Efficient oxidative cyclisation of acid hydrazides to 2,5-disubstituted 1,3,4-oxadiazoles catalysed by Bu_4NI with *t*-BuOOH as oxidant

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Acid hydrazides or araldehyde *N*-acylhydrazones can be converted in good yields to, respectively, symmetrical or unsymmetrical, 2,5-disubstituted 1,3,4-oxadiazoles at 60 °C by a Bu_4NI-catalysed procedure which requires the presence of a base and 2.5 equiv. of *t*-butyl hydroperoxide.

Keywords: hydrazides, *N*-acylhydrazones, oxadiazoles, oxidation, metal-free reactions

The 2,5-disubstituted, 1,3,4-oxadiazole ring system as a basic structure unit occurs in many biologically active natural and synthetic compounds as well as in optoelectronic functional materials.[1–5] For example, raltegravir, a clinically used antiretroviral drug for the treatment of HIV infection, possesses the 2,5-disubstituted, 1,3,4-oxadiazole ring system.[6] As a consequence, extensive efforts have been directed toward the development of methods for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles, including cyclodehydration of 1,2-diacylhydrazines in a dehydrating media or in the presence of an acidic catalyst, such as $POCl_3$,[7] TsCl,[8] or silica sulfuric acid;[9] oxidative cyclisation of N-acylhydrazones with various oxidising agents such as $Cu(OTf)_2$,[10] NCS[11] or Dess–Martin reagent;[12] and one-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from acid hydrazines and carboxylic acid derivatives or aldehydes promoted by ceric ammonium nitrate,[13] permanganate under microwave conditions,[14] or trichloroisocyanuric acid.[15]

Acid hydrazides can be oxidised to aldehydes or carboxylic acid derivatives with various oxidants, such as tetravalent lead reagents,[16] hypervalent iodine compounds,[17] permanganate,[18] a copper(II) catalyst,[19] ceric ammonium nitrate[20] or *N*-bromosuccinimide.[21] In some cases, *N*, *N*′-diacylhydrazines can be obtained with oxidising reagents such as oxone,[22] halogens,[23] or aryl sulfonyl peroxides.[24,25] To our knowledge, only a few papers mentioned the transformation of acid hydrazides to 2,5-disubstituted, 1,3,4-oxadiazoles as byproducts, albeit in very low yields.[16]

In recent years, catalytic oxidative organic transformations under metal free conditions, especially using I_2 or iodides as catalysts, have drawn considerable attention.[26–28] Systems like Bu_4NI*t*-butyl hydroperoxide (TBHP) and I_2\TBHP have been widely used for the formation of C–O,[29–31] C–N[32–34] bonds and heterocycles.[35–36] Inspired by these developments and in continuation of our efforts on metal free oxidative reactions,[37–39] we now report an efficient procedure for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from acid hydrazides or *N*-acylhydrazones catalysed by Bu_4NI with TBHP as an oxidant.

A screen of suitable conditions for the one pot transformation of acid hydrazides to symmetrical 2,5-disubstituted, 1,3,4-oxadiazoles was carried out with benzohydrazide **1a** as the test substrate and the results are shown in Table 1. Reaction of **1a** with a hexane solution of TBHP (2.5 equiv.) in MeOH at 60 °C in the presence of 10 mol% of Bu_4NI and 15 mol% of K_2CO_3 or 1,4-diazabicyclo-[2,2,2]-octane (DABCO) gave the known 2,5-diphenyl 1,3,4-oxadiazole **3a** in 47 and 22% yield, respectively (Table 1, entries 1 and 2). When mixed bases,

Table 1 Optimisation of reaction conditions[a] for the conversion of benzohydrazide **1a** to 2,5-diphenyl-1,3,4-oxadiazole **3a**

1a **3a**

Entry	I Source	Base	Oxidant	Solvent	Yield/%[b]
1	Bu_4I	K_2CO_3	TBHP	MeOH	47
2	Bu_4I	DABCO	TBHP	MeOH	25
3	Bu_4I	K_2CO_3/DABCO (1:1)	TBHP	MeOH	67
4	Bu_4I	K_2CO_3/DABCO (1:2)	TBHP	MeOH	75
5	Bu_4I	***K_2CO_3/DABCO (2:1)***	***TBHP***	***MeOH***	***87***
6	Bu_4I	Na_2CO_3/DABCO (2:1)	TBHP	MeOH	80
7	Bu_4I	Cs_2CO_3/DABCO (2:1)	TBHP	MeOH	83
8	Bu_4I	K_2CO_3/DBU (2:1)	TBHP	MeOH	65
9	Bu_4I	K_2CO_3/Et_3N (2:1)	TBHP	MeOH	Trace
10	Bu_4I	K_2CO_3/DABCO (2:1)	TBHP	CH_3CN	45
11	Bu_4I	K_2CO_3/DABCO (2:1)	TBHP	DMSO	38
12	Bu_4I	K_2CO_3/DABCO (2:1)	TBHP	$ClCH_2CH_2Cl$	Trace
13	NaI	K_2CO_3/DABCO (2:1)	TBHP	MeOH	Trace
14	I_2	K_2CO_3/DABCO (2:1)	TBHP	MeOH	39
15	Bu_4I	K_2CO_3/DABCO (2:1)	TBHP	MeOH	73[c]
16	Bu_4I	K_2CO_3/DABCO (2:1)	H_2O_2	MeOH	Trace
17	–	K_2CO_3/DABCO (2:1)	TBHP	MeOH	Trace
18	Bu_4I	–	TBHP	MeOH	Trace
19	Bu_4I	K_2CO_3/DABCO (2:1)	–	MeOH	Trace

