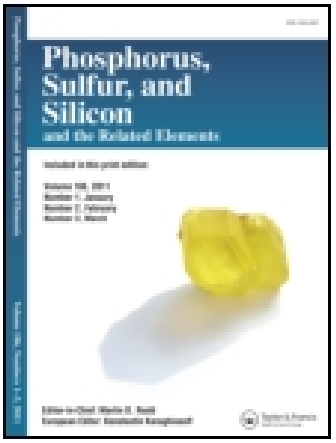


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

# Ultrasound-Mediated Willgerodt-Kindler Reactions: Non-thermal Synthesis of Thioacetamides

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Published online: 24 Aug 2011.

To cite this article: Mohammad M. Mojtahedi, Tooba Alishiri & M. Saeed Abaee (2011) Ultrasound-Mediated Willgerodt-Kindler Reactions: Non-thermal Synthesis of Thioacetamides, Phosphorus, Sulfur, and Silicon and the Related Elements, 186:9, 1910-1915, DOI: 10.1080/10426507.2010.550269

To link to this article: http://dx.doi.org/10.1080/10426507.2010.550269

*Phosphorus, Sulfur, and Silicon*, 186:1910–1915, 2011

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2010.550269



# ULTRASOUND-MEDIATED WILLGERODT–KINDLER REACTIONS: NON-THERMAL SYNTHESIS OF THIOACETAMIDES

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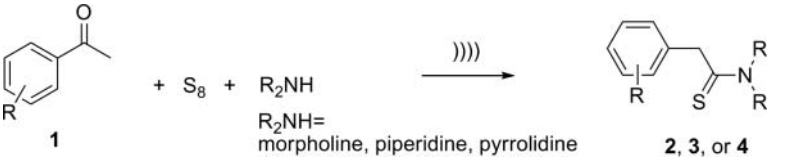
*Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran*

## GRAPHICAL ABSTRACT




**Abstract** *Non-thermal, solvent-free condensation of several aryl methyl ketones with amines and elemental sulfur is efficiently conducted using ultrasonic irradiation within short time periods. Consequently, various thioacetamides are conveniently synthesized. Similar experiments at controlled temperature (25 ± 1° C) resulted in comparable yields, showing the promotional role of ultrasound irradiation in the progress of the reaction.*

**Keywords** Multicomponent; Willgerodt–Kindler reaction; ultrasound irradiation; solvent-free; thioacetamide

## INTRODUCTION

Currently, multicomponent reactions (MCRs)[1] are considered as one of the key synthetic strategies in organic chemistry[2] since they offer a combination of more than two reactants in one pot and allow direct access to complex target molecules in a single step. In this context, oxidative condensation of acetophenone derivatives with elemental sulfur and amines, known as the Willgerodt–Kindler reaction,[3] has served as an important MCR in synthetic organic chemistry, leading to the formation of phenylthioacetamides, which are known to possess a variety of biological[4] and medicinal[5] properties. In addition, the thioacetamide products are conveniently converted to their corresponding arylacetic acid derivatives,[6] which in fact exhibit a vast range of biological activities[7] and are used as key

Received 4 August 2010; accepted 15 December 2010.
Partial financial support by the Ministry of Science, Research, and Technology of Iran is greatly acknowledged.
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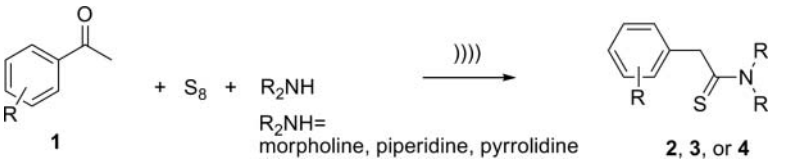
intermediates in the preparation of other synthetic targets.[8] The Willgerodt–Kindler reaction traditionally requires high-temperature treatment of the reactants in various solvents.[9] Although several modern methods using solvent-free systems,[10] ionic liquid media,[11] and microwave irradiation[12] are developed in recent years, there is still a demand for procedures capable of conducting the reaction under more environmentally friendly and milder conditions.

