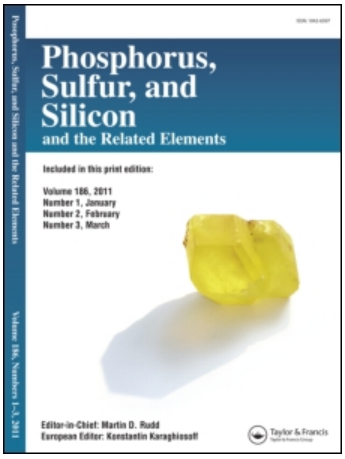

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A Novel, One-Pot Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazoles Using 1,4-Bis(Triphenylphosphonium)-2-Butene Peroxodisulfate

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Online publication date: 24 February 2010

To cite this Article Badri, Rashid and Gorjizadeh, Maryam(2010) 'A Novel, One-Pot Synthesis of 2,5-Disubstituted-1,3,4-Oxadiazoles Using 1,4-Bis(Triphenylphosphonium)-2-Butene Peroxodisulfate', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 3, 544 — 549
To link to this Article: DOI: 10.1080/10426500902840887
URL: http://dx.doi.org/10.1080/10426500902840887

Phosphorus, Sulfur, and Silicon, 185:544–549, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500902840887

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A NOVEL, ONE-POT SYNTHESIS OF 2,5-DISUBSTITUTED-1,3,4-OXADIAZOLES USING 1,4-BIS(TRIPHENYLPHOSPHONIUM)-2-BUTENE PEROXODISULFATE

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An efficient and convenient synthesis of 1,3,4-oxadiazoles from aromatic aldehydes, acyl hydrazide, and 1,4- bis(triphenylphosphonium)-2-butene peroxodisulfate is reported.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Acyl hydrazide; aromatic aldehyde; 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate; oxadiazole

INTRODUCTION

1,3,4-Oxadiazole derivatives have been reported to possess significant pharmacological[1] and biological activities including antimicrobial,[2] antifungal,[3] and anti-inflammatory.[4] 2,5-Disubstituted-1,3,4-oxadiazoles were disclosed as a broad-spectrum insecticide acaricide having potential agricultural use.[5] The common synthetic route to 1,3,4-oxadiazole involves the cyclization of diacylhydrazines and thiosemicarbazides. Typically, this reaction is carried out by using thionyl chloride,[6] phosphorous oxychloride,[7] phosphorous pentoxide,[8] triphenylphosphine,[9] or tosyl chloride/pyridine.[10] In these methods, the reaction conditions tend to be harsh, and long reaction times are generally needed. An alternative route to 1,3,4-oxadiazoles by oxidative cyclization from the corresponding acylhydrazones proceeds with lead tetraacetate,[11] lead(IV) oxide,[12] potassium permanganate,[13] or electrochemical methods.[14] These protocols are routinely multistep in nature. Few reliable, simple examples have been reported for the one-pot synthesis of 1,3,4-oxadiazoles.[15]

Peroxodisulfate ion is an excellent and versatile oxidant, used mostly for the oxidation of compounds in aqueous solution.[16] In spite of the great convenience of using $K_2S_2O_8$, $Na_2S_2O_8$, or $(NH_4)_2S_2O_8$ and relatively high oxidation potential, oxidation by peroxodisulfate generally does not proceed at a convenient rate. This can be largely attributed to the

Received 19 November 2008; accepted 23 February 2009.
We thank Shahid Chamran University for financial support of this work.
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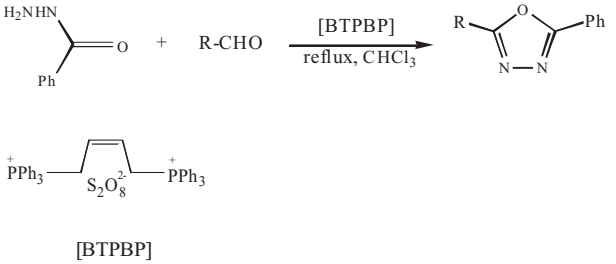
rate-limiting homolysis given in Equation (1), which has an activation energy of approximately 30 kcal/mol.

