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A panoramic view on synthetic applications of α-oxothioamides: a highly regioselective synthesis of 2-acyl-4-(het)arylthiazoles and thioethers†

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Highly regioselective synthesis of 2-acyl-4-(het)arylthiazoles and thioethers by the reaction between α-oxothioamides and α-bromoketones in the absence of base in DMF and in the presence of triethylamine in acetonitrile, respectively, has been reported. This thiazole synthesis is an important extended work of the Hantzsch thiazole synthesis, which overcomes the drawbacks of earlier reported methods. The probable mechanisms for the formation of thiazoles and thioethers are also presented.

Introduction

Thiazoles occupy a prominent position in medicinal chemistry due to their various biological activities such as anti-bacterial,[1] antihypertensive,[2] anti-inflammatory,[3] anti-oxidant,[4] antitumor,[5] anti-HIV,[6] antihyperlipidemic,[7] antiprotozoal,[8] antitubercular[9] and antimalarial.[10] Besides, they are present in natural products,[11] agrochemicals,[12] drugs[13] and materials.[14] Some biologically important thiazole derivatives are listed in Fig. 1. On the other hand, it is noteworthy to mention that thioethers are present in pharmaceuticals and natural products.[15] Because of their vast existence and applications, development of new methods for the synthesis of thiazoles and sulfides have gained paramount importance.

Our literature survey on the synthesis of thiazoles reflected that the Hantzsch synthesis[16] is the conventional method, which entails the reaction between thioamides and α-halocarbonyl compounds. Since an enormous number of methods for the synthesis of thiazole have been reported, we converged our presentation on modified Hantzsch thiazole reactions. Thus, thiourea,[17] thioamides[18–20] and substituted thioureas[21] gave thiazoles when reacted with α-halocarbonyl compounds. Alternatively, reaction of ethyl 3-bromo-2-oxopropanoate with thioamides furnished thiazoles.[22,23] Other methods involve reaction of thioamides with alkynyl(aryl)iodonium salts[24] and 1*H*-1-(1′-alkynyl)-5-methyl-1,2,3-benziodoxathiole 3,3-dioxides.[25] Substrate modified approaches are the reaction of β-keto esters with tribromoisocyanuric acid followed by cyclization with thiourea[26] and α-halogenation of β-keto esters with *N*-bromosuccinimide followed by reaction with thiourea.[27] In addition, α-halocarbonyl compounds in the Hantzsch synthesis are replaced by α-tosyloxy ketones.[28] Recently, reaction between α-oxo-1*H*-indole-3-thioacetamides and 2-bromo-1-(1*H*-indol-3-yl)ethanones produced (4-(1*H*-indol-3-yl)thiazol-2-yl)(1*H*-indol-3-yl)methanones.[29] Unfortunately, this report suffers from the generality of the protocol and long reaction time. To the best of our knowledge, a detailed or a general examination of α-oxothioamides with α-halocarbonyl compounds is not reported. As a consequence, we present the modified Hantzsch thiazole synthesis in this article, which fills the aforementioned void.

On the other hand, thioethers are present in pharmaceuticals and natural products.[30,31] They can be synthesized classically by the thiol alkylation or arylation.[32,33] The most recent methods include reaction of redox-active esters with thiosulfonates,[34] thiolation of alkyl oxalates,[35] reaction between 4-alkyl-1,4-dihydropyridines and thiosulfonates,[36] and others.[37] These methods suffer from limitations such as use of malodorous thiols, formation of stoichiometric amounts of thiol byproducts and disulfides as impurities in the presence of air. We present

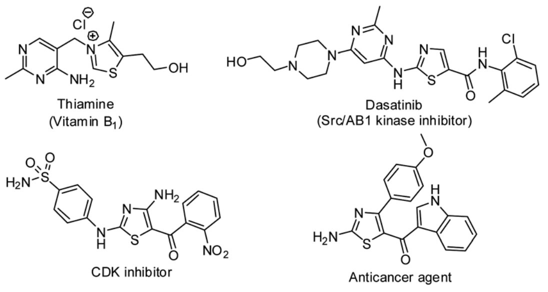

Fig. 1 Biologically important thiazole derivatives.

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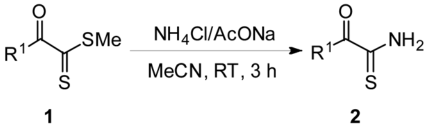
herein α-oxothioamides as thionating agent from which thioethers are formed upon reaction with α-bromoketones.

In continuation of our efforts in organic synthesis[38–44] we have recently reported the synthesis of quinoxalines,[45,46] thiazoles[47] and benzoxazoles[45] from α-ketodithioesters. In this direction, we have recently reported the synthesis of α-ketothioamides and explored their applications for the synthesis of 3,5-bis(acyl)-1,2,4-thiadiazoles.[48] In extension of this work, we report herein an important extended Hantzsch thiazole synthesis by the reaction of α-ketothioamides with α-bromoketones in the absence of a base. Besides, we have also demonstrated α-ketothioamides as an excellent thionating reagent for the synthesis of thioethers from α-bromoketones in the presence of a base.

