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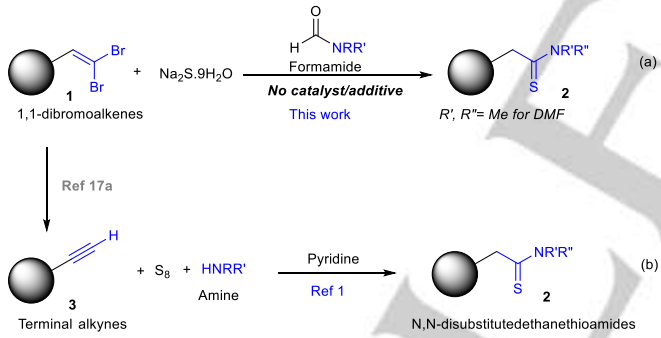
Catalyst/Additive-free Synthesis of Substituted Thioamides from *gem*-Dibromoalkenes and Sodiumsulfide

Ashok K. Morri, [a] Yadagiri Thummala,[a] Ramesh Adepu,[a] Gangavaram V. M. Sharma,[a] Subhash Ghosh,[a] Venkata Ramana Doddi*[b]

Dedicated Prof. H. Ila on her 74th birthday

Abstract: The three component reaction of 1,1-dibromoalkene, sodiumsulfide and *N*-substituted formamide for the synthesis of disubstituted thioamides has been developed. Various dibromoalkene derivatives were found to be compatible under these conditions and gave corresponding thioamides in good to excellent yields.

Understanding a reaction' pathway/mechanism often leads to correlations between systems not otherwise obviously related. Synthesis of thioamides from alkynes or its derivatives is one of the interesting transformation with different possible pathways (Scheme 1).[1,2] Some interesting methods have been reported for the synthesis of thioamides from different starting materials like amides,[3a-e] amines,[3f-h] carboxylic acids,[4] aldehydes,[5] ketones,[6] and nitriles.[7] Out of which, synthesis of thioamides starting from acetylenes, sulfur and amines in the presence of pyridine is one of the most efficient and atom economical method (Scheme 1b).[2] The catalyst or additive is usually employed in the aforesaid synthetic methods for the synthesis of thioamides starting from various starting materials.



Scheme 1. Our method of Synthesis of N,N-dimethylethanethioamides comparison with the recent literature.

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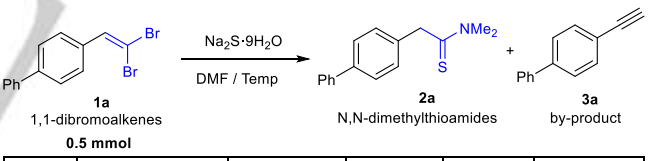
Thioamides are an important class of functional groups used in the synthesis of several sulfur containing heterocyclic compounds and polypeptides.[8] Thioamide functionality containing several compounds are having significant medicinal properties includes immunosuppressive activity,[9] opioid activity[10] and antituberculotic activity.[11] Thioamide group was used instead of amide group in peptides and other compounds to monitor the biological,[12] physical,[13] stability,[14] catalytic[15] functions of target molecules or structural changes in proteins.[16] Owing to their synthetic and biological importance, the motivation exists for discovering new and efficient strategies for the synthesis of thioamides.

We have been working on the substrates 1,1-dibromoalkenes, since we first reported their use in the synthesis of terminal acetylenes.[17] Terminal acetylenes in the presence of pyridine are best used for the synthesis of thioamides (Scheme 1b), and since, acetylenes are to be synthesized from 1,1-dibromoalkenes,[17] therefore, our attention turned to work on the synthesis of thioamides starting directly from 1,1-dibromoalkenes (Scheme 1a). We have chosen formamide DMF as solvent for this reaction as it is well evident from the previous reports that DMF can also act as dimethylamine source.[7]



S. No.	$Na_2S·9H_2O$ (equiv)	DMF (mL)	Temp °C	Time (h)	Yield[b] %	
					2a	**3a**
1	1	1	RT	24	-	23
2	2	1	60	8	-	28
3	1.5	1	120	16	25	-
4	**2.5**	**1**	**120**	**1**	**91**	**-**
5	2.5	2	120	1	85	-

[a] Reaction conditions: 1a (0.5 mmol), Sodium sulfide ($Na_2S·9H_2O$, 2.5 equiv), DMF (1 mL) at 120 °C. [b] Isolated yields.