[a] Reaction conditions: **1a** (1 mmol), I Source (0.1 mmol), base (0.15 mmol), oxidant (2.5 mmol), in solvent (3 mL) at 60 °C.
[b] Isolated yield.
[c] 70% TBHP in water was used.

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such as K_2CO_3/1,4-diazabicyclo-[2,2,2]-octane (DABCO) or K_2CO_3/1,8-diazabi-cyclo[5.4.0]-undec-7-ene (DBU), were used instead of K_2CO_3 alone, higher yields of product were obtained in most cases (Table 1, entries 3–8). However, when 10 mol% K_2CO_3 and 5 mol% triethylamine were employed in the reaction, no desired product was formed (Table 1, entry 9). It was found that 10 mol% K_2CO_3 and 5 mol% of DABCO was the best combination. Optimisation of the solvent revealed that MeOH was superior to CH_3CN, DMSO and $ClCH_2CH_2Cl$ (Table 1, entries 10–12). The use of Bu_4NI as catalyst provided the best result for this transformation (Table 1, entry 5). When other iodides were used as catalyst, the desired product **2a** was generated in low yield (Table 1, entries 13 and 14). The oxidant also showed a key role in this transformation and lower yields of products were isolated when 70% TBHP in water or H_2O_2 was used as the oxidant instead of TBHP solution in hexane (Table 1, entries 15 and16). Blank tests showed that the desired product was not formed in the absence of catalyst, base or oxidant (Table 1, entries 17–19). The optimised procedure was chosen as follows: reaction in MeOH at 60 °C for 4h in the presence of 10 mol% K_2CO_3, 5 mol% DABCO, 10 mol% BuN_4I and 2.5 equiv. of TBHP (entry 5).

Under the optimised conditions, the scope of the reaction was tested for the synthesis of other symmetric 2,5-disubstituted 1,3,4-oxadiazoles (Table 2). We were delighted to observe tat numerous useful functional groups were well tolerated, including alkyl, methoxy, halo and nitro substituents. When alkyl substituents, such as Me- or Me_3C-, were on the benzene ring, moderate to good yield of products were isolated (Table 2, entries 1–5). 4-Methoxylbenzohydrazide was so easily oxidised to *t*-butyl *p*-methoxyperoxybenzoate and only 45% of 2,5-bis(4-methoxyphenyl)- 1,3,4-oxadiazole **3f** was obtained (Table 2, entry 6). When an electron-withdrawing group (Cl, Br, I or NO_2) was on the benzene ring, good yields of product were obtained (Table 2, entries 7–11). With substrate **1l** a heteroaromatic hydrazide the desired 2,5-disubstituted 1,3,4-oxadiazole was also obtained in 55% yield (entry 12).

In an effort to synthesise unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles via the same procedure, crossed condensation of different acid hydrazides was then tested. However, treatment of a 1:1 mixture of acid hydrazide **1a** and **1g** with Bu_4NI/TBHP system under the optimised conditions gave a mixture of crossed condensation product **3p** and self condensation products **3a** and **3g** in 1:2.1:1.8 ratios.

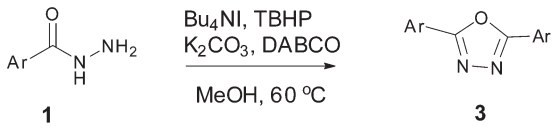
To make the method more practical, we explored Bu_4NI/TBHP catalytic system for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles from *N*-acylhydrazones. *N*-benzoylhydrazones derived from aromatic arylaldehydes bearing electron-donating or electron-withdrawing groups on the benzene ring could be smoothly converted into the corresponding products in yields ranging from 75 to 94% (Table 3, entries 2–7). Substrates derived from heterocyclic aldehydes, such as furfural and 2-thiophenecarboxaldehyde, also gave the corresponding products in moderate yields (Table 3, entries 8 and 9).

