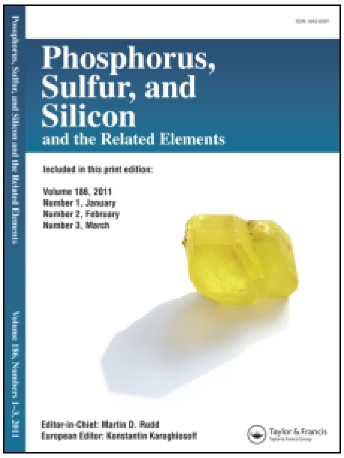

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The Different, but Interesting Behaviors of Benzyl Systems in the Willgerodt-Kindler Reaction under Solvent-Free Conditions

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THE DIFFERENT, BUT INTERESTING BEHAVIORS OF BENZYL SYSTEMS IN THE WILLGERODT-KINDLER REACTION UNDER SOLVENT-FREE CONDITIONS

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*On the benzyl system, bearing various functional groups, have been carried out the Willgerodt-Kindler reaction to obtain thiobenzmorpholide (**1**). The reactions, under solvent-free conditions, were performed in both classical (reflux, room temperature) and nonclassical (microwave) conditions to attempt our elucidation of the reactions pathways. Unlike benzylamine and benzyl mercaptan, benzyl halides give poor result due to the type of amine. The experimental results suggest that the proposed reaction pathway involves the oxidation coupling of benzylic substrates, followed by a thiolation step and an attack of the amine on the thiolated product to give (**1**).*

Keywords: Benzyl system; solvent-free conditions; the Willgerodt-Kindler reaction

Since thioamides have found widespread applications as intermediates in medicine and organic synthesis[1–4] their syntheses have attracted attention in the various field of chemistry.[5–8] The Willgerodt-Kindler reaction is one of the oldest and well-known methods for the synthesis of thioamides.[9–11] In the reaction, the starting materials are reacted with sulfur and primary or secondary amines to give thioamides with the same number of carbon atoms.

The present study is focused on the Willgerodt-Kindler reactions of compounds bearing benzyl skeletons. We believe that the use of novel nonclassical procedures and modern laboratory facilities allows us to extend our knowledge of the Willgerodt-Kindler reaction with new

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TABLE I The Formation of Thiobenzmorpholide (**1**) from Various Starting Materials Under Different Procedures[a]

Entry	Substrate	Microwave (3 min) 1 (%)	Classical heating (4 h) 1 (%)	Room temperature (4 h) 1 (%)
1	$PhCH_2SH$	99	98	19
2	$PhCH_2NH_2$	95	95	55
3	$PhCH_2Cl$[b]	17	11	6
4	$PhCH_2Br$[b]	10	5	4
5	$PhCH_2OH$	5	5	4
6	$PhCH_3$	5	4	2

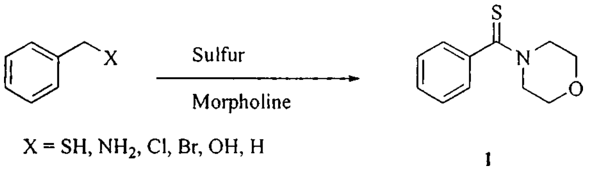
[a] The reactions were monitored by TLC and the product characterized by its spectral data. (Thiobenzmorpholide (**1**): Yellow crystals, IR (cm^{-1}) 820 (m), 1010 (m), 1100 (s), 1230 (m), 1430 (m), 1505 (s), 2810 (m), 2900 (m); ^{1}H-NMR (90 MHz, $CDCl_3$) δ 7.25 (s, 5H), 4.30 (t, 2H), 3.75 (t, 2H), 3.45 (s, 4H); ^{13}C-NMR (25 MHz, $CDCl_3$) δ 201.45, 142.23, 128.55, 128.24, 125.64, 66.42, 66.19, 52.23, 49.29, MS, m/e (rel. intensity %) 207 (M^+, 40), 121 (100), 86 (20), 77 (40).)

[b] The main products is N-benzyl morpholine (83–95%).

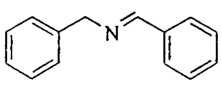
viewpoints. It is also of interest to know whether these compounds show similar behavior in the Willgerodt-Kindler reaction.

The reactions were carried out based on our established optimum reaction conditions.[12] All starting materials were treated with two equivalents of sulfur and three of morpholine. Under solvent-free conditions, benzylic compounds were treated with sulfur and morpholine and gave thiomorpholide **1** in low to high yields.

The results from different types of benzylic compounds are arranged in Table I. All the results clearly show that thermal effect is the only factor for promotion of the reaction. Microwave activation is due to its super-heating effects. Conducting the reaction at room temperature may offer the possibility of obtaining reactive intermediates whose isolation at higher temperature would be impossible.



