Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Efficient and rapid route to thioamides via modified Willgerodt-Kindler reaction of quinaldine and picolines under microwave irradiation

Firouz Matloubi Moghaddam[a]; Hassan Zali Boinee[a]; Salman Taheri[a]
[a] Department of Chemistry, Sharif University of Technology, Tehran, Iran

To cite this Article Moghaddam, Firouz Matloubi , Boinee, Hassan Zali and Taheri, Salman(2004) 'Efficient and rapid route to thioamides via modified Willgerodt-Kindler reaction of quinaldine and picolines under microwave irradiation', Journal of Sulfur Chemistry, 25: 6, 407 — 412
To link to this Article: DOI: 10.1080/17415990412331327369
URL: http://dx.doi.org/10.1080/17415990412331327369

J. Sulfur Chemistry
Vol. 25, No. 6, December 2004, 407–412

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Efficient and rapid route to thioamides via modified Willgerodt–Kindler reaction of quinaldine and picolines under microwave irradiation

FIROUZ MATLOUBI MOGHADDAM*, HASSAN ZALI BOINEE and SALMAN TAHERI

Sharif University of Technology, Department of Chemistry, PO Box 11365-9516 Tehran, Iran

(*Received 27 June 2004; in final form 11 September 2004*)

Various thioamides, especially thiobenzanilides and thioacetomorpholides, bearing a heterocycle ring were efficiently prepared by a modified Willgerodt–Kindler reaction of quinaldine and α- and γ-picoline with anilines and morpholine in the presence of sulfur, and a catalytic amount of DABCO under microwave irradiation.

Keywords: Thioamide; Willgerodt–Kindler reaction; Microwave irradiation; Picolines

1. Introduction

Thioamides are of importance in medicinal chemistry [1] due to their biological activity, *e.g.* against bacterial infection [2], as fungicides [3], herbicides [4], and antiulcerative agents [5]. Apart from these applications, thioamides are valuable building blocks for the synthesis of five- and six-membered heterocycles [6]. The Willgerodt–Kindler reaction is a well-known method for the synthesis of thioamides. In the original Willgerodt–Kindler reaction, ketones and aldehydes were found to react with sulfur and secondary amines to give terminal thioamides. This reaction already has been extended from its original form to encompass many other functional groups such as unsaturated hydrocarbons, nitriles, amines, imines, epoxides and alcohols [7].

Various attempts have been made for the preparation of thioamides from the corresponding picolines and quinolines. For instance, γ-picoline was thermally treated with *m*-anilines in the presence of sulfur to give the corresponding thioanilides along with a small amount of benzothiazoles [8]. These reactions were found to take place in low yields (10–35%) and to require long reflux times (6–24 h)

Recently, we have shown the efficiency of microwave heating for the synthesis of thioamides from styrenes, aldehydes, ketones, and nitriles [9]. In recent years, the concept of accelerating synthetic transformations through microwave activation has created much interest in organic

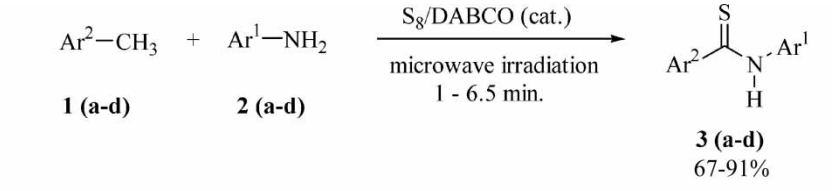
* Corresponding author. E-mail: matloubi@sharif.edu

J. Sulfur Chemistry
ISSN 1741-5993 print; ISSN 1741-6000 online
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990412331327369

synthesis. In particular, the use of dedicated microwave ovens that enable the rapid and safe heating of reaction mixtures with online temperature monitoring has greatly increased the general acceptance of the microwave heating method [10].

