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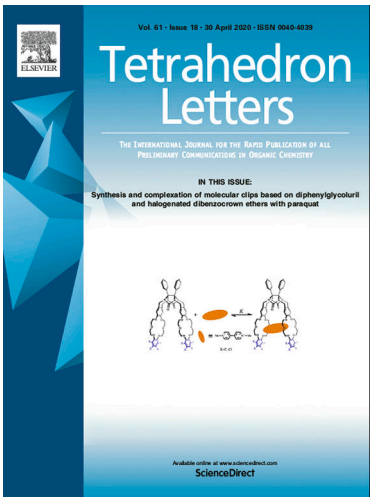

One-pot synthesis of 4-aryl-2-aminothiazoles from styrenes and thioureas promoted by tribromoisocyanuric acid

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Graphical Abstract

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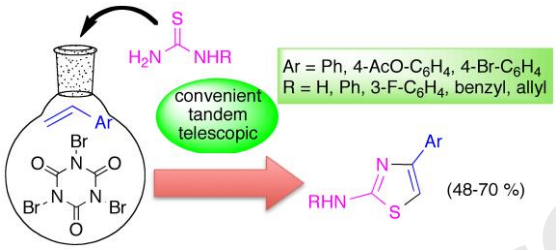

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One-pot synthesis of 4-aryl-2-aminothiazoles from styrenes and thioureas promoted by tribromoisocyanuric acid

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ABSTRACT

A simple and efficient one-pot protocol has been developed for the conversion of styrenes into 4-aryl-2-aminothiazoles using readily available starting materials. Tribromoisocyanuric acid was successfully used for the co-bromination and oxidation of styrenes to give phenacyl bromides, which in the presence of thioureas produced the corresponding 4-aryl-2-aminothiazoles in 48-70% yield. The protocol involves three reactions in one process: a tandem (formation of phenacyl bromides from styrenes) followed by a telescoped (conversion to thiazole) reaction.

Heterocyclic scaffolds are present in diverse molecules of significant interest in several branches of chemistry (e.g. medicinal chemistry, industry, agriculture and textile dyes). Among the vast number of *N*-heterocycles, the thiazole group (1,3-thiazole) is a privileged structural motif associated with bioactive compounds, as well as an important building block for materials science.[1] In particular, the 2-aminothiazole subclass is present in several drugs and natural products with broad biological and pharmacological activities (e.g. anticancer, antiviral, antimicrobial, antiprion, anti-inflammatory and psychotropic activities).[2] It also plays an important role as corrosion inhibitors[3] and fluorophores.[4] Figure 1 shows the diversity of structures that are found in important clinical drugs bearing the pharmacophoric 2-aminothiazole scaffold.

Due to the importance and utility of 2-aminothiazoles, diverse synthetic methods have been described for their preparation and the chosen strategy is highly dependent on the substitution pattern of the target molecule. In the particular case of 4-aryl-2-aminothiazoles, the classical Hantzsch condensation[5] of α-haloacetophenones (phenacyl halides) with thioureas is still a subject of study.[6] Useful methodologies include the metal-catalyzed decomposition of styryl azides in the presence of thiocyanates,[7] a multicomponent reaction of phenacyl bromides, amines and trimethylsilyl isothiocyanate,[8] or the condensation of thioureas with *in situ* formed phenacyl halides from acetophenones,[9] styrenes[10] and alkylarenes[11] (Scheme 1), among many others.[12] Although these are valuable approaches, many of them suffer from drawbacks, especially from the standpoint of the availability of starting materials, use of harsh reaction conditions and toxic chemicals.

