# Efficient Synthesis of Thiobenzanilides by Willgerodt–Kindler Reaction with Base Catalysts

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*Received 2 July 2007*

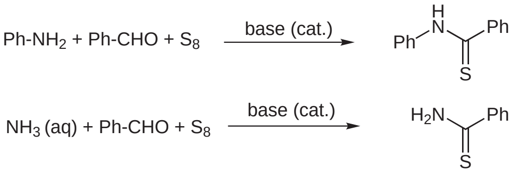
**Abstract:** Willgerodt–Kindler reaction between anilines and benzaldehydes readily proceeded in the presence of catalytic amount of $Na_2S·9H_2O$ to give thiobenzanilides in moderate to good yields. The base catalyst was also available for preparation of primary thiobenzamide.

**Key words:** sulfur, catalysis, condensation, aromatic amines, thioamides

Thioamides have been used in the field of medical and organic chemistry[1,2] and aromatic thioamides have been notably valuable building blocks for preparation of biologically relevant five- and six-membered heterocycles. Thioamides have also attracted recent attention in inclusion chemistry, transition-metal coordination chemistry, and materials science.[3]

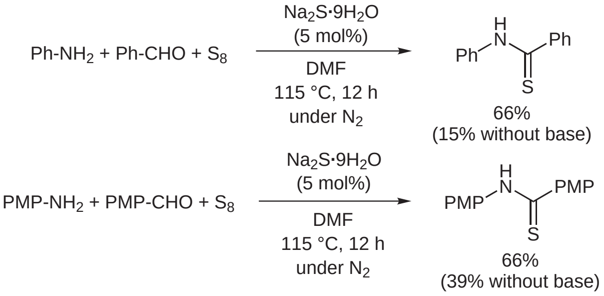
The Willgerodt–Kindler (WK) reaction is extensively used to synthesize various thioamides.[1f,4] However, to our knowledge, there have been only a few reports on the preparation of aromatic thioamides such as thiobenzanilide using the WK reaction,[5] and the yields have been low unless severe reaction conditions or microwave techniques are employed.[6]

Thiobenzanilide and its derivatives have generally been prepared by thionation of the corresponding benzanilides with Lawesson's reagent or $P_2S_5$.[7] To eliminate the limitations of the WK reaction, we have carried out the modification of the reaction conditions and found that addition of catalytic amount of base such as $Na_2S·9H_2O$ was efficient for the preparation of thiobenzanilides. There have been a few reports that addition of bases raised yields in WK reactions,[8] however, a usability of base catalysts for synthesis of thiobenzanilides has not been examined. We report here the efficient modification of WK reaction for preparation of thiobenzanilides, as shown in Scheme 1. The synthetic protocol is also available for preparation of primary thiobenzamide.



**Scheme 1**

The reaction of benzaldehyde with aniline and 4-anisidine in the presence of sulfur under the conditions of the conventional WK reaction afforded the corresponding thiobenzanilides in low to moderate yields (15% and 39% yields, respectively, as shown in Scheme 2); these results are consistent with reported literatures.[5a,c] The first step of the WK reaction is considered to involve cleavage of the S–S bond of elemental sulfur caused by nucleophilic attack of amine to form polysulfide anions in a reversible way.[4] The less basic amines, such as aniline, lead to only little formation of the polysulfide anions. In contrast, addition of a small amount (5 mol%) of $Na_2S·9H_2O$ in the reaction mixtures improved the reaction as shown in Scheme 2.



**Scheme 2**

To optimize the reaction conditions, the WK reaction of benzaldehyde and aniline with sulfur was carried out under various conditions. As shown in Table 1, the WK reaction of benzaldehyde and aniline with sulfur smoothly proceeded by the addition of $Na_2S·9H_2O$ as the base catalyst. The yield increased with an increase in the base content, and 91% yield was attained with 15 mol% of $Na_2S·9H_2O$. The yield was comparable to reported yields for WK reaction using microwave tequnique.[6] Use of other bases such as *t*-BuOK, DMAP, and $Et_3N$ gave thiobenzanilide in moderate (40–62%) yields.

