

Extension of the Willgerodt–Kindler reaction: protected carbonyl compounds as efficient substrates for this reaction

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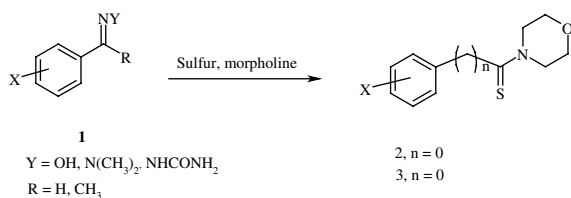
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Abstract—Nitrogen derivatives of carbonyl compounds such as oximes, hydrazones, and semicarbazones were found to be excellent candidates for the Willgerodt–Kindler reaction. They can be used directly in a solvent-free reaction, under both classical and microwave conditions, to give the corresponding thiomorpholides in good yields.
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1. Introduction

Recent studies on the Willgerodt–Kindler reaction in our laboratory^{1–5} have been directed toward its further development in synthesis. This reaction is a well known method for the synthesis of thioamides.⁶ In the original Willgerodt–Kindler reaction, ketones and aldehydes were found to react with sulfur and secondary amines to give terminal thioamides as a result of consecutive oxidations and rearrangements. Thioamides have often appeared in the literature as versatile intermediates in medical and organic chemistry.^{7–11} Very recently, we reported the direct and fast conversion of thiomorpholides into the corresponding thioesters.¹²



The present study is focused on Willgerodt–Kindler reactions of nitrogen derivatives of carbonyl compounds such as oximes, hydrazones, and semicarbazones which,

to our best knowledge, have not been studied in the literature. Although they are useful protecting groups, a disadvantages of these derivatives are the conditions required for their cleavage and regeneration to the parent carbonyl compound. In general, when faced with the problem of preparing a thioamide from the corresponding carbonyl group in a polyfunctional molecule, its preservation throughout the entire sequence of synthetic reactions is necessary. On the other hand, the regeneration of a carbonyl group from a protected derivative may result in a decrease of the total yield of the reaction sequence together with an additional step. Moreover, during the regeneration of a carbonyl group the selection of the appropriate reagent, which is inert to other functional groups in the molecule can be a significant problem. Therefore, it is of interest to determine whether a derivative of a carbonyl compound can be subjected directly to the Willgerodt–Kindler reaction conditions to give the corresponding thiomorpholides.

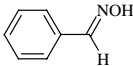
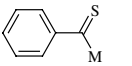
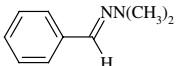
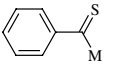
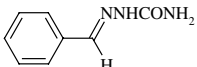
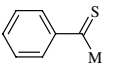
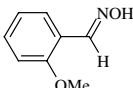
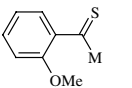
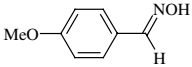
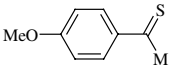
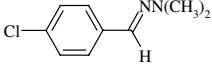
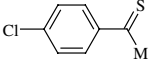
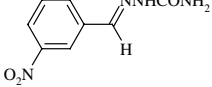
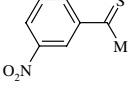
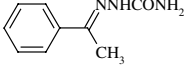
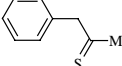
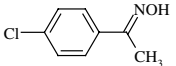
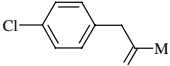
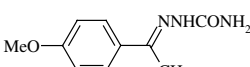
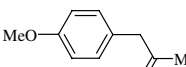
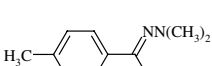
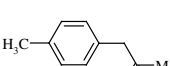
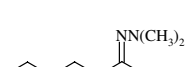
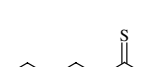
Herein we report the direct synthesis of thiomorpholides **2** and **3** from protected aldehydes and ketones using optimized reaction conditions. The crude reaction mixtures were directly analyzed by GC–MS and/or subjected to column chromatography. All the products were characterized by ¹H NMR and MS spectral data and were similar to those reported in the literature. The reaction conditions and yields of the products **2** and **3** are given in Table 1.

In conclusion, we have shown that the Willgerodt–Kindler reaction can be conducted with a variety of substrates, as shown in Table 1. Although the yields from the carbonyl

Keywords: Protected carbonyl compounds; Willgerodt–Kindler reaction; Thiomorpholides; Solvent-free conditions.

