Ultrasound-promoted Kabachnik–Fields Synthesis of Novel Coupled Chromonyl-thiadiazolyl Derivatives.

Presented By

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Abstract:

The work reports facile synthesis of novel ten α-aminophosphonate derivatives coupled with 3-formyl chromone moiety, namely diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl)phosphonate **6(a-j).** The derivatives **6(a-j)** were synthesized through one-pot three component Kabachnik-Fields reaction, by using ultrasound in presence of zirconium oxychloride ($ZrOCl_2$) as a catalyst, to give the final compounds in better yields and in shorter reaction time. Thiadiazole and its derivatives possess a broad range of biological and pharmacological properties. 5-substituted phenyl-1,3,4-thiadiazol-2-amine is widely used as starting material for the synthesis of a broad range of heterocyclic compounds and as substrates for drug synthesis. Several 3-formylchromone derivatives possess a broad range of biological and pharmacological properties. The α-amino phosphonate derivatives constitute an important class of organophosphorus compounds on account of their versatile biological activity. Considering the importance of the three pharmacophores, promoted us to club all pharmacophores in a single molecule using green protocol. The Principles of Green chemistry are followed while performing the synthesis.

Keywords: Kabachnik-Fields reaction; Ultrasound, thiadiazol; 3-formyl chromone; α-amino phosphonate; zirchonium oxychloride.

Contents

- Introduction
- Materials and methods
- Scheme of synthesis
- Result & Discussion
- Spectral characterization
- Conclusion
- References

INTRODUCTION

In recent years, numerous promising multicomponent reactions have appeared as an innovative synthetic platform in the field of organic chemistry. This boosted not only drug discovery but also the construction of new synthetic skeletons. Multicomponent reactions triggered new synthetic applications in organic chemistry. Among many multicomponent reactions reported so far, we were particularly interested in exploring Kabachnik-Fields reaction because it can afford α-amino phosphonates in good yield. The Kabachnik -Fields reaction is one of the well known multicomponent reaction. The Kabachnik -Fields reaction corresponds to the classical method for the synthesis of organophosphorus compounds. It was discovered in 1952 independently by Kabachnik and Medved' [1] and Fields [2]. The reaction occurs in a three-component system consisting of a hydrophosphoryl compound, a carbonyl compound and an amine and results in α-aminoalkylphosphonates commonly named as α -amino phosphonates.

Recently, α-aminophosphonates have attracted the attention of organic chemists due to their biological activities, such as antibiotic, enzyme inhibitor, HIV protease and as anti-tumor agents [3].

α-Aminophosphonic acids, considered as phosphorus analogues of α-amino acids, have attracted much attention in drug research due to their low mammalian toxicity. The α-aminophosphonates are considered to be structural analogues of α -amino acids and transition state mimics of peptide hydrolysis [4]. In agrochemistry α-aminophosphonates are used as plant growth regulators, herbicides, insecticides and fungicides [5]. Several α-aminophosphonates have also been used in organic synthesis. For example, phosphorylated allenes are used as versatile building blocks in organic synthesis [6].

They are important targets in the development of antibiotics, antiviral species, antihypertensives, and antitumour agents based on their effect as inhibitors of GABA-receptors, enzyme inhibitors and anti-metabolites [7–13]. Diaryl α-amino-phosphonate derivatives are selective and highly potent inhibitors of serine proteases, and thus can mediate the patho-physical processes of cancer growth, metastasis, osteoarthritis or heart failure [14]. Dialkylglycine decarboxylase [13] and leucine aminopeptidase [15] are also inhibited by α -amino-phosphonates. Cyanoacrylate [16] and amide derivatives [17] of α-aminophosphonates are active antiviral compounds and inactivators of the tobacco mosaic virus.

Certain α-aminophosphonates were proved to be suitable for the design of continuous drug release devices due to their ability to increase the membrane permeability of a hydrophilic probe molecule [18].

