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A facile route for the synthesis of vinyl-substituted 1,3,4-oxadiazoles

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Abstract An efficient synthesis of vinyl-substituted 1,3,4-oxadiazoles using *o*-nitrophenyl sulfoxide precursor via *syn*-elimination reaction using sodium acetate in THF is described. This method is cost effective as it uses cheap *o*-nitrothiophenol and can be used in the synthesis of vinyl intermediates during synthesis of bioactive compounds, which avoids the use of any toxic metals.

Keywords Vinyl 1,3,4-oxadiazole · *o*-Nitrothiophenol · *β-Syn* elimination · *o*-Nitrophenyl sulphoxide

Introduction

1,3,4-oxadiazoles are privileged structural units, not only in pharmaceutical chemistry [1, 2] but also in pesticide chemistry [3, 4], polymer chemistry [5–7], and material science [8–10]. Among 1,3,4-oxadiazoles, vinyl-substituted 1,3,4-oxadiazoles are versatile intermediates used for the synthesis of complex natural products and biologically active compounds, which are observed in a wide range of pharmacological and therapeutic agents, such as antiallergic, antibacterial, and anti-HIV [11, 12]. Some vinyl-substituted 1,3,4-oxadiazole derivatives play an important role as useful additives in material chemistry [13, 14].

There are several synthetic approaches reported in the literature for the synthesis of vinyl 1,3,4-oxadiazole. The most common approach involves the conventional way of dehydration of acyl hydrazide (Route A) [15, 16]. This method has certain drawbacks as it involves the synthesis of α,β-unsaturated hydrazide intermediate. During the synthesis of α,β-unsaturated hydrazide, the predominant product is pyrazolidinone due to hydrazinolysis and an undesired subsequent intramolecular

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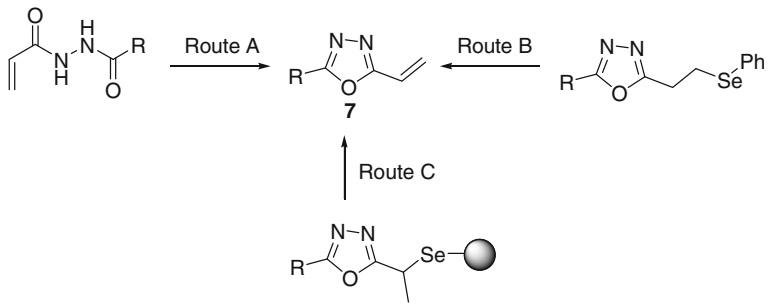


Scheme 1 Literature-reported methods for the synthesis of vinyl-substituted 1,3,4-oxadiazole

Michael-type cyclisation [17–19]. Another disadvantage of the cyclocondensation method is the complicated isolation procedure and low yield because of the reactive terminal double bond present in vinyl oxadiazole, which undergoes polymerization at higher reaction temperatures [20]. A second approach involves *syn* elimination of phenylselanylethyl-substituted oxadiazole (Route B) [21]. This approach has the advantage over the conventional method, such as good yield and simple work-up procedure. A third approach involves the use of polymer-bound selenopropionic acid (Route C) [22] (Scheme 1). But both these approaches demand the use of selenium metal which is carcinogenic and genotoxic and has little benefit in the synthesis of bioactive compounds.

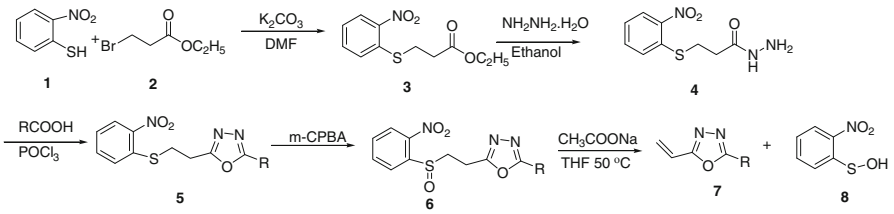
Results and discussion

Taking into account the pharmacological importance of vinyl oxadiazole intermediates, and as part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds [23–26], we have focused on the development of the synthesis of this nucleus which does not involve any toxic metal.