The role of ultrasonic irradiation in boosting the reactivity and selectivity of synthetic organic reactions is widely demonstrated in recent years.[13] Consequently, several protocols are developed to perform chemical reactions in shorter time periods and under more environmentally benign conditions. Some illustrative instances include the use of sonochemistry in multi-component procedures,[14] synthesis of heterocyclic compounds,[15] organometallic chemistry,[16] protection of functional groups,[17] cycloadditions,[18] and ring opening of epoxides.[19] Based on our previous experiences in sonochemistry[20] and in continuation of our attempts to develop green chemical methodologies,[21] we now report a novel procedure for solvent-free Willgerodt–Kindler reactions using ultrasound irradiation (Scheme 1).



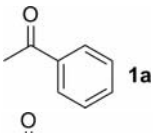
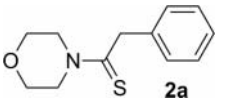
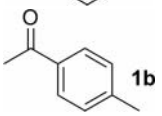
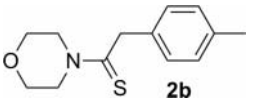
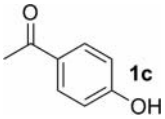
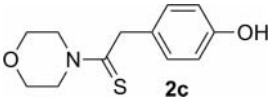
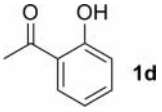
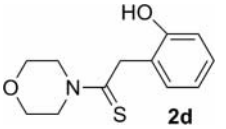
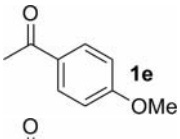
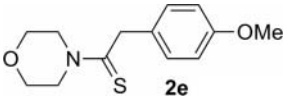
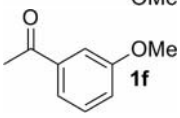
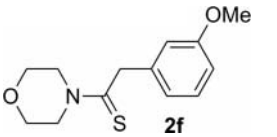
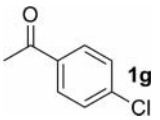
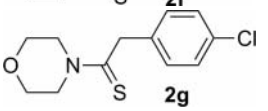
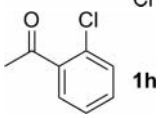
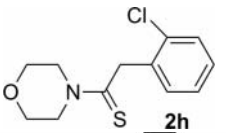
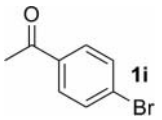
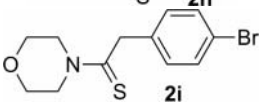
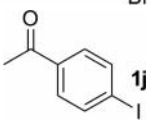
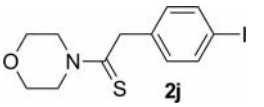
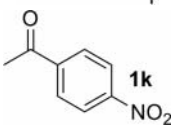
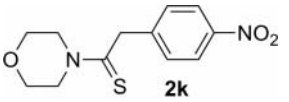
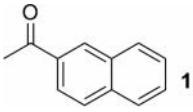
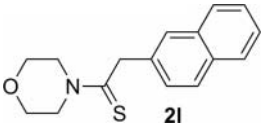

**Scheme 1**

## RESULTS AND DISCUSSION

First, a 1.0:1.2:1.4 mixture of acetophenone, sulfur, and morpholine was sonicated under various sets of conditions. The best results were obtained in the presence of no solvent, leading to the formation of 1-morpholino-2-phenylethanethione **2a** only after 10 min of sonication (Table 1, entry 1). The solid product was extracted from the reaction mixture and recrystallized from diethyl ether. Control experiments showed the crucial role of the ultrasonic irradiation in the reaction and excluded the effect of a possible simultaneous thermal activation. In other words, when the same reaction was conducted at a constant temperature of 25 ± 1° C, comparable results were obtained but after 5–6 min of excess sonication. Alternatively, in the absence of irradiation, no formation of **2a** was noticed. To show the diversity of the method, other derivatives of acetophenone-bearing electron-releasing (entries 2–5), electron-withdrawing (entries 6–11), and naphthyl substituents (entry 12) were used. In all cases, the desired products were obtained in good yields. In addition, the rates of all reactions were relatively high and not much relation between the activities and the physical specifications of the starting acetophenones could be concluded.

