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Chapter 2: Synthesis and applications of α-oxothioamides

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Abstract: α-Oxothioamides play an important role in the synthesis of several heterocycles. Herein, we summarize the synthesis and applications of α-oxothioamides. Particularly, the detailed synthetic studies of thiazoles, thiadiazoles and α-oxoamidines, which are derived from α-oxothioamides are presented.

Keywords: α-oxodithioesters, α-oxoamidines, α-oxothioamides, thiazoles.

1 Introduction

α-Oxothioamides are useful synthons for the synthesis of various sulphur and/or nitrogen containing five/six-membered heterocycles. For instance, a highly regioselective synthesis of 2-acyl-4-(het)arylthiazoles and thioethers was developed from the reaction between α-oxothioamides with phenacyl bromides in the absence and presence of base respectively (Suresh et al., 2023). Similarly, synthesis of 1,2,4 thiadiazoles was achieved *via* oxidative dimerization of α-oxothioamides in the presence of molecular iodine (Suresh et al., 2023). Recently, a regioselectively α-oxoamidines were synthesized from the acid-catalyzed condensation reaction between primary/secondary amines with oxothioamides (Honnabandar et al., 2025). To the best of our knowledge, we are the first to develop the synthesis of α-oxothioamides from α-oxodithioesters (Kiran et al., 2019; Kiran et al., 2020; Kiran et al., 2021; Shivaraj et al., 2023; Kiran et al., 2023; Swaroop et al., 2025; Suresh et al., 2025; Suresh et al., 2025; Swaroop et al., 2025; Swaroop et al., 2025). Furthermore, we are actively involved in organic synthesis (Rajeev et al., 2018; Dukanya et al., 2019; Swaroop et al., 2020; Santhosh et al., 2023; Preetham et al., 2023). Besides, we are also studying biological applications of synthesized compounds (Shivaprasad et al., 2013; Abdel-Wahab et al., 2018; Swetha et al., 2020; Suresh et al., 2023; Suresh et al., 2024).

In this chapter, we present the synthesis of thiazoles, 1,2,4-thiadiazoles and α-oxoamidines from α-oxothioamides. This chapter is helpful for many chemists to develop novel ideas for the synthesis of different heterocycles.

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2.0 Methods and materials

All chemicals were sourced from commercial suppliers located in India and were used as such. The progress of the reactions were checked by thin layer chromatography (commercially available pre-coated plates, MERCK 60F254, 0.25 mm thickness) and UV rays were used for visualization. NMR spectra were recorded with an Agilent NMR spectrometer. Chemical shifts (δ) are given in ppm. $CDCl_3$ was used as solvent. Coupling constants (*J*) are presented in *Hz*. Mass spectra were obtained by using Waters-SynaptG2 mass spectrometer.

3.0 Results and discussion

3.1 Synthesis of α-oxothioamides

According to earlier reported protocols, α-ketodithioesters **1** were prepared (Suresh et al., 2023), which were treated with stoichiometric amounts of ammonium chloride and anhydrous sodium acetate in acetonitrile solvent, to get α-oxothioamides **2** (Suresh et al., 2023) (Fig. 1).

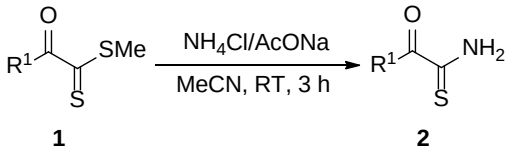


Fig. 1. Synthesis of α-oxothioamides

3.2 Synthesis of thiazoles

A highly regioselective synthesis of thiazoles and thioethers from the reaction between α-oxothioamides and phenacyl bromide has been presented. This synthesis is an example for the extended work of traditional Hantzsch thiazole synthesis which overcomes the limitations of earlier reported protocols. Thus, using key intermediate **2**, optimization of reaction conditions was performed for the synthesis of thiazoles by the reaction between α-oxothioamides **2a** and phenacyl bromide **3a** in the presence of triethylamine in acetone solvent unfortunately 2,2'-thiobis(1-phenylethanone) **5a** was formed and this product was confirmed by analytical characterizations (Fig. 2, Table 1). After multiple attempts, thiazoles **4a** was obtained when performed the same reaction in the absence of base (entry 2, Table 1). While doing solvent screening, DMF was found to be the best solvent to synthesize further derivatives (entry 3, Table 1). On the other hand, acetonitrile in triethylamine was suitable for the synthesis of 2,2'-thiobis(1-phenylethanone) (entry 6, Table 1).

