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Graphical Abstract

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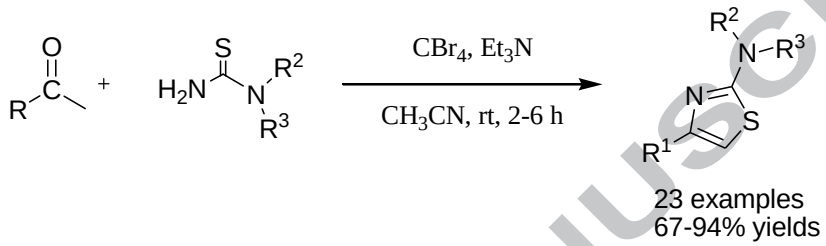

23 examples
67-94% yields

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Carbon tetrabromide mediated oxidative cyclocondensation of ketones and thioureas: an easy access to 2-aminothiazoles

Twinkle Keshari, Ritu Kapoorr, Lal Dhar S. Yadav*
Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211002, India

* Corresponding author. Tel.: +91 532 2500652; fax: +91 532 2460533; *E-mail address*: ldsyadav@hotmail.com (L.D.S. Yadav)

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ABSTRACT

A simple, mild and efficient one-pot method for the synthesis of substituted 2-aminothiazoles has been reported. The reaction involves the formation of sulfenyl bromide as an umpolung intermediate of nucleophilic sulfur, which is responsible for C-S bond formation leading to oxidative cyclization of ketones and thioureas to furnish the desired products. Carbon tetrabromide was used as a convenient and mild brominating reagent under basic condition at room temperature to give 2-aminothiazoles in good to excellent yields.

The thiazole ring constitutes a broad spectrum of compounds useful in the field of agriculture and medicinal chemistry.[1,2] Moreover, aminothiazole heterocycles have been explored as building blocks in organic synthesis and material science.[3] Aminothiazoles are also a privileged structural motif in numerous biologically active molecules.[4] They have been employed for the preparation of different important drugs required for the treatment of tuberculosis,[5a] inflammations,[5a,6,7] allergies,[8] hypertension,[9] schizophrenia,[10] bacterial and HIV infections[5a,11-13] and human lymphatic filarial parasite (Fig. 1).[14] In addition, aminothiazoles are also known to be ligands of estrogen receptors as well as of adenosine receptor antagonists.[15] Analogs of aminothiazole have also agricultural importance for being used as fungicides.[16]

In view of widespread biological applications and physiochemical properties of 2-aminothiazole and its derivatives, several synthetic protocols have been developed for their synthesis. The most popular protocol involves cyclocondensation of halo-carbonyl compounds with thioureas or thioamides called Hantzsch thiazole synthesis.[17] Other reported methods include synthesis using various catalysts such as silica chloride,[18] iodine,[19] 1,3-di-*n*-butylimidazolium tetrafluoroborate,[20] cyclodextrin, ammonium 1,2-molybdophosphate,[21,22] ionic liquid[23] and $NaICl_2$.[24] Recently, Wang and coworkers obtained 2-aminothiazoles by KI/NH_4NO_3 catalysed aerobic oxidative cyclization of ketones and thioureas in ionic liquid.[23] Furthermore, Telvekar et. al. have also developed a synthetic method for 2-aminothiazoles using aqueous $NaICl_2$.[24]

Carbon tetrabromide is a commercially available and cheap reagent, which has found various applications in organic transformations.[25] One of the most impressive and current applications of CBr_4 is its use as an efficient reagent for the umpolung activity of sulfur species.[26] Inspired by these results, we attributed CBr_4 as an efficient thiophilic mediator in our protocol. Thus, keeping the above points in view and our ongoing efforts for devising practical synthesis of bioactive heterocyclic compounds,[27] we envisaged a novel, efficient protocol for the synthesis of 2-aminothiazoles from simple and readily available ketones and thioureas in the presence of a base, using CBr_4 as a promoter in a one-pot procedure (Scheme 1).