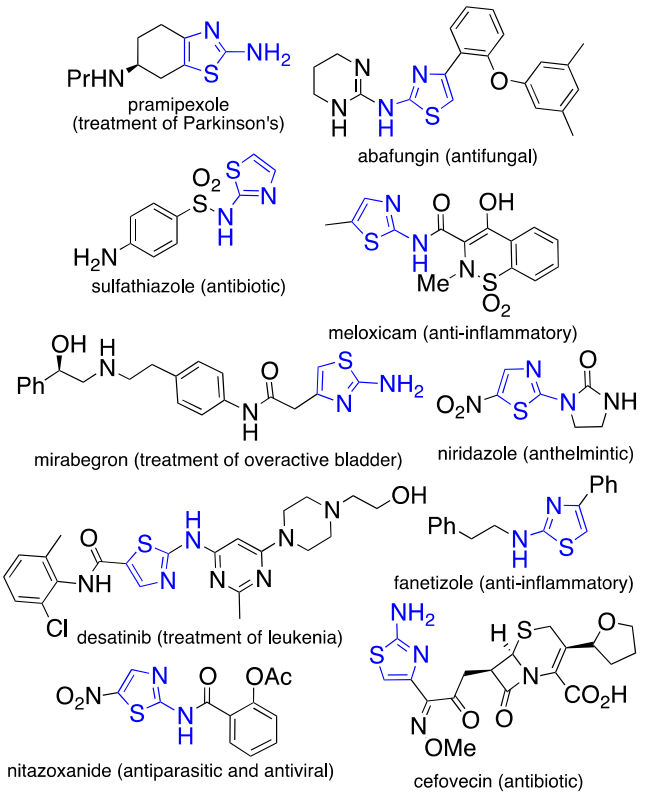

Figure 1. Selected examples of clinical drugs containing the 2-aminothiazole scaffold.

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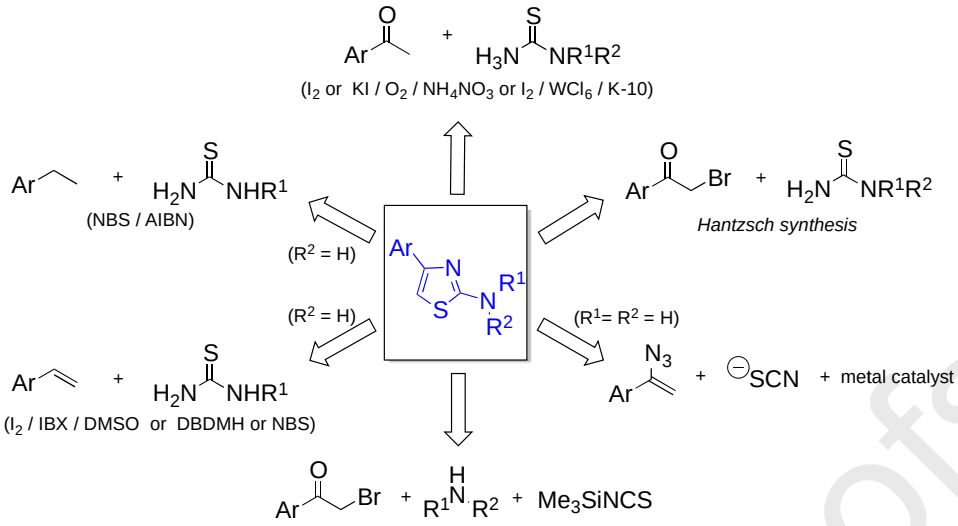


Scheme 1. Methodologies for the preparation of 4-aryl-2-aminothiazoles.

In light of growing environmental concerns, research efforts are especially focused on heterocyclic construction processes that are step- and atom-economic. In this regard, besides classical methodologies to access 2-aminothiazoles, new approaches have been reported in the literature by telescoping multi-step reactions (i.e. execution of multiple transformations, quenches and workup procedures without the isolation of intermediates), which avoids handling and exposure to hazardous or toxic compounds and minimizes the number of synthetic steps, purification processes and, consequently, chemical waste.[13] In this context, pot-economy approaches involving *N*-halo reagents are widespread in the literature for the synthesis of heterocycles.[14] Among the *N*-halo reagents, trihaloisocyanuric acids (Fig. 2) are effective and stable electrophilic halogenating reagents that are commercially available or prepared from readily accessible materials.[15] From a green chemistry point of view, they present a higher atom economy and are able to transfer up to three halogen atoms to a substrate.[16] In addition, in reactions involving trihaloisocyanuric acids, the cyanuric acid by-product can be reused to produce additional trihaloisocyanuric acid.[17] Recently, we published an efficient telescoped preparation of 2-aminothiazoles 5-carboxylates from thioureas and β-keto esters mediated by tribromoisocyanuric acid.[18]

