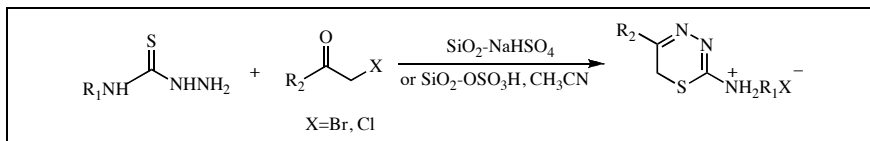


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5-Aryl-6*H*-1,3,4-thiadiazin-2-aminium and 5-aryl-*N*-phenyl-6*H*-1,3,4-thiadiazin-2-aminium salts have efficiently been synthesized from the reaction of thiosemicarbazide and α -haloketones in acetonitrile at room temperature using i) silica supported sodium hydrogen sulfate and ii) silica sulfuric acid as reusable heterogeneous catalysts. The experimental procedure is simple and the products are obtained in high yields.

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INTRODUCTION

As part of a continuing program of exploratory research in heterocyclic chemistry [1], we turned our attention to the 1,3,4-thiadiazines, which are one of the most thoroughly investigated isomers out of the six theoretically possible thiadiazines [2]. A literature survey on 1,3,4-thiadiazine derivatives, revealed that compounds with this moiety in their structure have shown anti-inflammatory [3], analgesic [4,5], antimicrobial [6], antiedematous [7], fungicidal [8,9], and muscle relaxant activity [10].

In recent years, silica supported reagents have attracted considerable attention because of their higher catalytic activity due to a larger surface area and better selectivity. Moreover, silica supported reagents have high mechanical and thermal stability, ease of handling, low toxicity, non-corrosiveness, easy separation of the catalyst after completion of the reaction and reusability of the catalyst, which make them promising for both academic and industrial applications. Recently, it has been reported that sodium hydrogen sulfate adsorbed on silica gel has a

higher catalytic activity than most other catalysts, which are sensitive to moisture and also very expensive [11].

Moreover, silica sulfuric acid has been found to be a superior proton source for preparation of organic compounds and has been used in many types of reactions such as oxidation, carbon-carbon bond formation and cycloaddition [12].

With all the aforementioned in mind, it occurred to us that silica supported sodium hydrogen sulfate ($\text{SiO}_2-\text{NaHSO}_4$), as well as silica sulfuric acid ($\text{SiO}_2-\text{OSO}_3\text{H}$), may be an effective, versatile and reusable catalysts for the preparation of 1,3,4-thiadiazines.

The main synthetic approach to these heterocycles involves condensation of thiosemicarbazides with α -haloketones [3].

It has been mentioned that the reaction, however, can be complex and the products are dependent on the nature of the substituents in each of the reactants (in which an aromatic substituent at the 5-position results in an increase of ring stability), the polarity of the solvent used and the reaction temperature [13-15]. It has also been reported that in conc. mineral acids, rearrangement to five membered

Table 1

Synthesis of 5-Aryl-(*N*-phenyl)-6*H*-1,3,4-thiadiazin-2-aminium Salts

Entry	R ₁	R ₂	SiO ₂ -NaHSO ₄		SiO ₂ -OSO ₃ H		mp °C[lit. mp]
			Time (h)	Yield (%)	Time(h)	Yield (%)	
1	H	C ₆ H ₅ -	¾	85	1.5	80	200.6-201[17]
2	H	4 - MeO- C ₆ H ₄ -	½	82	1	94	188-189[17]
3	H	4 - Br - C ₆ H ₄ -	½	98	1	92	216-217[17]
4	H	4 - NO ₂ - C ₆ H ₄ -	½	91	1	83	228-228.5[17]
5	H	2,4 -di-Cl- C ₆ H ₃ -	1	75	4	53	169-170[18]
6	Ph	C ₆ H ₅ -	3	96	4	75	172-173[19]
7	Ph	4 - MeO- C ₆ H ₄ -	3	81	4	88	184.8- 185.5
8	Ph	4 - Br - C ₆ H ₄ -	3	97	4	85	199.5-200
9	Ph	2,4 -di-Cl- C ₆ H ₃ -	3	74	4	43	186-187[10]
10	H	CH ₃ -	2	82	3	70	168.5-169.5[14]

heterocycles will occur; especially for those thiadiazines with an aliphatic substituent at the 5-position [14].