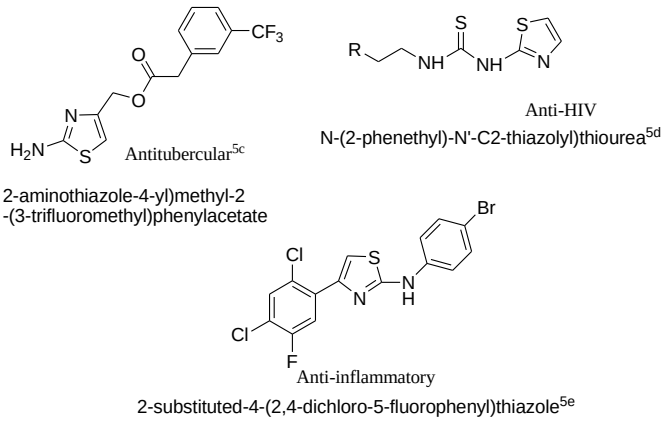
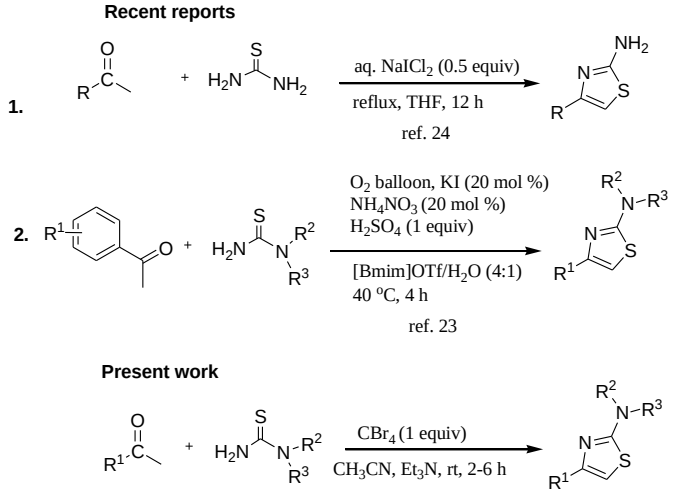


Figure 1. Some drugs containing 2-aminothiazole moiety.

In order to investigate our envisaged protocol, we commenced with the study of a model reaction by stirring a reaction mixture of ketone **1a** (1.0 mmol), thiourea **2a** (1.0 mmol), CBr_4 (1.0 mmol) and triethylamine (1 equiv) as a base in CH_3CN (3 mL) at rt for 2 h. To our delight, 2-aminothiazole **3a** was obtained in an excellent yield of 89% (Table 1, entry 1). Encouraged by this result, we focused our effort to know the minimum time required for completion of the reaction and it was found to be two hours. With this gratifying result in our hand, we proceeded to ensure the necessity of the reaction parameters. A series of control experiments were performed, which revealed that there was no

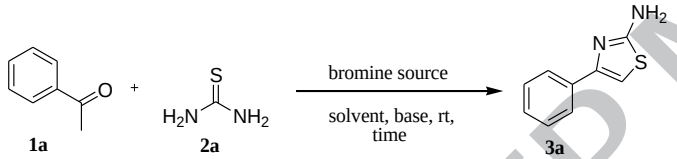


Scheme 1. Transition metal free synthesis of 2-aminothiazoles.

product formation in the absence of a bromine source or a base (Table 1, entry 1 vs 2 and 3), which signifies the necessity of a base and a reaction mediator.

Table 1

Optimization of reaction conditions[a]



1a **2a** **3a**

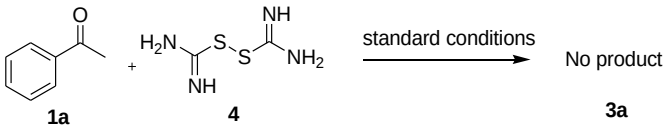
Entry	Bromine source (equiv)	Base	Solvent	Time (h)	Yield[b] (%)
1	CBr_4 (1.0)	Et_3N	CH_3CN	2	89
2	CBr_4 (1.0)	-	CH_3CN	6	n.r.[c]
3	-	Et_3N	CH_3CN	6	n.r.
4	CBr_4 (1.0)	Et_3N	THF	6	20
5	CBr_4 (1.0)	Et_3N	DMF	6	30
6	CBr_4 (1.0)	Et_3N	CH_2Cl_2	6	55
7	CBr_4 (1.0)	Et_3N	C_2H_5OH	6	15
8	CBr_4 (0.5)	Et_3N	CH_3CN	2	68
9	CBr_4 (1.5)	Et_3N	CH_3CN	2	89
10	TBAB[d] (1.0)	Et_3N	CH_3CN	6	30
11	NBS (1.0)	Et_3N	CH_3CN	6	35
12	CBr_4 (1.0)	DABCO	CH_3CN	6	18
13	CBr_4 (1.0)	DBU	CH_3CN	6	20
14	CBr_4 (1.0)	iPr_2NEt	CH_3CN	6	30

