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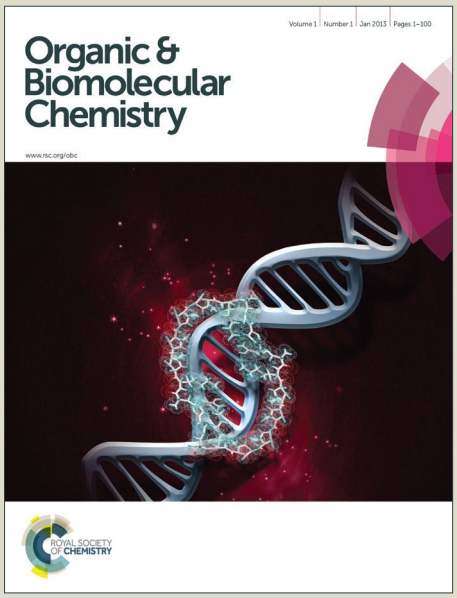

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ARTICLE

I_2 mediated synthesis of 5-substituted-3-methyl/benzyl-1,3,4-oxadiazol-2(*3H*)-ones via sequential condensation/ oxidative cyclization and rearrangement

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A simple and efficient iodine-assisted protocol for synthesis of 5-substituted-3-methyl/benzyl-1,3,4-oxadiazol-2(*3H*)-ones has been developed. The reaction involves a sequential condensation followed by tandem oxidative cyclization and rearrangement of readily available methyl/benzyl carbazates and aldehydes as starting substrates. The presence of iodine and base promotes an intramolecular C-O bond formation, followed by Chapman-like rearrangement of methyl/benzyl group at 90 °C in the hydrazone intermediate formed during the condensation step. This transition-metal-free approach has been adopted to generate a variety of oxadiazolones under mild conditions in good to excellent yields.

INTRODUCTION

Nitrogen and oxygen containing heterocycles are an important class of compounds, and constitute many biologically potent molecules.[1] In this series, 1,3,4-oxadiazol-2(*3H*)-one is a privileged five-membered heterocycle, and has a revitalized interest due to its broad pharmaceutical scope encompassing activities such as antibacterial,[2] antitubercular,[3] anti-tumor and anti HCV,[4] inhibition of selective monoamine oxidase B[5] and hormone sensitive lipase (HSL).[6] These rings are also important structural components of agrochemicals such as herbicides, and fungicides. The research on environmentally benign protoporphyrinogen oxidase (PPO) inhibiting molecules has led to the emergence of oxadiazon (**A**) and oxadiargyl (**B**) bearing a 1,3,4-oxadiazol-2(*3H*)-one core as commercial herbicides (**Fig. 1**).[7] In addition, oxadiazolones which have recently been reported as tetrazole and carboxylic acid bioisosteres,[8] can be applied to novel drug design. 5-substituted-3-methyl/benzyl-1,3,4-oxadiazol-2-ones are also found to act as an essential part of the pharmacophore in openers of large-conductance Ca^{2+}-activated potassium (Maxi-K) channels (**C**),[9] fungicides (**D**)[10] and function tools in chemical science (**Fig. 1**).

Since these molecules are of considerable interest owing to their wide commercial application, several strategies targeting the synthesis of 5-substituted-3-methyl/benzyl-1,3,4-oxadiazol-2-ones have been developed over the years.

Generally, these methodologies can be divided into three classes (Scheme 1): (a) substitution of 5-substituted-1,3,4-oxadiazol-2-(3H)-ones with alkyl halide[5] (b) cyclization of *N*-substituted-acylhydrazines in the presence of phosgene[9] or selenium-activated carbon monoxide[11] and *N*-acylhydrazine-1,2-dicarboxylates on heating[12] (c) transformations/conversions of heterocyclic rings.[13, 14]

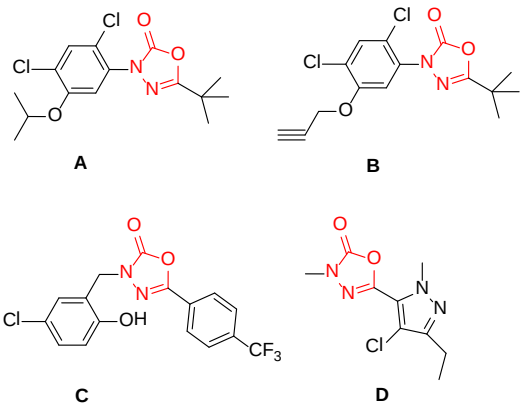

Fig. 1 Structures of pharmacologically potent 1,3,4-oxadiazol-2(*3H*)-ones

Although these procedures are useful for construction of 1,3,4-oxadiazolone cores, they suffer from limitations of multistep synthesis, use of expensive and toxic reagents and catalysts, elevated temperatures, long reaction time, laborious reaction procedures, and low product yields. Therefore development of mild, efficient, and atom-economical methods for direct installation of a methyl/benzyl moiety to the structurally diverse 1,3,4-oxadiazolone scaffold remains highly desirable.

