Article

Iron Nitrate-Mediated Selective Synthesis of 3-Acyl-1,2,4-Oxadiazoles from Alkynes and Nitriles: The Dual Roles of Iron Nitrate

Qilong Bian, Cunluo Wu, Jiangpei Yuan, Zuodong Shi, Tao Ding, Yongwei Huang, Yuanqing Xu, and Hao Xu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b03070 • Publication Date (Web): 29 Jan 2020

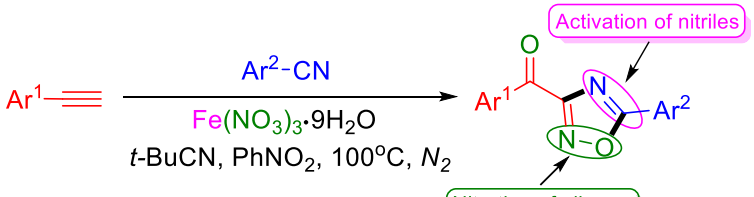
Iron Nitrate-Mediated Selective Synthesis of 3-Acyl-1,2,4-Oxadiazoles from Alkynes and Nitriles: The Dual Roles of Iron Nitrate

Qilong Bian,[a] Cunluo Wu,[a] Jiangpei Yuan,[a] Zuodong Shi,[a] Tao Ding,[a] Yongwei Huang,[b] Yuanqing Xu*,[a] and Hao Xu*,[a]

[a]Institute of Functional Organic Molecular Engineering, College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, China.

[b]College of Basic Medical Science, Henan University, Kaifeng 475004, China.

Supporting Information Placeholder



- *Dual roles of Fe(NO$_3$)$_3$*
- *High chemoselectivity*
- *Distinguished activation on nitriles shown by Fe(III)*

ABSTRACT: A direct strategy for the selective synthesis of 3-acyl-1,2,4-oxadiazoles from alkynes and nitriles has been developed under iron(III) nitrate-mediated conditions. The mechanism includes three sequential procedures: iron(III) nitrate-mediated nitration of alkynes leads to α-nitroketones, dehydration of α-nitroketones provides the nitrile oxides, and 1,3-dipolar cycloaddition of nitrile oxides with nitriles produces 3-acyl-1,2,4-oxadiazoles under iron-mediated conditions. Iron(III) nitrate plays dual roles in the nitration of alkynes and activation of nitriles while the formation of pyrimidine/isoxazole byproducts can be efficiently inhibited.

INTRODUCTION

The demand for functional 1,2,4-oxadiazoles has rapidly grown in many research fields.[1] Interest in 3-acyl-1,2,4-oxadiazoles has widely expanded due to their biological and pharmacological activities (Figure 1).[2] However, the methods for the direct synthesis of 3-acyl-1,2,4-oxadiazoles from readily available substrates remains very rare,[3] and most of them requires using of substrates as solvents. Moreover, nitriles are readily available and stable compounds containing carbon-nitrogen triple bonds. Some approaches to synthesize 1,2,4-oxadiazoles from nitriles and other readily available substrates have been developed,[4] but strong acid (such as *p*-toluenesulfonic acid[4a-b]) or strong nucleophiles (such as hydroxylamine[4c-d]) are always needed to activate the nitriles for satisfactory yields. In addition, 1,3-dipolar cycloaddition of nitrile oxides with nitriles is an efficient strategy for the synthesis of 1,2,4-oxadiazoles, but stoichiometric amounts of strong acid are always required for the activation of the nitriles.[4a-b,5] Therefore, the development of mild and convenient procedures to access 3-acyl-1,2,4-oxadiazoles from nitriles is still challenging and highly desirable.

Alkynes are an easily accessible class of chemicals and widely used in various transfromations.[6] The rich reactivity of alkynes makes them excellent substrates for the construction

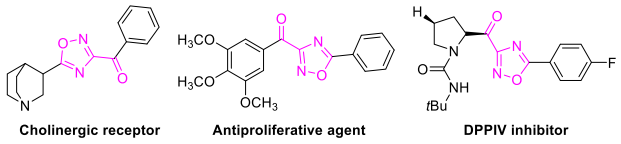
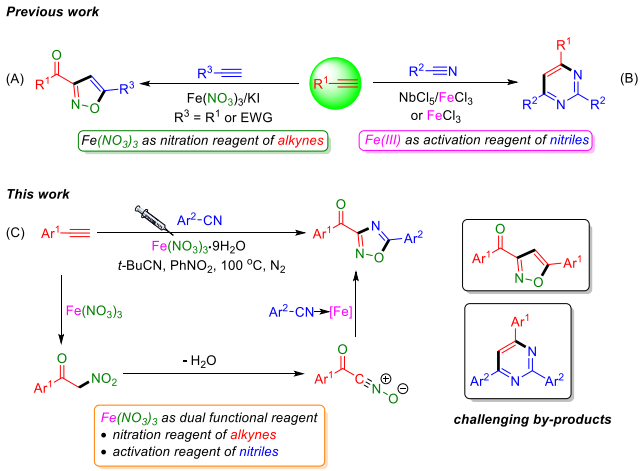


Figure 1. Examples of bioactive 3-acyl-1,2,4-oxadiazole molecules.

of diverse heterocycles such as oxazole,[7] isoxazole,[8] indole,[9] benzofuran,[10] pyrimidine,[11] 1,2,3-triazole[12] and benzothiazole.[13] However, to the best of our knowledge, there are no reported examples of the direct construction of 1,2,4-oxadiazole skeletons from alkynes.

Recently, an iron(III) nitrate-mediated synthesis of isoxazoles from alkynes via 1,3-dipolar cycloaddition has been developed by us.[8c] Here iron(III) nitrate is employed as a nitrating reagent, and terminal alkynes are nitrated to form the corresponding acyl nitrile oxides (1,3-dipolars). Furthermore,

Scheme 1. Iron Nitrate-Mediated Direct Synthesis Nitrogen-Containing Heterocycles from Alkynes

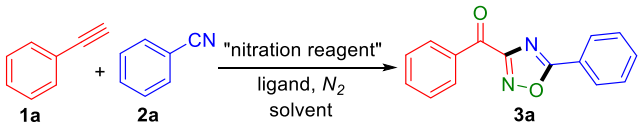


iron(III)-mediated/niobium-catalyzed [2+2+2] cycloaddition of nitriles and alkynes was developed to synthesize pyrimidines. The pyrimidines were produced with relatively low yields only under iron(III)-mediated conditions;[11b] iron(III) salt was used as an activation reagent of nitriles. Inspired by these results, we questioned whether iron(III) nitrate could play dual roles in both nitration of alkynes and activation of nitriles. By this design, 3-acyl-1,2,4-oxadiazoles could be selectively synthesized from alkynes and nitriles. In continuation of our endeavors towards efficient methods for the synthesis of *N*-heterocycles,[8c,14] we herein disclose an iron(III) nitrate-mediated selective synthesis of 3-acyl-1,2,4-oxadiazoles from alkynes and nitriles under strong-acid-free/strong-nucleophile-free conditions where iron(III) nitrate plays dual roles described above. Two main difficulties must be overcome for this transformation (Scheme 1): (1) Avoiding the formation of undesired byproducts such as pyrimidines and isoxazoles. According to previous reports, isoxazoles could be provided via nitration and cyclization of alkynes (Scheme 1A);[8c] and pyrimidines could also be formed from nitriles and alkynes under iron(III)-mediated conditions (Scheme 1B).[11b] (2) Activation stable nitriles and synthesis of 1,2,4-oxadiazole products selectively under strong-acid-free/strong-nucleophile-free conditions (Scheme 1C).

