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One Pot Synthesis of Phenyl-5-[2-(3-Trifluoromethyl-Phenyl)-Vinyl]-[1, 3, 4] Oxadiazole Derivative Under Ultrasonic Radiation

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Abstract:
An efficient and environmentally benign ultrasound-assisted one-pot synthetic method has been developed for the preparation of Phenyl-5-[2-(3-trifluoromethyl-phenyl)-vinyl]-1,3,4-oxadiazole derivatives**.** The protocol involves the in situ condensation of substituted benzoic acid hydrazides with 3-(trifluoromethyl)benzaldehyde, followed by intramolecular cyclodehydration under ultrasonic irradiation. The application of ultrasound significantly enhances reaction kinetics through acoustic cavitation, resulting in reduced reaction time, improved yields, and cleaner reaction profiles compared to conventional heating methods. The synthesized oxadiazole derivatives were obtained in good to excellent yields and characterized by standard spectroscopic techniques such as FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. The presence of the electron-withdrawing trifluoromethyl group is expected to enhance the physicochemical and biological properties of the synthesized compounds. This methodology demonstrates a green, rapid, and scalable approach for the synthesis of structurally diverse vinyl-substituted 1,3,4-oxadiazoles**,** aligning with current trends in sustainable heterocyclic chemistry. Ultrasound-assisted strategies have been widely reported to offer high efficiency, reduced energy consumption, and superior yields in oxadiazole synthesis. Additionally, one-pot cyclization of hydrazide-based intermediates remains a well-established route for constructing the 1,3,4-oxadiazole core.

Keyword: One pot,1,3,4-oxadiazole, 3-(3-(trifluoro methyl) phenyl) acrylic acid, Ultrasonic radiation,

Introduction:

Heterocyclic chemistry constitutes a foundational pillar of modern organic and medicinal chemistry, as a vast majority of biologically active molecules, pharmaceuticals, and agrochemicals incorporate heterocyclic scaffolds. Among these, five-membered heterocycles containing nitrogen and oxygen atoms have gained particular prominence due to their structural versatility and broad spectrum of biological activities. Within this class, 1,3,4-oxadiazole derivatives have emerged as highly significant motifs in drug design and synthetic chemistry. These compounds are recognized not only for their stability and ease of

functionalization but also for their role as bio isosteres of esters, amides, and carbamates, thereby improving pharmacokinetic and pharmacodynamic properties of lead molecules [1]. Consequently, the development of efficient, sustainable, and versatile synthetic strategies for 1,3,4-oxadiazoles continues to be an area of intense research interest. The biological and pharmaceutical relevance of 1,3,4-oxadiazole derivatives has been extensively documented. These compounds exhibit a wide array of biological activities, including antimicrobial, antifungal, anticancer, anti-inflammatory, anticonvulsant, and antiviral properties. Their therapeutic potential is attributed to their ability to interact with diverse biological targets such as enzymes, receptors, and nucleic acids. For instance, oxadiazole-containing molecules have been reported to act as inhibitors of bacterial growth and tumor cell proliferation, making them promising candidates in the development of new drugs [2]. Furthermore, the presence of the oxadiazole ring often enhances the metabolic stability of compounds by reducing susceptibility to hydrolysis and enzymatic degradation, thereby prolonging biological half-life.

Despite the growing importance of 1,3,4-oxadiazole derivatives, conventional methods for their synthesis present several limitations. Traditional approaches typically involve the cyclodehydration of diacylhydrazines or hydrazide intermediates using harsh dehydrating agents such as phosphorus oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), or concentrated acids. These reactions often require prolonged heating under reflux conditions, leading to high energy consumption and potential degradation of sensitive functional groups. Moreover, the use of toxic reagents and generation of hazardous by-products raises significant environmental and safety concerns. Multi-step procedures further reduce overall efficiency and yield, making these methods less suitable for large-scale or industrial applications [3]. Therefore, there is a pressing need for the development of greener, more efficient synthetic methodologies. The principles of **green chemistry**, which emphasize waste minimization, energy efficiency, and the use of safer reagents, have driven the exploration of alternative synthetic techniques. Among these, **ultrasound-assisted (sonochemical) synthesis** has emerged as a powerful and sustainable tool in organic synthesis. Ultrasound irradiation operates through the phenomenon of **acoustic cavitation**, which involves the formation, growth, and implosive collapse of microbubbles in a liquid medium. This collapse generates localized hotspots with extremely high temperatures (up to 5000 K) and pressures (up to 1000 atm), albeit for very short durations. These extreme conditions facilitate rapid bond formation and accelerate reaction rates without the need for harsh reagents or elevated bulk temperatures. As a result, ultrasound-assisted reactions often proceed under milder conditions with improved yields and selectivity [4]. In the context of heterocyclic synthesis, ultrasound irradiation has been successfully applied to a variety of transformations, including cyclization, condensation, and multicomponent reactions. Notably, ultrasound-assisted synthesis of 1,3,4-oxadiazoles has demonstrated significant advantages over conventional methods, such as reduced reaction times, higher product yields, and cleaner reaction profiles. Furthermore, the combination of ultrasound irradiation with **one-pot synthetic strategies**—where multiple reaction steps occur sequentially in a single reaction vessel—offers additional benefits in terms of operational simplicity, reduced solvent usage, and improved atom economy. One-pot methodologies eliminate the need for isolation and purification of intermediates, thereby enhancing overall efficiency and sustainability [5]. Recent literature highlights considerable progress in the development of one-pot and ultrasound-assisted methods for the synthesis of oxadiazole derivatives. For instance, several studies have reported the efficient synthesis of substituted oxadiazoles via condensation of hydrazides with aldehydes followed by cyclodehydration under ultrasonic conditions. Similarly, fluorinated oxadiazole derivatives have been synthesized using various catalytic and green chemistry approaches, demonstrating promising