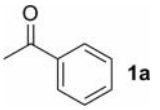
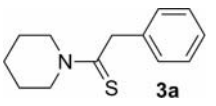
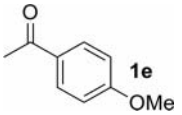
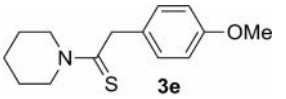
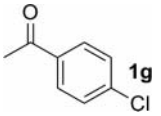
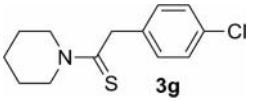
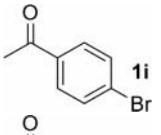
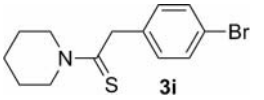
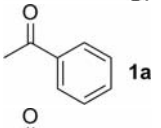
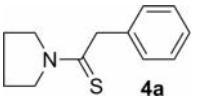
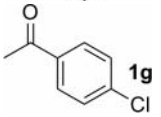
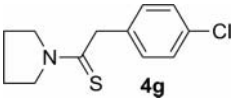
To further study the generality of the method, similar reactions were conducted using other amines (piperidine and pyrrolidine) and various acetophenone derivatives bearing different substituents, as shown in Table 2. These reactions led to relatively lower yields of the respective products within comparable time periods. This lower reactivity to participate in Willgerodt–Kindler reactions is usual for these amines and has been often observed by other researchers.[24,26,27]

**Table 1** Ultrasound-promoted Willgerodt–Kindler reactions with morpholine

| Entry | Substrate | Product | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  1a |  2a | 10 | 82 (Yadav et al., 2007)[11] |
| 2 |  1b |  2b | 15 | 75 (Yadav et al., 2007)[11] |
| 3 |  1c |  2c | 25 | 75 (Giordano et al., 2005)[5b] |
| 4 |  1d |  2d | 25 | 65 (Yadav et al., 2007)[11] |
| 5 |  1e |  2e | 15 | 65 (Yadav et al., 2007)[11] |
| 6 |  1f |  2f | 15 | 70 (Harrowven et al., 1999)[22] |
| 7 |  1g |  2g | 20 | 82 (Yadav et al., 2007)[11] |
| 8 |  1h |  2h | 20 | 84 (Rolfs and Liebscher, 1994)[23] |
| 9 |  1i |  2i | 20 | 80 (Yadav et al., 2007)[11] |
| 10 |  1j |  2j | 25 | 78 (Present work) |
| 11 |  1k |  2k | 20 | 85 (Yadav et al., 2007)[11] |
| 12 |  1l |  2l | 20 | 75 (Yadav et al., 2007)[11] |

[a]Isolated yields.

**Table 2** Ultrasound-promoted Willgerodt–Kindler reactions with other amines

| Entry | Substrate | Product | Time (min) | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  | 15 | 55 (Lee et al. 1988)[25] |
| 2 |  |  | 20 | 40 (Lee et al. 1988)[25] |
| 3 |  |  | 25 | 52 (Lee et al. 1988)[25] |
| 4 |  |  | 25 | 54 (Cornea et al. 1980)[26] |
| 5 |  |  | 10 | 68 (Sundberg et al. 1981)[27] |
| 6 |  |  | 15 | 60 (Rolfs and Liebscher 1994)[23] |

[a]Isolated yields.

In conclusion, we have reported a facile non-thermal Willgerodt–Kindler reaction using a sonochemical method. The reactions complete within a few minutes, yields are relatively high, no solvent or extra additive is required during the course of the reactions, and the method is environmentally safe. A comparison of the results with some other related methods is provided in Table 3, where the Willgerodt–Kindler reaction of acetophenone with morpholine is chosen as a standard reaction to show the advantages of the method. It could be concluded from the table that the reaction reaches completion within a relatively short time period as opposed to long-time high-temperature treatment required in thermal methods.

