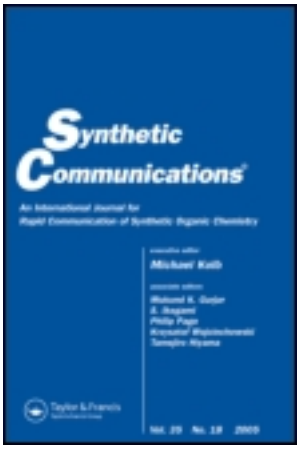

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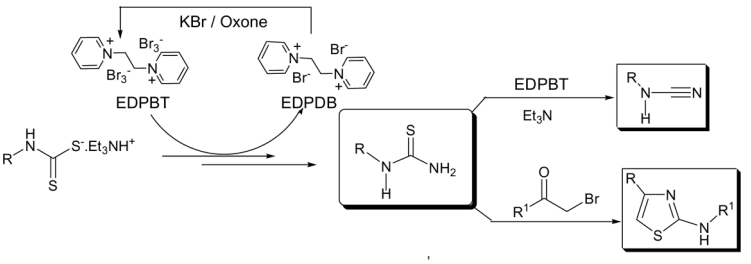
BROMINELESS BROMINE AS AN EFFICIENT DESULFURIZING AGENT FOR THE PREPARATION OF CYANAMIDES AND 2-AMINOTHIAZOLES FROM DITHIOCARBAMATE SALTS

Ramesh Yella, Veerababurao Kavala, and Bhisma K. Patel
Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, Assam, India

GRAPHICAL ABSTRACT



Abstract *In a one-pot procedure, bromineless brominating reagent 1,1′-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT) has been used as a desulfurizing agent in the preparation of organic cyanamides and substituted thiazoles starting from dithiocarbamic acid salts. In this approach, alkyl/aryl isothiocyantes were first obtained by the desulfurization of dithiocarbamic acid salts with EDPBT. The* in situ*–generated isothiocyanates reacts with an aqueous ammonia, forming alkyl or aryl thioureas, which on subsequent oxidative desulfurization with EDPBT led to the formation of corresponding cyanamides in good yields. Alternatively, an efficient one-pot synthesis of substituted thiazoles has been achieved by the condensation of the* in situ*–generated 1-aryl thioureas with the* in situ*–generated α-bromoketones from ketones, again using EDPBT. The reagent EDPBT can be easily prepared from the readily available reagents. Desulfurizing ability dominates over its brominating ability for substrates amenable to bromination.*

Keywords Cyanamide; desulfurizing agent; dithiocarbamate; ditribromide; thiazole

INTRODUCTION

Recently we have taken advantage of the desulfurizing ability of a hypervalent iodine reagent, diacetoxyiodobenzene (DIB), for the oxidative *N*-acylation of

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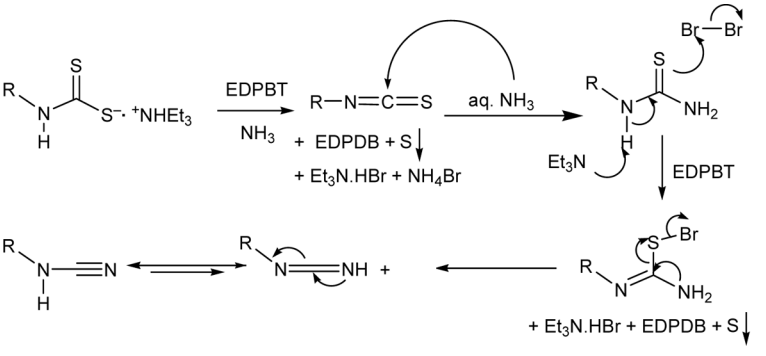
1,3-disubstituted thiourea,[1] in the preparation of isothiocyanates and for the construction of heterocycles[2a] and cyanamides,[2b] from dithiocarbamate salts. However, methods using a hypervalent iodine reagent are efficient but not economically viable when applied to large-scale reactions. In yet another related work, we have demonstrated that the hypervalency of iodine is not really essential, particularly for the transformation of dithiocarbamate to isothiocyanate[2a] and cyanamide,[2b] and at times molecular iodine[2c,d] and bromine equivalent 1,1′-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT)[3a,b] were found to be equally efficient.[3c] The advantage of the reagent EDPBT over conventional organic ammonium tribromides[4] has been reflected by a series of interesting organic transformations carried out in the past few years.[5a] Very recently, we have revealed its desulfurizing ability in the preparation of isothiocyanate from the corresponding dithiocarbamate salt.[3c] In this article, we demonstrate its utility in the construction of yet another useful organic functional group, cyanamide, and extending it further to an efficient one-pot synthesis of substituted thiazoles by using EDPBT as a key reagent.

RESULTS AND DISCUSSION

In this strategy, alkyl/aryl thioureas were prepared directly from dithiocrabamate salts and EDPBT in an aqueous ammonia (Scheme 1). The use of aqueous ammonia serves a dual purpose as a base in the first step to generate isothiocyanate from dithiocarbamate salt and as a nucleophile to form alkyl/aryl thioureas from the in situ–generated isothiocyanates.

However, when EDPBT was used instead of hypervalent iodine, ammonia was not that effective as a base in the second step and had to be replaced with a relatively stronger base, triethylamine. This in part may be due to the lesser thiophilicity of bromine as compared to the hypervalent iodine, DIB. Further, the relative acidity of the NH proton of dithiocarbamate salt is greater compared to NH protons of alkyl/aryl thiourea; hence, a stronger base is required for the latter. After completion of the reaction, precipitated spent reagent was filtered and washed with acetonitrile. Acetonitrile was removed and mixed with water (10 mL), and the product extracted with ethylacetate and purified over a short column of silica gel. The aqueous layer



Scheme 1. Proposed mechanism for the formation of cyanamide with in situ–generated isothiocyanate and alkyl/aryl thiourea.

containing the spent reagent 1,1′-(ethane-1,2-diyl)dipyridinium dibromide (EDPDB), along with the $Et_3N \cdot HBr$ and NH_4Br, were combined with the precipitated spent reagent obtained by filtration, and the ditribromide reagent (EDPBT) was regenerated using appropriate amounts of KBr and Oxone.[3] By employing this one-pot strategy, several aromatic cyanamides (**1a**–**10a**) could be successfully prepared from their dithiocarbamate salts (**1**–**10**) (Table 1). Although the overall isolated yields look moderate, considering the multistep process leading to the products, they should be considered good to excellent.

