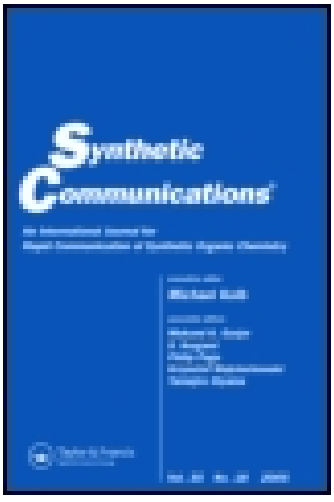

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$Y(OTf)_3$-Catalyzed, One-Pot Synthesis of 1,2,4-Oxadiazole Derivatives

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$Y(OTf)_3$-Catalyzed, One-Pot Synthesis of 1,2,4-Oxadiazole Derivatives

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Abstract: Direct one-step synthesis of 1,2,4-oxadiazole from ketones, nitriles, and nitric acid is described using yttrium triflate [$Y(OTf)_3$] as the catalyst. The salient features of this method include a simple procedure, mild condition, easy purification, and good yields.

Keywords: ketones, nitriles, 1,2,4-oxadiazole derivatives, yttrium triflate

The 1,2,4-oxadiazole derivatives are of significant importance to medicinal chemistry because they are found in many biologically active compounds. Publications have reported that substituted 1,2,4-oxadiazole derivatives have found applications in diverse therapeutic areas including as antikinetoplastid materials,[1] β_3 adrenergic receptor agonists,[2] anti-inflammatory substances,[3] muscarinic agonists,[4] and serotonineric antagonists.[5]

The widespread interest in 1,2,4-oxadiazole-containing structures has promoted extensive studies of their synthesis. These include the cycloaddition of nitrile oxides to amidoximes;[6] treatment of acylated amidoximes with bases such as NaH, NaOEt, or pyridine;[7] the *O*-acylation of amidoximes by an activated carboxylic acid derivative such as ester[5] or acid chlorides followed by cyclodehydration,[8] the *O*-acylation of *o*-vinylbenzamidoxime

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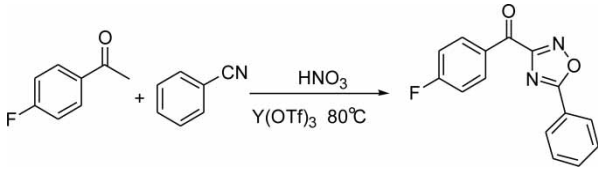
and trifluoroacetic anhydride in pyridine;[9] and condensation of nitriles, hydroxyl amine, and aldehydes under microwave irradiation.[10] Recently, Itoh and his coworkers reported the one-pot synthesis of 3-acetyl- and 3-benzoyl-1,2,4-oxadiazoles using $Fe(NO_3)_3$.[11] However, many of these processes suffer from limitations such as drastic reaction conditions, low yields, and tedious workup procedures.

During the past decade, rare-earth-metal triflates have been found to be unique Lewis acids. They are water-tolerant, reusable catalysts, and they can effectively promote carbon–carbon and carbon–heteroatom bond formation in good yields.[12] Because of their unique catalytic properties, rare-earth-metal triflates have been extensively used for a plethora of organic reactions. In our most recent work, we investigated the use of $Y(OTf)_3$ as a catalyst for the preparation of 1,2,4-oxadiazole derivatives. The reaction of ketones and nitriles with nitric acid in the presence of $Y(OTf)_3$ gave corresponding 1,2,4-oxadiazole derivatives in good yields (Scheme 1). Although there are several papers reporting the synthesis of 1,2,4-oxadiazole derivatives, there are few reports in the literature using ketones, nitriles, and nitric acid as starting materials in the presence of rare-earth-metal triflates as catalysts.