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†Electronic Supplementary Information (ESI) available: [Copies of ^{1}H NMR, ^{13}C NMR, and HR-MS for all the synthesized compounds, ORTEP and associated X-ray crystallographic data for **4o**, have been included.]. See DOI: 10.1039/x0xx00000x

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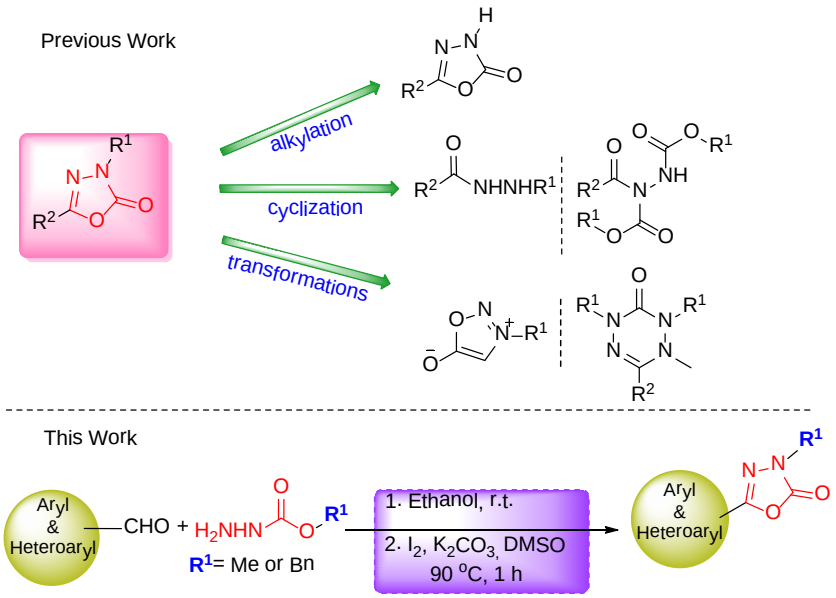

Scheme 1 An overview of various methods for the construction of 5-substituted-3-alkyl-1,3,4-oxadiazol-2(*3H*)-ones

In recent years, nonmetallic molecular iodine has emerged as a useful reagent in organic synthesis owing to its versatility, affordability, ready availability and environmental sustainability. Wu and co-workers have developed new synthetic routes for a variety of compounds using molecular iodine.[15-19] Several other groups have successfully employed iodine for the synthesis of pyrazole,[20] indole[21] and oxazole[22, 23] derivatives. More recently, various oxadiazole derivatives like symmetrical and unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles,[24,25] 2-amino-1,3,4-oxadiazoles[26], 3-amino-1,3,4-oxadiazoles[27] and α-keto-1,3,4-oxadiazoles[28] have also been synthesized using molecular iodine. However, preparation of 5-substituted-3-alkyl-1,3,4-oxadiazol-2(*3H)*-ones through direct oxidative cyclization of the corresponding carbazates is not yet reported in literature. Appreciating these findings, and anticipating the likelihood of an iminoether-amide rearrangement in 2-alkoxyoxadiazoles, we explored I_2-mediated tandem synthesis of 1,3,4-oxadiazol-2(*3H*)-one framework starting from methyl/benzyl carbazates and aldehydes as the substrates.

RESULT AND DISCUSSION

Transition metal-free approach that can construct the C–O bond through an intramolecular cyclisation[29, 30] motivated us initially, to investigate the oxidative cyclization of the purified 3-methoxy carbonylhydrazone (**3a**), prepared by condensation of benzaldehyde (**1a**) and methylcarbazate (**2**) in ethanol at room temperature (Table 1). Compound **3a** was treated with I_2 in the presence of K_2CO_3 in *N,N*-dimethylformamide (DMF) at 90 °C. On completion of reaction as seen on TLC, the workup afforded a single product in moderate yield (72%) which was purified by column chromatography, and confirmed as 3-methyl-5-phenyl-1,3,4-oxadiazol-2(*3H*)-one (**4a**) (Table 1). Apparently, the reaction seemed to involve the migration of methyl group from 2-methoxy-5-phenyl-1,3,4-oxadiazole generated *in situ* during the reaction, to *N*-3 resulting in **4a**. A similar 1,3-migratory rearrangement in oxadiazoles has previously been reported by Chapman and others.[31, 32] In order to confirm this observation, we carried out control experiment at 40 °C. At this temperature, the reaction went up till formation of oxadiazole, which was isolated and characterized by NMR.[33] However, on increasing the temperature to 90 °C, oxadiazole was found to rearrange to the isolated 1,3,4-oxadiazolone **4a**. Michel Golfier *et al.* earlier reported that in case of 2-alkoxy-5-aryl-l,3,4-oxadiazole as substrate, this rearrangement occurred near 180 °C in neat molten conditions (no reaction was found to occur in solution, at the same temperature).[31] Further, they also documented that this rearrangement was unusually fast in the solid crystalline state for some derivatives of 2-methoxy-5-aryl-l,3,4-oxadiazoles due to a double ionic mechanism, verified by theoretical and experimental results.[34] To the best of our knowledge, this is the first report where a solvent mediated rearrangement of 2-methoxy-5-substituted-1,3,4-oxadiazole derivatives at a much lower temperature is being demsonstrated.

In a quest to improve the yield of rearranged product **4a**, different solvents were screened. It was found that switching from DMF to DMSO (entry 2, Table 1) improved the yield of **4a** to 88%, while other solvents such as 1,4-Dioxane, Toluene, DimethylAcetamide, *N*-Methyl-2-pyrrolidone etc. were less effective for the reaction (entries 3-7). Encouraged by these preliminary results, we initiated further optimization with respect to catalyst, base, oxidant, and temperature. Use of

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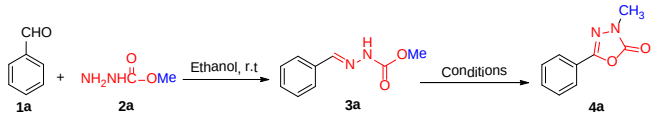
other catalysts known to furnish iodine like TBAI, DIB, and KI was found to be detrimental for the reaction, and gave **4a** in trace amounts (entries 8-10).