From our careful study of all the reported literature routes, we have come to the conclusion that we should introduce a non-metallic functional group that could be used to mask the vinylic functionality, which can serve as a pro-vinyl intermediate which can undergo *syn*-elimination to get vinyl-substituted oxadiazole.

Recently, in the literature, *o*-nitrophenyl sulfoxide was found to be an efficient precursor for the synthesis of various alkenes [27] and vinylglycines [28] via *syn*-periplanar *β*-elimination. We extended this methodology to develop a mild and efficient process for the synthesis of vinyl oxadiazole via *β*-elimination reaction. (Scheme 2).

We began the synthesis from ethyl *β*-bromo propionate, which condensed with *o*-nitrothiophenol to form sulphide **3**. Reaction of hydrazine hydrate with sulphide **3** gave hydrazide **4**, which in turn acylated and cyclized in the presence of phosphorus oxychloride to give nitrothiophenylethyl-1,3,4-oxadiazole **5**. Compound **5** underwent an oxidation reaction using *m*-chloroperbenzoic acid to form sulfoxide



Scheme 2 Synthesis of vinyl 1,3,4-oxadiazole

intermediate **6**, which was followed by sulfenic acid *syn*-elimination to obtain vinyl-substituted oxadiazoles **7** in good yield.

To optimize the reaction conditions for *β-syn* elimination reaction, precursor **6a** was used as model substrate. As a starting point, the *β-syn* elimination of *p*-nitrophenyl sulfoxide **6a** was carried out using sodium acetate in 10 volumes of toluene at reflux temperature; it completed within 2 h but provided a low yield (30 %). The reason for the low yield may be the higher temperature which leads to polymerization of the vinyl oxadiazole. We then carried out this reaction at a lower temperature using several solvents such as acetonitrile, dichloromethane, 1,4-dioxane, 1,2-dimethoxyethane, and THF, among which THF was found to be the best with 75 % yield at 50 °C. It was also observed that when the reaction was carried out at a higher temperature, the yield decreased considerably. We tested several bases such as sodium carbonate, potassium carbonate, and sodium acetate, of which sodium acetate provided better yields. Using the optimized reaction conditions, we examined the scope of this reaction and the results are summarized in Table 1. Electron-withdrawing substituted derivatives (**6j**) afforded product in 70 % yield with a faster reaction rate, while electron-donating substituents (**6b–e**) gave 55–60 % yield. The halo-substituted aromatic compounds (**6f–i**) gave a moderate

Table 1 Vinyl-substituted 1,3,4-oxadiazoles

R	Product	Yield	Product	Yield	Product	Yield
C_6H_5	5a	75	6a	78	7a	75
4-CH_3 C_6H_4	5b	71	6b	74	7b	55
4-OCH_3 C_6H_4	5c	62	6c	68	7c	57
Naphthyl	5d	73	6d	71	7d	49
3-CH_3 C_6H_4	5e	80	6e	76	7e	61
4-F C_6H_4	5f	79	6f	72	7f	69
4-Cl C_6H_4	5g	71	6g	73	7g	66
4-Br C_6H_4	5h	67	6h	69	7h	65
2-Br C_6H_4	5i	72	6i	73	7i	68
4-NO_2 C_6H_4	5j	69	6j	69	7j	70
i-C_3H_7	5k	65	6k	78	7k	48
CH_3	5l	63	6l	70	7l	50

yield at 65–69 %. We extended the scope of the reaction for aliphatic compounds (**6k–l**), which provided a lower yield (48–50 %) and slower reaction.

Experimental

Chemicals were procured from Aldrich Chemical (Bangalore, India). Reactions were monitored, and the purity of the products was checked by thin layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates with visualization by UV light. Melting points were determined on a Buchi Melting Point B-545 apparatus. The IR spectra (in KBr pellets) were recorded on a Hyper IR spectrophotometer. ^{1}H-NMR and ^{13}C spectra were recorded on Bruker (300 and 75 MHz) spectrometer instruments, respectively, in DMSO-d_6. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a MS-3200Q trap spectrometer. Elemental analysis was performed on a Carlo Erba CHNS-O 1108 Elemental analyzer.