Chromone and chromone derivatives are ubiquitous structures that constitute a variety of naturally occurring and synthetic bioactive compounds [19]. Chromones are oxygen-containing heterocycles with a benzoannelated γ-pyrone ring. Several biological activities have been ascribed to simple chromones and their analogues such as anti-inflammatory [20], antiplatelet [21], anticancer [22], antimicrobial [23], antiulcers [24], antioxidants [25], antiarrhythmic and hypotensive agents [26], aldose reductase and calpain inhibitors [27-29], MAO inhibition [30] Due to potential pharmacological properties, chromones are topic of great interest among a number of research groups.

Five membered aromatic systems having three hetero atoms at symmetrical position have interesting physiological properties [31, 32]. Sulphur-nitrogen heterocycles are important compounds due to their significant and versatile biological activity [33], and therefore these compounds have retained the interest of the researchers.

Among these, 1,3,4-thiadiazoles represent one of the most promising class of heterocycles in drug discovery. During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial [34, 35, 36], anti-inflammatory [37, 38, 39], anticonvulsants [40], antioxidant [41], anticancer [42] and antifungal [43] activities. The activity of 1,3,4-thiadiazoles is possibly due to the presence of the N–C–S moiety [44]. In view of these facts, we have synthesized novel 1,3,4-thiadiazole with spliced chromone and α-amino-phosphonate under ultrasound irradiation using Green protocol. Ultrasound assisted techniques were reported to be more effective in perspective of environment, reaction time, high yields, ease of work-up and isolation of products [45].

Ultrasound-promoted synthesis has various advantages over conventional synthesis techniques

- highly accelerated reaction rate,
- reasonable good yields,
- cheaper, very less amount of solvents required ,
- eco friendly method ,
- clean heating system, neat and clean synthetic protocol,
- milder reaction conditions.

Mechanism of ultrasound irradiation in synthesis:

The waves of ultrasound can be transmitted through any substance containing elastic property. The motion of these sounds is transferred to the particles of the environment, which vibrate in the route of the ultrasound wave. As the molecules oscillate, the molecular distance decreases in the compaction cycle and increases during rarefaction. When the molecular distance exceeds the critical amount necessary to hold the liquid perfect, the liquid collapse; bubbles and cavities are generated. This procedure (cavitation), refers to the generation and the energetic life of bubbles in liquids. The bubbles absorb energy from the waves of ultrasound and grow. Then bubble collapse consequences in pressure changes and high temperature. The solvent vapor suffers fragmentation to produce reactive particles, such as carbenes or free radicals. These high-energy particles are concentrated and lead to intermolecular reactions. In general, the yield of product increases, reactions occur faster, with lower temperatures and minor percentage of by-products achieved [10].

MATERIALS AND METHODS

General

All the reactions were performed in oven-dried glassware's. All reagents and solvents were used as obtained from the supplier or recrystallized /redistilled unless otherwise noted. The ultrasound sonicator (Sonics Vibra-cell, Modelno. VCX 500) equipped with solid synthetic probe, 13 mm in tip diameter, operating at 20 kHz with a maximum power output of 500 W, was used for synthesis of final title compounds. The purity of the synthesized compounds was monitored by ascending thin layer chromatography (TLC) on silica gel-G (Merck) coated aluminium plates, visualized by iodine vapour and melting points were determined in open capillary tubes. The homogeneity of the compounds was monitored by ascending thin layer chromatography(TLC) on silica gel-G (Merck) coated aluminium plates, visualized by iodine vapour**.**

The ^{1}H NMR and ^{13}C NMR spectra of synthesized compounds were recorded on Bruker Avance II 400 NMR Spectrometer at 400 MHz Frequency in deuterated DMSO and $CDCl_3$ and using TMS as internal standard (chemical shift δ in ppm). Mass spectra of some compounds were scanned on FTMS+p ESI full mass (100.00-1500.00).

Procedures:

Step I:General Procedures for the Synthesis of 3(a-j) using Ultra sound method

To the equimolar quantity of differently substituted benzoic acids **2(a-j)** (0.05 mol), thiosemicarbazide **(1)** (0.05 mol) in 5-8 ml of ethanol, catalytic amount of sulphuric acid was added and the reaction mixture was subjected to Ultrasound irradiation for 30-40 min at room temperature. The completion of the reaction was checked by TLC. After completion of the reaction, the reaction mixture was poured into the ice cold water, filtered, dried and recrystallized from ethanol.