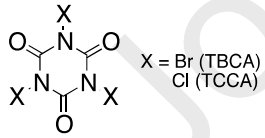
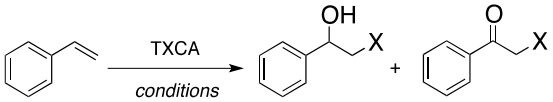


Figure 2. Trihaloisocyanuric acids.

Continuing our interest on the chemistry of trihaloisocyanuric acids,[19] we report herein the TBCA-promoted conversion of styrenes into 4-aryl-2-aminothiazoles through a pot-economic approach of three consecutive reactions in a single vessel.

There are several methodologies for the synthesis of phenacyl bromide from styrene using different oxidants.[20] Previously, we reported a convenient co-halogenation of alkenes with oxygenated nucleophiles promoted by trihaloisocyanuric acids.[21] Hence, the reaction of styrene with TBCA in aqueous acetone produced 2-bromo-1-phenylethanol with high regioselectivity. Therefore, we studied the possibility of the direct conversion of styrene into phenacyl bromide through a one-pot tandem reaction, with excess TBCA having a double action, i.e. as an electrophilic halogen source to form the bromohydrin and an oxidant to convert it into the haloketone. As can be seen in Table 1, the best results were obtained in water at 70 ºC for 2 h or in aqueous acetonitrile at room temperature for 20 h. Both conditions converted styrene into phenacyl bromide quantitatively, but we chose the first one as being optimal. Interestingly, although trichloroisocyanuric acid is known to oxidize alcohols to ketones,[22] the oxidation of the chlorohydrin to the phenacyl chloride was not effective and the utilization of a large excess of TCCA led to several products.

Table 1. Screening for the conversion of styrene into phenacyl halides.