RESULTS AND DISCUSSION

Considering that iron(III) nitrate as a nitrating reagent has many advantages such as environmental friendly and low cost,[3c,8c,15] and iron(III) nitrate-mediated system has shown good chemoselectivity via 1,3-dipolar cycloaddition with electron-deficient alkynes in the approach to isoxazles,[8c] we started our study by choosing phenylacetylene **1a** and benzonitrile **2a** as the model substrates to challenge the selective 1,3-dipolar cycloaddition with stable nitriles. The reaction conditions including nitrate salts, solvents and ligands were optimized. As shown in Table 1, iron(III) nitrate proved to be the optimal nitration reagent for this transformation (entries 1-8) because of higher activating ability for nitriles in this reaction. Different solvents were also screened, and nitrobenzene provided the highest yield (entries 8-14). The effects of ligands

Table 1. Screening of the Conditions[a]



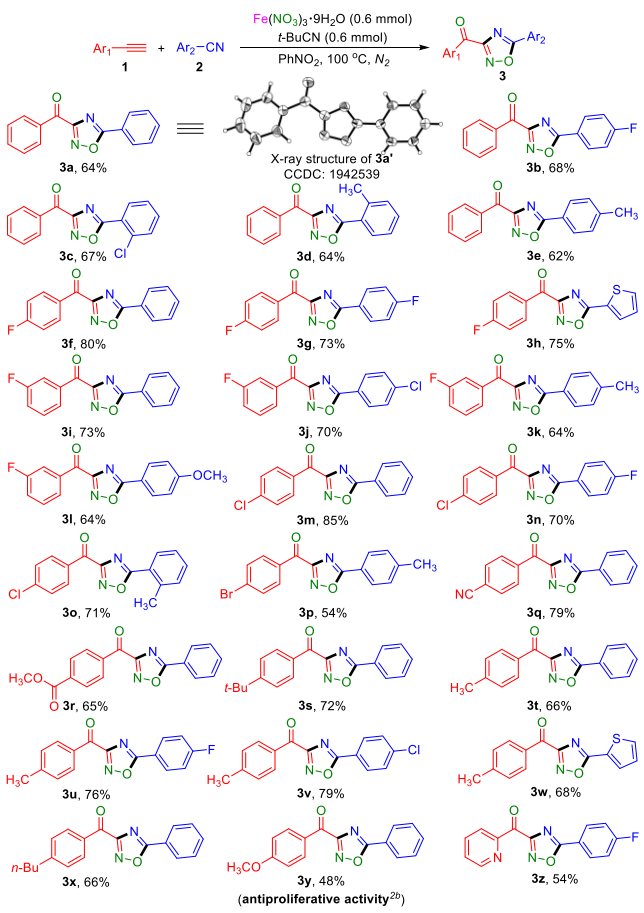
Entry	Nitration reagent	Solvent	Ligand	Yield[b](%)
1	$Zn(NO_3)_2{\cdot}6H_2O$	$PhNO_2$	*t*-BuCN	23
2	$Al(NO_3)_3{\cdot}9H_2O$	$PhNO_2$	*t*-BuCN	47
3	$Co(NO_3)_2{\cdot}6H_2O$	$PhNO_2$	*t*-BuCN	16
4	$Cu(NO_3)_2{\cdot}6H_2O$	$PhNO_2$	*t*-BuCN	36
5	KNO_3	$PhNO_2$	*t*-BuCN	0
6	$AgNO_2$	$PhNO_2$	*t*-BuCN	0
7	*t*-BuONO	$PhNO_2$	*t*-BuCN	0
8	**$Fe(NO_3)_3{\cdot}9H_2O$**	**$PhNO_2$**	***t*-BuCN**	**64**
9	$Fe(NO_3)_3{\cdot}9H_2O$	Toluene	*t*-BuCN	21
10	$Fe(NO_3)_3{\cdot}9H_2O$	Anisole	*t*-BuCN	43
11	$Fe(NO_3)_3{\cdot}9H_2O$	dioxane	*t*-BuCN	0
12	$Fe(NO_3)_3{\cdot}9H_2O$	THF	*t*-BuCN	0
13	$Fe(NO_3)_3{\cdot}9H_2O$	DMSO	*t*-BuCN	0
14	$Fe(NO_3)_3{\cdot}9H_2O$	DMF	*t*-BuCN	0
15	$Fe(NO_3)_3{\cdot}9H_2O$	$PhNO_2$	8-Oxine	31
16	$Fe(NO_3)_3{\cdot}9H_2O$	$PhNO_2$	*L*-Proline	44
17	$Fe(NO_3)_3{\cdot}9H_2O$	$PhNO_2$	Phen[c]	35
18	$Fe(NO_3)_3{\cdot}9H_2O$	$PhNO_2$	-	52
19[d]	$Fe(NO_3)_3{\cdot}9H_2O$	$PhNO_2$	*t*-BuCN	53

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol, 3.0 equiv), nitration reagent (0.6 mmol, 2.0 equiv), ligand (0.6 mmol, 2.0 equiv), solvent (1.0 mL) at 100 °C under nitrogen atmosphere; **1a** in solvent (0.5 mL) was slowly added by syringe pump to the mixture of all other reagents in solvent (0.5 mL) for 12 h at 100 °C, then the solution was stirred for another 24 h. [b]Isolated yield. [c]Phen = 1.10-Phenanthroline. [d]**1a** (0.3 mmol), **2a** (1.8 mmol, 6.0 equiv) $Fe(NO_3)_3{\cdot}9H_2O$ (0.6 mmol 2.0 equiv), *t*-BuCN (0.6 mmol 2.0 equiv) and $PhNO_2$ (1.0 mL) were directly stirred at 100 °C under nitrogen atmosphere.

were investigated, and *t*-BuCN was the best choice (entries 8 and 15-18).[8d,16] In addition, moderate yield could also be obtained when a greater amount of benzonitrile **2a** was directly added without use of syringe pump (entry 19).

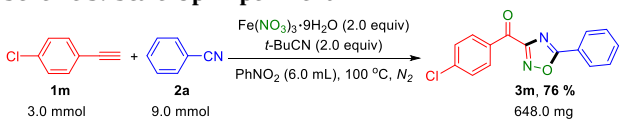
Under the optimized conditions (entry 8), the substrate scope for iron(III) nitrate-mediated selective synthesis of 1,2,4-oxadiazoles was examined, and various kinds of alkynes **1** and nitriles **2** including aromatic alkynes, heterocyclic alkynes, aromatic nitriles and heterocyclic nitriles could be transformed into the corresponding 3-acyl-1,2,4-oxadiazoles with moderate to good yields. As shown in Scheme 2, diverse electron-withdrawing groups (F, Cl, Br, COOR, CN; **3b-c**, **3f-r**, **3u-v**, **3z**) and electron-donating groups (Me, *n*-Bu, *t*-Bu, OMe; **3d-e**, **3k-l**, **3o-p**, **3s-y**) in the substituents were well tolerated in this transformation. Furthermore, the aromatic alkynes with electron-withdrawing groups promoted higher yields (to give **3m**), because self-coupling of aromatic alkynes could be weakened by electron-withdrawing groups. The position of substituents on the phenyl groups did not obviously affect the product yields **(3d** *vs.* **3e, 3f** *vs.* **3i)**. Additionally, there were some limitations for this transformation (Table S1),

Scheme 2. Substrate Scope of Alkynes and Nitriles[a, b]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol, 3.0 equiv), $Fe(NO_3)_3·9H_2O$ (0.6 mmol, 2.0 equiv), *t*-BuCN (0.6 mmol, 2.0 equiv), $PhNO_2$ (1.0 mL) at 100 °C under nitrogen atmosphere; **1** in $PhNO_2$ (0.5 mL) was slowly added by syringe pump to the mixture of all other reagents in $PhNO_2$ (0.5 mL) for 12 h at 100 °C, then the solution was stirred for another 24 h. [b]Isolated yield.