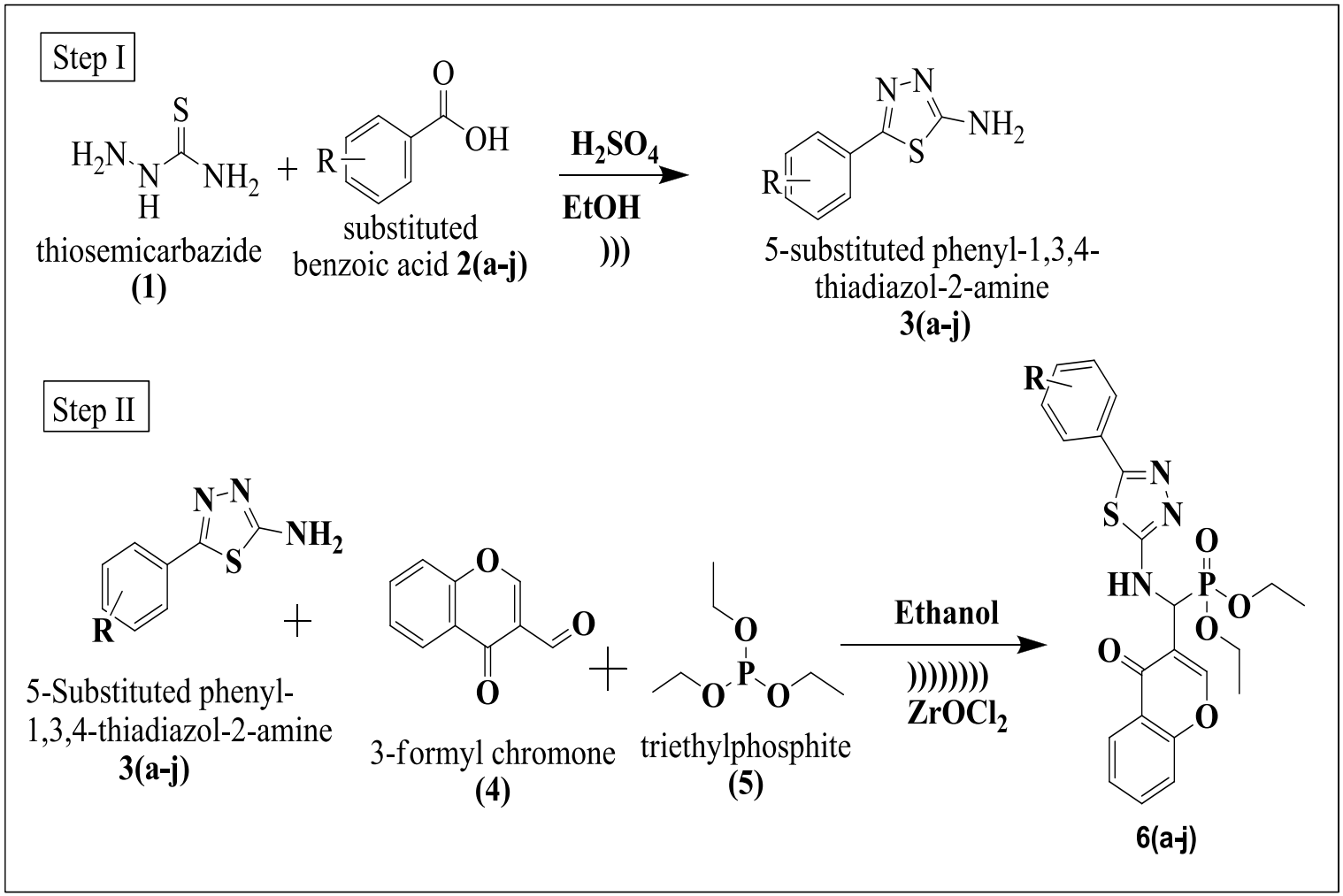
Step II: General procedure for synthesis of diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives 6(a-j) under ultrasound irradiation.