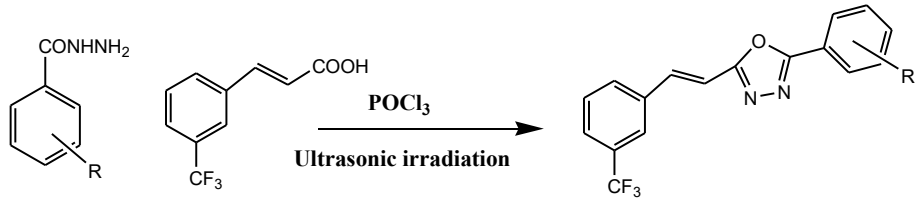
biological activities. However, despite these advances, the synthesis of **vinyl-substituted trifluoromethyl oxadiazoles** using ultrasound-assisted one-pot methods remains relatively underexplored. The introduction of a vinyl group in conjugation with a trifluoromethyl-substituted aromatic ring is expected to further enhance electronic delocalization and biological activity, yet systematic studies in this area are scarce.

This gap in the literature underscores the need for the development of novel synthetic strategies that combine the advantages of ultrasound irradiation, one-pot methodology, and fluorine chemistry. In particular, there is limited research focusing on the efficient construction of Phenyl-5-[2-(3-trifluoromethyl-phenyl)-vinyl]-1,3,4-oxadiazole derivatives, which represent a unique class of compounds with potential applications in medicinal chemistry. Therefore, the primary objective of the present study is to develop an efficient, green, and rapid ultrasound-assisted one-pot synthetic protocol for the preparation of these novel oxadiazole derivatives. The proposed method aims to overcome the limitations of conventional approaches by reducing reaction time, minimizing the use of hazardous reagents, and improving overall yield and sustainability. Additionally, the study seeks to explore the structural and electronic features imparted by the trifluoromethyl and vinyl substituents, thereby contributing to the broader understanding of structure–activity relationships in fluorinated heterocycles. In conclusion, this work is expected to provide a valuable contribution to the field of heterocyclic chemistry by offering a practical and environmentally friendly approach to the synthesis of complex oxadiazole derivatives. The integration of ultrasound-assisted techniques with one-pot synthesis not only aligns with the principles of green chemistry but also opens new avenues for the development of biologically active molecules with enhanced properties. published on 1,3,4-Oxadiazole derivatives suggesting methods of synthesis and their applications as pharmacological agents such as antitumor[6,7]. antiviral [8], antifungal [9,10], anticancer [11], antibacterial [12,13], anti-inflammatory [14,15], It has been well established that fluorinated heterocycles in particular CF_3 substituted have got a significant place in modern medicinal chemistry [16].

EXPERIMENTAL

Chemistry. All solvents and reagents were purchased from Merck India Ltd and are of AR Grade and used without further purification. Melting Points were determined by the open capillary method and reported as uncorrected. The reaction was monitored by thin layer chromatography, which was performed on Merck precoated plates (silica gel. 60 F254,0.25 mm) and was visualized by fluorescence quenching under UV light (254 nm). ^{1}H NMR spectra were recorded on Bruker DRX 500 spectrometer at 400 MHz using d6-DMSO and $CDCl_3$ as solvent, and TMS as internal standard

Reaction Scheme



1a-d 2 3 a-d

Synthesis of 2-(3-(trifluoromethyl)styryl)-5-phenyl-1,3,4-oxadiazole derivative (3a-d)

A mixture of substituted benzoic acid hydrazide **(1a-d)** (0.01mol with 3-(3 (trifluoromethyl)phenyl) acrylic acid (**2**) (0.01mol) suspended in phosphorus oxytrichloride (10ml) The reaction mixture in an ultrasonic bath. Sonicate for 10–15 minutes at room temperature. The progress of the reaction was monitored by TLC. After completing the reaction mixture was cooled and poured onto crushed ice dropwise with continuous stirring. The separated solid mass was neutralized with Sodium bicarbonate. The mixture was left overnight at Room temperature. The resulting solid thus obtained was collected by filtration, washed well with cold water, dried, and recrystallized from absolute ethanol.