As can be seen from Table 1, this strategy was successful even when an electron-withdrawing substituent such as the -NO_2 group (Table 1, entry 5) was attached to the aromatic ring. Substrates amenable to ring bromination (**7**, **8**) and α-bromination (**9**) gave their corresponding cyanamides without undergoing bromination. This method also worked well for the preparation of hindered and disubstituted substrate (**10a**) starting from corresponding dithiocarbamate (**10**). Cyanamides of aliphatic amines (**11** and **12**) and benzylic amines (**13** and **14**) were obtained from their dithiocarbamate salts in one pot.

Dithiocarbamate salts derived from chiral amines (**15** and **16**) yielded their cyanamides **15a** and **16a** respectively in excellent yields with retention of optical activity as shown in Scheme 2. Surprisingly, the magnitudes of the specific rotation of both amines and cyanamides were found to be identical. Finally, cyanamide of homoveratrylamine (**17a**) was obtained successfully in good yield from its dithiocarbamate salt (**17**).

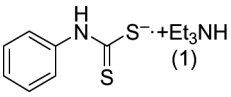
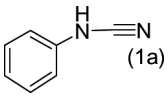
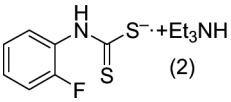
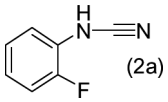
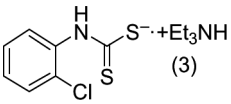
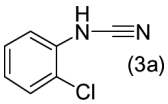
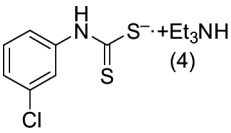
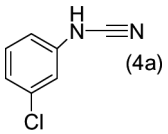
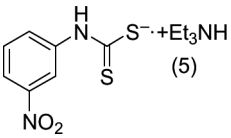
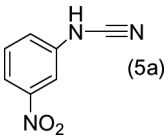
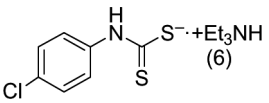
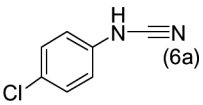
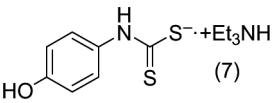
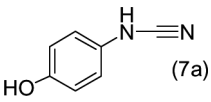
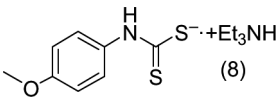
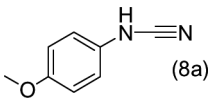
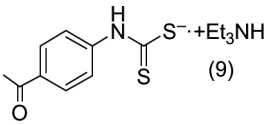
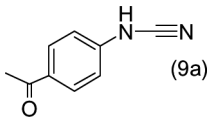
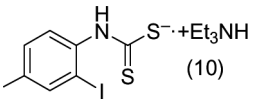
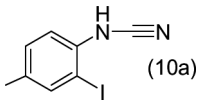
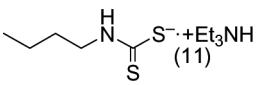
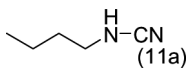
After successfully preparing a series of cyanamides, we thought of exploiting the in situ–generated 1-arylthiourea for the construction of substituted thiazoles by treating it with the in situ–generated α-haloketones. Thiazole skeleton is present in several naturally occurring compounds such as peniciline and vitamin B1 (thiamin). Of late, thiazole derivatives have attracted interest because of their biological activities. Among these, the 2-aminothiazole ring system is a useful structural motif in medicinal chemistry, having application in drug development for the treatment of allergies,[8] hypertension,[9] inflammation,[10] schizophrenia,[11] bacterial infections,[12] and HIV.[13] These are also known to be ligands of estrogen receptors,[14] adenosine receptor antagonists,[15] and neuropeptide Y5 receptor.[16]

The most commonly adopted method for the synthesis of 2-amino thiazoles is the reaction of thiourea or thioamide with α-bromo ketones.[17] These reactions have been further improved using catalysts such as ammonium-I2-molybdophosphate (AMP)[18] and β-cyclodextrin in water,[19] conventional heating, and the use of microwaves in an alcoholic media[20] at ambient temperature or in an aqueous medium.[21]

Although some of the methods for preparation of thiazoles are effective, the drawback associated with most of the procedures reported is separate preparation of precursors, namely, α-bromoketone and thiourea. In our strategy, both these precursors can be synthesized from readily available substrates using a single recyclable reagent, EDPBT, which in turn can be prepared from commercially available starting materials. The reaction at ambient temperature and the use of aqueous medium associated with the one-pot procedure adds to the synthetic potential of this method.

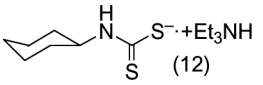
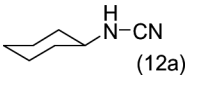
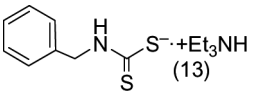
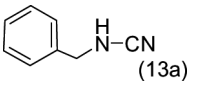
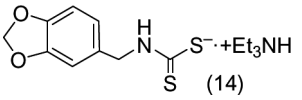
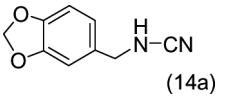
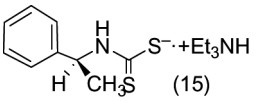
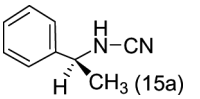
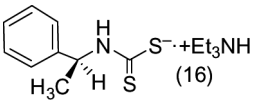
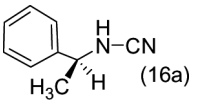
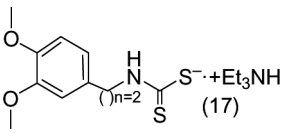
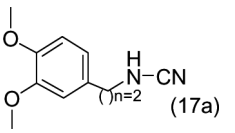
When phenyldithiocarbamate salt (**1**) was treated with EDPBT in the presence of aqueous ammonia, 1-phenylthiourea (**18**) was obtained directly. While EDPBT

