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A $KHSO_4$ mediated facile synthesis of 2-amino-1,3,4-oxadiazole derivatives

Binyu Long [a, b, 1], Binghua Tian [a, 1], Qiang Tang [a, b], Xiangnan Hu [a, b], Lei Han [a], Zifan Wang [a], Chenyu Wang [a], Yue Wu [a], Yu Yu [a, **], Zongjie Gan [a, *]

[a] Department of Medicinal Chemistry, College of Pharmacy, Chongqing Medical University, Chongqing, 400016, PR China
[b] Chongqing Research Center for Pharmaceutical Engineering, Chongqing Medical University, Chongqing, 400016, PR China

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ABSTRACT

A novel, efficient and mild $KHSO_4$ mediated synthesis for 2-amino-1,3,4-oxadiazoles has been established via the cyclodesulfurization of benzoylhydrazine and isothiocyanate derivatives in one pot. The reactions proceeded smoothly at room temperature and produced corresponding products in moderate to good yields. This protocol also showed good functional group tolerance.

1. Introduction

In the last few decades, the 2-amino-1,3,4-oxadiazoles, as a formidable class of heterocyclic compounds, contribute significantly to medicinal related fields due to their extensively original biological activities such as muscle relaxants [1], anti-cancer [2,3], antimicrobial [4], anti-proliferation [5], anti-inflammatory [6] and anti-mitosis [7]. For instance, the tubulin inhibitor IMC-038525 based upon this scaffold, exhibits remarkable anti-proliferative effects on cancer cells for the potential treatment of non-small-cell lung carcinoma [5]. In addition, compounds SMRB4-7 and Furamizole containing this core structure are also known to be anti-inflammatory and antibacterial compounds, respectively (Fig. 1). Inspired by the broad applications, exploitation of an efficient and environmental benign reaction route to 2-amino-1,3,4-oxadiazoles still holds its relevance.

A number of accessible methods for the construction of 2-amino-1,3,4-oxadiazoles have been developed in recent years. Cyclization of preformed thiosemicarbazides employing different catalytic reagents is the most well-designed and extensively explored synthetic protocol. A variety of desulfurization reagents including $POCl_3$ [8,9], concentrated sulfuric acid [10], Burgess reagent [11], N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide (EDCI) [12], O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU) [13], N, N′-diisopropylcarbodiimide (DIC) [14], o-iodoxybenzoic acid (IBX) [15], iodobenzenediacetate (IBD) [16], I_2/NaOH [17] and tosyl chloride [18] have been utilized (Scheme 1). However, most of the existing methods often suffer from several drawbacks, such as harsh reaction conditions, inconvenient handling, requirement of hazardous or expensive catalysts and so on. For example, Prabhu et al. [15] reported a one-pot oxidative cyclization of thiosemicarbazide derivatives to generate 2-amino-1,3,4-oxadiazoles wherein hypervalent iodine IBX was used. Similarly, Maghari et al. also developed a TBTU or DIC-mediated tandem cyclization of aryl hydrazides with ammonium thiocyanate in N, N-Dimethylformamide (DMF) at 50 °C for the formation of substituted 2-amino-1,3,4-oxadiazoles [13].

Therefore, there is a constant pursuit to develop a practical and cost-effective coupling reagent. Encouraged by our previous research [19], we herein wish to report a highly efficient promotor $KHSO_4$, which could effectively catalyze the cyclodesulfurization of thiosemicarbazide intermediates to afford 2-amino-1,3,4-oxadiazoles with moderate to good yields at room temperature. It is noteworthy that, instead of aforementioned reagents, the mild and environment friendly nature of $KHSO_4$ also made this reagent

* Corresponding author.
** Corresponding author.
E-mail addresses: yuyu3519@163.com (Y. Yu), gzj@cqmu.edu.cn (Z. Gan).
[1] These authors contributed equally to this work.

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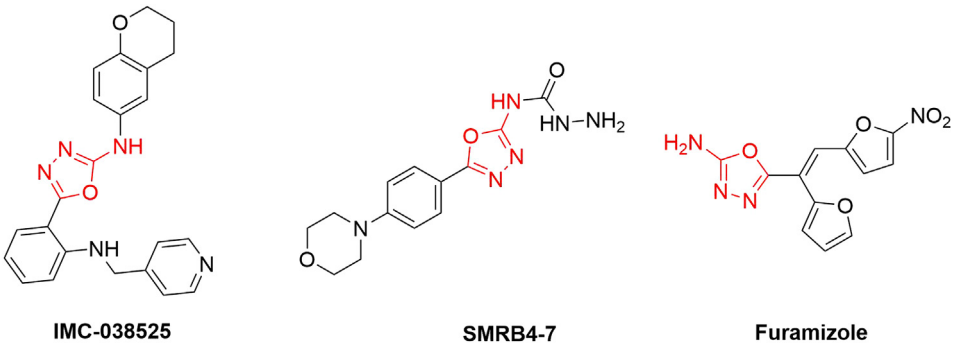
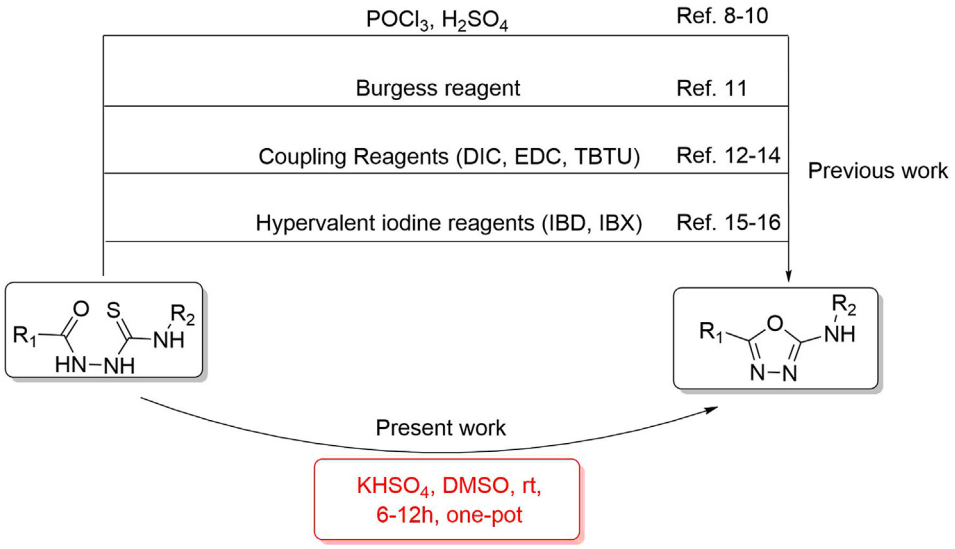