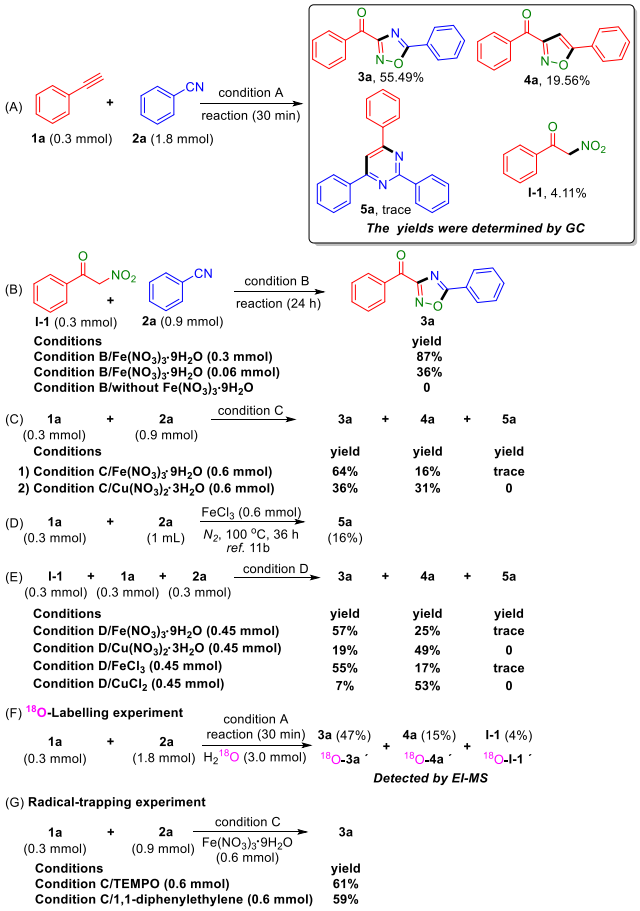
Scheme 3: Scale-Up Experiment



and only aromatic substrates were tolerated in this transformation. For example, aliphatic nitriles could not react with alkynes efficiently under standard conditions, and only self-coupling products of aromatic alkynes could be observed due to the difference of product stability. To demonstrate the synthetic utility of this reaction, methoxyl-substitued product **3y** with antiproliferative activity was successfully synthesized by our method. At last, a scale-up experiment (3.0 mmol) was also performed under iron(III)-mediated conditions (Scheme 3), and product **3m** was generated in 76 % yield.

To probe the possible reaction pathway, some control experiments were carried out (Scheme 4). First, the model reaction of **1a** with **2a** was monitored by gas chromatography (GC)

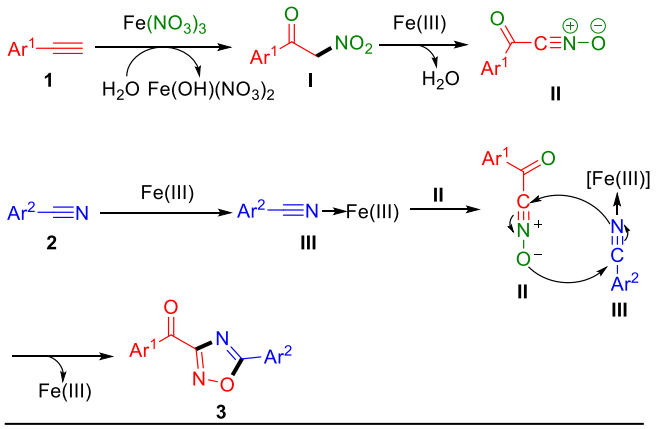
Scheme 4. Control Experiments for Mechanism Study[a]



[a]**Condition A**: **1a** (0.3 mmol), **2a** (1.8 mmol 6.0 equiv), $Fe(NO_3)_3·9H_2O$ (0.6 mmol 2.0 equiv), *t*-BuCN (0.6 mmol 2.0 equiv) and $PhNO_2$ (1.0 mL) were directly stirred at 100 °C under nitrogen atmosphere. **Condition B**: **I-1** (0.3 mmol), **2a** (0.9 mmol 3.0 equiv), *t*-BuCN (0.6 mmol 2.0 equiv) and $PhNO_2$ (1.0 mL) were directly stirred at 100 °C under nitrogen atmosphere. **Condition C**: **1a** (0.3 mmol), **2a** (0.9 mmol 3.0 equiv), nitrate salt (0.6 mmol 2.0 equiv), *t*-BuCN (0.6 mmol 2.0 equiv), $PhNO_2$ (1.0 mL) at 100 °C under nitrogen atmosphere; **1a** in $PhNO_2$ (0.5 mL) was slowly added by syringe pump to the mixture of all other reagents in $PhNO_2$ (0.5 mL) for 12 h at 100 °C, then the solution was stirred for another 24 h. **Condition D**: **1a** (0.3 mmol), **2a** (0.3 mmol 1.0 equiv), **I-1** (0.3 mmol 1.0 equiv), *t*-BuCN (0.45 mmol 1.5 equiv) and $PhNO_2$ (1.0 mL) were directly stirred at 100 °C under nitrogen atmosphere.

under $Fe(NO_3)_3$-mediated conditions. When the reaction time was reduced to 30 min and the substrates were directly added without use of syringe pump, the target product **3a** was provided in 55.49 % yield; meanwhile, *α*-nitroketone **I-1**, isoxazole and pyrimidine byproducts **4a** and **5a** were respectively determined to have 4.11 %, 19.56 % and trace yields (Scheme 4A; Figure S1-S4). Moreover, **I-1** could react with nitrile **2a** to generate the product **3a** in excellent yield under iron(III)-mediated conditions, and conversely no product was detected without the addition of iron(III) nitrate (Scheme 4B). In addition, when the model reaction was performed under standard conditions, a good yield of product **3a** could be isolated, only

Scheme 5. Possible Mechanism



small/trace amounts of **4a/5a** were detected, and no **I-1** was obtained (Scheme 4C1). Given the results above, **I-1** should be the intermediate for the method to produce 1,2,4-oxadiazole product **3a**, and was formed by the nitration of alkyne **(1a)** in the presence of $Fe(NO_3)_3$. Byproduct **4a** was formed by self-coupling of alkynes in the presence of the same nitrating reagents, while byproduct **5a** was formed via [2+2+2] cycloaddition of two nitriles **2a** with one alkyne **1a** under iron(III)-mediated conditions (Scheme 4D).[11b] There were notable competitions between the formation reactions of isoxazole/pyrimidine (**4a/5a**) and target 1,2,4-oxadizole (**3a)**. Additionally, $Fe(NO_3)_3$ is crucial for the target transformation not only as a nitrating reagent of alkynes but also an activating reagent of nitriles; and a satisfactory chemoselectivity was shown under $Fe(NO_3)_3$-mediated conditions.

Copper(II) nitrate is another efficient nitration reagent of alkynes in Xu's works.[8b,8d] To further explore the cause of the chemoselectivity shown by iron(III) nitrate, some comparison experiments with copper(II) were performed (Scheme 4C, 4E). Iron(III) showed higher activating ability for nitriles than alkynes, and copper(II) showed higher activating ability for alkynes. Furthermore, 1,3-dipolar cycloaddition with nitriles could proceed more smoothly under iron(III)-mediated conditions (Scheme 4C, 4E; entries 1-8 in Table 1).

To identify the source of oxygen atom in the acyl group of **I-1**, a ^{18}O-labelling experiment has been conducted, replacing $Fe(NO_3)_3{\cdot}9H_2O$ with anhydrous $Fe(NO_3)_3$ and $H_2{}^{18}O$ (Scheme 4F). But no obvious ^{18}O-labelling products could be detected by EI-MS (Figure S5). The results implied the oxygen atom in the acyl group of **I-1** was from nitro group of $Fe(NO_3)_3$, rather than from water molecules in the system. Finally, the radical trapping experiments were performed with 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) and 1,1-diphenylethylene respectively under standard conditions (Scheme 4G). And a radical mechanism could be ruled out, because no suppression effect was observed.

On the basis of control experiments above and previous reports,[8b-e,11b,17] a possible mechanism for the selective synthesis of 3-acyl-1,2,4-oxadiazoles is proposed in Scheme 5. At first, nitration of alkyne **1** gives adduct **I**,[8b,8d] and dehydration of **I** leads to **II** in the presence of iron(III) nitrate.[8e,18] Meanwhile, nitrile **2** coordinates with Fe(III) to afford the iron complex **III**. Finally, 1,3-dipolar cycloaddition of **II** with **III** provides the desired 1,2,4-oxadiazole product **3**, releasing the Fe(III) catalyst.

