Interesting Behavior of Acetone under the Willgerodt-Kindler Reaction Conditions

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A one-pot synthesis of thiomorpholides **1 – 3** is introduced. The Willgerodt-Kindler reaction of acetone with sulfur and morpholine gives selectively one of the products **1 – 4** depending upon the proper choice of the reaction condition. The formed products are strongly dependent on the experimental conditions. The pathways of the reaction toward the formation of each product are also proposed.

Key words: Acetone, Willgerodt-Kindler Reaction, Thiomorpholides

Introduction

Since thioamides have found widespread applications as versatile intermediates in medicine and organic synthesis [1 – 4], their syntheses have attracted attention in the various field of chemistry [5 – 8]. Although many different methods to prepare thioamides have been reported in the literature [9], the Willgerodt-Kindler reaction has so far found little attention. It has a rather bad reputation for not being very useful for preparative purpose due to the high reaction temperatures and long reaction periods together with poor yields [10]. In its original form, straight- or branched-chain aryl alkyl ketones were found to react with sulfur and secondary amines to give the terminal thioamides as a result of oxidation and rearrangement. The reaction is of wide scope and can be conducted with a variety of substrates and under different reaction conditions [10]. In some cases, unlike the normal Willgerodt-Kindler reaction, the carbonyl group has remained in the skeleton of the thioamide. Two factors have been suggested to keep the carbonyl group intact; one is the steric effect in hindered ketones [11] and the second is the donor group effect in adjacent to the carbonyl group [12].

In continuation of our investigation on this reaction [13 – 16], acetone has attracted our attention because it is of special interest due to the existence of acidic α-carbon at both side of its carbonyl group. Among four possible products **1 – 4**, to the best of our knowledge, synthesis of dithiomorpholide **4** was reported during the reaction of acetone with morpholine and sulfur in DMF at 80 °C for 1 h in 53% yield (Table 1, entry 1) [12].

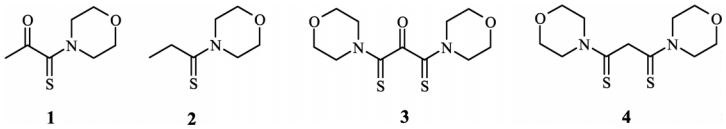
Herein, in an effort to improve the usefulness of the Willgerodt-Kindler reaction of acetone and to throw light on the reaction pathway, we have made a full study of the effects of the heating mode, time of reaction, and proportions of reagents to acetone, DMF, and water effect on the reaction.

There is, to the best of our knowledge, no report on the direct synthesis of **1 – 3** from the acetone. However, dithiomorpholide **3** has been prepared from the treatment of 1,3-dichloroacetone with morpholine and sulfur in DMF at room temperature in 31% yield [17]. Moreover, thiomorpholide **1** has been prepared from α-substituted acetone in 52% yield [17].

Result and Discussion

Optimization of the reaction

In order to find the optimal reaction conditions, we have considered several possible variations (*e.g.*, heating mode, time of reaction, proportions of reagents to acetone, and solvent effect), which may influence potentially on the reaction. Since the detailed mechanism of the reaction is not known, one cannot exclude interactions between the experimental variables. Therefore, any attempts at optimizing the reaction must make use of multivariate optimization strategies because adjusting one variable at a time usually fails to attain a true optimum in this reaction. The optimal condition of each product was achieved *via* several examinations and combination of these variations. The crude reac-



1 **2** **3** **4**

Scheme 1.

Table 1. Reaction conditions for the selective preparation of products **1 – 4**[a].

Entry	Reagents ratio[b]	Solvent	Reaction temperature	Time (min)	Yield (%)[c]				Ref.
					1	**2**	**3**	**4**	
1	1:5:4	DMF	80 °C	60	–	–	–	53	12
2	1:5:4	DMF	MW[d]	5	–	82	–	–	
3	1:2:2	–	25 °C	1440	71	3.5	1	–	
4	1:5:4	H_2O	80 °C	180	35	–	51	–	
5	1:5:4	H_2O	MW	5	7	–	73	–	

[a] The reactions were monitored by TLC and the products identified by GC-MS and NMR; [b] reagents = acetone: sulfur: morpholine, [c] yields are based on GC-MS analysis; [d] MW = microwave heating.

