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Synthesis of 5-Phenylthiazolamines Using Thiourea as an α-Bromination Shuttle

Irwan Iskandar Roslan,[a] Kian-Hong Ng,[a] Gaik-Khuan Chuah*[a] and Stephan Jaenicke*[a]

Abstract: A straightforward synthesis of 5-phenylthiazolamines via coupling of thiourea with phenylacetones, phenylacetophenones and β-tetralone has been developed. Thiourea acts as a substrate and an α-bromination shuttle, transferring Br from the brominating reagent, $CBrCl_3$, to the α-carbon of the carbonyl moiety before triggering a series of steps to form the final product. Isolated yields of 80 to 95 % were obtained. Key features of this protocol includes the minimal use of reagents (substrates, $CBrCl_3$ and $CsHCO_3$ as base), short reaction times under mild conditions (2-3 h at 80 °C) and ease of scale-up to gram quantities.

Figure 1. Representative biologically active thiazolamines.

Introduction

The thiazolamine moiety is an important structural motif that is present in many natural products, pharmaceuticals, and synthetic intermediates.[1] Some of these compounds possess medicinal and biological properties including antiHIV, anticancer, antimicrobial and antituberculosis activity (Figure 1).[2] In addition, thiazolamines have also found use in areas such as dyes, films and biophysical binding assays.[3] Due to the diverse properties and applications of thiazolamines, it is of interest to develop reliable and efficient protocols to construct these structural motifs. Over the years, various methods were reported in the literature, such as coupling of thiocyanates with vinyl azides[4] or oxime acetates,[5] three-component reactions involving thiocyanates, α-bromoketones and amines[6] and coupling of isothiocyanates amidines/guanidines and halomethylenes.[7] Nevertheless, the most commonly employed route is still the Hantzsch-type condensation of 2-bromoacetophenones with thioureas, forming 4-phenyl-thiazolamines.[8] The bromine at the α-carbon is necessary as a leaving group as no thiazolamine product can be formed without it. The α-bromoacetophenones have to be presynthesized, although *in-situ* α-halogenation of acetophenones, 1,3 dicarbonyl compounds and styrenes has since been reported.[9],[10] *N*-bromosuccinimide, *N*-iodosuccinimide, $NaICl_2$, I_2 or hypervalent iodine reagents are typically employed as the halogen source. Many of these reagents are highly exothermic or reactive which makes them difficult to handle and poses safety concerns when the reactions are to be carried out on a large scale.
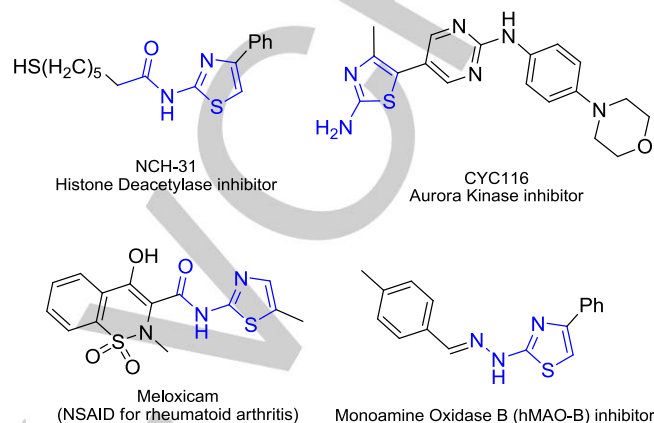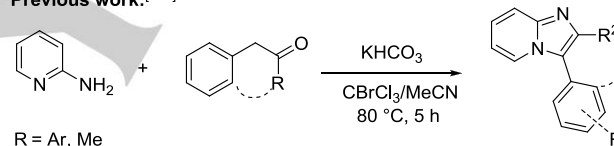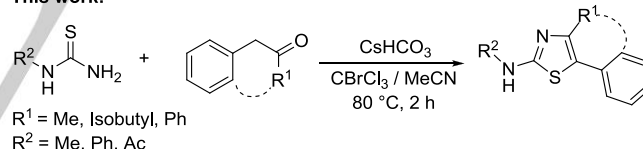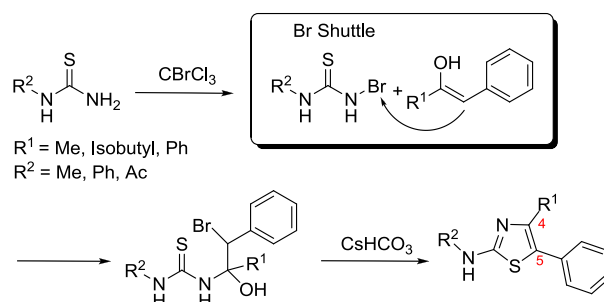

Scheme 1. Comparison of our previous and current work on the α-Br shuttle, including the reaction scheme for the latter.

