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An expeditious ultrasound-initiated green synthesis of 1,2,4-thiadiazoles in water

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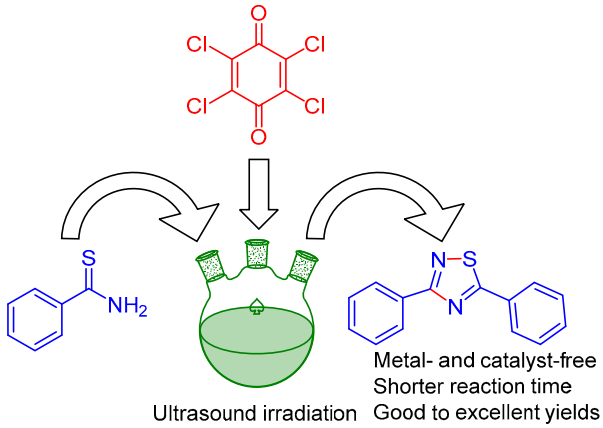


A convenient, environmentally benign, metal- and catalyst-free protocol has been developed for the conversion of thioamides to the corresponding 1,2,4-thiadiazole derivatives with chloranil under ultrasound irradiation in water at room temperature. This paper describes a general procedure for the synthesis of different 1,2,4-thiadiazoles in excellent yield in short reaction time *via* sonochemistry.

Keywords: aqueous medium, heterocycles, metal- and catalyst-free, one-pot synthesis, oxidative coupling, ultrasound irradiation.

The 1,2,4-thiadiazole is a priviledged heterocyclic scaffold because of its various biological activities and associated therapeutic applications. Despite these facts, the only commercially available 1,2,4-thiadiazole medication is antibiotic cefozopran,[1,2] but 1,2,4-thiadiazoles have a number of biological activities (Fig. 1).[3–10] 1,2,4-Thiadiazoles are privileged building blocks in the synthesis of many bioactive molecules for the treatment of human leukemia,[11] as cathepsin B inhibitors,[12] allosteric modulators,[13] factor XIIIa inhibitors,[14] non-ATP competitive glycogen synthase kinase 3 inhibitors,[15] dual 5-lipoxygenase and cyclooxygenase inhibitors.[16] Some of 1,2,4-thiadiazoles have superb thiol-catching properties[17] and show pronounced muscarinic[18] and cardioprotective properties.[19,20] They have been observed to have useful insecticidal, herbicidal, and fungicidal properties.[21]

In order to synthesize 1,2,4-thiadiazole derivatives under environmentally benign conditions, the combination of water and ultrasound technique has been applied. In this communication, metal- and catalyst-free dimerization of primary thioamide derivatives with chloranil in aqueous

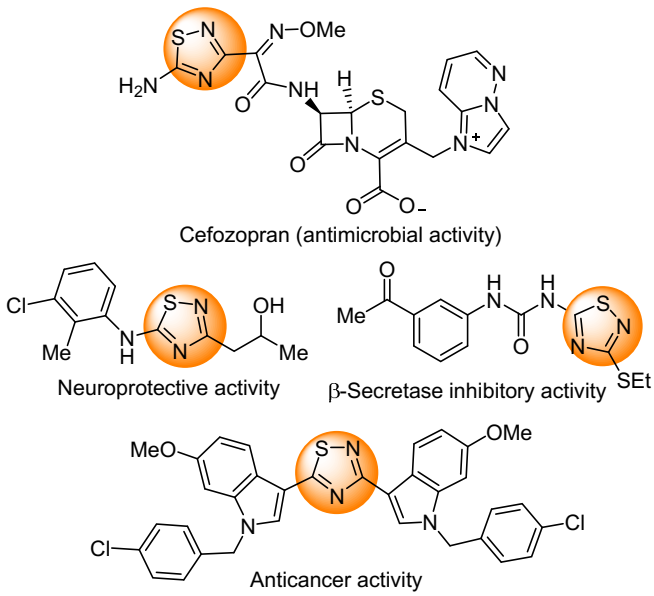


Figure 1. Biologically active 1,2,4-thiadiazoles.

medium under ultrasound irradiation is being reported for the first time.