CONCLUSION

In summary, we have developed a direct and simple method for the selective synthesis of 3-acyl-1,2,4-oxadiazoles from alkynes and nitriles via iron(III) nitrate-mediated 1,3-dipolar cycloaddition. The significance of this work lies in four points: 1) A direct construction of 1,2,4-oxadiazole skeleton from readily available alkynes has not been previously reported. 2) Iron(III) nitrate plays dual roles in the nitration of alkynes and activation of nitriles; and iron(III) shows distinguished activation on nitriles over copper(II) and other metal salts tested. 3) A good chemoselectivity for the target 3-acyl-1,2,4-oxadiazoles is shown under iron(III) nitrate-mediated conditions, and the formation of pyrimidine/isoxazole byproducts from alkynes/nitriles is efficiently inhibited. 4) The nitrile substrates could be activated and transformed into the corresponding 1,2,4-oxadiazole products under strong-acid-free/strong-nucleophile-free conditions; in precedent methods for the synthesis of 1,2,4-oxadiazoles from nitriles, strong acids or strong nucleophiles were always needed to activate the nitriles for a satisfactory yield. This method provides an opportunity for the modification and construction of functional 1,2,4-oxadiazole derivatives with diverse bioactivities.

EXPERIMENTAL SECTION

General Information. GC analysis was performed using gas chromatograph of Tianmei GC 7900. Melting points were recorded on SGW X-4. Mass spectra were recorded with a Bruker Daltonics ion trap mass spectrometry using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) techniques. High resolution mass spectra were recorded with a Bruker Daltonics Maxis Impact quadrupole-time of flight (QTOF) mass spectrometer using electrospray ionization (ESI). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz or 300 MHz spectrometers. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^1H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm) or were recorded using tetramethylsilane (TMS) in the solvent of DMSO-d_6 as the internal standard (^1H NMR: TMS at 0.00 ppm, DMSO-d_6 at 2.50 ppm; ^{13}C NMR: DMSO-d_6 at 39.51 ppm). All reactions were carried out under nitrogen atmosphere. Unless otherwise noted, all the materials are commercial without further purifications.

General Procedures for the Synthesis of 3-Acyl-1,2,4-Oxadiazols. Nitriles **2** (0.9 mmol, 3.0 equiv), $Fe(NO_3)_3{\cdot}9H_2O$ (0.6 mmol, 2.0 equiv), *t*-BuCN (0.6 mmol, 2.0 equiv) and $PhNO_2$ (0.5 mL) were added to a sealed Schlenk tube and stirred at 100 °C (oil bath) under nitrogen atmosphere. Then the solution of alkynes **1** (0.3 mmol 1.0 equiv) in $PhNO_2$ (0.5 mL) was slowly added to the Schlenk tube by syringe pump infusion (Figure S6) for 12 h. The reaction mixture was stirred for another 24 h and monitored by TLC. After the reaction was completed, the resulting solution was cooled down to room

temperature, which was evaporated in vacuum to obtain crude products. Finally, the crude products were purified by silica gel column chromatography to obtain target products **3a-z.**

3-Benzoyl-5-phenyl-1,2,4-oxadiazole ***(3a).***[3b,19] Eluent = petroleum ether/ethyl acetate (20:1). Yield 48 mg (64%), white solid, mp 91.3-92.7 °C (lit.[19] mp 92 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.24 (d, *J* = 7.6 Hz, 2H), 8.18-8.15 (m, 2H), 7.62-7.53 (m, 2H), 7.47-7.43 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 183.0, 176.5, 166.2, 135.1, 134.6, 133.4, 130.7, 129.2, 128.7, 128.5, 123.4. ESI-MS $[M+H]^+$ *m/z* 251.1. The structure of **3a** was further confirmed by X-ray crystallagraply (Scheme S1).

3-Benzoyl-5-(4-fluorophenyl)-1,2,4-oxadiazole ***(3b).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 55 mg (68%), white solid, mp 119.4-120.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29-8.22 (m, 4H), 7.67-7.63 (m, 1H), 7.53-7.49 (m, 2H), 7.24-7.19 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 182.9, 175.6, 167.1, 165.4 (d, *J* = 265.1 Hz), 135.0, 134.6, 131.0 (d, *J* = 9.4 Hz), 130.6, 128.7, 119.7 (d, *J* = 3.3 Hz), 116.7 (d, *J* = 22.4 Hz). ESI-HRMS $[M+H]^+$ m/z calcd for $C_{15}H_9FN_2O_2$ 268.0648, found 268.0623.

3-Benzoyl-5-(2-chlorophenyl)-1,2,4-oxadiazole ***(3c).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 57 mg (67%), white solid, mp 83.2-84.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.27 (d, *J* = 7.7 Hz, 2H), 8.14 (d, *J* = 7.7 Hz, 1H), 7.65-7.60 (m, 1H), 7.55-7.46 (m, 4H), 7.41-7.36 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 182.7, 175.2, 165.8, 135.1, 134.7, 134.1, 133.8, 132.4, 131.5, 130.7, 128.7, 127.2, 122.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_9ClN_2O_2$ 284.0453, found 284.0431.

3-Benzoyl-5-(2-methylphenyl)-1,2,4-oxadiazole ***(3d).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 51 mg (64%), yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.36-8.32 (m, 2H), 8.23-8.20 (m, 1H), 7.69-7.67 (m, 1H), 7.58-7.48 (m, 3H), 7.40-7.37 (m, 2H), 2.78 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 183.2, 177.2, 165.9, 139.5, 135.2, 134.6, 132.9, 132.1, 130.6, 130.7, 128.7, 126.4, 122.5, 22.1. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{12}N_2O_2$ 264.0899, found 264.0911.

3-Benzoyl-5-(4-methylphenyl)-1,2,4-oxadiazole ***(3e).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 49 mg (62%), white solid, mp 91.2-92.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.26 (d, *J* = 7.5 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.64-7.59 (m, 1H), 7.51-7.46 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 183.2, 176.7, 166.1, 144.4, 135.2, 134.5, 130.7, 129.9, 128.7, 128.5, 120.6, 21.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{12}N_2O_2$ 264.0899, found 264.0917.

3-(4-Fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3f).***[3a] Eluent = petroleum ether/ethyl acetate (20:1). Yield 64 mg (80%), white solid, mp 105.4-106.7 °C (lit.[3a] mp 106-108 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.35-8.31 (m, 2H), 8.17 (d, *J* = 7.4 Hz, 2H), 7.59-7.55 (m, 1H), 7.51-7.46 (m, 2H), 7.19-7.12 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.3, 176.6, 116.7 (d, *J* = 257.9 Hz), 166.0, 133.6, 133.5, 131.5 (d, *J* = 2.9 Hz), 129.3, 128.5, 123.2, 116.0 (d, *J* = 22.0 Hz). ESI-MS $[M+H]^+$ *m/z* 268.8.

3-(4-Fluorobenzoyl)-5-(4-fluorophenyl)-1,2,4-oxadiazole ***(3g).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 63 mg (73%), white solid, mp 124.3-125.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43-8.40 (m, 2H), 8.30-8.27 (m, 2H), 7.29-7.22 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 181.2, 175.7, 168.0 (d, *J* = 66.7 Hz), 166.0, 165.0 (d, *J* = 64.8 Hz), 133.6 (d, *J* = 9.7 Hz), 131.4, 131.0 (d, *J* = 9.4 Hz), 119.6 (d, *J* = 3.1 Hz), 116.7 (d, *J* = 22.4 Hz), 116.0 (d, *J* = 22.0 Hz). ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_8F_2N_2O_2$ 286.0554, found 286.0537.

3-(4-Fluorobenzoyl)-5-(2-thienyl)-1,2,4-oxadiazole ***(3h).*** Eluent = petroleum ether/ethyl acetate (10:1). Yield 62 mg (75%), white solid, mp 146.3-47.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.95 (d, *J* = 2.8 Hz, 1H), 7.64 (d, *J* = 4.9 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.17-7.14 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.5, 172.3, 165.8, 141.4, 133.4, 113.3, 133.1, 132.0, 129.1, 128.8, 124.6. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{13}H_7FN_2O_2S$ 274.0212, found 274.0220.