Fig. 1. Representative examples of biologically active derivatives featuring the 1,3,4-oxadiazoles scaffold.



Scheme 1. Literature and present protocols for the preparation of 2-amino-1,3,4-oxadiazoles.

attractive alternatives for desulfurization. To the best of our knowledge, this is the first report on the production of 2-amino-1,3,4-oxadiazoles through thiosemicarbazides catalyzed by $KHSO_4$.

2. Results and discussion

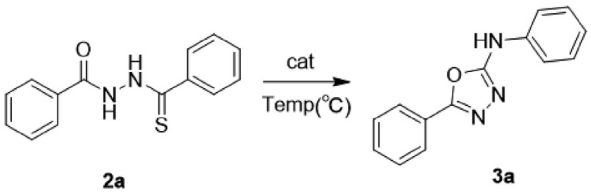
Our previous research [19] showed that $KHSO_4$ was able to catalyze the intramolecular cyclization of thioacylhydrazides, and also promoted us to envisage the use of $KHSO_4$ as a coupling agent in the synthesis of 2-amino-1,3,4-oxadiazoles. In an initial study using a model cyclization reaction of thiosemicarbazide **2a** prepared from benzohydrazide and phenyl isothiocyanate, it was observed that no final product was obtained in the absence of any catalyst (Table 1, entry 1), suggesting that a catalyst is essential for the reaction. Then the optimization of the reaction conditions was studied with different catalysts including 4-methylbenzenesulfonic acid (TsOH), H_2SO_4, Acetic acid (HAc), Lewis acids ($CaCl_2$, $FeCl_3$, $Cu(OAc)_2$) or inorganic salts ($KHSO_4$, Na_2SO_4, NH_4Cl, NaH_2PO_4). As shown in Table 1, preliminary experiments revealed that no reaction occurred or only trace amounts of product was afforded when the activator such as H_2SO_4, $KHSO_4$ or $NaHSO_4$ was replaced by other additives, which meant that the acidic catalysts with dehydration property might play a vital role in this series of reactions (Table 1, entries 1–12). Desired products were obtained in moderate yields in the presence of these three desulfurizing agents under mild conditions. Consequently, given that the economic attractiveness and environmental friendliness of $KHSO_4$, it was selected for further investigation.

Next, the effect of different amounts of catalyst on the reaction outcome was detected. As shown in Table 1, the efficacy of the catalyst positively correlated with its loadings at a certain range. There is a significant improvement of yield accompanied with the escalation of catalyst loading. A nearly ideal yield of 80 % was achieved when 6.0 equiv. of $KHSO_4$ was employed (Table 1, entry 13). Although the utilization of 9.0 equiv. of $KHSO_4$ provided the desired product in 85 % yield (Table 1, entry 14), 6.0 equiv. of $KHSO_4$ was sufficient and would be optimal. Moreover, it is pertinent to mention that no notable effect was observed when the reaction time was extended.

In order to investigate the effect of solvents, reactions were carried out in CH_2Cl_2, ethyl acetate (EA) and Tetrahydrofuran (THF), where no conversion was observed (Table 1, entries 15–17). Notably, increasing temperature could accelerate the reaction, but no obvious influence on the reaction yield was observed (Table 1, entries 18–20). Finally, according to the experimental data, the optimized parameters of reaction were selected as 6 equiv. of $KHSO_4$ in DMSO at room temperature.

In order to explore the generality of this reaction, various benzoylhydrazine derivatives were applied to this methodology under established optimized conditions. Experimental results associated were demonstrated in Table 2. Firstly, it was found that the electron-donating groups including $-CH_3$, $-OCH_3$, $-OC_2H_5$ and *t*-

Table 1
Optimization of the reaction conditions [a].