Acylhydrazones derived from different acid hydrazides were tested, too. The corresponding products were obtained in moderate to good yields (Table 3, entries 10–15). Especially, substrates derived from heterocyclic acid hydrazides, such as isonicotinyl hydrazide and 2-furoic hydrazide, showed good reactivity under this system (Table 3, entries 12, 13). Acylhydrazones derived from alkyl acid hydrazides, such as acetohydrazide and phenylacetic hydrazide, also reacted under the optimised conditions, giving 81% and 83% yields, respectively (Table 3, entries 14 and 15).

All but three of the 25 2,5-disubstituted 1,3,4-oxadiazoles that were synthesised were characterised by comparison of melting point and ^{1}H NMR with literature data. The three new compounds, **3o**, **3u** and **3v** were additionally characterised by ^{13}C NMR and Elemental Analysis.

To gain insights into the reaction pathway, several control experiments were carried out (Scheme 1). We first investigated the one-pot oxidation of acid hydrazides to symmetrical 2,5-disubstituted 1,3,4-oxadiazoles. When the reaction was performed for 25 min the generation of *N*-benzylidenebenzohydrazide **2a** could be identified as the expected intermediate.

Table 2 Yields[a] of symmetrical 2,5-disubstituted 1,3,4-oxadiazoles **3a–l** from acid hydrazides **1a–l** using the Bu_4NI/TBHP system (Method **A**[b])

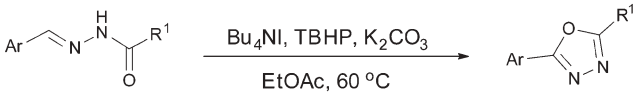


1 **3**

Entry	Ar	Yield/%
1	Ph	**3a**, 87
2	4-MeC_6H_4	**3b**, 85
3	3-MeC_6H_4	**3c**, 79
4	2-MeC_6H_4	**3d**, 83
5	4-$Me_3CC_6H_4$	**3e**, 68
6	4-$MeOC_6H_4$	**3f**, 45[c]
7	4-ClC_6H_4	**3g**, 80
8	2-ClC_6H_4	**3h**, 75
9	4-BrC_6H_4	**3i**, 81
10	3-IC_6H_4	**3j**, 86
11	3-$NO_2C_6H_4$	**3k** 84
12	2-Furyl	**3l**, 55

[a] Isolated yield.
[b] Reaction conditions: TBHP (2.5 mmol) in hexane was added dropwise over 2 h to a mixture of acid hydrazide (1 mmol), K_2CO_3 (0.1 mmol), DABCO (0.05 mmol) and Bu_4NI (0.1 mmol) in MeOH (3 mL) at 60 °C; the reaction was continued for another 2 h.
[c] Reaction was carried out at room temperature.

Table 3 Yields[a] of 2,5-disubstituted 1,3,4-oxadiazoles **3** from araldehyde *N*-acylhydrazone **2** using the Bu_4NI/TBHP system (Method **B**[b])



2 **3**

Entry	R^1	Ar	Yield [%]
1	Ph	Ph	**3a**,94
2	Ph	4-MeC_6H_4	**3m**,93
3	Ph	4-$MeOC_6H_4$	**3n**,94
4	Ph	3-$PhOC_6H_4$	**3o**,92
5	Ph	4-ClC_6H_4	**3p**, 91
6	Ph	4-BrC_6H_4	**3q**, 89
7	Ph	4-$NO_2C_6H_4$	**3r**, 83
8	Ph	2-Thienyl	**3s**, 88
9	Ph	2-Furyl	**3t**, 75
10	4-$MeOC_6H_4$	2-BrC_6H_4	**3u** 87
11	2-MeC_6H_4	3-$PhOC_6H_4$	**3v**, 89
12	4-Pyridinyl	Ph	**3w**, 80
13	2-Furyl	Ph	**3t**, 84
14	Me	Ph	**3x**, 81
15	Bn	Ph	**3y**, 83

[a] Isolated yield.
[b] Reaction conditions: *N*-acylhydrazone (0.5 mmol), K_2CO_3 (0.1 mmol), Bu_4NI (0.1 mmol), TBHP in water (1.25 mmol) in EtOAc (3 mL) at 60 °C for 1 h.