Results and discussion

We prepared required α-ketothioamides according to our earlier reported protocol.[48] Thus, α-ketodithioesters[45,47] **1** on treatment with stoichiometric amounts of ammonium chloride and anhydrous sodium acetate in acetonitrile furnished α-ketothioamides **2** (Scheme 1).

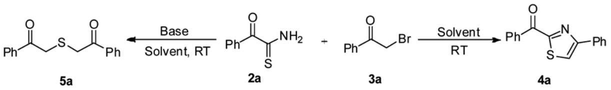


Scheme 1 Synthesis of α-ketothioamides.

Table 1 Optimization of reaction conditions for the synthesis of phenyl(4-phenylthiazol-2-yl)methanone **4a** and 2,2′-thiobis(1-phenylethanone) **5a**

Entry	Solvent	Base	Time (h)	Yield[a] (%) of **4a**	Yield[b] (%) of **5a**
1	Acetone	Et_3N	1		93
2	Acetone	—	2	90	—
3	DMF	—	1	93	—
4	MeCN	—	3	80	—
5	CH_2Cl_2	—	2	60	—
6	MeCN	Et_3N	0.5	—	95
7	DMF	Et_3N	1	—	90
8	MeOH	Et_3N	1	—	80
9	MeCN	K_2CO_3	1	—	90
10	Pyridine	Pyridine	2	—	Trace
11	MeCN	DMAP	2		40
12	MeCN	DIPEA	1.5		80

[a] Reaction conditions: **2a** (1 mmol), **3a** (1 mmol), solvent (5 mL). [b] Reaction conditions: **2a** (0.5 mmol), **3a** (1 mmol), base (1 mmol), solvent (5 mL).

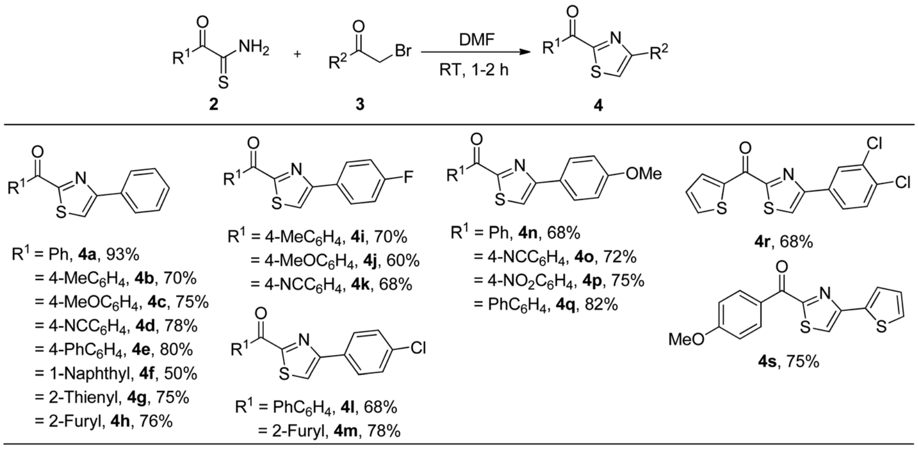


Scheme 2 Synthesis of phenyl(4-phenylthiazol-2-yl)methanone **4a** and 2,2′-thiobis(1-phenylethanone) **5a**.

With the key intermediates in hand, we started optimization of reaction conditions for the synthesis of phenyl(4-phenylthiazol-2-yl)methanone **4a** by reacting 2-oxo-2-phenylethanethioamide **2a** with phenacyl bromide **3a** in acetone in the presence of triethylamine (Table 1, Scheme 2). A product was obtained after an hour which was found to be 2,2′-thiobis(1-phenylethanone) **5a** based on spectroscopic data. Later, we tried the same reaction in the absence of triethylamine, which afforded anticipated product phenyl(4-phenylthiazol-2-yl)methanone **4a** in 90% yield (Table 1, entry 2). To improve the yield, we performed the same reaction in DMF, which furnished **4a** in 93% yield (Table 1, entry 3). Further, reactions in acetonitrile and dichloromethane resulted in decreased yield of **4a** (Table 1, entries 4 and 5). To screen the best condition for the formation of **5a**, we did the reaction **2a** with **3a** in the presence of triethylamine in acetonitrile, which produced **5a** in 95% yield (Table 1, entry 6). Change of solvent to DMF and methanol reduced the yield of **5a** (Table 1, entries 7 and 8). Change of base to potassium carbonate in acetonitrile gave **5a** in 90% yield (Table 1, entry 9). A reaction in pyridine as a solvent as well as base gave **5a** in trace amounts (Table 1, entry 10). Further, DMAP in acetonitrile furnished **5a** in 40% yield (Table 1, entry 11). Finally, a reaction with diisopropylethylamine (DIPEA) furnished **5a** in 80% yield (Table 1, entry 12). Thus, DMF and acetonitrile were found to be the best solvents for the formation of **4a** and **5a** in the absence and presence of triethylamine respectively.