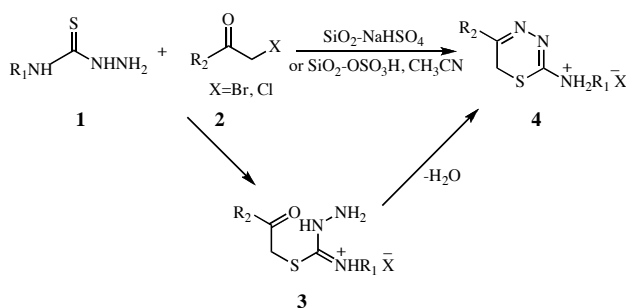
Recently, solid phase synthesis of amino-1,3,4-thiadiazines has been reported in the literature [16].

Because of the useful pharmacological activity and novelty of these heterocycles, and as the previously reported methods have a few drawbacks such as long reaction times, harsh refluxing conditions, formation of more than one product [13] and low product yields, we were encouraged to develop a simple and efficient method for the preparation of these compounds.

RESULTS AND DISCUSSION

In this report, 5-aryl-(*N*-phenyl)-6*H*-1,3,4-thiadiazin-2-aminium salts **4** were prepared, from the reaction of thiosemicarbazides **1** and α -haloketones **2** in acetonitrile at room temperature in the presence of solid supported reagents, i) $\text{SiO}_2\text{-NaHSO}_4$ and ii) $\text{SiO}_2\text{-OSO}_3\text{H}$ as catalysts (Scheme 1, Table 1).

Scheme 1



In our research, in order to achieve optimized condition, the reaction of thiosemicarbazide and phenacyl bromide (entry 1, Table 1) was initially performed in different solvents such as DMF, CH_3CN , EtOH and a mixture of EtOH, H_2O under neutral, acidic and basic conditions at room temperature, in which the best result was obtained with CH_3CN under acidic reagents such as (ZrCl_4 , ZnCl_2 , AlCl_3 , $\text{SiO}_2\text{-NaHSO}_4$ and silica sulfuric acid) (Table 2). We avoided using protic acids such as (HBr , HOAc , PTSA etc.), since in the presence of such acids, unwanted byproducts together with 1,3,4-thiadiazine will be formed [13-15]. When ZrCl_4 was used, the reaction went to completion very well at room temperature but we had difficulty in separating the ZrCl_4 from the products (since a small amount of ZrCl_4 is also dissolved in methanol). In the absence of any catalyst and in acetonitrile the intermediate **3** was obtained. Based on the above observations and as indicated in Table 2, $\text{SiO}_2\text{-NaHSO}_4$ and $\text{SiO}_2\text{-OSO}_3\text{H}$ which are both reusable and inexpensive catalysts were found to be the best catalysts for performing this reaction. Therefore, it seems that, the choice of the catalyst played an important role in this new

methodology. We have also found out that the reaction goes to completion using 1.2 mmol of thiosemicarbazide per 1 mmol of α -haloketones. Finally, we further investigated the best reaction conditions by using different amounts of $\text{SiO}_2\text{-NaHSO}_4$, and 200 mg was found to be the best amount and in the case of $\text{SiO}_2\text{-OSO}_3\text{H}$ [20], 230 mg was the optimized amount.