**Table 3** Comparison of the present work with some other related methods for the reaction of acetophenone with morpholine and sulfur

| Entry | Condition | Time | Yield (%) | Reference |
|---|---|---|---|---|
| 1 | Ultrasound irradiation | 10 min | 82 | Present work |
| 2 | Ionic liquid/110°C | 3 h | 92 | Yadav et al. (2007)[11] |
| 3 | Reflux | 20 h | 66 | Liu et al. (2006)[28] |
| 4 | *p*-$MeC_6H_4SO_3H$/120°C | 6 h | 41 | Giordano et al. (2009)[5a] |
| 5 | Microwave irradiation | 4 min | 50 | Nooshabadi et al. (1999)[12] |
| 6 | Quinoline/123°C | 2 h | 90 | Carison et al. (1986)[9] |
| 7 | 4-Me-morpholine/DMF/135°C | 6 h | 67 | Poupaert et al. (2004)[29] |

## EXPERIMENTAL

### General

The reactions were monitored by thin-layer chromatography (TLC). Fourier transform infrared (FT-IR) spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions were reported as wave numbers ($cm^{-1}$). Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ solutions on a FT-NMR Bruker Ultra Shield™ (500 MHz) instrument and the chemical shifts were expressed as $\delta$ units, with $Me_4Si$ as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at an ionization potential of 70 eV. All chemicals and reagents were purchased from commercial sources and were used without further purification. Sonication was performed using a Sartorius Ultrasonic-Homogenizer LABSONIC®P 230V/50 Hz instrument with a frequency of 24 KHz and a nominal power of 460 $W/cm^2$. The intensity level of irradiation was adjusted at the 80% level for the synthesis of the products. In all reactions, the tip of the sonotrode was located in the same position—just under the liquid surface—in order to obtain optimal sonication and reproducible results.

### Typical Procedure

A mixture containing an acetophenone derivative (2 mmol), sulfur (77 mg, 2.4 mmol), and morpholine (244 mL, 2.8 mmol) was sonicated in a 10-mL test tube for an appropriate length of time (as indicated in Table 1) until TLC showed complete disappearance of the starting materials. In the temperature-controlled experiments, reactions were performed in a water bath at $25 \pm 1^\circ$ C. After completion of the reactions, mixtures were diluted with diethyl ether and washed with brine. The organic phase was then dried by filtering through a short column of $Na_2SO_4$. The pure products were obtained either by recrystallization (in ether) or flash column chromatography of the residue (using a 1:4 mixture of EtOAC/hexane over silica gel). Products were identified based on their melting points and spectral data. Known structures were verified by comparison of their data with those reported in the literature.

### Spectral Data for the New Compound

**2-(4-Iodophenyl)-1-morpholinoethanethione (2j)**: m.p. 93–94° C; IR (KBr, $cm^{-1}$) 1498, 1109; $^1$H NMR ($CDCl_3$) $\delta$ 3.48 (t, $J = 5$ Hz, 2H), 3.65 (t, $J = 5$ Hz, 2H), 3.78 (t, $J = 5$ Hz, 2H), 4.31 (s, 2H), 4.38 (t, $J = 5$ Hz, 2H), 7.12 (d, $J = 8$ Hz, 2H), 7.69 (d, $J = 8$ Hz, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 50.3, 50.5, 51.2, 66.6, 66.8, 92.9, 130.3, 135.9, 138.4, 199.6; MS m/z (%) 347 ($M^+$, 25), 260 (12), 217 (15), 134 (74), 89 (100); Analysis calculated for $C_{12}H_{14}INOS$: C, 41.51; H, 4.06; N, 4.03. Found: C, 41.80; H, 4.09; N, 4.08.

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