Table 1: Optimization of reaction conditions for synthesis of 3-methyl-5-phenyl-1,3,4-oxadiazol-2(*3H*)-one.[a, b]



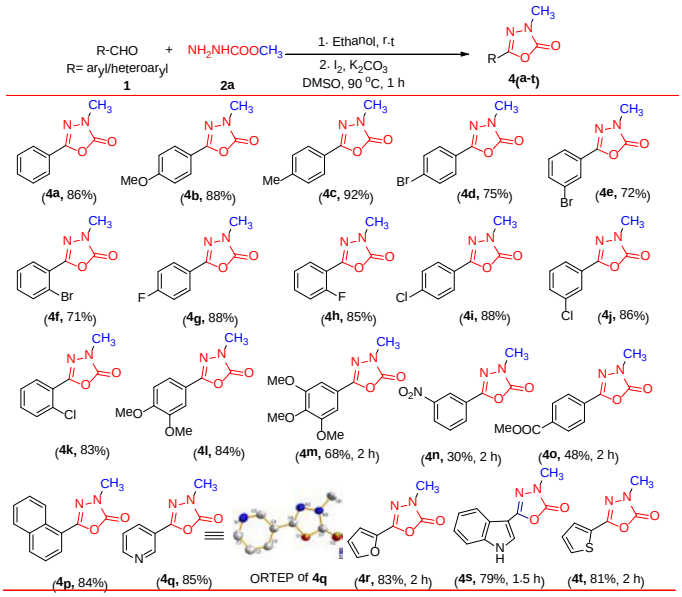
entry	reagent	base	solvent	yield[b] (%)
1.	Iodine	K_2CO_3	DMF	72
2.	**Iodine**	**K_2CO_3**	**DMSO**	**88**
3.	Iodine	K_2CO_3	1,4-Dioxane	Trace
4.	Iodine	K_2CO_3	Toluene	Trace
5.	Iodine	K_2CO_3	DMA	52
6.	Iodine	K_2CO_3	NMP	35
7.	Iodine	K_2CO_3	EtOAc	Trace
8.	TBAI	K_2CO_3	DMSO	Trace
9.	$PhI(OAc)_2$	K_2CO_3	DMSO	Trace
10.	KI	K_2CO_3	DMSO	18
11.	Iodine	Cs_2CO_3	DMSO	72
12.	Iodine	K_3PO_4	DMSO	29
13.	Iodine	KOH	DMSO	11
14.	Iodine	DBU	DMSO	Trace
15.	Iodine	NEt_3	DMSO	Trace
16.	Iodine	LiO^tBu	DMSO	Trace
17.	Iodine	K_2CO_3	DMSO	49[c], 38[d], 71[e],56[f]

[a] Reaction conditions: **1a** (0.18 mmol, 1.0 equiv.), **2a** (0.22 mmol, 1.0 equiv.), reagent (1.2 equiv.), base (3.0 equiv.) in DMSO, stirred at 90 °C in air for 1 hour. [b]HPLC yield. [c] I_2 used was 0.5 equiv. [d] K_2CO_3 used was 1.5 equiv. [e] 110 °C. [f] 70 °C.

Further optimization with respect to various organic and inorganic bases indicated potassium carbonate to be the base of choice, as it yielded the highest yield of **4a** (88% yield, entry 2). With other bases like Cs_2CO_3, K_3PO_4, KOH, DBU, Et_3N, and LiO^tBu (entries 11-17), the yields of product **4a** lowered significantly except for Cs_2CO_3 where moderate yield (72%, entry 11) was obtained. This suggested that organic bases were inferior to the inorganic carbonate bases for this reaction. Variation in amount of I_2 and K_2CO_3 was carried out next, and it was found that 1.2 equiv. of I_2 and 3 equiv. of K_2CO_3 were ideal for the reaction (entry 17). The effect of temperature on product yield was also monitored. Decreasing and increasing the temperature from 90 °C resulted in lower product yields (entry 17).

