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Willgerodt-Kindler reaction at room temperature: Synthesis of thioamides from aromatic aldehydes and cyclic secondary amines

Arun D. Kale, Yogesh A. Tayade, Sachin D. Mahale, Rahul D. Patil, Dipak S. Dalal*

Department of Organic Chemistry, School of Chemical Sciences, Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon 425 001, MS, India

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ABSTRACT

A simple method for the synthesis of thioamide derivatives in DMSO at room temperature and at 120 °C has been developed. Total 27 compounds were prepared under both conditions via a one-pot, three component reaction between substituted aromatic aldehydes, elemental sulfur powder, and cyclic secondary amines. By optimizing the mole ratio of sulfur powder and amines, we have successfully carried out Willgerodt-Kindler reaction of aromatic aldehydes at room temperature. At 120 °C, it is catalyst free reaction with lower reaction time whereas at room temperature, due to the additional amine molecule, Willgerodt-Kindler reaction of aromatic aldehydes is successfully carried out at room temperature. On gram-scale, the reaction is successfully attempted under both conditions with good yields.

1. Introduction

Thioamides have attracted the attention of scientific community from a long time due to its broad range of biological activities such as antioxidant, antimicrobial, anticonvulsant, antithyroid, anticancer activities [1], tuberculosis and leprosy [2]. Thioamides are also found in vital biological and pharmaceutical molecules, such as closthioamide [3a], hydroxymethyl thiolactam cyclothialidine [3b], and N-cyclohexylethyl-ETAV [3c], etc. Thioamides are key intermediates and valuable building blocks for preparation of biologically relevant heterocyclic scaffolds [4]. Thioamides have attracted recent attention in transition-metal coordination chemistry [5], polymer synthesis [6], inclusion chemistry and materials science [7]. Therefore, various approaches for the synthesis of thioamides have been developed.

The Willgerodt reaction was first described by Conrad Willgerodt in 1887, which involved the oxidation/rearrangement of a ketone to form a terminal amide [8]. After that in 1923, K. Kindler reported a modification of this reaction, which involved the reaction of aryl alkyl ketone, sulfur and a primary or secondary amine to afford the thioamide derivatives [9]. α-Ketothioamides were synthesized under solvent-free and non-catalyst conditions using IR energy as a source of activation [10]. Synthesis of thiomorpholide from substituted acetophenones in PEG-600 was also achieved [11]. Takaki Kanbara et al. [12] have reported the synthesis of thiobenzanilides from anilines and benzaldehydes in presence of catalytical amount of $Na_2S·9H_2O$. V. V. Kulganek and L. A. Yanovskaya [13] reported synthesis of thioamide derivatives by using *p*-toluene sulfonic acid as catalyst at different temperature (Scheme 1-a). The synthesis of thioamide was also attempted using 1-methyl-2-pyrrolidone as solvent under harsh reaction conditions, such as high temperature or microwave irradiation (Scheme 1-b) [14]. H. R. Darabi et al. [15] have used water as a solvent to carry out the Willgerodt-Kindler reaction (Scheme 1-c). The thioamides were synthesized by using primary amines, aldehyde, sulfur powder and K_2CO_3 in water (Scheme 1-d) [16]. Thioamides were also obtained by reaction of nitriles (Scheme 1-e) [17], arylacetic acids (Scheme 1-f) [18] and alkynes (Scheme 1-g) [19]. However, nitriles, arylacetic acids, and alkynes are not cheap starting materials. S. Chen et al. [20] reported synthesis of thioamide by using 1, 2-dibenzyldisulfane and difurfuryl disulfide using iodine as oxidant in DMSO as solvent (Scheme 1-h). Marta Feroci et al. [21] have recently reported synthesis of thioamide with three different protocols by using aldehydes, elemental sulfur and cyclic secondary amines (Scheme 1-i). In continuation of our work on thioamide synthesis [22], we have recently reported synthesis of thioamides

* Corresponding author.
E-mail addresses: dsdalal2007@gmail.com, dsdalal@nmu.ac.in (D.S. Dalal).

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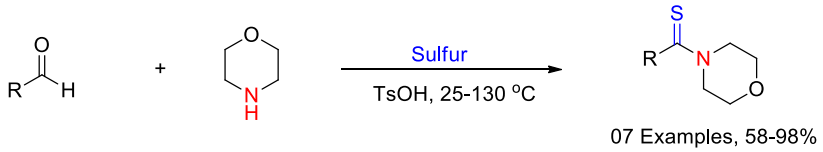
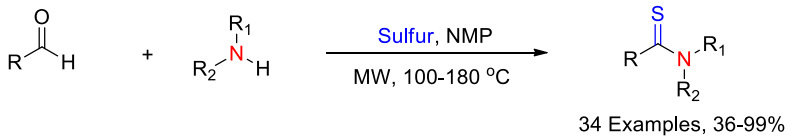
0040-4020/

Previous Reports:

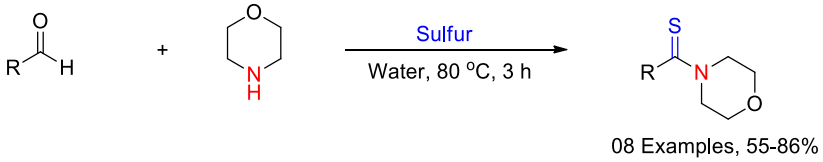
a) L. A. Yanovskaya, *et al.*[13]



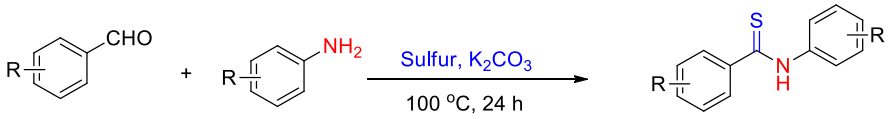
b) C. Oliver Kappe, *et al.*[14]



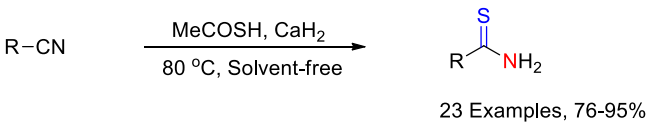
c) H. R. Darabi, *et al.*[15]



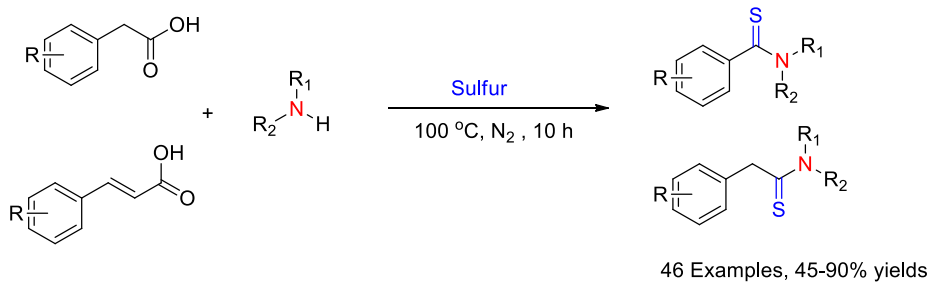
d) Xiangge Zhou, *et al.*[16]



e) P. N. Arunachalam, *et al.*[17]



f) K. N. Singh, et al.[18]



g) T. B. Nguyen, et al.[19]

Scheme 1. Previous work and our work for synthesis of thioamides.

using β-cyclodextrin as supramolecular catalyst in water (Scheme 1-j) [22d].

All reported methods for the synthesis of thioamide derivatives from aromatic aldehydes, nitriles, arylacetic acids, alkynes, and 1, 2-dibenzyldisulfane obtained satisfactory results. However, the synthetic methods reported in literature involved use of acid, base or neutral catalyst, higher reaction temperature, microwave irradiation, nitrogen atmosphere, requires higher reaction time and resulted in lower yields. For the first time, we are reporting the synthesis of thioamides using aromatic aldehydes, elemental sulfur and cyclic secondary amines at room temperature (1:4:2) and as well as at 120 °C (1:4:1) under catalyst free in DMSO solvent (Scheme 2). Willgerodt-Kindler reaction at room temperature and at 120 °C is significant for large scale preparation of thioamide derivatives.