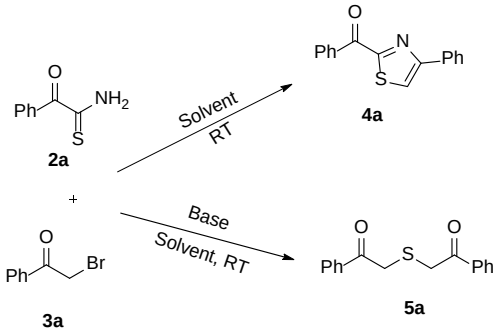


Fig. 2. Synthesis of phenyl(4-phenylthiazol-2-yl)methanone **4a** and **5a**

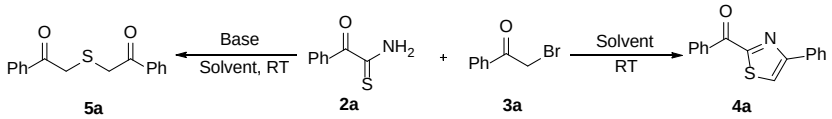
Generality and substrate scope for the synthesis of thiazoles and thioethers was explored using optimized reaction condition. Thus, various substituted α-oxothioamides and phenacyl bromides bearing electron rich and electron deficient substituents underwent smooth reaction in the presence and absence of base under standard optimized reaction condition leading to the formation of thiazoles **4a-s** (60-93%) and thioethers **5a-f** (69-95%) respectively (Table 2). The plausible reaction

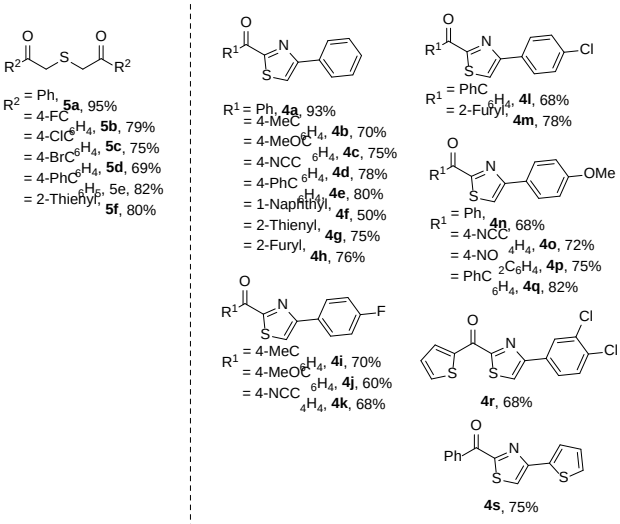
mechanism for the synthesis of 2-acyl-4-(het)arylthiazoles **4a** and 2,2'-thiobis(1-phenylethanone) **5a** is shown in Fig. 3.

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 (%) of **4a**	Yield (%) 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**

Table 2. Substrate scope for the synthesis of 2-acyl-4-(het)arylthiazoles **4a** and 2,2'-thiobis(1-phenylethanone) **5a**





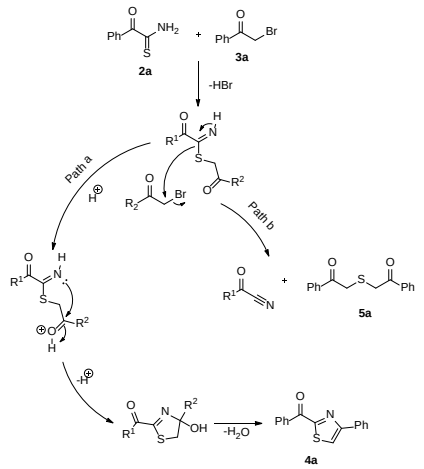


Fig. 3. Plausible reaction mechanism for the synthesis of 2-acyl-4-(het)arylthiazoles **4a** and 2,2'-thiobis(1-phenylethanone) **5a**