A mixture of substituted thiadiazole derivatives **3(a–j)** (0.05mol), 3-formyl chromone **(4)** (0.05mol), triethyl phosphite **(5)** (0.05mol) and the catalytic amount of zirconium oxychloride in absolute ethanol, was sonicated at a 25 °C temperature and frequency 20 kHz for a specified time as shown in Table **2**. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into the ice-cold water and filtered under suction; the precipitate thus obtained was washed with water and recrystallized from ethanol.

Identification

- Silica gel thin-layer chromatography (TLC)
- ^{1}H, ^{13}C and ^{31}P Nuclear Magnetic Resonance (NMR) spectroscopy
- Infrared (IR) spectroscopy

SCHEME OF SYNTHESIS



Scheme 1: Synthesis of Diethyl (4-oxo-4H-chromen-3-yl)(5-substituted phenyl-1,3,4-thiadiazol-2-ylamino)methyl phosphonate derivative **6(a-j).**

RESULTS AND DISCUSSION

Chemistry:

Here in we report the ultrasound promoted green synthesis of ten novel 3- Formyl Chromone Spliced Thiadiazole, α-Amino Phosphonate derivatives **6(a-j)** from three component reactions of an 3-formyl chromone (**4**), 5-substituted phenyl-1,3,4-thadiazole-2-amine **3(a-j)** and triethyl phosphite (**5**) in presence of ethanol as an solvent and $ZrOCl_2$ catalyst under ultrasound irradiation as shown in **Scheme 1**. 5-Substituted phenyl-1,3,4-thiadiazol-2-amine derivatives **3(a-j)** were synthesized by reacting thiosemicarbazide **(1)** (0.05 mol) with various substituted benzoic acid **2(a-j)** (0.05 mol) in ethanolic solvent in presences of catalytic amount of sulfuric acid under ultrasound irradiation. The synthesized compounds were characterized and confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, MS and elemental analyses. The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes and are uncorrected. Physical constant data for synthesized compounds diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate **6(a-j)** is as shown in **Table 1**.

Table 1. Physical characterization data of the synthesized compounds **6(a-j)**.

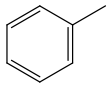
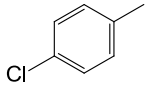
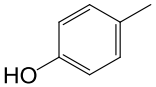
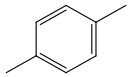
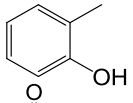
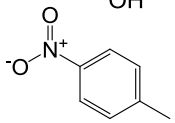
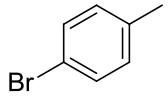
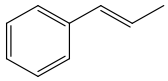
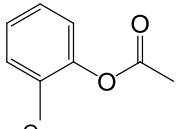
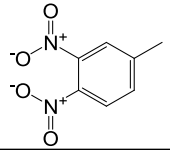
Code	R	Molecular formula	Molecular weight (gm)	% Yield	R_f value
6a		$C_{22}H_{22}N_3O_5PS$	471.47	90	0.45
6b		$C_{22}H_{21}ClN_3O_5PS$	505.91	92	0.35
6c		$C_{22}H_{22}N_3O_6PS$	487.47	95	0.35
6d		$C_{23}H_{24}N_3O_5PS$	485.49	90	0.35
6e		$C_{22}H_{22}N_3O_6PS$	487.47	89	0.50
6f		$C_{22}H_{21}N_4O_7PS$	516.46	88	0.40
6g		$C_{22}H_{21}BrN_3O_5$	550.36	94	0.35
6h		$C_{24}H_{24}N_3O_5PS$	497.50	92	0.40
6i		$C_{24}H_{24}N_3O_7PS$	529.50	87	0.35
6j		$C_{22}H_{20}N_5O_9PS$	561.46	84	0.45

Table 2: Details of synthesis of diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives **6(a-j)** under ultrasound irradiation.

