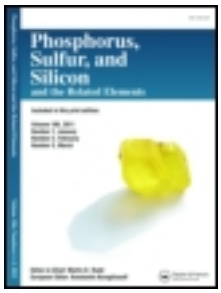

Phosphorus, Sulfur, and Silicon and the Related Elements

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# Synthesis of Phenylthioacetomorpholide: Effect of Substrate on the Willgerodt-Kindler Reaction

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# SYNTHESIS OF PHENYLTHIOACETOMORPHOLIDE: EFFECT OF SUBSTRATE ON THE WILLGERODT-KINDLER REACTION

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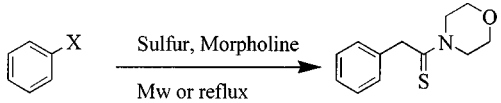
*The effect of substrates on the Willgerodt-Kindler reaction was studied. The existence of acidic protons on these substrates accerelates the formation of thiomorpholide was found.*

*Keywords:* Phenylthioacetomorpholide; the Willgerodt-Kindler reaction

Considering high usage potential of thioamides as intermediates in medicine and organic synthesis,[1–4] we believe that the limited application of the Willgerodt-Kindler will be sharply increased if the synthetic problems are overcome.[5]

Recently, we showed the efficiency of microwave heating for the Willgerodt-Kindler reaction of aryl alkyl ketones, compare to conventional heating.[6] In that article, we optimized the reaction by examination of parameters, such as the ratio of sulfur and morpholine to substrates and the time of irradiation.




**1a-1g** **2**

Here, in an effort to throw light on the substrate effect, we selected substrates, which contain different functional groups. All of the

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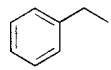
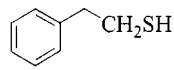
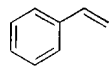
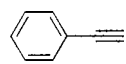
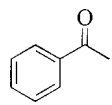
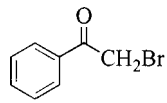
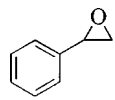
substrates have the same number of carbon atoms in their skeleton and are expected, under the same reaction conditions, to give product **1**. Among these substrates, to the best of our knowledge, the Willgerodt-Kindler reaction of only three compounds **1c–1e** were studied by us and others.[5–10]

We carried out the reactions under both microwave and classical heating. The reaction conditions and yields are given in Table I. The conclusions, which we have been able to draw from these data are:

**TABLE I** The Willgerodt-Kindler Reaction of the Substrates **1a–1g** with Morpholine and Sulfur[a]

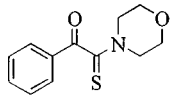
| | | Yield of **2** (%) | |
|---|---|---|---|
| Entry | Substrates **1** | MW[b] | Reflux[c] |
| a |  | 14 | 11 |
| b |  | 90 | 77 |
| c |  | 82 | 52 |
| d |  | 93 | 63 |
| e |  | 88 | 62 |
| f |  | 8 | 5 |
| g |  | 40 | 27 |

[a]The reactions were monitored by TLC and the product identified by GC-Mass[8] 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 5 CB was employed. Carrier gas was helium and inlet pressure was 14 psi.)

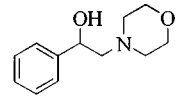
[b]The reaction mixture was exposed to microwave irradiation at 900 W for 4 min.

[c]The reaction mixture was refluxed for 2 h.

1. The compounds **1b–1e** give excellent yield of phenylthioacetomorpholide **2**.
2. Although the thiolation of **1a** is very difficult, the thiolated ethylbenzene, **1b**, is very active and gives **2** in excellent yield.
3. Phenylacetylene **1d** is much more acidic than styrene **1c**, which in turn is more acidic than ethyl benzene **1a**. This effect on the yield of product is clear.
4. Hydrogens at $\alpha$-position of carbonyl group of **1e** are acidic, which can be thiolated easier than that of ethyl benzene **(1a)**. This fact shows the carbonyl group serves to activate the $\alpha$-carbon.
5. The reaction of **1f** easily gave compound **3** as a main product in excellent yield. The reaction proceeds even at room temperature. It shows that existence of a leaving group at the $\alpha$-position of the carbonyl group accelerates the nucleophilic substitution.
6. In the case of epoxide **1g**, the low yield of the product **2** is due to formation of by-product **4**. The substrate undergoes the nucleophilic substitution and gives **4** in 42% yield.




**3**




**4**

In the case of **1e**, a GLC analysis of the reaction mixtures, conducted at room temperature, at various time intervals shows that the amount of **3** is higher than that of **2** up to first 2 h. It gradually decreased during 24 h. These facts show that carbonyl group is left, at first, intact and therein reduced to a methylene group by $H_2S$ in the final step.

Finally, we concluded the existence of a leaving group or acidic protons may accelerate the reaction.

Further work on the Willgerodt-Kindler reaction is in progress to extend the scope of the reaction by the use of different substrates.

## GENERAL PROCEDURE

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

In a typical experiments, a mixture of **1b** (2 mmol), morpholine (6 mmol), and sulfur (4 mmol) in an open pyrex glass flask was exposed to microwave* irradiation at 900 W for 4 min. After cooling, the

*The microwave oven used for this study was a domestic National Model NN-6755 with 7 power settings (90-900 W).

reaction product **2** was purified by silica gel chromatography by eluting with petroleum ether-ethyl acetate (8:2). The fractions were monitored by TLC.

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