2. Results & discussion

After studying the literature reports, it reveals that thioamide synthesis was carried out at higher temperature using acid, base or neutral catalyst. To attempt reaction at room temperature, we have optimized the solvent, temperature and mole ratios of aldehyde, secondary amine and sulfur. We have performed the model reaction using 4-chlorobenzaldehyde (1a; 1.0 equiv.), elemental sulfur

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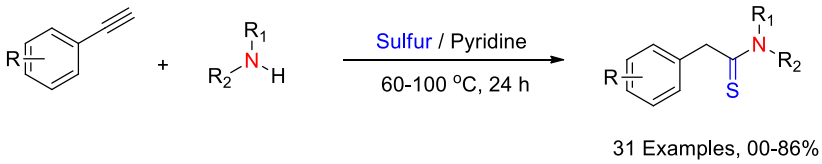
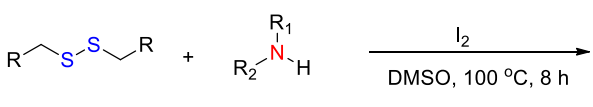


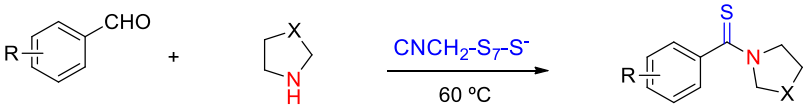
31 Examples, 00-86% yields

h) S. Chen, *et al.*[20]



26 Examples, 17-95% yields

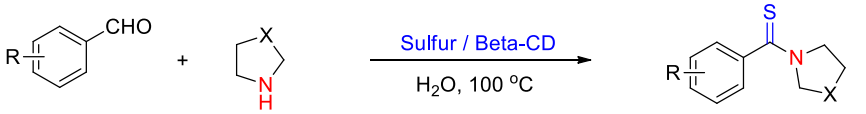
i) Marta Feroci, *et al.*[21]



X= CH_2-O, CH_2-CH_2, CH_2

18 Examples, tr-100%

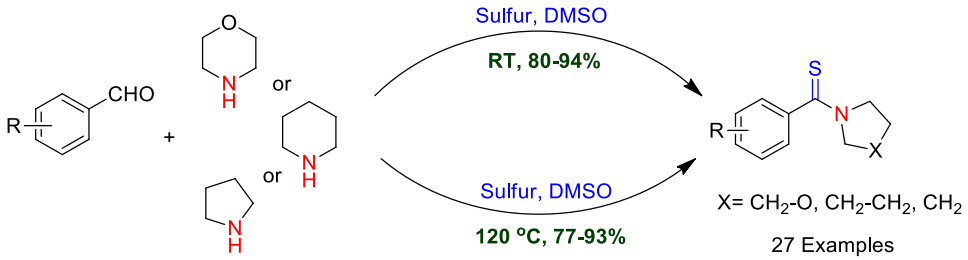
j) Dipak S. Dalal, *et al.*[22d]



X= CH_2-O, CH_2-CH_2, CH_2

21 Examples, 80-96%

This Work:



X= CH_2-O, CH_2-CH_2, CH_2

27 Examples

Scheme 1. (*continued*).

powder (2; 4.0 equiv.), and morpholine (3; 1.0 equiv.) in the absence of any catalyst in DMSO (10 mL) at room temperature. Interestingly, the reactants resulted in the formation of desired compound, 4-chlorophenyl (morpholino)methanethione (**4a**) in 78% yield on stirring for 56 h (Table 1, entry 1). Thus, to improve the reaction yield and time, in second experiment a mixture of 4-chlorobenzaldehyde (1a; 1.0 equiv.), elemental sulfur powder (2; 4.0 equiv.), and morpholine (3; 1.5 equiv.) in DMSO (10 mL) was stirred at room temperature for 24 h affording the 4-chlorophenyl (morpholino)methanethione (**4a**) in 90% yield (Table 1, entry 2). The best result was obtained with 4-chlorobenzaldehyde (1a; 1.0 equiv.), elemental sulfur powder (2; 4.0 equiv.), and morpholine (3; 2.0 equiv.) in DMSO (10 mL) at room temperature after 6 h affording the 4-chlorophenyl (morpholino)methanethione (4a) in 92% yield (Table 1, entry 3). This decrease in reaction time up to 6 h at room temperature (Table 1, entry 1 & 3) indicates that loading of second equivalent of amine increases the rate of reaction. Thereafter, the model reaction was carried out in different solvents at room temperature (Table 1, entries 4–14). The results showed that DMSO is the efficient solvent for the synthesis of aim product. However, the yield of aim product in DMSO was a bit higher than that of in DMF. No product formation was observed in EtOH, water, MeOH, DCM and THF (Table 1, entries 10–14). Whereas, trace product formation was observed in 1, 4-dioxane, toluene and ethyl acetate (Table 1, entries 7–9). Considering toxicity and yield of product, DMSO was chosen as optimizing solvent, while other solvents, such as EtOH, acetonitrile, 1,4-dioxane, water, MeOH, toluene, acetone, DCM, ethyl acetate, THF were not suitable for application of this synthesis (Table 1, entry 4–14), hence all the reactions were carried out in DMSO at room temperature.

We noted that the nucleophilicity of cyclic secondary amine is the key factor for the Willgerodt-Kindler reaction at room temperature. Too understood this, we have performed some control experiments using primary amines like aniline, 4-methoxy aniline and ethyl amine and acyclic secondary amines like diphenyl amine and diethyl amine at room temperature using 1:4:2 proportion of 4-chlorobenzaldehyde:sulfur:amine. Initially the colour of reaction mixture is colourless and it remains same after addition of sulfur powder. This indicates that the selected primary amines and acyclic secondary amines are not sufficiently nucleophilic to form polysulfide anions. Therefore, after 24 h of stirring in DMSO solvent, no product is obtained. Whereas in case of cyclic secondary amines,

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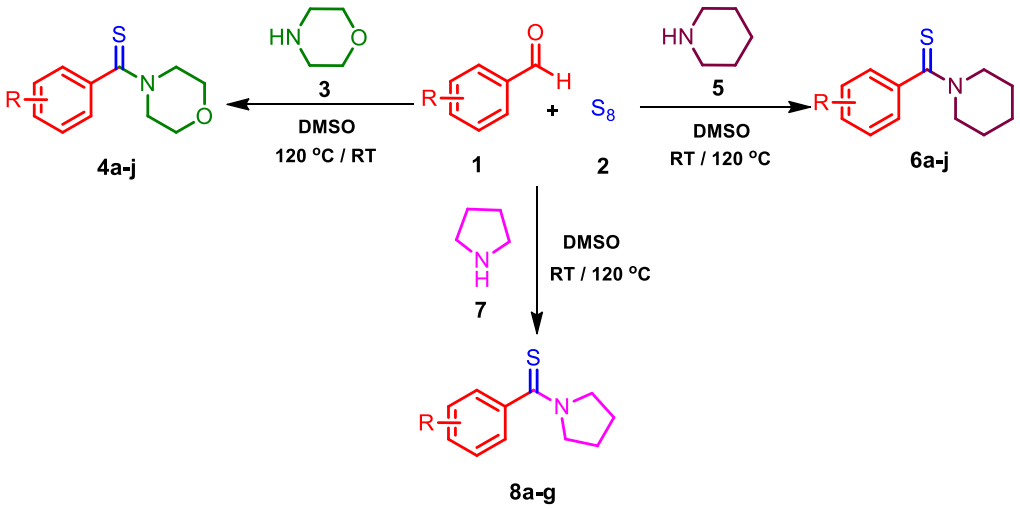
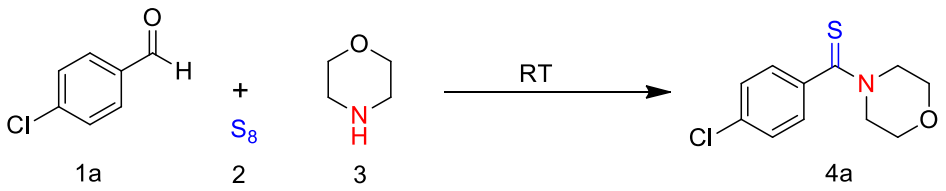


Scheme 2. General scheme for the synthesis of thioamide derivatives.

Table 1
Reaction optimization at room temperature.



