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MICROWAVE-ASSISTED RAPID HYDROLYSIS AND PREPARATION OF THIOAMIDES BY WILLGERODT-KINDLER REACTION

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Dedicated to Prof. Dr. Guy Solladie for his 60th birthday

ABSTRACT

Aldehydes and aryl alkyl ketones were efficiently transformed to thioamides with the same number of carbon atoms via Willgerodt-Kindler reaction under microwave irradiation in solvent-free conditions. The thioamides obtained were hydrolyzed to corresponding carboxylic acids with microwave dielectric heating in one minute. Both reactions are very fast and the yields are excellent.

Key Words: Thioamides; Hydrolysis; Willgerodt-Kindler reaction; Microwave; Monomode system.

Aryl and aryl alkyl thioamides and their corresponding carboxylic acids are useful organic compounds, versatile intermediates (1–3) and used as biologically

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active compounds such as pesticides (4,5), and anti-inflammatory (4,7), antiulcer (8), agents.

Although the classical Willgerodt-Kindler reaction of aldehydes and ketones provides useful routes to these compounds, a severe reaction condition (high temperature $\sim$200°C) and a long refluxing time in the order of hours is required (9). We (10,11) and others (12,13) have demonstrated the efficiency of microwave irradiation, especially the focused system for promoting organic reactions. In the present work, the preparation of thioamides via the Willgerodt-Kindler reaction and their hydrolysis to the corresponding carboxylic acids was investigated. Strauss *et al*. reported (14) the synthesis of phenylacetamide upon microwave heating using a microwave batch reactor (MBR). During the course of our investigation, a paper appeared on the Kindler-modification of aryl alkyl ketones under microwave irradiation with a domestic multi-mode oven (15). However, for the ketones, some further improvements were observed due to the use of a focused microwave digester (monomode system), instead of a domestic microwave oven. The reaction conditions were optimized by examining the different parameters such as time of irradiation, power of irradiation, the ratio of sulfur to secondary amine, and starting material. Morpholine as a cheap and technically available secondary amine was found to be most suitable. After performing several experiments, the best molar ratio was found to be substrate: sulfur: morpholine (1:2.5:3).

In a typical procedure, aldehyde or ketone (0.01 mol) was mixed with sulfur (0.025 mol) and morpholine (0.03 mol) in a closed Teflon vessel ($\sim$20 mL) and subjected to microwave irradiation (16) for four min. After conventional work-up, excellent yields of thioamides were obtained. For hydrolysis to corresponding carboxylic acids, the isolated thioamide (0.01 mol) was mixed with 5 mL of NaOH solution (15%) in a Teflon flask ($\sim$20 mL) and irradiated for one min.

Tables 1 and 2 show our results. Compared to results obtained with multimode domestic ovens, those achieved from monomode system by our method are clearly better (e.g., Table 1, entry 3, 85% versus 55%). We also examined the reaction of aldehydes, which, in general, produced excellent yields of thiomorpholides and their hydrolyzed products. To the best of our knowledge, the case of aldehydes has not studied yet by this methodology. The method has been applied to aromatic as well as aliphatic and α,β-unsaturated aldehydes (Table 2, entry 6,7). In conclusion, we have developed a rapid, mild, and high-yielding method for preparation and hydrolysis of thioamides by microwave activation. Further investigations of this reaction are now in progress in our laboratory.

EXPERIMENTAL

All products were known and identified either by their IR, NMR, or their physical data according to the literature (15,17,18).

