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Synthesis of 2-aminothiazoles from styrene derivatives mediated by 1,3-dibromo-5,5-dimethylhydrantoin (DBH)

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ABSTRACT

An efficient procedure for the synthesis of 2-aminothiazoles via DBH-mediated oxidative cyclization of styrenes and thioureas is reported. Various alkenes were successfully transformed to the corresponding 2-aminothiazoles in yields of 10–81% via a two-step one-pot manner using DBH as both the bromine source and oxidant. The method can be readily carried out in gram-scale and successfully applied to the synthesis of anti-inflammatory drug fanetizole using styrene as starting material.

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2-Aminothiazole ring systems are privileged structural motifs found in a great deal of biologically active compounds which are used to treat bacterial infections,[1] inflammation,[2] hypertension,[3] allergies,[4] schizophrenia,[5] cancer[6] and so on. Several compounds bearing 2-aminothiazole core have been approved as therapeutic drugs or under clinical trials (Fig. 1). In view of the importance of 2-aminothiazole ring in the pharmaceutical industry,[7] several methods have been developed for the construction of this scaffold from various starting materials. Traditional 2-aminothiazole formation was achieved by the Hantzsch reaction of α-halocarbonyl compounds and thioureas.[8] Recently, modified Hantzsch protocols were reported. The heterocycle-formation was promoted by various catalytic systems such as ammonium-12-molybdophosphate,[9] NaF,[10] β-cyclodextrin,[11] or catalyst-free in water[12]/ionic liquid,[13] or accelerated by microwave irradiation in ethanol.[14] To avoid direct handling of lachrymatic reagents, starting materials other than α-halocarbonyl compounds were also developed. Yadav reported $Cu(OTf)_2$-catalyzed coupling of α-diazoketones with thiourea to synthesize 2-aminothiazoles.[15] Zhao,[16] Kaushik,[17] Telvekar[18] and Yadav[19] presented their studies on the transformation of ketones to 2-aminothiazoles under various conditions. Halogenation followed by cyclocondensation of ketone with thiourea is also attractive, which is accessed by using iodine,[20] NBS,[21] and 1,3-dichloro-5,5-dimethylhydantoin[22] as halogen sources and catalyzed by nanoparticles. Transformation of phenylacetylenes to corresponding 2-aminothiazoles was also achieved, as reported by Nageswar.[23] Alkenes have been recognized as attractive starting materials for a number of organic transformations because they are inexpensive and readily available in chemical industry. Donohoe[24] and Kshirsagar[25] demonstrated the synthesis of 2-aminothiazoles from alkenes mediated by I_2/IBX in DMSO or NBS in water. Recently, our group reported that 1,3-dibromo-5,5-dimethylhydantoin (DBH) could be served as a powerful reagent in the transformation of alkenes to other versatile intermediates such as α-bromo/amino ketones, α,α-dibromoacetophenones, and amides.[26] Based on these works, we hypothesized that our strategy could be further expanded to the formation of 2-aminothiazoles. Herein, we would like to report a practical synthesis of 2-aminothiazoles by means of DBH-mediated oxidative cyclization of alkenes with thiourea under mild conditions.

According to our previous work in the conversion of olefins into

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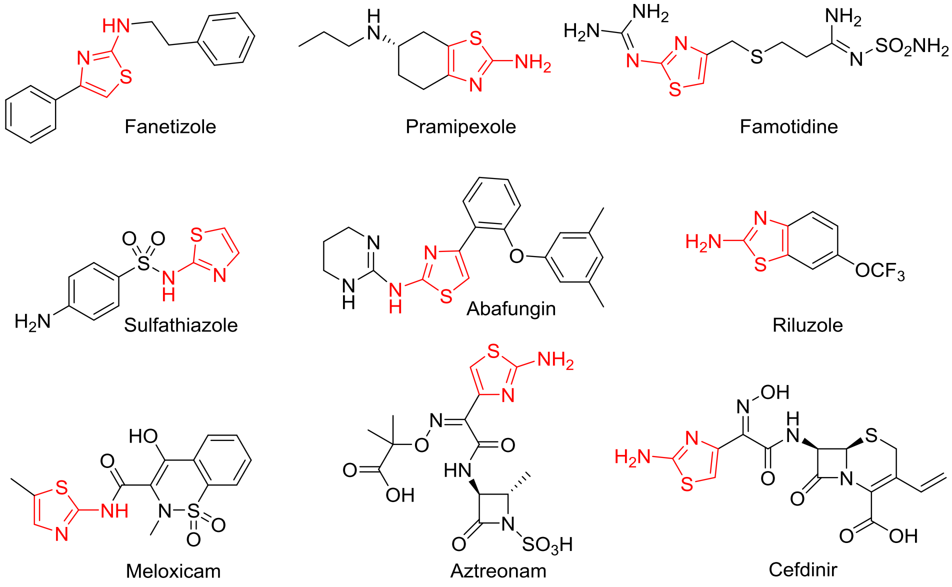

Fig. 1. Selected drugs bearing 2-aminothiazole scaffold.

