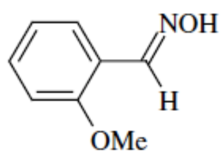
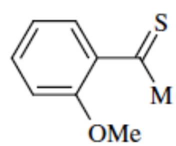
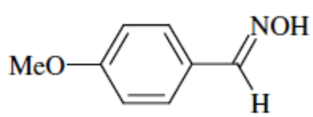
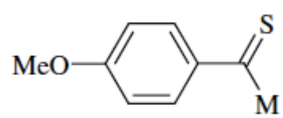
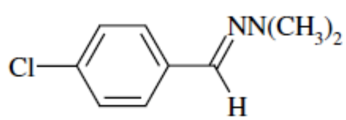
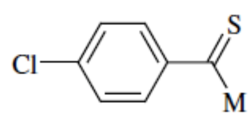
Y = OH, $N(CH_3)_2$, $NHCONH_2$

R = H, $CH_3$

2, n = 0

3, n = 0

Darabi, H., *et al*. *Tetrahedron Lett.,* **2004**, *45*, 4167.

| Entry | Substrates **1** | Products[a] | Yield (%)[b] | |
| --- | --- | --- | --- | --- |
| | | | Conventional heating[c] | MW[d] (min) |
| **a** |  |  | 65 | 70 (7) |
| **b** |  |  | 72 | 79 (10) |
| **c** |  |  | 83 | 72 (5) |
| **d** |  |  | 43 | 48 (7) |
| **e** |  |  | 75 | 80 (7) |
| **f** |  |  | 60 | 70 (10) |

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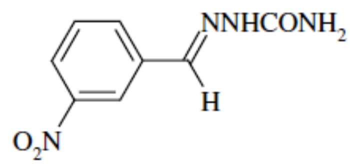
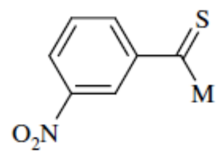
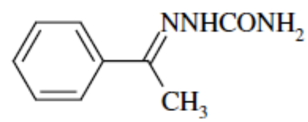
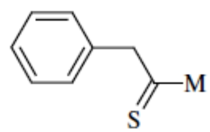
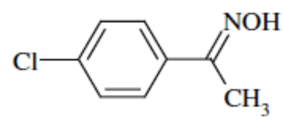
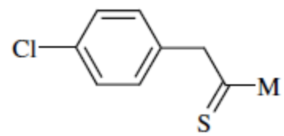
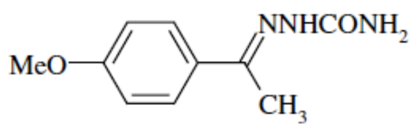
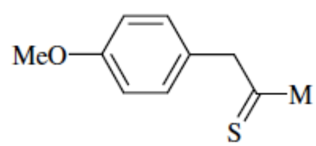
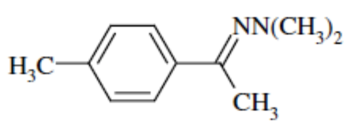
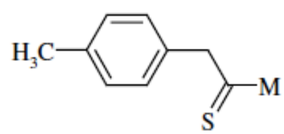
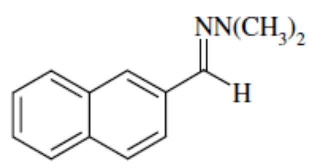
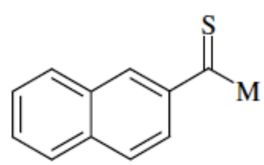
| Entry | Substrates **1** | Products[a] | Yield (%)[b] | |
|---|---|---|---|---|
| | | | Conventional heating[c] | MW[d] (min) |
| **g** |  |  | 55 | 72 (7) |
| **h** |  |  | 71 | 60 (7)[13] |
| **i** |  |  | 61 | 55 (7) |
| **j** |  |  | 41 | 44 (7) |
| **k** |  |  | 55 | 57 (7) |
| **l** |  |  | 65 | 73 (10) |