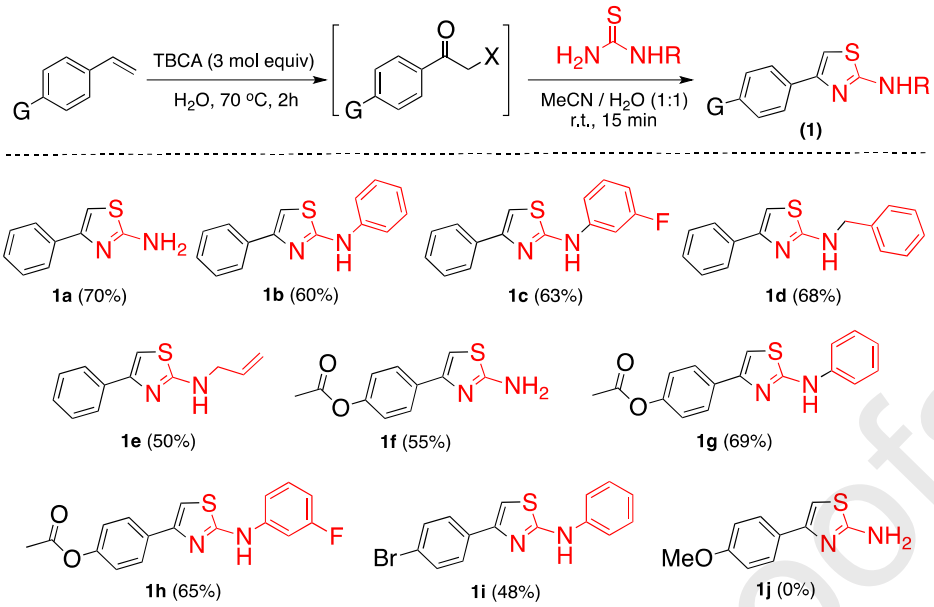


Solvent	Temp.	X^+ (equiv)	Time (h)	Alcohol/ ketone (%)[a]
MeCN/H_2O (4:1)	r.t.	Br (3.0)	15	48/52
MeCN/H_2O (4:1)	r.t.	Br (3.5)	15	25/75
MeCN/H_2O (4:1)	r.t.	Br (3.5)	20	0/100
Acetone/H_2O (30:1)	r.t.	Br (3.5)	24	25/75
H_2O	50 ºC	Br (3.0)	2	64/36
H_2O	70 ºC	Br (3.0)	2	0/100
H_2O	70 ºC	Br (2.1)	2	68/32
MeCN/H_2O (4:1)	r.t.	Cl (3.0)	24	59/41[b]
MeCN/H_2O (4:1)	r.t.	Cl (2.0)	24	93/7

[a]Determined by GC-MS.

[b]Formed along with a mixture of several products.

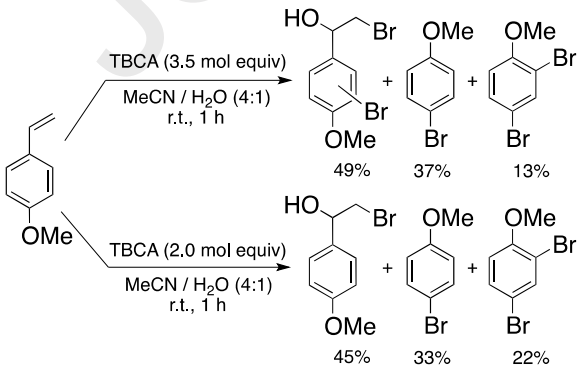
With these optimized conditions in hand, we studied the reaction of the *in situ* formed phenacyl bromide with thiourea, adjusting the solvent to a mixture of acetonitrile/water (1:1) and obtained 4-phenylthiazol-2-amine (**1a**) in 70% yield after an additional 15 min reaction at room temperature. The product was easily isolated by precipitation of the reaction media and was purified by recrystallization from aqueous ethanol. Extension of these optimized conditions to substituted styrenes and thioureas led to a series of 4-aryl-2-aminothiazoles (**1**) with different patterns of substitution on the aryl and amino groups (Scheme 2).



Scheme 2. 4-Aryl-2-aminothiazoles prepared from styrenes and TBCA.

It was observed that the nature of the thiourea does not affect the reaction. On the other hand, the group attached to the styrene ring plays an important role on the scope/yield of the reaction. Therefore, substrates bearing weakly electron-donating or withdrawing groups led to the corresponding 4-aryl-2-aminothiazoles in 48-70% yield. However, 4-methoxystyrene, which has a strong electron-donating group attached to the aromatic ring, led to a mixture of several products, none of which was the thiazole, as determined by GC-MS. In fact, when 4-methoxystyrene was subjected to the tandem co-bromination and oxidation reactions, a mixture of several S_EAr brominated products was obtained, including *ipso*-substitution, in only one hour at room temperature, even when using a stoichiometric amount of TBCA (Scheme 3). No carbonyl products were detected in the crude reaction mixtures by GC-MS.

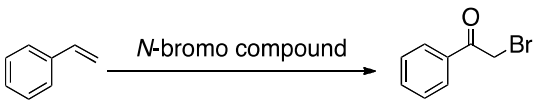
It is well-known that 4-methoxybenzyl alcohols give *ipso*-substitution products when reacting with electrophilic halogenating reagents.[23] In general, the *ipso*-substitution process competes with the oxidation and an investigation on the reaction pathway detected bromoacetaldehyde to support the process.[22b] Therefore, it is reasonable that 4-methoxystyrene undergoes co-bromination followed by *ipso* electrophilic aromatic substitution on the resulting bromohydrin, followed by arene bromination by the remaining TBCA.[24]



Scheme 3. Reaction of 4-methoxystyrene with TBCA.

