Synthesis of α-Ketothioamides via Willgerodt–Kindler Reaction of Arylglyoxals with Amines and Sulfur under Solvent-Free Conditions

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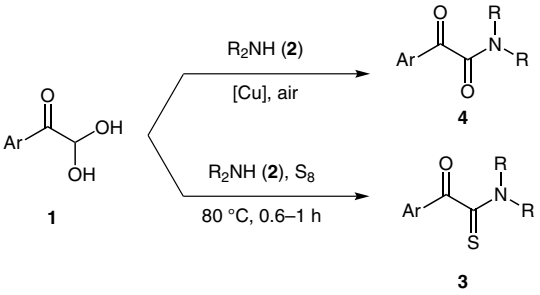
Abstract: Willgerodt–Kindler reaction of arylglyoxal hydrates with secondary amines and elemental sulfur under solvent-free conditions at 80 °C is developed, in which α-ketothioamides are obtained in 70–90% yield in 0.6–1 hour. The X-ray crystal-structure analysis for one compound was obtained.

Key words: α-ketothioamides, Willgerodt–Kindler reaction, arylglyoxals, green chemistry, solvent-free

The thioamides moiety is incorporated in the structure of many natural and unnatural products, such as closthioamide,[1] with a wide range of biological properties, such as pesticidal,[2] fungicidal,[3] insecticidal,[4] antioxidant,[5] antitubercular,[6] and anthelmintic activity.[7] Thioamides have also been widely used as building blocks in organic synthesis,[8] especially for the synthesis of heterocycles.[9] Furthermore, thioamides have a wide range of applications in the fields of peptide chemistry,[10] polymers,[11] and organocatalysis.[12] Numerous methods are available in the literature for the preparation of thioamides, including thionation of amides using P_4S_{10},[13] $(Me_3Si)_2S$,[14] $PSCl_3/H_2O/Et_3N$,[15] S_8/Cl_3SiH/amine,[16] ammonium phosphorodithioate,[17] and Lawesson's reagent,[18] and Friedel–Crafts reaction of aromatic compounds with KSCN in $MeSO_3H$.[19] The Willgerodt–Kindler reaction is extensively used to synthesize various thioamides,[20,5a] but suffers from disadvantages, such as long reaction times, low yields, and need for high reaction temperatures and toxic organic solvents.

Our recent review article on arylglyoxal chemistry[21] revealed that there is no report of the Willgerodt–Kindler reaction of arylglyoxals and this encouraged us to investigate the Willgerodt–Kindler reaction of arylglyoxal hydrates **1** with amines **2** and elemental sulfur to afford α-ketothioamides **3**. However, in previously reported Willgerodt–Kindler reactions of aryl methyl ketones, the corresponding α-ketothioamides were isolated as byproducts in very low yields.[22] Recently, Penieres-Carrillo et al.[23] reported the modified Willgerodt–Kindler reaction under uncatalyzed solvent-free conditions using IR energy to produce α-ketothioamides in 12–67% yield, in which the corresponding aryl methyl thioamides were also isolated in 0–42% yield. A number of limited different approaches for the synthesis of α-ketothioamides has been developed,[24] but these have disadvantages such as limited scope, expensive reagents or catalysts, and need for harsh reaction conditions. Recently, the copper-catalyzed aerobic oxidation of arylglyoxals in the presence of amines to produce α-ketoamides **4** was reported.[25] Herein we report a green and efficient route to synthesize the corresponding α-ketothioamides **3** in good to high yields in the absence of catalyst (Scheme 1).



Scheme 1 Willgerodt–Kindler reaction of arylglyoxal hydrates **1** with secondary amines **2**

For optimization of reaction conditions, we conducted the Willgerodt–Kindler reaction of phenylglyoxal hydrate, piperidine **2b**, and sulfur under different conditions. To maximize environmental acceptability, we carried out the reaction in water at different temperatures. At room temperature, the reaction time was long (over 24 h), and consequently 80 °C was chosen as the optimum temperature, which afforded the corresponding α-ketothioamide **3h** in 61% yield within one hour. Additionally, we found that a 1:2:2 ratio of phenylglyoxal/piperidine/sulfur was optimal for the generation of **3h**. In addition to the desired ketothioamide **3h**, the corresponding α-ketoamide **4** was obtained in low yield, which presumably results from hydrolysis of **3h** under the reaction conditions. To overcome this problem, we carried the similar reaction under solvent-free conditions at 80 °C to afford **3h** in 85% yield, without formation of the corresponding α-ketoamide **4**.

