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Short Communication

The *Willgerodt-Kindler* Reaction in Water: High Chemoselectivity of Benzaldehydes over Acetophenones

Kioumars Aghapoor, Farshid Mohsenzadeh, Golriz Khanalizadeh, and **Hossein R. Darabi***

Chemistry & Chemical Engineering Research Center of Iran, Tehran, Iran

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Summary. Water has been found for the first time as a useful solvent in the *Willgerodt-Kindler* (*WK*) reaction for the synthesis of benzothiomorpholides in high yield at 80°C for 3 h. This novel approach confronts the *WK* protocol with a new situation in which water not only is not regarded as a serious disadvantage but also is applied in this case as a useful solvent in the reaction. The basis of this finding is the presence of a methylene chain in the carbonyl substrates, which leads to the high reaction selectivity of benzaldehydes over acetophenones.

Keywords. *Willgerodt-Kindler* reaction; Selective thioamidation; Water.

Introduction

The three-component *Willgerodt-Kindler* (*WK*) reaction is well known as an important method for the synthesis of thioamides [1, 2]. In the original reaction, an aryl alkyl ketone or aryl aldehyde can be reacted with sulfur and a primary or secondary amine, and the product is the terminal thioamide **1** or **2** (Fig. 1) [1]. The importance of thioamides and their widespread applications as versatile intermediates in medicine and organic synthesis [3–7] have enlarged the synthesis utility of the *WK* reaction. In contrast, as the *WK* reaction is extendable to several substrates bearing various functional groups, such as alkynes, alkenes, nitriles, or amines, the range of synthetic routes toward the thioamides **1** and **2** becomes extended [1, 8–15].

One of the *WK* drawbacks is the presence of water in the reaction mixture, which retains the carbonyl group of substrate unchanged and leads to the formation

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

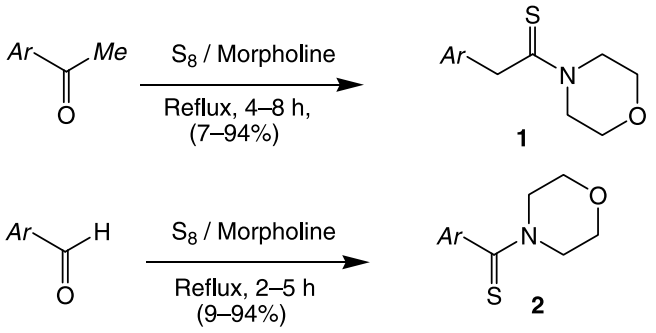


Fig. 1. The synthesis of terminal thioamides **1** and **2** under the *WK* reaction

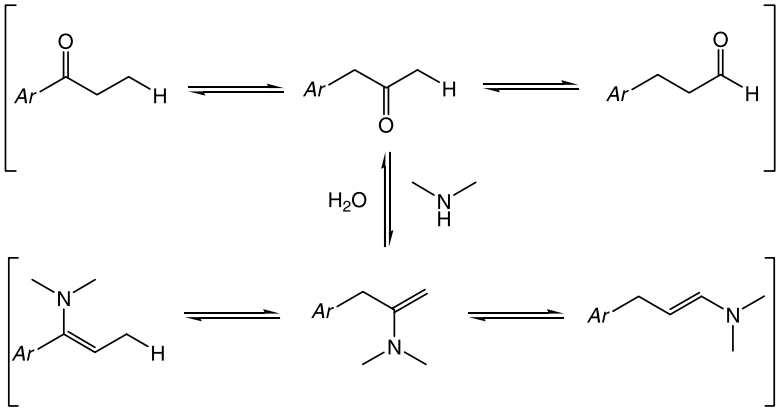


Fig. 2. Isomerization and the effect of water on enamines

of undesired by-product [11, 16]. Generally, it is often commented that all the experiments have to be carried out under anhydrous conditions. The excellent work by *Carmack et al.* [16, 17] has proved this claim and demonstrated that enamine as an intermediate plays a critical role in the migration of a carbonyl group back and forth along a chain of methylene units *via* a facile isomerization. This intermediate is unstable in the presence of water and hydrolyzes to the corresponding carbonyl substrate as shown in Fig. 2.

As was noted in several publications, benzaldehydes give consistently higher yields than acetophenones under anhydrous conditions in shorter periods of time [12–15]. The reason appears only to be explained by the presence of a methylene moiety in the carbonyl substrates.

In embracing the reaction principles and considering the important role of water and as well methylene units, and in continuation of our investigation on this reaction [8, 11, 14] we report a generally new approach to the synthesis of benzothioamides in water. Among various thioamides, the benzothioamide moiety in particular appears to be an interesting pharmacophore in medicinal chemistry, with widespread applications including estrogen receptor antagonists [18], antifungal [19] and antibacterial agents [20], and aldose reductase inhibitors [21]. Therefore, the development of an effective *WK* method for the synthesis of benzothioamides in aqueous media seems to be an important challenge.

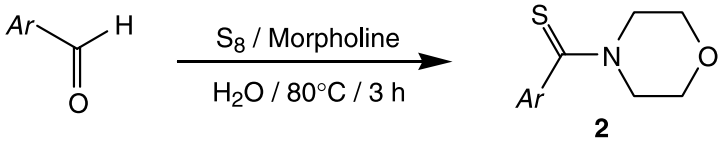
Results and Discussion

We first studied the *WK* reaction of benzaldehyde by screening the reaction conditions in water. In this study, morpholine as a secondary amine was applied because it has greater resistance to oxidation [22]. In an optimized experiment in water, benzaldehyde was treated with 3 equiv. of sulfur and morpholine at 80°C. The reaction resulted in the formation of the corresponding thioamide **2** after 3 h (Table 1, entry 1, 85%).