On the other hand, 1,2-dibenzoylhydrazine showed little reactivity under Method B (see Experimental), which confirmed that *N*-benzylidenebenzohydrazide is the main intermediate in this transformation (Scheme 1, **f**). Addition of 2,2,6,6-tetramethyl-1-piperidinyloxy(TEMPO), a radical-trapping reagent led to no formation of the desired product and as anticipated, the TEMPO adduct was obtained in 65% yield under the optimised conditions (Scheme 1, **a**). Similarly, if 1.2 equiv. of iodine were used instead of Bu_4NI/TBHP, no target product was obtained, too (Scheme 1, **b**). These observations implied that the direct oxidative cyclisation of acid hydrazides to symmetrical 2,5-disubstituted 1,3,4-oxadiazoles may involve a radical pathway. For the synthesis of **3a** from *N*-acylhydrazone **2a**, it was found that the radical-trapping reagent (TEMPO) had no effects on the yield of the desired product and if 1.2 equiv. of iodine were used instead of Bu_4NI/TBHP, excellent yields of the desired product could be obtained (Scheme 1, **c**, **d**). These results suggested that transformation of *N*-acylhydrazones to 2,5-disubstituted 1,3,4-oxadiazoles probably followed an iodine-catalysed mechanism. When *N*-benzylidenebenzohydrazide **2a** was reacted in the absence of base, no product was formed (Scheme 1, **e**). This result showed that base plays an important role in the oxidative cyclisation procedure.

On the basis of the results described above and previous reports,[16,34,40] a plausible mechanism is proposed in Scheme 2. For the one-pot transformation of hydrazide **1** to symmetrical 2,5-disubstituted 1,3,4-oxadiazoles **3**, aldehydes **4** may be formed first from hydrazide **1** following a radical pathway involving *t*-BuO. Condensation of the newly formed aldehyde **4** with hydrazide **1** gave *N*-acylhydrazone **2** *in situ*. The catalyst Bu_4NI was oxidised to I_2 by TBHP. Nucleophilic attack of the imine nitrogen of *N*-acylhydrazone **2** on molecular iodine led to cyclisation, as shown. The byproduct hydrogen iodide was then neutralised with a base and oxidised to iodine by TBHP to complete the catalytic cycle.

In conclusion, an efficient and simple procedure for the synthesis of symmetrical as well as unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles from acid hydrazides or *N*-acylhydrazones was developed. The reactions were carried out under mild conditions without the need of a transition-metal catalyst using easily available starting materials. Good functional group tolerance, mild reaction conditions and excellent yields of products make the procedure a good alternative for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.

Experimental

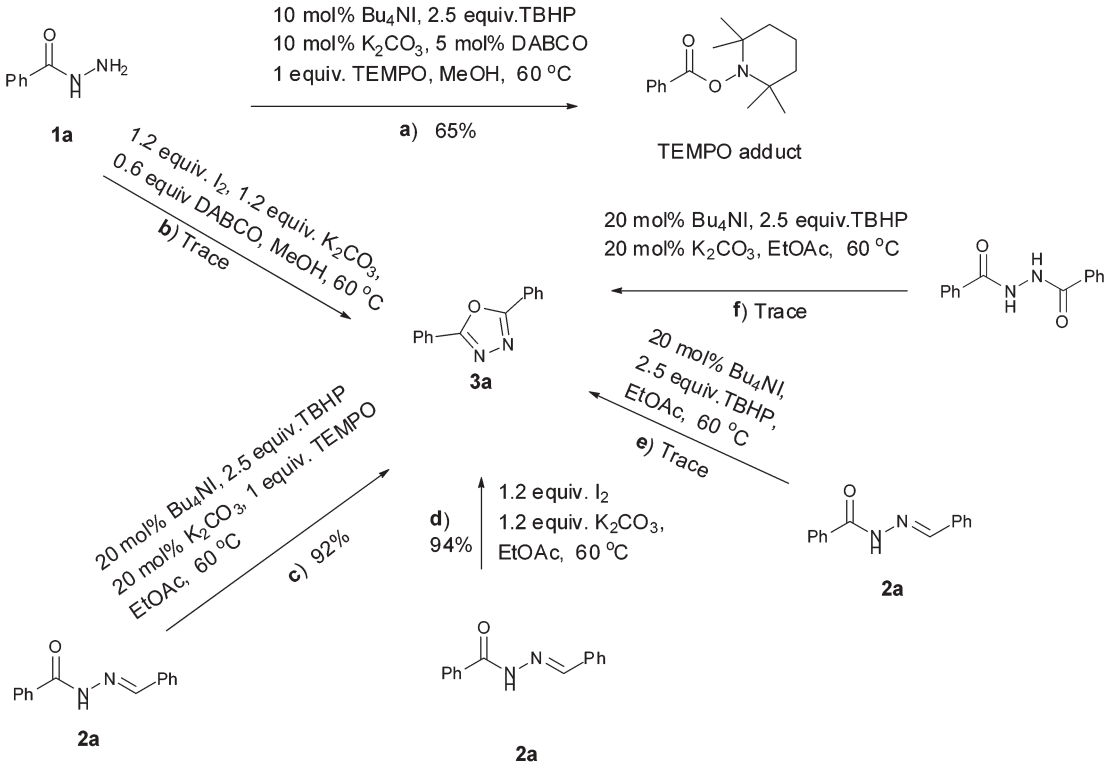
All solvents and reagents were obtained from commercially sources and used without further purification. NMR spectra were obtained on a Bruker Avance 500 spectrometer (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz) in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. Elemental analysis was performed at the elemental analysis of ISIC at EPFL. ESI-MS were recorded on a Thermal Finnigan TSQ Quantum ultra AM spectrometer using a TRB-5MS (30 m×0.25 mm×0.25 mm) column. Melting points were determined on a Yamato melting point apparatus Model MP-21. Silica gel (200–300 mesh) was used for column chromatographic separations and purifications. Petroleum ether (PE) refers to the fraction boiling at 60–90 °C. Most of the 2,5-disubstituted 1,3,4-oxadiazoles obtained are known compounds with physical and spectral properties in agreement with those reported in the literature closely.

