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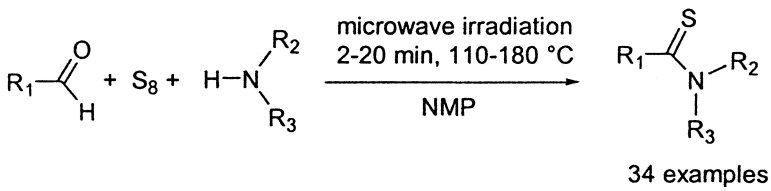

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Preparation of Thioamide Building Blocks via Microwave-Promoted Three-Component Kindler Reactions

Oleksandr I. Zbruyev, Nikola Stiasni, and C. Oliver Kappe*

Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

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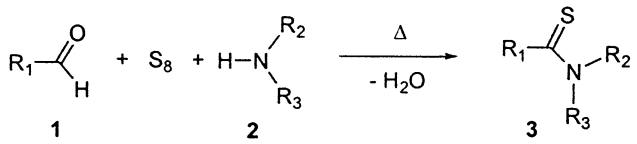
A microwave-enhanced variation of the Kindler thioamide synthesis is introduced. Taking advantage of the sealed vessel capabilities of a dedicated single-mode microwave reacto,r a diverse selection of 13 aldehyde and 12 amine precursors was utilized in the construction of a representative 34-member library of substituted thioamides. The three-component condensations of aldehydes, amines, and elemental sulfur were carried out using 1-methyl-2-pyrrolidone (NMP) as solvent employing microwave flash heating at 110−180 °C for 2−20 min. A simple workup protocol allows the isolation of synthetically valuable primary, secondary, and tertiary thioamide building blocks in 83% average yield and >90% purity.

Introduction

Thioamides are essential building blocks for the preparation of a number of biologically relevant heterocyclic scaffolds (that is, utilizing the Hantzsch thiazole synthesis).[1] Although many different methods to prepare thioamides have been reported in the literature,[2] the three-component coupling of an aldehyde **1**, elemental sulfur and an amine **2** (Scheme 1) has so far received comparatively little attention, in particular from the combinatorial chemistry community. This is despite the fact that this one-pot process, first reported by Kindler in 1923,[3] allows for an easy introduction of diversity into the thioamide backbone by simple variation of the aldehyde (R^1) and amine (R^2, R^3) components in the condensation step. Since a large number of aldehydes and primary/secondary amines are commercially available, a diverse set of synthetically useful thioamide products can potentially be prepared in one step using this method. However, the multicomponent process depicted in Scheme 1 has so far found only limited application because of the high reaction temperatures and long reaction times that are typically required.[4,5] In addition, the protocol is hampered by the fact that volatile amines or aldehydes cannot be used unless autoclave technology is employed.

In recent years, the concept of speeding up synthetic transformations by microwave activation has created a lot of interest in the organic[6] and combinatorial chemistry community.[7] In particular, the use of dedicated microwave reactors that enable the rapid and safe heating of reaction mixtures in sealed vessels under controlled conditions with on-line temperature and pressure monitoring has greatly increased the general acceptance of the microwave heating method. Therefore, it appeared to us that the use of microwave heating under sealed vessel (autoclave) conditions would provide an ideal and rapid method to synthesize thioamides in a combinatorial fashion according to the venerable, but underutilized, Kindler method. Here, we report a high-speed, one-pot protocol for the generation of diverse sets of thioamides from readily available aldehyde and amine precursors. It should be noted that very recently, the first reports on microwave-assisted Kindler reactions (and on related Willgerodt−Kindler processes) have appeared in the literature.[8] These studies employed domestic microwave ovens that did not allow accurate temperature measurements and, therefore, may prove difficult to reproduce. In addition, examples were restricted to two cyclic secondary amines (morpholine and piperazine) and, therefore, offered no diversity in a combinatorial context.[8]

Scheme 1



Results and Discussion

We have chosen the condensation of benzaldehyde (**1**, R_1 = Ph) with sulfur (S_8) and piperidine (**2**, R_2-R_3 = $-(CH_2)_5-$) as a suitable model reaction to investigate and optimize the microwave-assisted Kindler thioamide synthesis. This combination of building blocks involving cyclic amines and aromatic aldehydes has been well-studied in the literature and generally provides good yields of thioamide products upon heating of the neat reagents (or using suitable solvents).[5,9] Our initial experiments involved DMF as the solvent (2 mL) and an equimolar (2 mmol each) composition of the three building blocks. DMF effectively couples with microwave irradiation, that is, is able to convert electromagnetic energy of 2.45 GHz into heat energy,[10] leading to a rapid increase in temperature ("microwave flash heating"; see also Figure S1 in the Supporting Information). Single-mode microwave irradiation[11] of the equimolar mixture **1**/**2**/S_8 (Table 1, entry 1) under sealed-vessel conditions (2 min, 100 °C) produced a 57% isolated yield of the corresponding

* To whom correspondence should be addressed. Phone: +43-316-3805352. Fax: +43-316-3809840. E-mail: oliver.kappe@uni-graz.at.