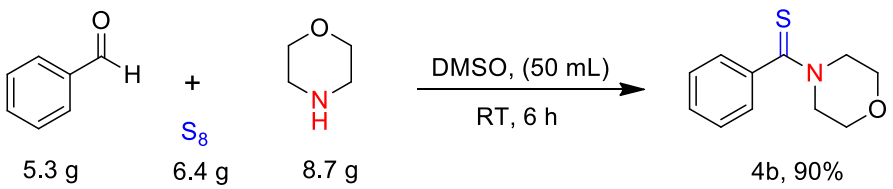
Entry	Solvent	Mole Ratio 1a: 2 : 3	Time (h)	Yield[a] (%)
1	DMSO	1:4:1	56	78
2	DMSO	1:4:1.5	24	90
3	**DMSO**	**1:4:2**	**6**	**92**
4	Acetonitrile	1:4:2	24	30
5	DMF	1:4:2	6	91
6	Acetone	1:4:2	24	65
7	1,4-Dioxane	1:4:2	24	Trace
8	Toluene	1:4:2	24	Trace
9	Ethyl acetate	1:4:2	24	Trace
10	EtOH	1:4:2	24	N.P.
11	Water	1:4:2	24	N.P.
12	MeOH	1:4:2	24	N.P.
13	DCM	1:4:2	24	N.P.
14	THF	1:4:2	24	N.P.

Reaction conditions: 4-Chlorobenzaldehyde (2 mmol), Morpholine (4 mmol), Sulfur powder (8 mmol) and Solvent (10 mL).
[a] Isolated yield.

the colourless reaction mass after addition of elemental sulfur powder turns to the reddish-brown colour.

The reaction of benzaldehyde, morpholine and elemental sulfur was successfully scaled-up (50 mmol) at room temperature (Scheme 3, yield 90%).

After getting the success at room temperature and to avoids the excess of cyclic secondary amine from the reaction, we have again optimized the solvent, temperature and mole ratios of aldehyde, secondary amine and sulfur. So, in our efforts, we have carried out optimization of the reaction conditions employing 4-chloro benzaldehyde (1a), elemental sulfur powder (2), and morpholine (3) as model reactants by varying different parameters (Table 2). In a first



Scheme 3. Gram-scale reaction for the synthesis of 4b at room temperature.

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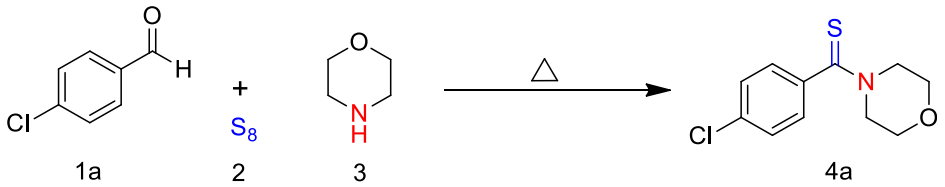
Table 2
Reaction optimization at higher Temperatures.



Entry	Solvent	Mole Ratio 1a: 2 : 3	Temp (°C)	Time (h)	Yield[a] (%)
1	DMSO	1:2:1	100	24	52
2	DMSO	1:2:1	120	24	64
3	DMSO	1:3:1	120	3	85
4	**DMSO**	**1:4:1**	**120**	**0.5**	**93**
5	DMSO	1:5:1	120	0.5	93
6	DMSO	1:4:1	80	6	75
7	DMSO	1:4:1	100	1	90
8	DMSO	1:4:1	130	0.5	93
9	DMSO	1:4:1	140	0.5	92
10	Toluene	1:4:1	110	30	31
11	1,4-Dioxane	1:4:1	100	15	70
12	DMF	1:4:1	100	1	85
13	DMF	1:4:1	120	1	90
14	Water	1:4:1	100	12	60

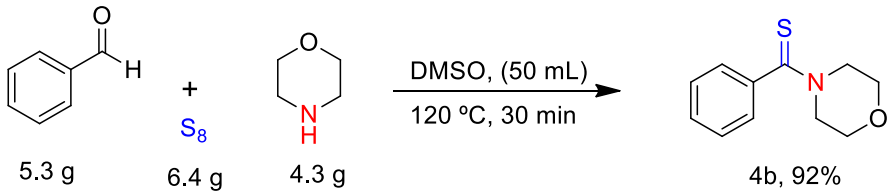
Reaction conditions: 4-Chlorobenzaldehyde (2 mmol), Morpholine (2 mmol), Sulfur powder (8 mmol) and Solvent (10 mL).
[a] Isolated yield.

experiment, 4-chloro benzaldehyde (**1a**; 1.0 equiv.), elemental sulfur powder (**2**; 2.0 equiv.), and morpholine (**3**; 1.0 equiv.) were heated at 100 °C with constant stirring for 24 h in DMSO (10 mL), the expected product 4-chlorophenyl (morpholino)methanethione (**4a)** was obtained in 52% yield (Table 2, entry 1). Thus, to increase the reaction yield, we studied the influence of reaction temperature at 120 °C and observed that after 24 h, the reaction yield increased moderately to 64% (Table 2, entry 2). The amount of elemental sulfur powder was playing the important role in the reaction. Hence, the amount of sulfur powder was optimized. Initially, the reaction by employing 3.0 equivalent of elemental sulfur powder at 120 °C gives 85% yield of product in 3 h (Table 2, entry 3). As the amount of elemental sulfur powder increases from 3.0 equivalents to 4.0 equivalents, it was observed that the yield of product increases with decrease in the reaction time (Table 2, entry 4). The 93% yield of product was obtained in the absence of a catalyst in DMSO at 120 °C within 30 min, the best molar ratio was found to be 1:4:1 (Table 2, entry 4). Further increase in the amount of element sulfur powder 5.0 equivalent, failed to improve the yield of product and time (Table 2, entry 5). Temperature is playing very important role in this transformation, at the low temperature (80 °C) there was a formation of 75% of product and required higher reaction time (Table 2, entry 6). As the temperature increases from 100 °C to 120 °C, the yields were found to increase while reaction time decreases (Table 2, entry 4 & 7). However, further increase of the temperature to 130 °C and 140 °C failed to improve the yield of product and time (Table 2, entry 8 & 9). We obtained the best results at 120 °C (Table 2, entry 4).

We next are inventing the possibility of improving the yield of the reaction at reflux in different solvents such as toluene, DMF, 1,4-dioxane and water at various temperatures. Among all these solvents (Table 2, entry, 10, 11, 12, 13 & 14), DMSO was found to be the best in terms of the yield of the product and time of completion compared with other organic solvents. In relation to the effect of different solvents, the use of DMF and DMSO encouraged the reaction to a high extent. When the reaction was carried out in DMF solvent at 120 °C (Table 2, entry 13), higher yields 90% was obtained. In 1, 4-dioxane after 15 h gives 70% yield of product (Table 2, entry 11). A lowest yield of 31% in 30 h (Table 2, entry 10) was obtained in non-polar toluene solvent. Also, when reactants were heated at 100 °C in water, only 60% yield of the product was obtained (Table 2, entry 14). Most importantly, for only few derivatives water is suitable solvent. However, none of used solvents could match the yield obtained in DMSO (Table 2, entry 4), hence all the reactions were performed in DMSO at the 120 °C. Thus, the catalyst free condition was achieved at 120 °C.

The reaction of benzaldehyde, morpholine and elemental sulfur was successfully scaled-up (50 mmol) at 120 °C (Scheme 4, yield 92%).

Aromatic aldehydes containing the electron donating, withdrawing, halogen, nitrile substituents on the aromatic ring were tested to afford the thioamide products. The position of the substituents on the aromatic ring was noticed to have some effects on the product yield and reaction time. As can be seen from Table 3,



Scheme 4. Gram-scale reaction for the synthesis of 4b at 120 °C.

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Table 3
Synthesis of various thioamide derivatives in DMSO.

