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Aqueous $NaHSO_4$ catalyzed regioselective and versatile synthesis of 2-thiazolamines

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Abstract The green acidic catalyst $NaHSO_4$ was used for the synthesis of some novel substituted 2-thiazolamines in water under mild conditions in high regioselectivity.

Keywords Heterocycles; Water; $NaHSO_4$; Regioselectivity; Green catalysis.

Introduction

Thiazoles represent a very important class of heterocycles. In Nature, the thiazolium ion is the chemically active center in the coenzyme derived from vitamin B (thiamin). A large number of thiazoles obtained from microbial and marine origins exhibit important biological effects, such as antitumor, antifungal, antibiotic, and antiviral activities [1]. Also, thiazoles have found broad application in the discovery and development of drugs used for the treatment of allergies [2], hypertension [3], and inflammation [4]. A novel field in which this building block has been utilized is thiazolium-based ionic liquids [5]. In view of these applications chemists are encouraged to find new versatile and efficient methodologies toward the synthesis of thiazoles.

The most widely used and classical synthesis approach to thiazoles involves the reaction of an α-halocarbonyl compound with a reactant bearing an N–C–S fragment such as thioamides, thioureas, or dithiocarbamic acid derivatives, which is known as the *Hantzsch* process [6]. A plethora of reagents and conditions have been used as a modification to the general reaction outlined by *Hantzsch*, such as solid supported thiazole synthesis [7], use of a heterogeneous silica chloride catalyst [8], aqueous phase synthesis in the presence of cyclodextrin [9], use of ammonium-12-molybdophosphate in methanol [10], microwave promoted synthesis in ethanol [11], *via* *Lawesson*'s reagent mediated cyclization [12], and the use of α-halocarbonyl substitutes [13].

Green chemistry principles have gained their position in the heart of chemistry research fields because of economic and health related aspects [14]. Recently, designing new methodologies based on greener solvents and catalysts are becoming very popular among chemists. Water as the prototypical green solvent has received considerable attention because it is not only inexpensive and environmentally friendly but also has unique antihydrophobic effects as discovered by *Breslow* and coworkers at the beginning of the 1980s [15]. When organic compounds are dispersed and suspended in water, their distinct insolubility in this medium causes them to associate, diminish their interface with water molecules, and increase the reaction rate [16]. So, the application of water as the reaction medium has been intensively expanded in the past two decades [17].

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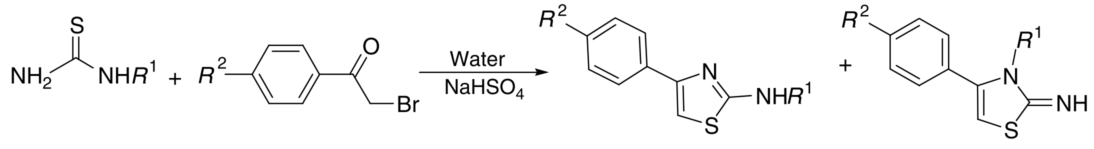


1 **2** **3** **4**

Scheme 1

Sodium hydrogen sulfate ($NaHSO_4$) has been utilized as a safe and efficient catalyst in a number of transformations and syntheses [18]. Some of these applications include selective removal of *N-Boc* protecting groups from protected amines [19a], synthesis of bis- and tris(indolylmethanes) [19b], mild nitrosation of secondary amines [19c], and 1,2-dihydroquinoline oxidation [19d]. This catalyst also avoids problems such as corrosion and harmfulness common to other protic acids, and can be handled easily for use in synthesis purposes.

As a part of our ongoing research program towards development of new and rapid methodologies for the synthesis of heterocyclic compounds [20], we present a new, convenient, efficient, and easy methodology for the synthesis of substituted 2-thiazolamines. Our initial aim was to overcome the limitations and drawbacks of reported methods. Therefore, we have come up with a rapid, efficient, and environmentally benign route to prepare these useful heterocycles, using aqueous $NaHSO_4$ as a safe, inexpensive, and efficient catalyst to promote the reaction.

Results and discussion

In this work, the *Hantzsch* process with new conditions is presented in which sodium hydrogen sulfate (30 mol%) is used in a small amount of water to catalyze the reaction (Scheme 1).

