

## SYNTHESIS OF ALIPHATIC THIOMORPHOLIDES BY WILLGERODT–KINDLER REACTION UNDER SOLVENT-FREE CONDITIONS

KIOUMARS AGHAPOOR, HOSSEIN REZA DARABI\*, KOUROSH TABAR-HEYDAR  
and LEILA NAKHSHAB

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

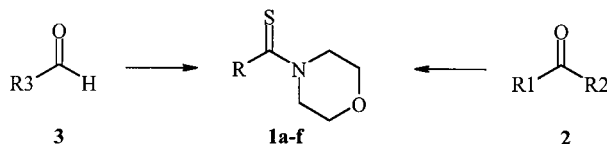
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The Willgerodt–Kindler reaction of aliphatic ketones and aldehydes with sulfur and morpholine under solvent-free conditions was performed in a domestic microwave oven. The method is simple, rapid and avoids prolonged heating with solvents.

**Keywords:** Aliphatic thiomorpholides; Willgerodt–Kindler reaction; Microwave activation; Solvent-free condition

In recent years, thioamides have often appeared in the literature as versatile intermediates in medicinal and organic chemistry [1–5]. They have also attracted attention in the field of peptide chemistry [6, 7]. Synthesis of thioamides have been accomplished in a number of ways. The Willgerodt–Kindler reaction is a well known method for the synthesis of thioamides [8]. In their original form, aryl alkyl ketones react with sulfur and secondary amines to give, via oxidation and rearrangement, terminal thioamides.

Our initial goal was to investigate the Willgerodt–Kindler reaction of aryl alkyl ketones under microwave irradiation. We have reported that carrying out the Willgerodt–Kindler reaction of aryl alkyl ketones in the microwave oven, under solvent-free conditions, enhances the reaction rate as compared to its conventional method together with an improved yield [9]. In continuation of our investigation of this reaction, we have also studied various substrates, in order to propose a reaction mechanism [10, 11].



The present study is focused on the Willgerodt–Kindler reactions of aliphatic ketones and aldehydes having not been studied in the literature, to our best knowledge, under microwave heating and solvent-free conditions. In a classical approach, a solution of aliphatic ketones

\* Corresponding author. E-mail: darabi@ccerci.ac.ir

TABLE I The Microwave-assisted Synthesis of Aliphatic Thiomorpholide **1a–f** under Solvent-free Conditions.\*

Entry	Substrates <b>2</b> and <b>3</b>	Substrate:sulfur: morpholine	Time (s)	Products <b>1</b>	
				R	Yield (%)
1	CH <sub>3</sub> CH <sub>2</sub> COCH <sub>3</sub>	1:2:1.5	180	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	70
2	CH <sub>3</sub> CH <sub>2</sub> COCH <sub>3</sub>	1:2:2	180	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	89
3	CH <sub>3</sub> CH <sub>2</sub> COCH <sub>3</sub>	1:2:3	180	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	85
4	CH <sub>3</sub> COCH <sub>3</sub>	1:2:2	180	C <sub>2</sub> H <sub>5</sub>	40
5	CH <sub>3</sub> CH <sub>2</sub> COCH <sub>2</sub> CH <sub>3</sub>	1:2:2	180	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	70
6	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> COCH <sub>3</sub>	1:2:2	180	<i>n</i> -C <sub>7</sub> H <sub>15</sub>	75
7	CH <sub>3</sub> CHO	1:2:2	90	CH <sub>3</sub>	68
8	CH <sub>3</sub> CH <sub>2</sub> CHO	1:2:2	90	C <sub>2</sub> H <sub>5</sub>	85
9	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> CHO	1:2:2	90	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	83
10	(CH <sub>3</sub> ) <sub>2</sub> CHCHO	1:2:2	90	iso-C <sub>3</sub> H <sub>7</sub>	91

\*The reactions were monitored by TLC and the product identified by GC-Mass and NMR. (GC-Mass Analysis: A fisons instruments gas chromatograph 8000 equipped to mass detector (trio 1000) with 70 ev was used. A 60 m × 0.25 mm column packed with WCOT fused silica CP-sil 5CB was employed, the carrier gas was helium and inlet pressure was 14 psi.)

were reacted with morpholine and sulfur in DMF at 110–130°C for 2–3 h and gave moderate yields of thiomorpholide (53–56%) [12].