[a]   Department of Chemistry, National University of Singapore, 3
        Science Drive 3, Singapore 117543.
        *E-mail: chmsj@nus.edu.sg; chmcgk@nus.edu.sg
        http://www.chemistry.nus.edu.sg/people/academic_staff/jaenicke.htm;
        http://www.chemistry.nus.edu.sg/people/academic_staff/chuahgk.htm

        Supporting information for this article is available on the WWW
        under http://dx.doi.org/xxxx

Instead of the common halogenation agents, we recently reported the use of $CBrCl_3$ as a convenient and safe bromine source.[11] Together with 2-aminopyridine which serves a dual role as a substrate and an α-bromination shuttle, bromine is transferred from $CBrCl_3$ to the α-carbon of its coupling partner,

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initiating a cascade reaction to form imidazo[1,2-*a*]pyridine (Scheme 1). The coupling of various 2-aminopyridines with dielectrophiles including 1,3-dicarbonyls, 1,3-cyclohexandione, phenylacetones, phenylacetophenones, and *β*-tetralone was successfully applied to give high yields of imidazo[1,2-*a*]pyridines under mild conditions. This reaction was done in one-pot without the need for transition metal catalysts and stoichiometric amounts of oxidants.

Having shown the versatility of this *α*-bromination shuttle system to various dielectrophiles, we were interested in whether thiourea could emulate the dual role played by 2-aminopyridine. Replacing the sp^2 N atom of the pyridine ring with the S atom of the thioketone moiety would allow access to 5-phenylthiazolamines instead of the ubiquitous 4-phenylthiazolamines.[9] Herein, we would like to report an efficient and rapid method to access phenylthiazolamines from the coupling of thiourea and its derivatives with phenylacetones, phenylacetophenones and *β*-tetralone (Scheme 1). To the best of our knowledge, this is the first protocol for the synthesis of 5-phenylthiazolamines that proceeds via *in-situ α*-bromination. It eliminates the need to employ *α*-brominated derivatives, which need to be presynthesized.
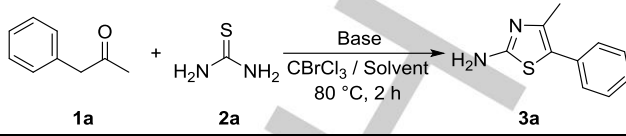
Results and Discussion

For the initial study, various bases were tested for the reaction system comprising phenylacetone **1a** (1 mmol) and thiourea **2a** (1.5 mmol) in a mixed solvent system of CBrCl$_3$/acetonitrile (1:14 v/v) at 80 °C (Table 1). Without a base, the desired product **3a** was not formed. The yield of the product increased in the order NaHCO$_3$ < KHCO$_3$ < CsHCO$_3$ and 92 % isolated yield was obtained after 2 h (Table 1, entries 2 - 4). The stronger base, K$_2$CO$_3$, was less suitable for the reaction with only 39 % isolated yield of **3a** while the reaction with Cs$_2$CO$_3$ gave several unidentified side products (Table 1, entries 5 & 6).

Next, various solvents were tested at 80 °C. The reaction was very sensitive to the type of solvent used. No reaction occurred in non polar and polar protic solvents. Only polar aprotic solvents such as DMF and MeCN were suitable (Table 1, entries 4, 7-11). With almost identical yields when employing DMF and MeCN as solvent, the latter was chosen due to its lower boiling point. It was satisfying that the amount of thiourea **2a** could be reduced to one equiv without a significant drop in yield (Table 1, entries 12 & 13). This sharply contrasts with the significant drop in yield when the reaction was conducted with one equiv of CBrCl$_3$ (Table 1, entry 14). Thus, the optimized conditions employed for subsequent reactions were 1 mmol of phenylacetone derivative, 1 mmol of thiourea **2a** and 1.1 equiv of CsHCO$_3$ in 3 mL of 1:14 (v/v) CBrCl$_3$/MeCN solvent mixture at 80 °C for 2 h.

Various phenylacetones were screened for their suitability under the optimized conditions (Table 2). Phenylacetones with methoxy substituent at the *ortho*-, *meta*- and *para*-position proceeded smoothly (Table 2, **3b** - **3e**). Even ethyl, chloro and

**Table 1.** Optimization parameters for the synthesis of phenylthiazolamine **3a**[a]

Entry	Solvent	Base	Yield of 3a (%)[b,c]
1	MeCN	-	0
2	MeCN	NaHCO$_3$	16
3	MeCN	KHCO$_3$	78 (70)
4	MeCN	CsHCO$_3$	95 (92)
5	MeCN	K$_2$CO$_3$	57 (39)
6	MeCN	Cs$_2$CO$_3$	-[d]
7	toluene	CsHCO$_3$	0
8	DCE	CsHCO$_3$	0
9	ethanol	CsHCO$_3$	0
10	dioxane	CsHCO$_3$	trace
11	DMF	CsHCO$_3$	96 (92)
12[e]	MeCN	CsHCO$_3$	95 (91)
13[f]	MeCN	CsHCO$_3$	94 (92)
14[g]	MeCN	CsHCO$_3$	67 (55)