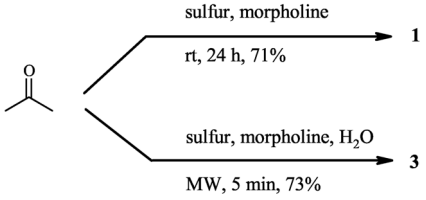
tion mixtures were directly analyzed by GC-MS and/or subjected to column chromatography. The identification of the isolated products was generally performed by ^{1}H NMR and MS spectral analyses. Table 1 lists some selected reaction conditions.

In an effort to optimize the order of addition of substrate and reagents in the reaction mixture, we considered the following five possible reaction sequences (acetone: sulfur: morpholine = 1:5:4): In the first set, a mixture of morpholine and acetone was stirred at 20 °C and then sulfur and DMF were added and stirred for 18 h at 20 °C. A mixture of **1** (50%) and **2** (11%) were prepared. In the second set, a mixture of DMF, acetone and morpholine was stirred at 20 °C and then sulfur was added. The mixture was heated for 2 h at 80 °C and gave **2** (43%) and **4** (56%). In the third set, acetone was added to a mixture of DMF, sulfur and morpholine and heated for 2 h at 80 °C and gave **2** (57%). In the fourth set, a mixture of DMF, sulfur and acetone was stirred for 2 h at 20 °C, and then morpholine was added to it. This mixture was heated for 2 h at 80 °C and gave **2** (57%). In the fifth set, acetone and, the reagents (sulfur, morpholine) were added to DMF and then the mixture was stirred for 12 h at 20 °C to give **2** in 80% yield.

We found some amounts of thioamide byproduct derived from dimethylamine as impurities, in all experimental sets except the fifth one, because of DMF decomposition. In the fourth set, this impurity was high.

Synthesis of thioamide **1**

Our initial experiment was carried out based on the last experimental set. Conducting the reaction at 20 °C



Scheme 2.

may offer the possibility of obtaining one product selectively. When the solvent-free reaction was carried out at room temperature for 24 h, thioamide **1** was formed as a major product, as judged by GC-MS measurement (Scheme 2, entry 3). The product **1** was separated chromatographically.

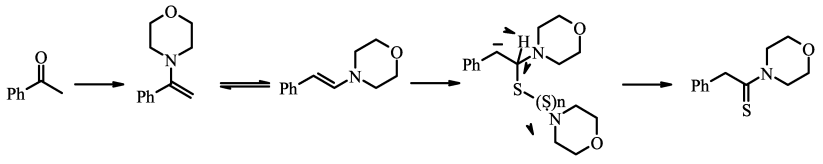
In addition to **1**, small amounts of **2** and **3** were detected on GC-MS analysis (**1**:**2**:**3** = 70:3.5:1). Under higher energy conditions, such as microwave heating or reflux, **1** was converted to **3** completely.