Result and Discussion:

The IR spectrum of compound **(3a)** shows characteristic absorption bands confirming the formation of the 1,3,4-oxadiazole ring and the presence of vinyl and aromatic functionalities. 1603 cm^{-1} (C=N stretching): This strong band corresponds to the azomethine (C=N) group of the 1,3,4-oxadiazole ring**,** confirming successful cyclization. 1094 cm^{-1} (C–O–C stretching)**:** This absorption is characteristic of the ether linkage within the oxadiazole ring, supporting ring formation. The ^1H NMR spectrum clearly supports the proposed structure through well-resolved signals corresponding to vinyl and aromatic protons. δ 5.70 (d, J = 16.52 Hz, 1H) δ 7.59 (d, J = 16.52 Hz, 1H) .These two doublets with a large coupling constant (J ≈ styryl moiety. The large J value strongly indicates anti (trans) configuration**.** The aromatic region (δ 7.60–8.17 ppm) accounts for protons from both Phenyl ring attached to oxadiazole and 3-trifluoromethyl substituted phenyl ring formation. δ 7.73 (d, J = 6.00 Hz, 1H) δ 7.89 (s, 1H). These peaks indicate protons influenced by Electron-withdrawing –CF_3 group Oxadiazole ring deshielding . The single at δ 8.08 (dd, J = 6.00, 7.48 Hz, 2H) and δ 8.17 (d, J = 7.48 Hz, 2H**)** correspond to the para-substituted phenyl ring attached to the oxadiazole moiety. The downfield shift (~8 ppm) reflects. This peak corresponds to the molecular ion, at 317 (M^+) confirming the molecular weight of the compound.

Spectral Characterization of Compound (3a-d)

The structure of compound (5a) was confirmed using IR, ^1H NMR, and mass spectrometry, all of which are consistent with the proposed 1,3,4-oxadiazole framework bearing a styryl moiety and a trifluoromethyl-substituted aromatic ring. The IR spectrum exhibits characteristic absorption bands supporting the formation of the oxadiazole ring and associated functional groups. A strong absorption band at 1603 cm^{-1} is attributed to C=N stretching vibration, which is diagnostic of the azomethine functionality within the 1,3,4-oxadiazole ring, confirming successful cyclization. The band observed at 1094 cm^{-1} corresponds to C–O–C stretching, indicative of the ether linkage present in the heterocyclic oxadiazole ring. Additionally, the band at 1507 cm^{-1} is assigned to aromatic C=C stretching**,** confirming the presence of phenyl rings, while the absorption at 986 cm^{-1} is characteristic of trans (E)-HC=CH out-of-plane bending, supporting the presence of a trans-vinyl group.

The ^1H NMR spectrum provides strong evidence for the proposed structure through well-resolved signals corresponding to vinyl and aromatic protons. Two distinct doublets at **δ** 5.70 (d, J = 16.52 Hz, 1H) and δ 7.59 (d, J = 16.52 Hz, 1H**)** are assigned to olefinic protons of the styryl group. The large coupling constant (J ≈ 16.5 Hz) is characteristic of trans (E)-configuration, confirming the anti-orientation of the vinyl protons. The aromatic region spanning δ 7.60–8.17 ppm accounts for protons from both the phenyl ring attached to the oxadiazole nucleus and the 3-trifluoromethyl-substituted phenyl ring. Signals at δ 7.73 (d, J = 6.00 Hz, 1H) and δ 7.89 (s, 1H) are attributed to aromatic protons influenced by the strong electron-

withdrawing –CF_3 group, which induces deshielding effects. Further, the signals at **δ** 8.08 (dd, J = 6.00, 7.48 Hz, 2H) and δ 8.17 (d, J = 7.48 Hz, 2H) correspond to the para-substituted phenyl ring attached to the oxadiazole moiety. The observed downfield chemical shifts (~8 ppm**)** reflect the electron-deficient nature of the aromatic system due to the adjacent heterocyclic ring. The mass spectrum displays a molecular ion peak at m/z = 317 (M^+)**,** which is in excellent agreement with the calculated molecular weight of the proposed compound, thereby confirming its molecular formula.