To evaluate the scope and limitations of this new methodology, various substituted phenacyl bromides with electron donating and withdrawing substituents were used to react with substituted thioureas (R^1 = H, *Me*, *Ph*; R^2 = H, O*Me*, Br, NO_2) (Table 1, products **3a**–**3k**). To optimize the reaction condition and find the optimal amount of catalyst, the process was performed under various conditions (Table 2).

Table 1 Aqueous $NaHSO_4$ catalyzed synthesis of 2-thiazolamines **3a**–**3k**

Product **3**	R^1	R^2	Time/min	Yield/%*
a	H	H	25	quantitative
b	H	O*Me*	30	81
c	H	Br	25	89
d	H	NO_2	10	quantitative
e	*Me*	H	30	82
f	*Me*	Br	45	85
g	*Me*	O*Me*	30	93
h	*Me*	NO_2	20	90
i	*Ph*	H	35	90
j	*Ph*	NO_2	5	quantitative
k	*Ph*	O*Me*	55	95

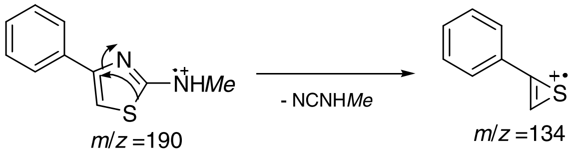
* Isolated yield

Table 2 Screening of the amount of solvent and catalyst in the synthesis of 4-phenyl-2-thiazolamine (**3a**)

Run no.	Solvent	Catalyst	Time/min	Yield/%*
1	H_2O	$NaHSO_4$ (10%)	120	90
2	H_2O	$NaHSO_4$ (20%)	90	90
3	H_2O	$NaHSO_4$ (30%)	25	quantitative
4	*Et*OH/H_2O (1:1)	$NaHSO_4$ (30%)	90	80
5	*Et*OH/H_2O (3:1)	$NaHSO_4$ (30%)	50	75
6	*Et*OH	$NaHSO_4$ (30%)	210	80

* Isolated yield

The most interesting piece of information in Table 2 is that upon going from aqueous ethanol to pure water as solvent, both the rate and the yield of reaction are improving. As indicated in Scheme 1, in the case of *N*-methyl- and *N*-phenylthiourea formation of both products **3** and **4** is possible. A previous study [21] has shown that in the presence of 10 *M* HCl in *Et*OH (1/2 *v/v*) the regioisomer **4** was formed, while changing the acidic condition led to a mixture of isomers **3** and **4**. It is interesting to point out that in the present study, running the reaction in aqueous sodium hydrogen sulfate at room temperature results in the formation of product **3** (R^1 = *Me*, *Ph*, R^2 = H) as the only product. The fragmentation pattern in mass spectra for compounds **3e**–**3k** is in agreement with the general pattern accepted for aro-



Scheme 2

matic thiazole ring substituents **3** and not for a dihydrothiazole **4**. For example, the peak with $m/z = 134$ ($M^+ - 56$) is due to the formation of 2-phenylthiiranium ion derived from the molecular ion by the loss of the NCNH*Me* fragment (Scheme 2). This is in accordance with the general pattern of fragmentation, which has been proposed for the 4-phenylthiazole ring system [22].

The reusability of the solution of 30 mol% $NaHSO_4$ in water was tested and the comparative results are shown in Table 3. When 30 mol% $NaHSO_4$ in 2 cm^3 water were used for each mmol of reactants, the products precipitated and could be easily isolated *via* simple filtration.

We then attempted to compare the reusability and regioselectivity observed for $NaHSO_4$ with other protic acids (H_2SO_4, HCl, HNO_3, HBr, and Na_2HPO_4). The results are presented in Table 4. In all cases the *Hantzsch* reaction was run with 30 mol% of each catalyst at room temperature, in which two products were detected in the reaction mixture by TLC and no remarkable regioselectivity was observed for most acids (entries 2–5, Table 4). Furthermore, the products did not precipitate during the reaction in contrast to what was seen with $NaHSO_4$ and therefore we were not able to reuse the reaction mixture (the catalyst). In these cases, we had to neutralize the reaction mixture in order to obtain the desired products. The results obtained for HCl (Table 4, entry 1) are in accordance to a previous study [21]. Aqueous $NaHSO_4$ is the only protic acid catalyst which is able to promote the convenient synthesis of 2-thiazolamines and its solution in water can be recovered easily and reused.

