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Na_2S-mediated thionation: an efficient access to secondary and tertiary α-ketothioamides via Willgerodt–Kindler reaction of readily available arylglyoxals with amines

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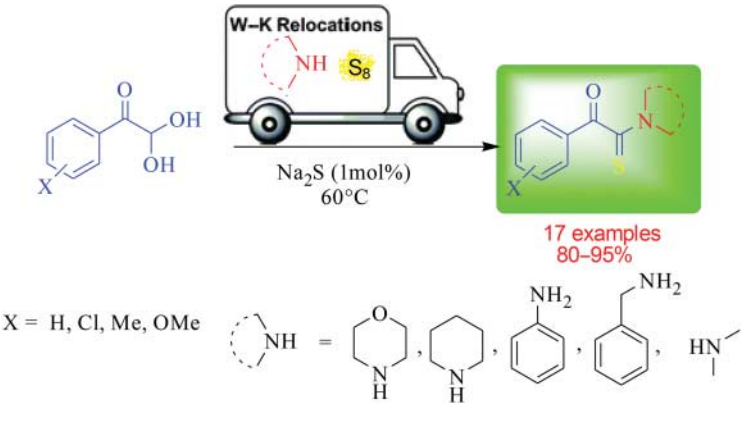
The task of this paper is to provide an efficient process for synthesis of secondary and tertiary α-ketothioamides via Willgerodt–Kindler reaction of readily available arylglyoxals with amines using Na_2S as an effective catalyst. A plausible role for Na_2S in the reaction of arylglyoxals with primary amines is proposed.



Keywords: thionation; α-ketothioamides; arylglyoxals; Willgerodt–Kindler reaction; thioamides

1. Introduction

Organosulfur compounds are valued not only for their rich and varied chemistry, but also for many important biological properties.[1] Thioamides are a class of organosulfur compounds that comprise a variety of derivatives that possess diverse physiological properties such as antigastric, antiulcer, antidiabetic, antitubercular, anti-inflammatory, antitumor, fungistatic, agricultural herbicides, antioxidant, molds and yeasts inhibitors.[2–10] The thioamide-NH is a stronger

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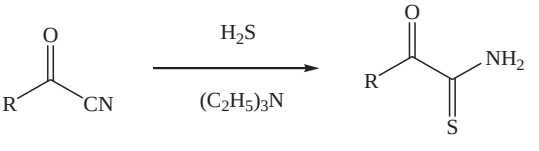
hydrogen bond donor than the amide NH, and the larger and less electronegative sulfur atom, relative to oxygen, is a weaker hydrogen bond acceptor.[11,12] These two factors combined may alter not only the hydrogen bonding ability at the receptor or enzyme level but also induce conformational changes and higher lipophilicity in the modified molecules. As a result, the substitution of thioamides for amides appears to be a promising and productive tool in drug discovery, inclusion chemistry, heterocycles synthesis and materials science.[13–21] On the other hand, α-ketothioamides have recently become a very important functional group in organic synthesis and medicinal chemistry.[22–24] These compounds have the potential to be converted into aryl glyoxalic acids.

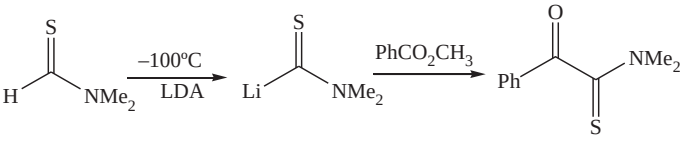
Not surprisingly, one of the most exploited routes to thioamides involves the Willgerodt–Kindler reaction (W–K reaction).[25] In the original W–K reaction, ketones and aldehydes were found to react with sulfur and secondary amines to give terminal thioamides as a result of consecutive oxidations and rearrangements. Several recent reviews have rendered the W–K reaction as a more attractive reaction to the medicinal and organic chemist.[26–32] The first step of the W–K reaction is considered to involve cleavage of the S–S bond of elemental sulfur caused by nucleophilic attack of amine to form polysulfide anions in a reversible way. The less basic amines lead to only little formation of the polysulfide anions.

