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Graphical Abstract

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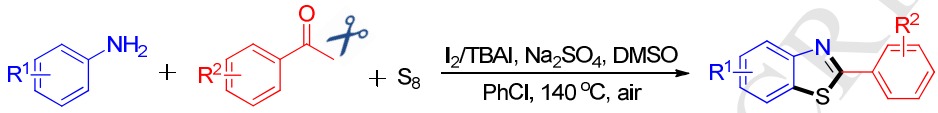

- metal-free
- C(CO)-C bond cleavage
- C-S/C-N bond formation
- broad substrates (25 examples, up to 81% yield)

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Efficient 2-Aryl Benzothiazole Formation from Acetophenones, Anilines, and Elemental Sulfur by Iodine-Catalyzed Oxidative C(CO)-C(alkyl) Bond Cleavage

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ABSTRACT

A novel and efficient iodine-catalyzed one-pot reaction of aromatic amines, acetophenones, and elemental sulfur for the synthesis of 2-aryl benzothiazoles is described. The process involves sequential C−S and C-N bond formation followed by C(CO)−C bond cleavage from readily accessible starting materials. A wide range of functional groups is tolerated under oxidant and metal-free condition and moderate to good product yields are obtained.

1. Introduction

Benzothiazole, as a privileged heterocyclic scaffold, is frequently found in diverse natural products and pharmacologically active molecules.[1] In particular, 2-aryl benzothiazoles have attracted increasing attention owing to its broad pharmacological profile.[2] For example, compound **A** possesses highly potent antiproliferative activity.[3] **B** exhibits significant activity against clinically relevant pathogens E. coli and S. aureus[4] and **C** enables a invasive diagnosis of Alzheimer's disease.[5] Furthermore, 2-aryl benzothiazoles can be employed as therapeutic agents by the virtue of their antitumor,[6] antiparasitic,[7] anti-inflammatory,[8] and anticonvulsant activities.[9] Thus, considerable research has been conducted on the synthesis of 2-aryl benzothiazoles over the past few decades.

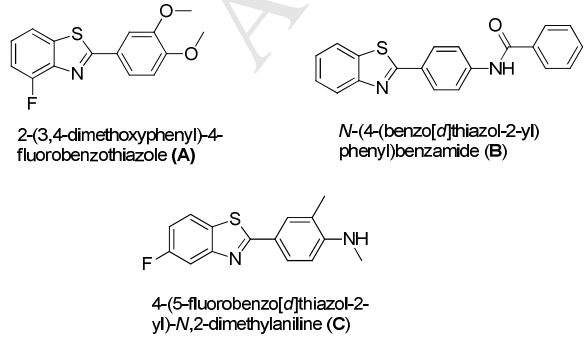
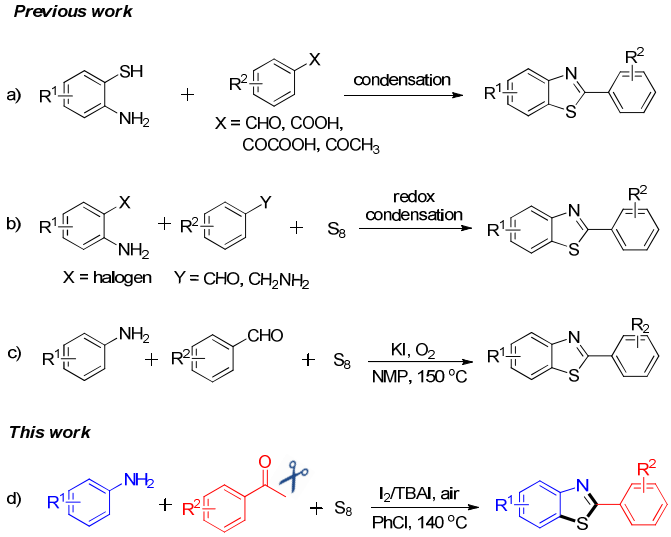


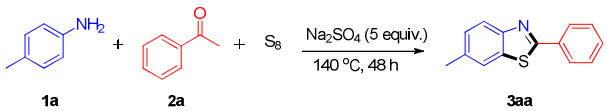
Figure 1. Pharmaceutical and bioactive compounds containing 2-aryl benzothiazoles

Traditional methods for the construction of 2-aryl benzothiazole skeleton involve the condensation of 2-aminothiophenol with carbonyl compounds such as aldehydes, carboxylic acids, acid chlorides and esters (Scheme 1, a).[10] Another approach requires the preparation of 2-aryl benzothiazoles *via* the reaction of 2-haloaniline and a sulfur source[11] or transition-metal-catalyzed intramolecular cyclization of thiobenzanilide (Scheme 1, b)[12]. However, these methods have



Scheme 1. Synthesis of 2-aryl benzothiazoles

Table 1. Optimization of reaction conditions[a]