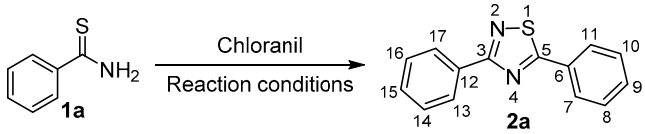
The reaction conditions were first optimized using equimolar amounts of thiobenzamide (**1a**) as a test substrate and chloranil. The reaction was carried out in H_2O while stirring at room temperature for 3 h and yielded only 20% of product **2a**. In the second run, the reaction mixture was refluxed for 3 h which gave low yield of the desired product (Table 1, entry 2). Further on heating the reaction mixture by conventional method at 50, 80, and 120°C under solvent-free conditions gave the desired product in 50–70% yield after 3 h (Table 1, entries 3–5). In order to improve the yield of the product, the reaction was performed under ultrasound irradiation at room temperature in H_2O. To our surprise, 95% yield was obtained in 3 min.

To investigate the effect of solvents, the reaction was carried out in different polar and nonpolar solvents. Although the desired product was obtained in both polar (H_2O, MeCN, THF, EtOH, 1,4-dioxane, $CHCl_3$, CH_2Cl_2, DCE, DMSO) and nonpolar solvents (PhH, PhMe), H_2O was found to be the best solvent for the dimerization of thiobenzamide with chloranil under ultrasound irradiation.

The formation of product **2a** was confirmed by spectral data. ^{1}H NMR spectrum shows doublets at 8.40 (2H, H-13,17), 8.06 ppm (2H, H-7,11), and multiplet at 7.56–7.48 ppm (6H, H-8,9,10,14,15,16).[22] ^{13}C NMR spectrum shows the characteristic peaks at 188.3 (C-3) and 174.0 ppm (C-5) which correspond to the 1,2,4-thiadiazole ring carbon atoms along with other aromatic carbon atoms at 133.1 (C-12); 132.1 (C-15); 130.9 (C-6); 130.5 (C-9); 129.4 (C-14,16); 128.9 (C-8,10); 128.5 (C-13,17); 127.7 ppm (C-7,11).

With optimized reaction conditions, the applicability of this methodology was examined with the different primary thiobenzamide derivatives, and the results are summarized in Table 2. These reaction conditions with chloranil as oxidant show extensive functional group tolerance and prove to be a general method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles. It was found that the reaction proceeds smoothly and provides an excellent yield of desired product within short period of time using thiobenzamide with electron-donating or electron-withdrawing substituent. Interestingly, thiobenzamide bearing halogen substituents such as chlorine and fluorine could also be reacted in efficient manner to obtain the desired products in good yield. Likewise, naphthalene-1-carbothioamide (**1i**) was successfully transferred into 3,5-di(naphthalen-1-yl)-

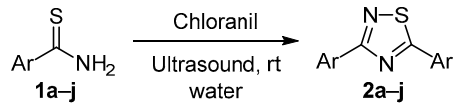
Table 1. Effect of reaction conditions on the yield of model compound **2a***

