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COMMUNICATION

10-Camphorsulfonic acid ((±)-CSA) catalyzed facile one-pot synthesis of a new class of 2, 5-disubstituted 1, 3, 4-oxadiazoles

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Abstract: A convenient, and efficient one-pot synthesis of 2,5-disubstituted-1,3,4-oxadizoles is described. Various Carboxylic acid hydrazides efficiently reacted with different carboxylic acid chlorides with 10-Camphorsulfonic acid. This methodology was successfully applied to synthesize a series of 2*H*-Chromene Substituted 1,3,4-Oxadiazole derivatives in good to high yields.

Keywords: 2,5-disubstituted- 1,3,4-oxadizoles; Chromene-substituted- 1,3,4-oxadizoles, 10- Camphorsulfonic acid ; Carboxylic acid hydrazides; Carboxylic acid chlorides.

1. Introduction

The study of heterocyclic chemistry is an enduring field in the branch of organic chemistry. More than half of the compounds produced by nature have heterocyclic rings in their structures. Amongst different heterocyclic systems, the chemistry of five membered heterocycles has gained importance as many of them exhibit pronounced bioactive nature. Particularly substituted 1,3,4-oxadiazoles have been much explored for their broad spectra of biological activities such as antibacterial [1-3], antimycobacterial[4], antifungal [5,6], anti-inflammatory[7], anti-allergy [8,9], analgesic[10], anticonvulsant[11], antihypoglycemic[12], anticancer[13] and insecticidal properties[14]. Moreover, 1,3,4-oxadiazoles were found wide usage as dyes, photosensitive and electrical materials[15]. Due to these broad applications, the chemistry of 1,3,4-oxadiazoles has evoked keen interest in the field of synthetic organic chemistry. Hence there is a need to develop newer synthetic routes, those should be more practical and more efficient pathways for 1,3,4-oxadiazoles.

Up to now various one-pot protocols are available in the literature for the synthesis of 1,3,4-oxadiazoles. Most of the 1,3,4-Oxadiazoles were synthesized by cyclodehydration of semicarbazide derivatives and oxidative cyclization of acyl-hydrozones. So far there are few efficient reagents were used for cyclo dehydration and oxidative cyclization reagents those are Burgess Reagent[16], T3P®[17], TsCl [18], EDCI[19], cyanuric chloride[20], XtalFluor-E[21], Dess–Martin reagent [22], bis (trifluoroacetoxy)iodobenzene (BTI)[23] , PbO_2 [24] etc.. Despite the wide generality and the high efficiency of the above mentioned methodologies, some limitations still remain. Those are, harsh regents, high cost of reagents, stability of reagents etc., and Very recently we reported an efficient, direct and common method for the synthesis of oxadiazoles, thiadiazoles and triazoles from various carboxylic acid hydrazides using the TMSNCS (trimethylsilyl isothiocyanate)[25-27]. As a part of our continued interest in the synthesis of heterocycles we wish to develop a convenient one-pot method for the synthesis of these useful heterocycles using reagents available to researchers worldwide.

Chromene derivatives are an important class of compounds, which are widely present in plants, including edible vegetables and fruits[28]. Synthetic analogues have been developed over the years, some of them display remarkable effects as pharmaceuticals[29], including antifungal[30], anti-microbial[31], molluscidial[32], anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactic characteristics[33]. The activities of chrome as well as the oxadiazoles leads us to synthesize a set of chromene substituted oxadiazole derivatives, while searching for new anti-cancerous inhibitors of an enzyme in an in house drug discovery program, we were interested in synthesizing the chromene substituted 1,3,4- and the 1,2,4-oxadiazoles in an efficient manner. Whereas an efficient one pot synthesis of chromene substituted 1,2,4-oxadazoles have been synthesized using PPTS (Pyridinium *p*-toluenesulfonate), their cytotoxicity evolution has been established[34]. Various 1,2,4-oxadiazole substituted 2*H*-Chromenes are found to have considerable anticancer activity, and their activity on cancer cell lines will be further explored.

Encouraged by these results it was envisaged to integrate the 1,3,4-oxadiazole moiety with a chromene frame work to study the cytotoxicity effect of the combined molecule. In this manuscript we investigated the synthetic utility of 10-Camphorsulfonic acid; to the best of our knowledge, the synthesis of 1,3,4-oxadiazoles utilizing 10-Camphorsulfonic acid as a reagent, has not been reported yet. 10-Camphorsulfonic acid is a versatile reagent in organic chemistry, which is widely used in asymmetric synthesis[35],Friedel–Crafts alkylation[36], oxidation of sulphides[37], selective inter-and intramolecular alcohol additions to *exo*-glycals[38], multi component reactions and Mannich reactions[39] and is been cheaper in operational cost. As a part of our studies on CAS, we investigated the synthetic utility of 10-Camphorsulfonic acid for the synthesis of 1,3,4-oxadiazoles. We report here in highly efficient one-step protocol to prepare 2,5-

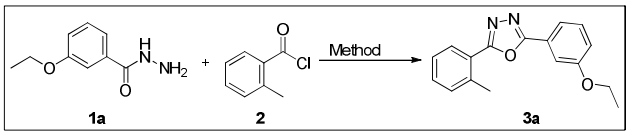
disubstituted 1,3,4-oxadiazoles from the reaction of various acid chlorides with different acyl hydrazides in the presence of catalytic amounts of 10-Camphorsulfonic acid (5 mol %) at elevated temperatures. The procedure does not require an anhydrous solvent, inert gas atmosphere and any chromatographic purification.