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol) and base (1.1 mmol) in 3 mL of 1:14 (v/v) CBrCl$_3$/solvent mixture (2.0 equiv wrt **1a**) at 80 °C for 2 h. [b] Yield (from GC) with respect to **1a**. [c] Isolated yields in parenthesis. [d] Reaction was very messy with lots of side products formed. [e] 1.25 equiv of **2a**. [f] 1.0 equiv of **2a**. [g] 1.0 equiv of CBrCl$_3$.

bromo substituents at the *para*-position were well tolerated with good yields (Table 2, **3f** - **3h**). It was gratifying that the "spicy pentanone", 4-methyl-1-phenyl-2-pentanone, used in food and fragrances and *β*-tetralone were also suitable coupling partners with thiourea, forming **3i** and **3j** with 89 and 80 % yield, respectively.
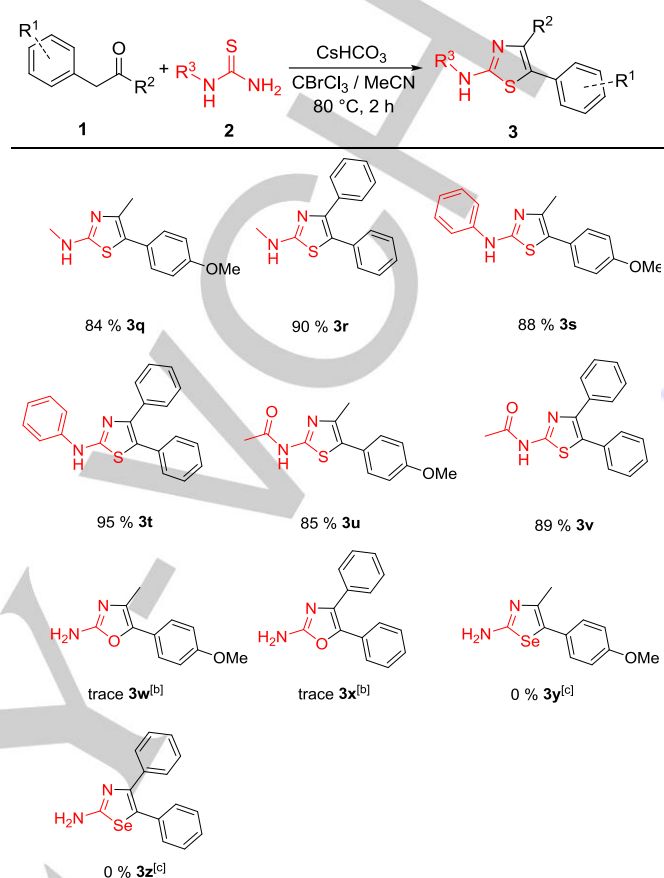
Six different phenylacetophenones were tested for their suitability under this reaction protocol. Substrates with both electron donating and electron withdrawing groups, including methyl, methoxy, fluoro, chloro and bromo substituent at either of the two phenyl moieties were all well tolerated and proceeded with good to excellent yields (Table 2, **3k** - **3p'**).

Next, screening of various *N*-substituted thioureas and their derivatives as coupling partners for 4-methoxyphenylacetone and phenylacetophenone was carried out (Table 3). Both *N*-methylthiourea and *N*-phenylthiourea were suitable coupling partners with 4-methoxyphenylacetone and phenylacetophenone proceeding with good to excellent yields (Table 3, **3q** - **3t**). Gratifyingly, even *N*-acetylthiourea, a substrate with an *α*-carbon, was well tolerated under the optimized conditions and coupled with 4-methoxyphenylacetone and phenylacetophenone to form **3u** and **3v** with 85 % and 89 % yields, respectively. These results show that the *α*-carbon of 4-methoxyphenylacetone and phenylacetophenone was more