A number of limited approaches for the synthesis of α-ketothioamides have been developed, but these have disadvantages such as limited scope, expensive reagents or catalysts, and need for harsh reaction conditions. The addition of H_2S onto acylcyanides according to Scheme 1 gave corresponding *N*-unsubstituted α-keto aryl thioamides.[33] However, the synthesis of α-ketothioamides is restricted to the *N*-unsubstituted derivatives.



Scheme 1. Synthesis of *N*-unsubstituted α-keto aryl thioamides.

Reaction of (*N*,*N*-dimethylthiocarbomyl) lithium with methyl benzoate, afforded α-keto aryl thioamides (Scheme 2).[34]

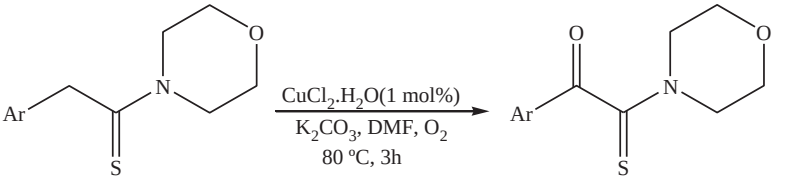


Scheme 2. Synthesis of α-keto aryl thioamides from dimethylthioformamide.

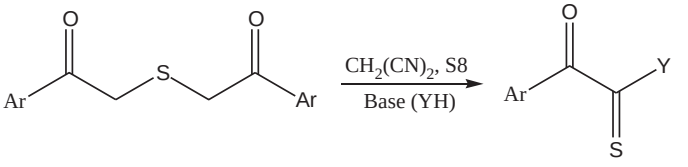
Recently, we have reported a procedure for the synthesis of α-ketothioamides from aryl thioacetamides using $CuCl_2 \cdot 2H_2O$ as a heterogeneous catalyst (Scheme 3).[35] However, this method is restricted to the aryl thioacetomorpholide derivatives.

Reaction of diphenacyl sulfides under Gewald conditions unexpectedly resulted in a narrow variety of α-keto aryl thioamides formation with good yields (Scheme 4).[36]

Arylglyoxals have been used as useful synthons in the organic synthesis.[37] Eftekhari and his co-workers have described a general synthesis of α-ketothioamides based on the W–K reaction of arylglyoxals with secondary cyclic amines and elemental sulfur.[38,39] The reaction was not



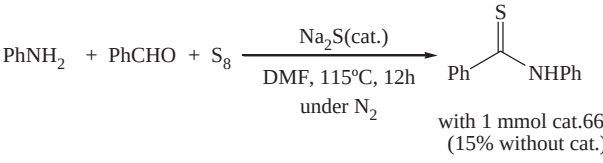
Scheme 3. Synthesis of α-keto aryl thioamides from dimethylthioformamide.



Scheme 4. Synthesis of α-keto aryl thioamides under Gewald conditions.

worked with aliphatic amines such as dimethylamine and benzylamine as well as with primary aromatic amine such as aniline.

It is evident that the need for the development of new, a broad scope and flexible method is required to access α-ketothioamides without using toxic reagents and avoiding extreme conditions. Recently, Kanbara reported that the addition of a small amount of Na_2S in the W–K reaction improved the reaction as shown in Scheme 4.[40] The W–K reaction between anilines and benzaldehyde proceeded in the presence of catalytic amount of Na_2S to give thiobenzanilides in moderate to good yields (Scheme 5).