1a 2a 3aa

Entry	Catalyst (mol %)	Additive	Solvent	Yield[b] (%)
1	I_2 (15)	-	PhCl	23
2	I_2 (50)	-	PhCl	trace
3	I_2 (15)	DMSO	PhCl	66
4	NH_4I (15)	DMSO	PhCl	41
5	KI (15)	DMSO	PhCl	47
6	TBAI (15)	DMSO	PhCl	trace
7	**I_2(15)/TBAI (20)**	**DMSO**	**PhCl**	**81**
8	I_2(15)/TBAB(20)	DMSO	PhCl	75
9	I_2(15)/TBAI (20)	DMSO	DMSO	68
10	I_2(15)/TBAI (20)	DMSO	Toluene	51
11	I_2(15)/TBAI (20)	DMSO	NMP	42
12[c]	I_2(15)/TBAI (20)	DMSO	PhCl	64
13[d]	I_2(15)/TBAI (20)	DMSO	PhCl	80
14[e]	I_2(15)/TBAI (20)	DMSO	PhCl	69

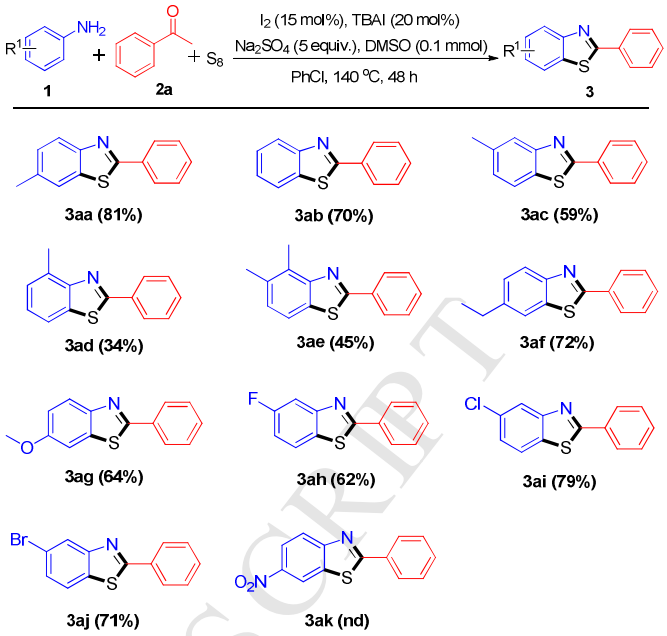
[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), S_8 (4 equiv.), catalyst (15 mol%), additive (0.15 mmol), Na_2SO_4 (5 equiv.), and solvent (0.6 ml) under air at 140 °C for 48h. [b]Yields of isolated products. [c]At 120 °C. [d]At 150 °C.[e]Without Na_2SO_4.

inherent drawbacks especially in the preparation of starting materials, which limit their synthetic applications. Recently, Deng et al. reported a more straightforward approach for the synthesis of 2-aryl benzothiazoles from amines, sulfur powder and benzaldehydes, which solved the problems well (Scheme 1, c).[13] Whereas, designing an effective strategy for preparing 2-aryl benzothiazoles from readily available starting materials and innocuous solvent in mild condition is still requisite. Herein, we developed an efficient procedure to synthesize 2-aryl benzothiazoles from anilines, elemental sulfur, and acetophenones which are cheap, commercially available and relatively stable, with a C(CO)-C(alkyl) bond cleavage (Scheme 1, d).

2. Results and discussion

Our initial efforts were focused on the reaction of *p*-toluidine **1a**, acetophenone **2a**, and elemental sulfur in the presence of 5 equiv Na_2SO_4 using I_2 as a catalyst at 140 °C. However, the desired product **3aa** was isolated in only 23% yield and increasing the amount of iodine ignificantly lowered the yield (Table 1, entries 1-2). To our delight, the addition of a small quantity of dimethyl sulfoxide (DMSO) afforded the desired product in 66% yield (Table 1, entry 3). These results indicated that the process required only catalytic dose of iodine and that DMSO catalyzed the oxidation of HI to iodine in the redox system. Next, various catalyst systems were examined for the reaction and the I_2 (15 mol %)/tetrabutylammonium iodide TBAI (20 mol%) system was found to be the most efficient (Table 1, entries 4-8). Further optimization based on solvent screening showed that PhCl was the most effective solvent for this reaction (Table 1, entries 9-11). The expected increase in product yield was not observed when the reactions were carried out at 120 °C and 150 °C (entries 12-13). In addition, a much lower yield was obtained when the reaction was carried out without anhydrous sodium sulfate, which serves as the drying

Table 2. Scope of substituted anilines

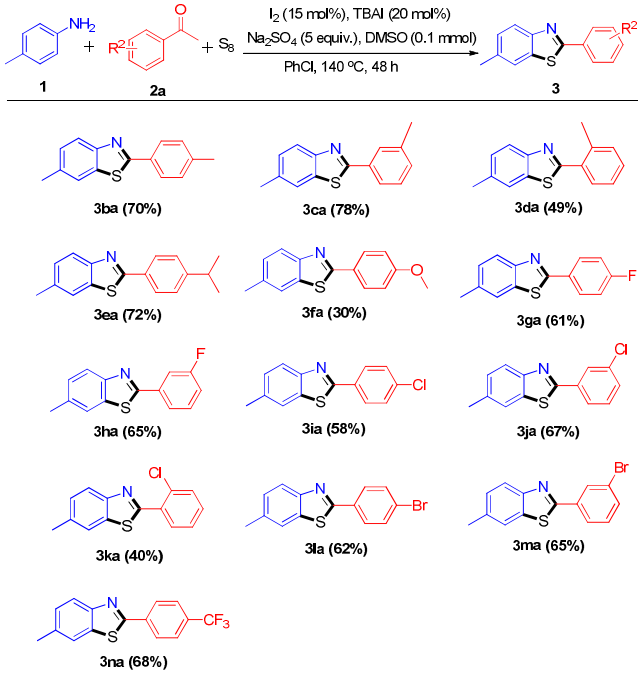


1 2a 3

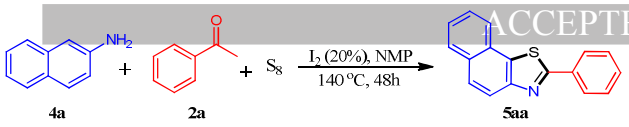
agent in this transformation. Hence, the optimal reaction condition was established as shown in entry 7 (Table 1).