2. Results and Discussions

We mainly focused on developing a facile procedure to generate 2*H*-Chromene substituted 1,3,4-oxadiazole library with a variety of substitution patterns. It requires to investigate the scope of the reaction by screening with various functionalities. In process of that we applied several traditional methodologies to react 2*H*-Chromene carboxylic acid hydrazide with several acid chlorides to obtain corresponding 1,3,4-oxadiazoles, which involved strong acidic conditions at elevated temperatures, which effects the ether linkage of the chromene ring, and narrows the convenient access of derivatized 1,3,4-oxadiazoles.

In process of evaluating best methodology, we cross checked various traditional methodologies by reacting 3-ethoxybenzohydrazide and *o*-toluoyl chloride to optimize the reaction conditions (**Scheme 1**). Different reagents and different solvents were screened for synthesizing 2,5-disubstited-1,3,4-oxadiazoles. The results were summarized in Table **1**. Among the all reagents 10-Camphorsulfonic acid were found to be the best reagent for obtaining 2, 5-disubstited-1,3,4-oxadiazoles with high yields.

Scheme-1: Methodology screening:



Scheme-1

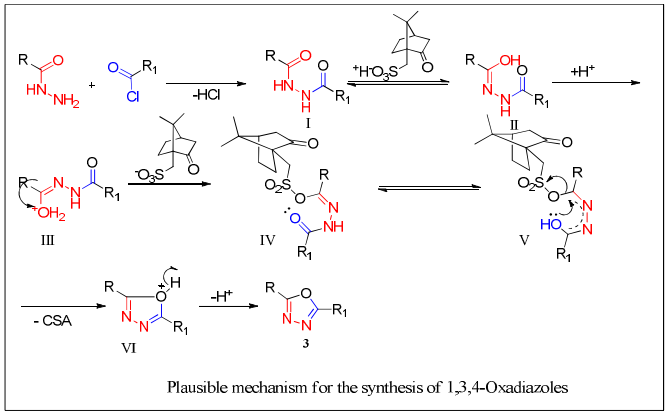
Table.1. Reaction system screening results

S No	Reagents	Reaction conditions	Yield
1	$POCl_3$	Reflux/8 h	35%
2	$SOCl_2$	Reflux/8 h	27
3	$InBr_3$ (5 mol%)	Dioxane/ 90°C	12%
4	$Cu(OTf)_2$ (5 mol%)	DMF/120°C/ 16 h	39%
5	p-TSA (5 mol%)	Dioxane/ 16 h	43%
6	PPTS 10 mol%)	DCE/90°C/ 16 h	52%
7	Burgess reagent	THF/ rt/5 h	44%
8	(±)-CSA (5 mol%)	Dioxane/100°C/ 16 h	75%
9	(±)-CSA(5mol%)	Dioxane/rt/ 36 h	15 %
10	(±)-CSA (5 mol%)	Dioxane/100°C/ 16 h	89%
11	(±)-CSA (5mol%)	Microwave/ 120°C/ 15 min	59 %

Note: 1. (±)-CSA: 10-Camphorsulfonic acid.

Having these preliminary observations in hand, we wished to extend our methodology to a variety of carboxylic acid hydrazides.

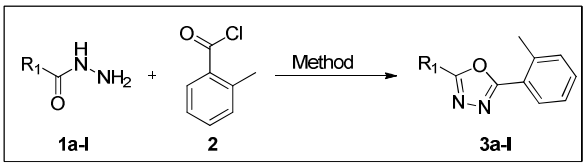
The plausible mechanism for the formation of 2,5-disubstituted 1,3,4-oxadiazoles were shown in **Scheme-2**. In which the carboxylic acid hydrazide reacts with acid chloride to form corresponding di-substituted carboxylic acid hydrazide (I), Which in turn undergoes enolization (II) followed by protanation (III) in presence of 10-Camphorsulfonic acid. Intermediate III in turn eliminates a water molecule and form a sulfonate complex (IV), which further undergoes enolization (V) followed by elimination of 10-Camphorsulfonic acid to form corresponding 1,3,4-oxadiazole (3).



Scheme-2

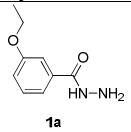
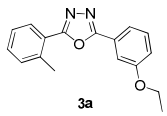
The reactions of **1a-l** with *o*-toluoyl chloride **(2) (Scheme-3)** in the presence of 5 mol % 10-Camphorsulfonic acid gave the 2,5-substituted-1,3,4-oxadiazoles (**3a-l**) with high yields (Table 2). As shown in Table.2, carboxylic acid hydrazides carrying an electron-withdrawing group or an electron-donating group reacted efficiently. *o,m,p*-substituted carboxylic acid hydrazides reacted more efficiently with o-toluoyl chloride resulted 2,5-substituted-1,3,4-oxadiazoles with high yields. We observed the more advantage of 10-Camphorsulfonic acid when compare to other acid catalysts, as the hydrazides having acid sensitive ether linkages **(3e, 3h, 3i, 3j)** also reacted well without failure. The hydrazides having heterocyclic compounds in their skeleton **(3k, 3l)** were also reacted efficiently.

