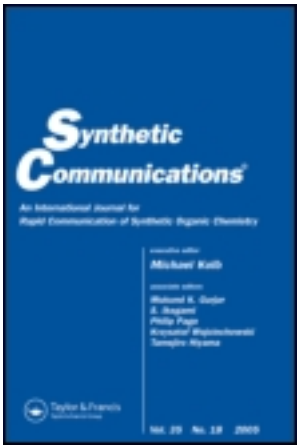

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Microwave Accelerated Solvent-Free Synthesis of 1,3,4-Oxadiazoles Using Polymer Supported Dehydration Reagent

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ABSTRACT

2-Aryl-5-(coumarin-3′-yl)-1,3,4-oxadiazoles are efficiently synthesized by microwave accelerated solvent-free procedure in high yield via the condensation of coumarin-3-carboxylic acid with (un)substituted benzoic acid hydrazides using poly(ethylene glycol) (PEG) supported dichlorophosphate as dehydration reagent.

Key Words: 1,3,4-Oxadiazole; Polymer supported reagent; Microwave irradiation; Solvent-free.

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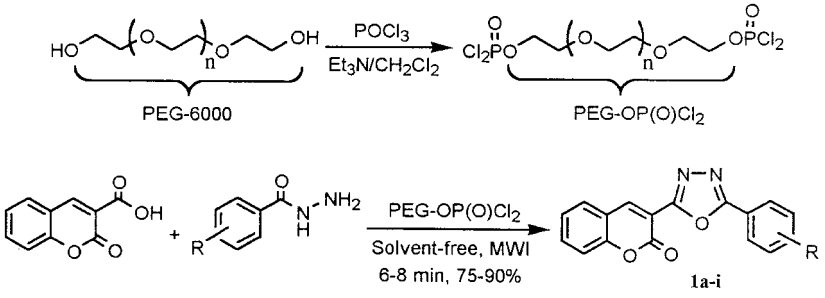
INTRODUCTION

1,3,4-Oxadiazole derivatives have been of interest to the medicinal chemists for many years because of their antimicrobial,[1] antimitotic,[2] antiinflammatory,[3] psychotropic,[4] antiaflatoxigenic,[5] and anticonvulsant[6] activities. 1,3,4-Oxadiazoles have been synthesized by traditional methodology via several approaches, three of the more popular being the cyclization of diacylhydrazides,[7] the cyclization of acylthiosemicarbazides,[8] and the oxidation of acylhydrozones.[9] However, long reaction procedure, extended reaction period at elevated temperature and harsh reagents, e.g., $SOCl_2$,[7] polyphosphoric acid[10] or sulfuric acid,[11] are usually encountered. Very recently, Brain[12] has reported a mild strategy for 1,3,4-oxadiazoles, which utilizes easily separated and recoverable polymer supported Burgess reagent as condensation reagent, and therefore represents a good alternative to 1,3,4-oxadiazoles. In this paper, we report a one-step solvent-free protocol for 1,3,4-oxadiazoles using more efficient poly(ethylene glycol) (PEG) supported dichlorophosphate as dehydration reagent.

The reaction of PEG-6000 with 2 eq. of phosphorus oxychloride in the presence of triethylamine afforded PEG supported dichlorophosphate in almost quantitative yield. The reaction proceeded at 0–5°C at the beginning, and at room temperature or 40°C since then. The product was obtained only by precipitation with ether. The finely mixed solid of coumarin-3-carboxylic acid with equivalent of various (un)substituted benzoic acid hydrazides and 1.2 eq. of PEG supported dichlorophosphate was irradiated in microwave oven to readily afford 2-aryl-5-(coumarin-3′-yl)-1,3,4-oxadiazoles (**1a–i**) in high yield (Sch. 1). The whole courses of reactions were easily monitored by TLC. All reactions can be completed within 6–8 min at 490-W microwave power with slightly quick rate for aryl rings bearing electron-donating groups and slightly slow for those bearing electron-withdrawing groups.



Scheme 1.

The desired products were easily isolated by washing away the polymer reagent with water, and the PEG was readily recovered from the aqueous solution by extraction. The results are outlined in Table 1.

In conclusion, we have devised a rapid, one-step and high yielding protocol for the preparation of 1,3,4-oxadiazoles including coumarin substituent. The features of simple work-up procedure, utilization of easily preparative and recoverable polymer supported reagent make this method suitable to high throughput and combinatorial synthesis of 1,3,4-oxadiazoles.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR spectrophotometer and ^{1}H NMR spectra on a Avanci-D2X-200 instrument using $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Elemental analyses were performed on a Vario El Elemental Analysis instrument. Melting points were determined with an electrothermal micromelting point apparatus and uncorrected. (Un)substituted benzoic acid hydrazides[13] were prepared according to literature procedure.

Preparation of PEG Supported Dichlorophosphate

To a solution of $POCl_3$ (0.93 mL, 10 mmol) in 20 mL of CH_2Cl_2, the mixture of PEG-6000 (30 g, 10 mmol OH) and Et_3N (1.67 mL, 12 mmol) in

Table 1. Solvent-free synthesis of **1a–i** under MWI using PEG supported reagent.