With the optimal reaction conditions in hand, we investigated the scope of anilines for this reaction. The results are summarized in Table 2. Anilines **1a**-**1g** containing electron-donating groups on the phenyl ring afforded the corresponding benzothiazoles in yields ranging from 34% to 81%. Anilines with substituents at the *para* and *meta*-positions provided higher yields than *ortho*-substituted anilines, which may be due to the effect of steric hindrance in the latter case. Substrates with electron-withdrawing groups at the *meta*-positions appeared compatible under the optimal reaction condition with excellent yields (**3ah**-**3aj**). Disappointingly, *p*-nitro-substituted aniline **1k** was not suitable for this transformation, which indicated that aniline might have

Table 3. Scope of substituted acetophenones.



1 2a 3



Scheme 2. Reaction conditions with respect to 2-aminonaphthalene

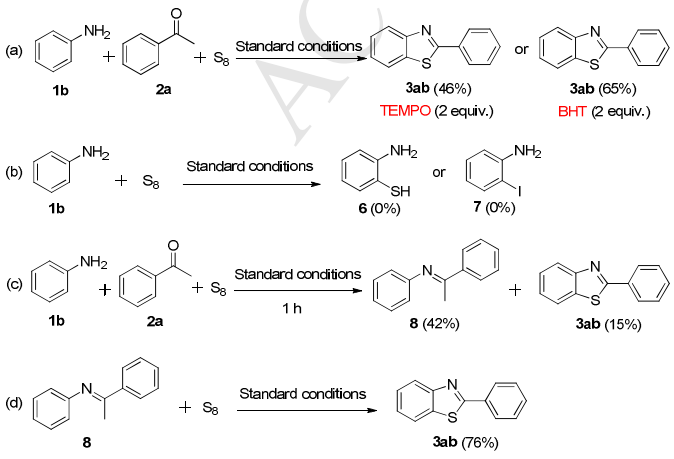
experienced a nucleophilic attack.

To further examine the scope and limitations of the reaction, we assessed various acetophenones (Table 3). Acetophenones with electron-donating groups smoothly reacted with the desired anilines and sulfur powder, affording the corresponding products (**3ba**-**3fa**). In the intermolecular effect, both *para* and *meta*-positions afforded good yields. In the case of *ortho* substituted acetophenone (**3da**), the yield was poor owing to the large *ortho* steric hindrance. Moreover, **2g**-**2n** including halogens such as F, Cl, Br and electron-withdrawing groups such as -CF_3 were tolerated well in this reaction and the corresponding products **3ga**-**3na** were obtained in reasonable yields of 40%-68%.

To further demonstrate the application of our protocol, we used 2-naphthalenamine as the substrate for this transformation (Scheme 2). Gratifyingly, 2-aminonaphthalene was also suitable for this transformation, and the desired product 2-phenylnaphtho[2,1-*d*]thiazole (**5aa**) was obtained in 66% yield.

To gain insight into the reaction mechanism, a sequence of control experiments was performed under the standard conditions, as shown in Scheme 3. First, when a radical scavenger such as TEMPO and BHT was added in the reaction, the desired transformation continued, thereby excluding any possible mechanism related to the generation of free radicals. Next, we speculated that 2-aminobenzenethiol or 2-iodoaniline may be a key intermediate before the cyclization reaction. Therefore, we conducted the next control experiment in the absence of acetophenone under standard conditions (Scheme 3, b), which revealed that aniline does not convert into **6** or **7** at all. Furthermore, the generation of imine **8** was superior when the reaction was performed within 1 h (Scheme 3, c). Moreover, imine **8** could convert into the final benzothiazole under the standard conditions (Scheme 3, d).

Based on our experiments and previous reports,[14] a plausible mechanism for the approach is proposed in Scheme 4. The reaction is initiated by the condensation of amine and acetophenone to produce Schiff's base **A**. Schiff's base **A** can be converted to a resonance structure **A'** at heating condition, which happens a nucleophilic attack on the elemental sulfur leading to intermediate **B**. **B** is then transformed into **C** *via* S_{n-1} extrusion and deprotonation. Subsequently, the active intermediate **C** is