Table 2

Optimization of the Reaction Condition Using Different Catalysts

Reagent	Time (h)	Condition	Yield (%)
-	5	R.T	Intermediate formed
ZrCl_4	5	R.T	not isolated
ZnCl_2	24	R.T	50
AlCl_3	2	R.T	40
$\text{SiO}_2\text{-NaHSO}_4$	0.75	R.T	85
$\text{SiO}_2\text{-OSO}_3\text{H}$	1.5	R.T	80

Thus, a range of 5-substituted 6*H*-1,3,4-thiadiazin-2-aminium salts (entries 2-10) were prepared under the optimized condition (Table 2), using i) $\text{SiO}_2\text{-NaHSO}_4$ and ii) $\text{SiO}_2\text{-OSO}_3\text{H}$ as catalysts.

In view of green chemistry, we then turned our attention towards the reusability of the catalysts. In order to achieve this, $\text{SiO}_2\text{-NaHSO}_4$ was prepared according to the literature method [20]. Thus, the reaction of thiosemicarbazide (1.2 mmol), phenacyl bromide (1 mmol) (entry 1, Table 1) and (200 mg) of $\text{SiO}_2\text{-NaHSO}_4$ was performed in acetonitrile (5 mL) at room temperature. After completion of reaction the solvent was removed in *vacuo* and to the residue MeOH (50 mL) was added and stirred for 1 hr. The catalyst was separated by filtration, washed with methanol, dried and reused for the subsequent run. It was noticed that the catalyst could be reused for at least four cycles (Table 3). $\text{SiO}_2\text{-OSO}_3\text{H}$ was next prepared according to the reported method [12a]. In a similar experiment the reaction of thiosemicarbazide (1.2 mmol), phenacyl bromide (1 mmol), and $\text{SiO}_2\text{-OSO}_3\text{H}$ (230 mg) was performed in acetonitrile (5 mL) at room temperature and as indicated in Table 3 the catalyst could be reused for at least three cycles.

It should be mentioned that in the case of entry 6 the free base has been isolated and its mp is reported.

Table 3

The Recycling of Silica Sulfuric Acid

Entry	$\text{SiO}_2\text{-NaHSO}_4$ Time (h)	Yield(%) ^b	$\text{SiO}_2\text{-OSO}_3\text{H}$ Time (h)	Yield (%) ^b
1	0.75	85	1.5	80
2	0.75	84	1.5	77
3	0.75	80	1.5	70
4	0.75	79	1.5	68

^b Isolated Yield.

CONCLUSION

In conclusion, we have developed a convenient, easy, and mild method for the synthesis of 5-aryl-6*H*-1,3,4-thiadiazin-2-aminium, 5-aryl-*N*-phenyl-6*H*-1,3,4-thiadiazin-2-aminium and 5-methyl-6*H*-1,3,4-thiadiazin-2-aminium salts in high yield, using low cost i) SiO₂-NaHSO₄ and ii) SiO₂-OSO₃H heterogeneous and reusable catalysts without heating the mixture which usually results in the formation of many by-products. Short reaction time, easy workup, formation of only one product (without any rearranged product) for both aliphatic and aromatic substituents at 5-position, are advantages of this new methodology and make it attractive for large scale operation.

EXPERIMENTAL

Melting points were determined on a Büchi B-540 instrument in open capillary tubes and are uncorrected. IR spectra were recorded on an ABB Bomem Model FTLA200-100 instrument. ¹H and ¹³C NMR spectra were measured with a Bruker DRX - 300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a High Resolution Agilent Technology EX mass spectrometer. Elemental analysis of new compounds was performed with a Vario EL III 0 Serial No. 11024054 instrument. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Chemicals were obtained from Merck and Sigma-Aldrich and used without further purification.