3-(3-Fluorobenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3i).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 59 mg (73%), white solid, mp 104.1-105.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.18 (d, *J* = 7.3 Hz, 2H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 9.4 Hz, 1H), 7.60-7.55 (m, 1H), 7.52-7.43 (m, 3H), 7.34-7.28 (m, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.6 (d, *J* = 2.6 Hz), 165.9, 164.3, 161.0, 136.8 (d, *J* = 6.9 Hz), 133.6, 130.4 (d, *J* = 7.7 Hz), 129.3, 128.5, 126.6 (d, *J* = 3.0 Hz), 123.1, 121.7 (d, *J* = 22.4 Hz), 117.3 (d, *J* = 21.3 Hz). ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_9FN_2O_2$ 268.0648, found 268.0637.

3-(3-Fluorobenzoyl)-5-(4-chlorophenyl)-1,2,4-oxadiazole ***(3j).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 64 mg (70%), white solid, mp 96.8-97.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28-8.24 (m, 2H), 8.14-8.12 (m, 1H), 8.03-8.01 (m, 1H), 7.54-7.49 (m, 1H), 7.37-7.35 (m, 1H), 7.26-7.21 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 181.4 (d, *J* = 2.6 Hz), 175.5, 165.9, 163.9, 161.4, 136.6 (d, *J* = 6.9 Hz), 135.6, 133.6, 130.6, 130.6 (d, *J* = 7.7 Hz), 128.5, 126.6, 126.6, 126.6, 124.7, 121.8 (d, *J* = 21.4 Hz), 117.3 (d, *J* = 23.4 Hz). ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_8FClN_2O_2$ 302.0258, found 302.0252.

3-(3-Fluorobenzoyl)-5-(4-methylphenyl)-1,2,4-oxadiazole ***(3k).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 54 mg (64%), white solid, mp 114.6-115.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.19-8.13 (m, 3H), 8.05 (d, *J* = 9.5 Hz, 1H), 7.58-7.51 (m, 1H), 7.42-7.36 (m, 3H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 181.8, 176.8, 165.9, 163.9, 161.4, 144.5, 137.0 (d, *J* = 6.8 Hz), 130.4 (d, *J* = 7.6 Hz), 130.0, 128.5, 126.6 (d, *J* = 3.0 Hz), 121.6 (d, *J* = 21.5 Hz), 120.5, 117.2 (d, *J* = 23.6 Hz), 21.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{11}FN_2O_2$ 282.0805, found 282.0807.

3-(3-Fluorobenzoyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole ***(3l).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 57 mg (64%), white solid, mp 126.6-127.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.23-8.16 (m, 3H), 8.08-8.04 (m, 1H), 7.58-7.51 (m, 1H), 7.43-7.36 (m, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 3.92 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 181.9, 176.6, 165.9, 163.9, 163.8, 161.4, 144.5, 137.0 (d, *J* = 7.0 Hz), 130.5, 130.4 (d, *J* = 7.6 Hz), 126.6 (d, *J* = 3.0 Hz), 121.6 (d, *J*

= 21.5 Hz), 117.2 (d, *J* = 23.6 Hz), 115.7, 114.7, 55.6. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{11}FN_2O_3$ 298.0754, found 298.0752.

3-(4-Chlorobenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3m).***[3a] Eluent = petroleum ether/ethyl acetate (20:1). Yield 73 mg (85%), yellow solid, mp 99.3-101.4 °C (lit.[3a] mp 100-102 °C). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34-8.31 (m, 2H), 8.25-8.22 (m, 2H), 7.67-7.61 (m, 1H), 7.58-7.50 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.7, 176.6, 166.0, 141.4, 133.6, 133.4, 132.1, 129.3, 129.1, 128.5, 123.2. ESI-MS $[M+H]^+$ *m/z* 284.9.

3-(4-Chlorobenzoyl)-5-(4-fluorophenyl)-1,2,4-oxadiazole ***(3n).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 64 mg (70%), yellow solid, mp 117.2-118.5 °C. ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 8.31-8.27 (m, 2H), 8.25-8.23 (m, 2H), 7.75-7.72 (m, 2H), 7.56-7.52 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, ppm) δ 182.3, 175.5, 166.5 (d, *J* = 256.2 Hz), 164.4, 140.4, 134.0, 132.6, 131.6 (d, *J* = 9.4 Hz), 129.5, 117.5 (d, *J* = 3.3 Hz), 116.7 (d, *J* = 22.4 Hz). ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{15}H_8FClN_2O_2$ 302.0258, found 302.0261.

3-(4-Chlorobenzoyl)-5-(2-methylphenyl)-1,2,4-oxadiazole ***(3o).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 64 mg (71%), yellow solid, mp 108.3-109.1 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.22 (d, *J* = 8.6 Hz, 2H), 8.10 (d, *J* = 7.3 Hz, 1H), 7.44-7.39 (m, 3H), 7.30-7.26 (m, 2H), 2.68 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.8, 177.3, 165.6, 141.3, 139.5, 133.4, 133.0, 132.0 132.1, 130.6, 129.1, 126.4, 122.4, 22.1. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{11}ClN_2O_2$ 298.0509, found 298.0523.

3-(4-Bromobenzoyl)-5-(4-methylphenyl)-1,2,4-oxadiazole ***(3p).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 55 mg (54%), white solid, mp 107.1-108.5 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25-8.22 (m, 2H), 8.16-8.13 (m, 2H), 7.72-7.70 (m, 22H), 7.38 (d, *J* = 8.0 Hz, 2H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 182.0, 176.8, 165.9, 144.5, 133.8, 132.1, 132.1, 130.2, 130.0, 128.5, 120.5, 21.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{11}BrN_2O_2$ 342.0004, found 341.9996.

3-(4-Cyanobenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3q).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 65 mg (79%), white solid, mp 170.1-171.5 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.22 (d, *J* = 8.3 Hz, 2H), 8.14 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.60-7.47 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 176.3, 167.6, 133.1, 132.6, 131.1, 129.2, 128.2, 128.0, 123.8, 118.2, 114.7. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_9N_3O_2$ 275.0695, found 275.0683.

3-(4-methylbenzoylformate)-5-phenyl-1,2,4-oxadiazole ***(3r).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 60 mg (65%), white solid, mp 90.1-91.2 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27-8.22 (m, 4H), 8.18 (d, *J* = 8.4 Hz, 2H), 7.63-7.61 (m, 1H), 7.59-7.55 (m, 2H), 3.97 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 176.0, 168.3, 166.4, 132.9, 132.4, 131.0, 130.0, 129.1, 128.2, 127.5, 124.1, 52.3. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{17}H_{12}N_2O_4$ 308.0797, found 308.0792.

3-(4-tert-Butylbenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3s).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 62 mg (72%), colourless liquid. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28-8.26 (m, 4H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.60-7.55 (m, 4H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 182.6, 176.4, 166.3, 158.7, 133.4, 132.6, 130.7, 129.2, 128.5, 125.8, 123.4, 35.3, 31.0. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1357.

3-(4-Methylbenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3t).***[3b,19] Eluent = petroleum ether/ethyl acetate (20:1). Yield 52 mg (66%), white solid, mp 116.2-117.5 °C (lit.[19] mp 115 °C). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.10 (d, *J* = 7.9 Hz, 4H), 7.52-7.47 (m, 1H), 7.44-7.39 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 2.31 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 182.5, 176.3, 166.2, 145.9, 133.4, 132.6, 130.8, 129.4, 129.2, 128.4, 123.3, 21.8. ESI-MS $[M+H]^+$ *m/z* 265.1.

3-(4-Methylbenzoyl)-5-(4-fluorophenyl)-1,2,4-oxadiazole ***(3u).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 64 mg (76%), white solid, mp 114.6-115.1 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.30-8.22 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.29-7.23 (m, 2H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.4, 174.5, 165.8 (d, *J* = 256.0 Hz), 165.2, 144.9, 131.6, 130.0 (d, *J* = 9.3 Hz), 129.8, 128.4, 119.7 (d, *J* = 3.3 Hz), 115.7 (d, *J* = 22.4 Hz), 20.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{11}FN_2O_2$ 282.0805, found 282.0801.