2. Results and discussion

The present study is focused on a modified Willgerodt–Kindler reaction of quinaldine and α- and γ-picoline with aniline derivatives in the presence of sulfur, a catalytic amount of DABCO, and under microwave irradiation (scheme 1).



a: Ar^1 = phenyl, Ar^2 = 2-quinolyl **b:** Ar^1 = *p*-tolyl, Ar^2 = 2-quinolyl

c: Ar^1 = *p*-tolyl, Ar^2 = 2-pyridyl **d:** Ar^1 = 2,4-dimethoxyphenyl, Ar^2 = 2-quinolyl

SCHEME 1

To the best of our knowledge, this reaction has not been reported in the literature, and also the less expensive methyl aromatic ketones are preferred over aldehydes. After performing several experiments involving the variation of molar proportions of the quinaldine and/or picolines, aniline derivatives, sulfur, and DABCO, we found that the best molar proportions for the reaction course were 2:1:1.2:0.05 respectively.

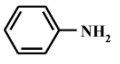
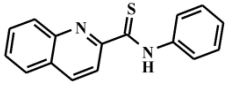
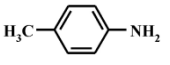
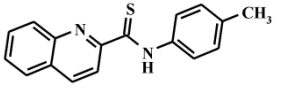
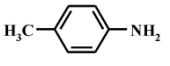
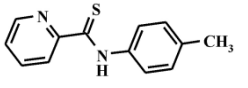
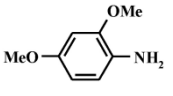
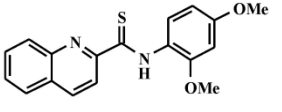
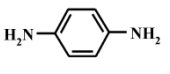
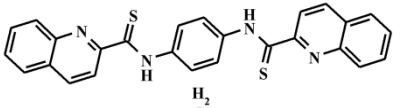
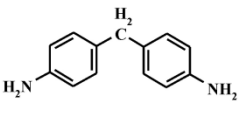
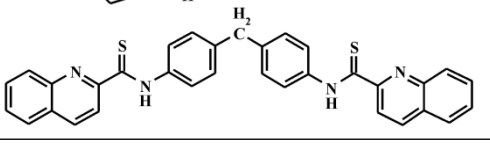
The reaction is performed in solvent-free conditions. In a typical procedure, quinaldine (10 mmol), aniline (5 mmol), S (6 mmol), and DABCO (0.25 mmol) were mixed in a reflux flask and irradiated in a monomode microwave oven [11] for 1–6.5 min in two steps. The resulting thioanilide was simply isolated from the reaction mixture by pouring the mixture into a polar solvent such as methanol. The excess of sulfur was removed by filtration, and the crude thioanilide was separated from the mother liquor. The purity of the crude products was more than 90% as determined by ^{1}H-NMR spectroscopy, and the final recrystallization led to pure products. The results are summarized in table 1.

We have also shown that our method could be extended to diamines (double-Willgerodt–Kindler reaction), leading to bisthioanilides (table 1, entries 5–7). It should be noted that even in these cases isolation of the final products was performed by simple filtration and the final crystallization in a suitable solvent.

We also examined the reaction of a secondary aliphatic amine such as morpholine with some heteroaromatics having an activated methylene group in the presence of sulfur and a catalytic amount of DABCO. It was found that in the case of γ-picoline and quinaldine the reaction is faster (1–2 min) and yields are very high (93 and 95%, respectively), whereas for 4-ethylpyridine the corresponding thioamide was obtained in moderate yield (57%) (table 1, entries 8–10).

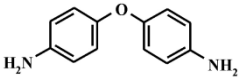
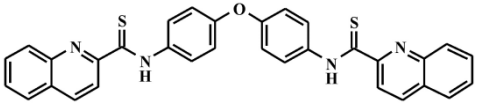
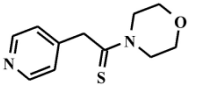
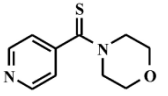
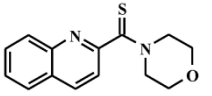
In conclusion we have developed a new method for the rapid conversion of quinaldine and/or picolines to the corresponding thioanilides and thioacetomorpholides. These valuable compounds could be used as versatile building block in heterocyclic chemistry [6]. They also have great importance in medicinal chemistry as well as in agriculture. The reaction time is very short (1–6.5 min) compared with the conventional methods (6–24 h) [8].

