Synthesis of 1,*n*-Acyloxy Thioamides by the Willgerodt-Kindler Reaction: Chemoselectivity of 1,3-Ketoesters over 1,3-Diketones

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Treatment of selected types of 1,3-ketoesters and their corresponding enamines by the Willgerodt-Kindler (WK) reaction afforded the corresponding 1,*n*-acyloxy thioamides. Based on the mechanistic study, the chemoselective thioamidation of 1,3-ketoesters occurs in the presence of 1,3-diketones.

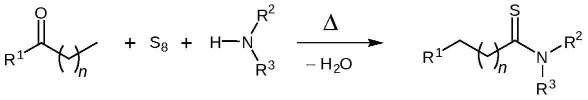
Key words: 1,*n*-Acyloxy Thioamides, Willgerodt-Kindler Reaction, Chemoselectivity

Introduction

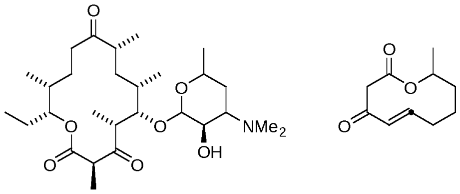
The importance of thioamides as versatile intermediates in the synthesis of pharmaceutically active compounds and in organic synthesis [1 – 4] have enlarged the synthetic utility of the Willgerodt-Kindler (WK) reaction. For instance, the incorporation of the thioamide functional group has provided a useful approach for the preparation of pharmacologically important peptides [5].

Thioamides are most often prepared by simple thionation of the corresponding amides with the aid of phosphorus pentasulfide or the Lawesson reagent [6, 7]. The practical use of this method is limited by the availability of the starting amide. Other methods for thioamide synthesis have been reviewed previously [6, 8, 9]. Recently, a direct synthesis of thioamides in a reaction related to the Friedel-Crafts synthesis, namely by reacting isothiocyanates with aromatic [10, 11] and heteroaromatic [12] compounds in the absence of Lewis acids, has been developed.

The three-component Willgerodt-Kindler (WK) reaction is well known as an alternative route for the synthesis of thioamides [13, 14]. In the original reaction, an aryl alkyl ketone or aryl aldehyde was reacted with sulfur and a primary or secondary amine, to give the terminal thioamide (Scheme 1) [13].



Scheme 1.

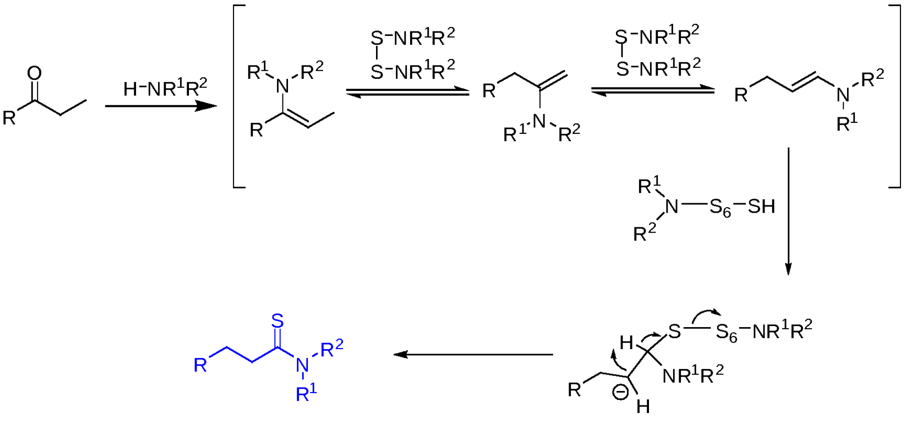


Scheme 2.

In continuation of our work on the WK reaction since 1999 [15], the synthesis of 1,5-acyloxy thioamides attracted our attention because these compounds serve as convenient building blocks in the heterocyclization process due to the existence of another reactive center in the molecule [16]. For example, 1,5-acyloxy thioamides are useful intermediates in the synthesis of macrolide antibiotics (Scheme 2) [17].

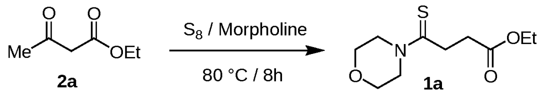
Results and Discussion

The excellent work by Carmack [18] has proved that an enamine plays a critical role as an intermediate in the migration of a carbonyl group back and forth along a chain of methylene units *via* a facile isomerization induced by catalytic action of a dithio-*bis*-amine generated from sulfur and amine (Scheme 3). In other words, the enamine is attacked by a dithio-*bis*-amine to form a highly reactive three-membered ring heterocyclic sulfur intermediate which facilitates the elimination-readdition of the amines reversibly along



Scheme 3. The terminal thioamide formation through the reversible enamine isomerization followed by an irreversible final WK oxidation.

Table 1. Optimization of the molar ratio of sulfur and morpholine to 1,3-ketoester **2a** for preparing **1a**.



