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Silica-Supported Dichlorophosphate as a Recoverable Cyclodehydrant: Expeditious Synthesis of [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazoles Under Microwave Irradiation

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Silica-Supported Dichlorophosphate as a Recoverable Cyclodehydrant: Expeditious Synthesis of [1,2,4]Triazolo [3,4-*b*][1,3,4]thiadiazoles Under Microwave Irradiation

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Abstract: An expeditious novel approach to 3,6-disubstituted [1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazoles using silica-supported dichlorophosphate as a recoverable cyclodehydrant, carboxylic acids and thiocarbohydrazide as starting materials, and microwave irradiation as thermal source was described. The protocol has advantages of concise synthetic step, short time, good yield, easy workup procedure, and no environmental pollution.

Keywords: Microwave irradiation, silica-supported dichlorophosphate, thiocarbohydrazide, [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole

INTRODUCTION

[1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole derivatives are important heterocyclic compounds with a wide range of pharmaceutical and biological activities, such as antibacterial,[1] fungicidal,[2] pesticidal,[3] and herbcidal[4] activities. Generally, 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazoles are synthesized by two routes[5] (Scheme 1): (i) 3-substituted

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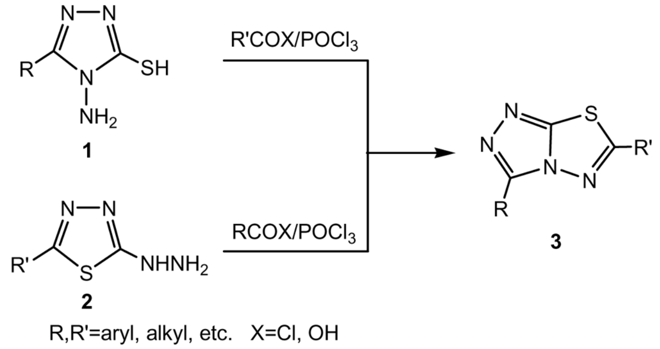


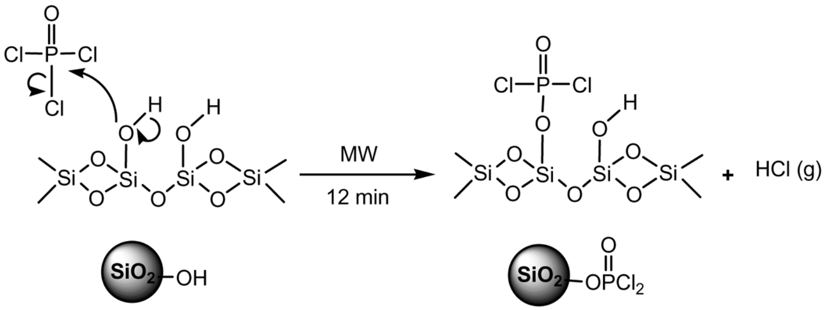
Scheme 1. Two routes for the synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

4-amino-5-mercapto-1,2,4-triazoles (**1**) reacted with carboxylic acids or acid chlorides using phosphorus oxychloride as cyclodehydrant; (ii) 2-substituted 5-hydrazino-1,3,4-thiadiazoles (**2**) reacted with carboxylic acids or acid chlorides using phosphorus oxychloride as cyclodehydrant. However, the preparation of intermediates **1** and **2** requires long steps, which often cause the poor overall yield of desired products. Furthermore, the resultant of liquid dehydrant, $POCl_3$, is difficult to separate and recover after the reactions, which usually causes heavy corrosive and environmental pollution.

In this article, we report a novel and expeditious route to synthesize 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles under microwave irradiation using silica-supported dichlorophosphate as an efficient and recoverable cyclodehydrant and carboxylic acids and thiocarbohydrazide as starting materials.

RESULTS AND DISCUSSION

Silica-supported dichlorophosphate was prepared by reaction of silica gel with phosphorus oxychloride under microwave irradiation (Scheme 2). The reaction could be completed within 12 min to afford the desired product in excellent yield. Figure 1 shows the infrared (IR) spectra of silica-supported dichlorophosphate and silica gel. Both IR spectra show the typical broad absorption peaks of Si-O-Si bond at 1103 cm^{-1}. Hydrogen-bonded silanol groups give bands in the region of 3300–3600 cm^{-1}. In particular, a new strong peak at 571 cm^{-1} is exhibited in the spectrum of silica-supported dichlorophosphate, which is attributable to the absorption



Scheme 2. Synthesis of silica-supported dichlorophosphate.

of P-Cl. The silica-supporting capacity for $POCl_2$ is ca. 2.81 mmol/g. The specific surface area for the sample is ca. 82 m^2/g.