Table 2. Scope of reaction (phenylacetones, phenylacetophenones and *β*-tetralone).[a]
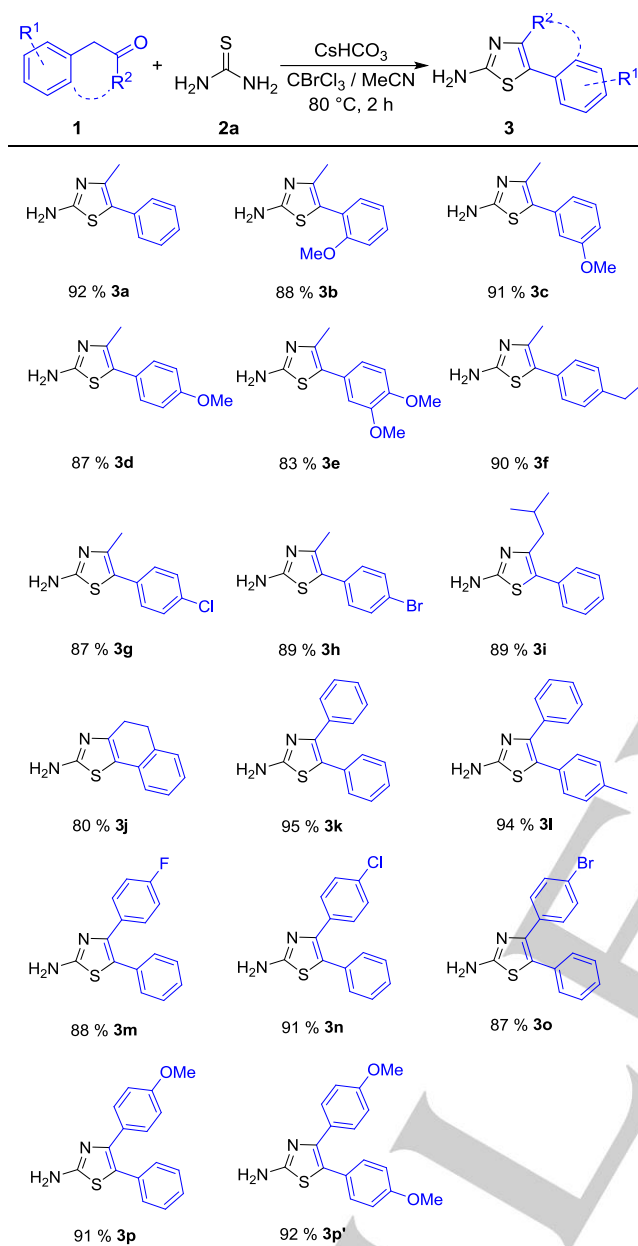
[a] Reaction conditions: **1** (1.0 mmol), **2a** (1.0 equiv) and CsHCO$_3$ (1.1 equiv) in 3 mL of 1:14 (v/v) CBrCl$_3$/MeCN mixture at 80 °C for 2 h. Percentage isolated yields.

Table 3. Scope of reaction (*N*-substituted thioureas, urea and selenourea).[a]

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 equiv) and CsHCO$_3$ (1.1 equiv) in 3 mL of 1:14 (v/v) CBrCl$_3$/MeCN mixture at 80 °C for 2 h. Percentage isolated yields. [b] Additional experiments using DMF instead of MeCN and longer reaction times of 24 h also produced traces of products or [c] no reaction.

group[10a] where both thiourea and selenourea coupled to *β*-ketoesters to form the thi/selen-azolamine products.

The reaction is proposed to follow a mechanism similar to that of the 2-aminopyridine/CBrCl$_3$ system (Figure 2). The reaction begins with the initial bromination of thiourea **2a** via a radical chain mechanism to form the *N*-brominated intermediate **A**.[12] An addition reaction of intermediate **A** with the enol form of phenylacetone **1a** forms the bromo-hemiaminal intermediate **B**.[13] Other than a substrate, thiourea **2a** doubles up as an *α*-bromination shuttle, transferring Br from CBrCl$_3$ to **1a**, releasing CHCl$_3$, which was detected via *in-situ* NMR.[11b] Dehydration of **B** forms the imine intermediate **C**. The S atom then attacks the *α*-carbon and an intramolecular cyclization ensues, forming the ionic salt **D**. Deprotonation by CsHCO$_3$ affords the desired product along with CO$_2$ and CsBr.

A scaled-up synthesis of **3t** was conducted to demonstrate the practical application of this protocol (Scheme 2). 15 mmol of phenylacetophenone and *N*-phenylthiourea were reacted

susceptible to *in-situ* *α*-bromination than the acetyl moiety of *N*-acetylthiourea. Unfortunately, urea was a rather sluggish substrate under the reaction protocol and only traces of **3w** and **3x** were seen. This result is expected as the O atom, being less nucleophilic than S, makes urea a much weaker substrate under this protocol. Interestingly, selenourea was unreactive and did not couple to either 4-methoxyphenylacetone or phenylacetophenone. This is in contrast to the findings by Rao's
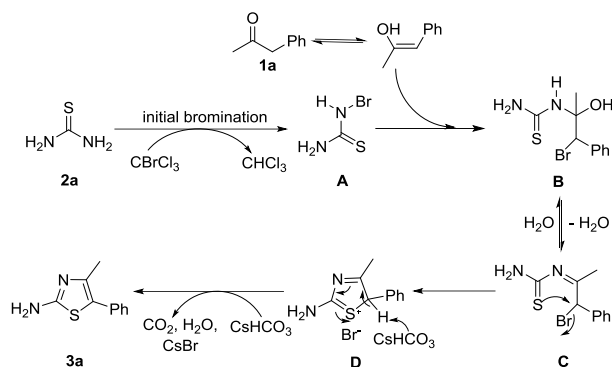
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Figure 2. Proposed mechanism.