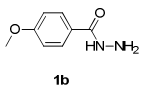
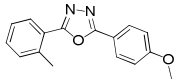
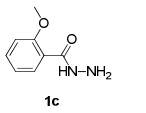
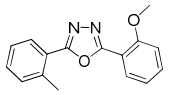
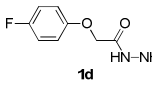
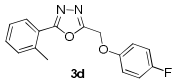
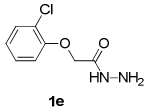
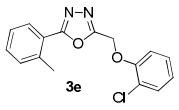
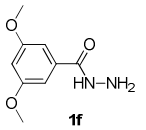
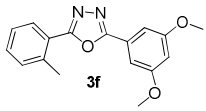
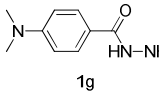
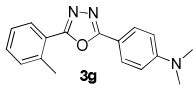
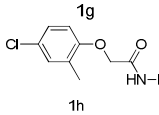
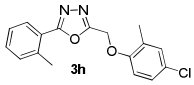
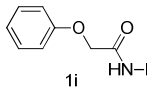
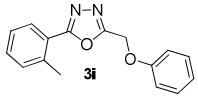
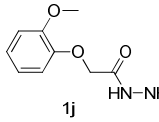
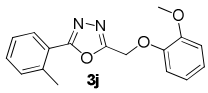
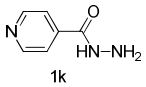
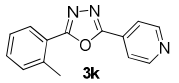
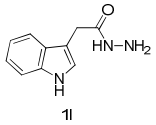
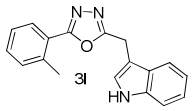
Scheme-3: Synthesis of 2, 5-subsitutied-1, 3, 4-oxadiazloes (3a-l)



Scheme-3

Table.2

Entry	Carboxylic acid hydrazides	Product	Yield (%)
1	 1a	 3a	89

2	 1b	 3b	92
3	 1c	 3c	90
4	 1d	 3d	78
5	 1e	 3e	80
6	 1f	 3f	83
7	 1g	 3g	85
8	 1h	 3h	79
9	 1i	 3i	77
10	 1j	 3j	76
11	 1k	 3k	87
12	 1l	 3l	86

2*H*-chromene-3-carboxylic acid hydrazide **(7)** was prepared using literature procedure[40] (Scheme-**4**).

Finally to demonstrate the generality of our methodology, we extend this methodology for the synthesis of a new class of 2*H*-chromenes substituted-1,3,4-oxadiazoles (Scheme-**5**), from 2*H*-Chromene acid hydrazides. The reaction of chromene-carboxylic acid hydrazides with different acid chlorides in the presence of 5 mole % of 10-Camphorsulfonic acid and resulted 2*H*-chromene substituted-1,3,4-oxadiazoles **(9a-n)** (Table.3)(Scheme-**5**) with good yields. To our delight, a variety of aromatic, hetero aromatic and aliphatic carboxylic acid chlorides bearing functional groups such as halo, methoxy, alkyl, participated effectively with chromene hydrazides and resulted chromene substituted-1,3,4-oxadiazoles with high yields (Table.3).

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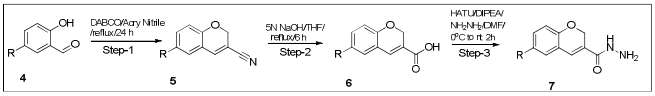
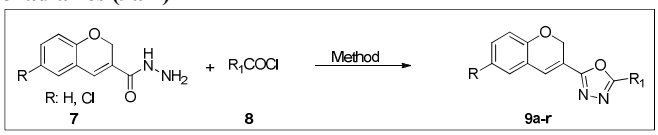
Scheme-4: Preparation of Chromene Hydrazides:



Scheme-4

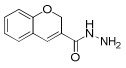
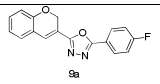
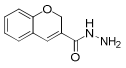
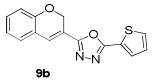
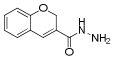
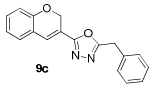
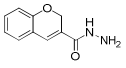
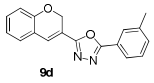
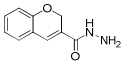
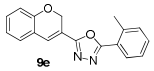
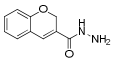
Scheme-5: Synthesis of Chromene substituted-1,3,4-oxadiazles (9a-r)



Method: 5 mol% 10-Camphorsulfonic acid/ Dioxane/100°C/16h

Scheme-5

Table.3. Synthesis of *2H*-chromene substituted-1,3,4-oxadiazoles.

Entry	Carboxylic acid Hydrazide	Acid Chlorides	Product	Yield (%)
1			 9a	88
2			 9b	79
3			 9c	75
4			 9d	83
5			 9e	88
6			9f	**75**
7			9g	86
8			9h	85
9			9i	89
10			9j	91
11			9k	83
12			9l	88
13			9m	88
14			9n	82

3. Conclusion

In summary we have developed an efficient one-pot synthetic methodology for the preparation of a new class of 2,5-disubstituted 1,3,4-oxadiazoles and 2*H*-Chromene substituted 1,3,4-oxadiazoles by reacting various carboxylic acid hydrazides with acid chlorides in the presence of 10-Camphorsulfonic acid. The significance of this method was, hydrazides containing acid sensitive groups **(3e, 3h, 3i, 3j)** were also converted to corresponding 2,5-disubstituted 1,3,4-oxadiazoles in good to high yields. The utility of the present method was successfully demonstrated for the synthesis of novel 2*H*-Chromene derivatives. The experimental procedure is operationally simple, does not require anhydrous solvent, inert gas atmosphere, any chromatographic purification, and avoids the use of harsh reagents.

4. Experimental Section

4.1. Chemistry

Melting points were determined in open capillaries on a Stuart apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 2:8). Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. All the appropriate acid chlorides and carboxylic acid hydrazides used for the preparation were purchased from commercial sources. Thin-layer chromatography (TLC) was performed on E.Merck AL silica gel 60 F254 plates and visualized under UV light. The IR spectra were recorded on a Perkin Elmer FT-IR spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian EM-360 spectrometer (300 MHz, 400MHz). The ^{13}C NMR spectra recorded in $CDCl_3$ on a Varian EM-360 spectrometer operating at (100 MHz). All the chemical shifts were reported in δ (ppm) using TMS as an internal standard.The mass spectrum were recorded on Agilent ion trap MS.