General procedure for the synthesis of 5-aryl-(*N*-phenyl)-6*H*-1,3,4-thiadiazin-2-aminium salts using silica supported NaHSO₄ (entries 1-10). To the stirred suspension of phenacyl bromide (**2**) (1 mmole), thiosemicarbazide (1.2 mmole) in acetonitrile (5 mL), SiO₂-NaHSO₄ (200 mg) was added at room temperature. After complete conversion Table 1 (3/4 hr), as indicated by TLC (EtOAc/MeOH), the solvent was removed *in vacuo* and to the residue MeOH (50 mL) was added and stirred for 1 hr. The catalyst was separated by filtration and the filtrate was evaporated *in vacuo*. The solids formed were then collected by filtration and recrystallized from methanol and ethyl acetate.

General procedure for the synthesis of 5-aryl-(*N*-phenyl)-6*H*-1,3,4-thiadiazin-2-aminium salts using Silica Sulfuric acid (entries 1-10). To the stirred suspension of phenacyl bromide (**2**) (1 mmole), thiosemicarbazide (**1**) (1.2 mmole) in acetonitrile (5 mL), silica sulfuric acid (230 mg) was added at room temperature. After complete conversion, Table 1 (1/2 hr) as indicated by TLC (EtOAc / MeOH), the solvent was removed *in vacuo* and to the residue MeOH (50 mL) was added and stirred for 1 hr. The catalyst was separated by filtration and the filtrate was evaporated *in vacuo*. The solids formed were then collected by filtration and recrystallized from methanol and ethyl acetate. All products are known compounds and were characterized by comparison of their spectral and physical data with those of known samples except (entries 7,8) which were identified by IR, ¹H NMR, ¹³C NMR, MS and CHN analysis.

5-(4-Methoxyphenyl)-*N*-phenyl-6*H*-1,3,4-thiadiazin-2-aminium bromide (entry 7). This compound was obtained as cream needles (MeOH/ EtOAc), mp = 184.8-185.5 °C; IR (KBr): ν_{max} = 3339, 3302, 3146, 1598, 1523 cm⁻¹; ¹H NMR (300MHz, CDCl₃): δ = 3.88 (s, 5H), 6.9-7(d, 2H, J = 8.86), 7.27-7.48 (m, 5H), 7.79-7.82(d, 2H, J = 8.87), 12.7(br, 2H); ¹³C NMR: (125MHz, DMSO-D₆): δ = 22.9, 55.6, 114.6, 124.02, 124.2, 127.2, 129.4, 129.5, 136.9, 152.04, 160.3, 162.4; MS (EI): m/z (%) = 51(7.22), 77(23.7), 133(100), 162(137.7), 297(65.4), 299(4.56), 375(0.15) 377 (for ⁷⁹Br) and 379 (for ⁸¹Br) [M⁺]. Anal. Calcd. For C₁₆H₁₆N₃OS: C, 50.80; H, 4.26; N, 11.11. Found: C, 50.40; H, 4.05; N, 11.05.

5-(4-Bromophenyl)-*N*-phenyl-6*H*-1,3,4-thiadiazin-2-aminium bromide (entry 8). This compound was obtained as colourless needles (MeOH/ EtOAc), mp = 199.5-200 °C; IR (KBr): ν_{max} = 3137, 2968, 2819, 1668, 1602, 1561, 1494, 1319, 1217, 1073, 1011, 837, 759cm⁻¹; ¹H NMR (500MHz, CDCl₃): δ = 3.9 (s, 2H), 7.2-7.3 (m, 2H), 7.70-7.73 (d, 2H, J = 8.25), 7.31-7.66 (m, 5H), 13.43(br, 2H); ¹³C NMR: (125MHz, DMSO-D₆): δ = 22.4, 124.5, 124.9, 127.4, 128.9, 129.5, 131.9, 132.1, 137.1, 150.3, 160.4; MS (EI): m/z (%) = 51(10), 77(29), 91(6), 102(46), 136(100), 183(36.5), 224(10), 313(4), 345(38), 347(40.9). Anal. Calcd. For C₁₅H₁₃BrN₃S: C, 42.18; H, 3.07; N, 9.8. Found: C, 42.13; H, 2.88; N, 9.8.

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