These preliminary results led us to extend the scope of the new synthesis system to various substrates. The data in Table 1 clearly show that the reaction of benzaldehyde derivatives in water gives the corresponding thioamides **2** (Table 1, entries 1–6) in high yields. The yields are highly dependent on the substrate used. For instance, aromatic heterocyclic substrates gave lower yields (Table 1, entries 7 and 8).

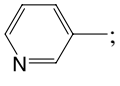
In sharp contrast, acetophenone, as expected, completely failed to produce the corresponding thioamide **1** under the same reaction conditions. This result

Table 1. The *WK* reaction of benzaldehydes in water



2

Entry	Product **2**[a, b, c]	Yield/%[d]
1	*Ph*.CS.*M*	85
2	4-*Me*.*Ph*.CS.*M*	84
3	4-*Me*O.*Ph*.CS.*M*	85
4	4-*Et*O.*Ph*.CS.*M*	83
5	4-Cl.*Ph*.CS.*M*	81
6	4-Me_2N.*Ph*.CS.*M*	86
7	*Py*.CS.*M*	70
8	*Th*.CS.*M*	55

[a] *M* =  ; [b] *Py* =  ; [c] *Th* =  ; [d] isolated yields

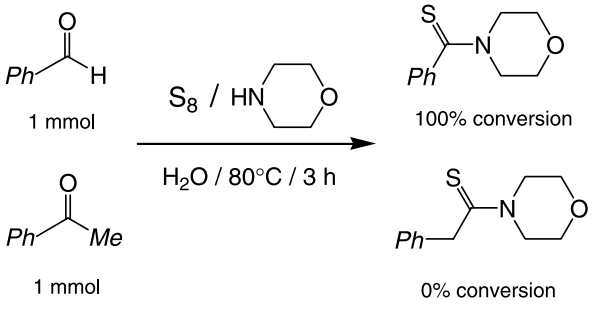
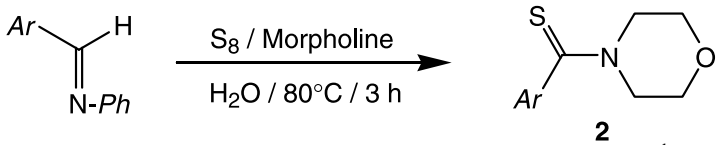


Fig. 3. Chemoselective thioamidation of benzaldehyde in the presence of acetophenone in water

Table 2. The *WK* reaction of benzaldimines in water



2

Entry	Product **2**[a]	Yield/%[b]
1	*Ph*.CS.*M*	80
2	4-*Me*.*Ph*.CS.*M*	82
3	4-*Me*O.*Ph*.CS.*M*	81
4	4-*Et*O.*Ph*.CS.*M*	80
5	4-Cl.*Ph*.CS.*M*	79
6	4-Me_2N.*Ph*.CS.*M*	83

[a] $M =$  ; [b] isolated yields

prompted us to explore the chemoselective *WK* reaction of benzaldehydes over acetophenones in water. For example, when an equimolar mixture of benzaldehyde and acetophenone was allowed to react with sulfur and morpholine in water only thioamide **2** was obtained, and acetophenone was recovered quantitatively (Fig. 3).

To extend this strategy, we carried out the *WK* reactions of aldimines in water under our optimized reaction condition and obtained the thiomorpholides **2** in high yields also (Table 2, entries 1–6).

In conclusion, we have established an applicable *WK* reaction method for the synthesis of benzothioamides in water. Considering the role of the methylene chain, we also discovered a simple and efficient method for the chemoselective thioamidation of benzaldehydes over acetophenones in the *WK* reaction. Therefore, the general *WK* protocol is confronted with a new situation in which water not only is not regarded as a serious disadvantage, but also is applied in this case as a useful solvent in the reaction. In general, we have presented a novel development in the application of this reaction which provides a powerful tool for selective benzothioamide synthesis in water.

Further studies of the *Willgerodt-Kindler* reaction of new substrates are now in progress in our laboratory to clarify the reaction mechanism of the present finding and to develop the application of this reaction.

Experimental

Morpholine was purified by refluxing for 24 h over Na and distillation. Benzaldehydes and purified sulfur were used. A GC-MS method for the analysis of mixtures was applied. A Fisons 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-MS was employed. Column temperature was programmed from 80 to 270°C at 10°C/min. Injection was performed at 280°C. The carrier gas was He and the inlet pressure was 14 psi. ^{1}H NMR spectra were recorded on Bruker 500 MHz spectrometers. All NMR samples were run in $CDCl_3$ and chemical shifts are expressed in ppm relative to internal *TMS*.

*General Experimental Procedure for the Synthesis of **2** in Water*

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

The aldehyde or aldimine (1 mmol), 2 mmol sulfur, 3 mmol morpholine, and 5 cm^3 H_2O are placed in a flask fitted with an air-cooled reflux condenser and stirrer. The mixture is heated at 80°C for 3 h. The dark-brown mixture is cooled to room temperature and the solid product is isolated by suction, and recrystallized from hot ethanol to remove the unreacted sulfur. Further purification (if necessary) can be achieved by recrystallization from *n*-hexane. The products **2** were generally pure as judged by TLC, GC-MS and ^1H NMR analysis.

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