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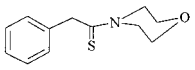
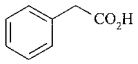
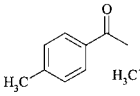
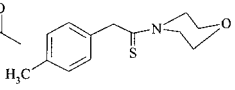
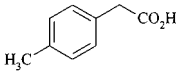
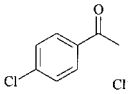
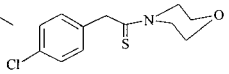
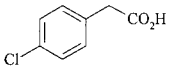
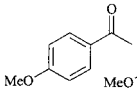
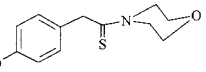
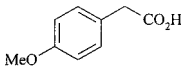
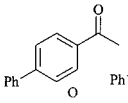
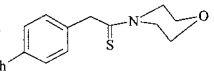
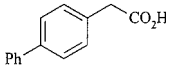
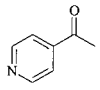
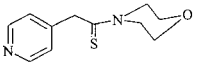
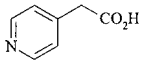
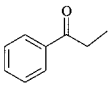
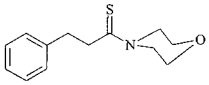
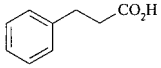
Table 1. Microwave-Promoted Willgerodt-Kindler Reaction of Ketones

Entry	Substrate	Morpholide[a]	(%) Yield (lit.)[b]	Carboxylic Acid[a]	Yield (%)
1			90 (81)		95
2			92 (74)		90
3			85 (55)		90
4			—		85[c]
5			95		90
6			90		88
7			—		45[c]

Note: [a] All products were characterized by m.p., IR, ^{1}H NMR, and their physical data were similar to those reported in the literature (15).
[b] All yields refer to isolated products.
[c] The yield for two steps.

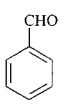
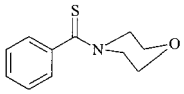
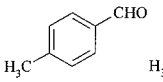
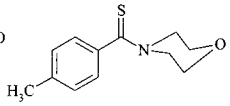
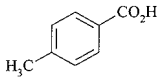
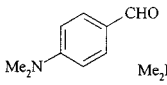
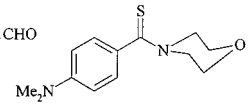
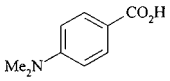
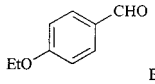
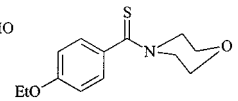
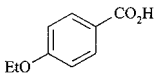
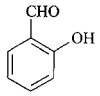
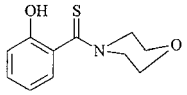
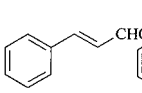
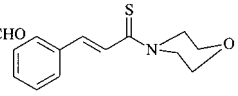
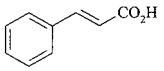
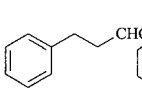
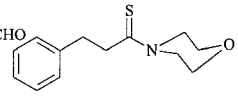
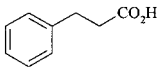
General Procedure for the Willgerodt-Kindler Reaction of Aldehydes and Ketones: (CAUTION—Noxious H_2S Generated)

A mixture of aldehyde or ketone (0.01 mol), morpholine (0.03 mol) and sulfur (0.025 mol) in a closed Teflon flask (~20 mL) was subjected to microwave irradiation for four min. Then the reaction mixture was poured on 50 mL chloroform and some active charcoal was added. After filtration and evaporation of the solvent, the solid residue was recrystallized from an ethanolic-aquatic mixture.

General Procedure for Hydrolysis of Thiomorpholides

Thiomorpholide (0.01 mol) was mixed with ~5 mL of NaOH (15%) in a Teflon flask (~20 mL) and exposed to microwave irradiation for one min. After

Table 2. Microwave Promoted Willgerodt-Kindler Reaction of Aldehydes

Entry	Substrate	Morpholide[a]	Yield (%)[b]	Carboxylic Acid[a]	Yield (%)[b]
1			93		97
2			95		95
3			100		97
4			95		93
5			65		90
6			—		56[c]
7			—		85[c]

[a] All thiomorpholides were characterized either by m.p., IR, ^{1}H NMR or by hydrolysis to their corresponding known carboxylic acids and their physical data were similar to those reported in the literature (19).
[b] All yields refer to isolated products.
[c] The yield for two steps.

cooling, the reaction mixture was made acidic with HCl (10%), and the crude acid was filtered and recrystallized from acetic acid and/or a mixture of ethanol and water.

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