General procedure for the Synthesis of 2,5-substituted-1,3,4-oxadiazoles (3a-l)*:* To a solution of carboxylic acid hydrazide **(1a-l)** (1.1 mmol) in dioxane (4 ml) was added 10-camphorsulfonic acid (0.055 mmol) followed by *o*-toluoyl chloride **(2)** (1.1 mmol), the resulted mixture was heated at 100°C for 16h. Then the reaction mixture was evaporated under vacumm, added saturated Na_2CO_3 (10 ml), then extracted into diethyl ether. Then the resulted organic layers were dried over Na_2SO_4 and distilled in vacumm to obtain 1,3,4-oxadiazole **(3a-l)** 75-92% without further purification.

2-(3-ethoxyphenyl)-5-(o-toluoyl)-1,3,4-oxadiazole (3a): Off white solid; yield 0.27 g (0.98 mmole, 89 %); M.R: 70-73 °C ; δH (400 MHz, $CDCl_3$) 8.00-7.98(d, 1H, J: 8Hz), 7.66-7.61(m, 2H), 7.40-7.36(t, 2H, J: 8Hz), 7.31-7.29(m, 2H), 7.04-7.02(d, 1H, J: 8Hz), 4.11-4.05(q, 2H, J: 4Hz), 2.74(s, 3H), 1.45-1.41(t, 3H, J; 5.3 Hz).; δC (100 MHz, $CDCl_3$) 164.60, 163.86, 159.15, 138.20, 131.60, 131.01, 130.01, 128.73, 125.98, 124.83,122.78,1128.93,118.23, 118.15, 112.10, 63.57, 22.07, 14.58; IR νmax (film): 3435, 2973, 2924, 1586, 1551, 1540, 1492, 1291, 1213, 1050, 730 cm-1; MS (EI) m/z 281.2 ($M+H^+$).

2-(4-methoxyphenyl)-5-(o-toluoyl)-1,3,4-oxadiazole (3b): Off-white solid; yield 0.29 g (1.1 mmole, 92 %); M.R: 123-126 °C; δH (400 MHz, $CDCl_3$) 8.07-8.05(d, 2H, J: 4Hz), 8.02-8.01(d, 1H), 7.43-7.32(m, 3H), 7.03-.701(d, 2H, J: 4Hz), 3.88(s, 3H), 2.76(s, 3H).; δC (100 MHz, $CDCl_3$) 164.35, 164.04, 162.27, 138.27, 131.71, 130.99, 128.83, 128.64, 126.09, 123.14, 116.47, 114.48, 55.42, 22.07; IR νmax (film): 3436, 2919, 2842, 1612, 1502, 1252, 1193, 1182, 1020, 844, 739 cm-1; MS (EI) m/z 267.2 ($M+H^+$).

2-(2-methoxyphenyl)-5-(o-toluoyl)-1,3,4-oxadiazole (3c): white solid; yield 0.29 g (1.08 mmole, 90 %); M.R: 96-99 °C ; δH (400 MHz, $CDCl_3$) 8.05-8.01(m, 2H), 7.51-7.46(t, 1H, J: 7.5 Hz), 7.42-7.29(m, 3H), 7.10-7.04(m, 2H), 3.97(s, 3H) , 2.75(s, 3H).; δC (100 MHz, $CDCl_3$)164.59, 162.89, 157.76, 138.17, 132.89, 131.58, 130.91, 130.26, 128.91, 126.00, 123.14, 120.63, 112.99, 111.86, 55.84, 21.88; IR νmax (film): 3435, 2921, 2033, 1716, 1604, 1534, 1496, 1434, 1260, 1018, 722 cm-1; MS (EI) m/z 267.1 ($M+H^+$).

***2-[(4-fluorophenoxy)methyl]-5-(o-toluoyl)-1,3,4-oxadiazole (3d)*:** Pale yellow solid; yield 0.24 g (0.84 mmole, 78 %) ; M.R: 101-104 °CδH (400 MHz, $CDCl_3$) 7.94-7.92(d, 1H, J: 8Hz), 7.42-7.40(d, 1H, J: 8Hz), 7.35-7.30(m, 2H), 7.01-6.99(d, 4H, J: 1Hz), 5.30(s, 2H), 2.69(s, 3H).; δC (100 MHz, $CDCl_3$) 166.02, 161.65, 159.22, 156.83, 153.66, 138.61, 131.76, 131.50, 129.07, 126.16, 122.50, 116.29, 116.01, 60.66, 22.00; IR νmax (film): 3436, 2922, 1541, 1507, 1491, 1218, 1042, 823, 727 cm-1; MS (EI) m/z 281.3 ($M+H^+$).

2-[(2-chlorophenoxy)methyl]-5-(o-toluoyl)-1,3,4-oxadiazole (3e) : Off white solid; yield 0.24 g (0.8 mmole, 80 %) ; M.R: 88-91 °C ; δH (400 MHz, $CDCl_3$) 7.96-7.94(d, 1H, J: 6Hz), 7.44-7.29(m, 4H), 7.27-7.22(m, 1H), 7.17-7.15(d, 1H, J: 6Hz), 7.15-6.96(t, 1H, J: 13.5 Hz), 5.41(s, 2H), 2.69(s, 3H).; δC (100 MHz, $CDCl_3$) 166.16, 161.39, 153.22, 138.62, 131.76, 131.52, 130.70, 129.15, 127.90, 126.19, 123.75, 123.28, 122.49, 114.97, 61.16, 22.00; IR νmax (film): 3434, 2921, 1608, 1541, 1488, 1281, 1229, 1040, 854, 744 cm-1; MS (EI) m/z 301.3 ($M+H^+$).