Typical procedure

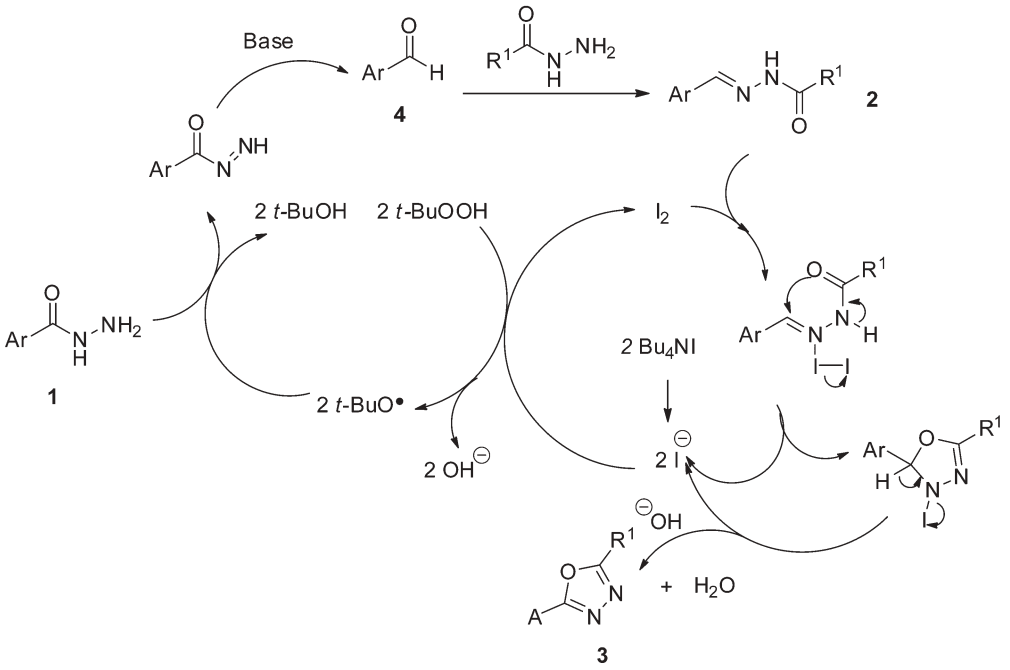
Preparation of acid hydrazides:[41] A mixture of carboxylic acid ester (10 mmol) and hydrazine hydrate (40.0 mmol, 80% in H_2O) in ethanol (20 mL) was refluxed overnight. After cooling to room temperature, the solution was concentrated *in vacuo* and the crude product was washed with hexane (2 × 10 mL) to give the corresponding acid hydrazide. Acid hydrazides **1b–m** all are known compounds and determined by comparison of melting points with literatures reported. **1a**, **1q**, **1r** were obtained from commercially sources and used without further purification.

Synthesis of N-acylhydrazones;general procedure[11]

N-acylhydrazones were prepared by the condensation of one equivalent of corresponding hydrazides and aldehydes in ethanolic medium



Scheme 1 Investigations into the reaction mechanism.



Scheme 2 Plausible mechanism of synthesis of 2,5-disubstituted 1,3,4-oxadiazoles.

under reflux condition for 10 h. The precipitates formed were filtered and washed with diethyl ether to afford the corresponding *N*-acylhydrazones. Most of the *N*-acylhydrazones obtained are known compounds with properties in close agreement with those reported in the literature. **2u** and **2v** are new compounds and ^{1}H NMR, ^{13}C NMR and HR-MS spectra data and elemental analyses are given.

N-(2-Bromobenzylidene)-4-methoxybenzohydrazide (**2u**): White solid, m.p. 164–165 °C (EtOH); ^{1}H NMR (DMSO-d_6): δ 11.99 (br, 1H, NH), 8.80 (s, 1H, CH), 7.92–8.00 (m, 3H, PhH), 7.67–7.68 (m, 1H, PhH), 7.35–7.45 (m, 2H, PhH), 7.04–7.06 (m, 2H, PhH), 3.83 (s, 3H, PhH); ^{13}C NMR: δ 163.05, 162.64, 145.79, 133.70, 133.63, 132.07, 130.12, 128.58, 127.68, 125.63, 123.95, 114.23, 55.93; HR-MS (*m/z*) (M+1) calcd for $C_{15}H_{13}BrN_2O_2$: 333.0168, found 333.0171.