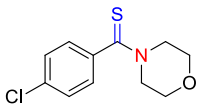
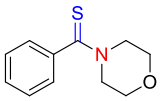
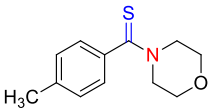
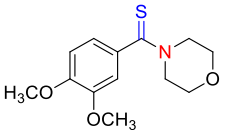
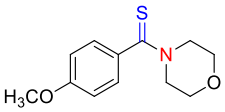
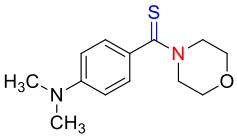
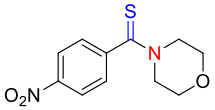
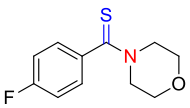
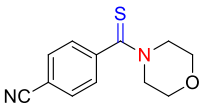
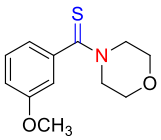
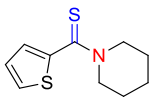
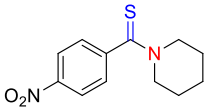
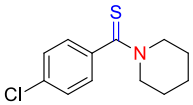
Entry	Product	Reaction Time		Product Yield (%)		M. P. °C
		RT (h)	120 °C (min)	RT	120 °C	
4a		6	30	92	93	138–140[13]
4b		6	30	91	91	136–138[23]
4c		7	120	86	84	126–128[23]
4d		14	120	91	91	154–156[22d]
4e		10	120	83	80	100–102[24]
4f		16	180	89	88	152–154[21]
4g		6	30	88	87	198–200[21]
4h		6	30	81	80	96–98[13]
4i		11	180	84	83	168–170[22d]
4j		11	160	80	77	132–134[26]
6a		9	90	83	80	84–86[27]
6b		6	30	91	90	176–178[22d]
6c		6	60	89	89	90–92[28]

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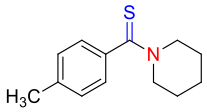
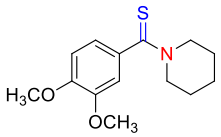
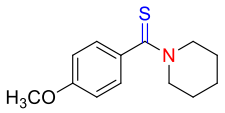
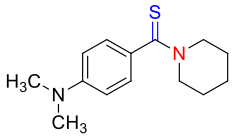
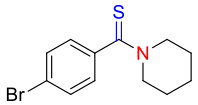
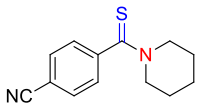
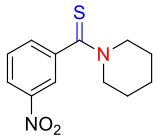
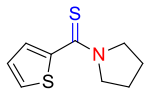
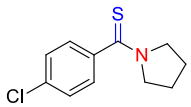
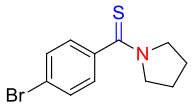
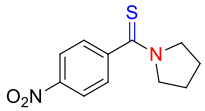
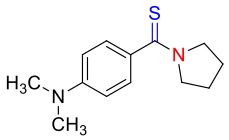
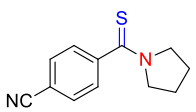
Table 3 (*continued*)

Entry	Product	Reaction Time		Product Yield (%)		M. P. °C
		RT (h)	120 °C (min)	RT	120 °C	
6d		6	140	85	84	96–98[28]
6e		14	120	86	87	98–100[29]
6f		11	160	83	82	110–112[22d]
6g		15	180	85	83	152–154[22d]
6h		15	90	81	79	118–120[22d]
6i		10	140	84	85	158–160[22d]
6j		7	70	82	81	74–76[21]
8a		7	30	94	93	84–86[22d]
8b		6	60	88	80	94–96[30]
8c		13	120	80	78	124–126
8d		6	30	90	88	148–150[21]
8e		15	120	84	83	96–98[22d]
8f		6	110	85	82	146–148[22d]

(*continued on next page*)

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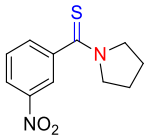
Table 3 (*continued*)

Entry	Product	Reaction Time		Product Yield (%)		M. P. °C
		RT (h)	120 °C (min)	RT	120 °C	
8g		7	60	83	84	102–104[21]

aromatic aldehydes containing electron-donating or electron-withdrawing substituents reacted successfully with cyclic secondary amines (morpholine, piperidine and pyrrolidine) to give corresponding thioamides in high yields and in short reaction time. The results showed that the aromatic aldehydes having substituent such as 4-NO_2 reacted speedily with morpholine/piperidine/pyrrolidine affording thioamide products with same reaction time (6 h and 0.5 h) at room temperature and 120 °C respectively (Table 3, entry 4a, 6b, 8d). Amongst all reactions, the reaction of 4-(dimethylamino)benzaldehyde with morpholine/piperidine/pyrrolidine at room temperature as well as at 120 °C required highest reaction time (Table 3, entry 4f, 6g, 8e). 3, 4-Dimethoxybenzaldehyde reacted with morpholine/piperidine at 120 °C to give 91% and 87% yields within 2 h and at room temperature to give 91% and 86% yields within 14 h respectively (Table 3, entry 4d and 6e). Aromatic aldehydes with electron-withdrawing groups at *meta*-position take more time for completion of reaction as compared to *para*-position (Table 3, entry 6j, 6b and 8g, 8d). This may be due to the increased reactivity of electron deficient aldehydes. Further, the heterocyclic aldehyde like thiophene-2-carboxaldehyde (Table 3, entries 6a and 8a) also gives smooth reaction to obtained corresponding products in high yields. However, reaction of 2-chlorobenzaldehyde with elemental sulfur powder and morpholine/piperidine/pyrrolidine in DMSO at room temperature as well as at 120 °C, no product formation was observed which may be due to the steric effect. Morpholino(4-nitrophenyl)methanethione (Table 3, entry 4g) has found to melt at higher temperature (198–200 °C) as compared to other derivatives. Lower melting point (72–74 °C) was observed for (4-chlorophenyl)(pyrrolidin-1-yl)methanethione (Table 3, entry 8b). During all addition of aromatic aldehydes with cyclic secondary amines in DMSO, the colourless reaction mass was observed and after addition of elemental sulfur powder, the reddish-brown colour of reaction mass was observed. After completion of reaction, the reaction mass is poured in to ice-water to obtain light yellow or off white or light brown solid. The residue was passed through the column chromatography with hexane as eluent to remove unreacted sulfur and to obtained yellow solid products. In all cases, the conversions were completed within 6–16 h at room temperature and 30–180 min at 120 °C with good to excellent yields of products. The temperature and mole ratios of reactants are playing key role in these reactions. The synthesized compounds were identified by their physical constants, FT-IR, ^{1}H NMR, ^{13}C NMR, CHNS elemental analysis, HRMS and comparison with authentic samples.

2.1. Plausible mechanism

Based on the previous literature [12,25], a possible mechanism is proposed in Fig. 1. The first step of this Willgerodt-Kindler reaction at room temperature is considered to involve cleavage of the S–S bond of elemental sulfur **III** caused by nucleophilic attack of morpholine **II** to form polysulfide anion **IV** in a reversible way. Meanwhile, the aldehyde **I** react with second molecule of morpholine **II** to form **V**. Intermediate **V** easily converted to intermediate **VI** in the presence of an amino sulfur species. Then, the nucleophilic attack of **IV** on **VI** affords intermediate **VII**. Due to the presence of the extra hydrogen on the methylene group of the imine, the intermediate **VII** oxidizes to release the final product **4a**. The used of two equivalents of cyclic secondary amine increases the rate of reaction and the Willgerodt-Kindler reaction take place at room temperature.

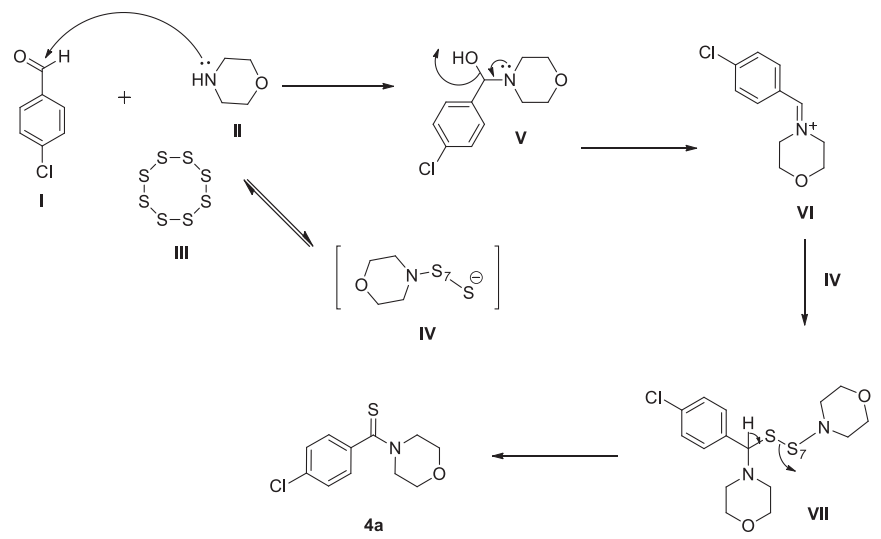


Fig. 1. Plausible mechanism for the formation of **4a**.