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Table 1. The direct synthesis of thiomorpholides from derivatives of carbonyl compounds

Entry	Substrates 1	Products ^a	Yield (%) ^b		Ref.
			Conventional heating ^c	MW ^d (min)	
a			65	70 (7)	3
b			72	79 (10)	3
c			83	72 (5)	3
d			43	48 (7)	14
e			75	80 (7)	15
f			60	70 (10)	1
g			55	72 (7)	14
h			71	60 (7) ¹³	1
i			61	55 (7)	1
j			41	44 (7)	1
k			55	57 (7)	14
l			65	73 (10)	1

^a M = morpholine.^b Yields are based on GC analysis.^c The reaction time is 3 h at 100 °C.^d MW = microwave irradiation.

derivatives in comparison with the analogous ketones and aldehydes under the same reaction conditions are slightly lower,^{1–3,6} the method is applicable to polyfunctional molecules due to its wide range of functional group toleration.

Further studies of the Willgerodt–Kindler reactions of new substrates are in progress in our laboratory.

2. General procedure

2.1. Caution

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

2.2. Solvent-free reaction under conventional heating

In a typical experiment, a mixture of substrate **1** (1 mmol), sulfur (4 mmol), and morpholine (6 mmol) was refluxed for 3 h. After cooling, the reaction product **2** or **3** was purified by silica gel column chromatography [petroleum ether–ethyl acetate (4:1)] and recrystallized from ethanol. The products **2** or **3** were generally pure as judged by TLC, GC–MS, and NMR analysis.

2.3. Solvent-free reaction under microwave heating

In a typical experiment, a mixture of substrate **1** (0.1 mmol), sulfur (0.4 mmol), and morpholine (0.6 mmol) in an open pyrex glass flask was exposed to microwave irradiation at 650 W between 5 and 10 min.¹⁶ The workup was performed using an identical procedure to that described above.

References and notes

1. Nooshabadi, M.; Aghapoor, K.; Darabi, H. R.; Mojtahedi, M. M. *Tetrahedron Lett.* **1999**, *40*, 7549.
2. Darabi, H. R.; Aghapoor, K.; Tabar-heydar, K. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 1189.
3. Aghapoor, K.; Darabi, H. R.; Nooshabadi, M.; Tabar-heydar, K. *Phosphorus, Sulfur and Silicon* **2002**, *177*, 1183.
4. Aghapoor, K.; Darabi, H. R.; Tabar-heydar, K.; Nakhshab, L. *Sulfur Lett.* **2002**, *25*, 259.
5. Darabi, H. R.; Aghapoor, K.; Nakhshab, L. *Z. Naturforsch.*, in press.
6. Brown, E. V. *Synthesis* **1975**, 358, and references cited therein.
7. (a) Padwa, A.; Scott Beall, L.; Heidelbaugh, T. M.; Liu, B.; Sheehan, S. M. *J. Org. Chem.* **2000**, *65*, 2684; (b) May, P. J.; Bradley, M.; Harrowven, D. C.; Pallin, D. *Tetrahedron Lett.* **2000**, *41*, 1627; (c) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 4443; (d) Metzner, P. *Synthesis* **1992**, 1185.
8. Spatola, A. F. In *Chemistry and Biochemistry of Amino acids, Peptides and Proteins*; Weinstein, B., Ed.; Marcel Dekker: New York, 1983; Vol. 7, pp 267–357, and references cited therein.
9. Hoeg-Jensen, T.; Olsen, C.; Holm, A. *J. Org. Chem.* **1994**, *59*, 1257.
10. Katritzky, A. L.; Moutou, J. L.; Yang, Z. *Synlett* **1995**, 99.
11. Murguia, M. C.; Rossi, R. A. *Tetrahedron Lett.* **1997**, *38*, 1335.
12. Darabi, H. R.; Aghapoor, K.; Tabar-heydar, K. *Monatsh Chem.* **2004**, *135*, 79.
13. Full details of the Willgerodt–Kindler reaction of **1h** and other semihydrazones under both microwave and conventional heating and possible reaction pathways are contained in a manuscript soon to be submitted.
14. Tominaga, Y.; Matsuoka, Y.; Oniyama, Y.; Uchimura, Y.; Komiya, H.; Hirayama, M.; Kohra, S.; Hosomi, A. *J. Heterocycl. Chem.* **1990**, *27*, 647.
15. Campaine, E.; Pragnell, M.; Haff, F. *J. Heterocycl. Chem.* **1968**, *5*, 141.
16. The microwave oven used for this study was a domestic National model NN-6755 with seven power settings (90–900 W).