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Sulphamic Acid as an Efficient Catalyst for Synthesis of Thiosemicarbazone Derivatives at Room Temperature

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ABSTRACT

Various thiosemicarbazone derivatives have been prepared from thisemicarbazide and substituted aromatic aldehyde in presence of sulphamic acid as mild, efficient, inexpensive, nontoxic catalyst and cost-effective catalyst at room temperature. It provides the products in excellent yields and in much shorter reaction time.

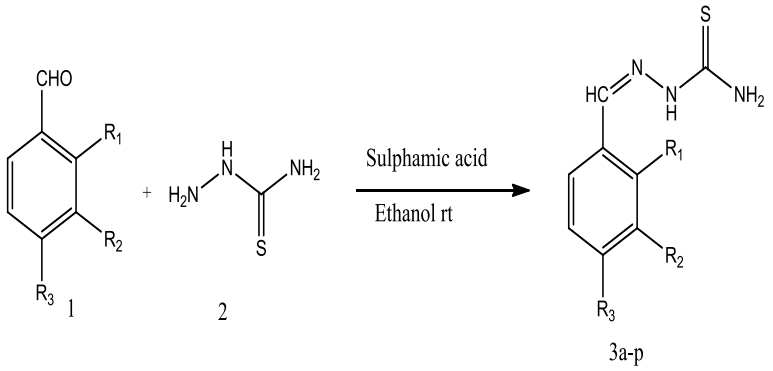
Keywords: Sulphamic acid, Aldehydes, Thiosemicarbazide

INTRODUCTION

Thiosemicarbazones are the condensation products of aldehydes and thiosemicarbazide have been associated with a diverse range of pharmacological properties. Thiosemicarbazone derivatives exhibit a great variety of biological activities, such as antitumor [1], antimicrobial [2], antineoplastic, anti-inflammatory [3], anti-convulsant, tuberculostatic [4], antifungal [5,6], antibacterial [7], antiviral [8], cytotoxicity [9] properties etc. Many of the synthetic approaches were reported to prepare thiosemicarbazone system involve heating the mixture of aldehyde and thiosemicarbazide in ethanol to reflux [10], acetic acid/ethanol reflux for [11,12], Conc. H_2SO_4/methanol [13]. All above mentioned reported methods involve the use of hazardous acids, long reaction times and tedious workup procedures.

Sulphamic acid is a white crystalline, nonvolatile, dry and odorless solid Bronsted acid [14]. It is commercially available and a very cheap chemical. It possesses distinctive catalytic features and displays an excellent catalytic activity over other acid-catalyzed organic transformations; recently sulphamic acid has been proved to be highly effective catalyst for the synthesis of Mannich-type reactions [15], Beckmann rearrangement of ketoxide [16], beiginally reaction [17], Bis-Lawsone derivatives [18], esterification [19], N-alkyl and N-aryl imides [20] etc. These properties prompted us to investigate the use of sulphamic acid for the synthesis of thiosemicarbazones.

In this paper, a practical procedure for preparation of thiosemicarbazone by reaction of aromatic aldehyde with thiosemicarbazide in alcohol in presence of catalytic amount of sulphamic acid at room temperature is reported (Scheme 1).



Scheme 1: Preparation of thiosemicarbazone

MATERIALS AND METHODS

Materials

All chemicals used in the synthesis were purchased from Sigma-Aldrich and S. D. Fine chem. Ltd. Mumbai.

Measurement

All the chemicals and solvents used in this work were of analytical reagent grade (anhydrous). Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded with a Shimadzu IR-408 spectrometer. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were determined in Dimethyl Sulfoxide-d6 (DMSO-d_6) solution on a Bruker Avance II (400 MHz) NMR Spectrometer and Tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded on a Waters, Q-TOF Micromass (LC-MS).