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3. Conclusion

In summary, we have developed a newer method for one-pot synthesis of thioamides from aromatic aldehydes, cyclic secondary amines, and elemental sulfur powder without using any external catalyst in DMSO solvent. All thioamides were synthesized under catalyst free conditions within 0.5–3 h at 120 °C with 77–93% yields and within 6–16 h at room temperature with 80–94% yields of products. The mole ratio for aldehydes: sulfur: amines was kept 1:4:1 at 120 °C and 1:4:2 at room temperature. By optimizing the mole ratios of aldehydes, sulfur and amine, we have carried out Willgerodt-Kindler reaction of aromatic aldehydes under catalyst-free condition at 120 °C. To best of our knowledge, this is first report on Willgerodt-Kindler reaction at room temperature. On gram-scale, the reaction is successfully attempted.

4. Experimental section

4.1. General information

All reactions were performed in DMSO and monitored by TLC analysis using Merck silica gel 60 F254 plates with fluorescent indicator (254 nm) and visualized with a UV lamp and without any special precautions in an atmosphere of air. All Chemicals were purchased from Spectrochem and DMSO (99.97%) and used as received without further purification. Melting points were measured in open capillary tubes and uncorrected. FT-IR spectra were obtained on Shimadzu IR-Affinity spectrometer (KBr Pellets). CHNS elemental analysis was performed on Thermo Finnigan CHNS analyzer model Flash 2000. ^{1}H NMR and ^{13}C NMR were recorded a Bruker Avance-II spectrophotometer operating at 400, 500 MHz and 100, 125 MHz. High resolution mass spectra (HRMS) were recorded a quadrupole time-of-flight (Q-TOF) mass spectrometer.

4.2. General procedure for synthesis of thioamide derivatives at room temperature

To a 25 mL round bottom flask containing DMSO (10 mL), aromatic aldehyde (2 mmol), morpholine or piperidine or pyrrolidine (4 mmol), and elemental sulfur powder (8 mmol) were added. The resulting reaction mixture was continuously stirred at room temperature and the progress of reaction was monitored by TLC (hexane:ethyl acetate, 8:2 ratio). After completion of the reaction, the reaction mixture was poured into ice-water mixture under vigorous stirring. The solid product was obtained by simple filtration, washed with water, and dried. The residue was passed through column chromatography to remove unreacted sulfur using hexane as eluent, and the pure product was obtained by passing ethyl acetate through the column.

4.3. General procedure for synthesis of thioamide derivatives at 120 °C

To a 25 mL round bottom flask containing DMSO (10 mL), aromatic aldehyde (2 mmol), morpholine or piperidine or pyrrolidine (2 mmol), and elemental sulfur powder (8 mmol) were added. The resulting reaction mixture was continuously stirred at 120 °C and the progress of reaction was monitored by TLC (hexane:ethyl acetate, 8:2 ratio). After completion of the reaction, the reaction mixture was poured into ice-water mixture under vigorous stirring. The solid product was obtained by simple filtration, washed with water, and dried. The residue was passed through column chromatography to remove unreacted sulfur using hexane as eluent, and the pure product was obtained by passing ethyl acetate through the column.

4.4. Gram-scale synthesis of morpholino(phenyl)methanethione (**4b**) at room temperature

To a 100 mL round bottom flask containing DMSO (50 mL), benzaldehyde (50 mmol), added slowly morpholine (100 mmol), during the addition of morpholine exotherm is observed at 25–35 °C and then added slowly elemental sulfur powder (200 mmol). The resulting reaction mixture was continuously stirred at room temperature for 6 h. After completion of the reaction, the reaction mixture was poured into ice-water mixture under vigorous stirring. The solid product was obtained by simple filtration, washed with water, dried and second lot extracted with ethyl acetate from filtrate removed the solvent under vacuum obtained crude product. The residue was passed through column chromatography to remove unreacted sulfur using hexane as eluent, and the pure product (4b) was obtained by passing ethyl acetate through the column (weight of product = 9.31 g, 90% yield).

4.5. Gram-scale synthesis of morpholino(phenyl)methanethione (**4b**) at 120 °C

To a 100 mL round bottom flask containing DMSO (50 mL), benzaldehyde (50 mmol), added slowly morpholine (50 mmol), during the addition of morpholine exotherm is observed at 25–32 °C and then added slowly elemental sulfur powder (200 mmol). The resulting reaction mixture was continuously stirred at 120 °C for 30 min. After completion of the reaction, the reaction mixture was poured into ice-water mixture under vigorous stirring. The solid product was obtained by simple filtration, washed with water, dried and second lot extracted from filtrate with ethyl acetate, removed the solvent under vacuum obtained crude product. The residue was passed through column chromatography to remove unreacted sulfur using hexane as eluent, and the pure product (4b) was obtained by passing ethyl acetate through the column (weight of product = 9.50 g, 92% yield).

4.6. Spectral data of compounds

4.6.1. 4-Chlorophenyl (morpholino)methanethione (**4a**) [13]

M.P. 138–140 °C; IR (KBr): 3012, 2949, 2835, 1591, 1477, 1438, 1226, 1116, 1089, 844, 819, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.34 (2H, dt, J = 8.56 & 2.17 Hz), 7.23 (2H, dt, J = 8.60 & 2.18 Hz), 4.41 (2H, t, J = 4.88 Hz), 3.88 (2H, t, J = 4.92 Hz), 3.65–3.58 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 199.5, 140.7, 134.9, 128.8, 127.4, 66.6, 66.4, 52.6, 49.6.

4.6.2. Morpholino(phenyl)methanethione (**4b**) [23]

M.P. 136–138 °C; IR (KBr): 3059, 2983, 2920, 2852, 1492, 1479, 1433, 1386, 1290, 1226, 1112, 871, 759, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.37–7.33 (3H, m), 7.28–7.26 (2H, m), 4.43 (2H, t, J = 4.75 Hz), 3.87 (2H, t, J = 5.00 Hz), 3.63 (2H, t, J = 4.50 Hz), 3.58 (2H, t, J = 4.75 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 200.9, 142.4, 128.8, 128.5, 125.8, 66.7, 66.5, 52.5, 49.5.

4.6.3. Morpholino(p-tolyl)methanethione (**4c**) [23]

M.P. 126–128 °C; IR (KBr): 2978, 2918, 2856, 1510, 1483, 1435, 1388, 1294, 1226, 1111, 1033, 873, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.19–7.18 (2H, m), 7.16–7.14 (2H, m), 4.42 (2H, t, J = 5.00 Hz), 3.86 (2H, t, J = 5.00 Hz), 3.62 (4H, brs), 2.34 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 201.3, 139.7, 139.0, 129.1, 126.0, 66.7, 66.5, 52.5, 49.7, 21.2.

4.6.4. (3,4-Dimethoxyphenyl)(morpholino)methanethione (**4d**) [22d]

M.P. 154–156 °C; IR (KBr): 2993, 2958, 2866, 2833, 1598, 1514,

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1483, 1440, 1301, 1269, 1111, 1062, 1020, 850, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 6.91 (1H, d, $J = 1.50$ Hz), 6.84–6.81 (2H, m), 4.41 (2H, brs), 3.88 (8H, brs), 3.65 (4H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 200.9, 149.7, 148.7, 135.0, 118.5, 110.6, 110.3, 66.7, 66.4, 56.0, 52.8, 49.9.

*4.6.5. (4-Methoxyphenyl)(morpholino)methanethione (**4e**) [24]*

M.P. 100–102 °C; IR (KBr): 3007, 2956, 2848, 2825, 1606, 1508, 1479, 1433, 1303, 1228, 1112, 1031, 873, 833, 783, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.28–7.26 (2H, m), 6.87–6.85 (2H, m), 4.41 (2H, brs), 3.86 (2H, brs), 3.81 (3H, s), 3.65 (4H, brs); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 201.1, 160.3, 134.8, 128.1, 113.7, 66.7, 66.5, 55.4, 52.8, 50.0.

*4.6.6. 4-(Dimethylamino)phenyl (morpholino)methanethione (**4f**) [21]*

M.P. 152–154 °C; IR (KBr): 3093, 2962, 2850, 1604, 1517, 1433, 1282, 1219, 1114, 1033, 821, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.29–7.27 (2H, m), 6.62–6.60 (2H, m), 4.41 (2H, brs), 3.76 (6H, brs), 2.97 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 202.0, 151.1, 129.6, 128.6, 111.0, 66.6, 53.0, 50.1, 40.2.