Entry	Catalyst (equiv.)	Temp (°C)	Solvent	Time (h)	Yield (%)[b]
1	–	25	DMSO	6	NR[c]
2	HAc (3.0)	25	DMSO	6	NR
3	TsOH (3.0)	25	DMSO	6	NR
4	$KHSO_4$ (3.0)	25	DMSO	6	53
5	H_2SO_4(3.0)	25	DMSO	6	65
6	$CaCl_2$ (3.0)	25	DMSO	6	NR
7	$FeCl_3$ (3.0)	25	DMSO	6	NR
8	$Cu(OAc)_2$ (3.0)	25	DMSO	6	NR
9	NaH_2PO_4 (3.0)	25	DMSO	6	NR
10	Na_2SO_4(3.0)	25	DMSO	6	NR
11	$NaHSO_4$(3.0)	25	DMSO	6	47
12	NH_4Cl (3.0)	25	DMSO	6	NR
13	$KHSO_4$ (6.0)	25	DMSO	6	80
14	$KHSO_4$ (9.0)	25	DMSO	6	85
15	$KHSO_4$ (6.0)	25	CH_2Cl_2	6	NR
16	$KHSO_4$ (6.0)	25	EA	6	NR
17	$KHSO_4$ (6.0)	25	THF	6	trace
18	$KHSO_4$ (6.0)	45	DMSO	6	81
19	$KHSO_4$ (6.0)	60	DMSO	6	84
20	$KHSO_4$ (6.0)	90	DMSO	2	86

[a] Reaction conditions: benzoylhydrazine (**1a**, 0.2 g, 1.5 mmol, 1.0 equiv.) and DMSO (3 mL).
[b] Isolated yield.
[c] No reaction.

Bu on the benzene ring of benzoylhydrazines showed higher reactivity, and generated corresponding products in 75–86 % yields (Table 2, **3a**-**3h**). Likewise, dimethoxy substituted substrate 3, 4-dimethoxybenzoylhydrazine **1i** was also found to be reactive and transformed into the target compound **3i** in 83 % yield. Meanwhile, as indicated by **3b, 3c** and **3d,** the position of the substituents on the phenyl ring had a minor impact on the reaction outcome. Moreover, it is important to note that 4-hydroxybenzoylhydrazine **1j** underwent the reaction smoothly and provided the desired product in 82 % yield, which indicated that this synthesis method was compatible when extended to substrates containing oxidant-sensitive group (Table 2, **3j**).

On the other hand, this reaction was also tolerant to benzoylhydrazines bearing electron-withdrawing groups such as F, Br, and Cl (Table 2, **3k**-**3m**), except for the strong electron withdrawing group NO_2, which was completely unfavorable for this reaction (data not shown). Particularly, for the product **3k**, the reaction time was extended to 12 h, which may be due to the high electrophilicity of 4-fulorobenzoylhydrazine. In addition, when the benzene ring was replaced by aliphatic groups, the reaction got more accomplished under the standard reaction conditions and resulted in inferior yields of products (Table 2, **3n-3p**). Furthermore, the present protocol was also proved to be compatible with the reactions of heterocyclic hydrazines, such as pyrimidine, thiophene and furan, and the corresponding products were isolated in 53–65 % yields (Table 2, **3q-3s**).

Next, we turned our attention to the substituted phenyl isothiocyanates. Similarly, this protocol can be extended to phenyl isothiocyanates bearing electron-donating groups as well. Treatment of **1a** with various isothiocyanates including aliphatic isothiocyanate produced the corresponding products in moderate to good yields (Table 3, **4a**-**4k**, 60–84 %). However, the present method was not suitable for isothiocyanate bearing strong electron-withdrawing groups either such as 4-nitrophenylisothiocyanate (data not shown).

Furthermore, the raw materials in this reaction were increased to gram-scale synthesis in order to examine the stability and efficiency of the reaction (Scheme 2). To our delight, the product purified by column chromatograph was ultimately obtained in 84 % yield.

A plausible mechanism for the formation of 2-amino-1,3,4-oxadiazoles, in accordance with the literature [13], is represented in Scheme 3. Initially, hydrazines were condensed with isothiocyanates to afford intermediate A. Then, the isomerization of intermediate A was promoted by $KHSO_4$, acting as a H^+ donor reagent, to afford intermediate B. Subsequent intracyclization via the nucleophilic attack of carbonyl group on the thiol group of intermediate B provided the reactive intermediate C followed by desulfurization that finally furnished the target compounds 2-amino-1,3,4-oxadiazoles.

3. Conclusion

In summary, an environmental and economical one-pot synthetic method was proposed for the preparation of 2-amino-1,3,4-oxadiazoles. The uniqueness of the protocol lies in that the target compounds are synthesized through the cyclization of thiosemicarbazides intermediates in the presence of $KHSO_4$ at room temperature. The highlights of this reaction include good yields, good functional group tolerance, and mild reaction conditions, providing a better synthetic option for the synthesis of 2-amino-1,3,4-oxadiazoles.