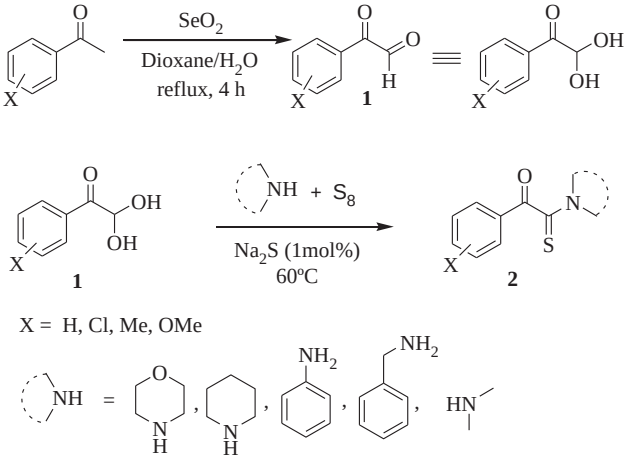
Scheme 5. Synthesis of thiobenzanilides in the presence of catalytic amount of Na_2S.

This encouraged us to investigate the W–K reaction for comprehensive synthesis of α-ketothioamides from readily available arylglyoxals using catalytic amount of Na_2S. To the best of our knowledge, this is the first demonstration for synthesis of secondary α-ketothioamides (Scheme 6).

2. Results and discussion

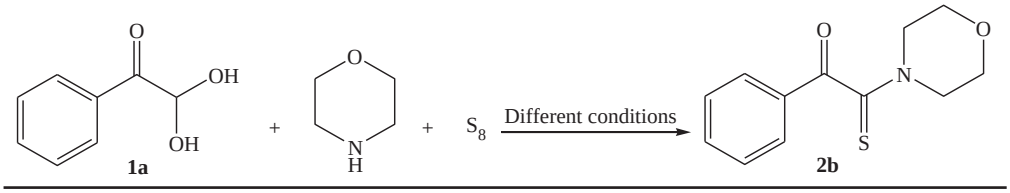
To find the optimal conditions, we conducted the W–K reaction of phenylglyoxal, morpholine and/or aniline under different conditions for the synthesis of tertiary α-ketothioamides and secondary α-ketothioamides, respectively (Tables 1 and 2). As shown in Table 1, 1-phenyl-2-(morpholin-1-yl)-2-thioxoethanone **2a** was obtained in good yield (95%) when a mixture of phenylglyoxal **1a**, morpholine and elemental sulfur were heated in the presence of Na_2S at 60°C under solvent-free condition for 10 min (Entry 10).

Our first experiment for optimization of reaction conditions of phenylglyoxal with aniline, showed that the presence of Na_2S is required to achieve the synthesis of secondary



Scheme 6. The W–K reaction of arylglyoxals **1** with primary and secondary amines.

Table 1. Optimization conditions of the W–K reaction for the synthesis of tertiary α-ketothioamides[a].



Entry	Solvent	Catalyst	T (°C)	Time (h)	Yield (%)[b]
1	H_2O	–	r.t	24	–
2	H_2O	Na_2S	r.t	24	trace
3	H_2O	Na_2S	60	4	78
4	DMF	–	r.t	24	–
5	DMF	Na_2S	r.t	24	trace
6	DMF	Na_2S	60	4	84
7	Solvent-free	–	r.t	24	80
8	Solvent-free	–	60	4	85
9	Solvent-free	Na_2S	r.t	4	90
10	**Solvent-free**	**Na_2S**	**60**	**0.16**	**95**
11	Solvent-free	Na_2S	60	24	–[c]

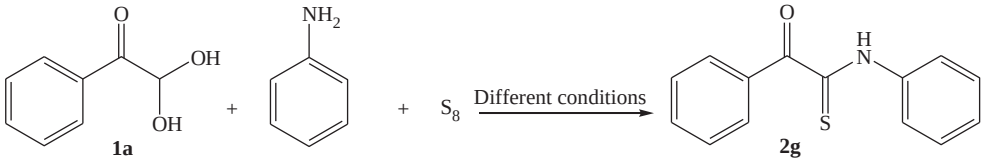
[a]Reaction conditions: solvent (5 mL), phenylglyoxal (1 mmol), morpholine (2 mmol), S_8 (2 mmol) and catalyst (1 mol%).
[b]Isolated yield.
[c]Without S_8.

α-ketothioamide **2g** and no desired product was observed when the reaction was performed without Na_2S (Table 2).