At first, we carried out the reaction in benzonitrile at 80°C, taking a 1:1.1 mol ratio mixture of 4-fluoroacetophenone and nitric acid in the presence of 5 mol% $Y(OTf)_3$ for 4 hours to afford 3-(4-fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole in 54% yield (Table 1, entry 8). Encouraged by this result, we studied different reaction parameters, and the results are summarized in Table 1. Among the various metal triflates such as $Cu(OTf)_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Yb(OTf)_3$, $Eu(OTf)_3$, and $Y(OTf)_3$ studied for this reaction, $Y(OTf)_3$ was found to be the most effective catalyst in terms of reaction yields. Then, the reaction was performed in different amounts of $Y(OTf)_3$.

As shown in Table 1, no reaction was observed when the mixture was stirred under similar conditions in the absence of $Y(OTf)_3$, even after heating for 12 h (Table 1, entry 7). Furthermore, we have changed the amount of $Y(OTf)_3$ from 5 to 30 mol%, finding that the use of 10 mol% was optimal to ensure high reaction efficiency (85%, yield).

To optimize the temperature for the reaction, we carried out the reaction at temperatures ranging from 60 to 110°C (Table 2); we found that the yield of



Scheme 1.

Table 1. Optimization of the reaction conditions[a]

Entry	Catalyst	Catalyst (mol%)	Yield[b,c] (%)
1	$Cu(OTf)_2$	10	62
2	$Zn(OTf)_2$	10	59
3	$Mg(OTf)_2$	10	31
4	$Yb(OTf)_3$	10	83
5	$Eu(OTf)_3$	10	81
6	$Y(OTf)_3$	10	85
7	None	—	ND[d]
8	$Y(OTf)_3$	5	54
9	$Y(OTf)_3$	15	85
10	$Y(OTf)_3$	20	86
11	$Y(OTf)_3$	30	86

[a]Reaction conditions: 4-fluoroacetophenone (0.28 g, 2.0 mmol), HNO_3 (0.15 g, 2.2 mmol, conc. 95%), benzonitrile (1 mL), reaction temperature 80°C, reaction time 4 h.

[b]Isolated yields based on 4-fluoroacetophenone.

[c]The product was 3-(4-fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole.

[d]No product was detected.

product improved as the temperature increased from 60 to 80°C. The yield plateaued when the temperature further increased from 90 to 110°C. Therefore, a reaction of 80°C was considered to be most suitable.

Having established the optimized reaction conditions, we then successfully synthesized a variety of 1,2,4-oxadiazole derivatives (Scheme 2), and the results are summarized in Table 3.

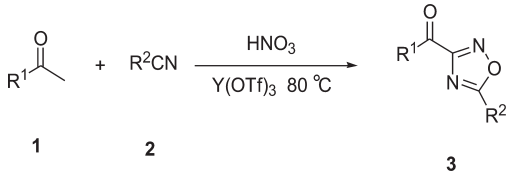
Table 2. Optimization of the reaction temperature[a]

Entry	Temperature (°C)	Yield[b,c] (%)
1	60	52
2	70	74
3	80	85
4	90	85
5	100	86
6	110	85

[a]Reaction conditions: 4-fluoroacetophenone (0.28 g, 2.0 mmol), HNO_3 (0.15 g, 2.2 mmol, conc. 95%), benzonitrile (1 mL), reaction time 4 h.

[b]Isolated yields based on 4-fluoroacetophenone.

[c]The product was 3-(4-fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole.



Scheme 2.

As shown in Table 3, acetonitrile (Table 3, entries 1–5), benzonitrile (Table 3, entries 6–11), and 2-fluorobenzonitrile (Table 3, entries 12–15) were used in this reaction. We found that the reactivity of acetonitrile was lower than aromatic nitriles in terms of reaction times and reaction yields. The reactions were completed within 10–30 h when using acetonitrile as substrate, much longer than that required for aromatic nitriles (4 h). Furthermore, relative low yields were obtained when using acetonitrile (Table 3, entries 1–5).

Moreover, several aromatic and aliphatic ketones were examined under the optimized conditions using 10 mol% of $Y(OTf)_3$. As shown in Table 3, we found that all the aromatic ketones must carry at least one electron-withdrawing group such as -Cl, -F, $-NO_2$, otherwise, the reaction could not perform smoothly to afford the products of 1,2,4-oxadiazoles. We investigated the reaction with aromatic ketones carrying electron-donating groups, such as acetophenone, 4-methyl-acetophenone, and 4-methoxy-acetophenone; unfortunately, we obtained the main products of furoxan derivatives, not the 1,2,4-oxadiazole derivatives that we desired.

