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The Rapid Synthesis of Thiomorpholides by Willgerodt-Kindler Reaction under Microwave Heating

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Abstract: The Willgerodt-Kindler reaction of several aryl alkyl ketones with sulfur and morpholine under solvent-free conditions was performed in a domestic microwave oven. Good yields were attained within a very short reaction time (between 3.5- 6 min.). © 1999 Published by Elsevier Science Ltd. All rights reserved.

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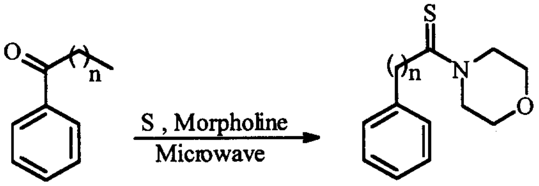
Apart from their widespread use as intermediates in organic synthesis,[1] thioamides have attracted attention in the field of peptide[2] chemistry, as well as in synthesis.[3-5] A traditional approach to their synthesis is the Willgerodt-Kindler reaction which has found only limited application because of the high reaction temperatures and long reaction periods required and the low to moderate yields obtained.[6] In its original form, straight- or branched-chain aryl alkyl ketones were found to react with sulfur and primary or secondary amines to give thioamides with the same number of carbon atoms.[7] The thiocarbonyl group of the product is always at the end of the chain.



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Since King *et al.* studied[8] the use of ten amines in this reaction and claimed that morpholine was the best amine to use, we utilized this in the Willgerodt-Kindler reaction.

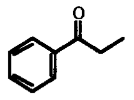
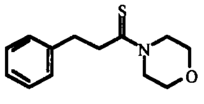
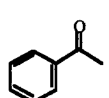
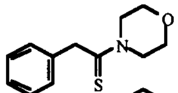
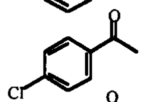
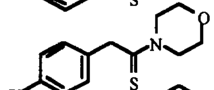
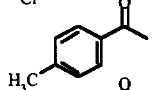
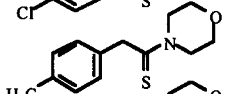
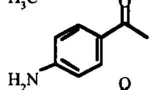
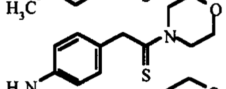
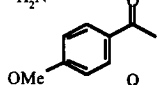
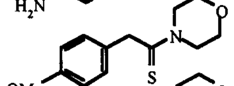
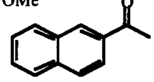
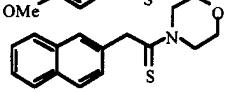
In the recent years, microwave technology has been used in combination with solvent-free techniques to improve many organic reactions.[9,10] This easy and environmental friendly technique has several advantages, mainly shorter reaction times, higher yields, and cleaner reaction products. Such reactions are also easier to work-up than reactions using classical heating.

We would like to report the synthesis of thioamides **2a-g** by the Willgerodt-Kindler reaction in a domestic microwave oven. Although Strauss *et al* reported[10, 11] the synthesis of acetamides by the Willgerodt reaction using a microwave batch reactor (MBR), the Willgerodt-Kindler reaction for the synthesis of thioamides has not, to the best of our knowledge, been reported yet. In a domestic microwave, aryl alkyl ketones **1a-g** were reacted with morpholine and sulfur under 900 W (2450 MHz) power irradiation in a few minutes either with or without added H-Y zeolite.

In order to find the optimal reaction conditions, as shown in table 1, several experiments were tried using three different sets of conditions. The optimal conditions were achieved by examination of various parameters (*e.g.* power of irradiation, time of irradiation, amounts of sulfur, and effects of H-Y zeolite as an acidic catalysis[12]). First of all, therefore, we checked the effect of the microwave power on the reaction rate. The ketone **1b** was irradiated under three different sets of power (270, 650, 900 W) for 4 minutes which gave **2b** in 5%, 20%, and 56% yield, respectively. This indicates that the rates of reaction rapidly increase when the power level is higher. The effects of both H-Y zeolite and amounts of sulfur on the reaction were also studied. A summary of the data found is given in table 1. The conclusions which we have been able to draw from these data are: 1) more increased time of irradiation does not increase the yield of products; 2) the best molar ratio is = ketones: sulfur: morpholine = 1: 2: 3; the use of more than three moles of sulfur does not increase the yield (set C); 3) the use of H-Y zeolite does not show a significant effect on the yield (compare sets A and B).

The mechanism of the Willgerodt-Kindler reaction is not completely known. All the facts points to a mechanism consisting of consecutive oxidations and reductions along the chain.[6,14] Further studies of this reaction are now in progress in our laboratory to elucidate the mechanism.

Table 1. The Willgerodt-Kindler reaction of ketones **1a-g** with morpholine and sulfur under microwave irradiation

Entry	Substrates 1	*Products 2*[a]	Time (min)	Isolated Yield (%) Series A[b]	 Series B[c]	 Series C[d]
a			4	10	16	40
b			4	50	56	81
c			6	40	45	55
d			4	44	53	74
e			3.5	42	47	65
f			5	49	56	72
g			4.5	56	61	75

a) The reactions were monitored by TLC and the products identified by their NMR, IR, and Mass spectra. b) Reaction conditions: the ratio of ketone: sulfur: morpholine is 1: 1: 2 together with H-Y zeolite. c) Reaction conditions: the ratio of ketone: sulfur: morpholine is 1: 1: 2 in absence of H-Y zeolite. d) Reaction conditions: the ratio of ketone: sulfur: morpholine is 1: 2: 3 in absence of H-Y zeolite.

In conclusion, this simple, convenient and fast method for the Willgerodt-Kindler reaction makes this reaction more useful in synthesis. While the classical reactions are normally conducted over several hours,[6-8] the microwave reactions were completed within few minutes.

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

In a typical experiment, a mixture of ketone **1b** (2 mmol), morpholine (6 mmol), and sulfur (4 mmol) in an open pyrex glass flask was exposed to microwave[15] irradiation at 900 W for 4 minutes. After cooling, the reaction product **2b** was purified by silica gel chromatography by eluting with petroleum ether-ethyl acetate (8:2). The fractions were monitored by TLC. While the known products **2b- 2f**[13a] and **2g**[5] were identified by their NMR, IR, and Mass spectra according to the literature, no spectral data of known **2a** was found.[7, 13b]

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[12]- Recently, Rolf *et al.* synthesized 2b in 49.5% with two hours reflux in an acidic condition: A. Rolf, J. Liebscher, *Org. Syntheses*, I. Shinkai Ed.; **1996**, vol 76, 257-263.
[13]- a) R. Carlson, T. Lundstedt, R. Shabana, *Acta. Chim. Scand., ser. B*, **1986**, 40, 534-544; b) **2a**: Colorless crystals, IR (cm^{-1}) 820 (m), 1010 (m), 1100 (s), 1230 (m), 1430 (m), 1505 (s), 2810 (m), 2900 (m); ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.12-4.25 (m, 12H), 7.25 (s, 5H); MS, m/e (rel. intensity %) 235 (M^+, 25), 202 (40), 148 (50), 130 (35), 105 (90), 91 (45), 86 (40), 77 (85).
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[15]- The microwave oven used for this study was a domestic National model NN-6755 with 7 power settings (90-900 W).