3.3 Synthesis of 1,2,4-thiadiazoles

Our group has reported the synthesis of 1,2,4-thiadiazoles by oxidative dimerization of α-oxothioamides using iodine as oxidizing agent. Thus, α-oxothioamides underwent reaction with molecular iodine (0.5 equiv.) to afford 3,5-diacyl-1,2,4-thiadiazoles (Fig. 4). For the synthesis of (1,2,4-thiadiazole-3,5-diyl)bis(phenylmethanone) **6a**, we oxidized 2-oxo-2-phenylethanethioamide **2a** using iodine in different solvents. The product **6a** was isolated in 64% yield in methanol and in 75% in acetonitrile (entries 2 and 3, Table 3). Later, the thiadiazole **6a** was formed in the highest yield (88%) in methanol and acetonitrile mixture (1:1) (entry 4, Table 3). Only 50% yield of **6a** was seen in toluene (entry 5, Table 3). Thus, mixture of methanol and acetonitrile in the ratio 1:1 was found to be the best solvent to synthesize further derivatives.

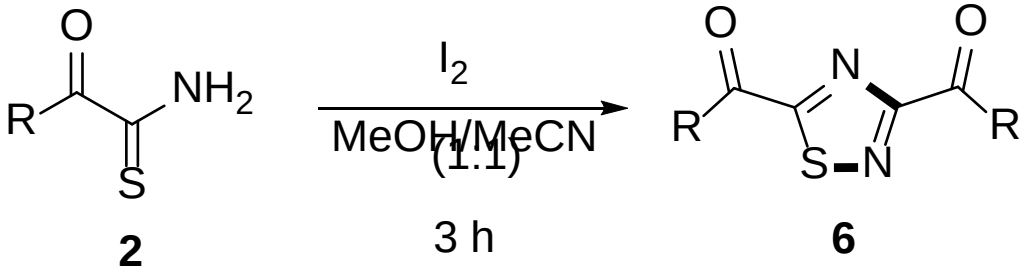


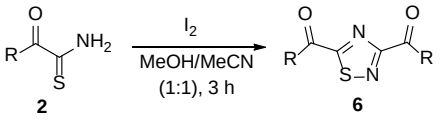
Fig. 4. Synthesis of 3,5-diacyl-1,2,4-thiadiazoles **6**

Table 3. Optimization of reaction conditions for the synthesis of 3,5-benzoyl-1,2,4-thiadiazoles **6a**

Entry	Solvent	Time (h)	Yield (%)
1	Methanol	6.0	64
2	Acetonitrile	4.0	75
3	Methanol: Acetonitrile	3.0	88
4	Toluene	5.0	50

With the optimization reaction condition in hand, we explored the generality for the synthesis of 1,2,4-thiadiazoles **6** (Table 4). Thus, various substituted α-oxothioamides **2** such as electron rich (methoxy, methyl, fluoro and bromo) and electron deficient (nitro and nitrile) and heteroaryl (thienyl, furyl) groups, underwent smooth reaction with molecular iodine to afford respective 1,2,4-thiadiazoles **6a-m** in 70-95% yields. The possible mechanism for the generation of 1,2,4-thiadiazoles **6** is given in Fig. 5.

Table 4. Substrate scope for 1,2,4-thiadiazoles synthesis



R= Ph, **6a**, 88%
= 3-MeC$_6$H$_4$, **6b**, 80%
= 4-MeC$_6$H$_4$, **6c**, 55%
= 3-MeO-C$_6$H$_4$, **6d**, 75%
= 4-MeO-C$_6$H$_4$, **6e**, 90%
= 4-FC$_6$H$_4$, **6f**, 75%
= 4-BrC$_6$H$_4$, **6g**, 78%
= 4-CNC$_6$H$_4$, **6h**, 85%
= 4-NO$_2$C$_6$H$_4$, **6i**, 80%
= 3-NO$_2$C$_6$H$_4$, **6j**, 60%
= Biphenyl, **6k**, 80%
= 2-Thienyl, **6l**, 95%
= 2-Furyl, **6m**, 70%