Table 1 Optimization study[a]

To examine the substrate scope of this reaction, wide range of 1,1-dibromoalkenes **1a-z** are subjected to the optimized reaction conditions (entry 4, Table 1) to give the corresponding *N,N*-dimethylethanethioamides **2a-z**. The 1,1-dibromoalkene substrates containing electron donating groups were converted to

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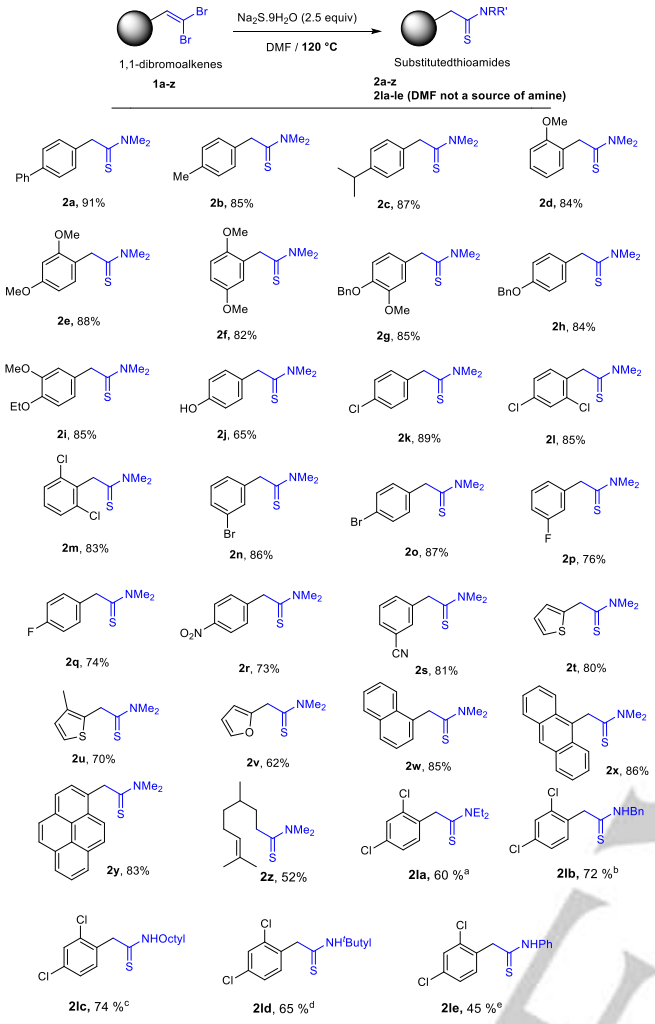
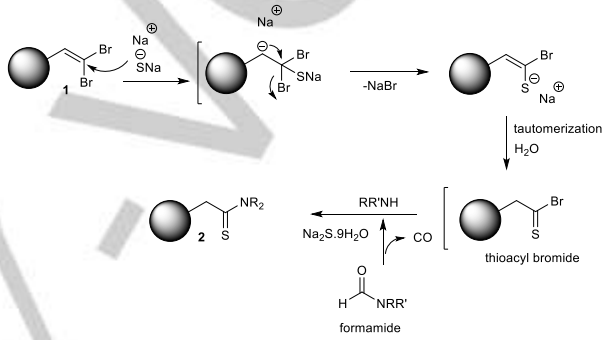


[a] Diethylamine, [b] Benzylamine, [c] Octylamine, [d] [t]Butylamine, [e] *N*-phenylformamide (PhNHCHO) are used as external amines in DMF.