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), base (1.0 equiv), bromine source (1.0 mmol) in a solvent (3 mL) were stirred at rt.
[b] Isolated yield of the product **3a**,
[c] n.r. = no reaction.
[d] TBAB = tetrabutylammonium bromide

Next, we optimized the reaction conditions with respect to the bromine source and base and the results are summarized in Table 1. Among CBr_4, TBAB and NBS, CBr_4 was found to act as the best bromine source in terms of the reaction time and yield (Table 1, entry 1 vs 10 and 11). The yield of **3a** was considerably reduced when the loading of CBr_4 was decreased from 1 equiv to 0.50 equiv (Table 1, entry 8). Moreover, the use of 1.5 equiv of CBr_4 instead of 1 equiv did not affect the yield (Table 1, entry 9). Different bases such as Et_3N, DABCO, DBU and iPr_2NEt were tested of which triethylamine proved to be the best (Table 1, entry 1 vs 12-14). CH_3CN was found the most suitable solvent among CH_3CN, THF, DMF, CH_2Cl_2 and C_2H_5OH (Table 1, entry 1 vs 4-7).

With the established reaction conditions in hand, scope of the reaction was investigated for the synthesis of 2-aminothiazoles as depicted in Table 2. The generality of protocol was evaluated across a wide variety of ketones and it was found that phenylethanones with an electron-donating substituent were more efficient as compared to those with an electron- withdrawing substituent on the phenyl ring (Table 2, entries 2-6 vs 7-9). Moreover, heterocyclic and aliphatic ketones were also well compatible with the present reaction conditions (Table 2, entries 11-14).

Further studies on various thioureas were carried out for the cyclization reaction with ketones and it was noted that alkyl thioureas like 1-butylthiourea and 1-benzylthiourea were successful to give target compounds (Table 3, entries 1 and 2). Aryl thioureas containing an electron-donating or an electron-withdrawing substituent on the phenyl ring were also suitable for the present method. However, an electron-withdrawing substituent slightly decreased the yield (Table 3, entries 5 and 6). *N, N*-Disubstituted thioureas such as morpholine-4-carbothioamide, piperidine-1-carbothioamide and 1-methyl-1-phenylthiourea also underwent efficient cyclocondensation to afford 2-aminothiazoles in excellent yields (Table 3, entries 7-9). When phenylethanone was reacted with formamidine disulfide **4** (a dimer of thiourea), the desired product **3** was not obtained under the optimal reaction conditions (Scheme 2). This ruled out the possibility of formation of the dimer of thiourea and subsequent nucleophilic attack of enol form of ketone to give the product **3a**[28]



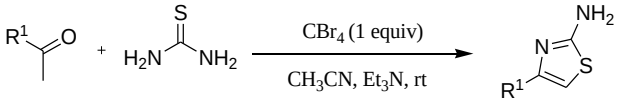
1a **4** **3a**

Scheme 2. Reaction with the dimer of thiourea.