Table 1. Preparation of cyanamides from dithiocarbamates and EDPBT[a]

Substrate	Product[b]	Yield (%)[c][Ref.]
 (1)	 (1a)	74[2b]
 (2)	 (2a)	65
 (3)	 (3a)	68[2b]
 (4)	 (4a)	70[2b]
 (5)	 (5a)	63[2b]
 (6)	 (6a)	60[2b]
 (7)	 (7a)	70[2b]
 (8)	 (8a)	72[6a]
 (9)	 (9a)	75[2b]
 (10)	 (10a)	63
 (11)	 (11a)	60[2b]

(*Continued*)

Table 1. Continued

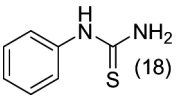
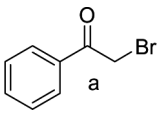
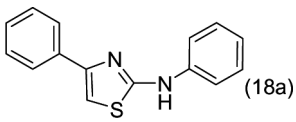
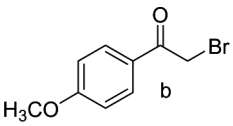
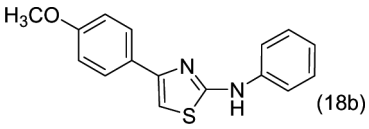
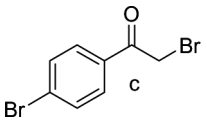
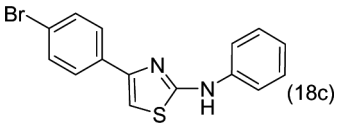
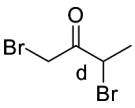
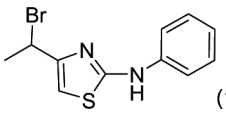
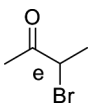
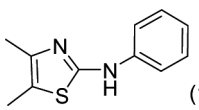
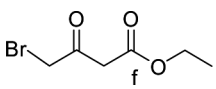
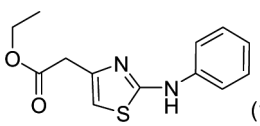
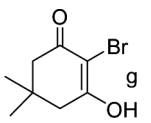
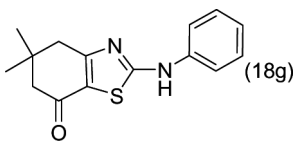
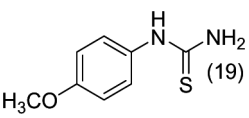
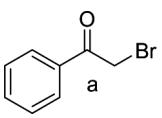
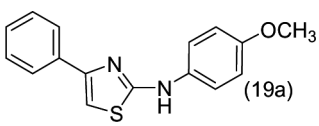
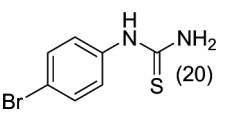
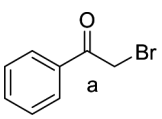
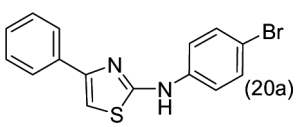
Substrate	Product[b]	Yield (%)[c][Ref.]
 (12)	 (12a)	72[2b]
 (13)	 (13a)	73[2b]
 (14)	 (14a)	74[2b]
 (15)	 (15a)	69[6b]
 (16)	 (16a)	69[7]
 (17)	 (17a)	65

[a]Reactions were monitored by TLC.
[b]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR.
[c]Isolated yield.

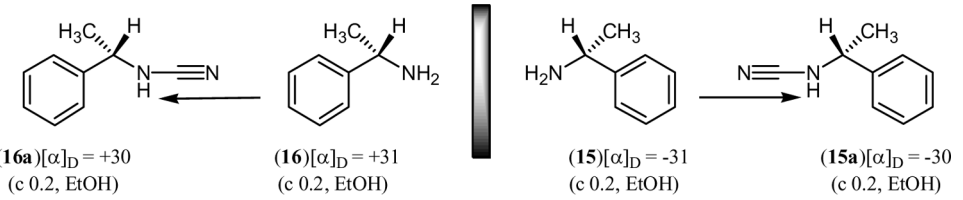
acts as a desulfurizing agent,[3c] the aqueous ammonia acts as a base in the formation of the intermediate isothiocyanate and as a nucleophile in the formation of 1-phenylthiourea (Scheme 1). Since EDPBT used here is 0.5 equivalent (being a ditribromide reagent, the bromine content is 1 equivalent), the reaction stops at the thiourea stage and does not lead to cyanamide. In another flask, α-bromoketone was prepared using EDPBT according to our recently reported procedure,[3a,b] which was then added to the flask after getting rid of the excess ammonia. The thiourea (being an S-based nucleophile particularly toward softer electrophiles[5d–f]) attacks the bromomethyl carbon, forming S-alkylated product (**X**). Intramolecular attack of the NH_2 group of the intermediate on the carbonyl group would give the intermediate tertiary alcohol (**Y**), which undergoes acid-catalyzed E1 elimination in water, as has been proved by us.[5f] Thus the removal of the excess ammonia is essential in the previous step to facilitate an acid-mediated E1 process.

Starting from 1-phenyl thiourea (**18**), several thiazoles derivatives (**18a–c**) were prepared successfully as shown in Table 1. The presence of a thiazole skeleton has been confirmed by x-ray crystallography, as shown in Fig. 1.