The scope of the reaction was investigated using different arylglyoxal hydrates **1** (prepared by oxidation of acetophenones using SeO_2 in refluxing dioxane in the presence of water according to Riely et al.[26]) and different secondary amines **2** under solvent-free conditions at 80 °C. The results are summarized in Table 1.

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As shown in Table 1, arylglyoxals with electron-withdrawing groups, such as chloro and bromo, and with electron-donating substituents, such as methoxy, reacted well but in the case of 4-nitrophenylglyoxal the Willgerodt–Kindler reaction did not occur (Table 1, entries 15 and 22) and polymeric material was produced. This can be attributed to the reduction of the nitro group to an amine in the presence of elemental sulfur followed by the reaction with the carbonyl group of another arylglyoxal molecule. Heterocyclic amines **2a–c** worked well in the Willgerodt–Kindler reaction with arylglyoxals. However, reaction with secondary acyclic amines, such as diethylamine **2d**, led to a complex mixture of products. In the early stages of the reaction with diethylamine the corresponding α-ketothioamides could be identified using TLC, but these were then consumed under the reaction conditions. This can be attributed to low nucleophilicity and steric hindrance of the alkyl residue in diethylamine.

Table 1 Willgerodt–Kindler Reaction of Arylglyoxal Hydrates under Solvent-Free Conditions[a]

Entry	R_2NH **2**	Ar **1**	Product **3**	Yield (%)[b]
1	 **2a**	Ph	**3a**	90
2		4-ClC_6H_4	**3b**	70
3		4-BrC_6H_4	**3c**	80
4		4-PhC_6H_4	**3d**	80
5		3-$MeOC_6H_4$	**3e**	85
6		4-$MeOC_6H_4$	**3f**	75
7		3,4-$(MeO)_2C_6H_3$	**3g**	90
8	 **2b**	Ph	**3h**	90
9		4-ClC_6H_4	**3i**	78
10		4-BrC_6H_4	**3j**	80
11		4-PhC_6H_4	**3k**	85
12		3-$MeOC_6H_4$	**3l**	85
13		4-$MeOC_6H_4$	**3m**	85
14		3,4-$(MeO)_2C_6H_3$	**3n**	90
15		4-$O_2NC_6H_4$	–	–[c]
16	 **2c**	Ph	**3o**	90
17		4-ClC_6H_4	**3p**	83
18		4-BrC_6H_4	**3q**	70
19		3-$MeOC_6H_4$	**3r**	85
20		4-$MeOC_6H_4$	**3s**	85
21		3,4-$(MeO)_2C_6H_3$	**3t**	85
22		4-$O_2NC_6H_4$	–	90 –[c]
23	 **2d**	Ph	–	–[d]
24		4-ClC_6H_4	–	–[d]

[a] See also Scheme 1.
[b] Yields refer to isolated products.
[c] Polymeric material was produced.
[d] Nonidentified mixture was obtained.

A single crystal of 1-phenyl-2-(piperidin-1-yl)-2-thioxoethanone (**3h**) suitable for X-ray analysis[27] was obtained via slow evaporation and its ORTEP representation with atom numbering is shown in Figure 1. For crystal data, structure refinement details, selected bond distances, bond angles, and torsion angles of **3h** see Supporting Information.