With the set of optimized conditions, we investigated if the developed protocol could be executed in one pot. **1a** and **2a** were taken in DMSO and heated at 90 °C. When formation of **3a** was seen (as evident by TLC), I_2 and K_2CO_3 were added in the same pot and reaction was run up to 4 hours at 90 °C. It was found that the overall conversion was less, and only 58% product was isolated. To improve the efficacy of the reaction, a sequential approach was adopted. In this, after completion of the first-step involving condensation of **1a** and **2a** in ethanol, the solvent (ethanol) was evaporated under reduced pressure and the resulting crude **3a** was directly subjected to the above optimized reaction conditions (I_2, K_2CO_3, DMSO, 90 °C) resulting in the formation of **4a** in an equally good yield (88 %, Table 1). After determining the best conditions for a sequential tandem reaction, we investigated its generality and scope by reacting a range of aryl and heteroaryl aldehydes with methylcarbazate (Table 2). Under the optimal reaction conditions, mono-substituted benzaldehydes bearing both electron-donating and electron-withdrawing groups (bromo, chloro, fluoro) at *ortho-*, *meta-*, and *para-* positions were converted to the corresponding 5-substituted phenyl-3-methyl-1,3,4-oxadiazol-2(*3H*)-ones (**4b–k**) in good to excellent yields. No acceleration or retardation in the reaction rate was observed upon changing the position of the substituent on the phenyl ring. With di- and tri-substituted benzaldehydes also, the corresponding products were obtained in moderate to high yields (**4l** and **4m**). It is believed that steric hindrance might be responsible for the reduced yield in case of tri-substituted benzaldehyde (**4m**). However, reaction with benzaldehydes bearing strong electron-withdrawing groups such as NO_2 gave low yield of 3-methyl-5-(3-nitrophenyl)-1,3,4-oxadiazol-2(3H)-one (**4n**) due to incomplete Chapman-rearrangement, and the intermediate compound, 2-methoxy-5-(3-nitrophenyl)-1,3,4-oxadiazole was also isolated along with **4n** (see supporting data). With nitro- substitution at *ortho-* and *para-* positions of benzaldehyde, the corresponding 1,3,4-oxadiazol-2(*3H*)-ones were not obtained, and the reaction mixture was found to decompose after 1 h of stirring at 90 °C. A similar behavior was observed with benzaldehydes substituted with CN, and CF_3 groups at *para-* position. Surprisingly, however, reaction went smoothly with *para-*COOMe substituted benzaldehyde probably due to a weaker electron withdrawing infuence, and moderate yield of **4o** was obtained.

Table 2: Synthesis of 3-methyl-5-substitued-1,3,4-oxadiazol-2(*3H*)-one derivatives[a, b]

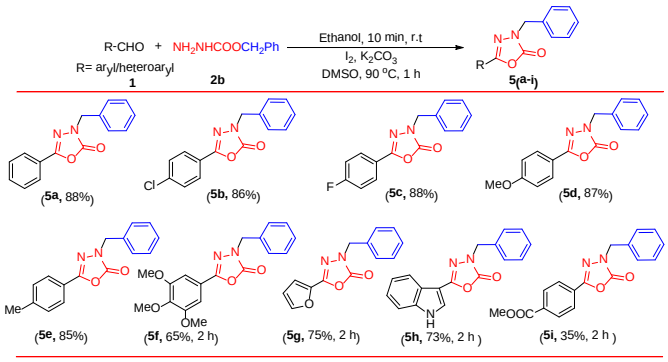


[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), iodine (0.6 mmol), K_2CO_3 (1.5 mmol) in DMSO (5 mL), stirred at 90 °C under air for 1 hour. [b]Isolated yield.

The reaction with other aromatic/heteroaromatic aldehydes such as α-naphthaldehyde, β-picolinaldehyde, furfural, β-indolylaldehyde and 2-formylthiophene also gave the desired products (**4p-4t**) in satisfactory yields. The structure of 3-methyl-5-(pyridin-3-yl)-1,3,4-oxadiazol-2(*3H*)-one (**4q**) (Table 2) was further confirmed by X-ray crystallography (see Supporting Information).

Fortified by the successful synthesis of an array of 3-methyl-5-substitued-1,3,4-oxadiazol-2(3H)-ones, we further extended the scope of this consecutive approach by replacing methylcarbazate with benzylcarbazate. Upon completion of condensation of benzylcarbazate **2b** and the corresponding aldehyde **1** in ethanol, the reaction mixture was concentrated, redissolved in DMSO, and treated with molecular iodine and potassium carbonate. Gratifyingly, stirring the resulting mixture at 90 °C for 1–2 h (see the Experimental Section) yielded the desired 3-benzyl-5-substitued-1,3,4-oxadiazol-2(3H)-ones (**5**) with a migrated benzyl group on the nitrogen of 1,3,4-oxazolidinone ring. This sequential synthesis protocol also endured substituted aromatics with electron withdrawing (chloro, fluoro) and electron donating groups (methyl, methoxy), as well as heteroaromatic aldehydes to provide a series of 3-benzyl-5-substitued-1,3,4-oxadiazol-2(*3H*)-one derivatives (**5b**-**5i**) in moderate yields (Table 3). With strong electron withdrawing groups such as NO_2 at *ortho-*, *meta-*, *para-* position or CN and CF_3 at *para-* position of substituted benzaldehydes, reaction with benzylcarbazate did not yield the desired 1,3,4-oxadiazol-2(*3H*)-ones. Instead, a decomposed reaction mixture was always observed. In contrast, *para-*COOMe substituted benzaldehyde tolerated the reaction conditions with benzyl carbazate as above with methylcarbazate, and yielded the corresponding oxadiazol-2-one **5i** albeit in low yield.

Table 3: Synthesis of 3-benzyl-5-substitued-1,3,4-oxadiazol-2(*3H*)-one derivatives[a, b]



[a]Reaction conditions: **1a** (0.5 mmol), **2b** (0.5 mmol), iodine (0.6 mmol), K_2CO_3 (1.5 mmol) in DMSO (5 mL), stirred at 90 °C under air for 1 hour. [b]Isolated yield.