Entry	Substrate : Sulfur : Morpholine (molar ratio)	Yield (%; GC)
1	1 : 1 : 2	45
2	1 : 2 : 2	73
3	1 : 2 : 3	79
4	1 : 3 : 6	76

the chain [20]. When the enamine reaches the terminal methyl group, final WK oxidation occurs irreversibly at the expense of the sulfur atom to produce an N,N-disubstituted thioamide.

Accordingly, the further a carbonyl group has to move to the end of a chain, the greater will be the opportunity for side-reactions to consume the intermediates; hence the yield of the ultimate thioamide decreases sharply [18 – 20]. Therefore, the study of a palpable model system for the WK reaction of aliphatic 1,3-ketoesters and 1,3-diketones demands the investigation on the shortest possible alkyl chains.

In consequence, we carefully selected the three types of 1,3-ketoesters **2a** – **c** which differ either in the length of the methylene chain or in the chain branching in order to have the shortest reaction time and the highest reaction yield. To gain more information on the reaction path, 1,3-diketones **2d** – **e** were also chosen.

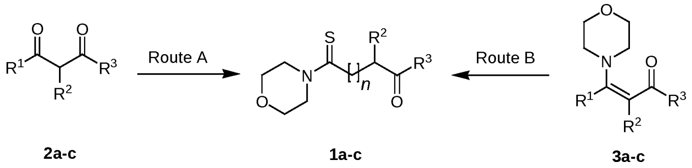
We first studied a reaction between 1,3-ketoester **2a**, sulfur and morpholine as a secondary amine [21] by screening the reaction conditions. In order to determine the optimum conditions, we examined the influence of the reaction time, reaction temperature, and molar ratio of sulfur and morpholine to substrate. Our observations revealed that the optimum conditions for this reaction in the absence of solvent is at 80 °C for 8 h, and that the best yield of **1a** is obtained under a 1 : 2 : 3 molar ratio (Table 1, entry 3).

Under the optimum conditions, the WK reactions of four other substrates **2b** – **e** were studied under classical and microwave heating. The yield of products under microwave heating did not differ significantly from those of classical conditiones, while the reaction progressed much faster. As expected, the yields of the thioamides **1a** – **c** sharply decrease when the length of the methylene chain increases or a chain branch is inserted in the molecule (Table 2, route A). Unlike **2a** – **c**, 1,3-diketones **2d** – **e** completely failed to produce the corresponding thioamides. This different behavior made us pose the question what happened during the reaction. Therefore, we synthesized enamines **3a** – **e** [22], as expected intermediates, and carried out their WK reactions under similar reaction condition.

As shown in Table 2, the reaction yields of enamino-esters **3a** – **c** are slightly improved when compared to those of **2a** – **c** (Table 2, route B). However, the WK reaction of enamino-ketones **3d** – **e** (similarly to their corresponding diketones **2d** – **e**) failed, too.

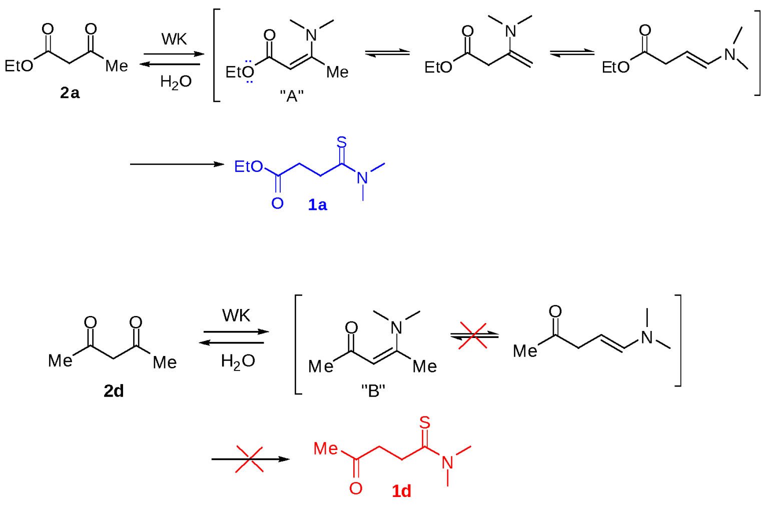
As shown in Scheme 4, enamino-ketone “B” as the first intermediate of **2d** has clearly a distinct nature in comparison to that of **2a**, *i. e.* the enamino-ester “A”. The enamino-ester “A” (unlike enamino-ketone “B”) is expected to move along a chain of methylene units *via* a facile isomerization to reach the end of a chain. The fact is that the ketonic moiety in **3d** – **e**, unlike that of **3a** – **c**, is strongly conjugated with an adjacent double bond of the enamine moiety and, therefore, prevents the further isomerization toward the end of the methylene chain.

Table 2. Synthesis of **1a – c** from **2a – c** and **3a – c** by the Willgerodt-Kindler reaction.