A polar solvent such as DMF was much better than H_2O and solvent-free conditions. The effect of temperature was also studied by carrying out the model reaction at room temperature and 60°C. It was observed that the yield was increased as the reaction temperature was raised to 60°C.

The optimized conditions are: phenylglyoxal (1 mmol), aniline (2 mmol), S_8 (2 mmol) and Na_2S (1 mol%) in DMF (5 mL) at 60°C for 4 h (Table 2, Entry 10).

Table 2. Optimization conditions of the W–K reaction for the synthesis of secondary α-ketothioamides[a].



Entry	Solvent	Catalyst	T (°C)	Time (h)	Yield (%)[b]
1	H_2O	–	r.t	24	–
2	H_2O	Na_2S	r.t	24	Trace
3	H_2O	Na_2S	60	4	60
4	Solvent-free	–	r.t	24	–
5	Solvent-free	–	60	24	Trace
6	Solvent-free	Na_2S	r.t	24	20
7	Solvent-free	Na_2S	60	4	73
8	DMF	–	r.t	24	–
9	DMF	Na_2S	r.t	24	34
10	**DMF**	**Na_2S**	**60**	**4**	**84**

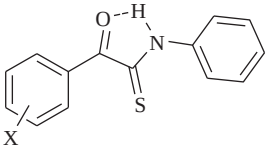


Figure 1. Intramolecular hydrogen bonding between the amine proton and the ketone group.

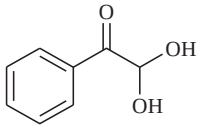
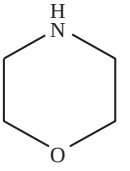
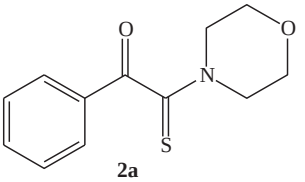
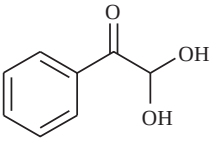
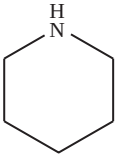
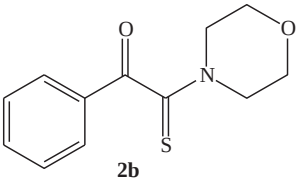
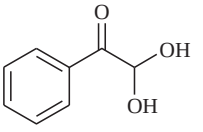
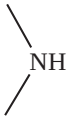
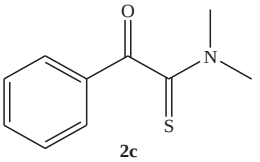
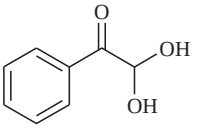
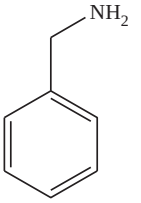
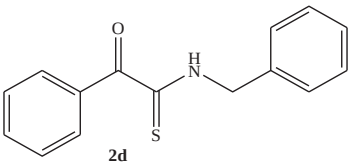
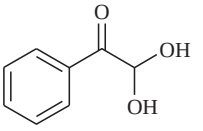
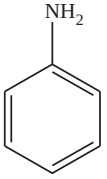
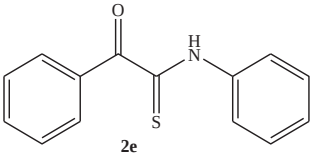
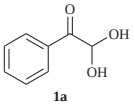
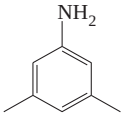
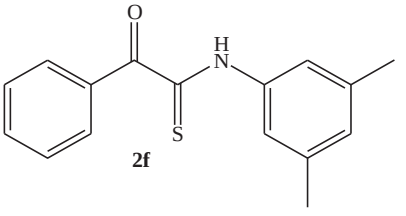
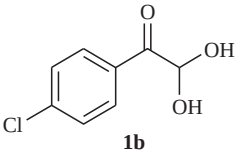
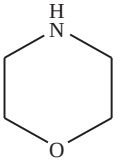
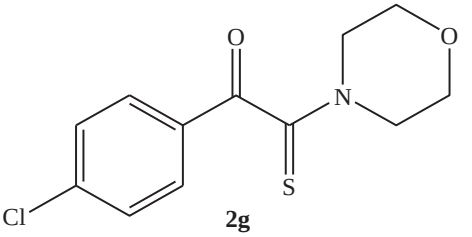
The structures of the desired products were confirmed by MS (electron ionization (EI) and ESI), ^{1}HNMR and ^{13}CNMR spectra. It should be mentioned that the structures of tertiary α-ketothioamides were confirmed by a comparison with authentic samples prepared by reported methods.[34,37] The characteristic signal for **2e** in the ^{1}HNMR spectrum was a broad resonance for the proton of the NH at 10.14 ppm. Intramolecular hydrogen bonding between the proton of amine and the ketone group, results in deshielding of the NH proton (Figure 1).