4. Experimental

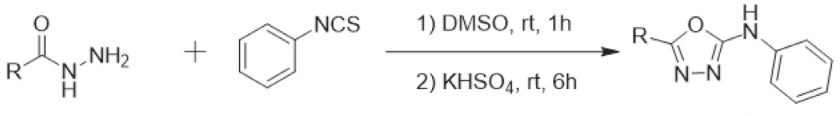
4.1. General information

Materials and chemicals utilized such as potassium bisulfate ($KHSO_4$, 99 %), dimethyl sulfoxide (DMSO, 99 %), phenyl isothiocyanate and benzoylhydrazine derivatives were commercially available and purchased from Adamas, Tansoole or Macklin in the current research. All reagents mentioned above were used without further purification unless otherwise noted. Melting points of the synthesized compounds were recorded using X-4 microscopic melting point apparatus. ^{1}H NMR and ^{13}C HNMR spectra were obtained using a Bruker-600 MHz spectrometer with DMSO-d_6 or $CDCl_3$ as solutions and TMS as the internal standard. Chemical shifts are reported in ppm and coupling constants (J) in Hz. HRMS spectra were obtained with an Aglient 6210 Triple Quad LC-MS instrument. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash column chromatography was carried out by using 200–300 mesh silica gel.

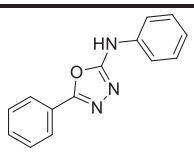
4.2. General procedure for the synthesis of 2-amino-1,3,4-oxadiazole derivatives (*3a-p, 4a-k*)

A solution of benzoylhydrazine (0.20 g, 1.5 mmol) and phenyl isothiocyanate (0.20 g, 1.5 mmol) in DMSO (3 mL) was stirred at room temperature for 1 h. Then, $KHSO_4$ (1.19 g, 8.75 mmol) was directly added to the stirred solution at the room temperature and reacted for another 6 h. After the completion of the reaction monitored by TLC, the solution was diluted with 30 mL water, and the resulting precipitate was separated by filtration or extracted with EA, concentrated and dried. The residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate to afford the target product.

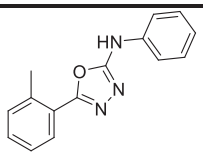
Table 2
Substrate scope with respect to substituted benzoylhydrazines[a].



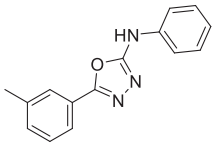
1a-1s 3a-3s



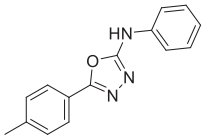
3a, 80%



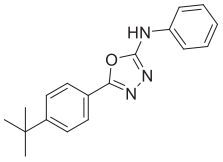
3b, 76%



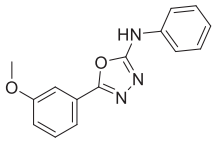
3c, 76%



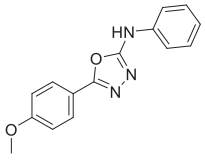
3d, 83%



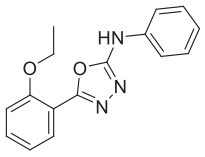
3e, 86%



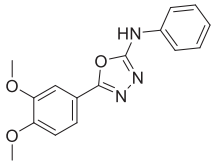
3f, 75%



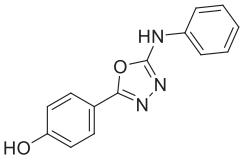
3g, 81%



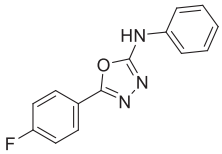
3h, 80%



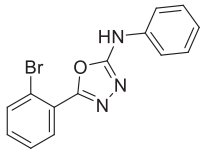
3i, 83%



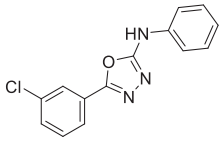
3j[b], 82%



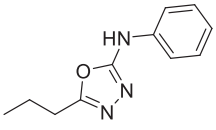
3k[c], 62%



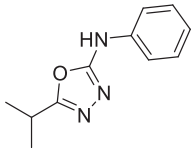
3l[b], 74%



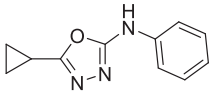
3m, 68%



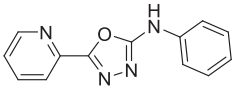
3n, 61%



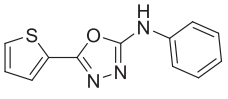
3o, 57%



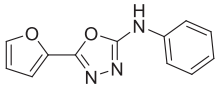
3p, 54%



3q, 53%



3r, 65%



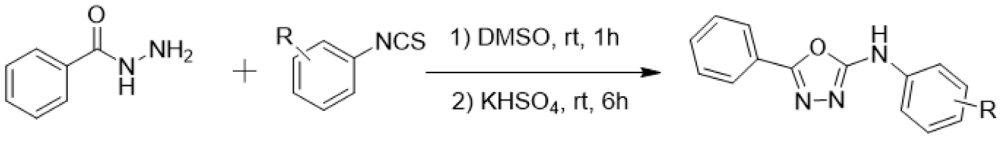
3s, 62%

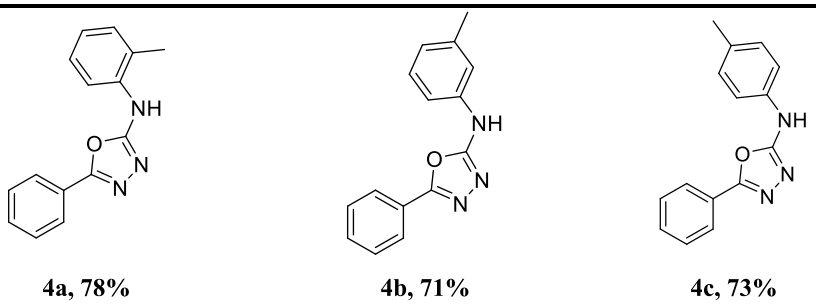
[a] Reagents and conditions: benzoylhydrazine derivatives (1.5 mmol), isothiocyanate derivatives (1.5 mmol), $KHSO_4$ (6.0 equiv.) and DMSO (3 mL), room temperature, air, isolated yield.