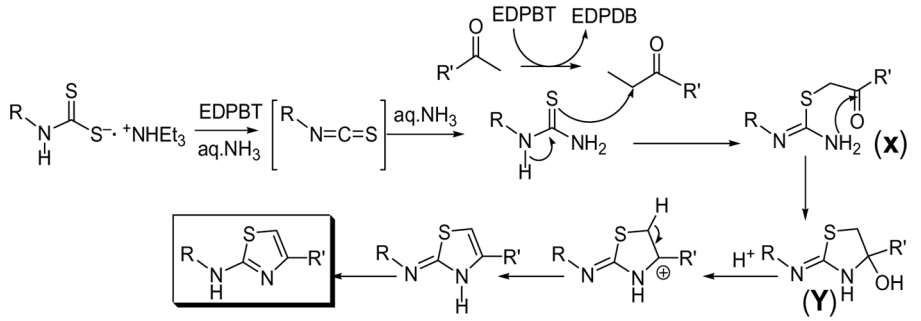
Table 2. One-pot preparation of 2-aminothiazoles[a]

Thiourea	α-Haloketone/alkyl halide	Product[b]	Yield (%)[c][Ref.]
 (18)	 a	 (18a)	72[21a]
	 b	 (18b)	76[21a]
	 c	 (18c)	73
	 d	 (18d)	55
	 e	 (18e)	55
	 f	 (18f)	60
	 g	 (18g)	61[21b]
 (19)	 a	 (19a)	69[21c]
 (20)	 a	 (20a)	65

[a]Reactions were monitored by TLC.
[b]Confirmed by IR, ^{1}H NMR, and ^{13}C NMR.
[c]Isolated yield.



Scheme 2. Specific rotations of chiral amines and their cyanamides.



Scheme 3. Proposed mechanism for the formation of thiazole.

Unsymmetrical ketones such as ethylmethyl ketone (d) gave two different products (**18d** and **18e**) depending on the reaction condition. This is because when bromination is allowed to continue for a longer period of time, dibrominated product (**d**) is obtained, giving the major thiazole product (**18d**). However, kinetically controlled bromination of ethylmethylketone gave the brominated product (**e**) leading to the thiazole (**18e**). Similarly, the thermodynamically stable brominated product (**f**)[22] of ethylacetoacetate gave exclusively thiazole derivative (**18f**). This type of isomerization or formation of thermodynamic stable brominated product is well documented in the literature.[22] Cyclic diketone gave exclusively the brominated product flanked by two carbonyl groups (i.e., kinetically stable product and the enol form),[23] which led to the formation of product (**18g**). Other in situ–generated thioureas such as **19** and **20** reacted with phenacyl bromide (**a**), giving thiazole derivatives **19a** and **20a** respectively in modest yield. The presence of the thiazole

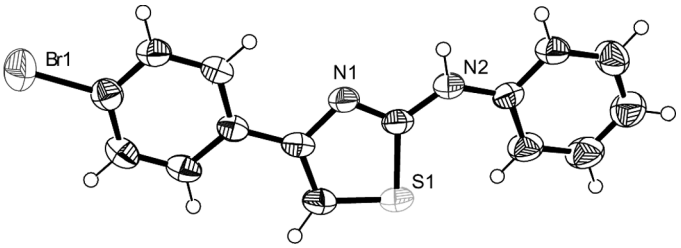


Figure 1. ORTEP view of **18c** with the atomic numbering scheme.

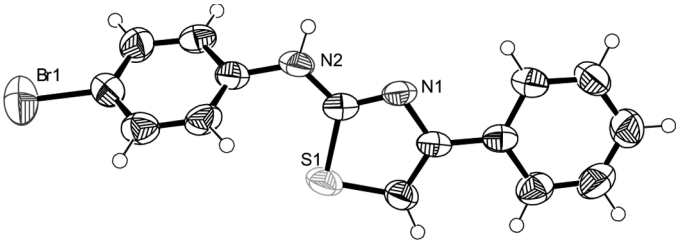


Figure 2. ORTEP view of **20a** with the atomic numbering scheme.

skeleton and the structure of **20a** has been further confirmed by x-ray crystallography as shown in Fig. 2.

CONCLUSION

In summary, bromineless brominating reagent has been used as a thiophilic reagent for the preparation of alkyl and aryl cyanamides from their dithiocarbamates in one pot. Subsequently, 2-amino thiazoles were synthesized by the condensation of the in situ–generated bromoketones and thioureas from their dithiocarbamates. Advantages of this protocol include ease of preparation of this reagent, facile isolation of products, and recyclability of the spent reagent, which make these methods environmentally acceptable. Although at first glance the product yields seem to be moderate, because these are actually three-step reactions in one pot, the yield can be considered very good.

EXPERIMENTAL

All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60–120 mesh) was used for the column chromatography. Reactions were monitored by thin layer chromatography (TLC) on silica gel $60\,F_{254}$ (0.25 mm). NMR spectra were recorded in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) with tetramethylsilane (TMS) as the internal standard for ^1H NMR (400 MHz) and in $CDCl_3$ or DMSO-d_6 solvent as the internal standard for ^{13}C NMR (100 MHz). Mass spectra were recorded using Waters MS system, Q-TOF premier, and data analyzed using Mass Lynx 4.1. Specific rotations were recorded on a Perkin-Elmer model 343 polarimeter. Elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer. Melting points were recorded on a Buchi B-545 melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer.

Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) at 298 K. Cell

parameters were retrieved using SMART[24] software and refined with SAINT[24] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS.[25] The structure was solved by direct methods implemented in the SHELX-97[26] program and refined by full-matrix least-squares methods on F2. All nonhydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Light yellow crystals were isolated in rectangular shape from ethylacetate and hexane at room temperature.