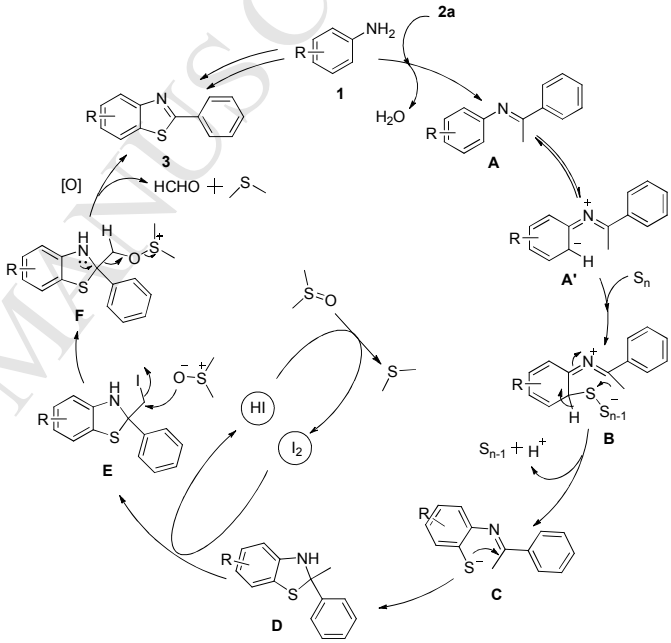


Scheme 3. Control experiments.

transformed into dihydro benzothiazole **D** *via* intramolecular cyclization. The methyl group of intermediate **D** is iodized to produce **E** and intermediate **E** possibly goes through a SN_2 reaction with DMSO to afford **F**. Intermediate **F** is oxidized to the desired product **3** along with the elimination of dimethyl sulfide and methanal.

3. Conclusion

In summary, we have developed an I_2-catalyzed three-component reaction for the synthesis of 2-aryl benzothiazoles from readily available anilines, acetophenones and elemental sulfur. Our protocol is advantageous in that it does not require pre-activation of the substrates or rigorous reaction conditions. In this reaction, the C(CO)−C(alkyl) bond in the acetophenones is cleaved, leading to the formation of C-N and C-S bonds for the construction of benzothiazole skeleton. In addition, various substituted acetophenones and anilines containing 2-naphthalenamine readily participate in the reaction with elemental sulfur to furnish the desired products in moderate to good yields.



Scheme 4. Proposed mechanism

4. Experimental section

4.1 General

^{1}H NMR, and ^{13}C NMR spectra were recorded on Bruker 400M and Mercury 300M in $CDCl_3$ or DMSO. All ^{1}H NMR and ^{13}C NMR chemical shifts were given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. All compounds were further characterized by HRMS; copies of their ^{1}H NMR and ^{13}C NMR spectra were provided. Products were purified by flash chromatography on 200–300 mesh silica gels. All melting points were determined without correction. All reagents were purchased commercially and used as received, unless otherwise noted.

4.2 Procedure for the synthesis of 3aa and 5aa

A mixture of acetophenone (**2a**, 0.2 mmol), *p*-toluidine (**1a**, 0.4 mmol), S_8 (0.8 mmol), I_2 (15 mol%), TBAI (20 mol%), DMSO (0.1 mmol) and sodium sulfate (1 mmol) in PhCl (0.6 mL)

was stirred at 140 °C for 48 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure to obtain the crude product. The residue was purified by silica gel chromatography (eluent: petroleum/ethyl acetate = 40/1) to obtain the desired product **3aa** as white solid.

A mixture of acetophenone (**2a**, 0.2 mmol), 2-aminonaphthalene (**4a**, 0.24 mmol), S_8 (0.6 mmol), and I_2 (20 mol%) in NMP (1 mL) was stirred at 140 °C for 48 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure to obtain the crude product. The residue was purified by silica gel chromatography (eluent: petroleum/ethyl acetate = 10/1) to obtain the desired product **5aa** as light yellow solid.

4.3 **Compound data of products 3 and 5aa**

*4.3.1. 6-methyl-2-phenylbenzo[d]thiazole (**3aa**)*

Compound **3aa** was isolated as a white solid (81% yield, 36.4 mg, mp: 121-123 °C). ^{1}H NMR (400 MHz,) δ 8.07 (ddd, *J* = 6.2, 1.9, 0.6 Hz, 2H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 0.6 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.30 (d, *J* = 8.2 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.2, 135.3, 135.1, 133.6, 130.7, 128.9, 127.8, 127.3, 122.6, 121.3, 21.5. HRMS (ESI): m/z calcd for $C_{14}H_{12}NS$ $(M+H)^+$ 226.0685; found: 226.0690.

*4.3.2. 2-phenylbenzo[d]thiazole (**3ab**)*

Compound **3ab** was isolated as a white solid (70% yield, 29.5 mg, mp: 114-117 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 – 8.03 (m, 3H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.42 (m, 4H), 7.42 – 7.32 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 154.1, 134.9, 133.5, 130.8, 128.9, 127.5, 126.2, 125.1, 123.1, 121.5. HRMS (ESI): m/z calcd for $C_{13}H_{10}NS$ $(M+H)^+$ 212.0529; found: 212.0533.

*4.3.3. 5-methyl-2-phenylbenzo[d]thiazole (**3ac**)*

Compound **3ac** was isolated as a yellow solid (59% yield, 26.5 mg, mp: 140-142 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 – 8.04 (m, 2H), 7.90 – 7.86 (m, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.24 – 7.18 (m, 1H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 154.4, 136.3, 133.7, 131.9, 130.8, 128.9, 127.4, 126.8, 123.2, 121.0, 21.4. HRMS (ESI): m/z calcd for $C_{14}H_{12}NS$ $(M+H)^+$ 226.0685; found: 226.0680.