*4.6.7. Morpholino(4-nitrophenyl)methanethione (**4g**) [21]*

M.P. 198–200 °C; IR (KBr): 3086, 3059, 2924, 2860, 1593, 1506, 1444, 1346, 1296, 1236, 1209, 1107, 1033, 879, 850, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.24–8.21 (2H, m), 7.45–7.43 (2H, m), 4.42 (2H, t, $J = 4.94$ Hz), 3.90 (2H, t, $J = 4.94$ Hz), 3.67 (2H, t, $J = 4.80$ Hz), 3.56 (2H, t, $J = 4.80$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 197.3, 147.9, 147.4, 126.7, 124.1, 66.5, 66.4, 52.5, 49.2.

*4.6.8. (4-Fluorophenyl)(morpholino)methanethione (**4h**) [13]*

M.P. 96–98 °C; IR (KBr): 3032, 2918, 2862, 1600, 1510, 1487, 1435, 1290, 1226, 1111, 1033, 875, 833, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.31–7.27 (2H, m), 7.06–7.03 (2H, m), 4.42 (2H, t, $J = 4.75$ Hz), 3.88 (2H, t, $J = 4.75$ Hz), 3.64 (2H, d, $J = 5.00$ Hz), 3.61 (2H, d, $J = 5.00$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 199.9, 163.8, 161.8, 138.5, 128.2, 128.1, 115.6, 115.4, 66.6, 66.4, 52.6, 49.7.

*4.6.9. 4-(Morpholine-4-carbonothloyl)benzonirile (**4i**) [22d]*

M.P. 168–170 °C; IR (KBr): 3014, 2980, 2846, 2227, 1506, 1487, 1446, 1288, 1232, 1120, 1033, 877, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.68–7.65 (2H, m), 7.38 (2H, dt, $J = 8.44$ & 1.69 Hz), 4.40 (2H, t, $J = 4.94$ Hz), 3.88 (2H, t, $J = 4.94$ Hz), 3.65 (2H, t, $J = 4.80$ Hz), 3.54 (2H, t, $J = 4.80$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 197.7, 146.2, 132.5, 126.5, 118.1, 112.3, 66.5, 66.3, 52.5, 49.2.

*4.6.10. (3-Methoxyphenyl)(morpholino)methanethione (**4j**) [26]*

M.P. 132–134 °C; IR (KBr): 3080, 2972, 2908, 2858, 1604, 1577, 1483, 1427, 1292, 1228, 1199, 1107, 1002, 842, 788, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.28–7.24 (1H, m), 6.88–6.85 (1H, m), 6.82–6.80 (2H, m), 4.42 (2H, t, $J = 4.92$ Hz), 3.87 (2H, t, $J = 4.92$ Hz), 3.80 (3H, s), 3.64–3.62 (2H, m), 3.60–3.59 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 200.4, 159.5, 143.6, 129.6, 117.7, 114.5, 111.4, 66.7, 66.4, 55.3, 52.4, 49.4; Anal. calcd. For $C_{12}H_{15}NO_2S$: C, 60.7; H, 6.4; N, 5.9; S, 13.5. Found: C, 60.8; H, 6.4; N, 5.9; S, 13.5. HRMS (ESI) calculated For $C_{12}H_{15}NO_2S$ [M+H]: 238.0902, Found: 238.0910.

*4.6.11. Piperidin-1-yl(thiophen-2yl)methanethione (**6a**) [27]*

M.P. 74–76 °C; IR (KBr): 3095, 2937, 2850, 1517, 1479, 1442, 1176, 1134, 1008, 844, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.37 (1H, dd, $J = 5.12$ & 1.12 Hz), 7.05 (1H, dd, $J = 3.64$ & 1.12 Hz), 6.95 (1H, dd, $J = 5.10$ & 3.66 Hz), 4.27 (2H, brs), 3.84 (2H, brs), 1.76 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.4, 145.0, 128.6, 126.4, 125.5, 53.7, 52.2, 26.9, 25.6, 24.2; Anal. calcd. For $C_{10}H_{13}NS_2$: C, 56.8; H, 6.2; N-6.6; S, 30.3; Found: C, 56.75; H, 6.2; N, 6.6; S, 30.35.

*4.6.12. (4-Nitrophenyl)(piperidin-1-yl)methanethione (**6b**) [22d]*

M.P. 176–178 °C; IR (KBr): 3061, 2935, 2856, 1591, 1512, 1438, 1340, 1249, 1207, 1103, 1012, 852, 752 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.21 (2H, dt, J = 8.50 & 2.25 Hz), 7.41 (2H, dt, J = 8.50 & 2.25 Hz), 4.34 (2H, t, $J = 5.50$ Hz), 3.48 (2H, t, $J = 5.75$ Hz), 1.86–1.81 (2H, m), 1.80–1.75 (2H, m), 1.61–1.57 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 195.9, 148.9, 147.2, 126.2, 124.0, 53.3, 50.3, 26.8, 25.4, 24.0.

*4.6.13. (4-Chlorophenyl)(piperidin-1-yl)methanethione (**6c**) [28]*

M.P. 120–122 °C; IR (KBr): 3074, 3018, 2935, 2858, 1589, 1454, 1433, 1298, 1240, 1141, 835, 810, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.33–7.30 (2H, m), 7.21 (2H, dt, $J = 8.32$ & 2.0 Hz), 4.33 (2H, t, $J = 5.44$ Hz), 3.51 (2H, t, $J = 5.62$ Hz), 1.84–1.72 (4H, m), 1.59–1.54 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 198.1, 141.6, 134.3, 128.6, 126.9, 53.2, 50.7, 26.9, 25.4, 24.1; Anal. calcd. For $C_{12}H_{14}NSCl$: C, 60.1; H, 5.9; N, 5.8; S, 13.4; Found: C, 60.0; H, 5.9; N, 5.8; S, 13.4.

*4.6.14. Piperidin-1-yl(p-tolyl)methanethione (**6d**) [28]*

M.P. 96–98 °C; IR (KBr): 3020, 2933, 2893, 1604, 1506, 1433, 1296, 1139, 1111, 1006, 950, 829, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, ppm) δ: 7.17 (2H, d, $J = 8.00$ Hz), 7.13 (2H, d, $J = 8.00$ Hz), 4.34 (2H, t, $J = 5.5$ Hz), 3.53 (2H, t, $J = 5.5$ Hz), 2.34 (3H, s), 1.82–1.78 (2H, m), 1.75–1.71 (2H, m), 1.57–1.53 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 199.9, 140.6, 138.4, 128.9, 125.5, 53.2, 50.7, 26.9, 25.5, 24.1, 21.4.

*4.6.15. (3,4-Dimethoxyphenyl)(piperidin-1-yl)methanethione (**6e**) [29]*

M.P. 98–100 °C; IR (KBr): 3076, 2949, 2937, 2848, 1598, 1514, 1485, 1269, 1232, 1147, 1018, 840, 825, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 6.88 (1H, d, $J = 1.72$), 6.85–6.80 (2H, m), 4.34 (2H, t, $J = 5.06$ Hz), 3.88 (6H, s), 3.57 (2H, t, $J = 5.46$ Hz), 1.82–1.73 (4H, m), 1.59–1.58 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 199.6, 149.3, 148.6, 136.0, 118.1, 110.6, 109.8, 56.0, 55.9, 53.3, 51.0, 27.0, 25.5, 24.2; Anal. calcd. For $C_{14}H_{19}NO_2S$: C, 63.4; H, 7.2; N, 5.3; S, 12.1; Found: C, 63.35; H, 7.2; N, 5.3; S, 12.1.

*4.6.16. (4-Methoxyphenyl)(piperidin-1-yl)methanethione (**6f**) [22d]*

M.P. 110–112 °C; IR (KBr): 3010, 2939, 2850, 1608, 1510, 1487, 1438, 1298, 1236, 1107, 1028, 835, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.20–7.17 (2H, m), 6.79–6.76 (2H, m), 4.26 (2H, t, $J = 5.25$ Hz), 3.73 (3H, s), 3.50 (2H, t, $J = 5.50$ Hz), 1.73–1.71 (2H, m), 1.69–1.65 (2H, m), 1.52–1.48 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 199.8, 159.8, 135.9, 127.5, 113.6, 55.4, 53.3, 51.0, 26.9, 25.5, 24.2.