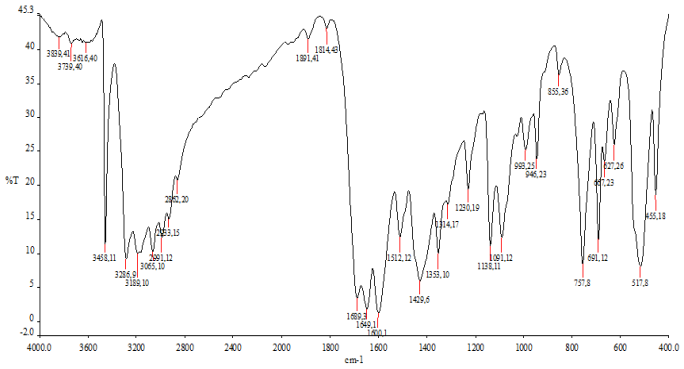
General procedure

A mixture of semithiocarbazide 2 (1 mmol), aromatic aldehyde 1 (1 mmol) and sulphamic acid (10 mmol %) were taken in 5 ml ethanol in a round bottomed flask and stirred for 10-30 min. The progress of reaction of was monitored by Thin Layer Chromatography (TLC), after total consumption of aldehyde; the mixture was poured into cold water. The solid separated was filtered, washed with water and recrystallized from ethanol to give the title compound 3.

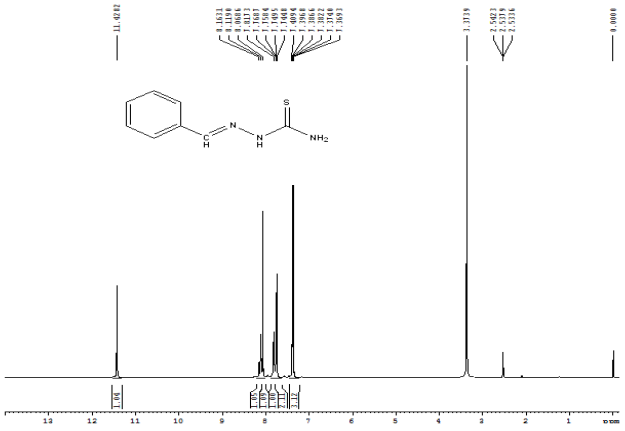
Spectral data for selected compounds

2-Benzylidenehydrazinecarbothioamide (**3a**)

IR (KBr) cm^{-1}: 3458, 3286, 1600, 1314; ^{1}H-NMR (DMSO d6, 400 MHz), δ(ppm): 7.36-7.40 (m, 3H, Ar-H), 7.74-8.76 (m, 2H, Ar-H), 7.81 and 8.11 (2Xs, 2H, –NH_2), 8.06 (s, 1H, CH), 11.42 (s, 1H, –NH–).



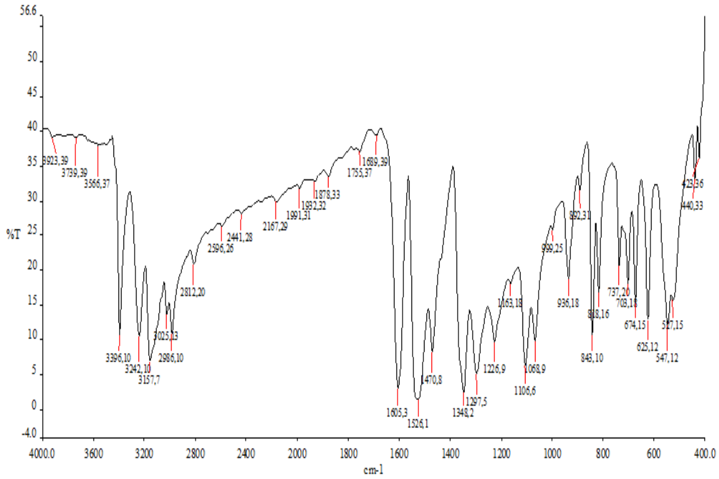
FTIR



^{1}H NMR

2-(3-Nitrobenzylidene)hydrazinecarbothioamide (**3b**)

IR (KBr) cm^{-1}: 3396, 3242, 1605, 1526, 1348, 1297; ^{1}H-NMR (DMSO d6, 400 MHz), δ(ppm): 7.69 (t, 1H, Ar-H), 8.14 (s, 1H, Ar-H), 8.19 (d, 1H, Ar-H), 8.24 (d, 1H, Ar-H), 8.30 and 8.30 (2 X s, 2H, –NH_2), 8.64 (s, 1H, CH), 11.62 (s, 1H,-NH-); MS 225.0(M+1).