*4.3.4. 4-methyl-2-phenylbenzo[d]thiazole (**3ad**)*

Compound **3ad** was isolated as a yellow liquid (34% yield, 15.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 2H), 7.74 – 7.68 (m, 1H), 7.50 – 7.44 (m, 3H), 7.29 – 7.24 (m, 2H), 2.81 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 153.5, 135.0, 133.9, 133.3, 130.6, 128.9, 127.5, 126.7, 125.0, 118.9, 18.3. HRMS (ESI): m/z calcd for $C_{14}H_{12}NS$ $(M+H)^+$ 226.0685; found, 226.0689.

*4.3.5. 4,5-dimethyl-2-phenylbenzo[d]thiazole (**3ae**)*

Compound **3ae** was isolated as a white solid (45% yield, 21.5 mg, mp: 77-79 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.51 – 7.42 (m, 3H), 7.17 (d, *J* = 8.1 Hz, 1H), 2.74 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 153.9, 134.1, 132.3, 131.5, 130.5, 128.9, 127.4, 127.3, 118.1, 19.6, 14.9. HRMS (ESI): m/z calcd for $C_{15}H_{14}NS$ $(M+H)^+$ 240.0842; found: 240.0840.

*4.3.6. 6-ethyl-2-phenylbenzo[d]thiazole (**3af**)*

Compound **3af** was isolated as a yellow solid (72% yield, 34.4 mg, mp: 39-42 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 0.8 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.30 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 152.3, 141.6, 135.1, 133.6, 130.6, 128.8, 127.3, 126.7, 122.7, 120.1, 28.8, 15.8. HRMS (ESI): m/z calcd for $C_{15}H_{14}NS$ $(M+H)^+$ 240.0842; found: 240.0847.

*4.3.7. 6-methoxy-2-phenylbenzo[d]thiazole (**3ag**)*

Compound **3ag** was isolated as a white solid (64% yield, 30.7 mg, mp: 118-120 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.89 (m, 3H), 7.51 – 7.39 (m, 3H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 157.6, 148.5, 136.3, 133.6, 130.4, 128.9, 127.1, 123.6, 115.6, 103.9, 55.7. HRMS (ESI): m/z calcd for $C_{14}H_{12}NOS$ $(M+H)^+$ 242.0634; found: 242.0630.

*4.3.8. 5-fluoro-2-phenylbenzo[d]thiazole (**3ah**)*

Compound **3ah** was isolated as a light yellow solid (62% yield, 28.4 mg, mp: 119-121 °C). ^{1}H NMR (300 MHz, CDCl3) δ 8.07 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.82 (dd, *J* = 8.8, 5.1 Hz, 1H), 7.75 (dd, J = 9.5, 2.5 Hz, 1H), 7.51 (dd, J = 6.4, 3.9 Hz, 3H), 7.16 (td, *J* = 8.8, 2.5 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 170.5, 163.5-160.3 (d, *J* = 241.5 Hz, 1C), 155.0-154.9 (d, *J* = 12.0 Hz, 1C), 133.3, 131.3, 130.3, 129.1, 127.5, 122.3-122.2 (d, *J* = 9.8 Hz, 1C), 114.0-113.7 (d, *J* = 24.8 Hz, 1C), 109.5-109.2 (d, *J* = 23.3 Hz, 1C). HRMS (ESI): m/z calcd for $C_{13}H_9FNS$ $(M+H)^+$ 230.0434; found: 230.0438.

*4.3.9. 5-chloro-2-phenylbenzo[d]thiazole (**3ai**)*

Compound **3ai** was isolated as a light yellow solid (79% yield, 38.6 mg, mp: 138-141 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 – 8.03 (m, 3H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.53 – 7.47 (m, 3H), 7.35 (dd, *J* = 8.5, 2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 154.9, 133.2, 133.1, 132.2, 131.3, 129.1, 127.5, 125.6, 122.9, 122.3. HRM (ESI): m/z calcd for $C_{13}H_9ClNS$ $(M+H)^+$ 246.0139; found: 246.0142.

*4.3.10. 5-bromo-2-phenylbenzo[d]thiazole (**3aj**)*

Compound **3aj** was isolated as a light yellow solid (71% yield, 40.9 mg, mp: 134-137 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.8 Hz, 1H), 8.05 (dt, *J* = 5.3, 2.0 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 155.2, 133.8, 133.1, 131.3, 129.1, 128.2, 127.6, 126.0, 122.6, 119.8. HRMS (ESI): m/z calcd for $C_{13}H_9BrNS$ $(M+H)^+$ 289.9634; found: 289.9635.

*4.3.11. 6-methyl-2-(p-tolyl)benzo[d]thiazole(**3ba**)*

Compound **3ba** was isolated as a white solid (70% yield, 33.4 mg, mp: 144-147 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 3H), 7.60 (d, *J* = 0.7 Hz, 1H), 7.29 – 7.21 (m, 3H), 2.44 (s, 3H), 2.38 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 152.1, 141.0, 134.9, 134.9, 130.9, 129.5, 127.7, 127.2, 122.4, 121.2, 21.5, 21.4. HRMS (ESI): m/z calcd for $C_{15}H_{14}NS$ $(M+H)^+$ 240.0842; found: 240.0845.