together with 16.5 mmol of $CsHCO_3$ as base in 45 mL of 1:14 (v/v) $CBrCl_3$/MeCN solvent mixture at 80 °C for 3 h. An isolated yield of 94 % of **3t** was obtained as a yellow solid after work-up and purification via column chromatography. This compares favorably with the isolated yield of 89 % obtained by Kodomari et al. from the coupling of silica-supported KSCN and alumina-supported aniline with desyl bromide.[14] Another protocol where *N*-phenylthiourea was coupled with desyl bromide gave an isolated yield of 98 % but microwave irradiation was required.[15] While all three methods give excellent yields of **3t**, the present protocol has the advantage that different phenylthiazolamines can be easily formed by *in-situ* α-bromination of the corresponding phenylacetophenones. In contrast, the other two methodologies would require derivatives of desyl bromide to be presynthesized as they are not commercially available. However, one limitation of our protocol is that it cannot be extended to urea and selenourea.
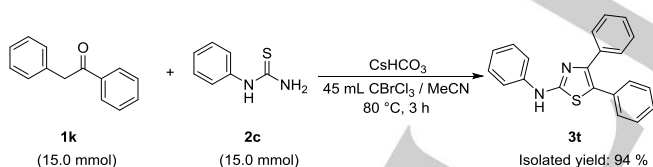
Scheme 2. Scaled-up synthesis of *N*-phenyl-substituted phenylthiazolamine **3t**.

Conclusions

In conclusion, we have demonstrated a straightforward protocol for the synthesis of 5-phenylthiazolamines via the coupling of thiourea with phenylacetones, phenylacetophenones and β-tetralones. This protocol employs a thiourea/$CBrCl_3$ α-bromination system to construct phenylthiazolamines by C-N/C-S bond formation. Thiourea has a dual role of a substrate and an α-bromination shuttle whereby the bromine atom is transferred from $CBrCl_3$ to the α-carbon. The *in-situ* bromination avoids the need to separately synthesize α-brominated derivatives. Besides a large scope, the reaction proceeds smoothly at relatively mild conditions and short reaction times. The scale-up to 15 mmol for

the synthesis of **3t** gave an isolated yield of 94 %. Hence, this protocol offers a practical and economical alternative to those previously reported in the literature.

Experimental Section

General Information

Thin layer chromatography (TLC) was performed using TLC silica gel 60 F_{254} glass plates. Silica gel 60 (230 – 400 mesh) was used for column chromatography. The ^{1}H NMR and ^{13}C NMR of samples in DMSO-d6 were measured using a Bruker Avance 300 (AV300) spectrometer with tetramethylsilane as an internal standard. For ^{1}H NMR spectra, chemical shifts were reported in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constant (Hz). Peaks at around 3.3 ppm correspond to water peak, which is inherent when using DMSO-d6 solvent. Detection of compounds by gas chromatography was performed using an Agilent 6890N gas chromatograph equipped with a HP-5 column and an FID detector. Analysis of samples by gas chromatography mass spectrometry was carried out using a Shimadzu QP5000. Mass spectra measurements were recorded on Bruker micrOTOFQII under electrospray ionization (ESI) mode. The following chemicals were obtained from Alfa-Aesar, Sigma-Aldrich, GCE Chemicals and TCI and used as received: $CBrCl_3$, $CsHCO_3$, MeCN, phenylacetones, and derivatives of phenylacetophenone and thiourea.

General procedure for formation of 5-phenylthiazolamines: A 10 mL round-bottomed flask was charged with phenylacetone **1a** (133.7 µL, 1.0 mmol), thiourea **2a** (76.1 mg, 1.0 mmol), $CsHCO_3$ (213 mg, 1.1 mmol and 3 mL of $CBrCl_3$/MeCN solvent mixture (1/14 v/v). The reaction mixture was stirred at 80 °C for 2 h. Thereafter, it was diluted with H_2O and extracted with EtOAc (15 mL × 5). The combined organic layers were washed with $NaHCO_3$ and brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed by rotary evaporation and the residue was cleaned up by column chromatography using ethyl acetate and hexane (v/v = 4/1) as eluent to afford **3a** in 92 % yield.