Compound	Time required for ultrasound method (minutes)
6a	40
6b	30
6c	35
6d	45
6e	50
6f	40
6g	35
6h	40
6i	35
6j	40

6a Diethyl (4-oxo-4H-chromen-3-yl)(5-phenyl-1,3,4-thiadiazol-2-ylamino)methyl phosphonate

Yield 90%; M. P.: 165-168°C ; IR (KBr ν_{max} in cm-1): 3363.25 (N-H stretching), 3016.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1725.02 (C-O stretching), 1665.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 663.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.29 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 4.70 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 5.05 (d, 1H, -CH), 7.41-8.08 (m, 10H, aromatic), 8.61 (s, 1H, -NH); ^{13}CNMR: (DMSO)δppm: 16.3, 16.3, 62.3, 62.3, 61.0, 128.7, 123.4, 129.2, 135.2, 125.8, 130.9, 116.9, 123.9, 133.5, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.90; Molecular formula: $C_{22}H_{22}N_3O_5PS$; Elemental Analysis: calculated: (C,H,N): 56.05, 4.70, 8.91; found: (C,H,N): 56.17, 4.82, 8.87

6b Diethyl(5-(4-chlorophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methyl phosphonate

Yield 92%; M. P.:135-137°C; IR (KBr ν_{max} in cm-1): 3303.25 (N-H stretching), 3096.12 (C-H stretching of aromatic), 2783.14 (C-H stretching of alkyl), 2241.73 (C=N Stretching), 1715.02 (C-O stretching), 1685.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 660.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.28 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 4.71 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 5.05 (d, 1H, -CH), 7.47-8.08 (m, 9H, aromatic), 8.61 (s, 1H, -NH); ^{13}C NMR: (DMSO) δ ppm: 16.3, 16.3, 62.3, 62.3, 61.6, 123.4, 135.2, 125.8, 128.9, 116.1, 129.3, 128.9, 129.3, 116.9, 123.9, 131.6, 183.0, 150.6, 157.2, 134.3, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.84; Molecular formula: $C_{22}H_{21}ClN_3O_5PS$; Elemental Analysis: calculated: (C,H,N): 52.23, 4.18, 8.31; found: (C,H,N): 52.35, 4.30, 8.27

6c diethyl (5-(4-hydroxyphenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methyl phosphonate

Yield 95%; M. P.:158-160°C ; IR (KBr ν_{max} in cm-1): 3303.25 (N-H stretching), 3106.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1709.02 (C-O stretching), 1675.10 (C=O stretching), 1527.35 (C-N Stretching), 1051.37 (O- stretching), 698.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.29 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.09 (d, 1H, -CH), 5.35 (s, 1H, OH), 6.87-8.08 (m, 9H, aromatic), 8.60 (s, 1H, -NH); ^{13}CNMR: (DMSO) δ ppm: 16.3, 16.3, 62.3, 62.3, 61.0, 123.4, 135.2, 125.8, 128.9, 116.4, 116.1, 128.9, 116.4, 116.9, 123.9, 126.1, 158.5, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.54; Molecular formula: $C_{22}H_{22}N_3O_6PS$; Elemental Analysis: calculated: (C,H,N): 54.21, 4.55, 8.62; found: (C,H,N): 54.32, 4.67, 8.58

6d Diethyl (4-oxo-4H-chromen-3-yl)(5-p-tosyl-1,3,4-thiadiazol-2-ylamino)methyl phosphonate

Yield 90%; M. P.: 159-161°C ; IR (KBr ν_{max} in cm-1): 3357.25 (N-H stretching), 3016.82 (C-H stretching of aromatic), 2763.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1705.02 (C-O stretching), 1695.10 (C=O stretching), 1597.35 (C-N Stretching), 1041.37 (O- stretching), 676.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.29 (t, 6H, 2×OCH$_2$CH$_3$), 2.34 (s, 3H, aromatic C-CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.09 (d, 1H, -CH), 5.35 (s, 1H, OH), 7.40-8.09 (m, 9H, aromatic), 8.60 (s, 1H, -NH); ^{13}CNMR:(DMSO) δppm: 16.3, 16.3, 21.3, 62.3, 61.0, 123.4, 135.2, 129.5, 125.8, 127.4, 116.1, 129.5, 127.4, 131.7, 123.9, 116.9, 123.9, 130.5, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.54; Molecular formula: $C_{23}H_{24}N_3O_5PS$; Elemental Analysis: calculated: (C,H,N): 56.90, 4.98, 8.66; found: (C,H,N): 57.02, 5.10, 8.62

6e diethyl (5-(2-hydroxyphenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methyl phosphonate