$$S_2O_8^{2-} \longrightarrow 2S\dot{O}_4 \quad (1)$$

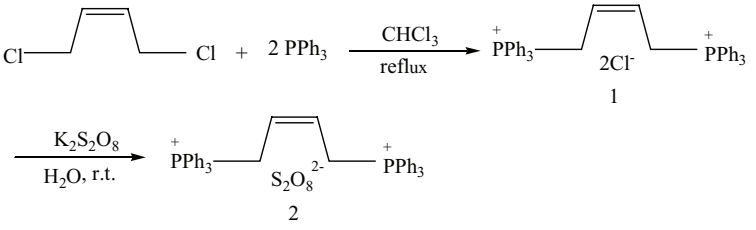
Thus certain limitations may be observed with these reagents. The decomposition of the peroxodisulfate ion requires strong mineral acids and heavy metal ions[17] as catalysts, and also protic and polar solvents are needed, so, recently the modification of $K_2S_2O_8$, $Na_2S_2O_8$, or $(NH_4)_2S_2O_8$ has attracted a great deal of attention.

In this article we report our efficient, one-pot, solution-phase preparation of 2,5-disubstituted-1,3,4-oxadiazoles directly from the acyl hydrazide and aromatic aldehydes using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an oxidant under non-aqueous and aprotic conditions (Scheme 1).



Scheme 1 Synthesis of 1,3,4-oxadiazoles from aromatic aldehyde, acyl hydrazide, and 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate as an oxidant.

This reagent can be readily prepared by adding an aqueous solution of potassium peroxodisulfate to a solution of 1,4-bis(triphenylphosphonium)-2-butene dichloride in water. This white solid is very stable and can be stored for months without losing its activity. It is soluble in acetonitrile, methanol, dichloromethane, chloroform, and ethyl acetate and is slightly soluble in CCl_4 and diethyl ether (Scheme 2).



Scheme 2 Preparation of 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate.

Compounds **1** and **2** were confirmed by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR.

RESULTS AND DISCUSSION

Stirring a mixture of compound **2**, acyl hydrazide, and an aromatic aldehyde in chloroform at reflux gave, after workup and isolation, the desired 1,3,4-oxadiazole compound in high yield. The results obtained are summarized in Table I.

As indicated in Table I, a variety of aromatic aldehydes bearing electron-releasing or electron-withdrawing substituents reacted smoothly and gave corresponding oxadiazoles in moderate to good yields.

The possible mechanism of the oxidation of the initially formed cyclic intermediate **I** in the presence of proxodisulfate involves an initial one electron transfer from **I** to the sulfate anion radical to give radical cation **II**. This radical cation loses a proton to form the intermediate **III**, which transfers an electron to the sulfate anion radical to form the cation and subsequently results in the aromatized product by homolysis. Before the use of oxidant **2**, we conducted the same reactions with all aldehydes of Table I under the same reaction conditions in the presence of $K_2S_2O_8$ as the oxidant, and found out that a mixture of possible desired and unidentified products was formed. The yields of isolated oxadiazoles were especially low, and the reaction times were higher than in the case of oxidant **2**. Also, the saturated form of compound **2** was prepared either via hydrogenation of compound **1** followed by $Cl^- \rightarrow S_2O_8{}^{2-}$ exchange or the reaction of 1,4-dichlorobutane with triphenylphosphine followed by anion exchange. Utilizing this saturated oxidant for the synthesis of oxadiazoles faces with long reaction times and lower yields than unsaturated oxidant **2** (see Scheme S1, available online in the Supplemental Materials).

The influence of the various solvents such as H_2Cl_2, CCl_4, $CHCl_3$, and CH_3CN on the yield of the reaction was investigated using benzaldehyde as the substrate. The obtained results showed that chloroform is the best choice for the oxidation reaction. This can be attributed to the enhanced solubilizing power of the solvent for the oxidant. In conclusion, the present work offers several advantages including a simple oxidation method, employing readily available reagents, high conversions, and high isolated yields, which make it a useful and attractive process for the synthesis of 1,3,4-oxadiazoles.