3-(4-Methylbenzoyl)-5-(4-chlorophenyl)-1,2,4-oxadiazole ***(3v).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 71 mg (79%), white solid, mp 109.3-110.9 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24-8.19 (m, 4H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 2.47 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 182.4, 175.5, 166.3, 146.0, 140.0, 132.6, 130.8, 129.7, 129.7, 129.5, 121.9, 21.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{16}H_{11}ClN_2O_2$ 298.0509, found 298.0504.

3-(4-Methylbenzoyl)-5-(2-thienyl)-1,2,4-oxadiazole ***(3w).*** Eluent = petroleum ether/ethyl acetate (10:1). Yield 55 mg (68%), white solid, mp 135.7-136.8 °C. ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 8.23-8.21 (m, 2H), 8.15 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.47-7.45 (m, 1H), 2.50 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, ppm) δ 182.9, 171.9, 166.1, 146.4, 135.3, 134.0, 132.8, 130.9, 130.0, 129.9, 124.4, 21.8. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{14}H_{10}N_2O_2S$ 270.0463, found 270.0449.

3-(4-Butylbenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3x).*** Eluent = petroleum ether/ethyl acetate (20:1). Yield 61 mg (66%), white solid, mp 103.6-104.4 °C. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.20-8.16 (m, 4H), 7.62-7.55 (m, 1H), 7.52-7.47 (m, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 1.60-1.55 (m, 2H), 1.13-1.26 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 182.6, 176.4, 166.3, 150.8, 133.4, 132.8, 130.9, 129.2, 128.9, 128.5, 123.4, 35.9, 33.1, 22.3, 13.9. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1342.

3-(4-Methoxybenzoyl)-5-phenyl-1,2,4-oxadiazole ***(3y).***[3b] Eluent = petroleum ether/ethyl acetate (10:1). Yield 40 mg (48%), White solid, mp 114.2-115.3 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.37-8.35 (m, 2H), 8.34-8.25 (m, 2H), 7.65-7.58 (m, 1H), 7.57-7.55 (m, 2H), 7.03-7.01 (m, 2H), 3.92 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 181.3, 176.3, 166.4, 164.9, 133.3, 133.2, 129.2, 128.5, 128.2, 123.5, 114.1, 55.6. ESI-MS $[M+H]^+$ *m/z* 280.9.

3-(2-Pyridinone)-5-(4-fluorophenyl)-1,2,4-oxadiazole ***(3z).*** Eluent = petroleum ether/ethyl acetate (5:1). Yield 44 mg (54%), white solid, mp 123.3-124.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.36-8.32 (m, 2H), 8.31-8.18 (m, 2H), 7.22-7.13 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 181.2, 175.7, 168.5, 166.0, 166.3 (d, *J* = 191.3 Hz), 164.2, 133.6, 133.5, 131.4 (d, *J* = 2.9 Hz), 131.1, 131.0, 119.6 (d, *J* = 3.3 Hz), 116.8 (d, *J* = 22.4 Hz), 116.2, 115.9. ESI-HRMS $[M+H]^+$ *m/z* calcd for $C_{14}H_8FN_3O_2$ 269.0601, found 269.0622.

3-Benzoyl-5-phenyl-isoxazol ***(4a).***[8c] Eluent = petroleum ether/ethyl acetate (20:1). Yellow solid, mp 78.2-81.5 °C (lit.[8c] mp 80.5-82.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.36-8.34 (m, 2H), 7.87-7.83 (m, 2H), 7.68-7.64 (m, 1H), 7.56-7.48 (m, 5H), 7.05 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 185.8, 170.8, 162.4, 135.7, 134.0, 130.7 (d, *J* = 3.3 Hz), 129.1, 128.6, 126.7, 126.0, 100.2. APCI-MS $[M+H]^+$ *m/z* 250.0.

2,4,6-triphenylpyrimidine ***(5a).***[20] Eluent = petroleum ether/ethyl acetate (50:1). White solid, mp 176.5-179.7 °C (lit.[20] mp 175-177 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.83-8.82 (m, 2H), 8.34-8.31 (m, 4H), 8.00 (s, 1H), 7.62-7.58 (m, 9H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, ppm) δ 164.7, 164.5, 138.2, 137.5, 130.8, 130.7, 128.9, 128.6, 128.5, 127.3, 110.2. ESI-MS $[M+H]^+$ *m/z* 309.2.

2-Nitro-1-phenylethanone ***(I-1).***[21] Eluent = petroleum ether/ethyl acetate (5:1). White solid, mp 103.2-105.3 °C (lit.[17] mp 105-107 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.89-7.87 (m, 2H), 7.71-7.67 (m 1H), 7.56-7.51 (m, 2H), 5.92 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 185.9, 135.1, 129.3, 128.2, 81.4. ESI-MS $[M-H]^-$ *m/z* 164.6.

Procedures for Scale-Up Experiment of 1m with 2a. Nitrile **2a** (927.9 mg, 9.0 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (2424 mg, 6.0 mmol), *t*-BuCN (498.6 mg, 6.0 mmol) and $PhNO_2$ (3.0 mL) were added to a sealed Schlenk tube and stirred at 100 °C (oil bath) under nitrogen atmosphere. Then the solution of alkyne **1m** (408.0 mg, 3.0 mmol) in $PhNO_2$ (3.0 mL) was slowly added to the Schlenk tube by syringe pump infusion for 12 h. The reaction mixture was stirred for another 24 h and monitored by TLC. After the reaction was completed, the resulting solution was cooled down to room temperature, which was evaporated in vacuum to obtain crude product. Finally, the crude product was purified by silica gel column chromatography to obtain target product **3m** in 76 % yield (648.0 mg).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental procedures, characterization data and copies of ^{1}H NMR and ^{13}C NMR spectra for the products.

AUTHOR INFORMATION

Corresponding Author

*E-mail: xuhao@henu.edu.cn.

*E-mail: 18937822307@163.com

ORCID

Hao Xu: 0000-0002-6069-3246

Notes The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by National Natural Science Foundation of China (Grant No. 21502042), Scientific Research Key Project Fund of Henan Provincial Education Department (No. 20A150002) and Postdoctoral Science Foundation of Henan University (No. 232939).

REFERENCES

(1) (a) Farooqui, M.; Pradhan, V.; Dar, B.; Bora, R. O. [1,2,4]-Oxadiazoles: Synthesis and Biological Applications. *Mini-Rev. Med. Chem*. **2014**, *14*, 355-369. (b) Abdildinova, A.; Gong, Y. D. Current Parallel Solid-Phase Synthesis of Drug-like Oxadiazole and Thiadiazole Derivatives for Combinatorial Chemistry. *ACS Comb. Sci.* **2018**, *20*, 309-329.

(2) (a) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; MacLeod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. J. Novel Quinuclidine-Based Ligands for the Muscarinic Cholinergic Receptor. *J. Med. Chem*. **1990**, *33*, 1128-1138. (b) Guan, Q.; Feng, D.-J.; Bai, Z.-S.; Cui, Y.-H.; Zuo, D.-Y.; Zhai, M.-A.; Jiang, X.-W.; Zhou, W.-B.; Bao, K.; Wu, Y.-L.; Zhang, W.-G. Microwave-Assisted Synthesis, Molecular Docking and Antiproliferative Activity of (3/5-Aryl-1,2,4-Oxadiazole-5/3-yl)(3,4,5-Trimethoxyphenyl) Methanone Oxime Derivatives. *Med. Chem. Comm.* **2015**, *6*, 1484-1493. (c) Koo, K. D.; Kim, M. J.; Kim, S.; Kim, K. H.; Hong, S. Y.; Hur, G. C.; Yim, H. J.; Kim, G. T.; Han, H. O.; Kwon, O. H.; Kwon, T. S.; Koh, J. S.; Lee, C. S. Synthesis, SAR, and X-ray Structure of Novel Potent DPPIV Inhibitors: Oxadiazolyl Ketones. *Med. Chem. Lett.* **2007**, *17*. 4167-4172.