N-(3-phenoxybenzylidene)-2-methylbenzohydrazide (**2v**): Light yellow solid, m.p. 156–158 °C (EtOH); ^{1}H NMR (DMSO-d_6): δ 11.74 (br, 1H, NH), 8.26 (s, 1H, CH), 7.35–7.48 (m, 6H, PhH), 7.25–7.32 (m, 2H, PhH), 7.15–7.19 (m, 2H, PhH), 7.05–7.10 (m, 2H, PhH), 6.96–6.97 (m, 1H, PhH); ^{13}C NMR: δ 165.702, 157.78, 147.08, 136.76, 136.36, 135.66, 130.69, 130.44, 127.91, 126.12, 124.35, 123.28, 120.83, 119.66, 119.49, 115.97; HR-MS (*m/z*) (M+1) calcd for $C_{21}H_{18}N_2O_2$: 331.1371, found 331.1372.

Preparation of anhydrous t-*butyl hydroperoxide in hexane*[42]

t-Butyl hydroperoxide in hexane was prepared according to the literature procedure with some modification. To a clean separatory funnel was added 10 mL of 70% TBHP in water, and hexane (12.5 mL) was added. The mixture was shaken several times and it should be noted that the gas produced in the process needed to be released quickly. Then, the aqueous layer was separated and the organic layer was dried with 4Å molecular sieves (5g) and stored in a brown glass bottle. The concentration of *t*-butyl hydroperoxide in hexane was determined by iodimetric analysis and the concentration found to be 5.03 M.

Method A: Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from acid hydrazides using a Bu$_4$NI/TBHP system: A 10 mL round-bottomed flask was charged with acid hydrazide (1 mmol), K_2CO_3 (0.1 mmol, 14 mg), DABCO (0.05 mmol, 6 mg), Bu_4NI (0.1 mmol, 37 mg) and MeOH (3 mL). The mixture was stirred at 60 °C and TBHP (2.5 mmol) was added dropwise over 2h; then the stirring was continued for another 2h. After the completion of the reaction, ethyl acetate (10 mL) was added and the mixture was washed with saturated $Na_2S_2O_3$ solution (5 mL), then with water (2×5 mL). The organic layer was dried by anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified on silica gel columns by using petroleum ether/ethyl acetate (10:1).

Method B: Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from araldehyde N-acylhydrazones using a Bu$_4$NI/TBHP system: A 10 mL round-bottomed flask was charged with *N*-acylhydrazone (0.5 mmol), K_2CO_3 (0.1 mmol, 14 mg), Bu_4NI (0.1 mmol, 37 mg), TBHP 70% in water (1.25 mmol) and ethyl acetate (3 mL). The mixture was stirred at 60 °C for 1h. After completion of the reaction, ethyl acetate (10 mL) was added and the mixture was washed with saturated $Na_2S_2O_3$ solution (5 mL), then with water (2×5 mL). The organic layer was dried by anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude products were purified on silica gel columns by using petroleum ether/ethyl acetate (10:1). All the products were characterised bymelting point and ^{1}H NMR; new compounds **3o**, **3u** and **3v** were additionally characterised by ^{13}C NMR and elemental analysis. Spectral data of the products are given below.

2,5-Diphenyl-1,3,4-oxadiazole (**3a**): White solid, m.p. 138–139 °C (lit.[11] 136–138 °C); ^{1}H NMR ($CDCl_3$): δ 7.53–7.58 (m, 6H, PhH), 8.17 (m, 4H, PhH).

2,5-Di-(p-tolyl)-1,3,4-oxadiazole (**3b**): White solid, m.p. 172–174 °C (lit.[12] 178 °C); ^{1}H NMR ($CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 4H, PhH), 7.33 (d, *J* = 8.0 Hz, 4H, PhH), 2.44 (s, 6H, CH_3).

2,5-Di-(m-tolyl)-1,3,4-oxadiazole (**3c**): White solid, m.p. 77–79 °C (lit.[10] 76–78 °C); ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 2H, PhH), 7.95 (d, *J* = 7.7 Hz, 2H, PhH), 7.43 (t, *J* = 7.7 Hz, 2H, PhH), 7.37 (d, *J* = 7.7 Hz, 2H, PhH), 2.47 (s, 6H, CH_3).

2,5-Di-(o-tolyl)-1,3,4-oxadiazole (**3d**): White solid, m.p. 127–128 °C (lit.[11] 123–125 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (m, 2H, PhH), 7.45 (m, 2H, PhH), 7.37 (m, 4H, PhH), 2.80 (s, 6H, CH_3).