*4.6.17. 4-(Dimethylamino)phenyl (piperidin-1-yl)methanethione (**6g**) [22d]*

M.P. 152–154 °C; IR (KBr): 3010, 2943, 2848, 1606, 1519, 1481, 1444, 1359, 1300, 1234, 1209, 1136, 1014, 850, 806, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.27–7.24 (2H, m), 6.63–6.61 (2H, m), 4.31 (2H, brs), 3.65 (2H, brs), 2.97 (6H, s), 1.79–1.58 (6H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 200.8, 150.8, 131.0, 128.1, 111.1, 53.6, 51.4, 40.3, 27.0, 25.5, 24.3.

*4.6.18. (4-Bromophenyl)(piperidin-1-yl)methanethione (**6h**) [22d]*

M.P. 118–120 °C; IR (KBr): 3070, 2943, 2852, 1583, 1498, 1435, 1290, 1242, 1136, 1010, 825, 808, 702, 588, 513 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.47 (2H, dt, J = 8.56 & 2.14 Hz), 7.15 (2H, dt, J = 8.44 & 2.12 Hz), 4.32 (2H, t, $J = 5.50$ Hz), 3.51 (2H, t, $J = 5.62$ Hz), 1.82–1.73 (4H, m), 1.59–1.54 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 197.9, 142.0, 131.5, 127.1, 122.4, 53.2, 50.6, 26.8, 25.4,

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24.0.

*4.6.19. 4-(Piperidin-1-carbonothioyl)benzonitrile (**6i**) [22d]*

M.P. 158–160 °C; IR (KBr): 2987, 2933, 2858, 2223, 1600, 1504, 1487, 1436, 1242, 1205, 1109, 1010, 840, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.65–7.63 (2H, m), 7.37–7.35 (2H, m), 4.33 (2H, t, $J = 5.50$ Hz), 3.46 (2H, t, $J = 5.75$ Hz), 1.85–1.80 (2H, m), 1.79–1.74 (2H, m), 1.60–1.55 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 196.4, 147.2, 132.4, 126.0, 118.3, 111.8, 53.2, 50.3, 26.8, 25.4, 24.0.

*4.6.20. (3-Nitrophenyl)(piperidin-1-yl)methanethione (**6j**) [21]*

M.P. 74–76 °C; IR (KBr): 3082, 3022, 2945, 2856, 1573, 1512, 1450, 1352, 1010, 808, 734, 686 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.18–8.16 (1H, m), 8.12 (1H, m), 7.62–7.59 (1H, m), 7.55 (1H, t, $J = 7.84$ Hz), 4.36 (2H, t, $J = 5.50$ Hz), 3.52 (2H, t, $J = 5.62$ Hz), 1.87–1.75 (4H, m), 1.63–1.61 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 195.7, 147.9, 144.4, 131.4, 129.6, 123.0, 120.5, 53.4, 50.6, 26.8, 25.4, 23.9.

*4.6.21. Pyrrolidin-1yl(thiophen-2-yl)methanethione (**8a**) [22d]*

M.P. 84–86 °C; IR (KBr): 3101, 2962, 2862, 1517, 1467, 1444, 1244, 1193, 1072, 844, 719 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.42 (1H, dd, $J = 5.12$ & 1.08 Hz), 7.28–7.27 (1H, m), 7.01 (1H, dd, $J = 5.08$ & 3.84 Hz), 4.02–3.98 (2H, m), 3.89–3.85 (2H, m), 2.08–2.03 (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 186.6, 146.4, 130.4, 126.8, 55.2, 54.3, 26.8, 24.4.

*4.6.22. (4-Chlorophenyl)(pyrrolidin-1yl)methanethione (**8b**) [30]*

M.P. 72–74 °C; IR (KBr): 3093, 3043, 2970, 2872, 1591, 1452, 1325, 1265, 1220, 1172, 1141, 1089, 958, 875, 817, 771, 435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, ppm) δ: 7.32 (2H, d, $J = 8.50$ Hz), 7.29 (2H, d, $J = 8.50$ Hz), 3.94 (2H, t, $J = 7.25$ Hz), 3.46 (2H, t, $J = 6.75$ Hz), 2.10–2.05 (2H, m), 2.00–1.95 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 195.8, 142.2, 134.8, 128.4, 127.2, 53.8, 53.5, 26.5, 24.6; Anal. calcd. For $C_{11}H_{12}NSCl$: C, 58.5; H, 5.4; N, 6.2; S, 14.2; Found: C, 58.6; H, 5.4; N, 6.2; S, 14.2.

*4.6.23. (4-Bromophenyl)(pyrrolidin-1yl)methanethione (**8c**)*

M.P. 124–126 °C; IR (KBr): 3041, 2968, 2872, 1737, 1585, 1471, 1450, 1392, 1325, 1269, 1220, 1172, 1147, 1070, 1001, 941, 873, 844, 813, 727 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, ppm) δ: 7.47 (2H, d, $J = 8.00$ Hz), 7.24 (2H, d, $J = 8.50$ Hz), 3.94 (2H, t, $J = 7.25$ Hz), 3.45 (2H, t, $J = 6.75$ Hz), 2.09–2.04 (2H, m), 2.00–1.96 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 195.7, 142.7, 131.4, 127.4, 122.8, 53.8, 53.5, 26.5, 24.6; Anal. calcd. For $C_{11}H_{12}NSBr$: C, 48.9; H, 4.5; N, 5.2; S, 11.9; Found: C, 48.8; H, 4.5; N, 5.2; S, 11.9.

*4.6.24. (4-Nitrophenyl)(pyrrolidin-1yl)methanethione (**8d**) [21]*

M.P. 148–150 °C; IR (KBr): 3070, 3057, 2956, 2872, 1593, 1512, 1438, 1342, 1103, 1037, 850, 827, 754, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.22 (2H, dt, $J = 8.80$ & 2.14 Hz), 7.52 (2H, dt, $J = 8.80$ & 2.15 Hz), 3.96 (2H, t, $J = 7.08$ Hz), 3.44 (2H, t, $J = 6.76$ Hz), 2.14–2.06 (2H, m), 2.06–2.01 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 193.9, 149.3, 147.3, 126.6, 123.8, 53.7, 53.3, 26.5, 24.5.

*4.6.25. 4-(Dimethylamino)phenyl (pyrrolidin-1yl)methanethione (**8e**) [22d]*

M.P. 96–98 °C; IR (KBr): 3034, 2974, 2870, 2804, 1606, 1523, 1442, 1267, 1124, 1022, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.39–7.37 (2H, m), 6.62–6.60 (2H, m), 3.96 (2H, t, $J = 7.08$ Hz), 3.61 (2H, t, $J = 6.68$ Hz), 2.97 (6H, s), 2.07–2.03 (2H, m), 1.95–1.91 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 197.5, 150.9, 131.4, 128.1, 110.8, 54.2, 53.9, 40.3, 26.6, 24.7.

*4.6.26. 4-(Pyrrolidine-1-carbonothioyl)benzonitrile (**8f**) [22d]*

M.P. 146–148 °C; IR (KBr): 3040, 2980, 2916, 2877, 2223, 1604, 1506, 1483, 1436, 1271, 1174, 1109, 1041, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 7.66 (2H, dt, $J = 8.44$ & 1.68 Hz), 7.46 (2H, dt, $J = 8.52$ & 1.77 Hz), 3.95 (2H, t, $J = 7.08$ Hz), 3.42 (2H, t, $J = 6.76$ Hz), 2.12–2.09 (2H, m), 2.03–1.99 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 194.3, 147.6, 132.3, 126.3, 118.3, 112.1, 53.7, 53.4, 26.5, 24.5.

*4.6.27. (3-Nitrophenyl)(pyrrolidin-1yl)methanethione (**8g**) [21]*

M.P. 102–104 °C; IR (KBr): 3074, 2974, 2870, 1525, 1492, 1444, 1354, 1265, 1151, 1076, 1024, 808, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, ppm) δ: 8.23–8.22 (1H, m), 8.20–8.18 (1H, m), 7.72 (1H, dt, $J = 7.72$ & 1.32 Hz), 7.56 (1H, t, $J = 7.90$ Hz), 3.98 (2H, t, $J = 7.08$ Hz), 3.49 (2H, t, $J = 6.72$ Hz), 2.15–2.07 (2H, m), 2.06–2.02 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 193.6, 147.8, 144.9, 131.7, 129.6, 123.3, 120.7, 53.9, 53.6, 26.5, 24.6.