The ^{1}H-decoupled ^{13}CNMR spectrum of **2e** showed 10 distinct resonances in agreement with the proposed structure, with the ketone and thioamide carbons appearing at $\delta = 189.70$ and 187.0 ppm, respectively, and 8 distinct resonances for the aromatic carbons between $\delta = 122.21$ and 137.84 ppm. The MS (EI) mass spectrum of **2g** clearly showed the presence of the molecular ion (241) [M^+]. MS (EI) analysis of α-ketothioamides revealed that their fragmentation followed a general pathway involving predominantly α-cleavage process from C–C bonds.

Using the optimized procedures (Tables 1 and 2), the reactions of arylglyoxals with various primary and secondary amines proceeded smoothly at 60°C in the presence of 1 mol% of Na_2S to afford α-ketothioamides. All the substrates consistently furnished the desired products in high yields and were not limited to aliphatic amines; aromatic amines also afforded the desired products in good yields (Table 3).

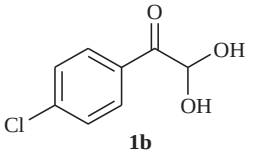
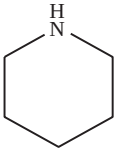
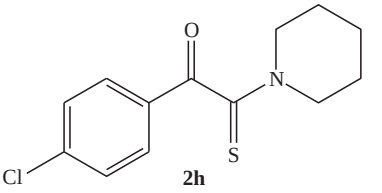
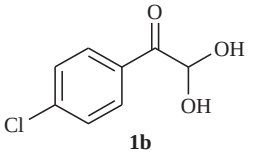
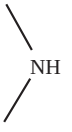
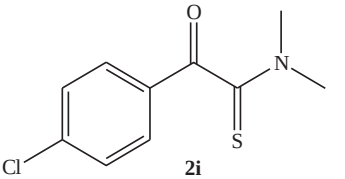
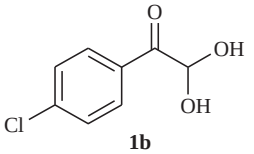
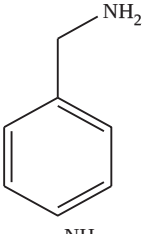
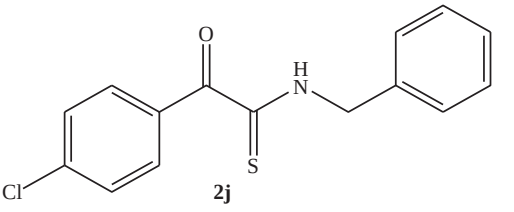
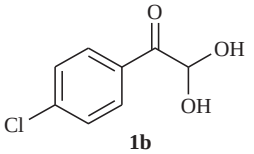
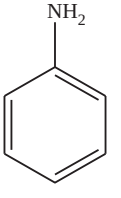
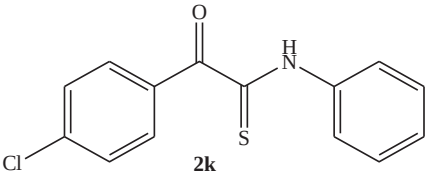
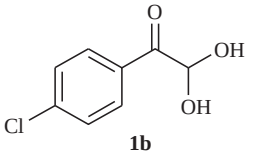
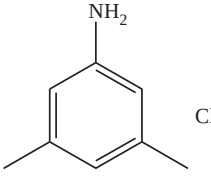
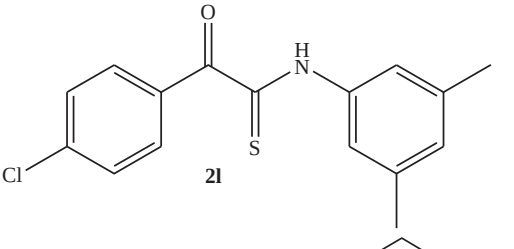
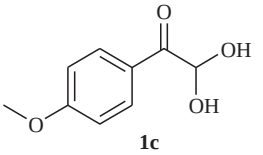
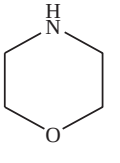
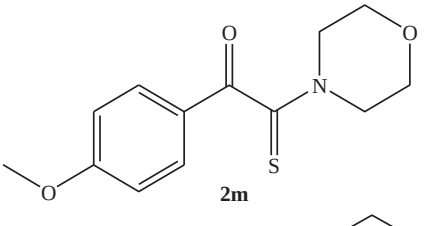
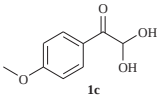
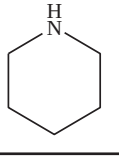
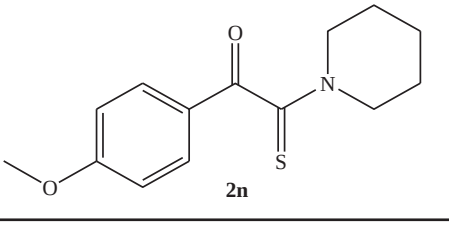
A plausible role for Na_2S in the W–K reaction of arylglyoxals with primary amines such as aniline is shown in Scheme 7. The suspension of elemental sulfur in the DMF solution of aniline remained unreacted because of the poor nucleophilicity of aniline. The addition of a small amount of Na_2S into the reaction mixture caused is considered to initiate the nucleophilic cleavage of the elemental sulfur ring to give the polysulfide anions as depicted in Scheme 6. The sulfur in polysulfides acts as a thiolating agent; the presence of small amounts of Na_2S has a