2-(3,5-dimethoxyphenyl)-5-(o-toluoyl)-1,3,4-oxadiazole (3f) : Off white solid; yield 0.25 g (0.81 mmole,83 %); M.R: 159-163 °C ; δH (400 MHz, $CDCl_3$) 8.02-8.00(d, 1H, J: 6Hz), 7.70-7.66(m, 2H), 7.45-7.32(m, 3H), 6.99-6.97(d, J: 6Hz), 3.99(s, 3H), 3.96(s, 3H), 2.76(s, 3H).; δC (100 MHz, $CDCl_3$) 164.44, 164.06, 151.95, 149.32, 138.28, 131.70, 131.03, 128.83, 126.08, 123.08, 120.32, 116.52, 111.07, 109.41, 56.09, 22.03; IR νmax (film): 3436, 2917, 1606, 1498, 1431, 1264, 1142, 1027, 726 cm-1; MS (EI) m/z 297.2 ($M+H^+$).

***N,N-dimethyl-4-[5-(o-touolyl)-1,3,4-oxadiazol-2-yl]aniline (3g)*:** Off-white solid; yield 0.26 g (0.93 mmole, 85 %) ; M.R: 130-133 °C ; δH (300 MHz, $CDCl_3$) 8.05-7.96(m, 4H), 7.47-7.31(m, 4H), 6.77-6.75(d, 2H, J: 4Hz), 3.06(s, 6H), 2.75(s, 3H); δC (100 MHz, $CDCl_3$) 164.79, 163.74, 152.29, 138.11, 131.62, 131.15, 130.69, 128.92, 128.26, 126.02, 123.45, 111.57, 40.05, 29.65, 22.07; IR νmax (film): 3437, 2922, 1614, 1504, 1363, 1196, 1050, 944, 739 cm-1; MS (EI) m/z 280.3 ($M+H^+$).

***2-[(4-chloro-2-methyl-phenoxy)methyl]-5-(o-toluoyl)-1,3,4-oxadiazole (3h)*:** Off-white solid; yield 0.23 g (0.71 mmole, 79 %); M.R: 111-114 °C ; δH (400 MHz, $CDCl_3$) 8.05-8.03(d, 1H, J:4Hz), 7.94-7.92(d, 1H, J:8Hz), 7.45-7.30(m, 4H), 7.14-7.12(d, 1H, J:8Hz), 6.95-6.93(d, 1H, J: 6Hz), 5.32(s, 2H), 2.78(s, 3H), 2.69(s, 3H).; δC (100 MHz, $CDCl_3$) 166.05, 161.70, 154.38, 138.46, 131.80, 131.54, 131.17, 130.90, 129.32, 128.94, 126.77, 126.20, 123.02, 122.53, 112.86, 60.42, 22.19, 16.05; IR νmax (film): 3436, 2921, 1541, 1492, 1250, 1043, 1022, 803, 726 cm-1; MS (EI) m/z 315.1 ($M+H^+$).

2-(o-toluoyl)-5-(phenoxymethyl)-1,3,4-oxadiazole (3i) : White solid; yield 0.25 g (0.92 mmole, 77 %); M.R: 72-76 °C ; δH (400

MHz, $CDCl_3$) 7.93-7.91(d, 1H, J: 4Hz), 7.41-7.37(t, 1H, J: 8Hz), 7.32-7.27(m, 4H), 7.04-6.99(m, 3H), 5.33(s, 2H), 2.69(s, 3H).; δC (100 MHz, $CDCl_3$) 165.92, 161.80, 157.52, 138.52, 131.68, 131.39, 129.64, 129.04, 126.09, 122.50, 122.09, 114.81, 59.85, 21.96; IR νmax (film): 3436, 2957, 2921, 1601, 1542, 1495, 1220, 1042, 748, 725 cm-1; MS (EI) m/z 267.4 ($M+H^+$).

***2-[(2-methoxyphenoxy)methyl]-5-(o-toluoyl)-1,3,4-oxadiazole (3j)*:** Off-white solid; yield 0.23 g (0.77 mmole, 76 %); M.R: 78-82 °C ; δH (400 MHz, $CDCl_3$) 7.94-7.92(d, 1H, J: 8Hz), 7.41-7.38(t, 1H, J: 6Hz), 7.32-7.26(m, 2H), 7.11-7.09(d, 1H, J: 8Hz), 7.03-6.99(t, 1H, J: 6Hz), 6.92-6.87(m, 2H), 5.38(s, 2H), 3.85(s, 3H), 2.67(s,3H).; δC (100 MHz, $CDCl_3$) 165.83, 161.96, 150.05, 146.79, 138.46, 131.61, 131.28, 129.04, 126.02, 123.34, 122.53, 120.83, 116.02, 112.16, 61.46, 55.77, 21.93; IR νmax (film): 3062, 2921, 2582, 1591, 1507, 1256, 1213, 10165, 729 cm-1; MS (EI) m/z 297.2 ($M+H^+$).

***2-(o-toluoyl)-5-(4-pyridyl)-1,3,4-oxadiazole (3k)* :** Pale yellow solid; yield 0.3 g (1.26 mmole, 87 %); M.R: 128-131°C ; δH (300 MHz, $CDCl_3$) 8.86-8.84(d, 2H, J: 3Hz), 8.06-8.04(d, 1H, J: 6Hz), 8.00-7.98(d, 2H, J: 3Hz), 7.47-7.45(d, 1H, J: 6Hz), 7.41-7.38(d, 3H, J: 3Hz), 2.78(s, 3H).; δC (100 MHz, $CDCl_3$) 165.75, 162.33, 150.92, 138.74, 131.95, 131.74, 131.06, 129.11, 126.30, 122.43, 120.31, 22.11; IR νmax (film): 3431, 3035, 2924, 2348, 1605, 1535, 1458, 1254, 1059, 728 cm-1; MS (EI) m/z 238.1 ($M+H^+$).