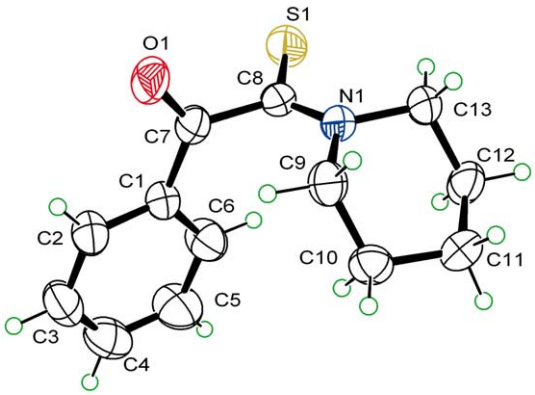
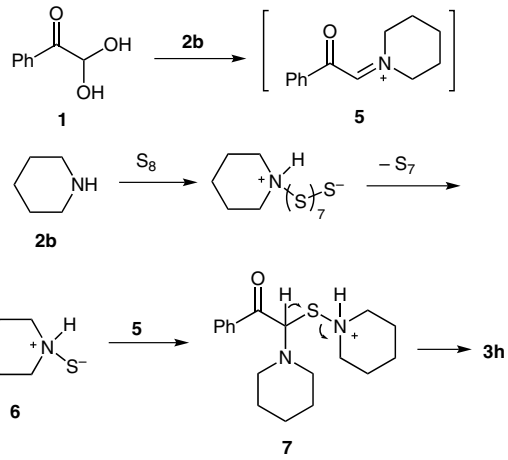


Figure 1 ORTEP representation of the crystal structure of **3h** (35% ellipsoid probability)

A plausible mechanism for the Willgerodt–Kindler reaction of phenylglyoxal with piperidine **2b** and elemental sulfur is shown in Scheme 2. Firstly, iminium salt **5** is produced by condensation of phenylglyoxal hydrate with **2b**. Subsequent nucleophilic addition of **2b** to sulfur, followed by elimination of S_7, piperidinium sulfide leads to **6**. Intermediate **7** is then produced by nucleophilic addition of **6** to iminium salt **5**, which is finally converted into the desired α-ketothioamide **3h** by the elimination of a molecule of piperidine.

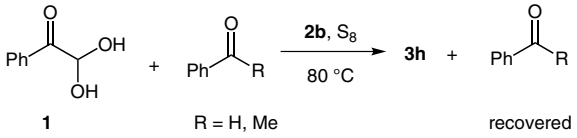


Scheme 2 Plausible mechanism for Willgerodt–Kindler reaction of phenylglyoxal with **2b** and sulfur

The Willgerodt–Kindler reaction of a primary amine, benzylamine, with phenylglyoxal hydrate and sulfur under the same conditions was also investigated but a complex mixture was produced. Finally, the reaction of an aromatic amine, aniline, with phenylglyoxal and sulfur, was carried out for an extended period, and the corresponding α-ketoimine was identified without incorporation of sulfur. This can be attributed to the low nucleophilicity of aniline too. As Okamoto et al.[28] have reported, we added Na_2S to the reaction mixture and this resulted in the disappearance of

the α-ketoimine, but a nonidentifiable mixture was obtained.

Another characteristic feature of the present protocol is the high chemoselectivity of the Willgerodt–Kindler reaction toward phenylglyoxal, in preference to benzaldehyde and acetophenone as shown in Scheme 3. Thus, when the reaction of phenylglyoxal with piperidine in the presence of one equivalent of either benzaldehyde or acetophenone was carried out under the same conditions, only **3h** was isolated and benzaldehyde or acetophenone was recovered.



Scheme 3 Chemoselectivity of the Willgerodt–Kindler reaction

In conclusion, we have reported an efficient and green methodology for the synthesis of α-ketothioamides via the Willgerodt–Kindler reaction of arylglyoxal hydrates with secondary amines and elemental sulfur under solvent-free conditions. Arylglyoxals with electron-donating and electron-withdrawing groups (except the nitro group) are good substrates. Heterocyclic secondary amines afford the corresponding α-ketothioamides in good to high yields, while reactions with secondary acyclic amines produce a nonisolable mixture. Reaction with primary amines does not occur. Finally, the reaction shows excellent chemoselectivity toward phenylglyoxal in preference to benzaldehyde and acetophenone.