*4.3.12. 6-methyl-2-(m-tolyl)benzo[d]thiazole(**3ca**)*

Compound **3ca** was isolated as a white solid (78% yield, 37.2 mg, mp: 72-75 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 2H), 7.61 (dd, *J* = 7.6, 0.5 Hz, 1H), 7.40 (d, *J* = 0.7 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.08 – 7.01 (m, 2H), 2.24 (s, 3H), 2.21 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 152.0, 138.6, 135.1, 134.9, 133.4, 131.4, 128.7, 127.7, 127.7, 124.6, 122.5, 121.2, 21.4, 21.2. HRMS (ESI): m/z calcd for $C_{15}H_{14}NS$ $(M+H)^+$ 240.0842; found: 240.0828.

*4.3.13. 6-methyl-2-(o-tolyl)benzo[d]thiazole (**3da**)*

Compound **3da** was isolated as a light yellow solid (49% yield, 23.4 mg, mp: 35-37 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.69 (s, 1H), 7.37 – 7.25 (m, 4H), 2.64 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 151.7, 136.9, 135.5, 134.9, 132.9, 131.3, 130.3, 129.6, 127.5, 125.9, 122.6, 120.9, 21.4, 21.3. HRMS (ESI): m/z calcd for $C_{15}H_{14}NS$ $(M+H)^+$ 240.0842; found: 240.0841.

*4.3.14. 2-(4-isopropylphenyl)-6-methylbenzo[d]thiazole (**3ea**)*

Compound **3ea** was isolated as a light yellow solid (72% yield, 38.4 mg, mp: 98-101 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 2H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.28 (dd, *J* = 8.3, 1.6 Hz, 1H), 2.97 (m, 1H), 2.48 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 152.2, 151.9, 135.1, 131.4, 127.8, 127.4, 127.0, 122.5, 121.3, 109.7, 34.1, 23.8, 21.5. HRMS (ESI): m/z calcd for $C_{17}H_{18}NS$ $(M+H)^+$ 268.1155; found: 268.1157.

*4.3.15. 2-(4-methoxyphenyl)-6-methylbenzo[d]thiazole (**3fa**)*

Compound **3fa** was isolated as a light yellow solid (30% yield, 15.3 mg, mp: 170-173 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.66 (s, 1H), 7.28 (d, *J* = 9.5 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 161.7, 152.3, 134.9, 134.9, 128.9, 127.8, 126.5, 122.3, 121.3, 114.3, 55.4, 21.5. HRMS (ESI): m/z calcd for $C_{15}H_{14}NOS$ $(M+H)^+$ 256.0791; found: 256.0789.

*4.3.16. 2-(4-fluorophenyl)-6-methylbenzo[d]thiazole (**3ga**)*

Compound **3ga** was isolated as a white solid (61% yield, 29.6 mg, mp: 160-162 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.99 (m, 2H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.28 (ddd, *J* = 8.3, 1.1, 0.6 Hz, 1H), 7.19 – 7.10 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 – 165.6 (d, *J* = 21.8 Hz, 1C), 162.6, 152.1, 135.4, 135.1, 130.0 – 129.9 (d, *J* = 3.0 Hz, 1C), 129.3 – 129.2 (d, *J* = 8.3 Hz, 1C), 127.9, 122.6, 121.3, 116.2 – 115.9 (d, *J* = 22.5 Hz, 1C), 21.5. HRMS (ESI): m/z calcd for $C_{14}H_{11}FNS$ $(M+H)^+$ 244.0591; found: 244.0594.

*4.3.17. 2-(3-fluorophenyl)-6-methylbenzo[d]thiazole (**3ha**)*

Compound **3ha** was isolated as a white solid (65% yield, 31.5 mg, mp: 96-99 °C). ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.58 (s, 1H), 7.38 (td, *J* = 8.2, 5.8 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.16 – 7.08 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 164.5 – 161.2 (d, *J* = 245.3 Hz, 1C), 151.9, 135.7, 135.6, 135.0, 130.5 – 130.4 (d, *J* = 7.5 Hz, 1C), 127.9, 123.0, 122.9 – 122.7 (d, *J* = 18.0 Hz, 1C), 121.2, 117.6 – 117.3 (d, *J* = 21.0 Hz, 1C), 114.1 – 113.8 (d, *J* = 23.3 Hz, 1C), 21.5. HRMS (ESI): m/z calcd for $C_{14}H_{11}FNS$ $(M+H)^+$ 244.0591; found: 244.0594.

*4.3.18. 2-(4-chlorophenyl)-6-methylbenzo[d]thiazole (**3ia**)*

Compound **3ia** was isolated as a light yellow solid (58% yield, 30.0 mg, mp: 182-187 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.69 (s, 1H), 7.49 – 7.43 (m, 2H), 7.31 (dd, *J* = 8.3, 1.2 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 152.1, 136.7, 135.6, 135.1, 132.2, 129.2, 128.5, 128.1, 122.7, 121.4, 21.6. HRMS (ESI): m/z calcd for $C_{14}H_{11}ClNS$ $(M+H)^+$ 260.0295; found: 260.0291.