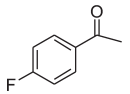
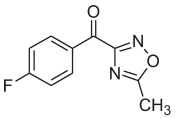
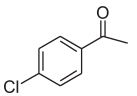
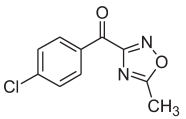
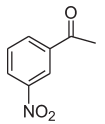
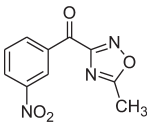
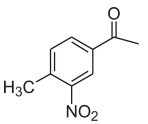
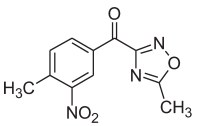
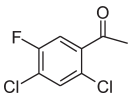
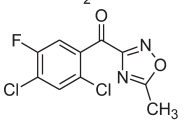
A probable mechanism for the reaction may be postulated as shown in Scheme 3. In this reaction mechanism, the enolization **4** of ketones was accelerated by $Y(OTf)_3$, followed by the nitration of ketones. The formation of nitrile oxides **6** proceeds via the acid-catalyzed dehydration of α-nitroketones **5**, and the 1,2,4-oxadiazole derivatives **3** were obtained by the 1,3-dipolar cycloaddition to nitriles.[11,13]

In conclusion, we have developed an efficient reaction protocal for the synthesis of 1,2,4-oxadiazole derivatives using ketones, nitriles, and nitric acid as starting materials in the prence of $Y(OTf)_3$ as a catalyst. The easy workup procedure, relatively short reaction times, and good yields make this method a valid contribution to the existing methologies.

EXPERIMENTAL

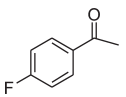
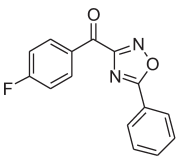
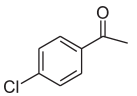
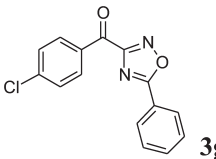
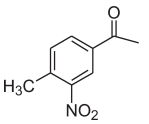
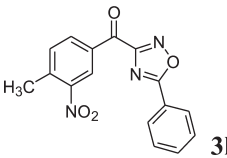
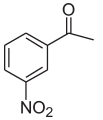
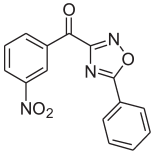
All reagents were commercial available and used without any purification. The melting points were recorded on a digital melting-point apparatus WRS-1B and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer. IR measurements were carried out with

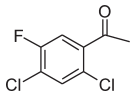
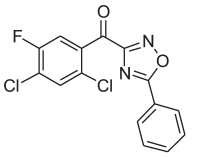
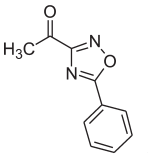
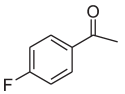
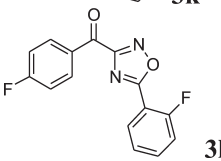
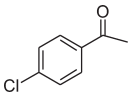
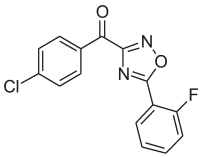
Table 3. $Y(OTf)_3$-catalyzed synthesis of 1,2,4-oxadiazole derivatives[a]

Entry	Ketones **1**	Nitriles **2**	Time (h)	Products	Yield[b] (%)
1		CH_3CN	18	 **3a**	49
2		CH_3CN	18	 **3b**	47
3		CH_3CN	24	 **3c**	69
4		CH_3CN	24	 **3d**	73
5		CH_3CN	30	 **3e**	68

(*continued*)

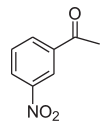
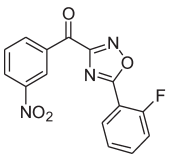
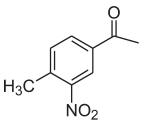
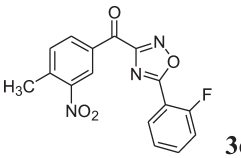
Table 3. Continued