Table 3. Efficient synthesis of secondary and tertiary α-ketothioamides 2a–2q[a].

Entry	Arylglyoxal	Amine	α-ketothioamides	Yields (%)
1	 **1a**		 **2a**	95
2	 **1a**		 **2b**	90
3	 **1a**		 **2c**	95
4	 **1a**		 **2d**	85
5	 **1a**		 **2e**	84
6	 **1a**		 **2f**	80
7	 **1b**		 **2g**	90

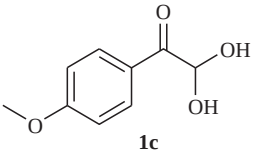
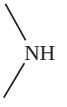
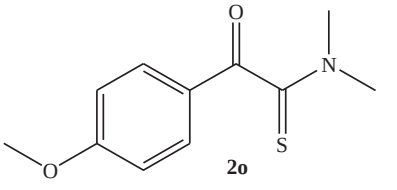
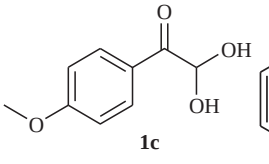
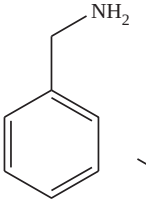
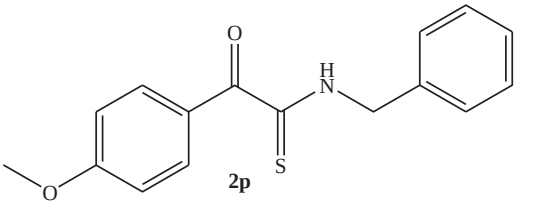
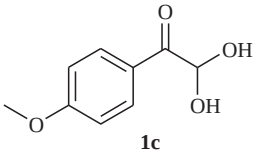
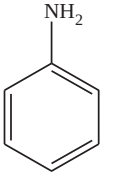
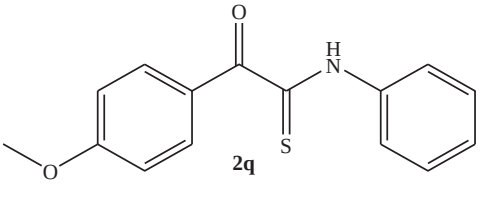
(*Continued*)

Table 3. Continued.

