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$FeCl_3$ Catalyzed Synthesis of 2, 5-Disubstituted 1, 3, 4-Oxadiazoles

E. Pravardhan Reddy, Gangadhar Thalari*

Department of Chemistry, Osmania University, Hyderabad, **INDIA**

Email:gangadharchemou@gmail.com

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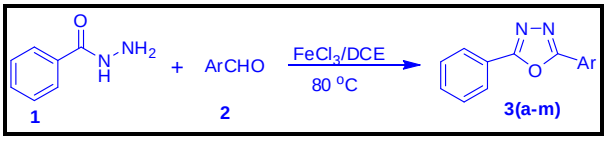
ABSTRACT

An efficient development for the one-pot synthesis of 2, 5-disubstituted 1, 3, 4-oxadiazoles have been developed using $Fecl_3$ as catalyst. The reaction was successful with a broad range of substrates such as aldehyde and aryl hydrazides to afford the corresponding unsymmetrical 2, 5-disubstituted 1, 3, 4-oxadiazoles. This is easy going reaction conditions, cost-effective reagents and short reaction time are advantages of this method.

Graphical Abstract



Oxidative Cyclization of N-arylhydrazones.

Keywords: $FeCl_3$, Aldehyde, 1, 3,4-Oxadiazoles, Oxidative Cyclization.

INTRODUCTION

Nitrogen containing aromatic compounds has gained considerable importance globally not only due to their prevalence in natural products [1] but also due to their interesting pharmacological [2], photochemical and optoelectronic properties [3]. In particular, five-membered ring heterocycles are of great interest due to their inherent biological activity [4]. Among them, oxadiazoles are privileged scaffolds in different areas of medicinal, pesticidal, polymer and receptor agonists, diuretic and antifungal etc [5, 6]. A number of compounds containing an oxadiazole moiety are in late stage clinical trials including zibotentan and furamizole. On the other hand, raltegravir, an antiretroviral drug for the treatment of HIV infection, has been launched into the market (Figure 1) [7].

The above diverse ranges of applications have driven the scientific community to develop novel and efficient synthetic methods for their preparation. As a result, there have been some reports on the preparation of 1,3,4-oxadiazoles, which involve mainly an oxidative cyclization of *N*-arylhydrazones using various oxidizing agents [8], cyclodehydration of 1, 2-diacylhydrazines [9] and a direct coupling of carboxylic acids or acyl chlorides with acid hydrazides or hydrazine's [10].

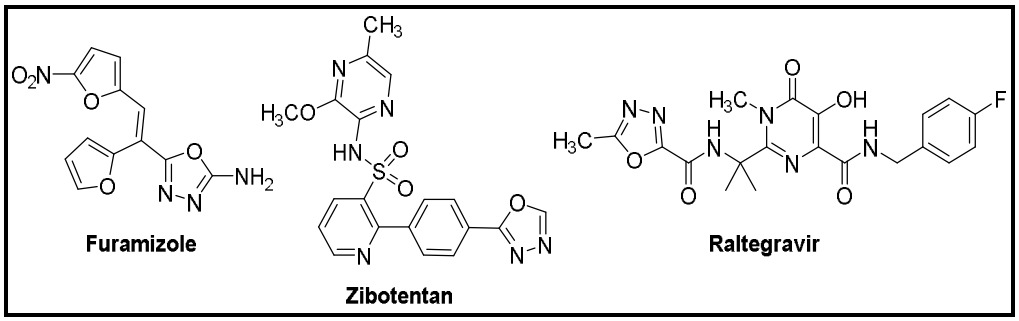


Figure 1. Oxadiazole containing drugs.

Despite of their potential use in oxadiazole synthesis, the majorities of them suffer from major drawbacks such as the use of strong alkaline or acidic conditions, highly toxic and corrosive reagents and also involves the use of costly reagents, elevated temperatures and longer reaction times. Inspired by the potential application of hypervalent metal reagents in organic synthesis, we would like to explore the readily available $FeCl_3$ reagents for the facile synthesis of 1, 3, 4-oxadiazoles.