[b] 25 °C, 8 h

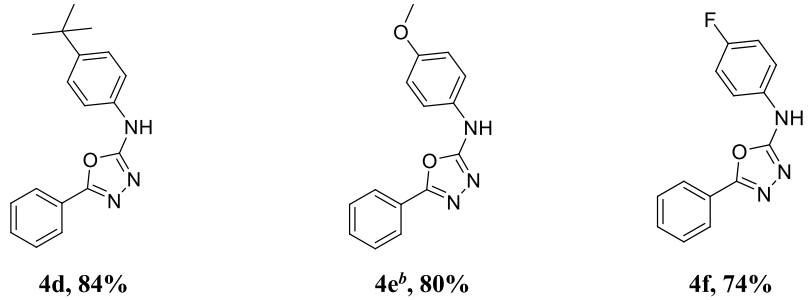
[c] 25 °C, 12 h

Table 3
Substrate scope with respect to substituted phenyl isothiocyanates[a].

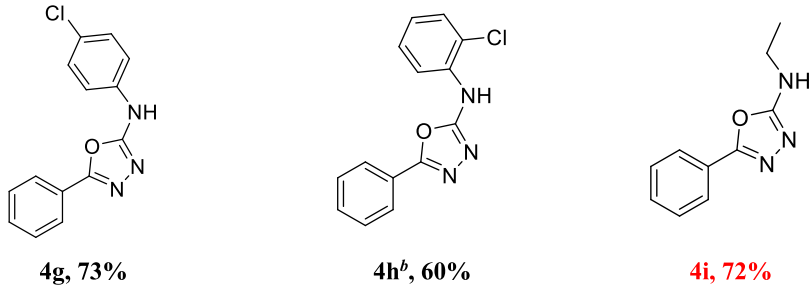




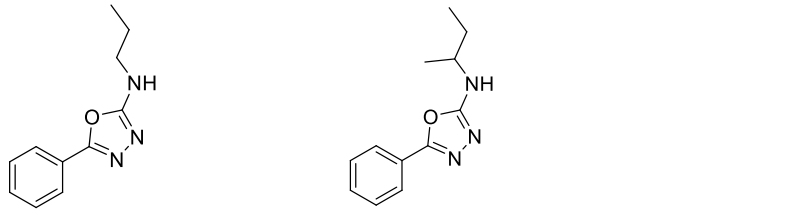
4a, 78% **4b, 71%** **4c, 73%**



4d, 84% **4e[b], 80%** **4f, 74%**



4g, 73% **4h[b], 60%** **4i, 72%**



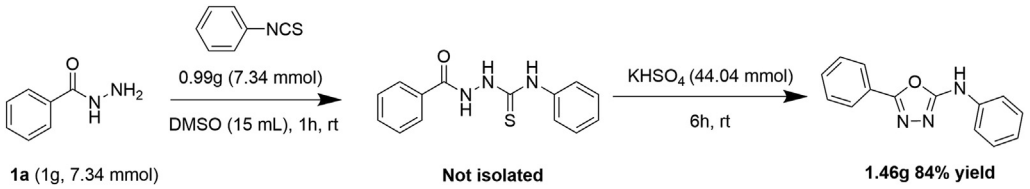
4j, 63% **4k, 60%**

[a] Reagents and conditions: benzoylhydrazine (**1a**, 0.2 g, 1.5 mmol, 1.0 equiv.), isothiocyanate derivatives (1.5 mmol), $KHSO_4$ (6.0 equiv.) and DMSO (3 mL), room temperature, air, isolated yield.
[b] 25 °C, 8 h

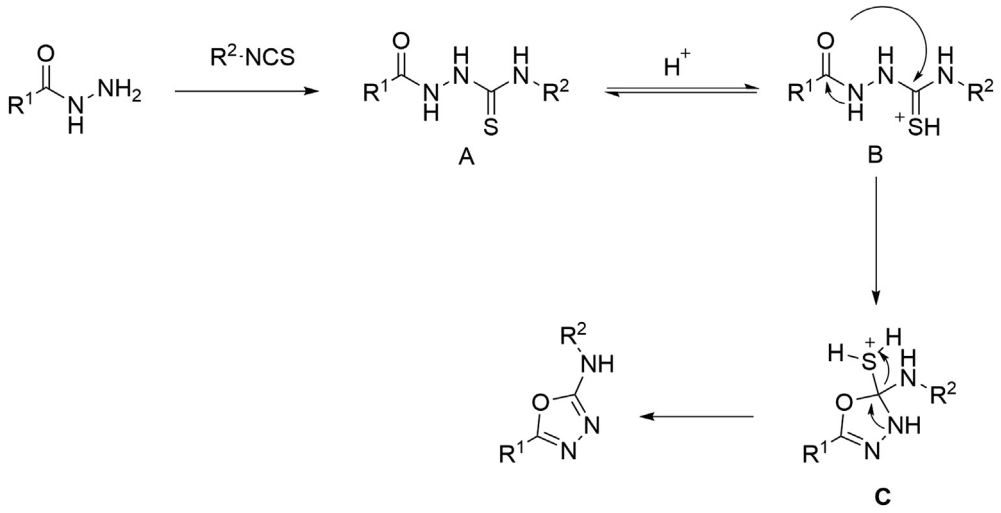
4.3. Product characterization data

N,5-diphenyl-1,3,4-oxadiazol-2-amine (**3a**) [20] obtained as red solid in 80 % yield; M.p. 207–209 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.68 (s, 1H), 7.98–7.82 (m, 2H), 7.69–7.50 (m, 5H), 7.40–7.33 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.39, 158.21, 139.11, 131.45, 129.83, 129.58, 126.02, 124.34, 122.37, 117.54. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{12}N_3O$: 238.0980; Found: 238.0984.