In conclusion, we reported a new, eco-friendly, and reusable catalytic system for the synthesis of 2-thiazolamines. Simple workup, easy recycling, reusability of the catalytic system, and the formation of some new and regioselective derivatives of 2-thiazolamines are the most important aspects of this process.

Table 3 Reusability of aqueous $NaHSO_4$ in synthesis of 4-phenyl-2-thiazolamine (**3a**)

Run no.	Time/min	Yield/%*
1	25	quantitative
2	35	95
3	40	91
4	60	90
5	90	75

* Isolated yield

Table 4 Comparison of regioselectivity for *Hantzsch* reaction in water for formation of product **3e** using some common protic acids

Entry	Catalyst*	Time/ min	Product **3e**/%**	Product **4e**/%**
1	HCl	15	10	80
2	H_2SO_4	25	30	60
3	HNO_3	35	50	50
4	HBr	15	50	50
5	NaH_2PO_4	60	50	50
6	$NaHSO_4$	30	82	–

* 30% of catalyst relative to mol of phenacyl bromide
** Isolated product

Experimental

Melting points were recorded on a Büchi B-540 apparatus. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ^1H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using *TMS* as an internal standard. Chemical shifts (δ) are reported relative to *TMS*, and coupling constants (J) are reported in Hz. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer with 70 eV ionization potential. Elemental analyses of new compounds were performed with a Vario EL III 0 Serial No. 11024054 instrument and their results agreed favorably with calculated values.

General experimental procedure for the synthesis of 2-thiazolamines in aqueous $NaHSO_4$

Thiourea or its *N*-methyl and *N*-phenyl derivatives (1 mmol) was dissolved in 2 cm^3 water containing 36 mg $NaHSO_4$ (30 mol%) and 1 mmol substituted phenacyl bromide was added to this solution. The mixture was stirred at room temperature and monitored by TLC (ethyl acetate:petroleum ether 1:3). After completion of the reaction, the precipitated solids which formed (2-thiazolamine hydrobromide) were collected by filtration and were then neutralized with 20% $NaHCO_3$ solution to afford the free base. The filtrate was reused five times. The products were further purified by recrystallization from a mixture of ethanol/water and washed with water to afford pure products.

N-Methyl-4-phenyl-2-thiazolamine (**3e**, $C_{10}H_{10}N_2S$)
White crystals, 0.155 g (82%), mp 134–136°C; IR (KBr): $\bar{\nu} =$ 3219, 3106, 3003, 2916, 1586, 1456, 1376 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 2.88$ (d, $J = 4.8$ Hz, 3H), 7.02 (s, 1H), 7.25 (t, $J = 4.2$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 2H), 7.55 (q, $J = 4.8$ Hz, 1H), 7.85 (d, $J = 4.2$, 2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 31.0$ ($NHCH_3$), 100.7, 125.6, 127.2, 128.4, 134.9, 150.2, 169.3 (N–C–S fragment in thiazole ring) ppm; MS (EI, 70 eV): m/z (%) = 190 (100) [M$^+$], 162 (33), 134 (40), 102 (20), 45 (10).

N-Methyl-4-bromophenyl-2-thiazolamine
(**3f**, $C_{10}H_9BrN_2S$)
White crystals, 0.229 g (85%), mp 146–148°C; IR (KBr): $\bar{\nu} =$ 3250, 3111, 3008, 2931, 1576, 1486, 1396 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 2.86$ (d, $J = 4.8$ Hz, 3H), 7.12 (s, 1H), 7.52 (t, $J = 2.1$ Hz, 1H), 7.55 (t, $J = 1.8$ Hz, 1H), 7.58 (q, $J = 5.1$ Hz, 1H), 7.76 (t, $J = 5.1$, 1H), 7.79 (t, $J = 5.1$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 30.9$ ($NHCH_3$), 101.7, 120.1, 127.6, 131.3 (C–Br phenyl ring), 134.1, 148.9 (C–N thiazole ring), 169.4 (N–C–S fragment in thiazole ring) ppm; MS (EI, 70 eV): m/z (%) = 270 (100) [M$^+$], 272 (98) [M$^+$ + 2], 240 (40), 214 (15), 182 (20), 133 (30), 89 (50), 45 (10).