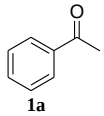
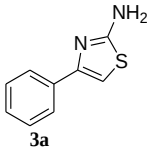
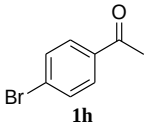
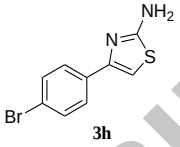
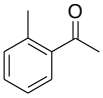
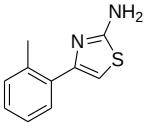
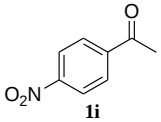
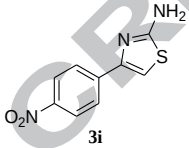
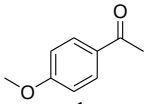
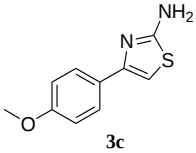
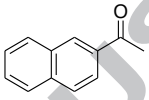
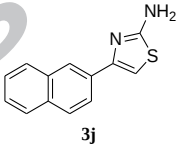
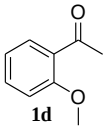
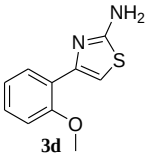
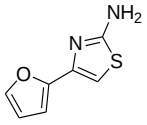
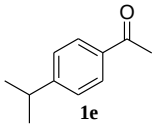
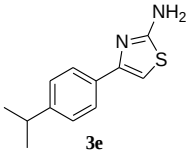
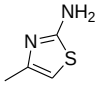
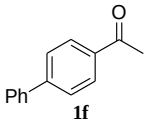
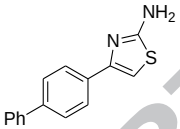
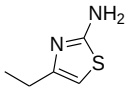
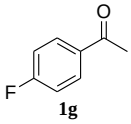
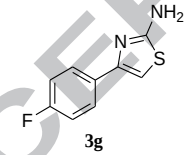
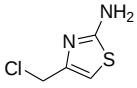
On the basis of the above observations and the literature reports,[26,28,29,30] a plausible mechanism for the formation of 2-aminothiazoles **3** is depicted in Scheme 3. Nucleophilic attack of the sulfur of thiourea (**1′**) on CBr_4 results in the formation of sulfur-centred electrophilic species **4.**[29,30] Then, enol form of **2**'of the ketone **2** attacks the electrophilic sulfur to give **5**, which undergoes cyclocondensation to give the desired product **3**. Bromoform was detected as a by-product in the reaction, which also supports the proposed mechanism. It is noteworthy that CBr_4 promoted formation of **4** with the umpolung reactivity of nucleophilic sulfur is the key step in the present heterocyclization.

In summary, we have developed a new and convenient route for the synthesis of 2-aminothiozoles from ketones and thioureas in a one-pot procedure. The reaction proceeds through carbon tetrabromide promoted in situ generation of electrophilic sulfenyl bromide, which has an umpolung activity of the nucleophilic sulfur. The method is metal-free, highly efficient and works in operationally simple manner at room temperature. Thus, it offers a superior alternative to the existing methods for the synthesis of 2-aminothiazoles.

Table 2
Scope of ketones[a]



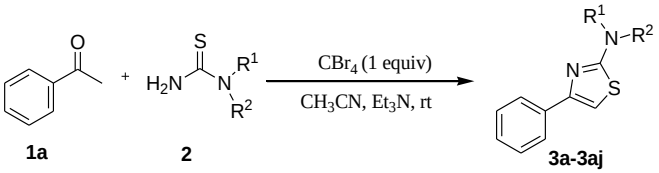
1 **2a** **3a-3n**

Entry	Ketone **1**	Product **3**	Time (h)	Yield (%)[b,c]	Entry	Ketone **1**	Product **3**	Time (h)	Yield (%)[b,c]
1	 **1a**	 **3a**	2	89	8	 **1h**	 **3h**	4	80
2	 **1b**	 **3b**	3	91	9	 **1i**	 **3i**	6	67
3	 **1c**	 **3c**	2	94	10	 **1j**	 **3j**	3	84
4	 **1d**	 **3d**	2	93	11	 **1k**	 **3k**	3	85
5	 **1e**	 **3e**	2	92	12	 **1l**	 **3l**	3	86
6	 **1f**	 **3f**	4	90	13	 **1m**	 **3m**	3	85
7	 **1g**	 **3g**	6	75	14	 **1n**	 **3n**	4	82