Synthesis of thioamide **2**

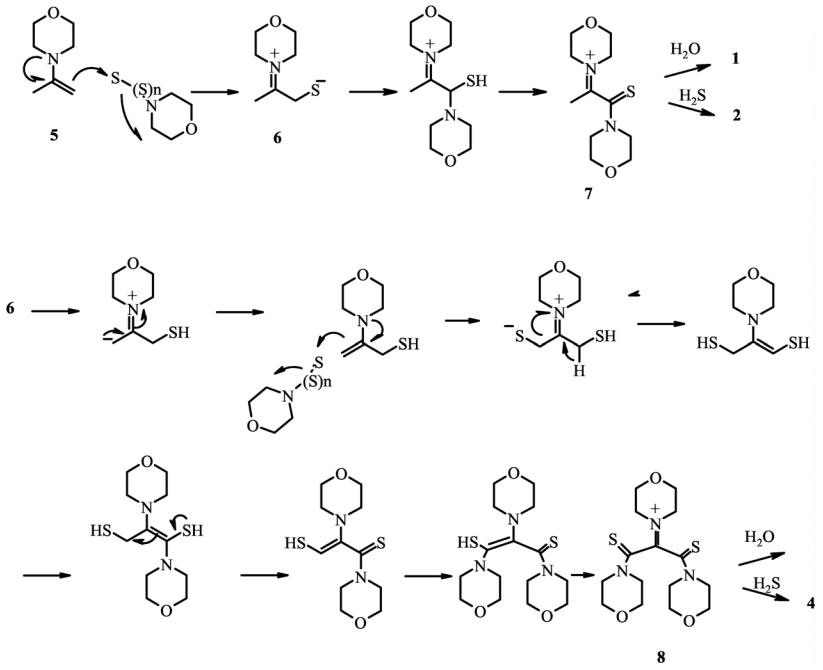
Viehe and co-workers have reported that the refluxing reaction of acetone with morpholine and sulfur in DMF gave dithiomorpholide **4** as the sole product (Table 1, entry 1) [12]. Surprisingly, when the reaction was carried out under microwave heating, the product **2**, instead of **4**, was obtained in 82% yield as the major product (Table 1, entry 2). When the excess of morpholine (10 equivalents) was employed a somewhat higher yield of product was obtained; however, the purity of the isolated thioamide **1** did not improve. The similar reaction in absence of DMF gave thiomorpholide **2** in 40% yield together with dithiomorpholide **3** in 45% yield [16]. These results show that DMF is an important parameter in the formation of products **2** and **4**.

Synthesis of dithioamide **3**

The optimum condition for product **3** appears to be the solvent-free reaction of acetone. Under microwave heating for 5 min, **3** was obtained in 73% yield (Scheme 2, entry 5). As we mention later, the first stage of this reaction is the formation of enamine and water. This water in the reaction mixture should have an effect on the formation of **1** and **3**, because it may retain the carbonyl group unchanged. Entry 4 in Table 1 con-



Scheme 3.



Scheme 4.

firms the strong effect of water in the reaction: When the reaction was carried out at 80 °C for 3 h in presence of water, it gave the products **1** and **3**.

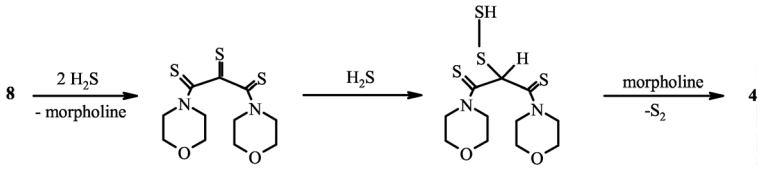
Reaction pathway

The mechanism of the Willgerodt-Kindler reaction has been the subject of much discussion and, although many suggestions have been put forward, no single mechanism accounts for all of the observations [10, 18, 19]. We feel that further extensions of the Willgerodt-Kindler reaction may be of assistance in elucidating the mechanisms of this reaction.

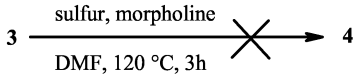
As shown in Scheme 3, Carmack has proposed a possible mechanism for the formation of simple thioamides, such as 2 [20]. Although the formation **2** is completely in agreement with this proposition, it is probably unreasonable to expect a single mechanism for this reaction to form all products **1** – **4**.

In line with numerous publications, we believe that reversible enamine formation is the first step of the reaction of ketones. When we examined the reaction of acetone and morpholine at room temperature, the enamine **5** was detected as determined by GC-MS technique in 65% yield. The solvent-free reaction of enamine **5** with sulfur under microwave heating for 3 min, gave a mixture of products **1** (39%), **2** (25%), **3** (7%) and **4** (1.5%). When we treated enamine **5** with sulfur in presence of water, products **1** and **3** were obtained in 39% and 10% yield, respectively. The reaction of enamine **5** with sulfur and morpholine at DMF for 2 h at 80 °C gave products **2** and **4**, in 60 and 30% yield, respectively. These results show that the presence of water in the reaction mixture will retain the carbonyl group unchanged. Therefore, DMF can trap water and deactivates its effect on the reaction.