The reaction conditions and yields of the product thiomorpholides **1a–f** are given in Table I. In order to find the optimal reaction conditions, we chose methyl ethyl ketone and some selected molar ratio of ketone: sulfur: morpholine, as shown in Table I. The effects of the sulfur:morpholine ratio on the reaction rate and yield of **1c** are clear. While the reaction of methyl ethyl ketone with sulfur and morpholine in molar ratio of 1:2:1.5 gives 70% yield, the best yield (89%) was obtained under an otherwise similar reaction with the molar ratio of 1:2:2 (entries 1–3).

A surprising result was observed in the reaction of acetone (entry 4). When acetone was heated under microwave conditions, the corresponding thiomorpholide **1b** was isolated in 40% yield. This low yield of product **1b** is due to the formation of other by-products [13].

As shown in Table I, the easier reaction of alkanals, relative to alkanones, is due to their terminal carbonyl group, which is without further rearrangement on carbon chains, and the corresponding thiomorpholide is formed.

The structures of all of the thiomorpholides were confirmed by mass spectra and NMR spectral data as shown in Table II. The thiocarbonyl group (C=S) was observed between 199 ppm and 211 ppm in the <sup>13</sup>C NMR spectra.

TABLE II Selected Spectral Data and Melting Point of Thiomorpholide **1a–f**.

Entry	R	<i>m.p.</i> (°C)	NMR (CDCl <sub>3</sub> /TMS), δ [ppm]		MS (EI, <i>m/z</i> )
			<sup>13</sup> C (C=S)	<sup>1</sup> H (morpholine)	
<b>a</b>	CH <sub>3</sub>	90 (90–92) <sup>14</sup>	199	3.65 (6H), 4.21 (2H)	145
<b>b</b>	C <sub>2</sub> H <sub>5</sub>	oil	203	3.70 (6H), 4.23 (2H)	159
<b>c</b>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	42 (40–42) <sup>12</sup>	206	3.75 (6H), 4.30 (2H)	173
<b>d</b>	iso-C <sub>3</sub> H <sub>7</sub>	40 (39–41) <sup>12</sup>	211	3.80 (6H), 4.40 (2H)	173
<b>e</b>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	oil	205	3.80 (6H), 4.34 (2H)	187
<b>f</b>	C <sub>7</sub> H <sub>15</sub>	34 (33–34) <sup>15</sup>	204	3.75 (6H), 4.35 (2H)	230

## GENERAL PROCEDURE

**Caution:** Experiments should be carried out in an efficient hood to avoid exposure to noxious vapors of hydrogen sulfide.

In a typical experiment, a mixture of ethyl methyl ketone (1 mmol) and sulfur (2 mmol) and morpholine (2 mmol) in an open Pyrex glass flask was exposed to microwave irradiation at 650 W for 3 minutes [16]. After cooling, the reaction product **1c** was purified on silica gel chromatography [petroleum ether–ethylacetate (3:1)] and recrystallized in ethanol (80%).

Thiomorpholide **1c**: mp: 42°C;  $^1\text{H}$  NMR (90 MHz,  $\text{CDCl}_3$ )  $\delta$  1.02 (t, 3H), 1.68 (m, 2H), 2.83 (t, 2H), 3.75 (m, 6H), 4.30 (m, 2H);  $^{13}\text{C}$  NMR (22.5 MHz,  $\text{CDCl}_3$ )  $\delta$  13.6, 23.5, 43.4, 49.8, 50.1, 66.3, 66.4, 206.2; IR (KBr) [ $\text{cm}^{-1}$ ] 2985, 1480; MS (EI),  $m/z$  (rel. intensity %) 173 ( $\text{M}^+$ , 70), 158, 144, 130, 86.

The products **1a–f** are generally pure as judged by TLC, GC-MS and NMR analysis.

Further studies of the Willgerodt–Kindler reaction of new substrates are now in progress in our laboratory to elucidate the reaction mechanism.

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- [16] The microwave oven used for this study was a domestic National model NN-6755 with 7 power settings (90–900 W).



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