With the optimized reaction conditions in hand, we next explored the generality of the method for the synthesis of 2-acyl-4-(het)arylthiazoles **4** from α-ketothioamides **2** and α-bromoketones **3** (Table 2). Thus, various α-oxodithioesters **2** containing electron donating groups (methyl and methoxy), electron withdrawing groups (cyano and phenyl), 1-naphthyl and heteroaryl groups (2-thienyl and 2-furyl) reacted smoothly with phenacyl bromide (**3a**) to furnish 2-acyl-4-phenylthiazoles **4a–h** in 50–93% yield. Similarly, electronically rich and deficient α-ketothioamides **2** underwent cyclization reaction with *p*-fluorophenacyl bromide (**3b**) to give respective thiazoles **4i–k** in 60–70% yield. In the same fashion, *p*-chlorophenacyl bromide (**3c**) furnished 2-acyl-4-(4-chlorophenyl)arylthiazoles **4l** and **4m** in 68% and 78% yield respectively by undergoing reaction with α-oxodithioesters substituted with biphenyl and 2-furyl moieties. Likewise, *p*-methoxyphenacyl bromide (**3d**) underwent cyclocondensation with electronically diverse α-oxodithioesters to produce 2-acyl-4-(4-methoxyphenyl)thiazoles **4n–q** in 68–82% yield. In parallel, 2-oxo-2-(thiophen-2-yl)ethanethioamide reacted with 3,4-dichlorophenacyl bromide (**3e**) to form (4-(3,4-dichlorophenyl)thiazol-2-yl)(thiophen-2-yl)methanone **4r** in 68% yield. Finally, a reaction between 2-oxo-2-(4-methoxyphenyl)ethanethioamide and 2-bromo-1-(thiophen-2-yl)ethanone (**3f**) yielded 4-methoxyphenyl(4-(thiophen-2-yl)thiazol-2-yl)methanone **4s** in 75%. Thus, α-haloketones containing electron donating and withdrawing groups did not affect the yield of products.

Table 2 Substrate scope for the synthesis of 2-acyl-4-(het)arylthiazoles



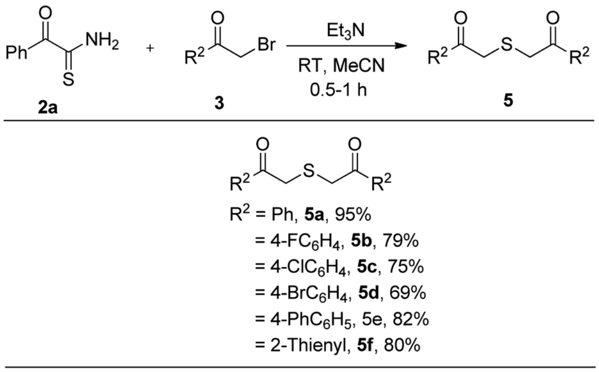
On the other hand, we reacted 2-oxo-2-phenylethanethioamide **2a** with various substituted phenacyl bromides which afforded thioethers **5a–e** in 69–95% yield (Table 3). Besides, 2-bromo-1-(thiophen-2-yl)ethanone reacted with **2a** to furnish 2,2′-thiobis(1-(thiophen-2-yl)ethanone) **5f** in 80% yield.

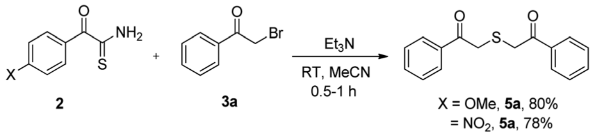
Later, we demonstrated that other electronically diverse α-oxothioamides **2** bearing methoxy and nitro groups behaved as excellent thionating agents for the synthesis of 2,2′-thiobis(1-phenylethanone) **5a** in 80% and 78% yield respectively (Scheme 3). To determine the generality of this protocol, we tested few reactions with *n*-butyl bromide and benzyl bromide, which did not produce anticipated thioethers **6** (Scheme 4).

The ORTEP diagram for one of the thiazoles (4-methoxyphenyl)(4-phenylthiazol-2-yl)methanone **4c** is given in Fig. 2.[49] Similarly, the diagram for one of the thioethers 2,2′-thiobis(1-(4-fluorophenyl)ethanone) **5b** is given in Fig. 3.[50]

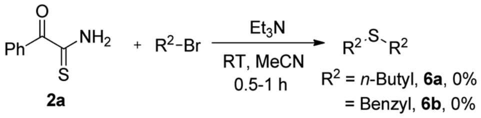
The probable mechanisms for the formation of 2-acyl-4-(het)arylthiazoles **4** and thioethers **5** are given in Scheme 5. For thiazoles, it involves nucleophilic attack of α-oxothiamide **2** to α-bromoketone **3** to give intermediate **7**, which is protonated to give cation **8**. This undergoes intramolecular cyclization to furnish dihydrothiazole intermediate **9**. Finally, dehydration of

Table 3 Substrate scope for the synthesis of 2,2′-thiobis(1-(het)arylethanones)





Scheme 3 Other thionating α-oxothioamides.



Scheme 4 Reaction of an α-oxothioamide with *n*-butyl and benzyl bromide.