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Table 1. Optimization of Microwave-Assisted Kindler Condensation of Benzaldehyde (1), Piperidine (2), and Sulfur (S) Furnishing Thioamide 3[a]

entry	**1**/**2**/S mmol[b]	solvent mL	temp °C	time min	yield %[c]
1	2/2/2	DMF [2]	100	2	57[d]
2	2/2/2	DMF [2]	120	2	64[e]
3	2/2.5/2.5	DMF [2]	120	2	85
4	2/3/2.5	DMF [2]	120	2	88
5	4/6/5	DMF [2]	120	2	91
6	4/6/5	DMF [2]	110	3	91
7	4/6/5	NMP [2]	110	3	95

[a] Scheme 1, R_1 = Ph, $R_2-R_3 = -(CH_2)_5$. [b] Molar weight of sulfur (S) = 32. [c] Isolated yields of pure (96%) product, except for entries 1 and 2. [d] ~80% purity of product (^{1}H NMR, GC/MS).

thioamide **3**; however, the purity of the product was only ~80%, as judged by ^{1}H NMR and GC/MS measurements. Raising the reaction temperature to 120 °C (entry 2) furnished a somewhat higher yield of product; however, the purity of the isolated thioamide did not improve. When an excess of both the amine and sulfur components was employed (entry 3) the yield and purity (>95%) of the thioamide improved markedly. After considerable experimentation involving variation of molar ratios of the three components (data not shown), we arrived at conditions for which a 50% excess of the amine and a 25% excess of sulfur were utilized (entry 4). These conditions consistently produced the highest yields of thioamide **3** and allowed the convenient isolation of the product by precipitation with water in a very high state of purity (96%), as judged by ^{1}H NMR and GC/MS with only trace amounts of sulfur being present as impurity.[12] Doubling the concentration of building blocks further increased the yield (entry 5), whereas a lower reaction temperature (110 °C) and longer reaction time (3 min) produced an identical result. Ultimately, we decided to use 1-methyl-2-pyrrolidone (NMP) as the solvent of choice in all Kindler-type transformations, since at higher reaction temperatures (>140 °C), DMF and *N*,*N*-dimethylacetamide (DMA) started to decompose, and small amounts of thioamide byproducts derived from dimethylamine were detected as impurities. However, this did not present a problem for the comparatively moderate temperatures (100−120 °C) used in the optimization studies presented in Table 1.

The above optimization studies therefore provide controlled microwave-assisted reaction conditions that allow a rapid and convenient access to thioamides derived from aromatic aldehydes and cyclic secondary amines (i.e., morpholine, pyrrolidine). Indeed, most of the successful examples of Kindler three-component couplings described in the literature involve these somewhat restricted building block combinations.[4,5,8,9]