In all three series, benzyl mercaptan and benzylamine exhibit the highest tendency to form thiomorpholide **1** (entries 1 and 2). However, benzyl halides mainly transformed into the N-benzyl morpholine (entries 3 and 4). In the case of toluene and benzyl alcohol considerable quantities of unreacted starting materials were recovered to show their low activity in the reaction (entries 5 and 6).



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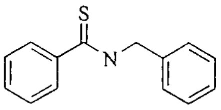
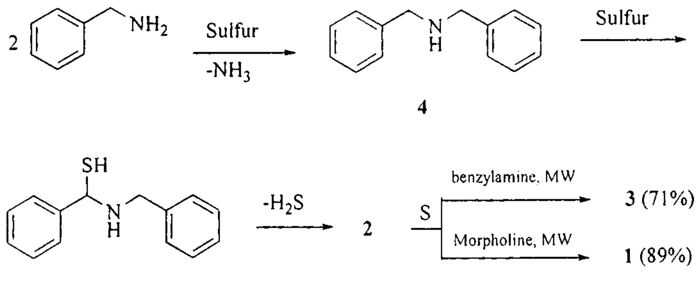


3

Although McMillan et al. reported the synthesis of **1** (41%) by the Willgerodt-Kindler reaction of benzyl amine under classical heating, they did not mention the formation of other products.[13] We, however, obtained **1** (95%) under microwave heating. The experimental data show that the reaction pathway, presented in Scheme 1, involves three basic steps.

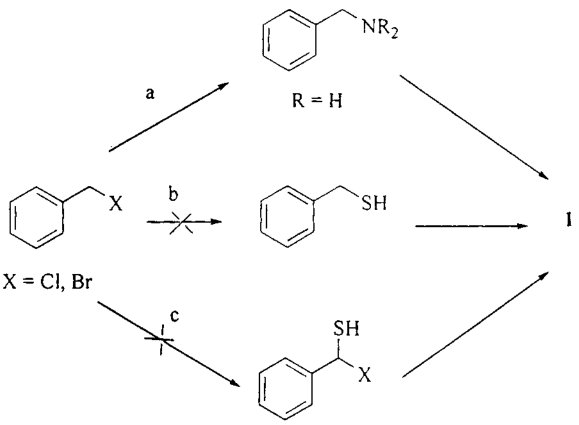
1. In the presence of sulfur, the oxidative coupling of benzylamine gives amine **4**.
2. Thiolation, followed by desulfurization of **4**, leads to Schiff base **2**. Of course, when either benzylamine or **4** were treated with sulfur at room temperature (1 h) in CH_2Cl_2, Schiff base **2** was the sole/isolated product (82–95%).
3. The Willgerodt-Kindler reaction of **2** under microwave heating affords the thioamides **1** or **3** in high yield.



SCHEME 1

The Willgerodt-Kindler reaction of benzyl mercaptan under microwave heating gave **1** in quantitative yield. Conducting the same reaction at room temperature gave dibenzyl disulfide[15] in 64% yield. Conducting the Willgerodt-Kindler reaction on dibenzyldisulfide under microwave heating resulted in further thiolation followed by an amination process to give **1**.

The other main objective in this study was to determine why other benzylic compounds gave low yields of **1**. This fact may pose the question us to what happened during the reaction. The Willgerodt reaction of benzyl chloride with sulfur and ammonium sulfide at 190°C gave benzamide in 60% yield.[14] The reaction of benzyl halides with a mixture of sulfur and amine may be performed in two ways. In the first, a nucleophilic substitution of amine or sulfur at the chlorine atom [or bromine atom] is expected to give benzylamine or benzyl mercaptan, respectively (path *a* and *b* is Scheme 2). In the second, addition of sulfur on a carbon atom is possible (path *c* in Scheme 2). When we applied the reaction of benzyl chloride with sulfur and morpholine, benzyl morpholide was obtained as a main product (entries 3 and 4 in Table I). This fact confirms that path *a* is the more feassible way. We also found that, under microwave heating, N-benzyl morpholine is inert to Willgerodt-Kindler reaction conditions, which is due to lack of formation of imine **2**. Therefore, the fact that benzyl halides do not give **1** is not due to their nature but to type of applied amine in the reaction.



SCHEME 2

The OH and H groups on benzyl skeleton are poor leaving groups, which under the reaction conditions are inert. Of course, the existence of trace amounts of by-products, such as methyl thiomorpholide, suggests that some of benzyl alcohol, like benzyl mercaptan, may convert to dibenzyl peroxide, which is an active radical source.

In general, it can be concluded that imine and dibenzyldisulfide are possible intermediates of this study. The experimental results suggest that the proposed reaction pathway involve the oxidative coupling of benzylic substrates, followed by a thiolation step and attack of an amine on the thiolated product to give **1**.

Further work on the Willgerodt-Kindler reaction is in progress to extend the scope of the reaction by using different substrates.

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