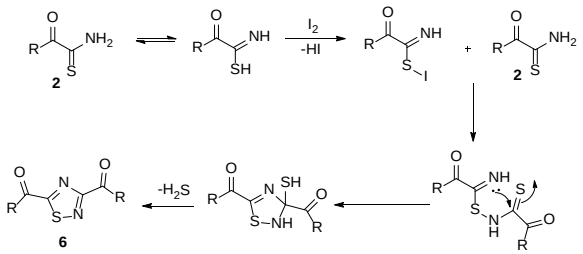


Fig. 5. Probable mechanism for the synthesis of 1,2,4-thiadiazoles **6**

3.4 Synthesis of α-oxoamidines

Amidines are an important class of compounds in organic chemistry occurs in drugs, natural products and agrochemicals (Kumamoto et al., 2009). Recently, our group has reported a regioselective synthesis of α-oxoamidines from acid-catalyzed condensation reaction between primary/secondary amines with 2-oxo-2-aryl-*N*-arylethanethioamides (Honnabandar et al., 2025). At the outset, *N*-aryl-α-oxothioamides were prepared by treating α-oxodithioesters with amines in the presence of sodium hydride in DMF under cold condition to get *N*-aryl-α-oxothioamides (Fig. 6). Then, the obtained *N*-aryl-α-oxothioamides underwent condensation reaction with primary or secondary amines in the presence of benzoic acid in toluene solvent to furnish α-oxoamidines in moderate to high yields (Fig. 7). While doing optimization, authors identified that benzoic acid in toluene at 80° C was found to be the best reaction condition.

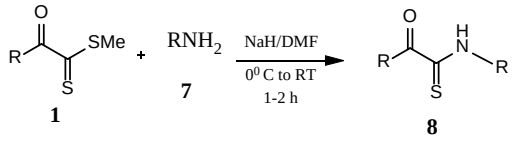


Fig. 6. Synthesis of N-aryl-α-oxothioamides **8**

Using optimized reaction condition, generality and substrate scope for the synthesis of α-oxoamidines was explored. Thus, subtrates *N*-aryl-α-oxothioamides **8** and primary or secondary amines **9** bearing substituents including electron-donating group and electron-withdrawing group undergo reaction in standard optimized conditions to furnish respective anticipated products in good to high yields **10a-r** (Table 5). Failed to get any products when acyclic amines were used as a starting material, which is one of the main limitations of this protocol. The main key features of this method includes, highly regioselective, easily available starting materials, attractive substrate scope and easy to handle. Suitable mechanism for the synthesis of α-oxoamidines **10** is as shown in Fig. 8.