***2-(1H-indol-3-ylmethyl)-5-(o-toluoyl)-1,3,4-oxadiazole (3l)* :** Off white solid; yield 0.26 g (0.9 mmole, 86 %); M.R: 138-141 °C; δH (400 MHz, $CDCl_3$) 8.52(brs, 1H), 7.83-7.81(d, 1H, J: 8Hz), 7.70-7.68(d, 1H, J: 8Hz), 7.35-7.32(m, 2H), 7.27-7.21(m, 2H), 7.20-7.11(m, 3H), 4.40(s, 2H), 2.62(s, 3H).; δC (100 MHz, $CDCl_3$) 165.33, 165.14, 138.19, 136.18, 131.57, 130.97, 128.82, 126.77, 125.98, 123.16, 122.95, 119.75, 118.55, 111.36, 108.06, 22.10; IR νmax (film): 3435, 2921, 1604, 1534, 1434, 1260, 1018, 722 cm-1; MS (EI) m/z 290.2 ($M+H^+$).

5.1. General procedure for the Synthesis of chromene substituted-1,3,4-oxadiazloes (9a-r)

To a solution of chromene carboxylic acidhydrazide (7) (1.3 mmol) in dioxane (4 ml) was added 10-camphorsulfonic acid (0.065 mmol) followed by acid chloride (8) (1.3 mmol), the resulted mixture was heated at 100°C for 16h. Then the reaction mixture was evaporated under vacumm, added saturated Na_2CO_3 (10 ml) .then extracted into diethyl ether. Then the resulted organic layers were dried over Na_2SO_4 and distilled in vacumm to obtain 1,3,4-oxadiazole **(9a-r)** 75-92% without further purification.

2-(2H-chromen-3-yl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (9a): Off-white solid; yield 0.27 g (0.84 mmole, 88%); M.R: 118-122 °C ; *δH* (400 MHz, CDCl3) 7.93-7.91(d, 1h, J:8Hz), 7.82-7.79(d, 1H, J: 12Hz), 7.54-7.49(q, 1H, J: 6.3 Hz), 7.39(s, 1H), 7.29-7.19(m, 2H), 6.99-6.96(t, 1H, J: 6Hz), 6.92-6.90(d, 1H, J:12Hz), 5.28(s, 2H).; δC (100 MHz, CDCl3) 164.08, 163.25, 162.02, 161.61, 154.72, 131.66, 130.92, 128.41, 128.22, 125.55, 122.79, 122.08, 120.94, 119.09, 118.88, 116.37, 115.70, 114.17, 113.93, 63.96, 29.67; IR νmax(film): 3436, 2924, 2854, 1744, 1640, 1604, 1455, 1211, 1123, 1033, 753, 726 cm-1; MS (EI) *m/z* 295.3 ($M+H^+$)

2-(2H-chromen-3-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (9b): pale yellow solid; yield 0.23 g (0.75 mmole, 79%); M.R: 181-184 °CδH (400 MHz, $CDCl_3$) 77.82-7.81(d, 1H,J; 4Hz), 7.57-7.56(s, 1H, J: 4Hz), 7.34(s, 1H), 7.25-7.17(m, 3H), 6.97-6.93(t, 1H, J: 8Hz), 6.90-6.88(d, 1H, J; 8Hz), 5.25(s, 2H).; δC (100 MHz, $CDCl_3$) 161.22, 160.54, 154.68, 131.53, 130.50, 130.08, 128.35, 128.25, 127.84, 124.94, 122.04, 121.02, 116.33, 115.68, 63.99; IR νmax (film): 3093, 2926, 2846, 1733, 1641, 1585, 1452, 1206, 1008, 851, 750, 721cm-1; MS (EI) m/z 283 ($M+H^+$)

***2-(2H-chromen-3-yl)-5-(benzyl)-1,3,4-oxadiazole (9c)*:** Gummy liquid; yield 0.23 g (0.71 mmole, 75%); δH (400 MHz, $CDCl_3$) 7.35-7.29(m, 5H), 7.21-7.19(d, 2H, J: 4Hz), 7.12-7.10(d, 1H, J: 8Hz),6.94-6.92(t, 1H, J: 4Hz), 6.87-6.85(d, 1H, J: 8Hz), 5.18(s, 2H), 4.32(s, 2H).; δC (100 MHz, $CDCl_3$) 165.09, 162.40, 154.61, 133.70, 131.44, 129.32, 128.97, 128.79, 127.74,127.63, 121.97, 120.91,116.27, 115.87, 63.96, 31.86; IR νmax (film): 3430, 2923, 2853, 1641, 1624, 1503, 1275, ,1261, 1122, 1018, 750 cm-1; MS (EI) m/z 291.3 ($M+H^+$).

***2-(2H-chromen-3-yl)-5-(m-toluoyl)-1,3,4-oxadiazole (9d)* :** White solid; yield 0.25 g (0.79 mmole, 83%); M.R: 112-116°C; δH (400 MHz, $CDCl_3$) 7.95-7.88(m, 2H), 7.41-7.30(m, 3H), 7.22-7.17(m, 2H), 6.97-6.93(t, 1H, J: 8Hz), 6.90-6.88(d, 1H, J: 8Hz), 5.27(s, 2H), 2.44(s, 3H).; δC (100 MHz, $CDCl_3$) 164.41, 161.68, 154.65, 138.99, 132.73, 132.46, 131.44, 128.97, 128.29, 127.64, 127.52, 127.40, 124.19, 124.05, , 123.82, 123.48, 122.01, 121.04, 116.30, 115.98, 64.02, 21.30;IR νmax (film): 3434, 3053, 2921, 2852, 1640, 1522, 1468, 1454, 1210, 1121, 1031, 996, 888, 750 cm-1; MS (EI) m/z 291.2 ($M+H^+$).