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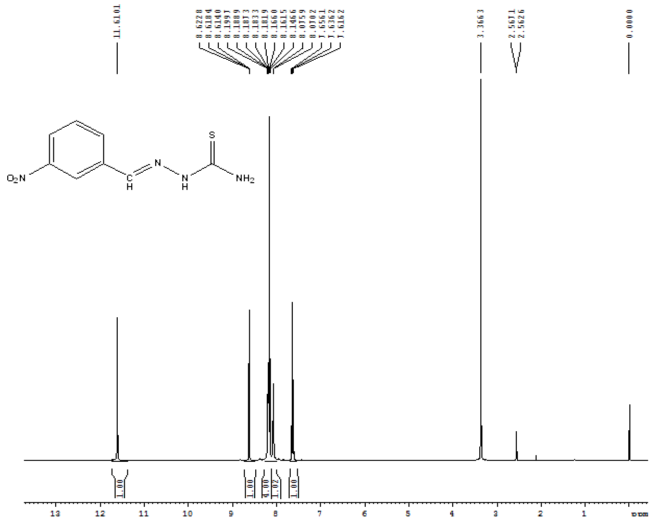
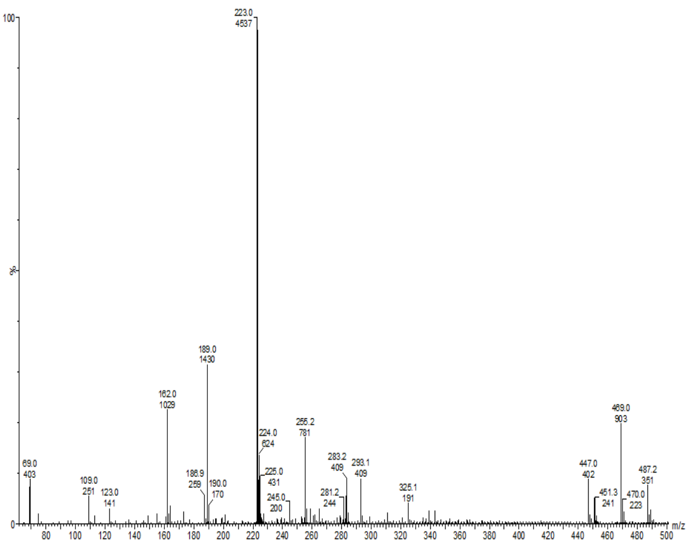


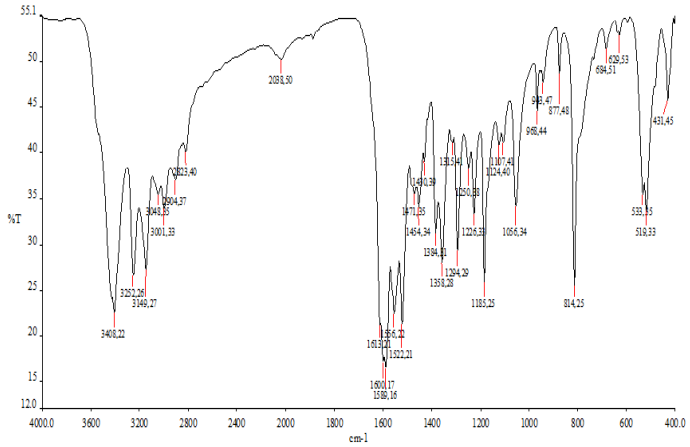
^{1}H-NMR



MS: 223.0(M-1), 225. 0 (M+1)