Based on literature reports[24, 25] and control experiments, a plausible mechanism for the formation of 1,3,4-oxadiazolones is outlined in Figure 2. The first step involves (1) condensation of aldehyde and carbazate to afford the key hydrazone intermediate **A**. The imine nitrogen of **A** attacks I_2 to form an iminium iodide **B**. (2) Subsequently, during oxidative cyclization, the iminium carbon in **B** is attacked intramolecularly by the amidic oxygen to afford intermediate (**C**). (3) A base assisted elimination and aromatization of **C** occurs to generate oxadiazole (**D**) with the release of hydroiodic acid (HI). (4) Finally, a Chapman-like[31, 34] rearrangement at 90 °C provides the desired oxadiazolone product (**E**).

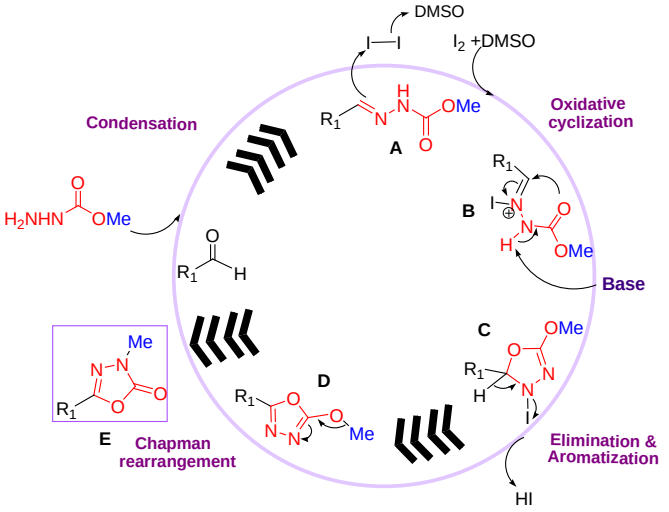


Fig. 2 Proposed mechanism for the formation of 5-substituted-3-alkyl-1,3,4-oxadiazol-2(*3H*)-ones

CONCLUSIONS

In summary, we have developed a method for the synthesis of 5-substituted-3-alkyl-1,3,4-oxadiazole-2-(*3H*)-ones starting from aldehydes and carbazates. The protocol involves a sequential condensation, oxidative cyclization, and a facile Chapman-like rearrangement in a tandem manner. The strategy is highly economical, and uses stoichiometric amounts of molecular iodine and potassium carbonate for effecting the reaction. It boasts of a transition metal-free route, and is highly versatile for synthesising a library of substituted-1,3,4-oxadiazole-2-(3H)-one derivatives in good to excellent yields.

EXPERIMENTAL SECTION

General Information:

All reactions were carried out under an air atmosphere in oven-dried round bottom flasks. Melting points were determined in open glass capillaries in an electrical melting point apparatus, and were uncorrected. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on a 0.25 mm silica gel plates (60F–254) and visualized under UV illumination at 254 nm. Further visualization was achieved by iodine vapour adsorbed on silica gel depending on the product type. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was performed on silica gel 100–200 mesh using a mixture of hexane and ethyl acetate as eluent, an isolated compounds were characterized

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by ^{1}H NMR, ^{13}C{1H} NMR, HRMS. NMR spectra for all the samples were measured in deuterochloroform ($CDCl_3$) and dimethylsufoxide-d_6 (DMSO-d_6). ^{1}H and ^{13}C-NMR spectra were recorded at ambient temperature on 300 MHZ and 75 MHz spectrometer using tetramethylsilane (TMS) as internal reference. The chemical shifts are quoted in δ units, parts per million (ppm) up field from the signal of internal TMS. ^{1}H NMR data is represented as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet), integration and coupling constant(s) *J* in Hertz (Hz). High resolution mass spectra (HRMS) were recorded on a Mass spectrometer using electrospray ionization-time of flight (ESI-TOF) reflectron experiments.

General procedure:

To a stirred solution of aldehyde (**1**, 0.5 mmol) in ethanol (1 mL), carbazate (**2**, 0.5 mmol) was added. The contents were stirred at room temperature until condensation was complete (monitored by TLC). Thereafter, the solvent was evaporated under reduced pressure, and the resulting residue was re-dissolved in dimethylsufoxide (DMSO) (5 mL), followed by addition of potassium carbonate (1.5 mmol) and iodine (0.6 mol) in sequence. The reaction mixture was stirred at 90 °C until complete conversion was observed (monitored by TLC, 1–2 h). After cooling to room temperature, it was treated with 5% $Na_2S_2O_3$ (20 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified through silica gel column chromatography using a mixture of ethyl acetate and hexane (0.7:9.3 to 2:8) as eluent to afford the corresponding 5-substituted-3-methyl/benzyl-1,3,4-oxadiazol-2(*3H*)-ones **4** and **5** in 65-92% yield.

3-methyl-5-phenyl-1,3,4-oxadiazol-2(*3*H)-one (4a):

0.5 mmol scale, yield 76 mg, 86%; white crystalline solid, m.p. 97-99 °C (lit.[12] m.p. 98.2-99.8 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (s, 2H), 7.42 (d, 3H, *J* = 7.2 Hz), 3.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.53, 152.88, 131.38, 128.87, 125.41, 123.75, 32.60; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_9N_2O_2$ 177.0659, found 177.0658.

5-(4-methoxyphenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4b):

Yield 91 mg, 88%; white solid, m.p. 132-134 °C (lit.[14] m.p. 133-135 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.76 (d, 2H, *J* = 8.4 Hz), 6.96 (d, 2H, *J* = 8.7 Hz), 3.86 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 162.20, 153.81, 153.21, 127.34, 116.31, 114.44, 55.44, 32.64; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{10}H_{11}N_2O_3$ 207.0764, found 207.0764.