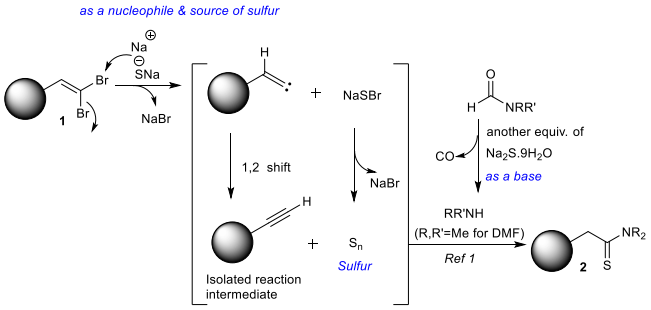
Scheme 2. Substrate scope of 1,1-dibromoalkenes for the synthesis of thioamides.

give the desired thioamides in 65–91% yields (**2a–i**; Scheme 2). It is worth noting that the phenol group sustained well under this conditions to give corresponding thioamide **2j** in 65 % yield. A number of halogenated substrates **1k-q** also reacted with sodium sulfide to give the expected products **2k-q** in very good yields. The bromo and chloro substituents are useful handles for further synthetic elaboration. Dibromoalkenes containing electron-withdrawing groups including fluoro **2p-q**, nitro **2r**, and cyano **2s** groups are also compatible with this protocol to give corresponding desired thioamides **2p-s**. The thioamidation of dibromoalkene containing heterocyclic substituents proceeded smoothly to give the desired products **2t-v** in very good yields, suggesting heterocyclic substrates other than simple aromatic substrates is also reactive. Moreover, by using polyaromatic substrates, this protocol could furnish thioamides **2w-y** in very good yields. Furthermore, aliphatic substrate citronellal derived 1,1-dibromoalkene also could give corresponding thioamide **2z**, albeit in low yield 54 %. Finally, we have performed reactions by the external supply of amines diethylamine, benzylamine, octylamine and tbutylamine instead of in situ formation of dimethylamine from the solvent DMF. Interestingly, corresponding *N,N*-diethylthioamide **2la** (Scheme 2), *N*-benzylthioamide **2lb**, N-octylthioamide **2lc** and *N*-tbutylthioamide **2ld**, (Scheme 2) formed in good yields. These experiments clearly shows that presence of external amines in the reaction leads to formation of corresponding *N,N*-disubstituted thioamides **2la-ld** instead of *N,N*-dimethylthioamide **2l**. The ability to synthesize *N*-substitutted thioamide **2le** by using *N*-phenylformamide (PhNHCHO) as an amine precursor demonstrates another niche for this protocol (Scheme 2), which clearly shows the compatibility of alkyl and aryl formamides in this transformation.



Scheme 3 Preliminary thoughts on reaction mechanism with thioacyl bromide as an intermediate

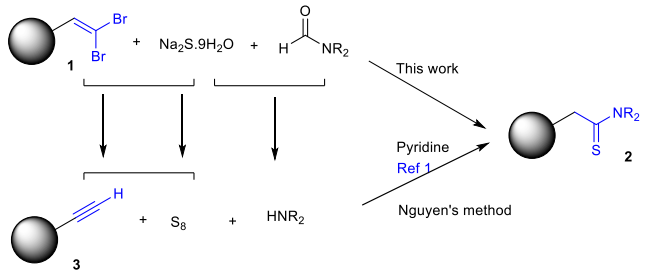
Initially, we thought, synthesis of thioamides **2** from 1,1-dibromoalkenes **1** proceeds through the reaction of in situ fomed thioacyl bromide with amine derived from formamide (Scheme 3). But, we have isolated an intermediate terminal alkyne **3** in this reaction (Table 1, entry 1). Therefore, it is concluded that reaction is proceeds through the formation of terminal alkyne **3** but not through the formation of thioacyl bromide as proposed in scheme 3.



Scheme 4 Proposed mechanism for the synthesis of *N,N*-disubstituted thioamides from 1,1-dibromo alkenes and formamide