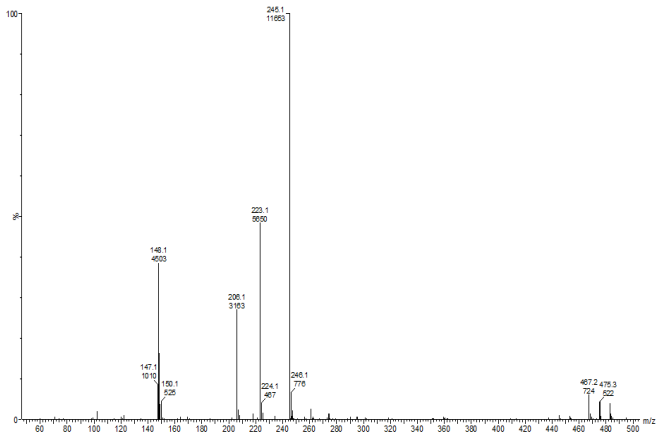
2-(4-(Dimethylamino)benzylidene)hydrazinecarbothioamide (**3c**)

IR (KBr) cm^{-1}: 3408, 3252, 1600, 1294; ^{1}H-NMR (DMSO d6, 400 MHz), δ(ppm): 2.97 (s, 6H, CH_3), 6.67 (d, 2H, *J*-8.0 Hz, Ar-H), 7.55 (d, 2H, *J*-8.0 Hz, Ar-H), 7.67 and 7.93 (2X s, 2H, $–NH_2$), 7.93 (s, 1H, CH), 11.17 (s, 1H, -NH-); MS 223.1 (M+1).



FTIR

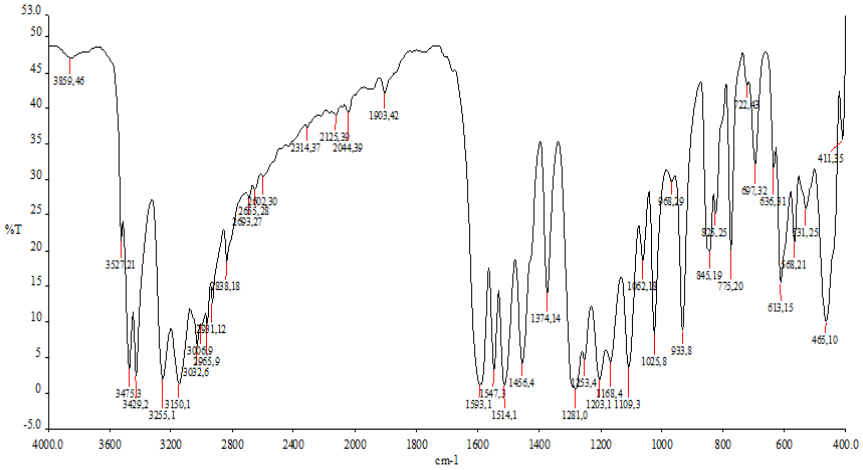
^{1}H-NMR



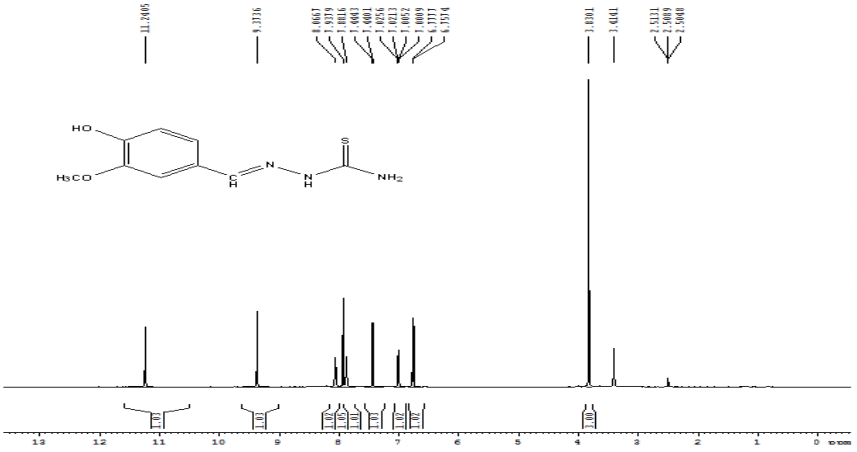
MS 223.1 (M+1)