Entry	Arylglyoxal	Amine	α-ketothioamides	Yields (%)
8	 **1b**		 **2h**	95
9	 **1b**		 **2i**	95
10	 **1b**		 **2j**	85
11	 **1b**		 **2k**	80
12	 **1b**		 **2l**	82
13	 **1c**		 **2m**	90
14	 **1c**		 **2n**	95

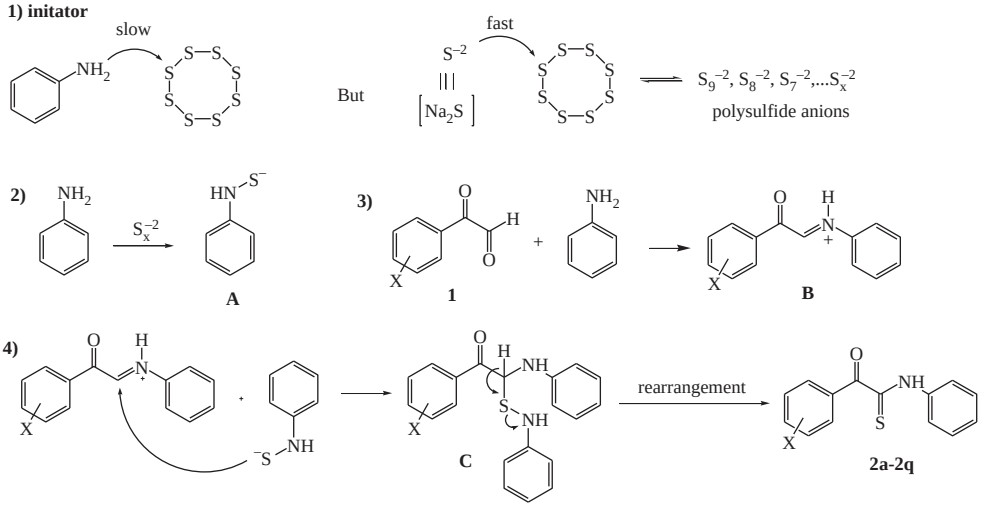
(*Continued*)

Table 3. Continued.

Entry	Arylglyoxal	Amine	α-ketothioamides	Yields (%)
15	 **1c**		 **2o**	95
16	 **1c**		 **2p**	80
17	 **1c**		 **2q**	80

[a]In Entries 3, 9 and 15 a dimethylamine solution 40% in H_2O was used.

favorable effect on thiolation.[40,41] Nucleophilic addition of aniline to polysulfide generated intermediate **A**. On the other hand, reaction of phenylglyoxal with aniline gave iminium salt **B**. Subsequent nucleophilic addition of **A** to iminium salt **B**, resulted intermediate **C**, which elimination of a molecule of aniline from **C** produced the desired α-ketothioamides **2a–2q**.



Scheme 7. Plausible role for Na_2S in the W–K reaction of arylglyoxals with primary amines.

In conclusion, we have reported an efficient Willgerodt–Kindler reaction for the synthesis of secondary and tertiary α-ketothioamides using Na_2S as an inexpensive catalyst with benign and easy workup, which make it a useful and attractive strategy for the synthesis of α-ketothioamides. The reaction also proceeds very well with primary aliphatic and aromatic amines and corresponding α-ketothioamides were produced in high yields.