Additionally, in a comparative study, the synthesis of phenacyl bromide and 4-phenylthiazol-2-amine (**1a**) was conducted stepwise and they were obtained in 80% and 76% yield, respectively. Thus, the overall yield of **1a** produced stepwise was lower than in the one-pot reaction (61% *versus* 70%). In addition, comparison of TBCA with similar *N*-bromo compounds, such as 1,3-dibromo-dimethylhydantoin (DBDMH) and *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$), for the conversion of styrene into phenacyl bromide is presented in Table 2. Our results show that although TBCA gave a lower yield, it has the advantage of possessing a higher atom efficiency (i.e. atom economy vs. chemical yield),[25] which is consistent with green chemistry principles.[26]

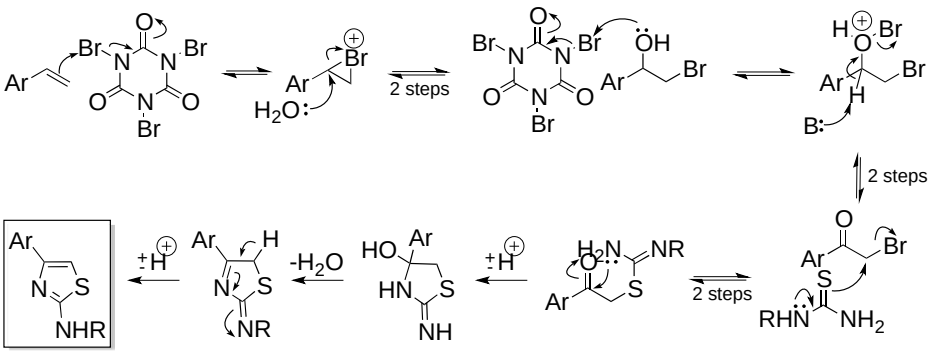
Table 2. Comparison of *N*-bromo compounds for the conversion of styrene into phenacyl bromide.



N-bromo compound	Yield (%)	Atom efficiency (%)	Ref.
DBDMH	85	39	20d
$TsNBr_2$	87	42	20c
TBCA	80	63	This work

A possible rationalization for the TBCA-promoted conversion of styrenes into 4-aryl-2-aminothiazoles involving co-halogenation, oxidation and oxidative cyclization steps is presented in Scheme 4. Initially, there is a regioselective co-halogenation of styrene promoted by TBCA, followed by oxidation of the bromohydrin by another equivalent of TBCA. Finally, nucleophilic attack of the thiourea on the phenacyl bromide, followed by condensation of the free amino, elimination and oxidation give the desired 4-aryl-2-aminothiazoles.

In summary, we have developed an efficient one-pot protocol for the synthesis of 4-aryl-2-aminothiazoles from styrenes and thioureas, which involves three reactions in only one process, i.e. a tandem (formation of phenacyl bromides) followed by a telescoped (convertion to thiazole) reaction. The experimental procedure is simple, the reagents are readily available, and there is no need for the manipulation of lacrymmatory phenacyl bromides, which makes our methodology attractive for a wide range of applications in organic synthesis.



Scheme 4. Possible rationalization for the TBCA-promoted conversion of styrenes into 4-aryl-2-aminothiazoles.

Acknowledgment

We thank CNPq and CAPES for financial support. We also thank Prof. Rafael Garrett da Costa and LBCD-LADETEC/IQ-UFRJ for the HRMS analyses.

Supporting Information

Supporting information is available which includes detailed experimental procedures, analytical data and copies of IR, MS, ^{1}H and ^{13}C spectrum of all synthesized compounds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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A pot-economy synthesis of 4-aryl-2-aminothiazoles from styrenes promoted by tribromoisocyanuric acid

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HIGHLIGHTS

- efficient conversion of styrenes into 4-aryl-2-aminothiazoles
- mild and safe reaction conditions
- simple experimental using readily avaiable materials
- a pot-economic approach in a single vessel
- tandem and a telescoped reactions

Declaration of interests

- ✓ ☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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