Yield 89%; M. P.:169-170°C ; IR (KBr ν_{max} in cm-1): 3363.25 (N-H stretching), 3016.12 (C-H stretching of aromatic), 2753.14 (C-H stretching of alkyl), 2281.73 (C=N Stretching), 1710.02 (C-O stretching), 1685.10 (C=O stretching), 1617.35 (C-N Stretching), 1081.37 (O- stretching), 663.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.29 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 4.70 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 5.08 (d, 1H, -CH), 5.35 (s, 1H, OH), 7.01-8.08 (m, 9H, aromatic), 8.55 (s, 1H, -NH); ^{13}CNMR: (DMSO) δ ppm: 16.3, 16.3, 62.3, 62.3, 61.60, 123.4, 135.2, 125.8, 128.9, 116.4, 116.1, 128.9, 116.4, 116.9, 123.9, 126.1, 158.5, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.04; Molecular formula: $C_{22}H_{22}N_3O_6PS$; Elemental Analysis: calculated: (C,H,N): 54.21, 4.55, 8.62; found: (C,H,N): 54.32, 4.67, 8.58

6f Diethyl(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methyl phosphonate

Yield 88%; M. P.: 130-132°C ; IR (KBr ν_{max} in cm-1): 3293.25 (N-H stretching), 3016.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1725.02 (C-O stretching), 1715.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 689.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.28 (t, 6H, 2×OCH$_2$<u>CH$_3$</u>), 4.71 (q, 4H, 2×O<u>CH$_2$</u>CH$_3$), 5.09 (d, 1H, -CH), 7.47-8.38 (m, 9H, aromatic), 8.61 (s, 1H, -NH); ^{13}CNMR:(DMSO) δppm:16.3, 16.3, 62.3, 62.3, 61.60, 123.4, 135.2, 125.8, 128.9, 116.4, 116.1, 128.9, 116.4, 116.9, 123.9, 126.1, 158.5, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.64; Molecular formula: $C_{22}H_{21}N_4O_7PS$; Elemental Analysis: calculated: (C,H,N): 51.16, 4.10, 10.85; found: (C,H,N): 51.28, 4.22, 10.81

6g diethyl (5-(4-bromophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methyl phosphonate

Yield 94%; M. P.: 138-140°C; IR (KBr v_{max} in cm-1): 3293.25 (N-H stretching), 3096.12 (C-H stretching of aromatic), 2763.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1715.02 (C-O stretching), 1675.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 668.39 (C-S Stretching); ^{1}HNMR: (DMSO) δ ppm: 1.28 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.05 (d, 1H, -CH), 7.40-8.08 (m, 9H, aromatic), 8.56 (s, 1H, -NH); ^{13}CNMR:(DMSO) δppm: 16.3, 16.3, 62.3, 62.3, 61.0, 123.4, 135.2, 125.8, 129.7, 116.1, 132.1, 129.7, 132.1, 116.9, 123.9, 132.5, 183.0, 150.6, 151.2, 123.1, 174.1, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.94; Molecular formula: $C_{22}H_{21}BrN_3O_5PS$; Elemental Analysis: calculated: (C,H,N): 48.01, 3.85, 7.63; found: (C,H,N): 48.13, 3.97, 7.59

6h (E)-diethyl (4-oxo-4H-chromen-3-yl)(5-styryl-1,3,4-thiadiazol-2-ylamino)methyl phosphonate

Yield 92%; M. P.:150-152°C ; IR (KBr vmax in cm-1): 3293.25 (N-H stretching), 3116.12 (C-H stretching of aromatic), 2703.14 (C-H stretching of alkyl), 2298.73 (C=N Stretching), 1710.02 (C-O stretching), 1705.10 (C=O stretching), 1527.35 (C-N Stretching), 1041.37 (O- stretching), 653.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.28 (t, 6H, 2×OCH$_2$CH$_3$), 4.71 (q, 4H, 2×OCH$_2$CH$_3$), 5.09 (d, 1H, -CH), 6.59-6.99 (m, 2H, -CH), 7.33-8.10 (m, 9H, aromatic), 8.55 (s, 1H, -NH); ^{13}CNMR:(DMSO)δppm:16.3, 16.3, 133.4, 116.9, 62.3, 62.3, 61.0, 127.9, 128.6, 128.6, 123,4, 135.29, 128.5, 125.8, 116.1, 128.5, 137.5, 116.9, 123.9, 183.0, 150.6, 157.2, 158.9, 164.2; ^{31}PNMR (200 MHz,$CDCl_3$) δ: 19.65; Molecular formula: $C_{24}H_{24}N_3O_5PS$; Elemental Analysis: calculated: (C,H,N): 57.94, 4.86, 8.45; found: (C,H,N): 58.06, 4.98, 8.41