2-(2H-chromen-3-yl)-5-(o-toluoyl)-1,3,4-oxadiazole (9e): White solid; yield 0.27 g (0.83 mmole, 88%); M.R: 116-120 °C; δH (400 MHz, $CDCl_3$) 8.01-7.99(d, 1H, J: 8Hz), 7.45-7.41(t, 1H, J: 8Hz), 7.37-7.33(m, 3H), 7.26-7.22(m, 1H), 7.19-7.18(d, 1H, J: 4Hz), 6.98-6.94(t, 1H, J: 8Hz), 6.92-6.90(d, 1H, J: 8Hz), 5.29(s, 2H), 2.74(s, 3H).; δC (100 MHz, $CDCl_3$) 164.52, 161.31, 154.67, 138.61, 131.82, 131.46, 131.38, 131.15, 129.01, 128.94, 128.31, 127.64, 126.17, 122.70, 122.01, 121.04, 116.31, 115.99, 64.03, 22.18; IR νmax (film): 3435, 2922, 2837, 1642, 1604, 1484, 1453, 1210, 1121, 1031, 889, 750, 727 cm-1; MS (EI) m/z 291.2 ($M+H^+$).

***2-(2H-chromen-3-yl)-5-cyclopropyl-1,3,4-oxadiazole(9f)*:** Gummy material ; yield 0.19 g (0.71 mmole, 75 %); δH (400 MHz, $CDCl_3$) 7.22-7.21(d, 1H, J: 4Hz), 7.18(s, 1H), 7.15-7.13(d, 1H, J: 8Hz), 6.90-6.87(d, 1H, J: 12Hz), 5.20(s, 1H), 2.22-2.18(m, 1H), 1.25-1.20(d, 4H,J: 5Hz).; δC (100 MHz, $CDCl_3$) 131.29, 128.19, 126.93, 121.97, 121.04, 120.85, 116.27, 115.94, 64.02, 29.68, 8.67, 6.48; IR νmax (film): 3442, 2923, 2857, 1636, 1456, 1275, 1261. 1019, 750 cm-1; MS (EI) m/z 241.3 ($M+H^+$).

***2-(2H-chromen-3-yl)-5-(3-fluoro-4-methyl-phenyl)-1,3,4-oxadiazole (9g)*:** Pale yellow solid; yield 0.19 g (0.81 mmole, 86 %); M.R: 185-188°C; δH (400 MHz, $CDCl_3$) 7.88-7.86(d, 1H, J: 8Hz), 7.83-7.80(dd, 1H, J: 4Hz), 7.35(s, 1H), 7.27-7.23(m, 1H), 7.20-7.18(d, 1H, J: 8Hz), 7.10-7.06(t, 1H, J: 8Hz), 6.99-6.95(t, 1H, J: 8Hz), 6.92-6.90(d, 1H, J: 8Hz), 5.27(s, 2H), 3.98(s, 3H).; δC (100 MHz, $CDCl_3$) 163.31, 161.61, 154.67, 153.50, 151.03, 150.89, 150.87, 131.51, 128.32, 127.69, 123.84, 122.04, 121.01, 116.32, 115.36, 114.96, 114.74, 113.47, 63.99, 56.32; IR νmax (film): 3437, 2924, 2852, 2601, 1744, 1640, 1623, 1503, 1454,1284, 1017, 883, 745 cm-1; MS (EI) m/z 325.2 ($M+H_2O^+$).

***2-(6-chloro-2H-chromen-3-yl)-5-(4-ethoxyphenyl)-1,3,4-oxadiazole (9h)*:** Off-white solid; yield 0.27 g (0.75 mmole, 85%); M.R: 174-176 °C ; δH (300 MHz, $CDCl_3$) 88.04-8.01(d, 2H, J: 4.5 Hz), 7.20-7.15(m, 2H), 7.02-6.99(d, 2H, J: 4.5Hz),

6.86-6.83(d, 1H, J: 9Hz), 5.28(s, 2H), 4.15-4.08(q, 2H, J: 3.5Hz), 1.48-1.44(t, 3H, J: 2Hz).; δC (100 MHz, $CDCl_3$) 164.53, 162.05, 160.97, 153.08, 30.83, 128.90, 127.53, 126.75, 125.86, 122.35, 117.62, 117.38, 115.72, 115.02, 64.22, 63.80, 14.67; IR νmax (film): 3209, 2978, 1609, 1496, 1268, 1179, 1043, 827, 807, 662 cm^{-1}; MS (EI) m/z 355.4 ($M+H^+$)

2-(6-chloro-2H-chromen-3-yl)-5-(3-fluorophenyl)-1,3,4-oxadiazole (9i): Off-white solid; yield 0.26 g (0.79 mmole, 89%); M.R: 169-173 °C ; δH (300 MHz, $CDCl_3$) 7.93-7.90(d, 1H, J: 9 Hz), 7.82-7.79(d, 1H, J: 9Hz), 7.56-7.49(m, 1H), 7.32-7.27(m, 2H), 7.24-7.18(m, 2H), 6.87-6.84(d, 1H, J: 9Hz), 5.31(s, 2H).; δC (100 MHz, $CDCl_3$) 163.51, 161.67, 157.23, 153.76, 147.86, 131.56,131.05, 130.96, 127.68, 126.89, 122.83, 122.12, 119.25,117.70,114.56,114.12, 64.10; IR νmax (film): 3446, 3053, 2854, 1636, 1538, 1485,1212, 861, 813, 645 cm-1; MS (EI) m/z 329.1 ($M+H^+$)