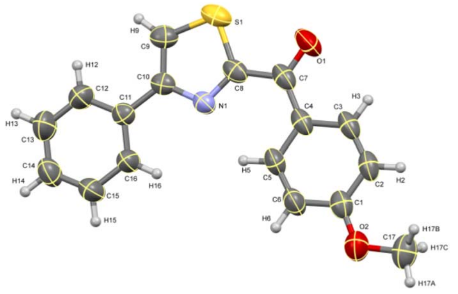


Fig. 2 ORTEP diagram of thiazole **4c**.

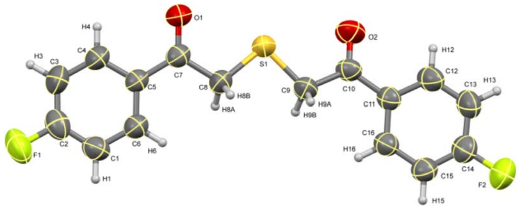
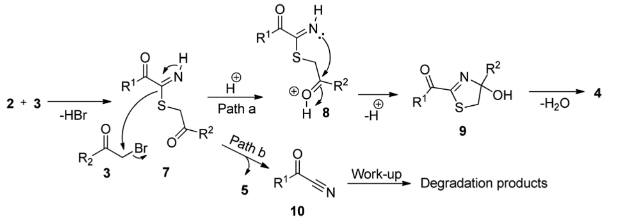


Fig. 3 ORTEP diagram of thioether **5b**.



Scheme 5 Probable mechanism for the formation of 2-acyl-4-(het) arylthiazoles **4**.

9 affords products **4** (path a). On the other hand, second nucleophilic substitution reaction by **7** onto **3** furnishes thioethers **5** and α-ketonitrile **10** (path b). Notably, we observed the degradation of byproduct **10** during work-up and isolation.

Experimental

Materials and methods

All reagents and solvents were purchased from commercial suppliers in India and were used without further purification. Reactions were monitored by TLC (commercially available precoated plates, MERCK 60F254, 0.25 mm thickness) and UV light was used for visualization. NMR spectra were recorded with a Agilant NMR spectrometer. Chemical shift (*δ*) values are given in ppm. $CDCl_3$ was used as solvent with reference to TMS. Coupling constant (*J*) values are given in Hz. Mass spectra were recorded by using Water-SynaptG2 mass spectrometer. The single-crystal X-ray diffraction data for the compounds were obtained with a Bruker Apex II CCD diffractometer using a Cu and Mo source at room temperature with the monochrome beam method. The structures were established *via* full-matrix least-squares methods using the SHELKS program.

Synthetic procedures

General procedure for the synthesis of 2-acyl-4-(het) arylthiazoles 4a–s. Equimolar ratio of α-oxothioamides **2** (1 mmol) and α-bromoketones **3** (1 mmol) were dissolved in DMF (5 mL) and allowed to stir at room temperature. The reactions were monitored by thin layer Chromatography (TLC). After the completion of the reaction, brine (25 mL) was added to the reaction mixture. It was then extracted with ethyl acetate twice (25 mL). The combined ethyl acetate layer was dried over anhydrous sodium sulphate and concentrated under reduced pressure. Later, the crude products were purified by column chromatography using a mixture of ethyl acetate in hexane (EtOAc : hexane: 80 : 20).

Phenyl(4-phenylthiazol-2-yl)methanone (4a). Yellow solid; 93% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 145–147 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3104, 1599, 1249, 1031, 782; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.59 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.94 (d, *J* = 7.6 Hz, 4H, Ar–H), 7.82 (s, 1H, Ar–H), 7.64 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.52–7.38 (m, 2H, Ar–H), 7.36 (t, *J* = 7.6 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 191.2, 183.7, 167.3, 157.5, 135.0, 133.7, 131.4, 131.1, 128.9, 128.6, 126.5, 119.7; HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{16}H_{11}NOS$: 266.0640; found: 266.0647.

(4-Phenylthiazol-2-yl)(*p*-tolyl)methanone (4b). Yellow solid; 70% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 136–138 °C; IR (KBr): ν_{max}(Nujol) cm^{-1} 3096, 1594, 1274, 1176, 846; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.52 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.96 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.82 (s, 1H, Ar–H), 7.46 (d, *J* = 4.0 Hz, 2H, Ar–H), 7.34 (t, *J* = 8.0 Hz, 3H, Ar–H), 2.44 (s, 3H, ArMe); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 195.3, 187.4, 171.8, 161.5, 148.8, 137.9, 135.7, 135.4, 133.3, 132.9, 130.6, 123.9, 25.9; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{13}NOS$ 280.0796 found 280.0798.

(4-Methoxyphenyl)(4-phenylthiazol-2-yl)methanone (4c). White solid; 75% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 100–102 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3093, 1597, 1172, 844; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.68 (d, *J* = 9.2 Hz, 2H, Ar–H), 7.95 (d, *J* = 7.2 Hz, 2H, Ar–H), 7.79 (s, 1H, Ar–H), 7.43 (m, 2H, Ar–H), 7.39 (t, *J* = 7.2 Hz, 1H, Ar–H), 7.01 (d, *J* = 8.8 Hz, 2H, Ar–H), 3.88 (s, 3H. MeO); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 181.8, 168.1, 164.1, 157.2, 133.8, 133.7, 128.7, 127.7, 126.4, 126.2, 119.5, 113.7, 55.5; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{13}NO_2S$ 296.0745 found 296.0748.