General procedure for the synthesis of ethyl 3-(2-nitrophenylthio)propanoate, 3

To a stirred mixture of 2-nitrothiophenol (10 mol) in DMF, anhydrous potassium carbonate (10 mmol) was added and stirred at room temparature for 6 h. The reaction was monitored by TLC. The reaction mixture was filtered and the filtrate was quenched in water. The product was extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated to get the crude product. The crude product was re-crystallized from ethanol. The yield was 70 %.

General procedure for preparation of 3-(2-nitrophenylthio)propanehydrazide, 4

To a stirred solution of ethyl 3-(2-nitrophenylthio)propanoate (10 mmol) in ethanol (30 mL), hydrazine hydrate (25 mmol) was added and heated to reflux for 4 h. The reaction was monitored by TLC. On cooling to 0 °C, the product separated out was filtered, and washed with chilled ethanol. The yield was 80 %.

General procedure for preparation of 2-{2-[(2-nitrophenyl)sulphanyl]ethyl}-5-substituted-1,3,4-oxadiazole, 5

The reaction mixture of *3*-(2-nitrophenylthio)propanehydrazide (**4**) and carboxylic acid (10 mmol) in phosphorus oxychloride (20 mL) was heated to reflux for 4 h, monitored by TLC, then evaporated to dryness in vacuum to get the crude product. The product was purified by column chromatography using silica gel and eluted with ethyl acteate/hexane to afford pure product **5**.

2-(4-Methoxyphenyl)-5-2-[2-(2-nitrophenylsulfanyl)ethyl]-1,3,4-oxadiazole (5c)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (m, 1H); 8.03 (d, J = 8.4 Hz, 2H), 7.27–7.56 (m, 3H), 7.04 (d, J = 8.4 Hz, 2H), 3.91 (s, 3H), 3.55 (t, 2H), 3.13 (t, 2H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 166.3, 164.3, 161.8, 145.1, 135.8, 134.1, 130.0, 129.1, 128.0, 126.1, 116.2, 114.1, 54.9, 29.4, 27.7; MS (*m/z*): 358.4 (M^+).

General procedure for the preparation of 2-(2-(2-nitrophenylsulfinyl)ethyl)-5-substituted-1,3,4-oxadiazole, 6

To a stirred solution of thio compound **5** (10 mmol) in MDC (10 mL), was added solution of *m*-CPBA (12 mmol) in MDC (5 mL) and the mixture was stirred for 3 h at room temperature, was monitored by TLC, then quenched with 5 % sodium bicarbonate solution. The organic layer was separated and the aqueous layer was extracted with MDC. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The product were purified by column chromatography using silica gel and eluted with ethyl acteate/hexane to afford pure product **6**.

2-(4-Methoxyphenyl)5-{2-[2(2-nitrophenyl)sulfinyl]ethyl}-1,3,4-oxadiazole (6c)

^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (m, 1H), 8.03 (d, J = 8.4 Hz 2H), 7.71–7.76 (m, 3H), 7.04 (d, J = 8.4 Hz, 2H), 3.29 (m, 2H), 3.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 162.3, 161.9, 144.8, 136.9, 134.8, 130.2, 128.1, 127.3, 125.3, 114.4, 113.5, 55.1, 47.6, 21.1; MS (*m/z*): 374.3 (M^+).

General procedure for the preparation of 5-vinyl-2-substituted 1,3,4-oxadiazoles, 7

To a stirred mixture of sulfoxide **6** (10 mmol) in THF (20 mL), sodium acetate (60 mmol) was added, and the mixture was heated to 50 °C for 4–8 h. The reaction mixture was monitored by TLC. The reaction mixture was cooled to room temperature, and the solid was removed by filtration through celite. The filtrate was concentrated in vacuum to get the crude product. The product were purified by column chromatography using silica gel and eluted with ethyl acteate/hexane (4:1) to afford pure product **7**.