2-(4-tert-butylphenyl)-5-(6-chloro-2H-chromen-3-yl)-1,3,4-oxadiazole(9j): Off-white solid; yield 0.30 g (0.81 mmole, 91%); M.R: 157-160 °C ; δH (300 MHz, $CDCl_3$) 8.05-8.01(d, 2H, J: 6 Hz), 7.56-7.53(d, 1H, J: 4.5Hz), 7.28-7.26(d,2H, J: 3Hz), 7.19-7.17(d, 2H, J: 3Hz), 6.86-6.83(d, 1H, J: 9Hz), 5.28(s, 2H), 1.37(s, 9H).; δC (100 MHz, $CDCl_3$) 164.59, 161.23, 155.79, 153.09, 130.90, 127.58, 126.94, 126.76, 126.12, 122.30, 120.63, 117.63, 117.29, 67.20, 35.13, 31.09; IR νmax (film): 3436, 2961, 1614, 1493, 1480, 1208, 1094,911, 713 cm-1; MS (EI) m/z 367.4 ($M+H^+$).

2-(6-chloro-2H-chromen-3-yl)-5-cyclopropyl-1,3,4-oxadiazole (9k): Off-white solid; yield 0.18 g (0.74 mmole, 83%); M.R: 114-117 °C ; δH (300 MHz, $CDCl_3$) 7.18-7.15(dd, 1H, J: 3Hz), 7.12-7.10(m, 2H), 6.84-6.81(d, 1H), 5.20(s, 2H), 2.26-2.18(m, 1H), 1.21-1.19(m, 4H).; δC (100 MHz, $CDCl_3$) 168.58, 160.85, 152.99, 130.78, 127.49, 126.72, 125.62, 122.24, 117.58, 117.30, 64.15, 11.03, 8.79, 6.46; IR νmax (film): 3436, 2961, 1614, 1493, 1480, 1208, 1094,911, 713 cm-1; MS (EI) m/z 275.3 ($M+H^+$).

2-(6-chloro-2H-chromen-3-yl)-5-phenyl-1,3,4-oxadiazole (9l): Off-white solid; yield 0.24g (0.78 mmole, 88%); M.R: 177-180 °C ; δH (300 MHz, $CDCl_3$) 8.13-8.10(d, 2H, J: 4.5Hz), 7.56-7.53(m, 3H), 7.30(s, 1H), 7.21-7.17(m, 2H), 6.86-6.84(d, 1H, J: 6Hz), 5.29(s, 2H).; δC (100 MHz, $CDCl_3$) 164.48, 161.43, 153.12, 132.07, 131.00, 129.14, 127.61, 127.09, 126.79, 126.43, 123.49, 122.25, 117.66, 117.20, 64.18; IR νmax (film): 3434, 3052, 1539, 1483, 1211, 1022, 809, 712, 684 cm-1; MS (EI) m/z 311.3 ($M+H^+$).

2-(6-chloro-2H-chromen-3-yl)-5-(2-thienylmethyl)-1,3,4-oxadiazole (9m): Off-white solid; yield 0.26 g (0.78 mmole, 88%); M.R: 148-151 °C ; δH (300 MHz, $CDCl_3$) 77.25-7.12(m, 4H), 7.02-6.99(m, 2H), 6.84-6.81(d, 1H, J: 9Hz), 5.21(s, 2H), 4.26(s, 2H). ; δC (100 MHz, $CDCl_3$) 164.32, 162.11, 153.07, 134.61, 131.02, 127.63, 127.28, 127.17, 126.78, 126.67, 125.57, 122.09, 117.63, 117.02, 64.09, 26.26; IR νmax (film): 3444, 2925, 1648, 1567, 1482, 1209, 988, 901, 827, 705 cm-1; MS (EI) m/z 331 ($M+H^+$).

2-butyl-5-(6-chloro-2H-chromen-3-yl)-1,3,4-oxadiazole (9n): Off-white solid; yield 0.212 g (0.73 mmole, 82%); M.R: 106-109 °C ; δH (300 MHz, $CDCl_3$) 7. 7.19-7.12(m, 3H), 6.84-6.81(d, 1H, J: 9Hz), 5.22(s, 3H), 2.92-2.87(t, 2H, 3.75 Hz), 1.86-1.76(p, 2H, J; 3.75Hz), 1.49-1.42(m, 2H), 1.00-0.95(t, 2H, J: 3.75Hz); δC (100 MHz, $CDCl_3$) 167.09, 153.04, 130.85, 127.53, 126.74, 125.99, 122.24, 117.61, 117.39, 64.19, 28.56, 25.12, 22.15, 13.56; IR νmax (film): 3430, 2957, 1645, 1566, 1481, 1208, 923, 814, 646 cm-1; MS (EI) m/z 291.3 ($M+H^+$).

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Graphical Abstract

10-Camphorsulfonic acid ((±)-CSA) catalyzed facile one pot synthesis of a new class of 2, 5-disubstituted 1, 3, 4-oxadiazoles

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A convenient, and efficient one-pot synthesis of 2,5-disubstituted-1,3,4-oxadizoles is described. Various carboxylic acid hydrazides efficiently reacted with different carboxylic acid chlorides with 10-Camphorsulfonic acid. This methodology was successfully applied to synthesize a series of 2*H*-chromene substituted 1,3,4-oxadiazole derivatives in good to high yields.