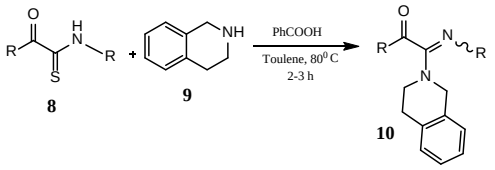


Fig. 7. Synthesis of α-oxoamidines **10**

Table 5. Substrate scope for the synthesis of α-oxoamidines **10**

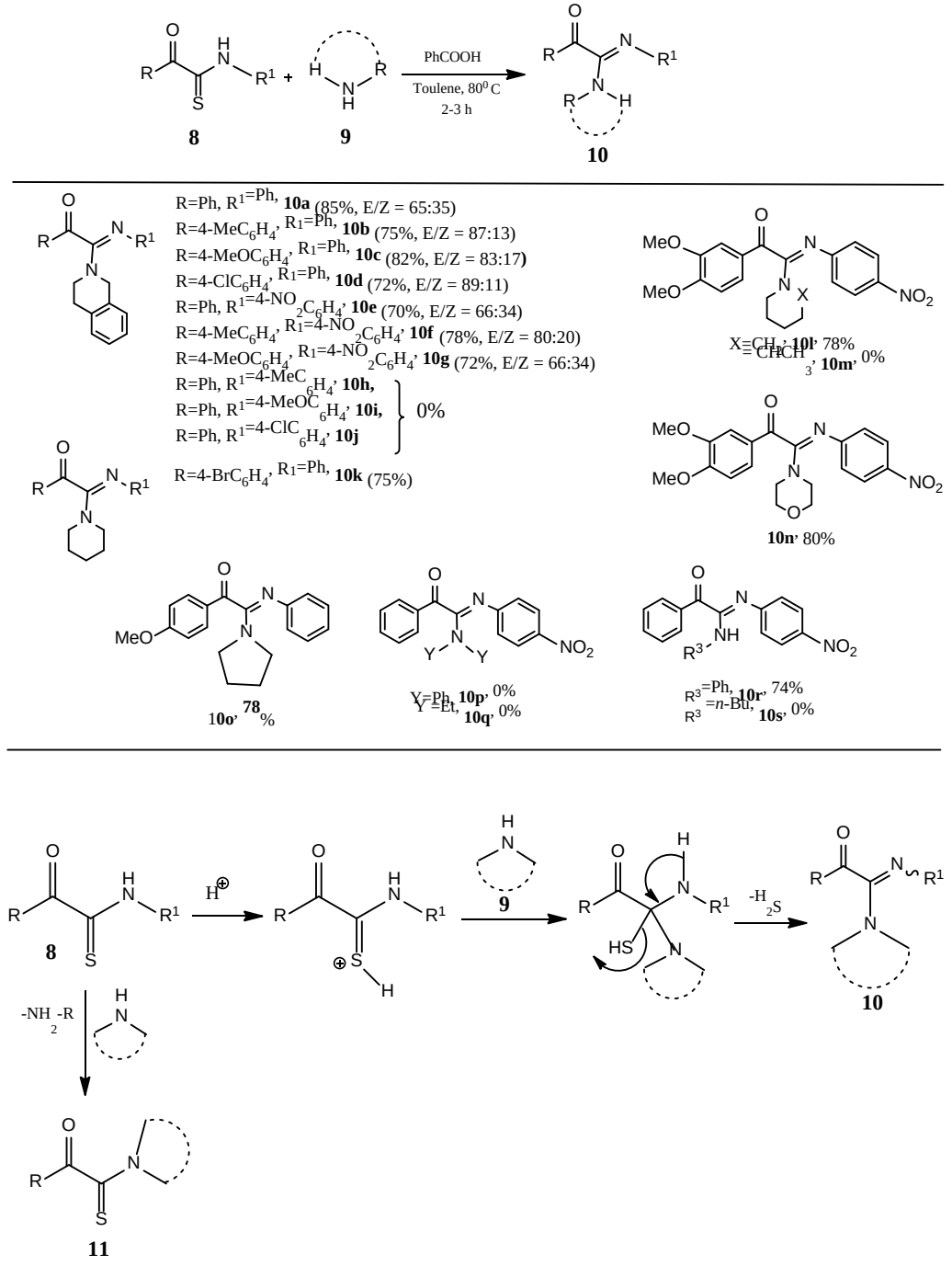


Fig. 8. Plausible reaction mechanism for the synthesis of α-oxoamidines **10**

Conclusions

In this chapter, we present the versatile reactivity of α-oxothioamides and reported the diverse synthetic methodologies for the construction of heterocyclic moieties. Firstly, α-oxothioamides involve in the regioselective synthesis of 2-acyl-4-(het)arylthiazoles and thioethers**.** Here α-oxothioamides act as both cyclization and thionating agents with α-bromoketones and it is an extended work of Hantzsch-thiazole synthesis offering improved yields, broader substrate scope, and mechanistic clarity. Consequently, α-oxothioamides are helpful for the synthesis of 3,5-bis(acyl)-1,2,4-thiadiazoles *via* oxidative dimerization using molecular iodine as a mild oxidant. This method explored the synthetic potential of α-oxothioamides in 1,2,4-thiadiazoles formation with excellent functional group tolerance and scalability. Finally, highly regioselective α-oxoamidines was achieved from the acid-catalyzed condensation reaction between α-oxothioamides and primary and secondary amines. This transformation highlights the selective nucleophilic attack at the thiocarbonyl over the carbonyl group. Overall, these strategies demonstrate that α-oxothioamides are used as versatile intermediates in organic synthesis, enabling the efficient construction of pharmaceutically relevant scaffolds such as thiazoles, thiadiazoles and amidines under mild and scalable conditions.

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