4-(4-Phenylthiazole-2-carbonyl)benzonitrile (4d). Yellow solid; 78% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 130–132 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3109, 1297, 755; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.66 (d, *J* = 12.0 Hz, 2H, Ar–H), 7.93 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.90 (s, 1H, Ar–H), 7.82 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.47 (d, *J* = 4.0 Hz, 2H, Ar–H), 7.41 (t, *J* = 6.0 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 186.4, 170.3, 162.1, 142.4, 137.4, 136.2, 135.9, 135.4, 133.1, 130.6, 125.0, 122.1, 120.7; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{10}N_2OS$ 291.0592 found 291.0596.

[1,1′-Biphenyl]-4-yl(4-phenylthiazol-2-yl)methanone (4e). Yellow solid; 80% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 100–102 °C; IR (KBr):ν_{max}(Nujol) cm^{-1} 3092, 1474, 1249, 952, 748; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.72 (d, *J* = 8.4 Hz, 2H, Ar–H), 8.01 (t, *J* = 6.8 Hz, 2H, Ar–H), 7.89 (s, 1H, Ar–H), 7.80 (d, *J* = 7.8 Hz, 2H, Ar–H), 7.71 (t, *J* = 7.2 Hz, 2H, Ar–H), 7.50–7.48 (m, 4H, Ar–H), 7.42 (d, *J* = 7.2 Hz, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*:183.6, 167.9, 157.9, 146.6, 140.2, 134.1,132.3, 132.1, 129.2, 128.9, 127.4, 127.2, 126.9, 126.7, 120.3, 120.1; HRMS (ESI) $[M + H]^+$ calculated $C_{22}H_{15}NOS$ 342.0953 found 342.0958.

Naphthalen-1-yl(4-phenylthiazol-2-yl)methanone (4f). Brown solid; 50% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 126–128 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3094, 1560, 1267, 884; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.54 (d, *J* = 12.0 Hz, 1H, Ar–H), 8.40 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.06 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.94 (t, *J* = 8.0 Hz, 2H, Ar–H), 7.89 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.86 (s, 1H, Ar–H), 7.60–7.52 (m, 4H, Ar–H), 7.38 (d, *J* = 4.0 Hz, 1H, Ar–H), 7.34 (d, *J* = 8.0 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*:191.2, 186.8, 168.1, 157.6, 133.8, 133.6, 133.1, 132.4, 132.0, 129.1, 128.6, 127.6, 126.6, 126.3, 125.6, 124.0, 120.4, 120.1. HRMS (ESI) $[M + H]^+$ calculated $C_{20}H_{13}NOS$ 316.0796 found 316.0789.

(4-Phenylthiazol-2-yl)(thiophen-2-yl)methanone (4g). Yellow solid; 75% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 130–132 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3110, 1474, 1262, 860, 640; ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 8.66 (t, *J* = 2.8 Hz, 1H, Ar–H), 8.0 (d, J = 1.2 Hz, 2H, Ar–H), 7.83 (s, 1H, Ar–H), 7.80 (d, J = 4.0 Hz, 1H, Ar–H), 7.47 (t, J = 6.8 Hz, 2H, Ar–H), 7.39 (d, J = 8.0 Hz, 1H, Ar–H), 7.23 (t, J = 5.6 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.2, 175.6, 166.5, 157.4, 139.3, 136.8, 136.6, 133.6, 128.8, 128.3, 126.5, 119.8; HRMS (ESI) $[M + H]^+$ calculated $C_{14}H_9NOS_2$ 272.0204 found 272.0209.

Furan-2-yl(4-phenylthiazol-2-yl)methanone (4h). Yellow solid; 76% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 126–128 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2923, 1476, 1189, 860; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.45 (s, 1H, Ar–H), 8.05 (d, J = 8.0 Hz, 2H, Ar–H), 7.93 (s, 1H, Ar–H), 7.89 (s, 1H, Ar–H), 7.56 (t, J = 8.0 Hz, 2H, Ar–H), 7.49 (d, J = 7.2 Hz, 1H, Ar–H), 6.77 (d, J = 1.6 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.0, 170.1, 161.6, 153.8, 152.7, 137.7, 132.9, 130.5, 130.4, 128.6, 123.6, 116.8; HRMS (ESI) $[M + H]^+$ calculated $C_{14}H_9NO_2S$ 256.0432 found 256.0438.