3. Experimental

3.1. *General procedure for the synthesis of arylglyoxals 1a–1c*

The arylglyoxals were prepared according to reported procedure with some improvements.[42] To a solution of SeO_2 (25 mmol) in dioxane (30 mL) containing H_2O (1 mL) was added an aryl methyl ketone (25 mmol). The solution was heated under reflux conditions for 6 h. Then the hot solution was decanted to remove the precipitated selenium. Distillation of dioxane was resulted a yellow liquid. Subsequently recrystallization of the liquid in hot H_2O obtained the corresponding arylglyoxals **1a–1c**.

3.2. *General procedure for the synthesis of secondary and tertiary α-ketothioamides 2a–2q*

Arylglyoxal **1** (1 mmol) was added to a mixture of amine (2 mmol), elemental sulfur (2 mmol) and Na_2S (1 mol%) in DMF (2 mL) or solvent free for primary amine and secondary amine, respectively, then heated at 60°C for 10 min-4 h (Tables 1 and 2). After completion of the reaction, monitored by TLC (*n*-hexane/EtOAc: 5/3), the obtained solid was removed by filtration. The unreacted sulfur and was removed by adding 5 ml EtOH, heating and then hot filtration. By cooling, corresponding α-ketothioamides were crystallized and separated by simple filtration. In the case of oily products, column chromatography was used for purification. Representative spectroscopic data of the α-ketothioamides **2a–2q**: *N-benzyl-2-oxo-2-phenylethanethioamide (2d)* ^{1}HNMR (250 MHz, $CDCl_3$) $\delta = 8.50$ (s, 1H, NH), 8.05 (d, $J = 7.75$, 2H, CH_{Ar}), 7.75 (d, $J = 8.50$, 2H, CH_{Ar}), 7.59 (t, $J = 7.25$, 2H, CH_{Ar}), 7.48–7.34 (m, 4H, CH_{Ar}), 4.93 (d, $J = 6.60$, 2H, CH_2). ^{13}C-NMR (62.50 MHz, $CDCl_3$) $\delta = 193.72$ (C=S), 187.72 (C=O), 136.32, 133.90, 130.74, 129.05, 128.53, 128.39, 128.02, 126.76, 49.22. MS (EI): m/z(%) = 255 (51) [M^+], 150 (7), 106 (88), 105 (79), 91 (100), 77 (48), 51 (12). **2**-*Oxo-N,2-diphenylethanethioamide (2e)* ^{1}HNMR (250 MHz, $CDCl_3$) $\delta = 10.14$ (s, 1H, NH), 8.09 (d, $J = 7.25$ Hz, 2H, CH_{Ar}), 8.02 (d, $J = 7.75$ Hz, 2H, CH_{Ar}), 7.63 (t, $J = 7.75$, 2H, CH_{Ar}), 7.53–7.63 (m, 4H, CH_{Ar}). ^{13}CNMR (62.5 MHz, $CDCl_3$) $\delta = 189.69$ (C=S), 186.97 (C=O), 137.85, 133.90, 131.2, 129.46, 129.16, 128.10, 127.34, 122.20. MS (EI): m/z(%) = 241 (73) [M^+], 136 (96), 109 (28), 105 (99), 77 (100), 51 (32). *N-benzyl-2-(4-methoxyphenyl)-2-oxoethanethioamide (2p)* ^{1}HNMR (250 MHz, $CDCl_3$) $\delta = 8.50$ (s, 1H, NH), 8.08 (d, $J = 10.0$ Hz, 2H, CH_{Ar}), 7.43–7.50 (m, 5H, CH_{Ar}), 6.93 (d, $J = 7.50$ Hz, 2H, CH_{Ar}), 4.93 (d, $J = 6.0$ Hz, 2H, CH_2), 3.89 (s, 3H, O–CH_3). ^{13}C-NMR (62.50 MHz, $CDCl_3$) $\delta = 194.33$ (C=S), 187.65 (C=O), 164.28, 133.40, 131.11, 128.99, 128.49, 128.30, 126.66, 113.54, 55.54, 49.22. MS (ESI): 286 [M+H]$^+$.]

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Supplemental data

Supplemental data for this article can be accessed at 10.1080/17415993.2014.955026.

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