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Appendix A. Supplementary data

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References

[1] (a) D.C. Schroeder, Chem. Rev. 55 (1955) 181–228;
(b) K. Gibinski, Curr. Med. Res. Opin. 7 (1981) 516–519;
(c) M. Shekarchi, M. Pirali-Hamedani, L. Navidpour, N. Adib, A. Shafiee, J. Iran. Chem. Soc. 5 (2008) 150–158;
(d) G. Brunhofer, C. Studenik, G. Ecker, T. Erker, Eur. J. Pharm. Sci. 42 (2011) 37–44;
(e) M.S. Chernovyants, N.V. Aleshina, J. Anal. Chem. 67 (2012) 214–218;
(f) M.S. Chernov'yants, A.O. Dolinkin, J. Struct. Chem. 51 (2010) 1176–1190;
(g) G.J. Corban, S.K. Hadjikakou, A.C. Tsipis, M. Kubicki, T. Bakas, N. Hadjiliadis, New J. Chem. 35 (2011) 213–224;
(h) W. Hu, H. Yu, Y. Chen, Y. Tsai, Y. Chen, C. Liao, L. Chang, J. Wang, Bioorg. Med. Chem. 16 (2008) 5295–5302.
[2] (a) H.V. Barnes, T. Bledsoe, J. Clin. Endocrinol. Metab. 35 (1972) 250–255;
(b) F. Wang, R. Langley, G. Gulten, L.G. Dover, G.S. Besra, W.R. Jacobs, J.C. Sacchettini, J. Exp. Med. 204 (2007) 73–78.
[3] (a) T. Lincke, S. Behnken, K. Ishida, M. Roth, C. Hertweck, Angew. Chem. 122 (2010) 2055–2057;
(b) P. Angehrn, E. Goetschi, H. Gmuender, P. Hebeisen, M. Hennig, B. Kuhn, T. Luebbers, P. Reindl, F. Ricklin, A. Schmitt-Hoffmann, J. Med. Chem. 54 (2011), 2207-2024;
(c) A. Bach, J.N.N. Eildal, N. Stuhr-Hansen, R. Deeskamp, M. Gottschalk, S.W. Pedersen, A.S. Kristensen, K. Strømgaard, J. Med. Chem. 54 (2011) 1333–1346.
[4] T.S. Jagodziński, Chem. Rev. 103 (2003) 197–228.
[5] K. Okamoto, J. Kuwabara, T. Kanbara, Chem. Lett. 44 (2015) 102–110.
[6] L. He, H. Zhao, P. Theato, Angew. Chem. 130 (2018) 2–5.
[7] (a) M. Akaiwa, T. Kanbara, H. Fukumoto, T. Yamamoto, J. Organomet. Chem. 690 (2005) 4192–4196;
(b) K. Okamoto, T. Kanbara, T. Yamamoto, A. Wada, Organometallics 25 (2006) 4026–4029.
[8] C. Willgerodt, Ber. Dtsch. Chem. Ges. 20 (1887) 2467–2470.
[9] K. Kindler, Justus Liebig's Ann. der Chemie. 431 (1923) 187–230.
[10] J.E. Valdez-Rojas, H. Ríos-Guerra, A.L. Ramírez-Sánchez, G. García-González, C. Álvarez-Toledano, J.G. López-Cortés, R.A. Toscano, J.G. Penieres-Carrillo, Can. J. Chem. 90 (2012) 567–573.
[11] S.S. Gawande, B.P. Bandgar, P.D. Kadam, S.S. Sable, Green Chem. Lett. Rev. 3

(2010) 315–318.
[12] K. Okamoto, T. Yamamoto, T. Kanbara, Synlett 17 (2007) 2687–2690.
[13] V.V. Kul'ganek, L.A. Yanovskaya, Bull. Acad. Sci. USSR Div. Chem. Sci. 28 (1979) 2402–2403.
[14] O.I. Zbruyev, N. Stiasni, C.O. Kappe, J. Comb. Chem. 5 (2003) 145–148.
[15] K. Aghapoor, F. Mohsenzadeh, G. Khanalizadeh, H.R. Darabi, Monatshefte für Chemie - Chem. Mon. 138 (2007) 61–65.
[16] H. Xu, H. Deng, Z. Li, H. Xiang, X. Zhou, Eur. J. Org. Chem. 2013 (2013) 7054–7057.
[17] K. Mahammed, V. Jayashankara, N. Premsai Rai, K. Mohana Raju, P. Arunachalam, Synlett 2009 (2009) 2338–2340.
[18] T. Guntreddi, R. Vanjari, K.N. Singh, Org. Lett. 16 (2014) 3624–3627.
[19] T.B. Nguyen, M.Q. Tran, L. Ermolenko, A. Al-Mourabit, Org. Lett. 16 (2014) 310–313.
[20] S. Chen, Y. Li, J. Chen, X. Xu, L. Su, Z. Tang, C.-T. Au, R. Qiu, Synlett 27 (2016) 2339–2344.
[21] M. Papa, I. Chiarotto, M. Feroci, ChemistrySelect 2 (2017) 3207–3210.
[22] (a) A.D. Jangale, P.P. Kumavat, Y.B. Wagh, Y.A. Tayade, P.P. Mahulikar, D.S. Dalal, Synth. Commun. 45 (2015) 376–385;
(b) P.P. Kumavat, A.D. Jangale, D.R. Patil, K.S. Dalal, J.S. Meshram, D.S. Dalal, Environ. Chem. Lett. 11 (2013) 177–182;
(c) A.D. Jangale, Y.B. Wagh, Y.A. Tayade, D.S. Dalal, Synth. Commun. 45 (2015) 1876–1886;
(d) Y.A. Tayade, A.D. Jangale, D.S. Dalal, ChemistrySelect 3 (2018) 8895–8900.
[23] F. Matloubi Moghaddam, L. Hojabri, M. Dohendou, Synth. Commun. 33 (2003) 4279–4284.
[24] S.D. Fazylov, O.A. Nurkenov, Z.S. Akhmetkarimova, D.R. Zhienbaeva, Russ. J. Gen. Chem. 82 (2012) 781–782.
[25] (a) J. Liu, S. Zhao, X. Yan, Y. Zhang, S. Zhao, K. Zhuo, Y. Yue, Asian J. Org. Chem. 6 (2017) 1764–1768;
(b) M. Carmack, J. Heterocycl. Chem. 26 (1989) 1319–1323;
(c) M. Carmack, M. Behforouz, G.A. Berchtold, S.M. Berkowitz, D. Wiesler, R. Barone, J. Heterocycl. Chem. 26 (1989) 1305–1318;
(d) X. Li, Q. Pan, R. Hu, X. Wang, Z. Yang, S. Han, Asian J. Org. Chem. 5 (2016) 1353–1358.
[26] (a) Brown, David; Hargreaves, Rodney B.; McLoughlin, Bernard J.; Mills, Stuart D,; US 4489074 A 19841218, 1984.
(b) Brown, David; Hargreaves, Rodney B.; McLoughlin, Bernard J.; Mills, Stuart D.; Eur. Pat. Appl. EP 80296 A1 19830601, 1983.
[27] A.R. Katritzky, R.M. Witek, V. Rodriguez-Garcia, P.P. Mohapatra, J.W. Rogers, J. Cusido, A.A.A. Abdel-Fattah, P.J. Steel, J. Org. Chem. 70 (2005) 7866.
[28] (a) S. Kato, H.K. Shibahashi, T.T. Tomonori, I. Noda, M. Mizuta, M. Goto, Liebigs Ann. Chem. 7 (1982) 1229–1244;
(b) D.V. Ramana, S.K. Viswanadham, Org. Mass Spectrom. 9 (1982) 409–415;
(c) A. Pal, N.D. Koduri, Z. Wang, E.L. Quiroz, A. Chong, M. Vuong, N. Rajagopal, M.R. Nguyen, P. Kenneth, S.R. Hussaini, Tetrahedron Lett. 58 (2017) 586–589.
[29] (a) C. Cercasov, G. Constantinescu, C. Doneanu, An. Univ. Bucur. Chim. 7 (1998) 71–78;
(b) S.M. Lempert, K. Lempert, P. Bruck, G. Toth, Electron deficient hetero-aromatic ammonioamidates, XIV, Acta Chim. Acad. Sci. Hung. 94 (1977) 391–401.
[30] (a) T. Hori, Y. Otani, M. Kawahata, K. Yamaguchi, T. Ohwada, J. Org. Chem. 73 (2008) 9102–9108;
(b) P.K. Bhattacharya, S. Bandyopadhyay, S.C. Pakrashi, Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem. 28 (1989) 673–674.

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