(4-(4-Fluorophenyl)thiazol-2-yl)(*p*-tolyl)methanone (4i). Yellow solid; 70% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 140–142 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3102, 1527, 1262, 1121, 835; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.40 (d, J = 12.0 Hz, 2H, Ar–H), 7.82 (dd, J = 8.0 Hz, 4.0 Hz, 2H, Ar–H), 7.66 (s, 1H, Ar–H), 7.25 (d, J = 8.0 Hz, 2H, Ar–H), 7.05 (dd, J = 4.0 Hz, 8.0 Hz, 2H, Ar–H), 2.36 (s, 3H, Ar-Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 189.7, 183.2, 167.8, 156.3, 144.7, 132.3, 131.4, 129.2, 128.2, 128.1, 119.1, 115.8, 21.9; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{12}FNOS$ 298.0702 found 298.0706.

(4-(4-Fluorophenyl)thiazol-2-yl)(4-methoxyphenyl)methanone (4j). Yellow solid; 60% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 128–130 °C; IR (KBr):ν_{max} (Nujol) cm^{-1} 3097, 1438, 1173, 880; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.65 (d, J = 9.2 Hz, 2H, Ar–H), 7.93–7.89 (m, 2H, Ar–H), 7.73 (s, 1H, Ar–H), 7.13 (d, J = 12.0 Hz, 2H, Ar–H), 7.01 (d, J = 12.0 Hz, 2H, Ar–H), 3.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.8, 168.2, 164.1,156.2, 133.8, 130.1, 128.2, 128.1, 127.7, 118.9, 115.8, 113.8, 55.6; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{12}FNO_2S$ 314.0651 found 314.0678.

4-(4-(4-Fluorophenyl)thiazole-2-carbonyl)benzonitrile (4k). Yellow solid; 68% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 134–136 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3093, 1449, 1278, 1031, 832; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.65 (d, J = 8.4 Hz, 2H, Ar–H), 7.91 (d, J = 8.0 Hz, 2H, Ar–H), 7.88 (d, J = 8.8 Hz, 2H, Ar–H), 7.82 (s, 1H, Ar–H), 7.15 (d, J = 8.4 Hz, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 182.3, 166.3, 164.3, 161.9, 156.9, 138.2, 131.9, 131.4, 128.3, 128.0, 120.3, 117.9, 116.6; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_9FN_2OS$ 310.0531 found 310.0538.

[1,1′-Biphenyl]-4-yl(4-(4-chlorophenyl)thiazol-2-yl) methanone (4l). Yellow solid; 68% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 90–92 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3091, 1477, 1258, 958, 746; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.59 (d, J = 12.0 Hz, 2H, Ar–H), 7.82 (d, J = 8.0 Hz, 1H, Ar–H), 7.79 (d, J = 8.8 Hz 2H, Ar–H), 7.75 (s, 1H, Ar–H), 7.69 (d, J = 8.4 Hz, 1H, Ar–H), 7.59 (d, J = 6.8 Hz, 2H, Ar–H), 7.39 (d, J = 8.0 Hz, 2H, Ar–H), 7.34 (d, J = 3.2 Hz, 2H, Ar–H), 7.33 (t, J = 2.4 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 196.8, 182.9, 167.7, 156.2, 146.2, 132.1, 131.9, 131.6, 130.8, 129.7, 129.2, 128.5, 127.7, 127.4, 120.2, 119.8; HRMS (ESI)$[M + H]^+$ calculated $C_{22}H_{14}ClNOS$ 376.0563 found 376.0569.

(4-(4-Chlorophenyl)thiazol-2-yl)(furan-2-yl)methanone (4m). Yellow solid; 78% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 134–136 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3126, 1463, 1280, 1012, 756; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.23 (d, J = 3.2 Hz, 1H, Ar–H), 7.80 (d, J = 7.2 Hz, 2H, Ar–H), 7.74 (d, J = 6.0 Hz, 2H, Ar–H), 7.35 (d, J = 7.6 Hz, 2H, Ar–H), 6.60 (s, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.7, 166.2, 156.2, 149.2, 148.8, 134.6, 132.1, 129.0, 127.5, 124.5, 119.8, 112.9; HRMS (ESI) $[M + H]^+$ calculated $C_{14}H_8ClNO_2S$ 290.0043 found 290.0049.

(4-(4-Methoxyphenyl)thiazol-2-yl)(phenyl)methanone (4n). Yellow solid; 68% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 136–138 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3104, 1599, 1249, 1031, 786; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.58 (d, J = 7.2 Hz, 2H, Ar–H), 7.85 (d, J = 9.2 Hz, 2H, Ar–H), 7.67 (s, 1H, Ar–H), 7.54 (t, J = 7.6 Hz, 1H, Ar–H), 7.51 (d, J = 7.6 Hz, 2H, Ar–H), 6.94 (d, J = 8.8 Hz, 2H, Ar–H), 3.81 (s, 3H, MeO); ^{13}C NMR ($CDCl_3$,100 MHz) δ: 183.6, 167.1, 160.0, 157.4, 135.1, 131.3, 128.2, 127.8, 127.7, 126.6, 118.4, 114.2, 55.4; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{13}NO_2S$ 296.0745 found 296.0749.