Table I Yield and physical characteristic of 1,3,4-oxadiazoles using 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate[a]

Entry	R	Yield[b](%)	Mp (°C)	Ref.
1	Ph	60	200–204	18
2	4-Cl–C_6H_4	73	216–218	18
3	4-Me–C_6H_4	81	219	18
4	4-MeO–C_6H_4	60	145–148	18
5	4-O_2N–C_6H4	72	244–246	18
6	3-O_2N–C_6H_4	75	188–189	18
7	4-I–C_6H_4	83	218	19
8	2,4-Cl_2–C_6H_3	69	102	20
9	3-Cl–C_6H_4	72	194	19
10	4-Br–C_6H_4	80	228	19
11	2-Furyl	68	99	21
12	3-Pyridyl	70	105–107	22

[a]Products were identified by comparison of their physical and spectral data with those of authentic samples.
[b]Isolated yields based on the aldehyde.

EXPERIMENTAL

All products were characterized by comparison of their physical data, IR, ^{1}H NMR, and ^{13} C NMR spectra with authentic samples. The IR spectra were recorded on a Bomem FT-IR Spectrometer. ^{1}H NMR and ^{13}C NMR spectra were taken on a 400 MHz Brucker Spectrometer. 1,4-Bis(triphenylphosphonium)-2-butene peroxodisulfate was prepared and other chemicals were purchased from the Merck Chemical Company, Darmstadt, Germany. The purity determination of the products and reaction monitoring were accomplished by TLC on polygram SILG/UV 254 plates.

Preparation of 1,4-Bis(triphenylphosphonium)-2-butene Dichloride (1)

To a solution of 1,4-dichlorobutene (0.63 g, 5 mmol) in $CHCl_3$ (10 mL) in a 50 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser, triphenylphosphine (2.62 g, 10 mmol) was added. The reaction mixture was refluxed for 2.5 h. The solution was cooled to room temperature, and then diethyl ether was added dropwise until an oily product was separated. The ether was removed by decantation, and acetone (40 mL) was added. The acetone solution, stirred for 40 min, afforded a white precipitate, which was filtered and then dried by anhydrous $CaCl_2$. Yield (80%), mp 278–279°C. IR (KBr): $\upsilon = 3053, 2755, 1613, 1575, 1478, 1437,754, 693, 556$ (cm^{-1}). ^{13}C NMR, ($CDCl_3$): $\delta = 20.7, 120.8, 132.15, 134.2, 137.01, 140.17$. ^{1}H NMR, ($CDCl_3$): $\delta = 5.7$ (dd, 4H), 6.3 (m, 2H), 7.79–8 (m, 30H). Anal. Calcd: C, 73.994; H, 5.544; P, 9.542; Cl, 10.920. found: C, 73.899; H, 5.552; P, 9.523; Cl, 10.897%.

Preparation of 1,4-Bis(triphenylphosphonium)-2-butene Peroxodisulfate (2)

In a 25 mL round-bottomed flask with a magnetic stirrer, a solution of $K_2S_2O_8$ (0.54 g, 2 mmol) in H_2O (5 mL) was prepared. Compound **1** (1.298 g, 2 mmol) was added to this solution, and the reaction mixture was stirred at ambient temperature for 3 h. The resulting white precipitate was filtered, washed with distilled water (10 mL), and dried in vacuo; yield (78%), mp 205–208°C. IR (KBr): $\upsilon = 3053, 2750, 1623, 1585, 1472, 1437, 750, 724, 689, 556$ (cm^{-1}). ^{13}C NMR, ($CDCl_3$): $\delta = 19.04, 119.45, 130.05, 133.98, 136.91, 138.8$. ^{1}H NMR, ($CDCl_3$): $\delta = 4.7$ (dd, 4H), 5.8 (m, 2H), 7.68–8 (m, 30H). Anal. Calcd: C, 62.350; H, 4.672; P, 8.039; S, 8.324. found: C, 62.345; H, 4.670; P, 8.036; S, 8.314%.

General Procedure for Preparation of 2,5-Disubstituted-1,3,4-oxadiazoles

To a solution of acyl hydrazide (1 mmol) and aromatic aldehyde (1 mmol) in chloroform (15 mL) in a 50 mL round-bottomed flask equipped with a condenser and a magnetic stirrer, 1,4-bis(triphenylphosphonium)-2-butene peroxodisulfate (1 mmol) was added in small portions. The reaction mixture was refluxed for 12 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, it was cooled to room temperature and filtered. Water (15 mL) was added and extracted with chloroform (3 × 15 mL). The combined organic layers solution was dried over $MgSO_4$. The solvent was concentrated in vacuo; the resulting product was directly charged on a small silica gel column and eluted with a mixture of diethyl ether and *n*-hexane (1:4) to afford the pure product.