To increase the structural diversity and synthetic value of thioamides **3** that can be accessed using this three-component process (Scheme 1), it appeared of prime interest to extend this reaction also to, for example, primary amines, ammonia, and to substituted aromatic and aliphatic aldehydes. Here, the number of successful high yielding examples reported in the literature is rather limited.[13] Taking advantage of the sealed vessel capabilities (max 20 bar) of the microwave synthesizer,[11] we particularly wanted to explore the use of volatile amine and aldehyde building blocks. With these issues in mind, a diverse selection of 13 aldehyde (**1**, R_1) and 12 amine (**2**, R_2R_3) building blocks was utilized in the construction of a representative 34-member library of substituted thioamides **3** (Table 2). As expected, cyclic secondary amines (i.e., piperidine, morpholine, pyrrolidine, *N*-phenylpiperazine) reacted in high yield with a variety of aromatic aldehydes (Table 2, entries 1−8), providing the anticipated thioamides. Here, both electron-donating and -withdrawing substituents were tolerated on the aromatic ring. In addition, heterocyclic aldehydes (entries 4 and 7) and phenyl acetaldehyde (entry 3) also provided high yields of product. Similar to the optimization work involving piperidine detailed above (Table 1), relatively moderate reaction conditions (110−130 °C for 2−10 min) were sufficient in order to achieve quantitative conversions. In contrast, reaction temperatures of up to 180 °C and somewhat longer reaction times were necessary in order to accomplish full conversions for most Kindler-type thioamide preparations involving primary amines (entries 9−30). In general, reactions could be carried out either in the 170−180 °C region for 3−7 min (for examples, see entries 9 and 11), or at somewhat lower temperatures at the expense of an increased reaction time (140−150 °C, 10−20 min). Both methods led to virtually identical results in terms of product yields; however, purities were somewhat higher using the lower temperatures. Since many of the more complex primary amines employed are not water-soluble, we have further reduced the amount of amine in the building block composition to 5 mmol (Table 2, entries 9−30), as compared to 6 mmol for the previous examples involving water-soluble secondary amines (Table 1). Successful examples of primary amines in the Kindler condensation include benzylamines (entries 9 and 10), phenethylamines (entries 11−23), cyclohexylamine (entries 24 and 25), and propylamine (entries 26−30). Note that because of the sealed vessel capabilities, the use of volatile building blocks such as propylamine did not present a major problem (in contrast to conventional open vessel protocols). In fact, even ammonia could be employed in these condensations (entries 31−34) employing a commercial 7 M solution of ammonia in methanol. Here, the pressure in the reaction vial increased to 13 bar (see Figure S1 in the Supporting Information) at 180 °C reaction temperature. Alternatively, these transformations involving ammonia could also be carried out without NMP as solvent, leading to similar yields of benzothioamide products (160 °C, 20 min). Note that it was also possible to use combinations of volatile aldehyde and amine precursors (entry 30).

In the majority of cases, workup of the reaction mixtures involved simply pouring the NMP solution onto ice/water and filtration of the solid material (Table 2, workup a). In cases in which the final reaction products did not solidify or were soluble in water, extractions with diethyl ether were performed (workup b). The purity of all those crude samples was at least 90% as determined by ^{1}H NMR and GC/MS measurements (see Supporting Information). In a few cases, it was necessary to purify the final products by flash chromatography (workups c and d). For most of the examples presented in Table 2, yields were above 90%. Only for

Table 2. Conditions and Yields for Synthesizing a 34-Member Library of Thioamides 3 (Scheme 1) via Microwave-Promoted Kindler Reactions[a]

entry	R_1	R_2, R_3	**1**/**2**/S, mmol[b]	temp, °C	time, min	yield[c] (%), workup[d]
1	Ph	$-(CH_2)_5-$	4/6/5	110	3	95, a
2	4-(NO_2)Ph	$-(CH_2)_5-$	4/6/5	130	2	94, a
3	$PhCH_2$	$-(CH_2)_5-$	4/5/4.5	100	3	73, c
4	3-indolyl	$-(CH_2)_5-$	4/5/4.5	100	8	72, a
5	3-(NO_2)Ph	$-(CH_2)_2O(CH_2)_2-$	4/6.4/5	110	3	92, a
6	3-(MeO)-4-(OH)Ph	$-(CH_2)_2O(CH_2)_2-$	4/6/4.8	120	10	92, a
7	2-thiophenyl	$-(CH_2)_2N(Ph)(CH_2)_2-$	4/5/4.5	120	3	99, a
8	4-(Me)Ph	$-(CH_2)_4-$	4/6/4.8	110	3	91, a
9	Ph	H, $PhCH_2$	4/5/4.5	170	3	>99, a
10	3-(Me)Ph	H, 3-(Cl)$PhCH_2$	4/5/4.5	140	12	85, c
11	Ph	H, $PhCH_2CH_2$	4/5/4.5	180	4	>99, a
12	3,4-(MeO)Ph	H, $PhCH_2CH_2$	4/5/4.5	140	10	99, a
13	4-(NMe_2)Ph	H, $PhCH_2CH_2$	4/5/4.5	140	12	>99, a
14	3-(Cl)Ph	H, $PhCH_2CH_2$	4/5/4.5	140	12	97, a
15	3-(NO_2)Ph	H, $PhCH_2CH_2$	4/5/4.5	150	10	>99, a
16	2-(Me)Ph	H, $PhCH_2CH_2$	4/5/4.5	160	20	43, d
17	2-thiophenyl	H, $PhCH_2CH_2$	4/5/4.5	140	14	99, a
18	pentyl	H, $PhCH_2CH_2$	4/5/4.5	140	10	39, d
19	4-(NMe_2)Ph	H, 2-(MeO)$PhCH_2CH_2$	4/5/4.5	140	12	>99, a
20	3-(Me)Ph	H, 2-(MeO)$PhCH_2CH_2$	4/5/4.5	140	12	>99, b
21	3-indolyl	H, 2-(MeO)$PhCH_2CH_2$	4/5/4.5	140	10	99, a
22	3,4-(MeO)Ph	H, 4-(F)$PhCH_2CH_2$	4/5/4.5	140	10	93, a
23	3-(Cl)Ph	H, 4-(F)$PhCH_2CH_2$	4/5/4.5	140	10	97, a
24	Ph	H, cyclohexyl	4/5/4.5	170	5	92, a
25	3-(Cl)Ph	H, cyclohexyl	4/5/4.5	140	10	98, a
26	Ph	H, propyl	4/5/4.5	150	5	93, a
27	4-(NMe_2)Ph	H, propyl	4/5/4.5	170	7	97, a
28	3-(Cl)Ph	H, propyl	4/5/4.5	140	12	90, a
29	3-(NO_2)Ph	H, propyl	4/5/4.5	150	12	95, a
30	pentyl	H, propyl	4/5/4.5	140	10	54, d
31	Ph	H, H	4/6/4.5	180	20	44, d
32	4-(Me)Ph	H, H	4/6/4.5	170	20	36, d
33	3-(Cl)Ph	H, H	4/6/4.5	170	20	46, d
34	4-(NMe_2)Ph	H, H	4/6/4.5	160	20	38, c