Procedure for scaled-up synthesis of 5-phenylthiazolamine 3t: A 100 mL round-bottomed flask was charged with 2-phenylacetophenone **1k** (2.94 g, 15.0 mmol), *N*-phenylthiourea **2c** (2.28 g, 15.0 mmol), $CsHCO_3$ (3.20 g, 16.5 mmol and 45 mL of $CBrCl_3$/MeCN solvent mixture (1/14 v/v) After stirring at 80 °C for 3 h, the reaction mixture was diluted with H_2O and extracted with EtOAc (200 mL × 5). The combined organic layers were washed with $NaHCO_3$ and brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed by rotary evaporation and the residue was cleaned up by column chromatography using hexane and ethyl acetate (v/v = 8/1) as eluent to afford **3t** in 94 % yield.

4-Methyl-5-phenylthiazol-2-amine (3a)

Obtained as a brown solid; yield: 175 mg (95 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.46-7.14 (m, 5H), 7.01 (s, 2H), 2.20 (s, *J* = 6.5 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.8, 143.2, 133.1, 128.7, 127.9, 126.0, 117.6, 16.2. HRMS (ESI) calcd for $C_{10}H_{11}N_2S$ [M+H]+: 191.0637; found 191.0640.

5-(2-Methoxyphenyl)-4-methylthiazol-2-amine (3b)

Obtained as a brown solid; yield: 194 mg (88 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.31-7.18 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 1H), 6.80 (s, 2H), 3.76 (s, 3H) 2.00 (s, 3H); 13C NMR (300 MHz, DMSO-d6) δ 166.8, 156.5, 144.3, 131.4, 128.6, 121.4, 120.3, 113.2, 111.5, 55.3, 16.1. HRMS (ESI) calcd for $C_{11}H_{13}N_2OS$ [M+H]+: 221.0743; found 221.0740.

5-(3-Methoxyphenyl)-4-methylthiazol-2-amine (3c)

Obtained as a brown solid; yield: 200 mg (91 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.27 (t, J = 7.8 Hz, 1H), 6.99 (s, 2H), 6.92-6.75 (m, 3H), 3.76 (s, 3H) 2.20 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.8, 159.3, 143.4, 134.4, 129.7, 120.3, 117.4, 113.4, 111.6, 55.0, 16.3. HRMS (ESI) calcd for $C_{11}H_{13}N_2OS$ [M+H]$^+$: 221.0743; found 221.0745.

5-(4-Methoxyphenyl)-4-methylthiazol-2-amine (3d)

Obtained as a brown solid; yield: 191 mg (87 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.24 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.85 (s, 2H), 3.76 (s, 3H) 2.13 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.2, 157.7, 141.9, 129.3, 125.3, 117.3, 114.1, 55.1 15.9. HRMS (ESI) calcd for $C_{11}H_{13}N_2OS$ [M+H]$^+$: 263.0849; found 263.0846.

5-(3,4-Dimethoxyphenyl)-4-methylthiazol-2-amine (3e)

Obtained as a brown solid; yield: 208 mg (83 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 6.94 (d, J = 8.1 Hz, 1H), 6.91-6.80 (m, 4H), 3.77 (s, 3H), 3.75 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.3, 148.7, 147.5, 142.2, 125.6, 120.6, 117.7, 112.1, 55.6, 55.5, 16.1. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2S$ [M+H]$^+$: 251.0849; found 251.0852.

5-(4-Ethylphenyl)-4-methylthiazol-2-amine (3f)

Obtained as a brown solid; yield: 197 mg (90 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.26-7.16 (m, 4H), 6.91 (s, 2H), 2.58 (q, J = 7.5 Hz, 2H), 2.17 (s, 3H), 1.17 (t, J = 7.5 Hz, 3H); 13C NMR (300 MHz, DMSO-d6) δ 165.5, 142.6, 141.7, 130.4, 128.0, 127.9, 117.6, 27.8, 16.2, 15.5. HRMS (ESI) calcd for $C_{12}H_{15}N_2S$ [M+H]$^+$: 219.0950; found 219.0953.

5-(4-Chlorophenyl)-4-methylthiazol-2-amine (3g)

Obtained as a yellow orange solid; yield: 196 mg (87 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.38 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.07 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.0, 144.0, 132.0, 130.5, 129.4, 128.6, 116.2, 16.2. HRMS (ESI) calcd for $C_{10}H_{10}ClN_2S$ [M+H]$^+$: 225.0248; found 225.0250.

5-(4-Bromophenyl)-4-methylthiazol-2-amine (3h)[16]

Obtained as an yellow orange solid; yield: 239 mg (89 %)/ ^{1}H NMR (300 MHz, DMSO-d6) δ 7.51 (d, J = 6.9 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H), 7.07 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.0, 144.0, 132.4, 131.5, 129.7, 118.9, 116.2, 16.3. HRMS (ESI) calcd for $C_{10}H_{10}BrN_2S$ [M+H]$^+$: 268.9743; found 268.9746.