2,5-Diphenyl-1,3,4-oxadiazole (entry 1). mp: 200–204°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.76 (m, 6H), 8.14–8.18 (d, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.73, 128.58, 129.01, 131.69, 164.17.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (entry 2). mp: 216–218°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.66 (m, 3H), 7.83–7.86 (d, 2H), 8.23–8.41 (d, 2H), 8.14–8.18 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.67, 125.98, 128.58, 128.63, 129.07, 130.18, 131.67, 135.81, 164.05.

2-(4-Metylphenyl)-5-phenyl-1,3,4-oxadiazole (entry 3). mp: 219°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H), 7.23 (d, 2H), 7.53–7.71 (m, 3H), 7.94–7.97 (d, 2H), 8.14–8.18 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 126.57, 123.78, 128.58, 128.93, 129.01, 129.97, 131.69, 142.21, 164.15.

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (entry 4). mp: 145–148°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 3H), 7.12 (d, 2H), 7.53–7.71 (m, 3H), 7.86 (d, 2H), 8.14–8.15 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5, 118.37, 118.98, 122.54, 123.73, 125.58, 129.07, 131.61, 164.11, 165.85.

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (entry 5). mp: 244–246°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.61 (m, 3H), 8.13–8.16 (d, 2H), 8.33–8.44 (d, 2H), 8.58 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.77, 122.98, 123.73, 125.60, 129.01, 131.68, 138.60, 149.85, 164.15.

2-(3-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (entry 6). mp: 188–189°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.61 (m, 3H), 8.03–8.06 (dd, 1H), 8.14–8.17 (d, 2H), 8.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.77, 123.08, 123.73, 128.60, 129.01, 131.28, 131.69, 134.85, 137.15, 1489.5, 164.18, 165.72.

2-(4-Iodophenyl)-5-phenyl-1,3,4-oxadiazole (entry 7). mp: 218°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.66 (m, 3H), 7.86 (d, 2H), 7.98–8.01 (d, 2H), 8.14–8.18 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 93.67, 122.18, 123.78, 128.65, 129.07, 131.68, 131.97, 138.83, 164.01.

2-(2,4-Dichlorophenyl)-5-phenyl-1,3,4-oxadiazole (entry 8). mp: 102°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.66 (m, 4H), 7.72 (s, 1H), 8.07 (d, 1H), 8.14–8.17 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.97, 123.74, 123.23, 128.55, 129.03, 131.69, 133.67, 134.19, 135.89, 138.02, 164.05, 166.12.

2-(3-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (entry 9). mp: 194°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.66 (m, 4H), 7.77–7.87 (dd, 1H), 7.97 (s, 1H), 8.14–8.17 (d, 2H), 8.71 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 120.67, 121.98, 123.73, 124.33, 128.54, 129.01, 130.67, 131.69, 133.89, 136.02, 164.05, 165.1.

2-(4-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (entry 10). mp: 228°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.57 (m, 3H), 7.66 (d, 2H), 7.79(d, 2H), 8.14–8.18 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.17, 123.48, 123.78, 128.55, 129.05, 131.58, 131.69, 164.01.

2-(2-Furyl)-5-phenyl-1,3,4-oxadiazole (entry 11). mp: 99°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (dd, 1H), 7.37 (d, 1H), 7.55–7.71 (m, 4H), 8.14–8.17 (d, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.48, 113.79, 123.73, 128.58, 129.03, 131.69, 141.89, 146.30, 152.85, 164.17.

2-(3-Pyridyle)-5-phenyl-1,3,4-oxadiazole (entry 12). mp: 105–107°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.71 (m, 3H), 7.82–7.87 (m, 2H), 8.14–8.17 (d, 2H), 8.78 (d, 1H), 9.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.77, 122.98, 123.73, 128.60, 129.03, 130.51, 131.69, 146.85, 157.05, 164.18.

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