(3) (a) Yu, C.-M.; Lei,M.; Su, W.-K.; Xie, Y.-Y. $Y(OTf)_3$-Catalyzed, One-Pot Synthesis of 1,2,4-Oxadiazole Derivatives. *Synth. Commun.* **2007**, *37*, 4439-4452. (b) Vale, J. A.; Faustino, W. M.; Zampieri, D. S.; Moran, P. J. S.; Rodrigues, J. A. R.; De sá, G. F. Lanthanide Nitrates as Lewis Acids in the One-Pot Synthesis of 1,2,4-Oxadiazole Derivatives. *J. Braz. Chem. Soc.* **2012**, *23*, 1437-1440. (c) Itoh, K.; Sakamaki, H.; Horiuchi, C. A. One-Pot Synthesis of 3-Benzoyl- and 3-Acetyl-1,2,4-Oxadiazole Derivatives Using Iron(III) Nitrate. *Synthesis-Stuttgart.* **2005**, *2005*, 1935-1938. (d) John, J. T.; Craig, J. D. Aroylnitrile Oxide Cyclizations. **1**. Synthsis of (3-Aroyl-1.2.4-Oxadiazol-5-yl)acetic Acids. *J. Heterocyclic Chem.* **1987**, *24*, 697-699. (e) Vincenzo, F.; Antonio, P. P.; Barbara, C.; Franco, G.; Domenico, S. The Boulton-Katritzky Reaction: A Kinetic Study of the Effect of 5-Nitrogen Substituents on the Rearrangement of Some (*Z*)-Phenylhydrazones of 3-Benzoyl-1,2,4-Oxadiazoles. *Eur. J. Org. Chem.* **2014**, *2014*, 7006-7014.

(4) (a) Augustine, J. K.; Akabote, V.; Hegde, S. G.; Alagarsamy, P. PTSA-$ZnCl_2$: An Efficient Catalyst for the Synthesis of 1,2,4-Oxadiazoles from Amidoximes and Organic Nitriles. *J. Org. Chem.* **2009**, *74*, 5640-5643. (b) Yoshimura, A.; Nguyen, K. C.; Klasen, S. C.; Postnikov, P. S.; Yusubov, M. S.; Saito, A.; Nemykin, V. N.; Zhdankin, V. V. Hypervalent Iodine-Catalyzed Synthesis of 1,2,4-Oxadiazoles from Aldoximes and Nitriles. *Asian J. Org. Chem.* **2016**, *5*, 1128-1133. (c) Outirite, M.; Lebrini, M.; Lagrenée, M.; Bentiss, F. New One Step Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles. *J. Heterocyclic Chem.* **2007**, *44*, 1529-1531. (d) Kaboudin, B.; Saadati, F. Magnesia-Supported Hydroxylamine Hydrochloride in the Presence of Sodium Carbonate as an Efficient Reagent for the Synthesis of 1,2,4-Oxadiazoles from Nitriles. *Tetrahedron Lett.* **2007**, *48*, 2829-2832.

(5) (a) Yoshimura, A.; Nguyen, K. C.; Klasen, S. C.; Saito, A.; Nemykin, V. N.; Zhdankin, V. V. Preparation, Structure, and Versatile Reactivity of Pseudocyclic Benziodoxole Triflate, New Hypervalent Iodine Reagent. *Chem. Commun.* **2015**, *51*, 7835-7838. (b) Nikodemiak, P.; Koert, U. Metal-Catalyzed Synthesis of Functionalized 1,2,4-Oxadiazoles from Silyl Nitronates and Nitriles. *Adv. Synth. Catal.* **2017**, *359*, 1708-1716.

(6) (a) Chinchilla, R.; Nájera, C. The Sonogashira Reaction: A Booming Methodology in Synthetic Organic Chemistry. *Chem. Rev.* **2007**, *107*, 874-922. (b) Johansson, J. R.; Beke-Somfai, T.; Stålsmeden, A. S.; Kann, N. Ruthenium-Catalyzed Azide Alkyne Cycloaddition Reaction: Scope, Mechanism, and Applications. *Chem. Rev.* **2016**, *116*, 14726-14768. (c) Willis, M. C. Transition Metal Catalyzed Alkene and Alkyne Hydroacylation. *Chem. Rev.* **2010**, *110*, 725-748. (d) Meldal, M.; Tornøe, C. W. Cu-Catalyzed Azide-Alkyne Cycloaddition. *Chem. Rev.* **2008**, *108*, 2952-3015.

(7) (a) Yang, W.-S.; Zhang, R.-L.; Yi, F.-Y.; Cai, M.-Z. A Heterogeneous Gold(I)-Catalyzed [2+2+1] Annulation of Terminal Alkynes, Nitriles, and Oxygen Atoms Leading to 2,5-Disubstituted Oxazoles. *J. Org. Chem.* **2017**, *82*, 5204-5211. (b) Yagyu, T.; Takemoto, Y.; Yoshimura, A.; Zhdankin, V. V.; Saito, A. Iodine(III)-Catalyzed Formal [2+2+1] Cycloaddition Reaction for Metal-Free Construction of Oxazoles. *Org. Lett.* **2017**, *19*, 2506-2509. (c) He, W.-M.; Li, C.-Q.; Zhang, L.-M. An Efficient [2+2+1] Synthesis of 2,5-Disubstituted Oxazoles via Gold-Catalyzed Intermolecular Alkyne Oxidation. *J. Am. Chem. Soc.* **2011**, *133*, 8482-8485. (d) Saito, A.; Taniguchi, A.; Kambara, Y.; Hanzawa, Y. Metal-Free [2+2+1] Annulation of Alkynes, Nitriles, and Oxygen Atoms: Iodine(III)-Mediated Synthesis of Highly Substituted Oxazoles. *Org. Lett.* **2013**, *15*, 2672-2675.

(8) (a) Gasparrini, F.; Giovannoli, M.; Misiti, D.; Natile, G.; Palmieri, G.; Maresca, L. Gold(III)-Catalyzed One-Pot Synthesis of Isoxazoles from Terminal Alkynes and Nitric Acid. *J. Am. Chem. Soc.* **1993**, *115*, 4401-4402. (b) Li, Y.-Y.; Gao, M.-C.; Liu, B.-X.; Xu, B. Copper Nitrate-Mediated Chemo- and Regio selective Annulation from Two Different Alkynes: A Direct Route to Isoxazoles. *Org. Chem. Front.* **2017**, *4*, 445-449. (c) Lai, Z.-Z.; Li, Z.-X.; Liu, Y.-W.; Yang, P.-K.; Fang, X.-M.; Zhang, W.-K.; Liu, B.-Y.; Chang, H.-B.; Xu, H.; Xu, Y.-Q. Iron-Mediated Synthesis of Isoxazoles from Alkynes: Using Iron(III) Nitrate as a Nitration and Cyclization Reagent. *J. Org. Chem.* **2018**, *83*, 145-153. (d) Gao, M.-C.; Li, Y.-Y.; Gan, Y.-S.; Xu, B. Copper Nitrate Mediated Regioselective [2+2+1] Cyclization of Alkynes with Alkenes: A Cascade Approach to D^2-Isoxazolines. *Angew. Chem. Int. Ed.* **2015**, *54*, 8919-8923. (e) Zhang, K.; Jelier, B.; Passera, A.; Jeschke, G.; Katayev, D. Synthetic Diversity from a Versatile and Radical Nitrating Reagent. *Chem. Eur. J.* **2019**, *25*, 12929-12939.

(9) (a) Li, H.; Zhu, Z.-H.; Zhang, F.; Xie, S.-H.; Li, H.-X.; Li, P.; Zhou, X.-G. Palladium Nanoparticles Confined in the Cages of MIL-101: An Efficient Catalyst for the One-Pot Indole Synthesis in Water. *ACS Catal.* **2011**, *1*, 1604-1612. (b) Djakovitch, L.; Dufaud, V.; Zaidi, R. Heterogeneous Palladium Catalysts Applied to the Synthesis of 2- and 2,3-Functionalised Indoles. *Adv. Synth. Catal.* **2006**, *348*, 715-724.