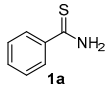
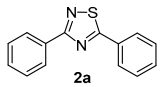
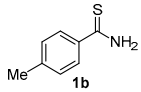
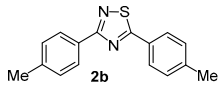
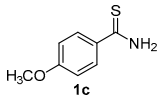
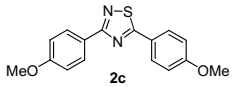
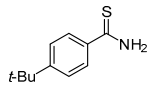
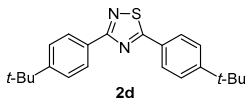
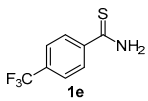
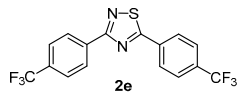
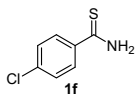
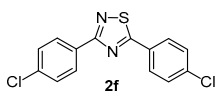
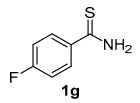
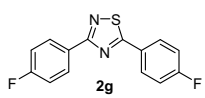
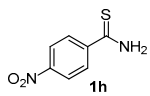
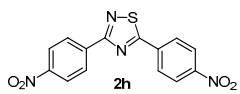
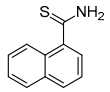
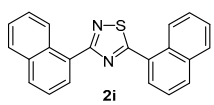
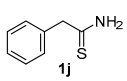
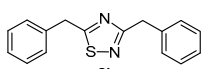


Entry	Reaction conditions	Solvent	Time	Yield**, %
1	Stirring, rt	H_2O	3 h	20
2	Stirring, reflux	H_2O	3 h	40
3	50°C	Solvent-free	3 h	50
4	80°C	Solvent-free	3 h	70
5	120°C	Solvent-free	3 h	70
6	**Ultrasound (US), rt**	**H_2O**	**3 min**	**95**
7	US, rt	MeCN	5 min	75
8	US, rt	THF	10 min	70
9	US, rt	EtOH	15 min	85
10	US, rt	1,4-Dioxane	12 min	65
11	US, rt	$CHCl_3$	8 min	78
12	US, rt	CH_2Cl_2	9 min	79
13	US, rt	DCE	7 min	82
14	US, rt	DMSO	10 min	78
15	US, rt	PhH	12 min	71
16	US, rt	PhMe	15 min	75

* Thiobenzamide (1.0 mmol) and chloranil (1.1 mmol), solvent (3 ml).
** Isolated yield.

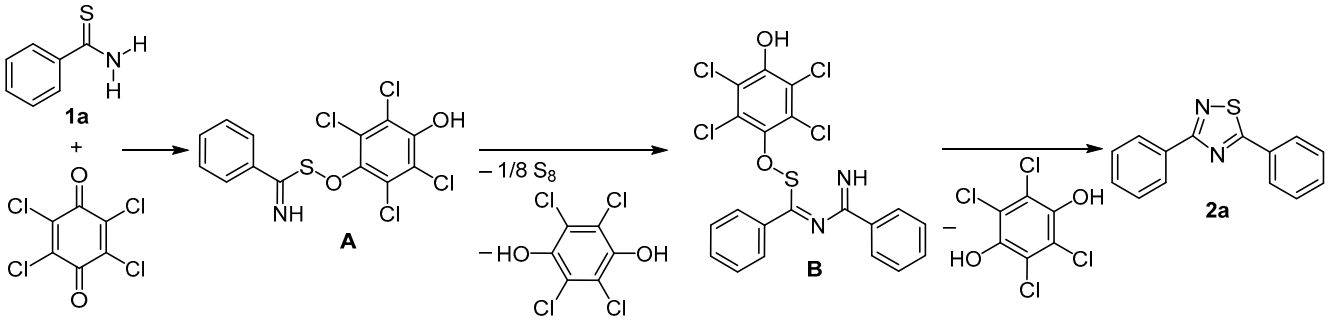
Table 2. Synthesis of thiadiazole derivatives **2a**–**j***



Entry	Substrate	Product	Time, min	Yield**, %
1			3	95
2			6	95
3			5	94
4			8	89
5			6	91
6			7	88
7			6	90
8			5	94
9			8	87
10			5	87

* Reaction conditions: substrate (1.0 mmol) and chloranil (1.1 mmol) were irradiated with ultrasound in H_2O (3 ml) at room temperature.
** Isolated yield.

Scheme 1. Proposed mechanism for the chloranil-mediated condensation of thiobenzamide.