General Experimental Procedure for the Preparation of Cyanamide

Ice-cooled aqueous ammonia (25%, 2 mL) was added to a stirred, ice-cold solution of dithiocarbamate salt **1** (0.542 g, 2 mmol) in acetonitrile (8 mL). EDPBT (0.666 g, 1 mmol) was added in pinches over a period of 10 min. The reaction mixture was stirred at room temperature for 30–40 min, and complete conversion to corresponding 1-phenyl thiourea was observed as judged from thin-layer chromatography (TLC). Excess ammonia was removed by heating the reaction mixture on a hot-water bath (60 °C) for 10 min. Triethylamine (1.1 mL, 8 mmol) was added followed by pinchwise addition of EDPBT (0.666 g, 1 mmol) at room temperature over a period of 10 min. The conversion of intermediate 1-phenylthiourea to corresponding cyanamide (**1a**) was observed within 10 min of complete addition of EDPBT. After completion of the reaction, some of the spent reagent was filtered and washed with acetonitrile. Acetonitrile was evaporated and mixed with water (10 mL), and the product was extracted with ethylacetate (2×10 mL), which was then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified over a short column of silica gel (hexane–ethylacetate, 8:2) to give 175 mg (74% yield) of **1b**.[2b]

General Experimental Procedure for the Preparation of Thiazole

Ice-cooled aqueous ammonia (25%, 2 mL) was added to a stirred, ice-cold suspension of dithiocarbamate **1** (540 mg, 2 mmol) in water (6 mL). EDPBT (666 mg, 1 mmol) was added in CH_3CN (4 mL) dropwise over a period of 15 min. After complete addition of EDPBT, the reaction mixture was allowed to stirred at room temperature for 30–40 min, and complete conversion to corresponding 1-phenyl thiourea was observed as judged from TLC. Excess ammonia was removed by a rotary evaporator, during which CH_3CN also was evaporated, leaving behind some in an aqueous layer.

Acetophenone (0.264 g, 2.2 mmol) was added to a solution of EDPBT (666 mg, 1 mmol) in acetonitrile (4 mL), and stirring continued for 45 min. During this period, the bromination of acetophenone (**a**) was complete as judged from the disappearance of the orange color of EDPBT. The supernatant containing the bromoketone was then directly filtered into a solution of the in situ–generated phenyl thiourea **18** in water (obtained previously) and stirred at room temperature. The reaction was completed within 1 h, as judged from TLC. After completion of the reaction, solvent (CH_3CN) was evaporated and extracted with ethyl acetate (2×20 mL). The ethyl acetate layer was washed with a saturated solution of $NaHCO_3$ (5 mL), dried over

anhydrous Na_2SO_4, concentrated under reduced pressure, and purified over a silica-gel column (hexane–EtOAc, 9:1:) to give 182 mg (74% yield) of **18a**.[21a]

Spectral Data

The new compounds were fully characterized by IR, NMR (^1H, ^{13}C), mass, and elemental analysis.

2-Fluoro-phenyl cyanamide (2a). White solid; mp 95 °C; ^1H NMR (400 MHz, $CDCl_3$): 6.87 (brs, 1H), 6.90–7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 110.9, 115.7, 115.9, 116.8, 124.1, 124.1 125.09, 125.12, 125.6, 125.8, 150.1, 152.5. IR (KBr, cm^{-1}): 3068, 2037, 1606, 1587, 1495, 1265, 1212, 1104, 941, 808, 752. $C_7H_5FN_2$ (136.13) calcd.: C, 61.76; H, 3.70; N, 20.58. Found: C, 61.80; H, 3.73; N, 20.53.

2-Iodo-4-methyl-phenyl cyanamide (10a). White solid; mp 144 °C; ^1H NMR (400 MHz, $CDCl_3$): 2.29 (s, 3H), 6.17 (brs, 1H), 7.17 (dd, 2H, $J = 8.2$ Hz), 7.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.4, 84.2, 110.7, 115.4, 130.9, 135.4, 139.6. IR (KBr, cm^{-1}): 3229, 2919, 2217, 1603, 1573, 1502, 1420, 1383, 1283, 1032, 866, 805. $C_8H_7N_2$ (258.06) calcd.: C, 37.23; H, 2.73; N, 10.86. Found: C. 37.27; H, 2.75; N, 10.84.

3,4-Dimethoxyphenylethyl cyanamide (17a). Gummy; ^1H NMR (400 MHz, $CDCl_3$): 2.84 (t, 2H, $J = 7.2$ Hz), 3.28 (q, 2H, $J = 7.2$ Hz), 3.83 (s, 3H), 3.84 (s, 3H), 4.37 (brs, 1H), 6.76 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 35.5, 47.5, 55.92, 55.95, 111.4, 111.9, 116.5, 120.9, 130.0, 147.8, 148.9. IR (KBr, cm^{-1}): 3274, 2937, 2219, 1592, 1517, 1464, 1262, 1236, 1156, 1142, 1026, 913. $C_{11}H_{14}N_2O_2$(206.24) calcd.: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.12; H, 6.80; N, 13.54.

4-(4-Bromophenyl)-*n*-phenylthiazol-2-amine (18c). White Solid; mp 156–158 °C; ^1H NMR (400 MHz, $CDCl_3$): 6.81 (s, 1H), 7.08 (m, 1H), 7.36 (m, 4H), 7.51 (d, 2H, $J = 8.4$ Hz), 7.71 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 102.4, 118.6, 121.9, 123.4, 127.9, 129.7, 131.9, 133.6, 140.4, 150.4, 165.2. IR (KBr, cm^{-1}): 3382, 3113, 1601, 1594, 1556, 1497, 1471, 1458, 1406, 1397, 1341, 1311, 1270, 1194, 1103, 1070, 1052, 1007, 914, 849, 829, 746, 726. HRMS (ESI): MH^+ found 330.9901; $C_{15}H_{11}BrN_2S$ requires 330.9905.

[4-(1-Bromo-ethyl)-thiazol-2-yl]-phenyl-amine (18d). Gummy; ^1H NMR (400 MHz, $CDCl_3$): 1.53 (s, 3H), 4.83 (q, 1H, $J = 6.4$ Hz), 6.40 (s, 1H), 7.05 (m, 1H), 7.24–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 22.4, 66.3, 101.5, 118.6, 123.4, 129.7, 140.4, 156.2, 166.1. IR (KBr, cm^{-1}): 3274, 3130, 2975, 1602, 1542, 1498, 1459, 1312, 1260, 1139, 1095, 1027, 964, 885, 749. $C_{11}H_{11}BrN_2S$ (283.19) calcd.: C, 46.65; H, 3.92; N, 9.89; S, 11.32. Found: C, 46.69; H, 3.88; N, 9.81; S, 11.21.