N-Methyl-4-methoxyphenyl-2-thiazolamine
(**3g**, $C_{11}H_{12}N_2OS$)
White crystals, 0.204 g (93%), mp 126–128°C; IR (KBr): $\bar{\nu} = 3266$, 3101, 3004, 2921, 1581, 1477, 1380 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 2.85$ (d, $J = 4.8$ Hz, 3H), 3.76 (s, 3H), 6.85 (s, 1H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.49 (q, $J = 4.8$ Hz, 1H), 7.75 (d, $J = 8.7$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 31.0$ ($NHCH_3$), 55.0 (O*Me*), 98.6, 113.8, 126.9, 127.8, 150.0 (C–O*Me* in phenyl ring), 158.6 (C–N thiazole ring), 169.3 (N–C–S fragment in thiazole ring) ppm; MS (EI, 70 eV): m/z (%) = 220 (100) [M$^+$], 192 (25), 149 (50), 121 (30), 77 (20), 45(20).

N-Methyl-4-nitrophenyl-2-thiazolamine (**3h**, $C_{10}H_9N_3O_2S$)
Light orange crystalline powder, 0.234 g (90), mp 214–217°C; IR (KBr): $\bar{\nu} = 3255$, 3111, 3003, 2916, 1601, 1498, 1378, 1335 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 2.89$ (d, $J = 4.5$ Hz, 3H), 7.43 (s, 1H), 7.71 (d, $J = 4.5$ Hz, 1H), 8.06 (dt, $J = 8.7$ Hz, $J = 2.1$, 2H), 8.22 (dt, $J = 8.7$ Hz, $J = 2.1$, 2H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 30.9$ ($NHCH_3$), 105.9, 123.9, 126.3, 140.8 (C–NO_2), 146.0, 148.1, 169.5 (N–C–S fragment in thiazole ring) ppm; MS (EI, 70 eV): m/z (%) = 235 (100) [M$^+$], 207 (70), 174 (35), 121 (20), 89 (50), 30 (25).

N-Phenyl-4-phenyl-2-thiazolamine (**3i**, $C_{15}H_{12}N_2S$)
White crystalline powder, 0.225 g (90%), mp 142°C (Ref. [23] 134–136°C); IR (KBr): $\bar{\nu} = 3250$, 3121, 3060, 2916, 1607 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 6.97$ (t, $J = 7.5$ Hz, 1H), 7.28–7.44 (m, 6H), 7.72 (d, $J = 8.1$ Hz, 2H), 7.90 (d, $J = 7.2$ Hz, 2H), 10.38 (s, 1H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 103.0$, 117.2, 121.6, 125.8, 127.8, 128.8, 129.2, 134.3, 141.1, 149.6, 163.4 ppm.

N-Phenyl-4-nitrophenyl-2-thiazolamine (**3j**, $C_{15}H_{11}N_3O_2S$)
Light orange crystalline powder, 0.295 g (quantitative), mp 226–229°C; IR (KBr): $\bar{\nu} = 3288$, 3145, 3102, 1622 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 6.98$ (t, $J = 6.0$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz), 7.72 (d, $J = 7.5$ Hz, 3H), 8.16 (d, $J =$ 4.5 Hz, 2H), 8.27 (d, $J = 4.5$ Hz, 2H); ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 108.0$, 117.0, 121.5, 124.2, 126.5, 129.1, 140.5, 141.0, 146.2, 148.1, 163.5 ppm; MS (EI, 70 eV): m/z (%) = 297 (100) [M$^+$], 267 (30), 251 (80), 150 (75), 104 (30).

N-Phenyl-4-methoxyphenyl-2-thiazolamine
(**3k**, $C_{16}H_{14}N_2OS$)
White crystalline powder, 0.268 g (95%), mp 182–184°C; IR (KBr): $\bar{\nu} = 3291$, 3159, 3098, 2951, 1617 cm^{-1}; ^{1}H NMR (300 MHz, *DMSO*-d$_6$): $\delta = 3.77$ (s, 3H, OCH_3), 6.97 (t, $J =$ 8.4 Hz, 3H), 7.14 (s, 1H), 7.34 (t, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 8.4$ Hz, 2H), 7.83 (d, $J = 8.4$ Hz, 2H), 10.35 (s, 1H, NH) ppm; ^{13}C NMR (75 MHz, *DMSO*-d$_6$): $\delta = 55.2$, 100.8, 114.1, 117.1, 121.5, 127.1, 127.1, 129.2, 141.1, 149.4, 159.0, 163.4 ppm; MS (EI, 70 eV): m/z (%) = 282 (100) [M$^+$], 150 (15), 93 (10), 64 (15).

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