1,2,4-thiadiazole **2i** in 87% yield (Table 2, entry 9) within few minutes. The results established that no significant electronic and steric effects of the substituents on the phenyl ring were observed. This reaction also gave good yield for 3,5-dibenzyl-1,2,4-thiadiazole **2j** (Table 2, entry 10). The corresponding products were obtained in good yield which show the wide scope of current methodology.

A control experiment was performed using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as radical trapping agent and it was observed that TEMPO does not quench the reaction. This shows that reaction does not proceed *via* radical intermediate and a nucleophilic pathway has been proposed. On the basis of product analysis, a mechanism for the chloranil-assisted dimerization of primary thiobenzamide is proposed in Scheme 1. Oxidative addition of thioamide **1a** to chloranil leads to intermediate **A**, which dimerizes forming intermediate **B**. Product **2a** is formed after cyclization of intermediate **B**.

In summary, we have developed a highly efficient and rapid conversion of primary thiobenzamides by chloranil in aqueous solution to the corresponding 1,2,4-thiadiazoles under ultrasonic irradiation. Ultrasound-induced dimerization of thiobenzamides using chloranil in water makes a highly efficient promoter system for the synthesis of 1,2,4-thiadiazoles in excellent yield in short reaction time. It is a valuable addition to the prevailing methods available for the synthesis of substituted 3,5-diaryl-1,2,4-thiadiazoles.

Experimental

IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500 and 125 MHz, respectively) using $CDCl_3$ as a solvent and TMS as internal standard. High-resolution mass spectra were measured on a Waters Quattro Micro mass spectrometer. Melting points were measured with a Stuart melting point apparatus SMP10. Ultrasonic irradiation was performed using a Sonics & Materials Vibra Cell Ultrasonic Processor VCX750 with a fixed power of 750 W, 20% amplitude, and a tapered micro tip was used as ultrasonic probe operating at a frequency of 20 kHz. Thin-layer chromatography was performed using pre-coated TLC silica gel 60 F_{254} plates from Merck. TLC plates were visualized by exposure to UV light with 254 nm wavelength lamp or in I_2 chamber. The column chromatography was performed on silica gel (60–120 mesh) using a mixture of EtOAc and hexane as an eluent. All the solvents and chemicals were purchased from commercial sources and were used without any further purification.

Synthesis of 1,2,4-thiadiazoles 2a–j (General method). A flask was charged with primary thiobenzamide **1a**–**j** (1.0 mmol) and chloranil (270 mg, 1.1 mmol) in H_2O (3 ml). The reaction mixture was irradiated with ultrasound at room temperature for appropriate time. The progress of reaction was monitored with TLC. After completion of the reaction, solvent was concentrated under reduced pressure, and the obtained residue was subjected to silica gel column chromatography purification (EtOAc–hexane) to obtain the desired products.

3,5-Diphenyl-1,2,4-thiadiazole (2a). Yield 226 mg (95%), white solid, mp 91–92°C (mp 90°C[22,23]), R_f 0.59 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 3050, 2922, 1599, 1464, 1407, 1315, 1270, 1171, 751. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.40 (2H, d, *J* = 8.1, H Ar); 8.06 (2H, d, *J* = 9.4, H Ar); 7.56–7.48 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 188.3; 174.0; 133.1; 132.1; 130.9; 130.5; 129.4; 128.9; 128.5; 127.7. Found, *m*/*z*: 239.0636 $[M+H]^+$. $C_{14}H_{11}N_2S$. Calculated, *m*/*z*: 239.0637.