2-(4-Hydroxy-3-Methoxy benzylidene) hydrazinecarbothioamide (**3e**)

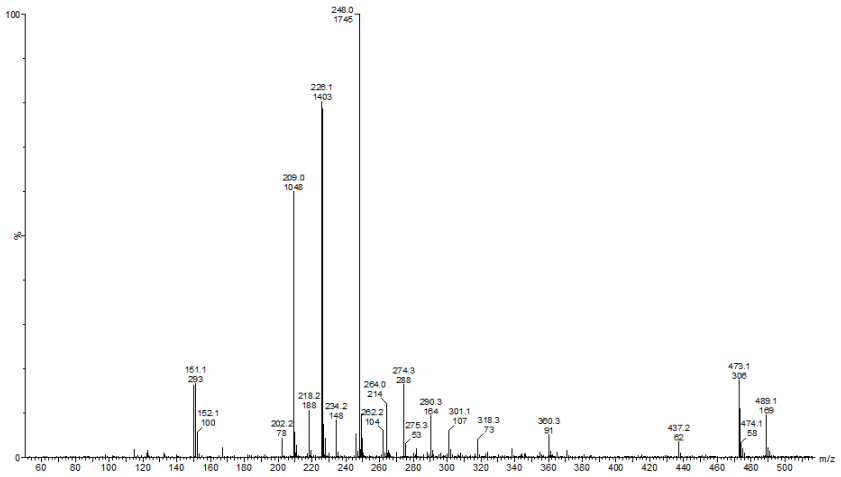
IR (KBr) cm^{-1}: 3475, 3429, 3255, 1593, 1281. ^{1}HNMR (DMSO d6, 400 MHz), δ(ppm): 6.77 (d, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 7.44(s, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 7.88 and 8.06 (2 X s, 2H, $–NH_2$), 9.37 (s, 1H, CH), 11.24 (s, 1H,-NH-); MS: 226.1 (M+1).



