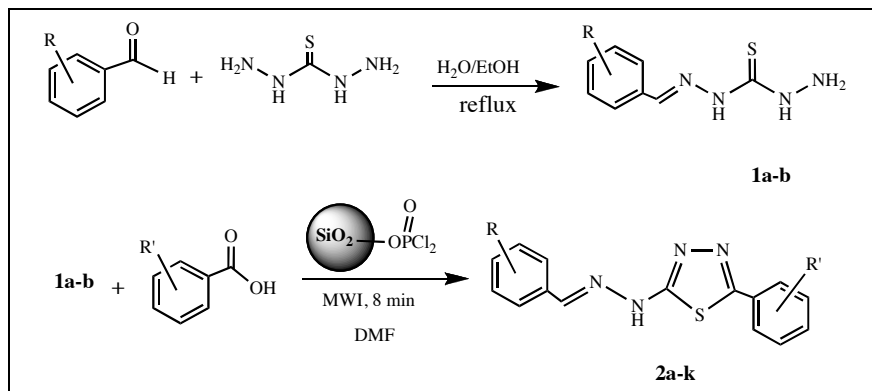


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(Un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones were efficiently synthesized by reactions of (un)substituted benzaldehyde thiosemicarbazones with aromatic carboxylic acids by using silica-supported dichlorophosphate as a recoverable dehydrant under microwave irradiation. The protocol has advantages of short reaction time, high yield, easy work-up procedure and no environmental pollution.

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INTRODUCTION

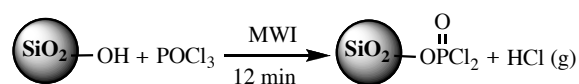
The compounds bearing a 1,3,4-thiadiazole moiety are of interest in medicinal and agricultural fields because of their wide range of biological activities, such as antibacterial [1], fungicidal [2], anticancer [3], anti-tubercular [4], anti-inflammatory [5] and leishmanicidal [6] activities. Especially (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones show the importance for their antitrypanosomal activity [7]. Fraga and coworkers [7] reported a synthetic route for (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones: Benzoic acid first reacted with thiosemicarbazide in liquid phosphorus oxychloride to synthesize 2-amino-5-phenyl-1,3,4-thiadiazole, then this amino-heterocyclic derivative was converted into 2-chloro-4-phenyl-1,3,4-thiadiazole by exploiting the diazotation and Sandmeyer reaction with CuCl. Heteroaromatic nucleophilic substitution of the chlorine atom of 2-chloro-4-phenyl-1,3,4-thiadiazole using hydrazine hydrate furnished the heterocyclic hydrazines, then acid catalyzed condensation of the hydrazines with the corresponding aromatic aldehydes in ethanol to give the target hydrazone derivatives. However, this route has long procedure, and need long reaction time, especially the liquid phosphorus oxychloride was used, which could cause corrosion and environmental pollution because of difficult separation after the reaction.

In this paper, we report a new, expeditious and eco-friendly route for the preparation of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones using thiosemicarbazide as starting material, easily recoverable silica-supported dichlorophosphate as dehydrant and microwave as heating source.

RESULTS AND DISCUSSION

Silica-supported dichlorophosphate was prepared by reaction of silica gel with phosphorus oxychloride under microwave irradiation (Scheme 1). The reaction could be completed within 12 min to afford the desired product in excellent yield.

Scheme 1



In order to explore the availability of silica-supported dichlorophosphate as a recoverable dehydrant under microwave irradiation, the synthesis of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones (**2a-k**) was tested (Scheme 2, Table 1). Firstly, thiosemicarbazide reacted with equivalent of aromatic aldehydes in aqueous ethanol medium at refluxing condition to give (un)substituted benzaldehyde thiosemicarbazones.

hydrazones (**1a-b**) in high yield. Provided the reactant ratio was carefully controlled, the reactions could afford the desired monosubstituted products in high selectivity, and no 1,5-disubstituted by-products were observed. Then the reactions of compounds **1a-b** with various aromatic acids to synthesize target products were attempted using silica-supported dichlorophosphate as dehydrant under microwave irradiation. It was found that the optimal conditions for the desired compounds **2a-k** were to irradiate the reaction mixture for 8 min at the power of 650 W using DMF as solvent. Benzoic acids bearing different substituents could react well with no significant difference. The silica-supported dehydrant could be separated and recovered from the resulting reaction mixture only by filtration, which could efficiently avoid the environmental pollution caused by using liquid POCl_3 .