*4.3.19. 2-(3-chlorophenyl)-6-methylbenzo[d]thiazole (**3ja**)*

Compound **3ja** was isolated as a yellow solid (67% yield, 34.7 mg, mp: 115-119 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.97 – 7.88 (m, 2H), 7.68 (s, 1H), 7.46 – 7.36 (m, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 151.9, 135.7, 135.3, 135.1, 134.9, 130.5, 130.1, 128.1, 127.1, 125.5, 122.8, 121.3, 21.5. HRMS (ESI): m/z calcd for $C_{14}H_{11}ClNS$ $(M+H)^+$ 260.0295; found: 260.0296.

*4.3.20. 2-(2-chlorophenyl)-6-methylbenzo[d]thiazole (**3ka**)*

Compound **3ka** was isolated as a light yellow solid (40% yield, 20.7 mg, mp: 102-105 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.15 (m, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.52 – 7.44 (m, 1H), 7.39 – 7.26 (m, 3H), 2.47 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 150.5, 136.1, 135.5, 132.4, 132.2, 131.5, 130.8, 130.6, 127.8, 126.9, 122.8, 120.9, 21.5. HRMS (ESI): m/z calcd for $C_{14}H_{11}ClNS$ $(M+H)^+$ 260.0295; found: 260.0294.

*4.3.21. 2-(4-bromophenyl)-6-methylbenzo[d]thiazole (**3la**)*

Compound **3la** was isolated as a white solid (62% yield, 37.4 mg, mp: 199-202 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 3H), 7.69 (s, 1H), 7.64 – 7.59 (m, 2H), 7.31 (dd, *J* = 8.4, 1.5 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 152.1, 135.7, 135.1, 132.6, 132.1, 128.7, 128.1, 125.1, 122.7, 121.4, 21.6. HRMS (ESI): m/z calcd for $C_{14}H_{11}BrNS$ $(M+H)^+$ 303.9790; found: 303.9795.

*4.3.22. 2-(3-bromophenyl)-6-methylbenzo[d]thiazole (**3ma**)*

Compound **3ma** was isolated as a white solid (65% yield, 39.2 mg, mp: 119-121 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (t, *J* = 1.8 Hz, 1H), 7.89 (ddd, *J* = 4.1, 3.3, 2.6 Hz, 2H), 7.63 – 7.58 (m, 1H), 7.54 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.32 – 7.23 (m, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 151.9, 135.7, 135.4, 135.1, 133.4, 130.3, 129.9, 128.0, 125.8, 123.0, 122.7, 121.3, 21.5. HRMS (ESI): m/z calcd for $C_{14}H_{11}BrNS$ $(M+H)^+$ 303.9790; found: 303.9786.

*4.3.23. 6-methyl-2-(4-(trifluoromethyl)phenyl)benzo[d]thiazole (**3na**)*

Compound **3na** was isolated as a white solid (68% yield, 39.8 mg, mp: 94-97 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.6 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.69 (m, 3H), 7.33 (dd, *J* = 8.4, 1.6 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 152.1, 136.9, 136.1, 135.4, 132.4, 132.0, 128.3, 127.6, 126.0 – 125.9 (q, *J* = 3.8 Hz, 1C), 123.1, 121.4, 21.6. HRMS (ESI): m/z calcd for $C_{15}H_{11}F_3NS$ $(M+H)^+$ 294.0559; found: 294.0562.

*4.3.24. 2-Phenylnaphtho[2,1-d]thiazole (**5aa**)*

Compound **5aa** was isolated as a light yellow solid (66% yield, 34.4 mg, mp: 102-105 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 – 8.01 (m, 3H), 7.94 (dd, *J* = 16.9, 7.6 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.60 – 7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 152.1, 133.6, 132.1, 130.9, 130.7, 128.9, 128.9, 127.9, 127.3, 127.2, 126.9, 125.9, 125.1, 121.6. HRMS (ESI): m/z calcd for $C_{17}H_{12}NS$ $(M+H)^+$ 262.0685; found, 262.0689.

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References and notes

1. (a) Wade, A. R.; Pawar, H. R.; Biware, M. V.; Chikate, R. C. *Green Chem.* **2015**, *17*, 3879. (b) Lyons, T. W.; Sanford, M. S.; *Chem. Rev.* **2010**, *110*, 1147. (c) Yu, C.; Lee, K.; You, Y.; Cho, E. J. *Adv. Synth. Cata.* **2013**, *355*, 1471. (d) Aiello, S.; Wells, G.;

Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135. (e) Li, Y. X.; Fu, Y. J.; Ren, C. J.; Tang, D.; Wu, P.; Meng, X.; Chen, B. H. *Org. Chem. Front.* **2015**, *2*, 1632. (f) Geng, J.; Li, M.; Wu, L.; Ren, J.; Qu, X. *J. Med. Chem.* **2012**, *55*, 9146.