General Procedure for the Preparation of Arylglyoxal Hydrates
Aryl methyl ketone (50 mmol) was added to a solution of SeO_2 (50 mmol) in dioxane (30 mL) containing H_2O (1 mL) and heated under reflux conditions for 4–6 h. Then the hot solution was decanted to remove the precipitated selenium. The dioxane was removed by distillation, and the obtained yellow liquid was recrystallized from hot H_2O to obtain the corresponding arylglyoxal.[26]

General Procedure for the Willgerodt–Kindler Reaction
A mixture of arylglyoxal hydrate **1** (1 mmol), amine **2** (2 mmol), and elemental sulfur (2 mmol) was heated at 80 °C for 0.6–1 h. After completion of the reaction, (as monitored by TLC, *n*-hexane–EtOAc, 7:3), the unreacted sulfur was removed by adding EtOH (2 mL), heating, and then filtering while hot. On cooling the filtrate, the corresponding α-ketothioamides crystallized and were isolated by filtration. Further purification for elemental analysis was carried out by recrystallization from *n*-hexane or EtOH. In the case of oily products, column chromatography was used for purification. All compounds were characterized spectrosopically. Compounds **3a**–**g**,**j**–**n**,**r**,**t** are novel and were also characterized by elemental analysis.[29]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are copies of the ^{1}H NMR and ^{13}C NMR spectra of all compounds.

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(29) **Spectroscopic and Analytical Data for Selected Novel Compounds**
1-(3,4-Dimethoxyphenyl)-2-(pyrrolidin-1-yl)-2-thioxo-ethanone (3g)
Dark yellow solid; mp 113–115 °C. FTIR (KBr): 2967 (CH), 1648 (C=O), 1589 (C=C), 1508 (C=S), 1451 (CH_2 bending), 1270 (CO), 1229 (CN), 1019 (C=S) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.63 (dd, *J* = 2.0, 8.4 Hz, 1 H, CH_{Ar}), 7.57 (d, *J* = 2.0 Hz, 1 H, CH_{Ar}), 6.90 (d, *J* = 8.4 Hz, 1 H, CH_{Ar}), 3.96–3.99 (m, 2 H, CH_2N), 3.98 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.56–3.59 (m, 2 H, CH_2N), 2.06–2.17 (m, 4 H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.1 (C=S), 188.3 (C=O), 154.3, 149.4, 126.0, 125.8, 111.1, 110.2, 56.2, 51.3, 26.1, 23.9. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.28. Found: C, 60.20; H, 6.13; N, 4.99.
1-(3-Methoxyphenyl)-2-morpholino-2-thioxoethanone (3r)
Dark yellow oil. FTIR (KBr): 2920 (CH), 1642 (C=O), 1600 (C=C), 1489 (C=S), 1435 (CH_2 bending), 1268 (CO), 1246 (CN), 1110 (C=S) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.56 (m, 2 H, CH_{Ar}), 7.40 (t, *J* = 8.0 Hz, 1 H, CH_{Ar}), 7.16–7.19 (m, 1 H, CH_{Ar}), 4.32–4.35 (m, 2 H, CH_2O), 3.90–3.93 (m, 2 H, CH_2O), 3.87 (s, 3 H, OCH_3), 3.70–3.72 (m, 2 H, CH_2N), 3.60–3.62 (m, 2 H, CH_2N). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 195.6 (C=S), 187.7 (C=O), 160.1, 134.5, 130.2, 122.8, 121.8, 113.4, 66.7, 55.6, 51.9, 47.1. Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.44; H, 5.39; N, 5.00.
1-(4-Methoxyphenyl)-2-morpholino-2-thioxoethanone (3s)
Yellow solid; mp 117–118.5 °C. FTIR (KBr): 3110, 2969 (CH), 1654 (C=O), 1595 (C=C), 1500 (C=S), 1437 (CH_2 bending), 1263 (CO), 1234 (CN), 1110 (C=S) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97–8.01 (m, 2 H, CH_{Ar}), 6.97–7.01 (m, 2 H, CH_{Ar}), 4.34–4.37 (m, 2 H, CH_2O), 3.92–3.94 (m, 2 H, CH_2O), 3.91 (s, 3 H, OCH_3), 3.70–3.73 (m, 2 H, CH_2N), 3.62–3.63 (m, 2 H, CH_2N). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 196.2 (C=S), 187.3 (C=O), 164.6, 132.3, 126.1, 114.3, 66.5, 55.7, 51.9, 47.1. Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.61; H, 5.80; N, 4.42.