4-(4-(4-Methoxyphenyl)thiazole-2-carbonyl)benzonitrile (4o). Yellow solid; 72% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 146–148 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3103, 1600, 1226, 1073, 835; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.65 (d, J = 8.0 Hz, 2H, Ar–H), 7.82 (dd, J = 8.0 Hz, 8 Hz, 4H, Ar–H), 7.76 (s, 1H, Ar–H), 6.97 (d, J = 8.0 Hz, 2H, Ar–H), 3.83 (s, 3H, MeO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 182.3, 165.9, 160.2, 157.9, 138.4, 132.2, 131.6, 127.9, 126.2, 119.3, 118.0, 116.5, 114.3, 55.2; HRMS (ESI) $[M + H]^+$ calculated $C_{18}H_{12}N_2O_2S$ 321.0698 found 321.0685.

(4-(4-Methoxyphenyl)thiazol-2-yl)(4-nitrophenyl)methanone (4p). Yellow solid; 75% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 138–140 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3103, 1600, 1226, 1073, 832; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.73 (d, J = 8.0 Hz, 2H, Ar–H), 8.37 (d, J = 9.2 Hz, 2H, Ar–H), 7.86 (d, J = 8.0 Hz, 2H, Ar–H), 7.79 (s, 1H, Ar–H), 6.98 (d, J = 12.0 Hz, 2H, Ar–H), 3.85 (s, 3H, MeO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 182.2, 165.8, 160.2, 158.0, 140.0, 132.2, 127.9, 127.3, 126.1, 123.3, 119.4, 114.3, 55.4; HRMS (ESI) $[M + H]^+$ calculated $C_{17}H_{12}N_2O_4S$ 341.0596 found 341.0597.

[1,1′-Biphenyl]-4-yl(4-(4-methoxyphenyl)thiazol-2-yl)methanone (4q). Yellow solid; 82% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 102–104 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3094, 1476, 1260, 943, 782; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.69 (d, J = 8.0 Hz, 1H, Ar–H), 7.54 (d, J = 12.0 Hz, 2H, Ar–H), 7.91 (d, J = 8.0 Hz, 1H, Ar–H), 7.81–7.71 (m, 3H, Ar–H), 7.64 (d, J = 8.0 Hz, 2H, Ar–H), 7.47 (d, J = 8.0 Hz, 2H, Ar–H), 7.41 (t, J = 8.0 Hz, 1H, Ar–H), 7.28 (s, 1H, Ar–H), 6.99 (d, J = 8.0 Hz, 1H, Ar–H), 3.85 (s, 3H, MeO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 183.5, 160.0, 157.4, 155.3, 146.1, 139.9, 131.8, 131.5, 128.6, 127.5, 127.2, 126.8, 126.5, 123.7, 116.8, 114.3, 55.4; HRMS (ESI) $[M + H]^+$ calculated $C_{23}H_{17}NO_2S$ 373.1092 found 373.1011.

(4-(3,4-Dichlorophenyl)thiazol-2-yl)(thiophen-2-yl)methanone (4r). Yellow solid; 68% yield (R_f = 0.525 in hexane/EtOAc 80 : 20 v/v); mp: 142–144 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3097, 1507, 1356, 1035, 774; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.60 (t, J = 4.0 Hz, 1H, Ar–H), 8.0 (s, 1H, Ar–H), 7.83 (s, 1H, Ar–H), 7.81 (d, J = 8.8 Hz, 1H, Ar–H), 7.78 (d, J = 2.0 Hz, 1H, Ar–H), 7.76 (d, J = 2.0 Hz, 1H, Ar–H), 7.24 (d, J = 2.4 Hz, 1H, Ar–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:

175.3, 167.1, 154.8, 139.0, 137.1, 136.8, 133.5, 130.1, 128.3, 128.1, 125.6, 125.4, 120.9, 120.6; HRMS (ESI) $[M + H]^+$ calculated $C_{14}H_7Cl_2NOS_2$ 339.9424 found 339.9465.

(4-Methoxyphenyl)(4-(thiophen-2-yl)thiazol-2-yl)methanone (4s). Yellow solid; 75% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 126–128 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2928, 1432, 1235, 1171, 843; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.59 (d, $J = 7.2$ Hz, 2H, Ar–H), 7.56 (s, 1H, Ar–H), 7.42 (t, $J = 2.4$ Hz, 1H, Ar–H), 7.23 (d, $J = 1.2$ Hz, 1H, Ar–H), 7.0 (d, $J = 1.2$ Hz, 1H, Ar–H), 6.93 (d, $J = 8.8$ Hz, 2H, Ar–H), 3.81 (s, 3H, MeO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 181.5, 168.0, 164.2, 151.7, 137.6, 134.0, 133.7, 127.6, 118.3, 117.8, 113.8, 113.6, 55.3; HRMS (ESI) $[M + H]^+$ calculated $C_{15}H_{11}NO_2S_2$ 302.3913 found 302.3918.

General procedure for the synthesis of thioethers 5a–f

A mixture of α-oxothioamides **2** (0.5 mmol), α-bromoketones **3** (1 mmol) and triethylamine (1 mmol) were stirred in acetonitrile (5 mL) at room temperature. The reactions were monitored by TLC. After the completion of the reaction, water (25 mL) was added to the reaction mixture. It was then extracted with ethyl acetate twice (25 mL). The combined ethyl acetate layer was washed with brine (25 mL) and dried over anhydrous sodium sulphate and concentrated under reduced pressure. Later, the crude products were purified by column chromatography using a mixture of ethyl acetate in hexane (EtOAc : hexane::80 : 20).