4-Isobutyl-5-phenylthiazol-2-amine (3i)

Obtained as a brown solid; yield: 208 mg (89 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.40-7.28 (m, 4H), 7.23 (t, J = 6.9 Hz, 1H), 6.95 (s, 2H), 2.37 (d, J = 7.2 Hz, 2H), 2.10-1.96 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.9, 146.8, 133.0, 128.6, 126.4, 118.4, 38.1, 27.9, 22.4. HRMS (ESI) calcd for $C_{13}H_{17}N_2S$ [M+H]$^+$: 233.1107; found 233.1105.

4,5-Dihydronaphtho[2,1-d]thiazol-2-amine (3j)

Obtained as a brown solid; yield: 162 mg (80 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.20 (s, 2H), 7.16-7.07 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 2.89 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H); ^{13}C NMR (300 MHz, DMSO-d6) δ 167.2, 149.6, 132.4, 131.0, 127.5, 126.8, 124.6, 121.7, 115.8, 28.3, 24.9. HRMS (ESI) calcd for $C_{11}H_{11}N_2S$ [M+H]$^+$: 203.0637; found 203.0639.

4,5-Diphenylthiazol-2-amine (3k)[16]

Obtained as a yellow solid; yield: 239 mg (95 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.40 (d, 2H), 7.29-7.13 (m, 10H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.3, 145.0, 135.5, 132.9, 129.0, 128.7, 128.5, 128.1, 127.3, 127.0, 119.2. HRMS (ESI) calcd for $C_{15}H_{13}N_2S$ [M+H]$^+$: 253.0794; found 253.0792.

4-Phenyl-5-p-tolylthiazol-2-amine (3l)

Obtained as a yellow solid; yield: 251 mg (94 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.39 (d, J = 7.8 Hz, 2H), 7.29-7.19 (m, 3H), 7.13-7.01 (m, 6H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.8, 144.5, 136.4, 135.5, 129.8, 129.3, 128.8, 128.4, 128.0, 127.2, 119.2, 20.7. HRMS (ESI) calcd for $C_{16}H_{15}N_2S$ [M+H]$^+$: 267.0950; found 267.0952.

4-(4-Fluorophenyl)-5-phenylthiazol-2-amine (3m)

Obtained as a yellow solid; yield: 237 mg (88 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.48-7.37 (m, 2H), 7.32-7.12 (m, 7H), 7.06 (t, J = 8.9 Hz, 2H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.3, 162.9, 159.7, 143.9, 132.7, 131.9, 131.8, 130.5, 130.4, 129.0, 128.8, 127.1, 119.0, 115.1, 114.8. HRMS (ESI) calcd for $C_{15}H_{12}FN_2S$ [M+H]$^+$: 271.0700; found 271.0697.

4-(4-Chlorophenyl)-5-phenylthiazol-2-amine (3n)

Obtained as a yellow solid; yield: 261 mg (91 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.39 (d, J = 8.4 Hz, 2H), 7.32-7.13 (m, 9H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.3, 143.5, 134.2, 132.5, 131.8, 130.1, 129.0, 128.8, 128.1, 127.2, 119.7. HRMS (ESI) calcd for $C_{15}H_{12}ClN_2S$ [M+H]$^+$: 287.0404; found 287.0407.

4-(4-Bromophenyl)-5-phenylthiazol-2-amine (3o)

Obtained as a yellow solid; yield: 289 mg (87 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.42 (d, J = 8.1 Hz, 2H), 7.36-7.15 (m, 9H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.3, 143.6, 134.6, 132.5, 131.0, 130.4, 129.0, 128.8, 127.2, 120.4, 119.8. HRMS (ESI) calcd for $C_{15}H_{12}BrN_2S$ [M+H]$^+$: 330.9899; found 330.9895.

4-(4-Methoxyphenyl)-5-phenylthiazol-2-amine (3p)

Obtained as a yellow solid; yield: 257 mg (91 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.40-7.18 (m, 7H), 7.12 (s, 2H), 6.81 (d, J = 7.5 Hz, 2H), 3.72 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 167.0, 158.5, 144.8, 133.1, 129.7, 128.9, 128.7, 127.9, 126.8, 117.7, 113.4, 55.0. HRMS (ESI) calcd for $C_{16}H_{15}N_2OS$ [M+H]$^+$: 283.0900; found 283.0903.

4,5-bis(4-Methoxyphenyl)thiazol-2-amine (3p')

Obtained as a yellow solid; yield: 286 mg (92 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.31 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H) 6.99 (s, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 165.4, 158.3, 158.2, 143.8, 130.3, 129.5, 127.9, 125.1, 117.6, 114.2, 113.4, 55.1, 55.0. HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2S$ [M+H]$^+$: 313.1005; found 313.1004.