FTIR



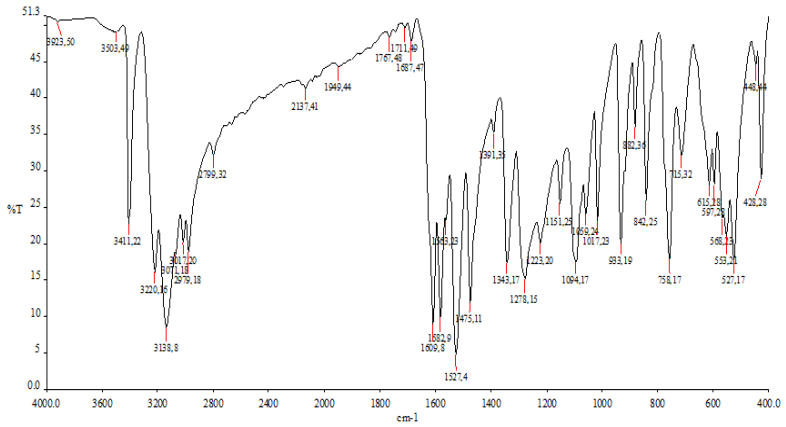
^{1}H-NMR



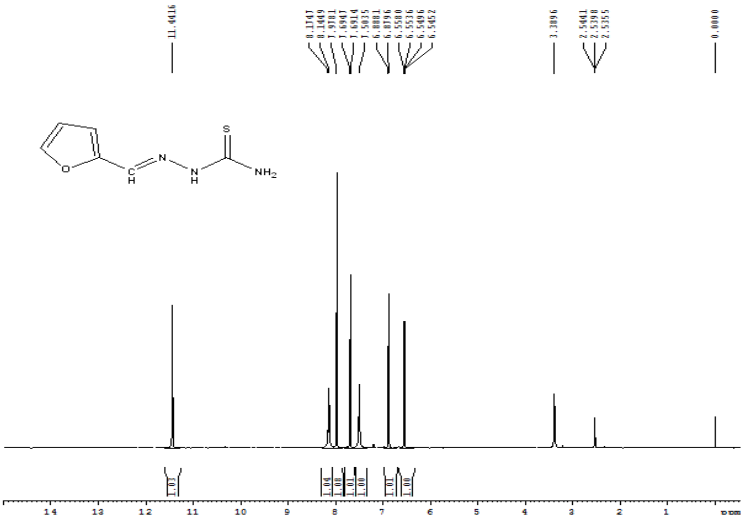
MS: 226.1 (M+1)

1-((furan-2-yl)methylene)thiosemicarbazide (**3g**)

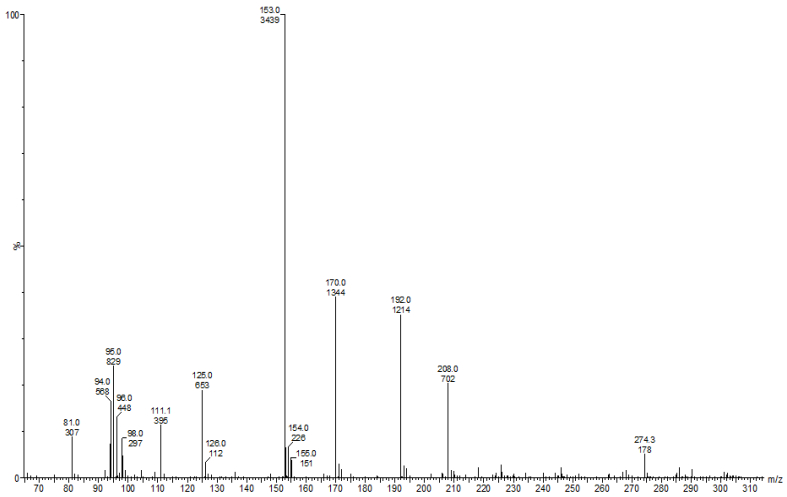
IR (KBr) cm^{-1}: 3411, 3220, 1609, 1278. ^{1}H-NMR (DMSO d6, 400 MHz), δ(ppm): 6.55 (s, 1H, Ar-H), 7.69 (m, 1H, Ar-H), 7.97 (m, 1H, Ar-H), 7.50 and 8.14 (2Xs, 2H, –NH_2), 7.97 (s, 1H, CH), 11.42 (s, 1H, -NH-); MS: 154.0 (M+1).