To explore the availability of silica-supported dichlorophosphate as a recoverable cyclodehydrant under microwave irradiation, the synthesis of 3,6-diphenyl [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole (**4a**) by reacting benzoic acid with thiocarbohydrazide was selected as a model synthetic reaction. The optimal reaction conditions including reactant ratio, reaction time, and microwave power were investigated. It was found that when the ratio of benzoic acid, thiocarbohydrazide, and silica-supported dichlorophosphate was 2.2:1:2.2 and the microwave power was 650 W, the reaction gave the best yield for **4a** within 8 min. Using similar conditions, a series of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**4a**–**j**) were synthesized in excellent yield (Table 1, Scheme 3). The different substituents on the aromatic rings have no significant effect on the reaction conditions and the reaction yields. After the reactions, the

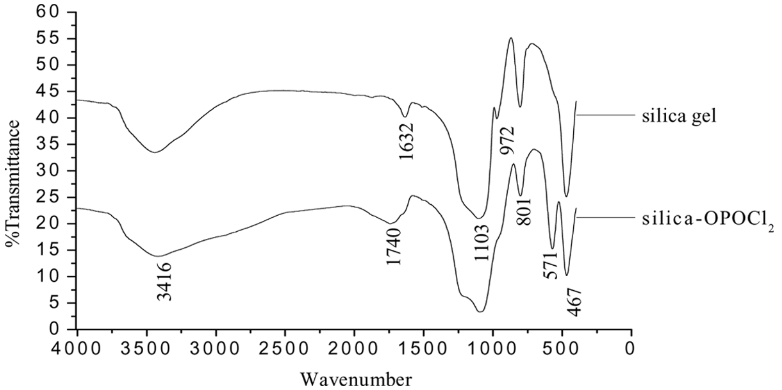
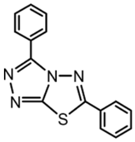
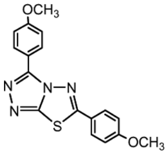
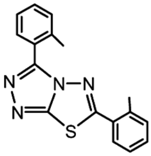
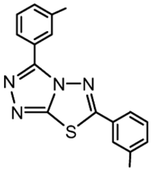
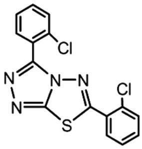
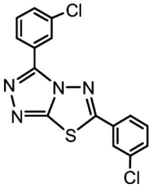
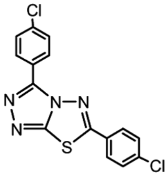


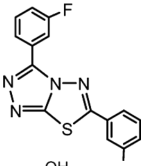
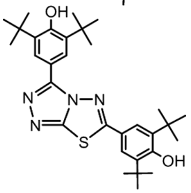
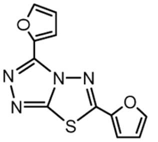
Figure 1. IR spectra of silica gel and silica-supported dichlorophosphate.

Table 1. Synthesis of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles (**4a–j**)

Compound	R	Product	Mp. (lit.) (°C)	Yield (%)[a]
4a	C_6H_5		200–202 (204–205)[6]	88
4b	$4\text{-}CH_3OC_6H_4$		160–162	84
4c	$2\text{-}CH_3C_6H_4$		120–122	83
4d	$3\text{-}CH_3C_6H_4$		124–126	84
4e	$2\text{-}ClC_6H_4$		220–222	80
4f	$3\text{-}ClC_6H_4$		196–194	81
4g	$4\text{-}ClC_6H_4$		214–216 (235–236)[7]	81

(*Continued*)

Table 1. Continued

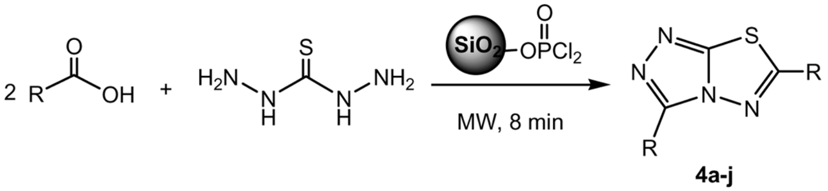
Compound	R	Product	Mp. (lit.) (°C)	Yield (%)[a]
4h	3-FC$_6$H$_4$		190–192	79
4i	3,5-((CH$_3$)$_3$C)$_2$-4-(OH)-C$_6$H$_2$		160–162	87
4j	Fur-2-yl		202–204 (204–206)[8]	84

[a]The yields refer to the isolated product.

resultant of silica-supported cyclodehydrant could be easily isolated and recovered from the reaction system by only filtration, and this efficiently avoided the corrosion and pollution caused by using liquid cyclodehydrant, such as phosphorus oxychloride. The pure product could be readily obtained by evaporating off the solvent and washing with water.