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# Domino Reactions

2-aminobenzo[*b*]thiophenes

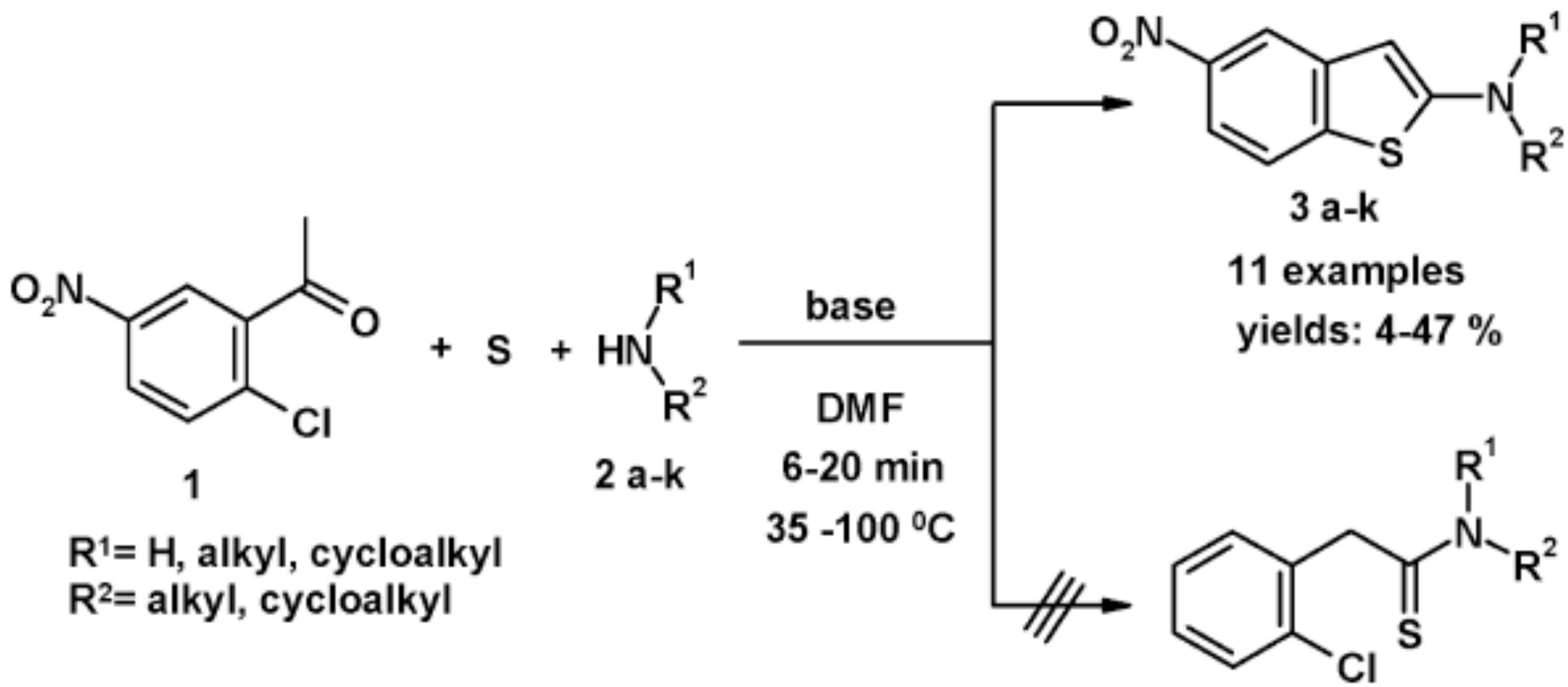


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**TABLE 1. Reaction Conditions and Yields of 2-Aminobenzo[*b*]thiophenes**

| entry | $R^1$ | $R^2$ | ratio of amine/S/base | temp (°C) | time (min) | yield of **3** (%) |
|---|---|---|---|---|---|---|
| **3a** | Me[a] | H | 3/5/3 | 60 | 10 | 46 |
| **3b** | allyl | H | 2.17/5/0 | 45 | 10 | 47 |
| **3c** | *n*-butyl | H | 3.2/3/2 | 60 | 8 | 36 |
| **3d** | benzyl | H | 3.8/5/0 | 60 | 10 | 30 |
| **3e** | *iso*-propyl | H | 2.3/5/0 | 60 | 10 | 14 |
| **3f** | cyclopentyl | H | 2.15/5/0 | 60 | 10 | 40 |
| **3g** | cyclohexyl | H | 1.95/5/0 | 35 | 6 | 19 |
| **3h** | Me[a] | Me | 1.5/1.5/1.5 | 100 | 180 | 4 |
| **3i** | $-(CH_2)_5-$ | | 3.7/3/2 | 60 | 15 | 31 |
| **3j** | $-(CH_2)_6-$ | | 1.2/1.5/1.5 | 100 | 20 | 10 |
| **3k** | $-(CH_2CH_2OCH_2CH_2)-$ | | 1.4/5/1.5 | 100 | 12 | 12 |

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# Thank You