(10) (a) Rubio-Marqués, P.; Rivero-Crespo, M. A.; Leyva-Pérez, A.; Corma, A. Well-Defined Noble Metal Single Sites in Zeolites as an Alternative to Catalysis by Insoluble Metal Salts. *J. Am. Chem. Soc.* **2015**, *137*, 11832-11837. (b) Bruneau, A.; Gustafson, K. P. J.; Yuan, N.; Tai, C. W.; Persson, I.; Zou, X.-D.; Bäckvall, J. Synthesis of Benzofurans and Indoles from Terminal Alkynes and Iodoaromatics Catalyzed by Recyclable Palladium Nanoparticles Immobilized on Siliceous Mesocellular Foam. *Chem. Eur. J.* **2017**, *23*, 12886-12891.

(11) (a) Low, C. H.; Rosenberg, J. N.; Lopez, M. A.; Agapie, T. Oxidative Coupling with Zr(IV) Supported by a Noninnocent Anthracene-Based Ligand: Application to the Catalytic Cotrimerization of Alkynes and Nitriles to Pyrimidines. *J. Am. Chem. Soc.* **2018**, *140*, 11906-11910. (b) Fuji, M.; Obora, Y. $FeCl_3$-Assisted Niobium-Catalyzed Cycloaddition of Nitriles and Alkynes: Synthesis of Alkyl- and Arylpyrimidines Based on Independent Functions of $NbCl_5$ and $FeCl_3$ Lewis Acids. *Org. Lett.* **2017**, *19*, 5569-5572.

(12) (a) Kalisiak, J.; Sharpless, K. B.;Fokin, V. Efficient Synthesis of 2-Substituted-1,2,3-Triazoles. *Org. Lett.* **2008**, *10*, 3171-3174. (b) Campbell-Verduyn, L. S.; Mirfeizi, L.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. Phosphoramidite Accelerated Copper(I)-Catalyzed [3+2] Cycloadditions of Azidesand Alkynes. *Chem. Commun.* **2009**, *16*, 2139-2141.

(13) Huang, Y.-B.; Yan, D.-H.; Wang, W.; Zhou, P.-Q.; Wu, W.-Q.; Jiang, H.-F. Controllable Assembly of the Benzothiazole Framework Using a C≡C Triple Bond as a One-Carbon Synthon. *Chem. Commun.* **2018**, *54*, 1742-1745.

(14) (a) Su, H.-M.; Wang, L.-Y.; Rao, H.-H.; Xu, H. Iron-Catalyzed Dehydrogenative sp3-sp2 Coupling via Direct Oxidative C-H Activation of Acetonitrile. *Org. Lett.* **2017**, *19*, 2226-2229. (b) Xu, H.; Ma, S.; Xu, Y.-Q.; Bian, L.-X.; Ding, T.; Fang, X.-M.; Zhang, W.-K.; Ren, Y.-R. Copper-Catalyzed One-Pot Synthesis of 1,2,4-Triazoles from Nitriles and Hydroxylamine. *J. Org. Chem.* **2015**, *80*, 1789-1794. (c) Pan, L.-Y.; Lai, Z.-Z.; Ding, T.; Fang, X.-M.; Zhang, W.-K.; Xu, H.; Xu, Y.-Q. Base-Mediated Synthesis of Unsymmetrical 1,3,5-Triazin-2-aminesvia Three-Component Reaction of Imidates, Guanidines, and Amidesor Aldehydes. *J. Org. Chem.* **2017**, *82*, 10043-10050. (d) Li, S.-Y.; Pan, W.-N.; Wu, S.-X.; Bu, X.-B.; Xin, S.-G.; Yu, J.-P.; Xu, H.; Yang, X.-B. Visible-Light-Induced Tandem Radical Addition-Cyclization of 2-Aryl Phenyl Isocyanides Catalysed by Recyclable Covalent Organic Frameworks. *Green Chem.* **2019**, *21*, 2905-2910.

(15) (a) Taniguchi, T.; Ishibashi, H. Iron-Mediated Radical Nitro-Cyclization Reaction of 1,6-Dienes. *Org. Lett.* **2010**, *12*, 124-126. (b) Naveen, T.; Maity, S.; Sharma, U.; Maiti, D. A Predictably Selective Nitration of Olefin with $Fe(NO_3)_3$ and TEMPO. *J. Org. Chem.* **2013**, *78*, 5949-5954.

(16) (a) Ito, M.; Itazaki, M.; Nakazawa, H. Selective Double Hydrosilylation of Nitriles Catalyzed by an Iron Complex Containing Indium Trihalide. *ChemCatChem.* **2016**, *8*, 3323-3325. (b) Ito, M.; Itazaki, M.; Nakazawa, H. Selective Double Hydroboration and Dihydroborylsilylation of Organonitriles by an Iron-indium Cooperative Catalytic System. *Inorg. Chem.* **2017**, *56*, 13709-13714. (c) Fier, P. S.; Hartwig, J. F. Copper-Mediated Fluorination of Aryl Iodides. *J. Am. Chem. Soc.* **2012**, *134*, 10795-10798. (d) Fier, P. S.; Luo, J.; Hartwig, J. F. Copper-Mediated Fluorination of Arylboronate Esters. Identification of a Copper(III) Fluoride Complex. *J. Am. Chem. Soc.* **2013**, *135*, 2552-2559.

(17) (a) Maity, S.; Manna, S.; Rana, S.; Naveen, T.; Mallick, A.; Maiti, D. An Efficient and Stereoselective Nitration of Mono- and Di-Substituted Olefins with $AgNO_2$ and TEMPO. *J. Am. Chem. Soc.* **2013**, *135*, 3355-3358. (b) Manna, S.; Maity, S.; Rana, S.; Agasti, S.; Maiti, D. *ipso*-Nitration of Arylboronic Acids with Bismuth Nitrate and Perdisulfate. *Org. Lett.* **2012**, *14*, 1736-1739. (c) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. Stereoselective Nitration of Olefins with ^{t}BuONO and TEMPO: Direct Access to Nitroolefins under Metal-free Conditions. *Org. Lett.* **2013**, *15*, 3384-3387. (d) Manna, S.; Jana, S.; Saboo, T.; Maji, A.; Maiti, D. Synthesis of (*E*)-Nitroolefins Via Decarboxylative Nitration Using *t*-Butylnitrite (*t*-BuONO) and TEMPO. *Chem. Commun.* **2013**, *49*, 5286-5288. (e) Agasti, S.; Maiti, S.; Maity, S.; Anniyappan, M.; Talawar, M. B.; Maiti, D. Bismuth Nitrate as a Source of Nitro Radical in *ipso*-Nitration of Carboxylic Acids. *Polyhedron*. **2019**, *172*, 120-124.

(18) Barrow, S. J.; Easton, C. J. Exploiting the 1,3-Dithiane of 2-Oxopropanenitrile Oxide to Limit Competing Dimerization in 1,3-Dipolar Cycloaddition Reactions. *Tetrahedron Lett.* **1997**, *38*, 2175-2178.

(19) Ruccia, M.; Spinelli, D. Transformation of 1,2,4-Oxadiazole Derivatives into 2H-1,2,3-Triazole Derivatives. *Gazz. Chim. Ital.* **1959**, *89*, 1654-1669.

(20) Satoh, Y.; Yasuda, K.; Obora, Y. Strategy for the Synthesis of Pyrimidine Derivatives: $NbCl_5$-Mediated Cycloaddition of Alkynes and Nitriles. *Organometallics* **2012**, *31*, 5235-5238.

(21) Gowda, A. N.; Roy, A.; Kumar, S. Synthesis and Characterisation of Novel Isoxazole-Based Banana Liquid Crystals from Naturally Occurring Curcumin. *Liq. Cryst.* **2016**, *43*, 175-182