3-methyl-5-(p-tolyl)-1,3,4-oxadiazol-2(*3*H)-one (4c):

Yield 87 mg, 92%; white crystalline solid, m.p. 105-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.61 (d, 2H, *J* = 7.2 Hz), 7.19 (d, 2H, *J* = 6.9 Hz), 3.42 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.49, 153.01, 141.83, 129.49, 125.33, 120.95, 32.48, 21.43; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{10}H_{10}N_2NaO_2$ 213.0634, found 213.0637.

5-(4-bromophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4d):

Yield 95 mg, 75%; white crystalline solid, m.p. 134-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.63 (d, 2H, *J* = 8.4 Hz), 7.56 (d, 2H, *J* = 8.4 Hz), 3.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.41, 152.27, 132.28, 126.91, 126.07, 122.71, 32.79; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8BrN_2O_2$ 254.9764, found 254.9765

5-(3-bromophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4e):

Yield 91 mg, 72%; white solid, m.p. 97-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.97 (s, 1H), 7.74 (d, 1H, *J* = 7.8 Hz), 7.62 (d, 1H, *J* = 8.1 Hz), 7.36-7.31 (m, 1H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.40, 151.73, 134.46, 130.53, 128.45, 125.67, 124.06, 123.07, 32.84; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8BrN_2O_2$ 254.9764, found 254.9768.

5-(2-bromophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4f):

Yield 90 mg, 71%; white solid, m.p. 70-71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.70 (d, 2H, *J* = 7.5 Hz), 7.41-7.33 (m, 2H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.40, 151.77, 134.76, 132.22, 130.40, 127.55, 124.67, 120.72, 32.88; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8BrN_2O_2$ 254.9764, found 254.9769.

5-(4-fluorophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4g):

Yield 85 mg, 88%; white crystalline solid, m.p. 87-89 °C (lit.[14] mp 86-88 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.71-7.67 (m, 2H), 7.07-7.01 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.50 (d, $^{1}J_{CF}$ = 251.2 Hz), 153.48, 152.21, 127.75 (d, $^{3}J_{CF}$ = 9 Hz), 120.11 (d, $^{4}J_{CF}$ = 3.7 Hz), 116.24 (d, $^{2}J_{CF}$ = 21.7 Hz), 32.63; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8FN_2O_2$ 195.0564, found 195.0565.

5-(2-fluorophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4h):

Yield 82 mg, 85%; white crystalline solid, m.p. 62-64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.64-7.59 (m, 1H), 7.37-7.24 (m, 1H), 7.14-7.07 (m, 2H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.73 (d, $^{1}J_{CF}$ = 257.2 Hz), 153.09, 149.61, 149.57, 133.54 (d, $^{3}J_{CF}$ = 8.4 Hz), 128.25, 124.51 (d, $^{4}J_{CF}$ = 3.7 Hz), 116.82 (d, $^{2}J_{CF}$ = 20.2 Hz), 112.13 (d, $^{2}J_{CF}$ = 11.1 Hz), 32.71; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8FN_2O_2$ 195.0564, found 195.0564.

5-(4-chlorophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4i):

Yield 92 mg, 88%; white crystalline solid, m.p. 135-137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.73 (d, 2H, *J* = 8.4 Hz), 7.42 (d, 2H, *J* = 8.4 Hz), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.45, 152.21, 137.68, 129.33, 126.78, 122.27, 32.77; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8ClN_2O_2$ 211.0269, found 211.0268.

5-(3-chlorophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4j):

Yield 90 mg, 86%; white solid, m.p. 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.75 (s, 1H), 7.65 (d, 1H, *J* = 6.9 Hz), 7.43-7.38 (m,

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2H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.33, 151.75, 135.07, 131.45, 130.30, 129.33, 125.42, 123.54, 32.78; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8ClN_2O_2$ 211.0269, found 211.0269.

5-(2-chlorophenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4k):

Yield 87 mg, 83%; white crystalline solid, m.p. 83-85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.73 (d, 1H, *J* = 6.9 Hz), 7.47-7.31 (m, 3H), 3.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.10, 150.93, 132.21, 131.97, 131.34, 129.68, 126.94, 122.47, 32.72; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8ClN_2O_2$ 211.0269, found 211.0272.

5-(3,4-dimethoxyphenyl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4l):

Yield 99 mg, 84%; white solid, m.p. 145-148 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.42 (dd, 1H, J_1 = 8.4 Hz, J_1 = 2.1 Hz), 7.31 (d, 1H, *J* = 1.8 Hz), 6.92 (d, 1H, *J* = 8.4 Hz), 3.93 (s, 6H), 3.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.74, 153.11, 151.86, 149.29, 119.23, 116.27, 111.06, 107.88, 56.00, 32.63; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{11}H_{13}N_2O_4$ 237.0870, found 237.0870.

3-methyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2(*3*H)-one (4m):

Yield 90 mg, 68%; white solid, m.p. 135-137 °C (lit.[12] m.p. 136.9-138.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.06 (s, 2H), 3.90 (s, 9H), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.59 (here three quaternary carbon merged and gave one peak), 152.90, 140.90, 118.76, 102.71, 60.90, 56.22, 32.66; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{12}H_{15}N_2O_5$ 267.0975, found 267.0974.