2,2′-Thiobis(1-phenylethanone) (5a). Yellow solid; 95% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 140–142 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2982, 1176, 678; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (d, $J = 8.0$ Hz, 4H, Ar–H), 7.49 (t, $J = 6.8$ Hz, 2H, Ar–H), 7.36 (t, $J = 6.8$ Hz, 4H, Ar–H), 3.89 (s, 4H, $(CH_2)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 193.7, 134.9, 133.2, 128.3, 128.2, 37.2; HRMS (ESI) $[M + H]^+$ calculated $C_{16}H_{14}O_2S$ 271.0793 found 271.0798.

2,2′-Thiobis(1-(4-fluorophenyl)ethanone) (5b). Yellow solid; 79% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 134–136 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2954, 1216, 1279, 670; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.92 (dd, $J = 9.2$ and 8.8 Hz, 4H, Ar–H), 7.08 (d, $J = 8.4$ Hz, 4H, Ar–H), 3.87 (s, 4H, $(CH_2)_2$; ^{13}C NMR($CDCl_3$, 100 MHz) δ: 192.5, 167.2, 164.6, 131.6 ($J = 30.0$ Hz), 116.0, 37.4; HRMS (ESI) $[M + H]^+$ calculated $C_{16}H_{12}F_2O_2S$ 307.0604 found 307.0612.

2,2′-Thiobis(1-(4-chlorophenyl)ethanone) (5c). Yellow solid; 75% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 130–132 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2930, 1399, 1009, 987, 683; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.81 (d, $J = 8.0$ Hz, 4H, Ar–H), 7.35 (d, $J = 8.0$ Hz, 4H, Ar–H), 3.85 (s, 4H, $(CH_2)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 193.4, 140.8, 134.2, 130.8, 129.7, 38.0; HRMS (ESI) $[M + H]^+$ calculated $C_{16}H_{12}Cl_2O_2S$ 339.0013 found 339.0018.

2,2′-Thiobis(1-(4-bromophenyl)ethanone) (5d). Yellow solid; 69% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 138–140 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2952, 1289, 988, 643; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.75 (d, $J = 8.8$ Hz, 4H, Ar–H), 7.55 (d, $J = 8.4$ Hz, 4H, Ar–H), 3.85 (s, 4H, $(CH_2)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 193.7, 134.6, 132.7, 130.7, 129.5, 38.0; HRMS (ESI) $[M + H]^+$ calculated $C_{16}H_{12}Br_2O_2S$ 428.8983 found 428.8985.

2,2′-Thiobis(1-([1,1′-biphenyl]-4-yl)ethanone) (5e). Yellow solid; 82% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 158–160 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 2923, 1184, 688; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.99 (d, $J = 8.0$ Hz, 4H, Ar–H), 7.63 (d, $J = 8.8$ Hz, 4H, Ar–H), 7.57–7.55 (m, 5H, Ar–H), 7.42–7.39 (m, 5H, Ar–H), 3.97 (s, 4H, $(CH_2)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 194.3, 146.8, 140.2, 134.6, 129.8, 129.5, 128.9, 127.9, 127.8, 38.2; HRMS (ESI) $[M + H]^+$ calculated $C_{28}H_{22}O_2S$ 423.1419 found 423.1423.

2,2′-Thiobis(1-(thiophen-2-yl)ethanone) (5f). Yellow solid; 80% yield ($R_f = 0.525$ in hexane/EtOAc 80 : 20 v/v); mp: 145–146 °C; IR (KBr): ν_{max} (Nujol) cm^{-1} 3012, 1289, 992, 688; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.72 (d, $J = 4.0$ Hz, 2H, Ar–H), 7.62 (d, $J = 4.8$ Hz, 2H, Ar–H), 7.09 (t, $J = 4.0$ Hz, 2H, Ar–H), 3.86 (s, 4H, $(CH_2)_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 187.7, 142.8, 135.0, 129.0, 128.3, 38.0; HRMS (ESI) $[M + H]^+$ calculated $C_{12}H_{10}O_2S_3$ 282.9921 found 282.9926.

Conclusions

In conclusion, we have developed a highly regioselective synthesis of 2-acyl-4-(het)arylthiazoles by the reaction between α-oxothioamides and α-bromoketones in the absence of any base. It should be noted with main concern that the reaction reported herein is an important extended work of the Hantzsch thiazole synthesis, which overcomes the limitations of earlier reported protocols. On the other hand, the same reaction, in the presence of a base yielded thioethers in a highly regioselective fashion. Further studies on synthetic applications of α-oxodithioesters and α-oxothioamides are underway in our laboratory.

Author contributions

R. N. Suresh: methodology, conceptualization, analysis. T. R. Swaroop: writing – review and editing. D. Gowda: writing – methodology, conceptualization, analysis. K. Mantelingu: writing – review and editing. K. S. Rangappa: writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

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