Table 1. Microwave-assisted Willgerodt-Kindler reaction of heteroaromatics having an activated methylene group.

Entry	Amine	Thioamide[a]	Compound	Time (t/min)	M.p. (°C) (literature)	Yield (%)[b]
1			**3a**	3	110–111 (109–110) [12c]	91
2			**3b**	2.5	116–117 (117–118) [12c]	87
3			**3c**	3	98–99.5 (101–102) [12d]	67
4			**3d**	4	132–136	78
5			**3e**	6	299–303 (306) [12f]	39
6			**3f**	5	221–223 (214–215) [12f]	42

(*continued*)

Table 1. Continued.

Entry	Amine	Thioamide[a]	Compound	Time (t/min)	M.p. (°C) (literature)	Yield (%)[b]
7			**3g**	6.5	205–207	58
8			**3h**	2	105–107 (104–105) [12e]	57
9			**3i**	2	151–152 (153) [12e]	93
10			**3j**	1	173–174 (172–174) [12a]	95

[a]All known compounds gave satisfactory and spectroscopic analysis compared to the authentic samples and literature [12].
[b]All yields refer to isolated products and are based on the amine as limiting reagent.

3. Experimental

All products gave satisfactory spectroscopic data. FT IR spectra were recorded for samples as KBr pellets on a Nicolet spectrometer (Magna 550). A Bruker (DRX-500 Avance) NMR spectrometer was used to record the ^{1}H NMR spectra. All NMR spectra were determined in $CDCl_3$ at ambient temperature. Melting points were determined on a Büchi B540 apparatus.

3.1 *General Procedure for the preparation of thioamides*

Caution: All experiments should be carried out in an efficient hood to avoid exposure to noxious hydrogen sulfide vapors.

In a typical experiment, a mixture of quinaldine (10 mmol), aniline (5 mmol), sulfur (6 mmol), and DABCO (0.25 mmol) was charged in a two-necked flask (25 mL) fitted with a condenser and thermometer probe. Irradiation (two-step) was performed at 500 W in such a way that in the initial step the temperature of the reaction mixture rose from room temperature to 100 °C (during 2 min), and in the second step from 100 °C to 140 °C in 3 min. After cooling, the reaction mixture was poured into methanol (25 mL) and the precipitate was filtered off. The filtrate was evaporated to one half the original volume, then left in a refrigerator. The crude solid was filtered off, and recrystallized from ethanol.

3.2 *Spectroscopic data for the compounds 3a–3k*

3a: Orange crystals (MeOH); mp 110–111 °C; ^{1}H NMR 12.27 (s, 1H), 9.20 (d, *J* 8.5 Hz, 1H), 8.18 (d, *J* 7.9 Hz, 2H), 8.11 (d, *J* 8.4 Hz, 1H), 7.71 (d, *J* 8.6 Hz, 1H), 7.45 (t, *J* 7.2 Hz, 1H), 7.41 (d, *J* 8.1 Hz, 1H), 7.25 (m, 3H), 7.08 (t, *J* 7.1 Hz, 1H); IR 3630, 1592, 1530, 1375 cm^{-1}.

3b: Orange crystals (MeOH); mp 116–117 °C; ^{1}H NMR 12.27 (s, 1H), 9.22 (d, *J* 8.6 Hz, 1H), 8.14 (d, *J* 8.2 Hz, 2H), 8.11 (d, *J* 8.5 Hz, 1H), 7.69 (d, *J* 8.6 Hz, 1H), 7.54 (t, *J* 7.2 Hz, 1H), 7.41 (d, *J* 8.1 Hz, 1H), 7.23 (t, *J* 7.3 Hz, 1H), 7.08 (d, *J* 8.1 Hz, 2H), 2.16 (s, 3H); IR 3415, 1607, 160, 1461 cm^{-1}.