3-methyl-5-(3-nitrophenyl)-1,3,4-oxadiazol-2(*3*H)-one (4n):

Yield 32 mg, 30%; white solid, m.p. 133-135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.70 (s, 1H), 8.36 (d, 1H, *J* = 6.3 Hz), 8.14 (d, *J* = 6.3 Hz), 7.70 (s, 1H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.20, 151.11, 148.65, 130.91, 130.66, 125.87, 125.54, 120.62, 33.01; (ESI) *m/z* $[M+H]^+$ calc. for $C_9H_8N_3O_4$ 222.0509, found 222.0528.

Methyl 4-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl) benzoate(4o):

Yield 56 mg, 48%; white solid, m.p. 153-155 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.13 (d, 2H, *J* = 8.1 Hz), 7.90 (d, 2H, *J* = 8.1 Hz), 3.95 (s, 3H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.03, 153.47, 152.24, 132.63, 130.17, 127.58, 125.46, 52.45, 32.87; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{11}H_{10}N_2NaO_4$ 257.0533, found 257.0538.

3-methyl-5-(naphthalen-2-yl)-1,3,4-oxadiazol-2(*3*H)-one (4p):

Yield 95 mg, 84%; white crystalline solid, 110-113 °C (lit.[12] m.p. 112-115 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 8.69 (d, 1H, *J* = 8.1), 7.72-7.64 (m, 3H), 7.43-7.34 (m, 2H), 7.22 (t, 1H, *J* = 7.6), 3.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.13, 153.01, 133.65, 132.33, 129.18, 128.80, 127.92, 127.58, 126.51, 125.45, 124.76, 119.62, 32.74; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{13}H_{11}N_2O_2$ 227.0815, found 227.0815.

3-methyl-5-(pyridin-3-yl)-1,3,4-oxadiazol-2(*3*H)-one (4q):

Yield 75 mg, 85%; pale yellow crystalline solid, m.p. 124-127 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 9.08 (t, 1H, *J* = 1.5 Hz), 8.74 (dd, 1H, J_1 = 4.8 Hz, J_2 = 1.5 Hz), 8.01 (dt, 1H, J_1 = 8.1 Hz, J_2 = 2.1 Hz), 7.43 (dd, 1H, J_1 = 8.1 Hz, J_2 = 4.8 Hz), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$):153.14, 152.03, 150.91, 146.67, 132.58, 123.59, 120.22, 32.77; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_8H_8N_3O_2$ 178.0611, found 178.0611.

5-(furan-2-yl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4r):

Yield 69 mg, 83%; white solid, m.p. 92-95 (lit.[14] m.p. 91-93 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.59 (dd, 1H, J_1 = 1.8 Hz, J_2 = 0.6 Hz), 6.97 (dd, 1H, J_1 = 3.6 Hz, J_2 = 0.6 Hz), 6.56 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.8 Hz), 3.5 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 152.79, 146.52, 145.55, 138.93, 113.44, 111.90, 32.81; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_7H_7N_2O_3$ 167.0451, found 167.0456.

5-(1H-indol-2-yl)-3-methyl-1,3,4-oxadiazol-2(*3*H)-one (4s):

Yield 84 mg, 79%; pale yellow solid, m.p. 128-131 °C; ^{1}H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): 10.90 (s, 1H), 7.96 (d, 1H, *J* = 6.9 Hz), 7.63 (s, 1H), 7.39 (d, 1H, *J* = 6.9 Hz), 7.20-7.11 (m, 2H,) 3.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ and DMSO-d_6): 148.76, 146.91, 131.84, 121.92, 119.04, 118.28, 116.52, 115.79, 107.34, 95.69, 27.73; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{11}H_{10}N_3O_2$ 216.0768, found 216.0767.

3-methyl-5-(thiophen-2-yl)-1,3,4-oxadiazol-2(*3*H)-one (4t):

Yield 74 mg, 81%; white solid, m.p. 106-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.59 (s, 1H), 6.97 (d, 1H, *J* = 3.6 Hz), 6.56-6.55 (m, 1H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 152.79, 146.51, 145.55, 138.92, 113.44, 111.90, 32.80; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_7H_7N_2O_2S$ 183.0223, found 183.0220.

3-benzyl-5-phenyl-1,3,4-oxadiazol-2(*3*H)-one (5a)

Yield 111 mg, 88%; white crystalline solid, m.p. 114-116 °C (lit.[12] mp 112-114 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.84 (d, 2H, J_1 = 6.6 Hz), 7.48-7.38 (m, 8H), 4.98 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.57, 153.35, 135.01, 131.54, 128.91, 128.87, 128.39, 128.33, 125.71, 123.88, 49.79; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{15}H_{13}N_2O_2$ 253.0972, found 253.0971.

3-benzyl-5-(4-chlorophenyl)-1,3,4-oxadiazol-2(*3*H)-one (5b):

Yield 121 mg, 86%; white solid, m.p. 89-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (d, 2H, *J* = 8.4 Hz), 7.31-7.25 (m, 7H), 4.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.33, 152.53, 137.76, 134.84, 129.31, 128.90, 128.46, 128.36, 126.97, 122.33, 49.86; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{15}H_{11}ClN_2NaO_2$ 309.0401, found 309.0406.