5-Phenyl-2-vinyl-1,3,4-oxadiazole (7a)

Oil, [Lit 21]; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11–8.09 (m, 2H), 7.56–7.51 (m, 3H), 6.84–6.76 (m 1H,), 6.38–6.34 (d, 1H), 5.88–5.86 (d, 1H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.24, 163.64, 131.87, 129.09, 127.02, 124.92, 123.77, 120.05; IR υ_{max} (cm^{-1}) 3,065, 2,927, 1,552, 1,536, 1,465, 780, 706, 690; MS (*m/z*): 173 (M^+)Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76 %, H, 4.68 %, N, 16.27 %; Found: C, 69.81 %, H, 4.78 %, N, 16.19 %.

5-(4-Methylphenyl)-2-vinyl-1,3,4-oxadiazole(7b)

Colourless oil, ^1H NMR (300 MHz, $CDCl_3$) δ ^1H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.78–6.71 (m, 1H), 6.59–5.96

(m, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 168.6, 141.4, 129.4, 128.5, 127.2, 123.8, 120.5, 21.4; MS: *m/z* 133(100), 187.2 (M^+); IR υ_{max} (cm^{-1}) 3,063, 2,981, 1,540, 1,311, 1,290, 835, 696, 600; MS (*m/z*): 184 (M^+); Anal. Calcd for $C_{11}H_{10}N_2O$: C, 65.34 %, H, 4.98 %, N, 13.85 %; Found: C, 65.50 %, H, 5.08 %, N, 17.00 %.

5-(4-Methoxyphenyl)-2-vinyl-1,3,4-oxadiazole(7c)

Off white solid, mp: 79–81 °C, [Lit 22: 80–82 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, $J = 9.0$ Hz, 2H), 6.85 (d, $J = 9.0$ Hz, 2H,), 6.67–6.59 (m, 1H), 6.19–5.68 (m, 2H), 3.71 (s, 3H,). ^{13}C NMR (75 MHz, $CDCl_3$): δ163.61, 162.68, 161.94, 128.20, 124.02, 119.53, 115.61, 114.01, 54.99; IR υ_{max} (cm^{-1}) 3,063, 2,981, 1,540, 1,311, 1,290, 835, 696, 600; MS (*m/z*): 203.2 (M^+); Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34 %, H, 4.98 %, N, 13.85 %; Found: C, 65.50 %, H, 5.08 %, N, 17.00 %.

2-(Naphthalen-2-yl)-5-vinyl-1,3,4-oxadiazole (7d)

Off white solid, mp: 79–81 °C; ^{1}H NMR ($CDCl_3$) δ 8.08–7.99 (m, 2H), 7.64–7.60 (m, 2H), 7.57–7.53 (m, 1H), 7.42–7.40 (d, $J = 8.4$ Hz, 1H,), 7.26–7.19 (m, 1H), 6.16–6.00 (m, 2H), 5.34–5.31 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 160.3, 134.34, 130.66, 130.06, 129.75, 128.59, 128.37, 127.44, 126.74, 125.42, 120.82; IR υ_{max} (cm^{-1}) 3,063, 2,981, 1,540, 1,311, 1,290, 835, 696, 600; MS (*m/z*): 223.1 (M^+); Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66 %, H, 4.54 %, N, 12.60 %; Found: C, 75.70 %, H, 4.62 %, N, 12.75 %.

Conclusion

In summary, we have described a new method for the synthesis of vinyl-substituted 1,3,4-oxadiazole using o-nitro phenyl sulfoxides as an efficient synthetic precursor. The advantage of this new method is the use of a very mild condition for *β-syn* elimination which avoids the polymerization of the vinyl group of synthesized vinyl-substituted oxadiazole. This method is cost effective as it uses cheap *o*-nitrothiophenol and can be used in synthesis of vinyl intermediates during synthesis of bioactive compounds, which avoids the use of any toxic metals.

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