*2,5-Bis-(4-*t*-butyl-phenyl)-1,3,4-oxadiazole* (**3e**): White solid, m.p. 139–140 °C (lit.[7] 145 °C); ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J* = 8.5, 4H, PhH), 7.54 (d, *J* = 8.5 Hz, 4H, PhH), 1.35 (s, 12H, CH_3).

2,5-Bis-(4-methoxyphenyl)-1,3,4-oxadiazole (**3f**): White solid, m.p. 158–160 °C (lit.[11] 158–160 °C); ^{1}H NMR ($CDCl_3$): δ 8.06 (d, *J* = 8.8 Hz, 4H, PhH), 7.03 (d, *J* = 8.8 Hz, 4H, PhH), 3.90 (s, 6H, CH_3).

2,5-Bis-(4-chlorophenyl)-1,3,4-oxadiazole (**3g**): White solid, m.p. 248–250 °C (lit.[11] 250–251 °C);. ^{1}H NMR ($CDCl_3$): δ 8.08 (d, *J* = 8.5 Hz, 4H, PhH), 7.53 (d, *J* = 8.5 Hz, 4H, PhH).

2,5-Bis-(2-chlorophenyl)-1,3,4-oxadiazole (**3h**): White solid, 97–98 °C (lit.[10] 94–96 °C); ^{1}H NMR ($CDCl_3$): δ 8.08 (d, *J* = 8.5 Hz, 4H, PhH), 7.53 (d, *J* = 8.5 Hz, 4H, PhH).

2,5-Bis-(4-bromophenyl)-1,3,4-oxadiazole (**3i**): White solid, m.p. 219–221 °C (lit.[43] 219–220 °C); ^{1}H NMR ($CDCl_3$): δ 8.00 (d, *J* = 8.5 Hz, 4H, PhH), 7.68 (d, *J* = 8.5 Hz, 4H, PhH).

2,5-Bis-(3-iodophenyl)-1,3,4-oxadiazole (**3j**): White solid, m.p. 233–235 °C (lit.[44] 230–233 °C); ^{1}H NMR ($CDCl_3$). δ 8.47 (s, 2H,

PhH), 8.12 (d, *J* = 7.7 Hz, 2H, PhH), 7.90 (d, *J* = 7.7 Hz, 2H, PhH), 7.28 (t, *J* = 7.7 Hz, 2H, PhH).

2,5-Bis-(3-nitrophenyl)-1,3,4-oxadiazole (**3k**): Light yellow solid, m.p. 226–228 °C (lit.[45] 225–227 °C); ^{1}H NMR ($CDCl_3$): δ 9.01 (s, 2H, PhH), 8.57 (m, 2H, PhH), 8.48 (m, 2H, PhH), 7.82 (t, *J* = 8.0 Hz, 2H, PhH).

2,5-Di-(furan-2-yl)-1,3,4-oxadiazole (**3l**): Yellow solid, m.p. 134–136 °C (lit.[10] 136–138 °C); ^{1}H NMR ($CDCl_3$): δ 7.68 (m, 2H, ArH), 7.25 (m, 2H, ArH), 6.63 (m, 2H, ArH).

2-p-Tolyl-5-phenyl-1,3,4-oxadiazole (**3m**): White solid, m.p. 124–125 °C (lit.[11] 121–122 °C); ^{1}H NMR ($CDCl_3$): δ 8.14–8.16 (m, 2H, PhH), 8.03–8.05 (m, 2H, PhH), 7.54–7.56 (m, 3H, PhH), 7.33–7.35 (m, 2H, PhH), 2.46 (s, 3H, CH_3).

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3n**): White solid, m.p. 148–149 °C (lit.[11] 149–150 °C); ^{1}H NMR ($CDCl_3$): δ 8.13–8.15 (m, 2H, PhH), 8.08–8.10 (m, 2H, PhH), 7.53–7.55 (m, 3H, PhH), 7.04–7.05 (m, 2H, PhH), 3.90 (s, 3H, CH_3).

2-(3-Phenoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**3o**): White solid, m.p. 129–130 °C; ^{1}H NMR ($CDCl_3$): δ 8.13–8.14 (m, 2H, PhH), 7.88–7.90 (m, 1H, PhH), 7.79 (s, 1H, PhH), 7.49–7.57 (m, 4H, PhH), 7.37–7.41(m, 2H, PhH), 7.10–7.20 (m, 2H, PhH), 7.08–7.09(m, 2H, PhH); ^{13}C NMR: δ 164.72, 164.13, 158.04, 156.48, 131.87, 130.63, 130.05, 129.13, 127.02, 125.47, 124.04, 123.78, 121.93, 121.65, 119.27, 116.95; Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.34; H, 4.40; N, 8.85%.

