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].

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 heterocycl-
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 palatable 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 conditions, 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 enamino 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>α</th>
<th>Yield (Route A; %)ᵃ</th>
<th>Yield (Route B; %)ᵃ</th>
<th>Yield (Route A; %)ᵇ</th>
<th>Yield (Route B; %)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>H</td>
<td>OEt</td>
<td>1</td>
<td>79 (40)</td>
<td>81 (43)</td>
<td>81 (45)</td>
<td>83 (46)</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Et</td>
<td>OEt</td>
<td>1</td>
<td>45 (30)</td>
<td>51 (40)</td>
<td>54 (38)</td>
<td>60 (41)</td>
</tr>
<tr>
<td>c</td>
<td>n-Pr</td>
<td>H</td>
<td>OEt</td>
<td>3</td>
<td>22 (10)</td>
<td>28 (12)</td>
<td>29 (12)</td>
<td>35 (15)</td>
</tr>
<tr>
<td>d</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>1</td>
<td>no reaction</td>
<td>no reaction</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
<tr>
<td>e</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>1</td>
<td>no reaction</td>
<td>no reaction</td>
<td>no reaction</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

ᵃ GC yield; isolated yield is given in parentheses; ᵇ S₈ / morpholine / 80 °C / 8 h; ᵇ S₈ / 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 chemo-selective 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 thioamination 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 Na2SO4. 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 1H NMR, 13C 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-morpholin-4-thioxobutanoate (1a)

1H NMR (500 MHz, CDCl3): 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). – 13C NMR (125 MHz, CDCl3): 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-morpholin-4-thioxobutanoate (1b)

1H NMR (500 MHz, CDCl3): 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). – 13C NMR (125 MHz, CDCl3): 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-morpholin-6-thioxohexanoate (1c)

1H NMR (500 MHz, CDCl3): 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). – 13C NMR (125 MHz, CDCl3): 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).


[21] Morpholine has greater resistance to oxidation in comparison to other secondary amines.


[23] A domestic microwave oven from National (model NN-6755 operating at 2450 MHz, 900 W power) was used for all syntheses.