Entry	Ketones **1**	Nitriles **2**	Time (h)	Products	Yield[b] (%)
6			4	 **3f**	85
7			4	 **3g**	83
8			4	 **3h**	84
9			4	 **3i**	82

10			4	 **3j**	80
11			4	 **3k**	46
12			4	 **3l**	79
13			4	 **3m**	74

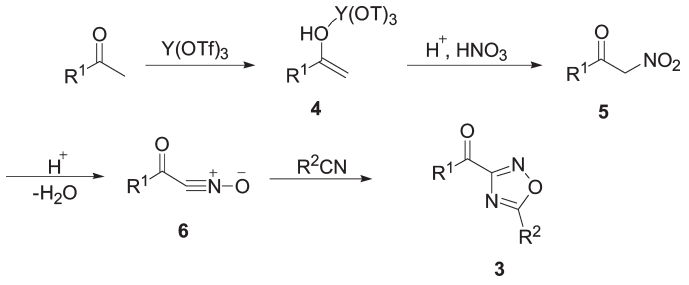
(*continued*)

Table 3. Continued

Entry	Ketones **1**	Nitriles **2**	Time (h)	Products	Yield[b] (%)
14			4	 **3n**	80
15			4	 **3o**	81

[a]Reaction conditions: ketones (2.0 mmol), HNO_3 (0.15 g, 2.2 mmol, conc. 95%), nitriles (1 mL), reaction temperature 80°C, catalyst $Y(OTf)_3$ 10 mol%.

[b]Isolated yields based on ketones.



Scheme 3.

Nicolet Aviatar-370 instrument. Mass spectra were measured with a Thermo Finnigan LCQ-Advantage. Elemental analyses (C, H, N, S) were performed on a Fisons EA 1110 CHNS elemental analyzer.

General Procedure for the Preparation of 1,2,4-Oxadiazole Derivatives

A mixture of ketones (**1**, 2.0 mmol) and HNO_3 (0.15 g, 2.2 mmol, conc. 95%) in nitriles (**2**, 1 mL) was stirred at 80°C in the presence of 10 mol% $Y(OTf)_3$ for the appropriate time (Table 3). After completion of the reaction as indicated by thin-layer chromatography (TLC), the mixture was diluted with AcOEt (20 mL) and washed with aq. $NaHCO_3$ solution (10 mL × 2) and sat. aq. NaCl (10 mL × 2). Then the organic phase was dried over $MgSO_4$ and concentrated in a vacuum. The residue was chromatographed on silica gel and eluted with petroleum ether–AcOEt (5:1) to give pure products **3**.

Spectral and Analytical Data

3-(4-Fluorobenzoyl)-5-methyl-1,2,4-oxadiazole (**3a**)

White solid; mp 82–83°C. IR (KBr): 1638, 1597, 1481, 1229, 907 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.36–8.39$ (m, 2H, ArH), 7.20–7.24 (m, 2H, ArH), 2.75 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.10$, 177.62, 167.97, 165.53, 165.40, 133.53, 133.44, 131.34, 116.14, 115.92, 12.35 ppm. MS (EI): m/z (%) = 206 (30) [M^+]. Anal. calcd. for $C_{10}H_7FN_2O_2$: C, 58.26; H, 3.42; N, 13.59. Found C, 58.22; H, 3.40; N, 13.63.

3-(4-Chlorobenzoyl)-5-methyl-1,2,4-oxadiazole (**3b**)

White solid; mp 108–110°C. IR (KBr): 1682, 1670, 1585, 1208, 911 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.28$ (d, 2H, $J = 8.0$ Hz, ArH), 7.52

(d, 2H, $J = 8.0$ Hz, ArH), 2.74 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.74$, 177.99, 165.83, 141.69, 133.58, 132.30, 129.44, 12.68 ppm. MS (EI): m/z (%) = 222 (30), 224 (11) [M^+]. Anal. calcd. for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found C, 53.99; H, 3.14; N, 12.60.