N-phenyl-5-(o-tolyl)-1,3,4-oxadiazol-2-amine (**3b**) [21] obtained as white solid in 76 % yield; M.p. 192–195 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.49–7.30 (m, 5H), 7.02 (t, J = 7.3 Hz, 1H), 2.64 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.04, 158.35, 139.18, 137.39 132.12, 130.98, 129.58, 128.28, 126.87, 123.40, 122.32, 117.52, 22.01. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O$: 252.1137; Found: 251.1144.



Scheme 2. Gram scale synthesis experiment.



Scheme 3. A plausible mechanism for the synthesis of 2-amino-1,3,4-oxadiazoles.

N-phenyl-5-(m-tolyl)-1,3,4-oxadiazol-2-amine (**3c**) obtained as pale red solid in 76 % yield; M.p. 203–205 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.66 (s, 1H), 7.73 (s, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.63 (d, J = 8.1 Hz, 2H), 7.47 (t, J = 7.7 Hz, 1H), 7.40-7.35 (m, 3H), 7.02 (t, J = 7.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.32, 158.27, 139.21, 139.12, 132.11, 129.74, 129.57, 126.39, 124.26, 123.20, 122.35, 117.52, 21.38. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{15}H_{14}N_3O$: 251.1137; Found: 251.1143.

N-phenyl-5-(p-tolyl)-1,3,4-oxadiazol-2-amine (**3d**) [22] obtained as pale-yellow solid in 83 % yield; M.p. 205–207 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 7.7 Hz, 2H), 7.44–7.31 (m, 4H), 7.02 (t, J = 7.3 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.19, 158.31, 141.43, 139.16, 130.36, 129.57, 126.01, 122.32, 121.61, 117.50, 21.55. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{15}H_{14}N_3O$: 252.1137; Found: 252.1140.

5-(4-(tertbutyl)phenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3e**) obtained as red solid in 86 % yield; M.p. 201–202 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.66 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.63-7.59 (m, 4H), 7.37 (t, J = 7.9 Hz, 2H), 7.02 (t, J = 7.3 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.21, 158.23, 154.29, 139.16, 129.57, 126.64, 125.89, 122.30, 121.63, 117.48, 35.22, 31.34. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{18}H_{20}N_3O$: 294.1606; Found: 294.1602.

5-(3-methoxyphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3f**) obtained as tan solid in 75 % yield; M.p. 155–157 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.54–7.45 (m, 2H), 7.42–7.32 (m, 3H), 7.18–7.11 (m, 1H), 7.02 (t, J = 7.3 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.38, 160.09, 158.07, 139.08, 131.14, 129.58, 125.51, 122.38, 118.35, 117.54, 117.47, 110.82, 55.82. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{15}H_{14}N_3O_2$: 268.1086; Found: 268.1090.

5-(4-methoxyphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3g**) [23] obtained as pale red solid in 81 % yield; M.p. 196–198 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 7.85–7.78 (m, 2H), 7.68 - 7.58 (m, 3H), 7.54 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.76, 160.00, 158.16, 139.22, 129.55, 127.81, 122.23, 117.44, 116.78, 115.28, 55.92. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{15}H_{14}N_3O_2$: 268.1086; Found: 268.1090.

5-(2-ethoxyphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3h**) obtained as white solid in 80 % yield; M.p. 150–152 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.54 (s, 1H), 7.76-7.73 (m, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.57–7.49 (m, 1H), 7.36 (t, J = 7.9 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.3 Hz, 1H), 4.18 (q, J = 6.9 Hz, 2H), 1.39 (t, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.50, 157.13, 156.81, 139.29, 133.06, 130.25, 129.56, 122.25, 121.14, 117.44, 114.00, 113.68, 64.61, 15.05. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{16}H_{16}N_3O_2$: 282.1243; Found: 282.1248.

5-(3,4-dimethoxyphenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3i**) obtained as white solid in 83 % yield; M.p. 171–174 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.47-7.40 (m, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 7.3 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.01, 158.20, 151.56, 149.53, 139.20, 129.56, 122.23, 119.33, 117.43, 116.72, 112.54, 108.90, 56.16, 56.04. HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{16}H_{16}N_3O_3$: 298.1192; Found: 298.1192.

4-(5-(phenylamino)-1,3,4-oxadiazol-2-yl) phenol (**3j**) obtained as white solid in 82 % yield; M.p. 237–239 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.55 (s, 1H), 10.17 (s, 1H), 7.77–7.70 (m, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.36 (t, J = 7.9 Hz, 2H), 7.00 (t, J = 7.3 Hz, 1H), 6.97–6.91 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.42, 159.81, 158.44, 139.28, 129.54, 127.95, 122.15, 117.40, 116.57, 115.18. HRMS (ESI): HRMS (ESI): m/z [M+H]$^+$ Calcd for $C_{14}H_{12}N_3O_2$: 254.0930; Found: 254.0929.