2. (a) Sun, Y.; Jiang, H.; Wu, W.; Zeng, W.; Wu, X.; *Org. Lett.* **2013**, *15*, 1598. (b) Yao, S.; Schafer-Hales, K. J.; Belfield, K. D.; *Org. Lett.* **2007**, *9*, 5645. (c) Meazza, M.; Tur, F.; Hammer, N.; Jφrgensen, K. A. *Angew. Chem. Int. Ed.* **2017**, *56*, 1634. (d) Penteado, F.; Vieira, M. M.; Perin, G.; Alves, D.; Jacob, R. G.; Santib, C.; Lenardão, E. J. *Green Chem*, **2016**, *18*, 6675. (e) Inamoto, K.; Hasegawa, C.; Kawasaki, J.; Hiroya, K.; Doi, T. *Adv. Synth. Catal*. **2010**, *352*, 2643.
3. Mortimer, C. G.; Wells, G.; Crochard, J. P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179.
4. Singh, M.; Singh, S. K.; Gangwar, M.; Nath, G.; Singh, S. K. *RSC Adv*. **2014**, *4*, 19013.
5. Weekes, A. A.; Westwell, A. D. *Curr. Med. Chem*. **2009**, *16*, 2430.
6. (a) Bradshaw, T. D.; Westwell, A. D. *Curr. Med. Chem.* **2004**, *11*, 1241. (b) Chen, Y. X.; Quian, L.; Zuang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330. (c) Jin, H. L.; Cheng, T. X.; Chen, J. X. *Appl. Organometal. Chem*. **2011**, *25*, 238.
7. (a) Neres, J.; Brewer, M. L.; Ratier, L.; Botti, H.; Buschiazzo, A.; Edwards, P. N.; Mortenson, P. N.; Charlton, M. H.; Alzari, P. M.; Frasch, A. C.; Bryce, R. A.; Douglas, K. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 589. (b) Nguyen, T. B.; Pasturaud, K.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2015**, *17*, 2562. (c) Liu, Y. F.; Guo, X.; Tang, D.; Wang, J.; Wu, P.; Han, J. W.; Chen, B. H. *Chinese J. Chem.*, **2017**, *35*, 1222.
8. (a) Wang, X.; Sarris, K.; Kage, K. *J. Med. Chem*. **2009**, *52*, 170. (b) Guntreddi, T.; Vanjari, R.; Singh, K. N. *Org. Lett.* **2015**, *17*, 976. (c) Wu, J.; Xie, Y. J.; Chen, X. G.; Deng, G. J. *Adv. Synth. Catal.* **2016**, *358*, 3206.
9. (a) Rana, A.; Siddiqui, N.; Khan, S. A.; Haque, S. E.; Bhat, M. A. *Eur. J. Med. Chem.* **2008**, *43*, 1114. (b) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (c) Ma, X. T.; Yu, L.; Su, C. L.; Yang, Y. Q.; Li, H.; Xu, Q. *Adv. Synth. Catal*. **2017**, *359*, 1649.
10. (a) Tale, R. H. *Org. Lett.* **2002**, *4*, 1641. (b) Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835. (c) Yoo, W. J.; Yuan, H.; Miyamura, H.; Kobayashi, S. *Adv. Synth. Catal*. **2011**, *353*, 3085. (d) Bahrami, K.; Khodaei, M.; Nejati, A. *Green Chem.* **2010**, *12*, 1237. (e) Chhabra, M.; Sinha, S.; Banerjee, S.; Paira, P. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 213. (f) Sharma, H.; Singh, N.; Jang, D. O. *Green Chem.* **2014**, *16*, 4922.
11. (a) Yang, Z.; Hu, R. H.; Li, X. T.; Wang, X.; Gu, R.; Han, S. Q. *Tetrahedron Lett.* **2017**, *58*, 2366. (b) Deng, H.; Li, Z.; Ke, F.; Zhou, X. *Chemistry* **2012**, *18*, 4840. (c) Duan, F. F.; Song, S. Q.; Xu, R. S. *Chem. Commun.* **2017**, *53*, 2737. (d) Huang, Y. B.; Yan, D. H.; Wang, X; Zhou, P. Q.; Wu, W. Q.; Jiang, H. F. *Chem. Commun.* **2018**.
12. (a) Cheng, Y.; Peng, Q.; Fan, W.; Li, P. *J. Org. Chem.* **2014**, *79*, 5812. (b) Feng, E. G.; Huang, H.; Zhou, Y.; Ye, D. J.; Jiang, H. L.; Liu, H. *J. Comb. Chem.* **2010**, *12*, 422. (c) Alla, S. K.; Sadhu, P.; Punniyamurthy, T. *J. Org. Chem.* **2014**, *79*, 7502. (d) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261; (e) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (f) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147.
13. Che, X.; Jiang, J.; Xiao, F.; Huang, H.; Deng, G. J. *Org. Lett.* **2017**, *19*, 4576.
14. (a) Che, X.; Jiang, J.; Xiao, F.; Huang, H.; Deng, G. J. *Org. Lett.* **2017**, *19*, 4576. (b) Liao, Y;. Qi, H.; Chen, S.; Jiang, P.; Zhou, W.; Deng, G. J. *Org. Lett.* **2012**, *14*, 6004. (c) Ravi, O.; Shaikh, A.; Upare, A.; Singarapu, K. K.; Bathula, S. R. *J. Org. Chem.* **2017**, *82*, 4422. (d) Li, G.; Xie, H.; Chen, J.; Guo, Y.; Deng, G. J. *Green Chem.* **2017**, *19*, 4043. (e) Zhu, X. M.; Yang, Y. Z.; Xiao, G. H.; Song, J. X.; Liang, Y.; Deng, G. B. *Chem. Commun*. **2017**, *53*, 11917; (f) Deng, J. C.; Zhuang, S. B.; Liu, Q. Z.; Lin, Z. W.; Su, Y. L.; Chen, J. H.; Tang, R. Y. *RSC Adv*. **2017**, *7*, 54013.