Compounds **2a-k** were confirmed by ^1H NMR, IR and elemental analyses. ^1H NMR analyses show the proton peaks at 12.51-12.59 ppm for NH and 8.14-8.18 ppm for CH. IR spectra show the characteristic absorption at 3200-3217 cm^{-1} for NH.

In conclusion, silica-supported dichlorophosphate was found an efficient and recoverable dehydrant for the preparation of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones *via* a novel two-step route by reactions of thiocarbohydrazide with equivalent of aromatic aldehydes, followed by aromatic acids. This protocol has the advantages of no environmental pollution, short reaction period, high yield and simple work-up procedure.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Digilab FTS 3000 FTIR spectrophotometer and ^1H NMR spectra on a Mercury-400BB instrument using $(\text{CD}_3)_2\text{SO}$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Melting points were observed in an electrothermal melting point apparatus. Microwave reactions were conducted in a modified microwave oven fitted with a condenser (LG-WP650, China).

Thiocarbohydrazide was prepared according to literature procedure [12].

The preparation of silica-supported dichlorophosphate. The mixture of silica gel (1 g) and phosphorus oxychloride (6 mL) was stirred for 10 min at room temperature. Then the mixture was subjected to the microwave irradiation for total 12 min (1 min interval for each 3 min of irradiation) under the power of 455 W. Then the resulting mixture was washed with CH_2Cl_2 (3×5 mL) to remove the excess phosphorus oxychloride, and the solid was dried to give the product. Yield: 98%. IR (KBr): 571 ($\nu_{\text{P-Cl}}$). The silica supporting capacity for POCl_3 is ca 2.81 mmol/g.

The general procedure for the preparation of (un)substituted benzaldehyde thiocarbohydrazones (1a-b). To the solution of thiocarbohydrazide (15 mmol) in 50 mL of H_2O and 1 mL of acetic acid, aromatic aldehyde (10 mmol) in 20 mL of ethanol was added dropwise within 1 h at refluxing condition. After the addition, the mixture was further refluxed for 3 h. Then the precipitate was collected by filtration and washed with water (3×10 mL). The resulting solid was recrystallized from ethanol to give the product. The analytical data for **1a-b** are given below.

1a: Yield, 84%; m.p., 210-212°C (lit. 193-194°C) [13]. ^1H nmr (DMSO- d_6 , 400 MHz): δ 11.42 (s, 1H, NH), 9.82 (bs, 1H, NH), 8.03 (s, 1H, CH), 7.34-8.01 (m, 5H, Ar-H), 4.91 (bs, 2H, NH_2). ir (potassium bromide): 3258 (N-H), 3162 (N-H), 1263 (C=S) cm^{-1} . ms: m/z , 194 (M^+). Anal. Calcd. for $\text{C}_8\text{H}_{10}\text{N}_4\text{S}$: C, 49.46; H, 5.19; N, 28.84. Found: C, 49.52; H, 5.20; N, 28.77.

1b: Yield, 87%; m.p., 198-200°C. ^1H nmr (DMSO- d_6 , 400 MHz): δ 11.39 (s, 1H, NH), 9.81 (bs, 1H, NH), 8.02 (s, 1H, CH), 7.54-7.95 (m, 4H, Ar-H), 4.90 (bs, 2H, NH_2), 3.81 (s, 3H, CH_3). ir (potassium bromide): 3208 (N-H), 3100 (N-H), 1254 (C=S) cm^{-1} . ms: m/z , 224 (M^+). Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_4\text{OS}$: C, 48.20; H, 5.39; N, 24.98. Found: C, 48.30; H, 5.38; N, 24.89.