[a] All reactions were carried out utilizing controlled single-mode microwave irradiation under sealed vessel conditions in NMP (2 mL). For details, see text. For a graphical representation of all thioamide products **3**, see Figure S2 in the Supporting Information. [b] Molar weight of sulfur (S) = 32. [c] Isolated yields of crude (workups a and b) or purified (workups c and d) products. The purity of all compounds was >90% as by GC/MS. See the Supporting Information. [d] For details of the workup procedures, see the Experimental Section in the text.

aliphatic aldehydes (entries 3, 18 and 30) and for cases involving ammonia as amine building block (entries 31−34) were yields considerable lower. The reasons for these low yields were not investigated further. Other limitations of the Kindler method include the use of ortho-substituted aromatic aldehydes (see, for example, entry 16), and the use of aromatic amines, with both types of building blocks furnishing only moderate yields of the desired thioamide products. In the case of benzaldehyde and aniline, for example, very high reaction temperatures (200−250 °C) were required to afford the desired *N*-phenylbenzothioamide in ~30% yield with varying amounts of 2-phenylbenzothiazole (10−15%) being formed as a byproduct.[14]

The examples of thioamide preparations shown in Table 2 represent carefully optimized and fine-tuned reaction conditions for a representative set of building block combinations. Utilizing the advantages of modern microwave synthesizers, allowing either parallel or sequential processing,[7b] the protocol presented herein allows the rapid generation of diverse sets of thioamides using the general concept of the Kindler coupling, a reaction that to our knowledge has so far not been utilized in the context of a combinatorial approach. The thioamides accessible via this route (in particular for R_2 = H) are important building blocks in heterocyclic synthesis.[1]

General Microwave Procedure for the Synthesis of Thioamides 3.[11] Elemental sulfur, 2 mL of NMP, the corresponding amine **2**, and the appropriate aldehyde **1**, (in that order; for molar ratios, see Table 2) were charged into a large Smith process vial. After the addition of a Teflon-coated stirring bar, the vial was sealed with a Teflon septum and aluminum crimp, using the appropriate crimping tool. The mixture was heated in the single-mode microwave cavity (max power 300 W) for 2−20 min at 110−180 °C (see Table 2). After cooling, the usually dark brown reaction mixture was poured onto ice (40 g). In the case of a solid thioamide product, the precipitate was removed by filtration (workup a). In those instances for which the thioamide did not solidify, extraction with diethyl ether (3 × 20 mL) was performed, followed by washing (brine) and drying (sodium sulfate) of the combined organic phases and evaporation (workup b). In a few cases, purification of the crude materials (solids, workup c; or liquids, workup d) by silica gel flash chromatography had to be carried out in order to obtain thioamides with sufficient purity.