FTIR



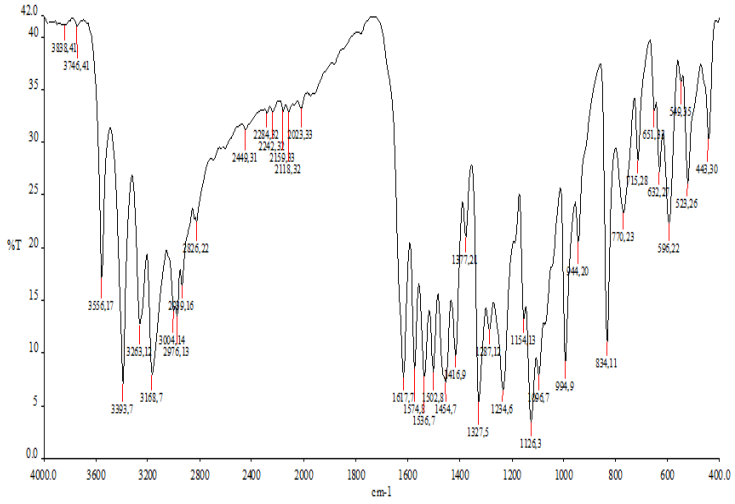
^{1}H-NMR



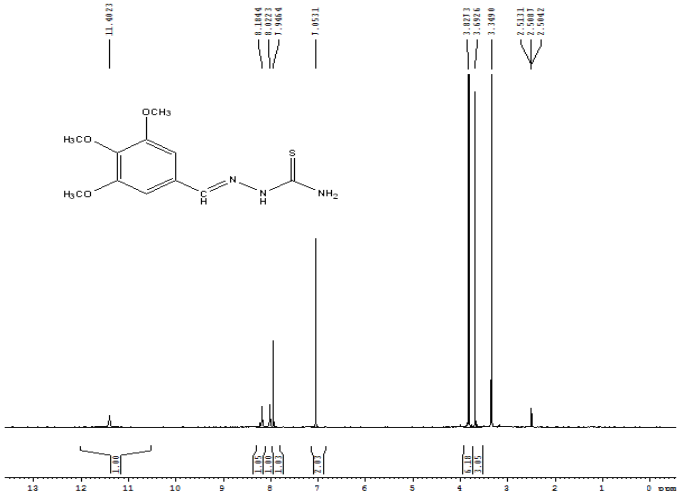
MS: 153 (M), 154 (M+1)

2-(3,4,5-Trimethoxy benzylidene) hydrazinecarbothioamide (3l)

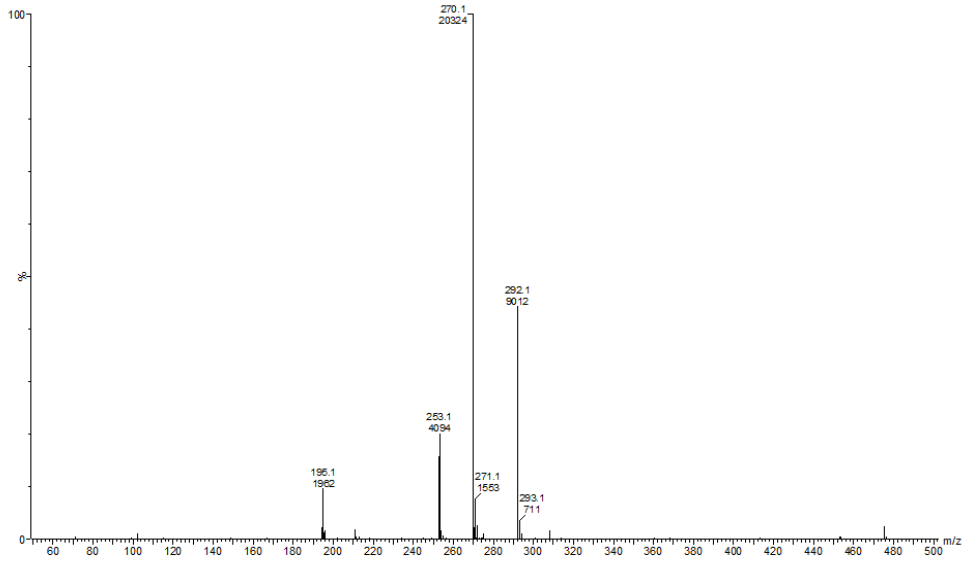
IR (KBr) cm^{-1}: 3393, 3263, 1617, 1287; ^{1}H-NMR (DMSO d6, 400 MHz), δ(ppm): 3.69(s, 3H, -OCH_3), 3.82(s, 6H, -OCH_3), 7.05 (s, 2H, Ar-H), 7.94 (s, 1H, CH), 8.02 and 8.18 (2 X s, 2H, –NH_2), 11.40 (s, 1H,-NH-). MS: 270.1 (M+1).