2-Phenyl-5-[2-(3-trifluoromethyl-phenyl)-vinyl]-[1,3,4]oxadiazole (3a).
Yield 88%; mp 153°C; IR (*v* max/cm^{-1}): 1603 (C=N), 1094 (C-O-C),1507 (C=C aromatic), 986 (HC=CH trans), ^{1}H NMR (400 MHz, DMSO-d6), δ, ppm: 5.7 (d, J=16.52 Hz,1H,), 7.59 (d, J=16.52 Hz,1H), 7.6 (d, J=7.08 Hz,1H), 7.67 (dd, J=7.76, 7.08 Hz, 1H), 7.69 (d, J=7.76 Hz, 1H), 7.73(d, J=6.00 Hz, 1H),7.89 (s, 1H), 8.08 (dd, J= 6.00,7.48 Hz, 2H),8.17 (d, J=7.48 Hz, 2H (MS *m/z*: (M^+) 317.

2-(4-Nitro-phenyl)-5-[2-(3-trifluoromethyl phenyl)-vinyl]-[1,3,4] oxadiazole (3b)
Yield 92 %; mp 208 °C; (*v*max/ cm^{-1}):1592(C=N), 1076 (C-O-C), 1482 (C=C aromatic), 1531, (Ar-NO_2) 966 (HC=CH trans), ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.26 (d, J=15 Hz,1H), 7.65 (d, J=15Hz, 1H), 7.76 (d, J=7.6, 1H),7.79 (d, J=7.76 Hz, 1H),7.84 (d, J=6.00 7.08 Hz, 1H),7.84 (d, J=7.08 Hz, 1H),7.84(s, 1H), 8.33 (d, J=5.4, 2H), 8.4 (d, J= 5.4, 2H). MS *m/z*: (M^+) 362.

2-(4-Chloro-phenyl)-5-[2-(3-trifluoromethyl-phenyl)-vinyl]-[1,3,4]oxadiazole (3c).
Yield 89 %; mp 146 °C; IR (*v*max/ cm^{-1}): 1597 (C=N), 1075 (C-O-C), 1474 (C=C aromatic), 973 (HC=CH trans).^{1}H NMR (400 MHz, DMSO-d6):δ, ppm: 7.6 (d, J= 16.48 Hz,1H), 7.65 (d, J=16.48 Hz, 1H), 7.67 (d, J= 8.24, 2H),7.87 (d, J=7.76 Hz, 1H),7.71 (dd, J=7.76, 8.24Hz, 1H), 7.73 (d, J=7.76 Hz, 1H), 8.12 (d, J=8.24 Hz, 2H), 8.19 (s, 1H). MS *m/z*: (M^+) 351.

2-(3-Nitro-phenyl)-5-[2-(3-trifluoromethyl phenyl)-vinyl]-[1,3,4]oxadiazole (3d)
Yield 90 %; mp 181°C; IR (*v*max/ cm^{-1}): 1524(C=N), 1068 (C-O-C), 1484 (C=C aromatic), 1524 (Ar-NO_2) , 983 (HC=CH trans), ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 7.18 (d, J=16.56 Hz, 1H), 7.58 (d, J=16.56Hz,1H), 7.61 (d, J=7.56 Hz,1H), 7.76 (d, J=8.04, 7.56 Hz,1H), 7.8 (d, J=8.04 Hz,1H), 7.87 (dd J= 7.44, 8.08 Hz,1H), 8.84 (d J= 8.08 Hz), 8.85 (d, J= 7.44 Hz,1H), 8.94 (s, 1H) MS *m/z*: (M^+) 362.

Conclusion:
In conclusion, a series of novel 2-(3-(trifluoromethyl)styryl)-5-phenyl-1,3,4-oxadiazole derivatives **(3a–d**) were successfully synthesized via an efficient cyclization reaction using substituted benzoic acid hydrazides and 3-(trifluoromethyl) cinnamic acid in the presence of phosphorus oxychloride under ultrasonic conditions. The adopted method proved to be simple, rapid, and effective, affording the desired compounds in good to excellent yields with high purity. The structures of the synthesized compounds were unambiguously confirmed through spectral analysis, including IR, ^{1}H NMR, and mass spectrometry. Characteristic IR absorptions corresponding to C=N and C–O–C functionalities confirmed the formation of the 1,3,4-oxadiazole ring, while the presence of trans-styryl moiety was supported by diagnostic out-of-plane bending vibrations. The ^{1}H NMR spectra further substantiated the proposed structures by exhibiting distinct signals for olefinic and aromatic protons, with large coupling constants clearly indicating the trans (E)-configuration of the vinyl group. Mass spectral data showing molecular ion peaks

consistent with calculated molecular weights provided additional confirmation. Overall, the study demonstrates a reliable synthetic route and comprehensive spectral validation for the development of structurally diverse oxadiazole derivatives. These compounds, bearing electron-withdrawing substituents such as $–CF_3$, $–NO_2$, and –Cl, may serve as promising candidates for further investigation in medicinal and material chemistry due to their potential biological and physicochemical properties.

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