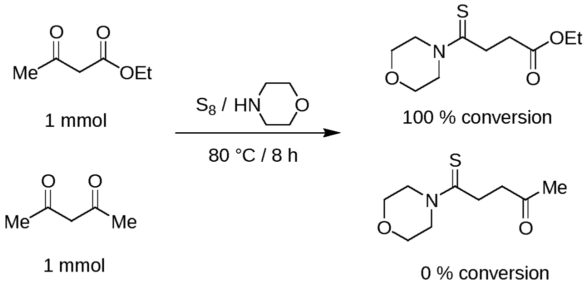


Entry	R^1	R^2	R^3	n	Yield (Route A; %)[a]		Yield (Route B; %)[a]	
					Classical[b]	Microwave[c]	Classical[b]	Microwave[c]
a	Me	H	OEt	1	79 (40)	81 (43)	81 (45)	83 (46)
b	Me	Et	OEt	1	45 (30)	51 (40)	54 (38)	60 (41)
c	n-Pr	H	OEt	3	22 (10)	28 (12)	29 (12)	35 (15)
d	Me	H	Me	1	no reaction	no reaction	no reaction	no reaction
e	Me	H	Et	1	no reaction	no reaction	no reaction	no reaction

[a] GC yield; isolated yield is given in parentheses; [b] S_8 / morpholine / 80 °C / 8 h; [c] S_8 / morpholine / microwave irradiation (900 W) / 3 min.



Scheme 4. Proposed WK reaction pathway for **2a** and **2d**.



Scheme 5. Chemoselective thioamidation of a 1,3-ketoester in the presence of a 1,3-diketone.

This hypothesis prompted us to explore the chemoselective WK reaction of 1,3-ketoesters over 1,3-diketones. For example, when an equimolar mixture of 1,3-ketoester **2a** and 1,3-diketone **2d** was allowed to react with sulfur and morpholine at 80 °C only thioamide **1a** was obtained, and 1,3-diketone **2d** was recovered quantitatively after the reaction mixture had been subjected to a standard aqueous quench (see Scheme 5).

Conclusion

In the present work, the Willgerodt-Kindler reaction is introduced as an alternative route for the synthesis of 1,*n*-acyloxy thioamides from 1,3-ketoesters and their homologous enamines. A mechanistic study led to the chemoselective thioamidation of 1,3-ketoesters in the presence of 1,3-diketones. This is a new finding for the WK reaction which can be helpful for elucidating its reaction pathway that still remains obscure [13, 18].

Experimental Section

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

*General procedure for the synthesis of **1** under classical conditions*

The 1,3-ketoester **2** or 1,3-enamino-ester **3** (1 mmol), sulfur (2 mmol) and morpholine (3 mmol) are placed in a flask fitted with an air-cooled reflux condenser and stirrer. The obtained mixture is stirred and heated at 80 °C for 8 h. The dark-brown mixture is cooled to r. t., washed with water and then extracted with ethyl acetate. The organic layer is separated and dried over anhydrous Na_2SO_4. The purification is carried out by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1 : 3 v/v) to afford pure product **1**. The identification of the isolated products was performed by ^{1}H NMR, ^{13}C NMR and GC-MS spectral analyses.

*General procedure for the synthesis of **1** under microwave heating*

The 1,3-ketoester **2** or 1,3-enamino-ester **3** (1 mmol), sulfur (2 mmol) and morpholine (3 mmol) are placed in an open pyrex flask and heated under 900 W power irradiation for 3 min [23]. The work-up was performed using an identical procedure to that described above.

*Ethyl 4-morpholino-4-thioxobutanoate (**1a**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (t, 3H), 2.94 (m, 4H), 3.77 (m, 4H), 3.85 (t, 2H), 4.18 (t, 2H), 4.37 (q, 2H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2, 33.5, 35.8, 49.9, 50.2, 60.7, 66.3, 66.5, 172.6, 201.6. – MS (EI, 70 eV): *m/z* (%) = 231 (60) $[M]^+$, 166 (40), 158 (40), 144 (45), 86 (100).

*Ethyl 2-ethyl-4-morpholino-4-thioxobutanoate (**1b**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.8 – 0.9 (m, 5H), 1.1 (t, 3H), 2.4 (m, 1H), 2.9 (t, 2H), 3.9 (m, 8H), 4.1 (q, 2H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.3, 13.9, 15.6, 42.1, 46.8, 49.8, 49.9, 60.1, 66.2, 66.3, 175.5, 193.5. – MS (EI, 70 eV): *m/z* (%) = 259 (30) $[M]^+$, 226 (25), 214 (30), 186 (30), 144 (50), 130 (30), 112 (60), 86 (90), 29 (100).

*Ethyl 6-morpholino-6-thioxohexanoate (**1c**)*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.3 (t, 3H), 1.8 (m, 4H), 2.4 (t, 2H), 2.9 (t, 2H), 3.8 (m, 6H), 4.2 (q, 2H), 4.4 (t, 2H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7, 24.9, 28.9, 34.2, 43.5, 50.4, 50.5, 60.8, 66.9, 70.0, 173.7, 203.7. – MS (EI, 70 eV): *m/z* (%) = 259 (35) $[M]^+$, 226 (30), 214 (35), 145 (30), 112 (45), 86 (100), 71 (45), 43 (55), 29 (40).

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