5-Methyl-3-(3-nitrobenzoyl)-1,2,4-oxadiazole (**3c**)

Pale yellow crystal; mp 135–137°C. IR (KBr): 1680, 1621, 1533, 1206, 872 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.18$ (s, 1H, ArH), 8.67 (d, 1H, $J = 8.0$ Hz, ArH), 8.54 (d, 1H, $J = 8.0$ Hz, ArH), 7.80 (dd, 1H, $J = 8.0$ Hz, ArH), 2.79 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.48$, 178.12, 165.14, 148.30, 135.90, 134.84, 130.01, 128.56, 125.49, 12.35 ppm. MS (EI): m/z (%) = 233 (30) [M^+]. Anal. calcd. for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found C, 51.57; H, 2.99; N, 18.09.

5-Methyl-3-(4-methyl-3-nitrobenzoyl)-1,2,4-oxadiazole (**3d**)

Yellow crystal; mp 112–114°C. IR (KBr): 1678, 1527, 1345, 1210, 869 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.96$ (s, 1H, ArH), 8.46 (d, 1H, $J = 8.0$ Hz, ArH), 7.56 (d, 1H, $J = 8.0$ Hz, ArH), 2.77 (s, 3H, CH_3), 2.72 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.18$, 177.99, 165.25, 149.37, 140.14, 133.98, 133.81, 133.41, 126.94, 30.73, 12.36 ppm. MS (EI): m/z (%) = 248 (50) [$M + H^+$]. Anal. calcd. for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67; N, 17.00. Found C, 53.38; H, 3.66; N, 16.89.

3-(2,4-Dichloro-5-fluorobenzoyl)-5-methyl-1,2,4-oxadiazole (**3e**)

White solid; mp 74–75°C. IR (KBr): 3034, 1692, 1587, 1255, 852 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.58$ (d, 1H, $J = 6.4$ Hz, ArH), 7.52 (d, 1H, $J = 8.4$ Hz, ArH), 2.74 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.42$, 178.52, 165.60, 157.70, 155.19, 135.01, 134.96, 132.45, 128.32, 126.35, 126.16, 118.65, 118.40, 12.41 ppm. MS (EI): m/z (%) = 274 (21) [M^+]. Anal. calcd. for $C_{10}H_5Cl_2FN_2O_2$: C, 43.67; H, 1.83; N, 10.18. Found C, 43.60; H, 1.88; N, 10.20.

3-(4-Fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole (**3f**)

White solid; mp 106–108°C. IR (KBr): 1687, 1600, 1467, 1217, 914 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.43$ (dd, 2H, $J_1 = 5.2$ Hz, $J_2 = 8.4$ Hz, ArH), 8.27 (d, 2H, $J = 8.0$ Hz, ArH), 7.67 (t, 1H, $J = 8.0$ Hz, ArH), 7.59 (t, 2H, $J = 8.0$ Hz, ArH), 7.22–7.26 (m, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.33$, 176.65, 168.06, 165.50, 166.13, 133.65, 133.56, 131.56, 129.29, 128.54, 123.30, 116.18, 115.96 ppm. MS (EI): m/z (%) = 268 (25) [M^+]. Anal. calcd. for $C_{15}H_9FN_2O_2$: C, 67.16; H, 3.38; N, 10.44. Found C, 67.10; H, 3.44; N, 10.49.

3-(4-Chlorobenzoyl)-5-phenyl-1,2,4-oxadiazole (**3g**)

White solid; mp 100–102°C. IR (KBr): 1687, 1561, 1461, 1218, 912 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.34$ (d, 2H, $J = 8.4$ Hz, ArH), 8.29 (d, 2H, $J = 7.8$ Hz, ArH), 7.68 (t, 1H, $J = 7.8$ Hz, ArH), 7.60 (t, 2H, $J = 7.8$ Hz, ArH), 7.56 (t, 2H, $J = 7.8$ Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.72$, 176.68, 166.01, 141.42, 133.58, 133.39, 132.08, 129.29, 129.16, 128.53, 123.22 ppm. MS (EI): m/z (%) = 284 (40), 286 (12) [M^+]. Anal. calcd. for $C_{15}H_9ClN_2O_2$: C, 63.28; H, 3.19; N, 9.84. Found C, 63.24; H, 3.22; N, 9.78.