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**3p**): White solid, m.p. 161–162 °C (lit.[11] 161–162 °C); ^{1}H NMR ($CDCl_3$): δ 8.14–8.16(m, 2H, PhH), 8.09–8.11 (m, 2H, PhH), 7.52–7.57 (m, 5H, PhH).

2-(4-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (**3q**): White solid, m.p. 169–170 °C (lit.[11] 169–170 °C); ^{1}H NMR ($CDCl_3$): δ 8.13–8.15 (m, 2H, PhH), 8.01–8.03 (m, 2H, PhH, 7.68–7.70 (m, 2H, PhH), 7.55–7.57 (m, 3H, PhH).

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (**3r**): Yellow solid, m.p. 200–201 °C (lit.[10] 196–198 °C); ^{1}H NMR ($CDCl_3$): δ 8.41–8.43 (m, 2H, PhH), 834–8.35 (m, 2H, PhH), 8.15–8.18 (m, 2H, PhH), 7.56–7.62 (m, 3H, PhH).

2-(Thiophen-2-yl)-5-phenyl-1,3,4-oxadiazole (**3s**): White solid, m.p. 112–113 °C (lit.[11] 114–115 °C); ^{1}H NMR ($CDCl_3$): δ 8.12–8.14 (m, 2H, PhH), 7.85–7.86 (m, 1H, PhH), 7.54–8.59 (m, 4H, ArH), 7.20–7.22 (m, 1H, ArH).

2-(Furan-2-yl)-5-phenyl-1,3,4-oxadiazole (**3t**): White solid, m.p. 100–102 °C (lit.[11] 98–100 °C); ^{1}H NMR ($CDCl_3$): δ 8.13–8.15 (m, 2H, PhH), 7.68–7.69 (m, 1H, PhH), 7.52–8.57 (m, 3H, ArH), 7.25–7.26 (m, 1H, ArH), 6.64–6.65 (m, 1H, ArH).

2-(2-Bromophenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (**3u**): White solid, m.p. 139–141 °C; ^{1}H NMR ($CDCl_3$): δ 8.09–8.10 (m, 2H, PhH), 8.04–8.05 (m, 2H, PhH), 7.45–7.49 (m, 1H, PhH), 7.38–7.41 (m, 1H, PhH), 7.03–7.05 (m, 2H, PhH), 3.90 (s, 3H, CH_3); ^{13}C NMR: δ 165.10, 163.08, 162.55, 134.60, 132.41, 131.65, 128.92, 127.65, 125.40, 121.46, 116.18, 114.59, 55.52; Anal. Calcd for $C_{15}H_{11}BrN_2O_2$: C, 54.40; H, 3.35%; N, 8.46. Found: C, 54.35; H, 3.40; N, 8.35%.

2-(3-Phenoxyphenyl)-5-o-tolyl-1,3,4-oxadiazole (**3v**): White solid, m.p. 98–100 °C; ^{1}H NMR ($CDCl_3$): δ 8.01–8.03 (m, 1H, PhH), 7.86–7.88 (m, 1H, PhH), 7.77–7.78 (m, 1H, PhH), 7.49(t, *J* = 8.0 Hz, 1H, PhH), 7.33–7.45(m, 5H, PhH), 7.16–7.19(m, 2H, PhH), 7.07–7.09 (m, 2H, PhH), 2.75(s, 3H, CH_3); ^{13}C NMR: δ 165.01, 163.70, 158.10, 156.40, 138.51, 131.86, 130.64, 130.06, 129.02, 126.24, 125.53, 124.08, 122.89, 121.79, 121.57, 119.36, 116.83, 22.19; Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found C 76.70; H, 5.00; N, 8.47%.

4-(5-Phenyl-1,3,4-oxadiazol-2-yl)-pyridine (**3w**): White solid, m.p. 154–156 °C (lit.[14] m.p. 153 °C); ^{1}H NMR ($CDCl_3$): δ 8.86 (d, *J* = 5.9 Hz, 2H, ArH), 8.15–8.18 (m, 2H, ArH), 8.03–8.04 (m, 2H, PhH), 7.57–7.60 (m, 2H, PhH).

2-Methyl-5-phenyl-1,3,4-oxadiazole (**3x**): White solid, m.p. 114–116 °C (lit.[9] 116 °C); ^{1}H NMR ($CDCl_3$): δ 8.02 (d, *J* = 8 Hz, 2H, PhH), 7.46–7.53 (m, 3H, PhH), 2.61 (s, 3H, CH_3).

2-Benzyl-5-phenyl-1,3,4-oxadiazole (**3y**): White solid, m.p. 100–102 °C (lit.[46] 102.3–102.8 °C); ^{1}H NMR ($CDCl_3$): δ 8.00–8.02 (m, 2H, PhH), 7.47–7.52 (m, 3H, PhH), 7.34–7.38 (m, 4H, PhH), 7.29–7.31 (m, 1H, PhH), 4.29 (s, 2H, CH_2).

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