In contrast, the synthesis of **4a** was also tested by the traditional heating method. However, after 10 h reflux in ethanol, only 51% yield of **4a** was obtained.

In conclusion, we have developed an expeditious, novel method to 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles by the



Scheme 3. Synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

reactions of aromatic carboxylic acids with thiocarbohydrazide using silica-supported dichlorophosphate as a recoverable cyclodehydrant and microwave irradiation as thermal source. The features of short reaction time, good reaction yield, no environmental pollution, and simple workup procedure make this protocol a good alternative to the synthesis of the corresponding heterocyclic compounds.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Digilab FTS 3000 Fourier transform (FT)-IR spectrophotometer and ^{1}H NMR spectra on a Mercury-400BB instrument using $CDCl_3$ 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[9] and silica-supported dichlorophosphate[10] were prepared according to the literature procedure.

General Procedure for the Preparation of 3,6-Disubstituted [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles (4a–j)

Silica-supported dichlorophosphate (4.4 mmol) was added to the solution of aromatic carboxylic acid (4.4 mmol) and thiocarbohydrazide (2 mmol) in 25 mL of ethanol. The mixture was subjected to the microwave irradiation at reflux condition for 8 min under the power of 650 W. The completion of the reaction was monitored by thin-layer chromatography (TLC). Then the resulting mixture was filtered to recover the silica-supported reagent, which could be reused after regeneration, and the filtrate was evaporated off the solvent. The resulting solid was washed with cold ethanol (5 mL) and water (10 mL) and recrystallized from DMF–EtOH–H_2O (1:5:1) to give the product. The analytical data for compounds **4a–j** are given next.

Data

Compound **4a**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58–8.34 (m, 10H, Ar-H). IR (KBr, ν, cm^{-1}): 1676, 1514, 1466, 1380, 1237, 684. Anal. calcd. for $C_{15}H_{10}N_4S$: C, 64.73; H, 3.62; N, 20.13. Found: C, 64.60; H, 3.61; N, 20.18.

Compound **4b**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.02–8.35 (m, 8H, Ar-H), 3.89 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 1690, 1611, 1512, 1431, 1257, 693. Anal. calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.25; H, 4.16; N, 16.51.

Compound **4c**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39–8.28 (m, 8H, Ar-H), 2.43 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 1650, 1608, 1519, 1461, 1269, 684. Anal. calcd. for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29. Found: C, 66.77; H, 4.62; N, 18.24.

Compound **4d**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–8.21 (m, 8H, Ar-H), 2.42 (s, 6H, CH_3). IR (KBr, ν, cm^{-1}): 1651, 1607, 1514, 1462, 1261, 680. Anal. calcd. for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29. Found: C, 66.72; H, 4.60; N, 18.35.

Compound **4e**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54–8.23 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 1606, 1540, 1496, 1448, 1243, 691. Anal. calcd. for $C_{15}H_8Cl_2N_4S$: C, 51.89; H, 2.32; N, 16.14. Found: C, 51.78; H, 2.31; N, 16.20.

Compound **4f**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60–8.40 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 1608, 1496, 1472, 1460, 1248, 694. Anal. calcd. for $C_{15}H_8Cl_2N_4S$: C, 51.89; H, 2.32; N, 16.14. Found: C, 52.00; H, 2.30; N, 16.09.

Compound **4g**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71–8.33 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 1626, 1595, 1472, 1468, 1259, 697. Anal. calcd. for $C_{15}H_8Cl_2N_4S$: C, 51.89; H, 2.32; N, 16.14. Found: C, 51.98; H, 2.34; N, 16.19.

Compound **4h**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–8.21 (m, 8H, Ar-H). IR (KBr, ν, cm^{-1}): 1591, 1480, 1460, 1453, 1261, 692. Anal. calcd. for $C_{15}H_8F_2N_4S$: C, 57.32; H, 2.57; N, 17.83. Found: C, 57.41; H, 2.56; N, 17.88.

Compound **4i**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, 2H, Ar-H), 7.75 (s, 2H, Ar-H), 5.76 (s, 1H, OH), 5.54 (s, 1H, OH), 1.51 (s, 36H, CH_3). IR (KBr, ν, cm^{-1}): 1600, 1514, 1465, 1419, 1240, 700. Anal. calcd. for $C_{31}H_{42}N_4O_2S$: C, 69.63; H, 7.92; N, 10.48. Found: C, 69.71; H, 7.93; N, 10.54.

Compound **4j**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.79–8.12 (m, 6H, Fu-H). IR (KBr, ν, cm^{-1}): 1623, 1593, 1520, 1508, 1254, 699. Anal. calcd. for $C_{11}H_6N_4O_2S$: C, 51.16; H, 2.34; N, 21.69. Found: C, 51.21; H, 2.35; N, 21.73.

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