3,5-Bis(4-methylphenyl)-1,2,4-thiadiazole (2b). Yield 253 mg (95%), white solid, mp 135°C (mp 135–137°C[23]), R_f 0.55 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2962, 1402, 1317, 1011, 842, 735. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.27 (2H, d, *J* = 8.1, H Ar); 7.94 (2H, d, *J* = 8.0, H Ar); 7.36–7.29 (4H, m, H Ar); 2.48–2.39 (6H, m, 2CH_3). ^{13}C NMR spectrum, δ, ppm: 188.1; 173.9; 142.6; 140.6; 130.5; 130.0; 129.5; 128.4; 128.3; 127.6; 21.8; 21.7. Found, *m*/*z*: 267.0948 $[M+H]^+$. $C_{16}H_{15}N_2S$ Calculated, *m*/*z*: 267.0950.

3,5-Bis(4-methoxyphenyl)-1,2,4-thiadiazole (2c). Yield 280 mg (94%), yellow solid, mp 139–140°C (mp 138–140°C[24]), R_f 0.60 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2990, 2872, 1632, 1443, 1255, 1295, 1032, 835. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.32 (2H, d, *J* = 8.9, H Ar); 7.98 (2H, d, *J* = 8.8, H Ar); 7.02–6.99 (4H, m, H Ar); 3.91–3.86 (6H, m, 2OCH_3). ^{13}C NMR spectrum, δ, ppm: 187.5; 173.5; 162.6; 161.4; 130.0; 129.3; 126.2; 123.9; 114.7; 114.1; 55.7; 55.5. Found, *m*/*z*: 299.0845 $[M+H]^+$. $C_{16}H_{15}N_2O_2S$. Calculated, *m*/*z*: 299.0849.

3,5-Bis(4-*tert*-butylphenyl)-1,2,4-thiadiazole (2d). Yield 312 mg (89%), white solid, mp 91–92°C (mp 91–93°C[24]), R_f 0.52 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2974, 2905, 1724, 1609, 1472, 1495, 1323, 1134, 835. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.32 (1H, d, *J* = 8.4, H Ar); 7.98 (1H, d, *J* = 8.3, H Ar); 7.59 (2H, d, *J* = 8.4, H Ar); 7.55–7.52 (2H, m, H Ar); 7.48 (2H, d, *J* = 8.4, H Ar); 1.38 (9H, s, $C(CH_3)_3$); 1.33 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 188.0; 174.0; 155.7; 153.7; 130.5; 128.3; 128.3; 127.5; 126.3; 125.8; 35.3; 35.0; 31.4; 31.3. Found, *m*/*z*: 351.1887 $[M+H]^+$. $C_{22}H_{27}N_2S$. Calculated, *m*/*z*: 351.1889.

3,5-Bis[4-(trifluoromethyl)phenyl]-1,2,4-thiadiazole (2e). Yield 340 mg (91%), white solid, mp 82–83°C (mp 81°C[23]), R_f 0.56 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2927, 1742, 1469, 1319, 1268, 1128, 1063, 894. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.51 (2H, d, *J* = 8.0, H Ar); 8.18 (2H, d, *J* = 8.0, H Ar); 7.83–7.75 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J,* Hz): 187.0; 172.7; 135.6; 133.7 (q, *J* = 32.7); 132.46; 132.2 (q, *J* = 32.4); 128.7; 127.9; 126.4 (q, *J* = 3.7); 125.8 (q, *J* = 3.7); 124.0 (q, *J* = 271.0); 123.7 (q, *J* = 271.0). Found, *m*/*z*: 375.0412 $[M+H]^+$. $C_{16}H_9F_6N_2S$. Calculated, *m*/*z*: 375.0385.

3,5-Bis(4-chlorophenyl)-1,2,4-thiadiazole (2f). Yield 270 mg (88%), white solid, mp 161–162°C (mp 159.7–160.8°C[25]), R_f 0.55 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2925, 1741, 1464, 1424, 1091, 1013, 829, 738. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.31 (2H, d, *J* = 8.6, H Ar); 7.98 (2H, d, *J* = 8.6, H Ar); 7.52–7.46 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 187.2; 173.0; 138.3; 136.8; 131.3; 129.8; 129.8; 129.2; 129.1; 128.9. Found, *m*/*z*: 306.9856 $[M+H]^+$. $C_{14}H_9Cl_2N_2S$. Calculated, *m*/*z*: 306.9858.