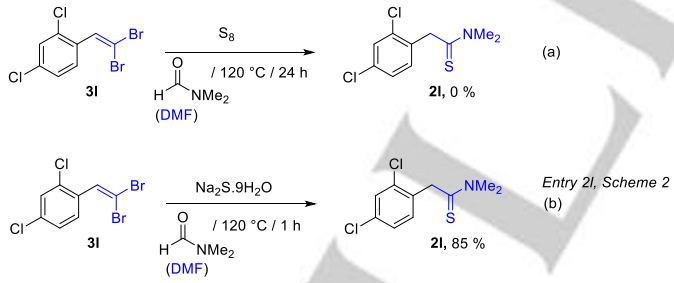
A new plausible mechanism is suggested sulfidesulfurin Scheme 4. The reaction starts with a sodium sulfide mediated formation of terminal alkynes **3** from 1,1-dibromoalkenes **1**. Herein, we propose the nucleophilic attack of sulfide (1 mol) on the bromine atom to give carbene along with another intermediate sodium hypobromothioite NaSBr (Scheme 4). Carbene undergoes 1,2-H

shift to give the terminal alkyne intermediate and simultaneously another intermediate sodium hypobromothioite NaSBr undergo elimination of sodium bromide NaBr to give elemental sulfur (S_n). On the other hand, hydrated sodium sulfide is also basic in nature and it's another molar equivalent induces the cleavage of dialkyl formamides to give amine RR'NH_2.[19] Hence, this reaction needs minimum two equivalents of sodium sulfide to complete the reaction (2.5 equiv, entry 4, Table 1). The subsequent step involves the three component reaction of *in situ* formed three intermediates elemental sulfur S_n, amine RR'NH_2 and terminal alkyne **3** to give corresponding thioamide **2** as proposed by Nguyen *et al*[1] (Scheme 4).



Scheme 5 Our method in comparison with previous method.

We can visualize the present developed method as as a triple telescopic reaction to the method developed by Nguyen *et al* (Scheme 5). Three starting materials used in Nguyen's method can be obtained from their precursors used in this present method (Scheme 5). Two starting materials terminal alkyne **3** and sulfur S_8 can be obtained from the reaction of their two precursors 1,1-dibromoalkene and sodiumsulfide. Another starting material amine HNR_2 can be obtained from base induced cleavage of precursor formamide R_2NCHO (Scheme 5). Further, our results are in full accordance with the results obtained by Nguyen *et al*.[1]



Scheme 6 Control experimentssulfide

A control experiment on the substrate **1l** with elemental sulfur S_8 instead of sodium sulfide Na_2S was conducted in order to confirm the essential role of sodium sulfide in this method (Scheme 6a). There was no product formation even after prolonged time 24 h (Scheme 6a) and we knew the same reaction in the presence of sodium sulfide gives our desired product **2l** (Scheme 6b). These findings confirm elemental sulfur cannot act as nucleophile on 1,1-dibromoalkene **1l** and hence no reaction. These observations in Scheme 6 also further confirms the essential role of Na_2S for the *in situ* formation of three starting materials reported in Nguyen's method (Scheme 5).

Conclusions

In summary, an efficient synthetic procedure for generating *N,N*-disubstituted thioamides by the reaction of 1,1-dibromoalkene, $Na_2S{\cdot}9H_2O$ and formamide R_2NCHO. The wide substrate scope of the reactants allowed synthesis of corresponding thioamides in good to excellent yields. No additive or catalyst used in this reaction unlike previously reported methods employed. Control experiments and optimization studies supported our newly proposed mechanism and confirmed the reaction proceeds through the formation of terminal alkyne intermediate not thioacyl bromide. This developed method could be a better alternative to the methods starting from acetylenes or their derivatives for the synthesis of thioamides.

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Keywords: Dibromoalkene • Sulfide • Elemental sulfur • Thioamide • Formamide

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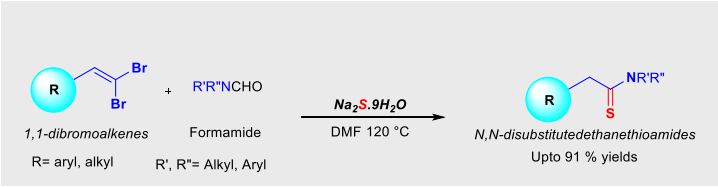

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Catalyst/Additive-free Synthesis of Substituted Thioamides from *gem*-Dibromoalkenes and Sodiumsulfide

Synthesis of thioamides from geminal dibromoalkenes, sodium sulfide and formamide have been reported under catalyst or additive free conditions . Control experiment and mechanistic studies revealed that necessary role of sodium sulfide in this overall transformation.

Key topic: Thioamides