4,5-Dimethyl-n-phenylthiazol-2-amine (18e). Yellow solid; mp 112–114 °C; ^1H NMR (400 MHz, $CDCl_3$): 2.18 (s, 3H), 2.32 (s, 3H), 7.02 (t, 1H, $J = 6.8$ Hz), 7.25–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 11.2, 14.7, 114.3, 118.3, 122.6, 129.5, 141.1, 142.9, 161.8. IR (KBr, cm^{-1}): 3241, 3194, 3138, 3068,

2916, 1605, 1569, 1499, 1458, 1424, 1376, 1328, 1297, 1222, 1195, 991, 874, 846, 746, 713, 685. $C_{11}H_{12}N_2S$ (204.29) calcd.: C, 64.67; H, 5.92; N, 13.71; S, 15.70. Found: C, 64.73; H, 5.96; N, 13.63; S, 15.73.

Ethyl-2-(2-(phenylamino)thiazol-4-yl)acetate (18f). Gummy; ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (t, 3H, $J = 7.2$ Hz), 3.64 (s, 2H), 4.17 (q, 2H, $J = 7.2$ Hz), 6.44 (s, 1H), 7.04 (m, 1H), 7.79–7.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3, 37.4, 61.2, 104.6, 118.6, 123.2, 129.6, 140.5, 144.7, 165.4, 170.7. IR (KBr, cm^{-1}): 3337, 3064, 2981, 1731, 1603, 1526, 1497, 1459, 1445, 1370, 1311, 1246, 1178, 1030, 994, 939, 851, 751. $C_{13}H_{14}N_2O_2S$ (262.33): calcd. C, 59.52; H, 5.38; N, 10.68; S, 12.22. Found: C, 59.48; H, 6.40; N, 10.54; S, 12.34.

4-Bromo-phenyl-(4-phenyl-thiazol-2-yl)-amine (20a). White solid; mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 6.83, (s, 1H), 7.24 (d, 2H, $J = 8.0$ Hz), 7.30 (m, 1H), 7.38 (m, 4H), 7.82 (d, 2H, $J = 8.0$ Hz), 8.00 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 102.3, 115.3, 119.8, 126.4, 128.2, 128.9, 132.4, 134.6, 139.6, 151.7, 164.3. IR (KBr, cm^{-1}): 3378, 3110, 2925, 1584, 1557, 1481, 1442, 1416, 1382, 1325, 1295, 1277, 1213, 1071, 1055, 1009, 915, 817, 770, 707. $C_{15}H_{11}BrN_2S$ (331.23) calcd. : C, 54.39; H, 3.35; N, 8.46; S, 9.68. Found: C, 54.33; H, 3.39; N, 8.52; S, 9.78.

Crystallographic Description of 18c

Crystal dimension (mm): $0.48 \times 0.28 \times 0.19$; $C_{15}H_{11}BrN_2S$, $Mr = 331.23$; orthorhombic, space group *Pbca*; a = 14.7566(9) Å, b = 5.7446(4) Å, c = 31.925(2) Å; $\alpha = \beta = \gamma = 90$, V = 2706.3(3) Å^3; Z = 8; $\rho_{cal} = 1.626$ mg/m^3; μ (mm^{-1}) = 3.178; F (000) = 1328; reflection collected/unique = 41573/4573; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] $R_1 = 0.0431$, $wR2 = 0.1312$, R indices (all data) $R_1 = 0.1126$; $wR_2 = 0.1700$, goodness of fit = 0.975. CCDC No. 739036.

Crystallographic Description of 20a

Crystal dimension (mm): $0.45 \times 0.28 \times 0.23$; $C_{15}H_{11}BrN_2S$, Mr = 331.23; triclinic, space group *P*-1; a = 5.7775(5) Å, b = 14.8715(12) Å, c = 16.3074(12) Å; α = 92.837(4), $\beta = 100.20$, $\gamma = 90.01$; V = 1377.23(19) (A^3); Z = 4; $\rho_{cal} = 1.597$ mg/m^3; μ (mm^{-1}) = 3.127; F (000) = 664; reflection collected/unique = 13454/4279; refinement method = full-matrix least-squares on F^2; final R indices [$I > 2\sigma_I$] $R_1 = 0.1261$, $wR_2 = 0.3114$, R indices (all data) $R_1 = 0.1604$; $wR_2 = 0.3183$, goodness of fit = 1.842. CCDC No. 739035.