3-(4-Methyl-3-nitrobenzoyl)-5-phenyl-1,2,4-oxadiazole (**3h**)

Yellowish crystal; mp 107–109°C. IR (KBr): 1656, 1596, 1270, 1164, 897 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.04$ (s, 1H, ArH), 8.51 (d, 1H, $J = 7.6$ Hz, ArH), 8.28 (d, 2H, $J = 7.6$ Hz, ArH), 7.68 (t, 1H, $J = 6.8$ Hz, ArH), 7.57–7.62 (m, 3H, ArH), 2.74 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.79$, 177.28, 166.09, 149.72, 140.55, 134.44, 134.29, 133.78, 129.67, 128.90, 127.43, 123.40, 21.16 ppm. MS (EI): m/z (%) = 309 (40) [M^+]. Anal. calcd. for $C_{16}H_{11}N_3O_4$: C, 62.14; H, 3.58; N, 13.59. Found C, 62.15; H, 3.66; N, 13.49.

3-(3-Nitrobenzoyl)-5-phenyl-1,2,4-oxadiazole (**3i**)

Yellowish crystal; mp 123–125°C. IR (KBr): 1683, 1607, 1529, 1346, 1209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.27$ (s, 1H, ArH), 8.72 (d, 1H, $J = 8.0$ Hz, ArH), 8.56 (d, 1H, $J = 8.0$ Hz, ArH), 8.28 (d, 2H, $J = 8.0$ Hz, ArH), 7.80 (t, 1H, $J = 8.0$ Hz, ArH), 7.69 (t, 1H, $J = 8.0$ Hz, ArH), 7.60 (d, 2H, $J = 8.0$ Hz, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.75$, 177.07, 165.69, 148.41, 136.19, 136.01, 133.79, 130.04, 129.29, 128.63, 128.57, 125.69, 122.99 ppm. MS (EI): m/z (%) = 295 (30) [M^+]. Anal. calcd. for $C_{15}H_9N_3O_4$: C, 61.02; H, 3.07; N, 14.23. Found C, 61.00; H, 3.12; N, 14.19.

3-(2,4-Dichloro-5-fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole (**3j**)

White solid; mp 121–123°C. IR (KBr): 1697, 1565, 1476, 1256, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.24$ (d, 2H, $J = 8.0$ Hz, ArH), 7.67 (t, 1H, $J = 8.0$ Hz, ArH), 7.56–7.60 (m, 4H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.77$, 177.46, 166.21, 157.82, 155.31, 135.20, 135.12, 133.75, 132.53, 129.34, 128.56, 128.55, 126.45, 126.26, 123.08, 118.79, 118.55 ppm. MS (EI): m/z (%) = 336 (25), 338 (16) [M^+]. Anal. calcd. for $C_{15}H_7Cl_2FN_2O_2$: C, 53.44; H, 2.09; N, 8.31. Found C, 53.40; H, 2.10; N, 8.28.

3-Acetyl-5-phenyl-1,2,4-oxadiazole (**3k**)

Pale yellow crystal; mp 46–48°C. IR (KBr): 2918, 1721, 1560, 1467, 1158 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.23$ (d, 2H, $J = 7.6$ Hz, ArH), 7.64 (t, 1H, $J = 7.6$ Hz, ArH), 7.56 (t, 2H, $J = 7.6$ Hz, ArH), 2.77 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 189.02$, 177.23, 166.34, 133.05, 129.22, 128.41, 123.27, 27.94 ppm. MS (EI): m/z (%) = 188 (30) [M^+]. Anal. calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found C, 63.77; H, 4.25; N, 14.92.