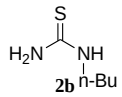
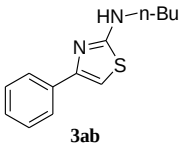
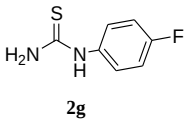
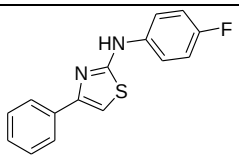
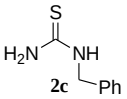
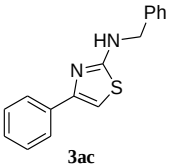
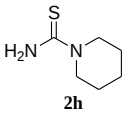
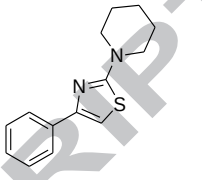
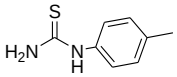
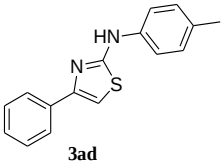
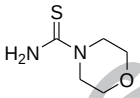
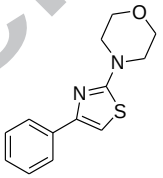
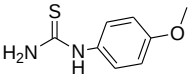
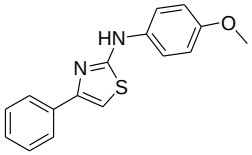
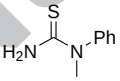
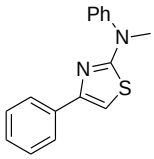
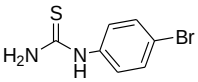
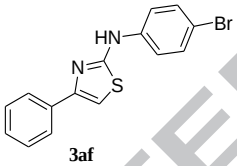
[a] For the experimental procedure, see Ref. 31
.[b] Isolated yield of the products **3**.
[c] All compounds are known and were characterized by comparison of their ^{1}H NMR, ^{13}C NMR and MS spectra with those reported in theliterature.[23,24]

Table 3

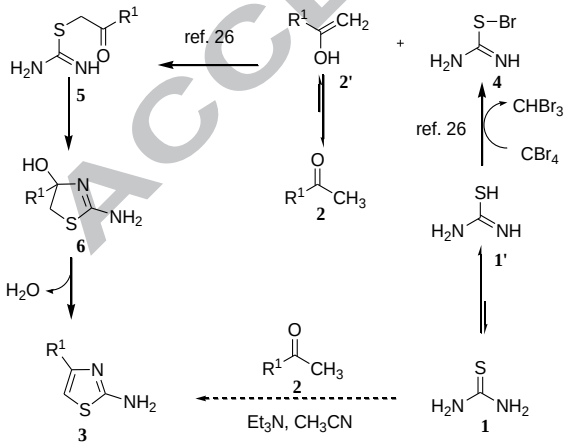
Scope of thioureas[a]



1a **2** **3a-3aj**

Entry	Thiourea **2**	Product **3**	Time (h)	Yield (%)[b,c]	Entry	Thiourea **2**	Product **3**	Time (h)	Yield (%)[b,c]
1	 **2b**	 **3ab**	3	90	6	 **2g**	 **3ag**	6	75
2	 **2c**	 **3ac**	3	88	7	 **2h**	 **3ah**	2	93
3	 **2d**	 **3ad**	3	93	8	 **2i**	 **3ai**	2	92
4	 **2e**	 **3ae**	2	92	9	 **2j**	 **3aj**	3	93
5	 **2f**	 **3af**	4	82					

[a] For the experimental procedure, see Ref. 31.
[b] Isolated yield of the products **3**.
[c] All compounds are known and were characterized by comparison of their ^{1}H NMR, ^{13}C NMR and MS spectra with those reported in the literature.[23,24]



Scheme 3. Plausible mechanism for the formation of 2-aminothiazoles.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi-----

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31. *General Procedure for the synthesis of 2-aminothiazoles* ***3*** *(Table 2, 3) from ketones and thioureas*: To a mixture of ketone (0.5 mmol) , thiourea (0.5 mmol) and triethylamine (0.5 mmol) in acetonitrile (3 mL) was added carbon tetrabromide (0.5 mmol) in a round bottom flask at room temperature and the reaction mixture was stirred for 2-6 h. After completion of the reaction (monitored by TLC), water (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the crude product. The resulting product was purified by silica gel column chromatography using a gradient mixture of hexane/ethyl acetate as eluent to afford an analytically pure sample of **3**. All the products are known compounds and were characterized by the comparison of their spectral data with those reported in the literature.[23,24]