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REFERENCES

1. Singh, C. B.; Ghosh, H.; Murru, S.; Patel, B. K. Hypervalent iodine(III)–mediated regioselective N-acylation of 1,3-disubstituted thioureas. *J. Org. Chem.* **2008**, *73*, 2924–2927.
2. (a) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. Desulfurization mediated by hypervalent iodine(III): A novel strategy for the construction of heterocycles. *Eur. J. Org. Chem*. **2008**, 6189–6196; (b) Ghosh, H.; Yella, R.; Ali, A. R.; Sahoo, S. K.; Patel, B. K. An efficient synthesis of cyanamide from amine promoted by a hypervalent iodine(III) reagent. *Tetrahedron Lett.* **2009**, *50*, 2407–2410; (c) Nath, J.; Ghosh, H.; Yella, R.; Patel, B. K. Molecular iodine–mediated preparation of isothiocyanates from dithiocarbamic acid salts. *Eur. J. Org. Chem*. **2009**, 1849–1851; (d) Nath, J.; Patel, B. K.; Jamir, L.; Bora, U.; Satyanarayana, K. V. V. V. V. A one-pot preparation of cynamide from dithiocarbamate using molecular iodine. *Green Chem*. **2009**, *11*, 1503–1506.
3. (a) Kavala, V.; Naik, S.; Patel, B. K. A new recyclable ditribromide reagent for efficient bromination under solvent-free condition. *J. Org. Chem*. **2005**, *70*, 4267–4271; (b) Kavala, V.; Naik, S.; Patel, B. K. A new recyclable ditribromide reagent for efficient bromination under solvent-free condition. *J. Org. Chem*. **2005**, *70*, 6556; (c) Yella, R.; Ghosh, H.; Murru, S.; Sahoo, S. K.; Patek, B. K. An efficient preparation of isothiocyanates from dithiocarbamates using bromineless brominating reagent. *Synth. Commun*. **2009**, *40*, 2083–2096.
4. (a) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. Regioselective bromination of organic substrates by tetrabutylammonium bromide promoted by V_2O_5-H_2O_2: An environmentally favorable synthetic protocol. *Org. Lett.* **2000**, *2*, 247–249; (b) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R.; Mandal, G. C. An environmentally benign synthesis of organic ammonium tribromides (QATB) and bromination of selected organic substrates by tetrabutylammonium tribromide (TBATB). *Tetrahedron Lett.* **1998**, *39*, 8163–8166; (c) Avramoff, M.; Weiss, J.; Schächter, O. The brominating properties of tetramethylammonium tribromide. *J. Org. Chem.* **1963**, *28*, 3256–3258; (d) Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. Bromination of phenols by use of benzyltrimethylammonium tribromide. *Chem. Lett*. **1987**, 627–630; (e) Jordan, A. D.; Luo, C.; Reitz, A. B. Efficient conversion of substituted aryl thioureas to 2-aminobenzothiazoles using benzyltrimethylammonium tribromide. *J. Org. Chem.* **2003**, *68*, 8693–8696; (f) Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Yamasaki, H.; Hirakawa, T.; Okamoto, T. Synthesis of dibromoacetyl derivatives by use of benzyltrimethylammonium tribromide. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2667–2668; (g) Salazar, J.; Dorta, R. Pentylpyridinium tribromide: A vapor-pressure-free, room-temperature, ionic liquid analogue of bromine. *Synlett* **2004**, 1318–1320; (h) Tanaka, K.; Shiraishi, R.; Toda, F. A new method for stereoselective bromination of stilbene and chalcone in a water suspension medium. *J. Chem. Soc., Perkin Trans. 1* **1999**, *21*, 3069–3070; (i) Markovic, R.; Baranac, M.; Dzambaski, Z. Sequential bromination-rearrangement of push–pull thiazolidines induced by pyridinium hydrobromide perbromide under homogeneous reaction conditions. *Heterocycles* **2004**, *63*, 851–860; (j) Fischer, L. F.; Fiecher, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p. 967; (k) Reeves, W. P.; Lu, C. V.; Schulmeier, B.; Jonas, L.; Hatlevik, O. Selective bromination of aromatic ethers with pyridinium hydrobromide perbromide. *Synth. Commun.* **1998**, *28*, 499–505; (l) Paquet, L. A. (Ed.). *Encyclopedia of Reagents for Organic Synthesis*; Wiley: NewYork, 1995; vol. 6, pp. 4738, 4370; (m) Muathen, H. A. 1,8-Diazabicyclo[5.4.0]undec-7-ene hydrobromide perbromide: A new mild stable brominating agent for aromatic compounds. *J. Org. Chem*. **1992**, *57*, 2740–2741; (n) Zolfigol, M. A.; Chehardoli, G.; Salehzadeh, S.; Adams, H.; Ward, M. D. {[K.18-Crown-6]Br_3}n: A unique tribromide-type and columnar nanotube-like

structure for the oxidative coupling of thiols and bromination of some aromatic compounds. *Tetrahedron Lett*. **2007**, *48*, 7969–7973.

5. (a) Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. 1′-(Ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) as a recyclable catalyst for acylation. *Arkivoc* **2006**, *11*, 21–36; (b) Kavala, V.; Murru, S.; Das, G.; Patel, B. K. Syntheses and regiochemistry of enol addition to 9-phenyl-9H-xanthen-9-ol. *Tetrahedron* **2008**, *64*, 3960–3965; (c) Kavala, V.; Murru, S.; Patel, B. K.; Das, G. Self-assembled superstructure of xanthene derivatives. *J. Chem. Crystallogr.* **2007**, *37*, 527–535; (d) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. It is "thiazolidene-2-imine" and not imidazole-2-thione as the reaction product of 1-benzoyl-3-phenylthiourea with Br_2/enolizable ketone. *Org. Lett.* **2006**, *8*, 5397–5399; (e) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. 3-Aryl-1-benzoylthioureas with α-bromoketones in water form 2-N-benzoyl-3-arylthiazol-2(3H)-imines, not 3-aryl-1-benzoylimidazoline-2-thiones. *J. Chem. Res*. **2007**, 136–137; (f) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. A convenient one-pot synthesis of thiazol-2-imines: Application in the construction of pifithrin analogues. *Tetrahedron* **2008**, *64*, 1931–1942; (g) Murru, S.; Kavala, V.; Singh, C. B.; Patel, B. K. A one-pot synthesis of 1,4-dithiins and 1,4-benzodithiins from ketones using the recyclable reagent 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT). *Tetrahedron Lett*. **2007**, *48*, 1007–1011; (h) Ghosh, H.; Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. A new facile synthetic method for the construction of 1,3-oxathiolan-2-ylidenes. *Tetrahedron Lett*. **2008**, *49*, 2602–2606; (i) Zolfigol, M. A.; Chehardoli, G.; Ghaemi, E.; Madrakian, E.; Zare, R.; Azadbakht, T.; Niknam, K.; Mallakpour, S. N-Bromo reagent-mediated oxidation of urazoles to their corresponding triazolinediones under mild and heterogeneous conditions. *Monatsh. Chem*. **2008**, *139*, 261–265.
6. (a) Chen, C.-Y.; Wong, F. F.; Huang, J.-J.; Lin, S.-K.; Yeh, M.-Y. Desulfurization and transformation of isothiocyanates to cyanamides by using sodium bis(trimethylsilyl)-amide. *Tetrahedron Lett.* **2008**, *49*, 6505–6507; (b) Kim, J.-J.; Kweon, D.-H.; Cho, S.-D.; Kim, H.-K.; Jung, E.-Y.; Lee, S.-G.; Falck, J. R.; Yoon, Y.-J. 2-Cyanopyridazin-3(2H)-ones: Effective and chemoselective electrophilic cyanating agents. *Tetrahedron* **2005**, *61*, 5889–5894.
7. Bruni, E.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. Synthesis of chiral 1,2-diamines. *Tetrahedron Lett.* **1989**, *30*, 1679–1682.
8. Hargrave, K. D.; Hess, F. K.; Oliver, J. T. N-(4-Substituted-thiazolyl)oxamic acid derivatives, new series of potent, orally active antiallergy agents. *J. Med. Chem*. **1983**, *26*, 1158–1163.
9. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor Jr., D. G.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. Structure–activity relationships of a series of 2-amino-4-thiazole-containing renin inhibitors. *J. Med. Chem.* **1992**, *35*, 2562–2572.
10. (a) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. 3-[1-(2-Benzoxazolyl)hydrazino]propanenitrile derivatives: Inhibitors of immune complex–induced inflammation. *J. Med. Chem*. **1988**, *31*, 1719–1728; (b) Clemence, F.; Le Martret, O.; Delevallee, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. 4-Hydroxy-3-quinolinecarboxamides with antiarthritic and analgesic activities. *J. Med. Chem*. **1988**, *31*, 1453–1462.
11. Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazolamines: A novel class of compounds with central dopamine agonist properties. *J. Med. Chem*. **1990**, *33*, 311–317.
12. Tsuji, K.; Ishikawa, H. Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601–1606.

13. Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noréen, R.; Öberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. Phenethylthiazolethiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors, 1: Synthesis and basic structure–activity relationship studies of PETT analogs. *J. Med. Chem.* **1995**, *38*, 4929–4936.
14. Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens. *Chem. Biol.* **1999**, *6*, 205–219.
15. van Muijlwijk-Koezen, J. E.; Timmerman, H.; Vollinga, R. C.; Frijtag von Drabbe Kunzel, J.; de Groote, M.; Visser, S.; Ijzerman, A. P. Thiazole and thiadiazole as as novel class of adenosine receptor antagonists. *J. Med. Chem.* **2001**, *44*, 749–762.
16. Nettekoven, M.; Guba, W.; Neidhart, W.; Mattei, P.; Pflieger, P.; Plancher, J.; Taylor, S. Aminothiazole derivatives as neuropeptide Y5 receptor ligands: Finding the balance between affinity and physicochemical properties. *Chem. Med. Chem.* **2006**, *1*, 45–48.
17. (a) Kazzouli, S. E.; Raboin, S. B.; Mouadbib, A.; Guillaumet, G. Solid support synthesis of 2,4-disubstituted thiazoles and aminothiazoles. *Tetrahedron Lett.* **2002**, *43*, 3193–3196; (b) Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. A convenient procedure for the solution-phase preparation of 2-aminothiazole combinatorial libraries. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1409–1414; (c) Kearney, P. C.; Fernendez, M.; Flygare, J. A. Traceless solid phase synthesis of 2-aminothiazoles. *J. Org. Chem.* **1998**, *63*, 196–200.
18. Das, B.; Reddy, V. S.; Ramu, R. A rapid and high-yielding synthesis of thiazoles and aminothiazoles using ammonium-12-molybdophosphate. *J. Mol. Catal. A: Chem*. **2006**, *252*, 235–237.
19. Narender, M.; Reddy, M. S.; Sridhar, R.; Nageswar, Y. V. D.; Rao, K. R. Aqueous phase synthesis of thiazoles and aminothiazoles in the presence of β-cyclodextrin. *Tetrahedron Lett.* **2005**, *46*, 5953–5955.
20. (a) Kabalka, G. W.; Mereddy, A. R. Microwave-promoted synthesis of functionalized 2-aminothiazoles. *Tetrahedron Lett.* **2006**, *47*, 5171–5172; (b) Prakash, R.; Kumar, A.; Aggarwal, R.; Prakash, O.; Singh, S. P. α,α-Dibromoketones: A superior alternative to α-bromoketones in Hantzsch thiazole synthesis. *Synth. Commun*. **2007**, *37*, 2501–2505.
21. (a) Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. Catalyst-free efficient synthesis of 2-aminothiazoles in water at ambient temperature. *Tetrahedron* **2008**, *64*, 5019–5022; (b) Dabholkar, V. V.; Mishra, S. K. J. Microwave-mediated synthesis of some novel heterocycles containing thiazole, oxazole, thiazine, oxazine, thiadiazine,and triazolo-thiadiazine moiety. *Ind. J. Chem. B* **2006**, *45B*, 2112–2117; (c) Prakash, O.; Pundeer, R.; Chaudhri, V. Organoiodine(III)-mediated one-pot synthesis of N-substituted 2-aminothiazoles. *J. Ind. Chem. Soc.* **2004**, *81*, 786–788.
22. Choi, H. Y.; Chi, D. Y. Nonselective bromination–selective debromination strategy: Selective debromination of unsymmetrical ketones on singly activated carbon against doubly activated. *Org. Lett.* **2003**, *5*, 411–414.
23. Khan, A. T.; Parvin, T.; Choudhury, L. H. Effects of substituents in the β-position of 1,3-dicarbonyl compounds in bromodmethylsulfonium bromide-catalyzed multicomponent reactions: A facile access to functionalized piperidines. *J. Org. Chem*. **2008**, *73*, 8398–8402.
24. SMART, SAINT, and XPREP. Siemens Analytical X-*ray* Instruments Inc.: Madison, Wisconsin, USA, 1995.
25. Sheldrick, G. M. *SADABS: Empirical Absorption and Correction Software*; University of Gottingen, Institut fur Anorganische Chemieder Universitat: Gottingen, Germany, 1999–2003.
26. Sheldrick, G. M. *SHELXS-97*. University of Gottingen: Gottingen, Germany, 1997.