The general procedure for the preparation of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones (2a-k). To the solution of (un)substituted benzaldehyde thiocarbohydrazones (**1a-b**) (2 mmol) and aromatic acids (2.2 mmol) in 6 mL of DMF, silica-supported dichlorophosphate (2 mmol, based on supported POCl_3) was added. Then the mixture was subjected to the microwave irradiation at the power of 650 W for total 8 min (2 min of irradiation followed by 1 min of interval). The completion of the reaction was monitored by TLC. The resulting mixture was filtered to recover the silica-supported reagent. The filtrate was poured into 20 mL of water, and the precipitate was collected by filtration, washed by cold ethanol (2×5 mL) and recrystallized

Scheme 2

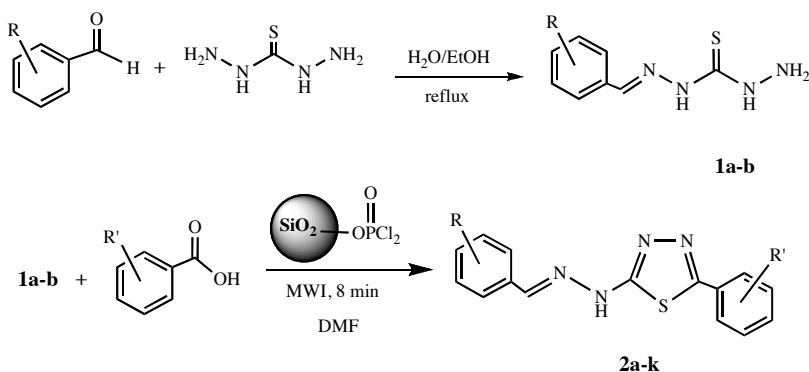


Table 1
Synthesis of (un)substituted benzaldehyde (5-aryl-1,3,4-thiadiazol-2-yl)hydrazones (**2a-k**).

Compd.	R	R'	Product	m.p. (lit.) (°C)	Yield (%) ^a
2a	H	H		242-244 (248) [8]	90
2b	H	4-CH ₃ O		234-236	87
2c	H	2-CH ₃		224-226	80
2d	H	3-CH ₃		202-204	84
2e	H	3-Cl		226-228	84
2f	H	4-Cl		188-190 (254-256) [9]	82
2g	4-CH ₃ O	H		206-208 (200) [10]	85
2h	4-CH ₃ O	4-CH ₃ O		182-184 (163-165) [11]	87
2i	4-CH ₃ O	4-Cl		212-214	83
2j	4-CH ₃ O	3-Cl		189-191	84
2k	4-CH ₃ O	2-CH ₃		208-210	81

^a Yields refer to the isolated products.

from DMF-EtOH-H₂O (2:5:1) to give the product. The analytical data for **2a-k** are given below.

2a: This compound was obtained as white crystal (DMF-EtOH-H₂O). ¹H nmr (DMSO-*d*₆, 400 MHz): δ 12.59 (s, 1H, NH), 8.14 (s, 1H, CH), 7.42-8.06 (m, 10H, Ar-H). ir (potassium bromide): 3200 (N-H) cm⁻¹. ms: *m/z*, 280 (M⁺). Anal. Calcd. for C₁₅H₁₂N₄S: C, 64.26; H, 4.31; N, 19.98. Found: C, 64.35; H, 4.29; N, 19.92.

2b: This compound was obtained as white crystal (DMF-EtOH-H₂O). ¹H nmr (DMSO-*d*₆, 400 MHz): δ 12.52 (s, 1H, NH), 8.16 (s, 1H, CH), 7.04-8.05 (m, 9H, Ar-H), 3.78 (s, 3H, CH₃). ir (potassium bromide): 3209 (N-H) cm⁻¹. ms: *m/z*, 310 (M⁺). Anal. Calcd. for C₁₆H₁₄N₄OS: C, 61.92; H, 4.55; N, 18.05. Found: C, 62.04; H, 4.57; N, 18.01.

2c: This compound was obtained as white crystal (DMF-EtOH-H₂O). ¹H nmr (DMSO-*d*₆, 400 MHz): δ 12.52 (s, 1H, NH), 8.14 (s, 1H, CH), 7.33-8.14 (m, 9H, Ar-H), 2.53 (s, 3H,

CH₃). ir (potassium bromide): 3205 (N-H) cm⁻¹. ms: *m/z*, 294 (M⁺). Anal. Calcd. for C₁₆H₁₄N₄S: C, 65.28; H, 4.79; N, 19.03. Found: C, 65.14; H, 4.80; N, 19.07.

2d: This compound was obtained as white crystal (DMF-EtOH-H₂O). ¹H nmr (DMSO-*d*₆, 400 MHz): δ 12.53 (s, 1H, NH), 8.15 (s, 1H, CH), 7.34-8.15 (m, 9H, Ar-H), 2.52 (s, 3H, CH₃). ir (potassium bromide): 3204 (N-H) cm⁻¹. ms: *m/z*, 294 (M⁺). Anal. Calcd. for C₁₆H₁₄N₄S: C, 65.28; H, 4.79; N, 19.03. Found: C, 65.37; H, 4.77; N, 18.99.