5-(4-Methoxyphenyl)-*N*,4-dimethylthiazol-2-amine (3q)

Obtained as a brown solid; yield: 197 mg (84 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.37 (q, J = 4.2 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 6.94 (d, J = 8.1 Hz, 2H), 3.76 (s, 3H), 2.80 (d, J = 4.2 Hz, 3H), 2.16 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.3, 157.8, 142.5, 129.4, 125.2, 116.9, 114.2, 55.1, 30.7, 16.2. HRMS (ESI) calcd for $C_{12}H_{15}N_2OS$ [M+H]$^+$: 235.0900; found 235.0897.

N-Methyl-4,5-diphenylthiazol-2-amine (3r)

Obtained as a yellow solid; yield: 266 mg (90 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 7.63 (q, J = 4.2 Hz, 1H), 7.44-7.37 (m, 3H), 7.32-7.17 (m, 8H), 2.88 (d, J = 4.2 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 166.9, 145.3, 135.5, 132.7, 128.9, 128.6, 128.5, 128.0, 127.3, 127.0, 118.6,

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30.8. HRMS (ESI) calcd for $C_{16}H_{15}N_2S$ [M+H]$^+$: 267.0950; found 267.0953.

5-(4-Methoxyphenyl)-4-methyl-*N*-phenylthiazol-2-amine (3s)

Obtained as a yellow solid; yield: 261 mg (88 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.14 (s, 1H), 7.67 (d, J = 8.7 Hz, 2H), 7.36-7.26 (m, 4H), 7.00-6.89 (m, 3H), 3.75 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 160.1, 158.2, 142.4, 141.2, 129.8, 128.9, 124.4, 121.1, 119.0, 116.9, 114.2, 55.1, 16.2. HRMS (ESI) calcd for $C_{17}H_{17}N_2OS$ [M+H]$^+$: 297.1056; found 297.1058.

N-4,5-triphenylthiazol-2-amine (3t)

Obtained as a yellow solid; yield: 313 mg (95 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.40 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 7.8 Hz, 2H), 7.41-7.19 (m, 10H), 6.98 (t, J = 7.4 Hz, 1H); ^{13}C NMR (300 MHz, DMSO-d6) δ 161.1, 145.1, 141.1, 135.2, 132.1, 129.2, 129.0, 128.7, 128.5, 128.2, 127.5, 121.4, 120.6, 117.1. HRMS (ESI) calcd for $C_{21}H_{17}N_2S$ [M+H]$^+$: 329.1107; found 329.1109.

N-(5-(4-Methoxyphenyl)-4-methylthiazol-2-yl)acetamide (3u)

Obtained as a brown solid; yield: 223 mg (85 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 12.02 (s, 1H) 7.36 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 3.78 (s, 3H), 2.30 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 168.2, 158.5, 154.5, 141.0, 129.8, 124.3, 123.3, 114.3, 55.2, 22.4,15.8. HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2S$ [M+H]$^+$: 263.0848; found 263.0846.

N-(4,5-Diphenylthiazol-2-yl)acetamide (3v)

Obtained as a yellow solid; yield: 263 mg (89 %). ^{1}H NMR (300 MHz, DMSO-d6) δ 12.29 (s, 1H), 7.44-7.26 (m, 10H), 2.18 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d6) δ 168.7, 155.8, 143.7, 134.7, 131.9, 129.2, 128.9, 128.4, 128.2, 127.9, 127.6, 125.2, 22.4. HRMS (ESI) calcd for $C_{17}H_{15}N_2OS$ [M+H]$^+$: 295.0900; found 295.0904.

Acknowledgements

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A wide array of 5-phenylthiazolamines with 80 to 95 % isolated yields was obtained via coupling of thiourea with phenylacetones, phenylaceto-phenones and β-tetralone. Thiourea acts as a substrate and an α-bromination shuttle, transferring Br from CBrCl$_3$ to the α-carbon of the carbonyl moiety.
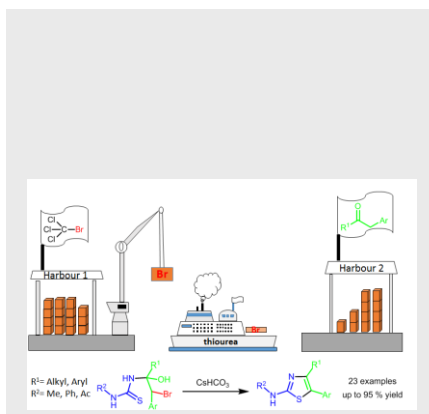
***In-situ* bromination**

Irwan Iskandar Roslan, Kian-Hong Ng, Gaik-Khuan Chuah*, Stephan Jaenicke*

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Synthesis of 5-Phenylthiazolamines Using Thiourea as an α-Bromination Shuttle