The reaction conditions of entry 9 in Table 1 were applied for various aromatic amines and aldehydes,[9] and the

***SYNLETT*** 2007, No. 17, pp 2687–2690
Advanced online publication: 25.09.2007
DOI: 10.1055/s-2007-991073; Art ID: U06207ST

**Table 1** WK Reaction of Aniline with Benzaldehyde[a]

| Entry | Base | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | – | 12 | 15 |
| 2 | $Et_3N$, 5 mol% | 12 | 40 |
| 3 | DMAP, 5mol% | 12 | 42 |
| 4 | *t*-BuOK, 5 mol% | 12 | 62 |
| 5 | $Na_2S{\cdot}9H_2O$, 1 mol% | 12 | 55 |
| 6 | $Na_2S{\cdot}9H_2O$, 5 mol% | 4 | 32 |
| 7 | $Na_2S{\cdot}9H_2O$, 5 mol% | 12 | 66 |
| 8 | $Na_2S{\cdot}9H_2O$, 10 mol% | 12 | 83 |
| 9 | $Na_2S{\cdot}9H_2O$, 15 mol% | 12 | 91 |
| 10 | $Na_2S{\cdot}9H_2O$, 20 mol% | 12 | 88 |

[a] Reaction conditions: aniline (6.0 mmol), benzaldehyde (4.0 mmol) and sulfur (5.0 mmol) in DMF (4 mL) at 115 °C.

[b] Isolated yield.

results are summarized in Table 2. $Na_2S{\cdot}9H_2O$ was efficient for the preparation of several thiobenzanilides. Disubstituted aromatic thioamides, which could not be prepared by the conventional WK reaction, were obtained in moderate yields (entries 5 and 6). $Na_2S{\cdot}9H_2O$ was also effective for the reaction of heteroaromatic amines and aldehydes (entries 8–10 and 12). New compounds (entries 8, 10, and 11) were characterized by NMR spectroscopy and elemental analysis.[10]

Scheme 3 shows a plausible role for $Na_2S{\cdot}9H_2O$ in the WK reaction. The suspension of elemental sulfur in the DMF solution of aniline remained unreacted because of the poor nucleophilicity of aniline. 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. Therefore, the base catalyst is considered to initiate the nucleophilic cleavage of the elemental sulfur ring to give the polysulfide anions as depicted in Scheme 3.

**Table 2** WK Reaction of Aromatic Amines, Arylaldehydes, and Sulfur with Catalytic Amount of $Na_2S{\cdot}9H_2O$[a]

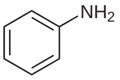
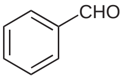
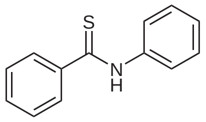
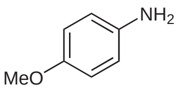
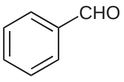
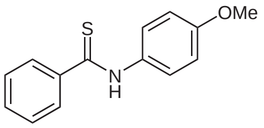
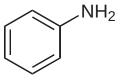
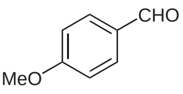
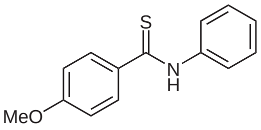
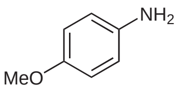
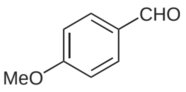
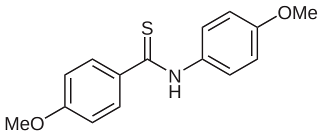
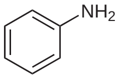
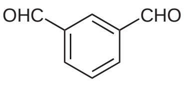
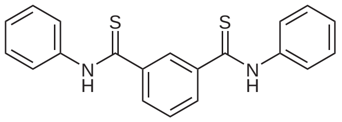
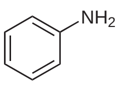
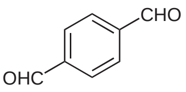
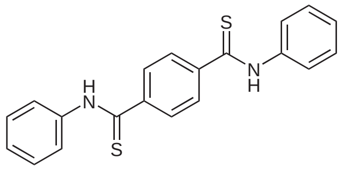
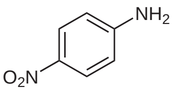
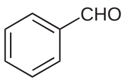
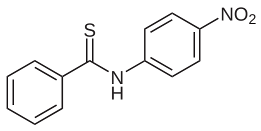
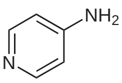
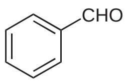
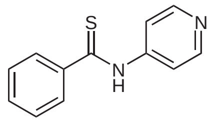
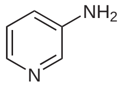
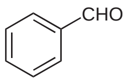
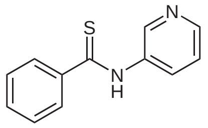
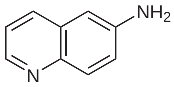
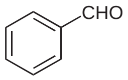
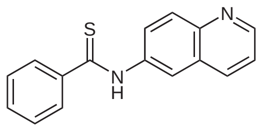
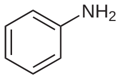
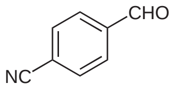
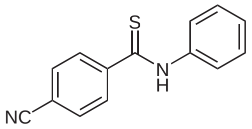
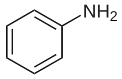
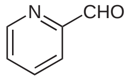
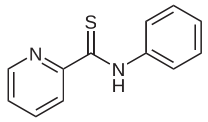
| Entry | Amine | Aldehyde | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  |  | 91 (15) |
| 2 |  |  |  | 92 (40[c]) |
| 3 |  |  |  | 78 (7) |
| 4 |  |  |  | 88 (39) |
| 5[d] |  |  |  | 48 (0[e]) |
| 6[d] |  |  |  | 40 (0[e]) |
| 7[f] |  |  |  | 40 (0[e]) |