2e: This compound was obtained as white crystal (DMF-EtOH-H₂O). ¹H nmr (DMSO-*d*₆, 400 MHz): δ 12.59 (s, 1H, NH), 8.15 (s, 1H, CH), 7.01-8.12 (m, 9H, Ar-H). ir (potassium bromide): 3210 (N-H) cm⁻¹. ms: *m/z*, 314 (M⁺). Anal. Calcd. for C₁₅H₁₁ClN₄S: C, 57.23; H, 3.52; N, 17.80. Found: C, 57.34; H, 3.53; N, 17.76.

2f: This compound was obtained as white crystal (DMF-EtOH-H₂O). ¹H nmr (DMSO-*d*₆, 400 MHz): δ 12.58 (s, 1H,

NH), 8.14 (s, 1H, CH), 7.06-8.04 (m, 9H, Ar-H). ir (potassium bromide): 3211 (N-H) cm^{-1} . ms: m/z , 314 (M^+). *Anal.* Calcd. for $\text{C}_{15}\text{H}_{11}\text{ClN}_4\text{S}$: C, 57.23; H, 3.52; N, 17.80. Found: C, 57.30; H, 3.51; N, 17.85.

2g: This compound was obtained as white crystal (DMF-EtOH- H_2O). ^1H nmr (DMSO- d_6 , 400 MHz): δ 12.57 (s, 1H, NH), 8.17 (s, 1H, CH), 7.06-8.06 (m, 9H, Ar-H), 3.75 (s, 3H, CH_3). ir (potassium bromide): 3213 (N-H) cm^{-1} . ms: m/z , 310 (M^+). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{OS}$: C, 61.92; H, 4.55; N, 18.05. Found: C, 61.88; H, 4.54; N, 18.00.

2h: This compound was obtained as white crystal (DMF-EtOH- H_2O). ^1H nmr (DMSO- d_6 , 400 MHz): δ 12.56 (s, 1H, NH), 8.18 (s, 1H, CH), 7.04-8.05 (m, 8H, Ar-H), 3.76 (s, 6H, CH_3). ir (potassium bromide): 3216 (N-H) cm^{-1} . ms: m/z , 340 (M^+). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$: C, 59.98; H, 4.74; N, 16.46. Found: C, 60.05; H, 4.75; N, 16.40.

2i: This compound was obtained as white crystal (DMF-EtOH- H_2O). ^1H nmr (DMSO- d_6 , 400 MHz): δ 12.58 (s, 1H, NH), 8.17 (s, 1H, CH), 7.05-8.06 (m, 8H, Ar-H), 3.75 (s, 3H, CH_3). ir (potassium bromide): 3216 (N-H) cm^{-1} . ms: m/z , 344 (M^+). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{OS}$: C, 55.73; H, 3.80; N, 16.25. Found: C, 55.80; H, 3.81; N, 16.21.

2j: This compound was obtained as white crystal (DMF-EtOH- H_2O). ^1H nmr (DMSO- d_6 , 400 MHz): δ 12.59 (s, 1H, NH), 8.17 (s, 1H, CH), 7.01-8.14 (m, 8H, Ar-H), 3.74 (s, 3H, CH_3). ir (potassium bromide): 3217 (N-H) cm^{-1} . ms: m/z , 344 (M^+). *Anal.* Calcd. for $\text{C}_{16}\text{H}_{13}\text{ClN}_4\text{OS}$: C, 55.73; H, 3.80; N, 16.25. Found: C, 55.66; H, 3.79; N, 16.29.

2k: This compound was obtained as white crystal (DMF-EtOH- H_2O). ^1H nmr (DMSO- d_6 , 400 MHz): δ 12.51 (s, 1H, NH), 8.16 (s, 1H, CH), 7.33-8.13 (m, 8H, Ar-H), 3.79 (s, 3H, CH_3), 2.53 (s, 3H, CH_3). ir (potassium bromide): 3213 (N-H)

cm^{-1} . ms: m/z , 324 (M^+). *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{OS}$: C, 62.94; H, 4.97; N, 17.27. Found: C, 63.04; H, 4.96; N, 17.22.

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