6i 2-(5-((diethoxyphosphoryl)(4-oxo-4H-chromen-3-yl)methylamino)-1,3,4-thiadiazol-2-yl)phenyl acetate

Yield 87%; M. P.:168-170°C ; IR (KBr vmax in cm-1): 3283.25 (N-H stretching), 3056.12 (C-H stretching of aromatic), 2773.14 (C-H stretching of alkyl), 2271.73 (C=N Stretching), 1715.02 (C-O stretching), 1695.10 (C=O stretching), 1598.35 (C-N Stretching), 1089.37 (O- stretching), 679.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.28 (t, 6H, 2×OCH$_2$<u>CH</u>$_3$), 2.28 (s, 3H, -CH$_3$), 4.71 (q, 4H, 2×O<u>CH</u>$_2$CH$_3$), 5.09 (d, 1H, -CH), 7.33-8.10 (m, 9H, aromatic), 8.55 (s, 1H, -NH); ^{13}CNMR:(DMSO) δppm: 16.3, 16.3, 20.3, 62.3, 62.3, 169.0, 61.0, 129.4, 126.0, 129.1, 135.2, 125.8, 127.9, 123.2, 116.1, 116.9, 123.9, 129.4, 151.1, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,CDCl$_3$) δ: 19.45; Molecular formula: $C_{24}H_{24}N_3O_7PS$; Elemental Analysis: calculated: (C,H,N): 54.44, 4.57, 7.94; found: (C,H,N): 54.56, 4.69, 7.90

6j Diethyl (5-(3,4-dinitrophenyl)-1,3,4-thiadiazol-2-ylamino)(4-oxo-4H-chromen-3-yl)methyl phosphonate

Yield 84%; M. P.:165-168°C; IR (KBr vmax in cm-1): 3303.25 (N-H stretching), 3106.12 (C-H stretching of aromatic), 2711.14 (C-H stretching of alkyl), 2225.73 (C=N Stretching), 1710.02 (C-O stretching), 1685.10 (C=O stretching), 1587.35 (C-N Stretching), 1091.37 (O- stretching), 673.39(C-S Stretching); ^{1}HNMR (400 MHz, DMSO, δ_H ppm): 1.29 (t, 6H, 2×OCH$_2$<u>CH</u>$_3$), 4.71 (q, 4H, 2×O<u>CH</u>$_2$CH$_3$), 5.05 (d, 1H, -CH), 7.10-8.08 (m, 5H, aromatic), 8.49 (s, 1H, -NH), 8.52-8.99 (m, 3H, aromatic); ^{13}CNMR:(DMSO) δppm:16.3, 16.3, 62.3, 62.3, 61.0, 123.4, 135.2, 125.8, 116.1, 134.5, 125.3, 123.7, 116.9, 123.9, 140.5, 144.8, 145.3, 183.0, 150.6, 157.2, 174.1, 164.2; ^{31}PNMR (200 MHz,CDCl$_3$) δ: 19.56; Molecular formula: $C_{22}H_{20}N_5O_9PS$; Elemental Analysis: calculated: (C,H,N): 47.06, 3.59, 12.47; found:(C,H,N):47.18, 3.71, 12.43

CONCLUSION

The novel ten diethyl ((4-oxo-4H-chromen-3-yl)((5-sustituted phenyl-1,3,4-thiadiazol-2-yl)amino)methyl) phosphonate derivatives **6(a-j)** were synthesized under ultrasound irradiation. The present protocol is also extendable to a wide variety of substrates. The advantages of this protocol are the use of eco-friendly catalyst, short reaction time, easy work-up, ease of product isolation, and high yield. The present protocol is also extendable to a wide variety of substrates.

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