Compound	R	Reaction time (min)	M.p. (°C)	Yield (%)[a]
1a	H	7	194–195	76
1b	2-Cl	8	205–207	81
1c	4-Cl	8	245–246	75
1d	3-O_2N	8	252–254	90
1e	4-O_2N	8	>300	75
1f	4-CH_3O	6	223–224	81
1g	3-CH_3	6	202–203	87
1h	4-I	7	294–296	85
1i	2-HO	6	>300	83

[a]Yields refer to the isolated products.

80 mL of CH_2Cl_2 was added dropwise at 0–5°C. Then the resulting solution was stirred for 2 hr at room temperature and refluxed for additional 5 hr. The insoluble solid was removed by filtration and the solution was concentrated to a third of its volume. Then appropriate ether was added and the precipitate was filtered to afford product as a white solid. Yield: 98%. M.p.: 52–53°C. IR (KBr, ν, cm^{-1}): 1036 (P═O).

General Procedure for the Preparation of Compound 1a–i

The mixture of coumarin-3-carboxylic acid (1 mmol), (un)substituted benzoic acid hydrazides (1 mmol), and PEG supported dichlorophosphate (1.2 mmol) was mixed using a pestle and mortar until a fine and homogeneous powder was obtained. Then the mixture was irradiated in a microwave oven for 6–8 min irradiating time at 490-W power by means of 1 min irradiation then 30 sec interval. The completion of reactions was monitored by TLC using ethyl acetate, acetone, and petroleum ether (1 : 1 : 2) as eluent. Then distilled water (20 mL) was added to the resulting mixture, and the precipitate was collected by filtration and recrystallized from EtOH to afford product. The physical and spectral data of compounds are shown below:

1a. White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.68 (s, 1H, ═CH), 6.89–8.04 (m, 9H, Ar-H). MS: m/z, 290 (M^+). IR (KBr, ν, cm^{-1}): 1732 (C═O), 1611, 1496 (C═N). Anal. Calcd. for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.22; H, 3.56; N, 9.71.

1b. White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.72 (s, 1H, ═CH), 7.05–8.19 (m, 8H, Ar-H). MS: m/z, 324 (M^+). IR (KBr, ν, cm^{-1}): 1749 (C═O), 1619, 1508 (C═N). Anal. Calcd. for $C_{17}H_9ClN_2O_3$: C, 62.88; H, 2.79; N, 8.63. Found: C, 62.96; H, 2.70; N, 8.75.

1c. White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.73 (s, 1H, ═CH), 7.04–8.20 (m, 8H, Ar-H). MS: m/z, 324 (M^+). IR (KBr, ν, cm^{-1}): 1749 (C═O), 1618, 1509 (C═N). Anal. Calcd. for $C_{17}H_9ClN_2O_3$: C, 62.88; H, 2.79; N, 8.63. Found: C, 62.79; H, 2.75; N, 8.56.

1d. White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.76 (s, 1H, ═CH), 7.10–8.29 (m, 8H, Ar-H). MS: m/z, 335 (M^+). IR (KBr, ν, cm^{-1}): 1758 (C═O), 1626, 1516 (C═N). Anal. Calcd. for $C_{17}H_9N_3O_5$: C, 60.90; H, 2.71; N, 12.53. Found: C, 60.81; H, 2.67; N, 12.64.

1e. White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.78 (s, 1H, ═CH), 7.11–8.30 (m, 8H, Ar-H). MS: m/z, 335 (M^+). IR (KBr, ν, cm^{-1}): 1759 (C═O), 1628, 1517 (C═N). Anal. Calcd. for $C_{17}H_9N_3O_5$: C, 60.90; H, 2.71; N, 12.53. Found: C, 60.99; H, 2.65; N, 12.45.

1f. White solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.70 (s, 1H, ═CH), 7.02–8.15 (m, 8H, Ar-H), 3.91 (s, 3H, OCH_3). MS: m/z, 320 (M^+). IR (KBr, ν,

cm^{-1}): 1746 (C═O), 1617, 1500 (C═N). Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.62; H, 3.70; N, 8.68.

1g. White solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.66 (s, 1H, ═CH), 6.82–8.01 (m, 8H, Ar-H), 2.39 (s, 3H, CH_3). MS: m/z, 304 (M^+). IR (KBr, ν, cm^{-1}): 1729 (C═O), 1610, 1493 (C═N). Anal. Calcd. for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21. Found: C, 70.92; H, 3.91; N, 9.14.

1h. White solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.77 (s, 1H, ═CH), 7.08–8.25 (m, 8H, Ar-H). MS: m/z, 416 (M^+). IR (KBr, ν, cm^{-1}): 1751 (C═O), 1619, 1512 (C═N). Anal. Calcd. for $C_{17}H_9IN_2O_3$: C, 49.06; H, 2.18; N, 6.73. Found: C, 48.93; H, 2.15; N, 6.66.

1i. White solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.72 (s, 1H, ═CH), 7.04–8.16 (m, 8H, Ar-H). MS: m/z, 306 (M^+). IR (KBr, ν, cm^{-1}): 1748 (C═O), 1619, 1502 (C═N). Anal. Calcd. for $C_{17}H_{10}N_2O_4$: C, 66.67; H, 3.29; N, 9.15. Found: C, 66.76; H, 3.35; N, 9.08.

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