3-benzyl-5-(4-fluorophenyl)-1,3,4-oxadiazol-2(*3*H)-one (5c):

Yield 119 mg, 88%; white solid, m.p. 93-95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.82-7.78 (m, 2H), 7.42-7.32 (m, 5H), 4.93 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.62 (d, $^1J_{CF}$ = 251.4 Hz), 153.44, 152.60, 134.89, 128.88, 128.43, 128.34, 127.99 (d, $^1J_{CF}$ = 8.8 Hz), 120.19, 116.28 (d, $^1J_{CF}$ = 22.3 Hz), 49.80; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{15}H_{11}FN_2NaO_2$ 293.0697, found 293.0701.

3-benzyl-5-(4-methoxyphenyl)-1,3,4-oxadiazol-2(*3*H)-one (5d):

Yield 123 mg, 87%; white solid, m.p. 116-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.75 (d, 2H, *J* = 8.7 Hz), 7.42-7.34 (m, 5H), 6.95 (d, 2H, *J* = 8.7 Hz) 4.94 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 162.22, 153.67, 153.43, 135.12, 128.84, 128.50, 128.29, 127.48, 116.31, 114.39, 55.43, 49.67; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{16}H_{14}N_2NaO_3$ 305.0897, found 305.901.

3-benzyl-5-(*p*-tolyl)-1,3,4-oxadiazol-2(*3*H)-one (5e):

Yield 117 mg, 88%; white solid, m.p. 96-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 7.68 (d, 2H, *J* = 7.5 Hz), 7.41-7.31 (m, 5H), 7.22 (d, 2H, *J* = 7.8 Hz), 4.92 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.63, 153.57, 142.09, 135.07, 129.61, 128.84, 128.33, 128.31, 125.69, 121.12, 49.73, 21.59; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1128.

3-benzyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2(*3*H)-one (5f):

Yield 111 mg, 65%; pale yellow solid, m.p. 106-109 °C (lit.[12] m.p. 107-110 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 7.40-7.35 (m, 5H), 7.05 (s, 2H), 4.95 (s, 2H), 3.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): 153.61, 153.51, 153.18, 141.07, 135.00, 128.85, 128.44, 128.34, 128.17, 126.33, 118.84, 103.00, 60.92, 56.28, 49.74; HRMS (ESI) *m/z* $[M+H]^+$ calc. for $C_{18}H_{19}N_2O_5$ 343.1288, found 343.1288.

3-benzyl-5-(furan-2-yl)-1,3,4-oxadiazol-2(*3*H)-one (5g):

Yield 91 mg, 75%; light brown semi solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (dd, 1H, J_1 = 1.8 Hz, J_2 = 0.9 Hz), 7.43-7.33 (m, 5H), 6.96 (dd, 1H, J_1 = 3.3 Hz, J_2 = 0.6 Hz), 6.53 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.8 Hz), 4.94 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 152.62, 146.72, 145.61, 138.95, 134.78, 128.87, 128.44, 128.39, 113.63, 111.95, 49.92; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{13}H_{10}N_2NaO_3$ 265.0584, found 265.0587.

3-benzyl-5-(1H-indol-3-yl)-1,3,4-oxadiazol-2(3H)-one (5h):

Yield 99 mg, 68%; pale yellow solid, m.p. 155-158; ^{1}H NMR (300 MHz, DMSO-d_6): 11.96 (s, 1H), 8.05 (s, 1H), 7.88 (d, 1H, *J* = 7.5 Hz), 7.52 (d, 1H, *J* = 7.5 Hz), 7.40-7.34 (m, 5H), 7.25-7.20 (m, 2H), 4.97 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): 153.18, 151.87, 136.92, 136.35, 129.17, 128.42, 128.33, 128.15, 123.90, 123.38, 121.60, 120.43, 112.93, 99.87, 49.22; HRMS (ESI) *m/z* $[M+Na]^+$ calc. for $C_{17}H_{13}N_3NaO_2$ 314.0900, found 314.0902.

Methyl 4-(4-benzyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)benzoate(5i):

Yield 54 mg, 35%; white solid, m.p. 120-122 °C; ^{1}H NMR (300 MHz, CDCl3): 8.10 (d, 2H, J = 8.1 Hz), 7.88 (d, 2H, J = 8.1 Hz), 7.41-7.36 (m, 5H), 4.96 (s, 2H), 3.93 (s, 3H); 13C NMR (75 MHz, CDCl3):166.05, 153.29, 152.49, 134.71, 132.64, 130.11, 128.92, 128.51, 128.39, 127.61, 126.97, 125.60, 65.35, 52.45, 49.95; HRMS (ESI) m/z $[M+Na]^+$ calc. for $C_{17}H_{14}N_2NaO_4$, 333.0846 found 333.0843.

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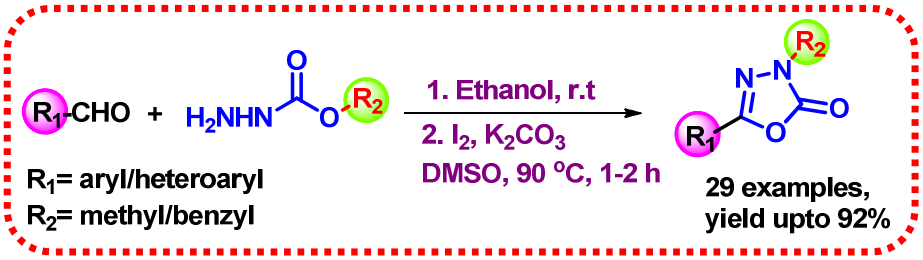

- One-pot tandem approach
- Transition Metal-free synthesis
- High yield