To answer the question whether a carbonyl group alone could be reduced to a methylene group, dithiomorpholide **3** was subjected to the same reaction condition. Treatment of **3** with sulfur and morpholine, under similar reaction conditions, failed to give **4** (Scheme 6).



Scheme 5.



Scheme 6.

We conclude that formation of **4** should pass through the formation of intermediate **8**. This result supports our suggested reaction pathway. The probable pathway of this reaction is outlined in Schemes 4 and 5.

In contrast to **3**, when **2** was subjected to the similar reaction conditions, a mixture of products **2** and **4** was formed. Therefore, we found that existence of hydrogen(s) on α-carbon at least on one side of the carbonyl group is necessary not only to promote the reaction but also to reduce the carbonyl group to a methylene group. While reduction of imines **7** or **8** in the presence of hydrogen sulfide may give products **2** and **4**, their oxidation by water leads to formation of products **1** and **3**. Therefore, attack on α-carbon is common to this reaction. Hydrogen sulfide can be produced from the morpholine/sulfur mixtures [21]. As shown in Scheme 5, the reduction of the iminium ion **7** or **8** to the methylene group can occur by the exothermic desulfurization of C=S group with H_2S in the presence of amines [19]. The results show that at any time subsequent to formation of enamine **5**, the initial attack at the α-carbon could occur.

In conclusion, we optimized the one-pot synthesis of products **1 – 3** from acetone together with the development of a general mechanism of the Willgerodt-Kindler reaction.

Experimental Section

Morpholine was purified by refluxing for 24 h over sodium and distillation. Anhydrous acetone and purified sulfur was used. A GC-MS method for the analysis of mixtures was applied; a Fisions instruments gas chromatograph 8000 connected to a 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 the inlet pressure was 14 psi.

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

Preparation of enamine **5***:* 1.16 g (20 mmol) of acetone was warmed with 3.48 g (40 mmol) of morpholine in 50 ml of DMF at 30 °C for 8 h. When the mixture was analyzed by GC-MS, it was found to consist of acetone (10%) in addition to the expected enamine **5** (65%).

Reaction of enamine **5** with sulfur and morpholine: 1.27 g (10 mmol) of enamine **5** was heated with 1.28 g of sulfur (40 mmol) and 4.35 g (50 mmol) of morpholine in 50 ml of DMF at 80 °C for 1 h. The products **2** and **4** were formed as determined by GC-MS.

Preparation of **1***:* Acetone (0.58 g, 10 mmol) was heated with sulfur (0.64 g, 20 mmol) and morpholine (1.74 g, 20 mmol) at 20 °C for 8 h. The reaction was monitored by GC showing 71% yield. The reaction mixture was purified by flash chromatography on silica gel using hexane-ether (1:1) and gave pure product **1** in 67% yield. M.p. 149 – 151 °C. – ^{1}H NMR (90 MHz, $CDCl_3$): $\delta = 2.46$ (s, 3H), 3.65 (m, 6H), 4.20 (d, 2H). – MS (EI): m/z (%) = 173 (15) [M^+], 130 (30), 115 (15), 86 (45), 43 (100).

Preparation of **2***:* A mixture of 0.58 g (10 mmol) of acetone and 1.60 g (50 mmol) of sulfur and 3.12 g (40 mmol) of morpholine in 10 ml of DMF was exposed to microwave irradiation for 5 min. The reaction was monitored by GC showing 82% yield. The reaction mixture was purified by flash chromatography on silica gel using hexane-ether (2:1) and gave pure product **2** in 76% yield [16].

Preparation of **3***:* A mixture of acetone (0.58 g, 10 mmol) and sulfur (1.60 g, 50 mmol) and morpholine (3.12 g, 40 mmol) in presence of a trace amount of water was exposed to microwave irradiation for 5 min. The reaction was monitored by GC showing 73% yield. The product was purified by flash chromatography on silica gel using ether as eluent to afford **3** as a yellow solid. After recrystallization from ethanol, the pure product **3** was obtained in 55% yield.

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