α-bromoketones,[26a] we treated styrene (0.5 mmol) with DBH (1.5 equiv) and 1% (v/v) tween-80 as an emulsifier in water at 60 °C for 1 h, followed by reaction with thiourea (1.5 equiv) at 80 °C for 2 h. To our glad, the reaction gave 4-phenylthiazol-2-amine (**2a**) in 81% yield (Table 1). Encouraged by this result, we next engrossed in exploring the substrate scope of the reaction with different substituted alkenes. As shown in Table 1, most 2-aminothiazoles were obtained in moderate to good yields regardless of an electron withdrawing or donating group on the benzene ring (**2c**-**2z**). Substrates bearing weak electron-donating group (alkyl group) were transformed to corresponding 2-aminothiazoles in good yields from 65% to 79% (**2c**-**2f**). However, this protocol did not work on styrenes bearing strong electron-donating group such as methoxyl group. On the contrary, derivatives with electron-withdrawing substituents gave desired products smoothly in yields from 32% to 71% (**2g**-**2r**, **2u**-**2z**). The effect of steric hindrance on the benzene ring was also observed. The yield of styrene derivative with *meta*-substituent was considerably lower than its *para*-counterparts (**2i**/**2j** *vs.* **2 g**/**2h**, **2 m**/**2n** *vs.* **2 k**/**2l**, and **2q**/**2r** *vs.* **2o**/**2p**); while for *ortho*-substituent, the yield was as low as about 10% (**2s**/**2t**). As shown in Table 1, not only terminal alkenes but also linear- and cyclic-internal styrene derivatives, provided satisfactory results (**2ac**/**2ad** and **2ag**/**2ah**). Furthermore, this protocol also worked well on aliphatic olefins (**2ae**/**2af**).

Subsequently, in order to evaluate the scalability of the method, the reaction of styrene was performed in a 1.0-g scale (Scheme 1), affording the 2-aminothiazole (**2a**) in satisfactory yield (79%).

Fanetizole (*N*-phenethyl-4-phenylthiazol-2-amine, Fig. 1) is an anti-inflammatory agent under clinical trials for the treatment of rheumatoid arthritis. This compound has been previously synthesized by coupling of 2-bromoacetophenone with *N*-phenethylthiourea.[12,13] Recently, Zhao[16] reported the oxidative cyclization of acetophenone and *N*-phenethylthiourea to yield fanetizole by using the combination of $KI/NH_4NO_3/H_2SO_4$ in [Bmim]OTf/H_2O and molecular oxygen as oxidant. According to our new protocol, commercial available and cheap styrene was treated with DBH, subsequently reacted with *N*-phenethylthiourea to afford fanetizole in 72% yield (Scheme 2), avoiding the using of 2-bromoacetophenone with serious lachrymatic property.

Based on our previous works and the disclosed reaction pathway,[26] we proposed a plausible mechanism of this reaction, as shown in Scheme 3. The reaction is initiated by halohydroxylation with DBH or active species HBrO to obtain 2-bromo-1-phenyl ethanol. The further bromination of this intermediate is investigated with DBH or HBrO as bromo source, followed by cleaving one molecule of HBr to give phenacyl bromide. Finally, the in situ generated phenacyl bromide reacts with thiourea smoothly to form aminothiazoles **2a**.

In summary, various alkenes were successfully transformed to corresponding 2-aminothiazoles in moderate to good yields via a two-step one-pot manner using DBH as both the bromine source and oxidant. This method is attractive because of the use of low-toxic reagents, readily available and inexpensive starting materials without preliminary functionalization, and mild conditions. The reaction can be readily carried out in gram-scale, providing a practical strategy for the preparation of 2-aminothiazole derivatives. The synthesis of anti-inflammatory drug fanetizole using styrene as starting material demonstrated a successful application of this method.

1. Experimental section

1.1. General information

All commercial reagents were used without further purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254). Preparative thin layer chromatography was performed on silica gel F254 glass plates (layer thickness 400–500 mm). Yields refer to isolated yields and spectroscopically pure compounds. Melting points were determined on a melting point apparatus in open capillaries and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz or Bruker Avance III 600 MHz spectrometer as indicated in the data list. Chemical shifts for proton nuclear magnetic resonance (^1H NMR) spectra are reported in parts per million relative to the signal residual ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm) or TMS. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.16 ppm or DMSO-d_6 multiplet at 39.52 ppm. The abbreviations s, d, t, q, br, and m stand for the resonance multiplicity singlet, doublet, triplet, quartet, broad and multiplet, respectively. High resolution mass

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