FTIR



^{1}H-NMR



MS: 270.1 (M+1)

Table 1: Synthesis of thiosemicarbazone derivatives[a]

Entry	R-CHO	Yield[b] (%)	Time (min)	Melting point (°C)	Product
1	C_6H_5	92	15	166-168	3a[c]
2	3-NO_2 C_6H_4	94	10	214-216	3b[c]
3	4-N, N-$(CH_3)_2$ C_6H_4	91	15	222-224	3c[c]
4	2-Cl C_6H_4	93	17	208-210	3d
5	3-OCH_3, 4-OH C_6H_3	90	25	200-202	3e[c]
6	3- Cl C_6H_4	91	23	190-192	3f
7	2-furyl	92	30	144-145	3g[c]
8	4- Cl C_6H_4	96	21	190-192	3h
9	4-HO C_6H_4	93	17	184-186	3i
10	2-$NO_2C_6H_4$	95	12	204-206	3j
11	4-OCH_3 C_6H_4	94	18	174-176	3k
12	3, 4, 5-$(OCH_3)_3$ C_6H_2	92	20	236-238	3l[c]
13	2-OCH_3 C_6H_4	94	15	206-208	3m
14	4-Fluoro C_6H_4	91	10	192-194	1n
15	2-naphthyl	93	20	222-224	1o
16	4-NO_2 C_6H_4	95	10	197-199	1p

[a]Reaction condition: semithiocarbazide 2 (1 mmol), aromatic aldehyde 1 (1 mol) and sulphamic acid (10 mol%) in 10 ml ethanol stirred at room temperature; [b]Isolated yields; [c]Synthesized compounds were characterized by spectral analysis such as FTIR, ^{1}H-NMR, Mass

RESULTS AND DISCUSSION

In this work, we would like to report a simple, efficient and rapid method for synthesis of thiosemicarbazone. Various aromatic aldehydes (1) react with thiosemicarbazide (2) catalyzed by sulphamic acid in ethanol at room temperature (Scheme 1). The reaction was rapidly completed and gave desired products in good to excellent yield. The resulting thiosemicarbazone (3a-p), reaction conditions, yields and physical constants are shown in Table 1. The structures of the products were supported by the IR, ^{1}H-NMR, mass and the previously reported melting points.

In order to investigate, the effect of amount of catalyst on the condensation, the reaction between benzaldehyde (1 mmol) and thiosemicarbazide (1 mmol) in ethanol and sulphamic acid as a catalyst at room temperature was selected as model reaction. This led to low yield (70%) of the product with 5 mmol% of catalyst. To enhance the yield of the desired product, the amount of catalyst was increased by 5 mmol%. With increasing the amount of the catalyst, the productivity of the reaction increased. As indicated in Table 2, maximum yield was obtained (92%) when the reaction was loaded with 10 mmol% of the catalyst. A further increasing of catalyst loading did not affect the yield. It was observed that the reaction the reaction was completed in 10-20 min with excellent yield. 2-furaldehyde (3g) requires somewhat longer time as compared to simple aromatic aldehyde as mentioned in Table 1.

After optimizing the conditions, we applied this protocol for synthesis of substituted thiosemicarbazone by using different aromatic aldehyde with a wide range of ortho, meta and para- substitutions in ethanol at room temperature starring conditions to establish the catalytic importance of sulphamic acid for this reaction. The corresponding results are given in Table 1. We found that the reaction proceeded efficiently by either electron-releasing or electron-withdrawing substituent on aryl ring of aldehyde. Based on such a good results, we synthesized differently substituted thiosemicarbazones (3a to 3p) with good to excellent yield.

Table 2: Optimization of the amount of catalyst at room temperature

Entry	Amount of catalyst (mmol%)	Time (min)	Yield[a] %
1	05	30	70
2	10	20	92
3	15	20	92
4	20	20	92

[a]Isolated yield

CONCLUSION

In summary, an efficient and mild protocol for the synthesis of semithiocarbazone derivative using sulphamic acid as an inexpensive heterogeneous catalyst has been developed. Short reaction times, high yields, easy work-up, low cost & easy availability of catalyst are the key advantages of this method.

ACKNOLEDGEMENT

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