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Supporting Information Available. ^{1}H NMR and GC/MS data, structures and systematic names of all 34 thioamide products **3**, and typical heating profiles for a microwave-assisted process. This material is available free of charge over the Internet at http://pubs.acs.org.

References and Notes

(1) Takahata, H.; Yamazaki, T. *Heterocycles* **1988**, *27*, 1953−1973. Hurd, R. N.; Delamater, G. T *Chem. Rev.* **1961**, *61*, 45−86.

(2) Schaumann, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 419−434.

(3) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187−230.

(4) For reviews on the Kindler reaction and related processes (e.g., the Willgerodt reaction), see the following: (a) Carmack, M.; Spielman, M. A. *Org. React.* **1946**, *3*, 83−107. (b) Brown, E. V. *Synthesis* **1975**, 358−375.

(5) For more recent applications, see the following: (a) Dutron-Woitrin, F.; Merenyi, R.; Viehe, H. G. *Synthesis* **1985**, 77−78. (b) Amupitan, J. O. *Synthesis* **1983**, 730. (c) Li, R.-T.; Ye, W.-Y. *Synth. Commun*. **1995**, *25*, 921−925. (d) You, Q.; Zhou, H.; Wang, Q.; Lei, X. *Org. Prep. Proced. Int.* **1991**, *23*, 435−438. (e) Stillings, M. R.; Welbourn, A. P.; Walter, D. S. *J. Med. Chem*. **1986**, *29*, 2280−2284. (f) Duceppe, J. S.; Gauthier, J. *J. Heterocycl. Chem*. **1985**, *22*, 305−310. (g) Greve, S.; Näther, C.; Friedrichsen, W. *Org. Lett.* **2000**, *2*, 2269−2270. (h) Kanabara, T.; Kawai, Y.; Hasegawa, K.; Morita, H.; Yamamoto, T. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 3739−3750.

(6) (a) Hayes, B. L. Microwave Synthesis: Chemistry at the Speed of Light; CEM Publishing: Matthews, NC, 2002. (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: New York; 2002. (c) For more information on microwave-assisted organic synthesis, see http://www.maos.net.

(7) For reviews on microwave-assisted combinatorial chemistry, see for example: Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (b) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314−320.

(8) (a) Moghaddam, F. M.; Ghaffarzadeh, M. *Synth. Commun.* **2001**, *31*, 317−321. (b) Gupta, M.; Paul, S.; Gupta, R. *Synth. Commun.* **2001**, *31*, 53−59. (c) Nooshabadi, M.; Aghapoor, K.; Reza Darabi, H.; Majid Mojtahedi, M. *Tetrahedron Lett.* **1999**, *40*, 7549−7552.

(9) (a) Tomchin, A. B. *Zh. Org. Chim.* **1981**, *17*, 589−595. (b) Kanyonyo, M. R.; Ucar, H.; Isa, M.; Carato, P.; Lesieur, D.; Renard, P.; Poupaert, J. H. *Bull. Soc. Chim. Belg.* **1996**, *105*, 17−22. (c) Cornea, F.; Cercasov, C.; Ciureanu, M. *Spectrochim. Acta Part A* **1980**, *36*, 775−782.

(10) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213−223.

(11) All microwave irradiation experiments were performed using the SmithSynthesizer from Personal Chemistry AB (ref 15). For a detailed description of this instrument, see the following: Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624−630.

(12) The use of excess sulfur does not create a problem for the purity of the final thioamide product so long as the amine is also used in excess. The reactive intermediates involved in the Kindler reaction are most likely polar water-soluble nitrogen−sulfur species formed from elemental sulfur and the amine, attacking the initially formed azomethine or aminal intermediates. For details, see ref 5h and the following: Carmack, M. *J. Heterocycl. Chem.* **1989**, *26*, 1319−1323.

(13) (a) Kanyonyo, M. R.; Gozzo, A.; Lambert, D. M.; Lesieur, D.; Poupaert, J. H. *Bull. Soc. Chim. Belg.* **1997**, *106*, 39−45. (b) Robbe, Y.; Fernandez, J.-P.; Chapat, J.-P.; Sentenac-Roumanou, H.; Fatome, M.; Subra, G. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 16−25.

(14) Bottcher, B.; Bauer, F. *Liebigs Ann. Chem.* **1950**, 568, 218−27.

(15) PersonalChemistry AB, Kungsgatan 76, SE-753 18 Uppsala, Sweden. Phone: +46-18-4899000. Fax: 46-18-4899100. http://www.personalchemistry.com

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