5-(4-fluorophenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3k**) obtained as yellow solid in 62 % yield; M.p. 239–242 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.00–7.91 (m, 2H), 7.62 (d,

J = 7.7 Hz, 2H), 7.47–7.40 (m, 2H), 7.40–7.33 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.78, 163.13, 160.41, 157.51, 139.08, 129.59, 128.62, 128.56, 122.40, 121.06, 117.55, 117.14, 116.99. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_3OF$: 256.0886; Found: 256.0885.

5-(2-bromophenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3l**) [24] obtained as white solid in 74 % yield; M.p. 186–189 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.05–7.95 (m, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.79-7.77 (m, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.55 (t, J = 7.9 Hz, 1H), 7.38 (t, J = 7.9 Hz, 2H), 7.03 (t, J = 7.3 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.60, 156.95, 138.94, 134.09, 132.11, 129.61, 128.35, 126.46, 124.99, 122.77, 122.52, 117.62. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_3OBr$: 316.0085; Found: 316.0087.

5-(3-chlorophenyl)-N-phenyl-1,3,4-oxadiazol-2-amine (**3m**) [13] obtained as pale-yellow solid in 68 % yield; M.p. 179–181 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.73 (s, 1H), 7.98–7.77 (m, 2H), 7.72–7.52 (m, 4H), 7.39-7.35 (m, 2H), 7.03 (t, J = 7.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.61, 157.08, 138.95, 134.41, 131.90, 131.20, 129.60, 126.26, 125.49, 124.64, 122.52, 117.63. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_3OCl$: 272.0591; Found: 272.0594.

5-propyl-N-phenyl-1,3,4-oxadiazol-2-amine (**3n**) obtained as white solid in 61 % yield; M.p. 109–111 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.54 (d, J = 7.7 Hz, 2H), 7.30–7.34 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 2.73 (t, J = 7.3 Hz, 2H), 1.74–1.66 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.25, 160.12, 139.39, 129.48, 121.98, 117.24, 26.73, 19.88, 13.82. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{11}H_{14}N_3O$: 204.1137; Found: 204.1140.

5-isopropyl-N-phenyl-1,3,4-oxadiazol-2-amine (**3o**) obtained as white solid in 57 % yield; M.p. 127–129 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.35 (s, 1H), 7.60-7.50 (m, 2H), 7.40–7.25 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H), 3.15–3.06 (m, 1H), 1.29 (d, J = 7.0 Hz, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.22, 160.09, 139.40, 129.48, 121.97, 117.23, 25.88, 20.19. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{11}H_{14}N_3O$: 204.1137; Found: 204.1139.

5-cyclopropyl-N-phenyl-1,3,4-oxadiazol-2-amine (**3p**) obtained as red solid in 54 % yield; M.p. 125–127 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.29 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 7.8 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 2.19–2.04 (m, 1H), 1.10–1.02 (m, 2H), 0.97–0.89 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.53, 159.53, 139.33, 129.46, 121.96, 117.19, 7.35, 6.11. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{11}H_{12}N_3O$: 202.0980; Found: 202.0980.

2-benzyl-5-(pyridin-2-yl)-1,3,4-oxadiazole (**3q**) [25] obtained as white solid in % yield; M.p. 227–229 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.75–8.72 (m, 1H), 8.14–8.07 (m, 1H), 8.04–7.98 (m, 1H), 7.62 (m, 2H), 7.58–7.55 (m, 1H), 7.43–7.33 (m, 2H), 7.04 (t, J = 7.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.00, 158.05, 150.53, 143.65, 138.96, 138.14, 129.61, 125.95, 122.54, 122.23, 117.61. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{13}H_{11}N_4O$: 239.0933; Found: 239.0931.

2-benzyl-5-(thiophen-2-yl)-1,3,4-oxadiazole (**3r**) [13] obtained as white solid in 65 % yield; M.p. 212–214 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.70 (s, 1H), 7.84–7.80 (m, 1H), 7.71–7.50 (m, 3H), 7.37–7.26 (m, 3H), 7.02 (t, J = 7.0 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.81, 154.63, 138.99, 130.38, 129.58, 129.01, 128.79, 125.42, 122.42, 117.54. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{12}H_{10}N_3OS$: 244.0545; Found: 244.0549.

2-benzyl-5-(furan-2-yl)-1,3,4-oxadiazole (**3s**) [21] obtained as white solid in 62 % yield; M.p. 184–186 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.99 (d, J = 1.6 Hz, 1H), 7.60 (d, J = 7.8 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.14 (d, J = 3.5 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 6.77 (dd, J = 3.5, 1.7 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 159.74, 151.44, 146.45, 139.40, 138.94, 129.59, 122.48, 117.55, 112.84, 40.54. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{12}H_{10}N_3O_2$: 228.0773; Found: 228.0775.