3-(4-Fluorobenzoyl)-5-(2-fluorophenyl)-1,2,4-oxadiazole (**3l**)

White solid; mp 114–116°C. IR (KBr): 1673, 1621, 1598, 1470, 1216 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.43$ (dd, 2H, $J_1 = 6.0$ Hz, $J_2 = 8.4$ Hz, ArH), 8.28 (t, 1H, $J = 7.2$ Hz, ArH), 7.66 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 8.0$ Hz, ArH), 7.22–7.39 (m, 4H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.08$, 173.82, 168.08, 165.52, 165.72, 162.25, 159.65, 125.52, 135.43, 133.66, 133.56, 131.50, 124.90, 117.38, 117.17, 116.20, 115.99 ppm. MS (EI): m/z (%) = 286 (50) [M^+]. Anal. calcd. for $C_{15}H_8F_2N_2O_2$: C, 62.94; H, 2.82; N, 9.79. Found C, 63.00; H, 2.77; N, 9.88.

3-(4-Chlorobenzoyl)-5-(2-fluorophenyl)-1,2,4-oxadiazole (**3m**)

White solid; mp 125–126°C. IR (KBr): 1682, 1620, 1468, 1222, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.32$ (d, 2H, $J = 8.4$ Hz, ArH), 8.26 (t, 1H, $J = 6.8$ Hz, ArH), 7.66 (m, 1H, ArH), 7.56 (d, 2H, $J = 8.4$ Hz, ArH), 7.28–7.38 (m, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.37$, 173.91, 165.54, 162.16, 159.57, 141.43, 135.52, 135.43, 133.26, 132.02, 131.18, 129.11, 124.85, 117.31, 117.11, 111.84, 111.72 ppm. MS (EI): m/z (%) = 302 (25) (M^+). Anal. calcd. for $C_{15}H_8ClFN_2O_2$: C, 59.52; H, 2.66; N, 9.25. Found C, 59.50; H, 2.58; N, 9.19.

5-(2-Fluorophenyl)-3-(3-nitrobenzoyl)-1,2,4-oxadiazole (**3n**)

Pale yellow crystal; mp 130–132°C. IR (KBr): 1684, 1620, 1534, 1348, 1211 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.27$ (s, 1H, ArH), 8.72 (d, 1H, $J = 7.6$ Hz, ArH), 8.56 (d, 1H, $J = 8.0$ Hz, ArH), 8.30 (t, 1H, $J = 7.2$ Hz, ArH), 7.80 (t, 1H, $J = 7.6$ Hz, ArH), 7.69 (m, 1H, ArH), 7.32–7.41 (m, 2H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.54$, 174.27, 165.37, 162.33, 159.73, 148.50, 136.21, 136.01, 135.78, 135.69, 131.29, 130.08, 128.69, 125.71, 125.01, 117.46, 117.26, 111.80, 111.59 ppm. MS (EI): m/z (%) = 313 (40) [M^+]. Anal. calcd. for $C_{15}H_8FN_3O_4$: C, 57.52; H, 2.57; N, 13.41. Found C, 57.48; H, 2.55; N, 13.46.

5-(2-Fluorophenyl)-3-(4-methyl-3-nitrobenzoyl)-1,2,4-oxadiazole (**3o**)

Yellow crystal; mp 107–109°C. IR (KBr): 1679, 1618, 1553, 1353, 1203 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.03$ (s, 1H, ArH), 8.51 (dd, 1H, $J_1 = 0.8$ Hz, $J_2 = 8.0$ Hz, ArH), 8.28 (m, 1H, ArH), 7.67 (m, 1H, ArH), 7.58 (d, 1H, $J = 8.4$ Hz, ArH), 7.31–7.41 (m, 2H, ArH), 2.73 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 180.12$, 174.10, 165.36, 162.27, 159.67, 149.45, 140.24, 135.69, 135.60, 134.09, 133.47, 131.25, 127.03, 124.96, 117.41, 117.21, 111.82, 111.70, 20.76 ppm. MS (EI): m/z (%) = 327 (25) [M^+]. Anal. calcd. for $C_{16}H_{10}FN_3O_4$: C, 58.72; H, 3.08; N, 12.84. Found C, 58.77; H, 3.05; N, 12.88.

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