3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole (2g). Yield 246 mg (90%), white solid, mp 186–187°C (mp 188.1–188.6°C[25]), R_f 0.54 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2926, 2855, 1741, 1547, 1514, 1463, 1226, 835, 739. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.37 (2H, dd, *J* = 8.9, *J* = 5.5, H Ar); 8.04 (2H, dd, *J* = 8.8, *J* = 5.2, H Ar); 7.23–7.16 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 187.1; 172.9; 165.1 (d, *J* = 252.0); 164.4 (d, *J* = 249.0); 130.6 (d, *J* = 8.6); 129.8 (d, *J* = 8.8); 129.3 (d, *J* = 3.1); 127.2 (d, *J* = 3.3); 116.7 (d, *J* = 22.1); 115.9 (d, *J* = 21.8). Found, *m*/*z*: 275.0448 $[M+H]^+$. $C_{14}H_9F_2N_2S$. Calculated, *m*/*z*: 275.0449.

3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2h). Yield 309 mg (94%), yellow solid, mp 200–201°C (mp 201–203°C[24]), R_f 0.54 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 2924, 2853, 1602, 1536, 1470, 1351, 851, 716. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.58 (2H, d, *J* = 8.9, H Ar); 8.43–8.37 (4H, m, H Ar); 8.25 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum, δ, ppm: 186.5; 172.3; 150.0; 149.3; 137.8; 135.6; 129.5; 128.6; 124.9; 124.3.

3,5-Di(naphthalen-1-yl)-1,2,4-thiadiazole (2i). Yield 294 mg (87%) white solid, mp 119–120°C (mp 120–121°C[25]), R_f 0.52 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 3040, 2925, 1722, 1476, 1384, 1241, 1049, 795, 76. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.22 (1H, d, *J* = 8.5, H Ar); 8.96 (1H, d, *J* = 8.1, H Ar); 8.50 (1H, dd, *J* = 7.2, *J* = 1.2, H Ar); 8.09–8.05 (2H, m, H Ar); 8.03 (1H, d, *J* = 8.2, H Ar); 7.99–7.95 (2H, m, H Ar); 7.69–7.57 (6H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 187.1; 174.1; 134.3; 134.2; 132.4; 131.3; 131.2; 130.3; 130.2; 130.1; 129.4; 128.8; 128.7; 128.2; 127.9; 127.4; 126.9; 126.5; 126.2; 125.6; 125.3. Found, *m*/*z*: 339.0948 $[M+H]^+$. $C_{22}H_{15}N_2S$. Calculated, *m*/*z*: 339.0950.

3,5-Dibenzyl-1,2,4-thiadiazole (2j). Yield 231 mg (87%), yellow oil, R_f 0.63 (hexane–EtOAc, 9:1). IR spectrum, ν, cm^{-1}: 3089, 1590, 1398, 1032, 832. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.50 (2H, d, *J* = 7.2, H Ar); 7.72–7.66 (1H, m, H Ar); 7.57–7.53 (2H, m, H Ar); 7.43–7.33 (4H, m, H Ar); 7.29–7.25 (1H, m, H Ar); 4.47 (4H, s, 2CH$_2$). ^{13}C NMR spectrum, δ, ppm: 187.3; 177.0; 136.9; 134.8; 134.3; 131.3; 129.3; 128.9; 128.8; 127.1; 39.7; 37.6. Found, *m*/*z*: 267.0954 $[M+H]^+$. $C_{16}H_{15}N_2S$. Calculated, *m*/*z*: 267.0950.

Supplementary information file containing HRMS, ^{1}H and ^{13}C NMR spectra of products **2a**–**j** is available at the journal website at http://link.springer.com/journal/10593.

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