3c: Orange crystals (MeOH); mp 98–99.5 °C; ^{1}H NMR 12.1 (s, 1H), 9.01 (d, *J* 7.9 Hz, 1H), 8.13 (d, *J* 4.1 Hz, 1H), 8.08 (d, *J* 8.1 Hz, 2H), 7.15 (t, *J* 7.7 Hz, 1H), 7.03 (d, *J* 8.1 Hz, 2H), 6.71 (t, *J* 5.0 Hz, 2H), 2.14 (s, 3H); IR 3415, 1630, 1538, 1384 cm^{-1}.

3d: Yellow crystals (MeOH); mp 132–136 °C; ^{1}H NMR 13.12 (s, 1H), 9.98 (d, *J* 8.9 Hz, 1H), 9.27 (d, *J* 8.6 Hz, 1H), 8.20 (d, *J* 8.4 Hz, 1H), 7.69 (d, *J* 8.6 Hz, 1H), 7.46 (t, *J* 7.0 Hz, 1H), 7.40 (d, *J* 8.0 Hz, 1H), 7.24 (t,*J* 7.9 Hz, 1H), 6.53 (d, *J* 2.5 Hz, 1H), 6.46 (d, *J* 6.5 Hz, 1H); IR 3407, 1615, 1538, 1400 cm^{-1}.

3e: Yellow crystals (MeOH); mp 159–161 °C; ^{1}H NMR 12.02 (s, 2H), 9.02 (d, *J* 8.6 Hz, 2H), 8.07 (d, *J* 8.4 Hz, 2H), 7.98 (d, *J* 8.6 Hz, 2H), 7.91 (d, *J* 8.4 Hz, 4H), 7.62 (d, *J* 8.1 Hz, 2H), 7.58 (t, *J* 7.3 Hz, 2H), 7.40 (t, *J* 7.4 Hz, 2H); IR 3423, 1623, 1515, 1392 cm^{-1}.

3f: Lustrous yellow crystals (EtOH); mp 221–223 °C; ^{1}H NMR 12.28 (s, 2H), 9.00 (d, *J* 8.6 Hz, 2H), 8.37 (d, *J* 8.6 Hz, 2H), 8.21 (d, *J* 8.3 Hz, 2H), 8.13 (d, *J* 8.3 Hz, 4H), 7.94 (d, *J* 8.0 Hz, 2H), 7.84 (t, *J* 7.2 Hz, 2H), 7.68 (t,*J* 7.1 Hz, 2H), 7.37 (d,*J* 8.1 Hz, 4H), 4.13 (s, 2H); ^{13}C NMR 188.0, 150.8, 145.2, 139.7, 137.8, 137.5, 131.0, 130.0, 129.8, 129.5, 128.6, 128.1, 123.4, 121.7, 41.7; IR (KBr) 3645, 1592, 1507, 1384 cm^{-1}.

3g: Lustrous orange crystals (EtOH); mp 205–207 °C; ^{1}H NMR 12.27 (s, 2H), 9.00 (d, *J* 8.6 Hz, 2H), 8.37 (d, *J* 8.6 Hz, 2H), 8.21 (d, *J* 5.2 Hz, 2H), 8.18 (d, *J* 6.7 Hz, 4H), 7.94 (d, *J* 8.0 Hz, 2H), 7.84 (t, *J* 7.1 Hz, 2H), 7.68 (t, *J* 7.2 Hz, 2H), 7.21 (d, *J* 8.8 Hz, 4H); ^{13}C NMR 188.1, 155.5, 150.8, 145.3, 137.7, 134.8, 131.0, 130.0, 129.6, 128.6, 128.1, 124.9, 121.6, 119.6; IR (KBr) 3569, 1592, 1500, 1384 cm^{-1}.

3h: White crystals (EtOH); mp 105–107 °C; ^{1}H NMR 8.58 (d, *J* 5.74 Hz, 2H), 7.26 (d, *J* 5.17 Hz, 2H), 4.53 (t, *J* 4.85 Hz, 2H), 4.33 (s, 2H), 3.77 (t, *J* 4.85 Hz, 2H), 3.59 (t, *J* 4.85 Hz, 2H), 3.74 (t, *J* 4.85 Hz, 2H); IR (KBr) 3035, 1653, 1510, 1385 cm^{-1}.