**Table 2** WK Reaction of Aromatic Amines, Arylaldehydes, and Sulfur with Catalytic Amount of $Na_2S{\cdot}9H_2O$[a] (continued)

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

[a] Reaction was carried out in analogy with entry 9 in Table 1.

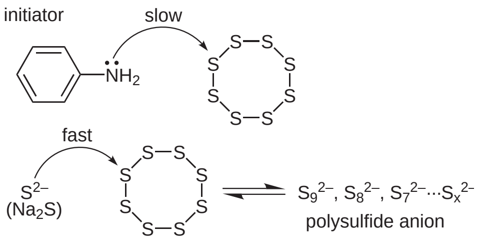
[b] Isolated yield; the data obtained in the absence of base is shown in parentheses.

[c] From ref. 5c.

[d] Aniline (3 equiv) was used.

[e] Not detected by TLC.

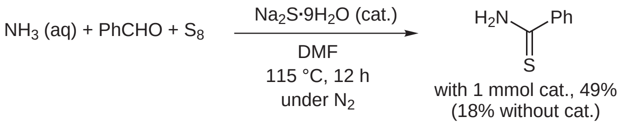
[f] $Na_2S{\cdot}9H_2O$ (5 mol%) was used.



**Scheme 3**

There have been numerous investigations concerning the reaction of elemental sulfur in amines or ammonia,[11] however, the behavior and the fate of sulfur in those media have not yet been fully elucidated. From changes of the absorption spectra and conductivity of those media, Davis et al. suggested that the color change of the reaction media results from the formation of polysulfide anions and that the related ions were generated by the initial nucleophilic attack of amines on the sulfur ring.[11a]

$Na_2S{\cdot}9H_2O$ was also usable for the preparation of primary thiobenzamide. In contrast to extensive study on the reaction of elemental sulfur with ammonia,[11e] only a few reports concerning the WK reaction of benzaldehyde with ammonia were reported; the reaction gave thiobenzamide in moderate yield under microwave irradiation.[1f] The addition of the base catalyst was also effective for the WK reaction of benzaldehyde with aqueous ammonia,[12] and the yield was improved as shown in Scheme 4.



**Scheme 4**

In summary, we succeeded in improving the preparation of thiobenzanilides and primary thiobenzamide by the WK reaction under mild conditions. The base catalyst was applicable for the preparation of various thiobenzanilides, and the results will contribute to the expanded use of the WK reaction.

## Acknowledgment

The authors gratefully thank Dr. T. Koizumi of Tokyo Institute of Technology for useful discussion. The authors are grateful to the Chemical Analysis Center of University of Tsukuba, for measurements of NMR spectra and elemental analysis.

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(9) **Experimental Procedure** (Table 1, entry 9): $Na_2S·9H_2O$ (216 mg, 15 mol%) was added to a mixture of sulfur (160 mg, 5 mmol as elemental sulfur) and aniline (0.55 mL, 6 mmol) in DMF (4 mL), and the suspension was stirred at 115 °C for 0.5 h under nitrogen. After the mixture was cooled to r.t., benzaldehyde (0.41 mL, 4 mmol) was added, and was stirred at 115 °C for 12 h under nitrogen. After cooling to r.t., the resulting solution was quenched with sat. aq $NH_4Cl$ solution (50 mL) and extracted with $CHCl_3$ (50 mL). The organic fraction was thoroughly washed with $H_2O$ (2 × 50 mL) and dried with anhyd $Na_2SO_4$. After concentration, the resulting crude product was purified by chromatography on silica gel with $CHCl_3$ to afford *N*-phenylthiobenzamide as a yellow powder (780 mg, 91% yield); mp 99 °C, lit.[7] 99 °C.