5-phenyl-N-(o-tolyl)-1,3,4-oxadiazol-2-amine (**4a**) [23] obtained as green solid in 78 % yield; M.p. 150–153 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.66 (s, 1H), 7.90–7.80 (m, 2H), 7.78–7.75 (m, 1H), 7.57–7.55 (m, 3H), 7.26–7.22 (m, 2H), 7.05 (t, J = 7.3 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.58, 158.47, 137.14, 131.33, 131.12, 129.80, 129.50, 127.01, 125.91, 124.46, 124.33, 121.49, 18.39. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O$: 252.1137; Found: 252.1142.

5-phenyl-N-(m-tolyl)-1,3,4-oxadiazol-2-amine (**4b**) [13] obtained as yellow solid in 71 % yield; M.p. 138–140 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.93–7.87 (m, 2H), 7.62–7.56 (m, 3H), 7.47–7.40 (m, 2H), 7.25 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.40, 158.17, 139.05, 138.83, 131.43, 129.82, 129.42, 126.00, 124.35, 123.14, 118.02, 114.78, 21.77. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O$:252.1137; Found: 252.1143.

5-phenyl-N-(p-tolyl)-1,3,4-oxadiazol-2-amine (**4c**) [13] obtained as white solid in 73 % yield; M.p. 212–214 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.94–7.84 (m, 2H), 7.64–7.54 (m, 3H), 7.51 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.49, 158.09, 136.63, 131.38, 131.24, 129.96, 129.82, 125.97, 124.39, 117.59, 20.80. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O$: 252.1137; Found: 252.1143.

N-(4-(*tert*-butyl) phenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4d**) obtained as white solid in 84 % yield; M.p. 233–235 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.56 (s, 1H), 7.94–7.85 (m, 2H), 7.61–7.55 (m, 3H), 7.53 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 1.28 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.54, 158.11, 144.75, 136.56, 131.39, 129.83, 126.22, 125.97, 124.39, 117.36, 34.42, 31.73. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{18}H_{20}N_3O$: 294.1606; Found: 294.1609.

N-(4-methoxyphenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4e**) [18] obtained as white solid in 80 % yield; M.p. 207–210 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.00–7.79 (m, 2H), 7.68–7.63 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.65, 157.99, 154.95, 132.37, 131.32, 129.80, 125.92, 124.43, 119.08, 114.83, 55.72. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O_2$: 268.1086; Found: 268.1091.

N-(4-fluorophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4f**) [18] obtained as white solid in 74 % yield; M.p. 237–240 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.92 - 7.86 (m, 2H), 7.70 - 7.62 (m, 5H), 7.22 (t, J = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.39, 158.59, 158.23, 157.01, 135.58, 131.47, 129.83, 126.02, 124.31, 119.17, 119.12, 116.26, 116.11. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_3OF$: 256.0886; Found: 256.0891.

N-(4-chlorophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4g**) [13] obtained as pale-yellow solid in 73 % yield; M.p. 265–266 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.87 (s, 1H), 7.88–7.92 (m, 2H), 7.64 (d, J = 8.2 Hz, 2H), 7.43–7.53 (m, 3H), 7.43 (d, J = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.15, 158.38, 138.10, 131.54, 129.84, 129.46, 126.07, 125.98, 124.24, 119.12. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_3OCl$: 272.0591; Found: 272.0594.

N-(2-chlorophenyl)-5-phenyl-1,3,4-oxadiazol-2-amine (**4h**) obtained as yellow solid in 60 % yield; M.p. 136–139 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.96–7.84 (m, 2H), 7.61–7.56 (m, 3H), 7.50–7.54 (m, 1H), 7.44–7.37 (m, 1H), 7.20–7.11 (m, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.97, 158.96, 135.73, 131.56, 130.31, 129.84, 128.45, 126.06, 125.34, 124.41, 124.26, 122.65. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_3OCl$: 272.0591; Found: 272.0596.

N-ethyl-5-phenyl-1,3,4-oxadiazol-2-amine (**4i**) [26] obtained as white solid in 72 % yield; M.p. 109–111 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.84–7.80 (m, 2H), 7.78–7.70 (m, 1H), 7.56–7.49 (m, 3H), 3.30 - 3.26 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz,

DMSO-d_6) δ 163.93, 157.93, 130.87, 129.69, 125.54, 124.77, 37.90, 15.01. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{10}H_{12}N_3O$: 190.0980; Found: 190.0986.

N-propyl-5-phenyl-1,3,4-oxadiazol-2-amine (**4j**) obtained as yellow solid in 63 % yield; M.p. 97–99 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.83 - 7.78 (m, 3H), 7.55 - 7.50 (m, 3H), 3.21 (q, J = 6.9 Hz, 2H), 1.63 - 1.56 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.11, 157.85, 130.84, 129.68, 125.52, 124.79, 44.83, 22.55, 11.71. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{11}H_{14}N_3O$: 204.1137; Found 204.1142.

N-isobutyl-5-phenyl-1,3,4-oxadiazol-2-amine (**4k**) obtained as white solid in 60 % yield; M.p. 99–101 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.85–7.79 (m, 2H), 7.67 (d, J = 7.9 Hz, 1H), 7.55–7.48 (m, 3H), 3.59–3.52 (m, 1H), 1.66–1.46 (m, 2H), 1.19 (d, J = 6.5 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.63, 157.70, 130.82, 129.69, 125.50, 124.81, 50.92, 29.17, 20.44, 10.82. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{12}H_{16}N_3O$: 218.1293; Found: 218.1300.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132382.

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