3i: White crystals (EtOH); mp 151–152 °C; ^{1}H NMR 8.63 (d, *J* 5.9 Hz, 2H), 7.17 (d, *J* 5.9 Hz, 2H), 4.42 (t, *J* 4.8 Hz, 2H), 3.89 (t, *J* 4.9 Hz, 2H), 3.66 (t, *J* 5.0 Hz, 2H), 3.55 (t, *J* 4.5 Hz, 2H); IR (KBr) 3023, 1645, 1530, 1386 cm^{-1}.

3j: Yellow crystals (MeOH); mp 173–174 °C; ^{1}H NMR 8.24 (d, *J* 8.5 Hz, 1H), 8.1 (d, *J* 8.5 Hz, 1H), 7.86 (d, *J* 8.1 Hz, 1H), 7.78 (t, *J* 7.1 Hz, 1H), 7.74 (d, *J* 8.5 Hz, 1H), 7.61 (t, *J* 7.2 Hz, 1H), 4.54 (t, *J* 4.9 Hz, 2H), 4.00 (t, *J* 4.9 Hz, 2H), 3.79 (t, *J* 3.9 Hz, 2H), 3.74 (t, *J* 5.0 Hz, 2H); IR (KBr) 3057, 1639, 1510, 1392 cm^{-1}.

References

[1] Smith, J., Liras, J. L., Schneider, S. E. and Anslyn, E. V., 1996, *J. Org. Chem.*, **61**, 881.
[2] Mallams, A. K., Morton, J. B., and Reichert, P. J., 1981, *J. Chem. Soc., Perkin Trans. 1*, 2186.
[3] Schroeder, D. C., 1955, *Chem. Rev.*, **55**, 181.
[4] Sarkis, G. Y., Faisal, E. D., 1985, *J. Heterocycl. Chem.*, **22**, 137.
[5] Gibinski, K., 1981, *Curr. Med. Res. Opin.*, **7**, 516.
[6] (a) Jagodzinski, S. T., 2003, *Chem. Rev.*, **103**, 197–227; (b) Griffin, T. S., Woods, T. S., Klayman, D. L., 1975, In *Advances in Heterocyclic Chemistry*, A. R. Katritzky, A. J. Boulton (Eds), vol. 18, p. 99, Academic Press, New York; (c) Matloubi Moghaddam, F., Zali Boinee, H., 2003, *Tetrahedron Lett.*, **44**, 6253; (d) Matloubi Moghaddam, F. and Zali Boinee, H., 2004, *Tetrahedron*, **60**, 6085.
[7] Brown, E. V., 1975, *Synthesis*, 358.
[8] Hisano, T., Yabuta, Y., 1973, *Chem. Pharm. Bull.*, **21**, 511.
[9] (a) Matloubi Moghaddam, F., Ghaffarzadeh, M. and Dekamin, M., 2000, *J. Chem. Res.* (***S***), 228; (b) Matloubi Moghaddam, F. and Ghaffarzadeh, M., 2001, *Synth. Commun.*, **31**, 317; (c) Matloubi Moghaddam, F., Hojabri, L. and Dohendou, M., 2003, *Synth. Commun.*, **33**, 4276.
[10] Zbruyev, O. I., Stiasni, N. and Kappe, O., 2003, *J. Comb. Chem.* **5**, 145.
[11] Milestone ETHOS-MR, microwave laboratory system.
[12] (a) Malan, L. R. and Dean, P. M., 1947, *J. Am. Chem. Soc.*, **69**, 1797; (b) Schmitt, J. and Suquet, M., 1956, *Bull. Soc. Chim. Fr.*, 755; (c) Schmitt, J. and Suquet, M., 1960, *Bull. Soc. Chim. Fr.*, **8**, 51; (d) Saikachi, H. and Hisano, T., 1959, *Chem. Pharm. Bull*, **7**, 349; (e) Porter, H. D., 1954, *J. Am. Chem. Soc.*, **76**, 127; (f) Chupakhin, O. N., Pushkareva, Z. V. and Darienko, E. P., 1963, *Zh. Obshch. Khim.*, **33**, 2401.