(10) ***N*-(4-Methoxyphenyl)thiobenzamide** (Table 2, entry 2): yellow powder; mp 135 °C, lit.[7] 135 °C.
**4-Methoxy-*N*-phenylthiobenzamide** (Table 2, entry 3): yellow powder; mp 154 °C, lit.[7] 153–154 °C.
**4-Methoxy-*N*-(4-methoxyphenyl)thiobenzamide** (Table 2, entry 4): yellow powder; mp 148 °C, lit.[7] 148 °C.
**1,3-Bis(anilinothiocarbonyl)benzene** (Table 2, entry 5): yellow powder; mp 243–244 °C, lit.[2a] 242–244 °C.
**1,4-Bis(anilinothiocarbonyl)benzene** (Table 2, entry 6): yellow powder; mp 280–281 °C, lit.[2a] 280–282 °C.
***N*-(4-Nitrophenyl)thiobenzamide** (Table 2, entry 7): yellow powder; mp 145–146 °C, lit.[13] 145 °C.
***N*-(4-Pyridyl)thiobenzamide** (Table 2, entry 8): yellow powder; mp 187–188 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 11.99 (s, 1 H), 9.59 (d, $J$ = 6.4 Hz, 2 H), 8.00 (d, $J$ = 6.4 Hz, 2 H), 7.78 (d, $J$ = 7.6 Hz, 2 H), 7.55 (t, $J$ = 7.6 Hz, 1 H), 7.47 (t, $J$ = 7.6 Hz, 2 H). $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$): δ = 199.35, 150.17, 146.64, 142.78, 130.99, 128.00, 127.37, 116.67. Anal. Calcd for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.07; S, 14.96. Found: C, 67.32; H, 4.52; N, 13.15; S, 14.88.
***N*-(3-Pyridyl)thiobenzamide** (Table 2, entry 9): yellow powder; mp 140–141 °C, lit.[14] 140–141 °C.
***N*-(6-Quinolyl)thiobenzamide** (Table 2, entry 10): orange powder; mp 177–179 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 12.03 (s, 1 H), 8.90 (br, 1 H), 8.56 (br, 1 H), 8.38 (d, $J$ = 8.0 Hz, 1 H), 8.05–8.11 (m, 2 H), 7.89 (d, $J$ = 7.6 Hz, 2 H), 7.53–7.56 (m, 2 H), 7.49 (t, $J$ = 7.6 Hz, 2 H). $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$): δ = 199.81, 151.99, 147.55, 144.08, 139.55, 137.49, 132.50, 130.65, 129.67, 129.29, 129.08, 128.86, 123.41, 123.00. Anal. Calcd for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.62; H, 4.51; N, 10.60; S, 11.97.
**4-Cyano-*N*-phenylthiobenzamide** (Table 2, entry 11): orange powder; mp 130–131 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 12.01 (s, 1 H), 7.91–7.93 (br, 4 H), 7.83 (d, $J$ = 8.0 Hz, 2 H), 7.44 (t, $J$ = 8.0 Hz, 2 H), 7.29 (t, $J$ = 8.0 Hz, 1 H). $^{13}$C{$^1$H} NMR (100 MHz, DMSO-$d_6$): δ = 195.16, 146.14, 139.47, 131.96, 128.42, 127.95, 126.42, 123.74, 118.27, 112.54. Anal. Calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76. Found: C, 70.85; H, 4.45; N, 11.71.
***N*-Phenyl-2-pyridinethioamide** (Table 2, entry 12): orange-yellow powder; mp 45 °C, lit.[15] 45 °C.

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(12) **Preparation of Thiobenzamide** (Scheme 4): $Na_2S·9H_2O$ (244 mg, 1 mmol) was added to a mixture of sulfur (160 mg, 5 mmol as elemental sulfur) and 28% aq $NH_3$ (3 mL, ca. 44 mmol) in DMF (4 mL), and the suspension was stirred at 115 °C for 0.5 h under nitrogen. After the mixture was cooled to r.t., benzaldehyde (0.41 mL, 4 mmol) was added, and stirred at 115 °C for 12 h under nitrogen. After cooling to r.t., the resulting solution was quenched with sat. aq $NH_4Cl$ solution (50 mL) and extracted with $CHCl_3$ (50 mL). The organic fraction was thoroughly washed with $H_2O$ (2 × 50 mL) and dried with anhyd $Na_2SO_4$. After concentration, the resulting crude material was purified by chromatography on silica gel with $CHCl_3$–$Et_2O$ (100:0–20:80) to afford thiobenzamide as a pale yellow powder (270 mg, 49% yield); mp 118 °C, lit.[7b] 117–118 °C.

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