MATERIALS AND METHODS

^1H NMR ^{13}C NMR spectra were recorded on Bruker Avance 500 MHz, 400 MHz and 300 MHz. For ^1H NMR, tetramethylsilane (TMS) was used as internal standard (δ = 0) and the values are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet, brs = broad), and the coupling constants in Hz. For ^{13}C NMR, $CDCl_3$ (δ = 77.27) was used as internal standard and spectra were obtained with complete proton decoupling. Low-resolution MS and HRMS data were obtained using VG AutoSpec triple sector MS. Melting points were measured on Triad Scientific micro melting point apparatus.

General procedure: A mixture of aryl aldehyde (1 mmol) and benzhydrazide (1 mmol) was heated at 80^0C for 30 min and then cooled to 0^0C. To this mixture, $FeCl_3$ (1.2 mmol) were added in DCE. The resulting solution was allowed to stir for 1.5 h at 80^0C. Up on completion, the mixture was quenched with water and washed with sodium chloride solution and extracted with ethyl acetate. Removal of the solvent followed by purification on silica gel afforded the pure 1, 3, 4-oxadiazole.

2, 5-Diphenyl-1,3,4-oxadiazole (3a): Solid, m.p. 137-138^{0}C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.09 (m, 4H), 7.62-7.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 131.7, 129.0, 126.9, 123.8. MS (ESI): *m/z* 223 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_{10}N_2O$ = 223.0872 $(M+H)^+$, Found 223.0874.

2-(2-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (3b): Solid, m.p. 95-96^{0}C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20-8.09 (m, 1H), 8.05-7.99 (m, 1H), 7.60-7.44 (m, 2H), 7.17- 7.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 163.3, 157.8, 132.9, 131.4, 130.3, 128.9, 126.8, 124.1, 120.6, 113.0, 111.9, 55.9. MS (ESI): *m/z* 253 $(M+H)^+$; HRMS (ESI) calcd for $C_{15}H_{12}N_2O_2$ = 253.1390 $(M+H)^+$, Found 253.1393.

2-(3,4-Dimethoxyphenyl)-5-phenyl-1,3,4-oxadiazole (3c): Solid, m.p. 106-108^{0}C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22-8.05 (m, 2H), 7.71 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.58-7.51 (m, 3H), 6.99 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 151.9, 149.5, 131.6, 129.0, 126.8, 124.0, 120.4, 116.5, 111.1, 109.5, 56.2, 56.0. MS (ESI): *m/z* 283 $(M+H)^+$; HRMS (ESI) calcd for $C_{16}H_{14}N_2O_3$ = 283.1121 $(M+H)^+$, Found 283.1126.

2-Phenyl-5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-oxadiazole (3d): Solid, m.p. 120-121^{0}C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.59-7.52 (m, 3H), 7.37 (s, 2H), 3.99 (s, 6H), 3.94 (s, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 164.5, 153.6, 141.7, 141.1, 133.1, 131.7, 129.0, 127.9, 126.9, 123.8, 118.9, 104.2, 61.0, 56.4; MS (ESI): *m/z* 313 $(M+H)^+$; HRMS (ESI) calcd for $C_{17}H_{16}N_2O_4$ = 313.1187; found: 313.1189.

2-(2-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (3e): Solid, m.p. 190-191^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.01 (m, 4H), 7.87-7.70 (m, 2H), 7.63-7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 161.1, 133.0, 132.4, 132.1, 131.6, 129.1, 127.1, 124.6, 123.3, 118.6; MS (ESI): *m/z* 268 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_9N_3O_3$ = 268.1390 $(M+H)^+$, Found 268.1393.

2-(p-Tolyl)-5-(3, 4, 5-trimethoxyphenyl)-1, 3, 4-oxadiazole (3f): Solid, m.p. 121-122^{0}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.41-7.31 (m, 1H), 3.98 (s, 2H), 3.94 (s, 1H), 2.45 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 164.2, 153.6, 142.2, 129.7, 126.8, 121.1, 119.1, 104.1, 61.0, 56.4, 21.6. MS (ESI): *m/z* 327 $(M+H)^+$; HRMS (ESI) calcd for $C_{18}H_{18}N_2O_4$ = 327.2490 $(M+H)^+$, Found 327.2493.

2-(3-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (3g): Solid, m.p. 114-115^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.7 Hz, 1H), 8.17- 8.12 (m, 2H), 8.11-8.08 (m, 1H), 7.69 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.60-7.52 (m, 4H), 7.42 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.2, 134.6, 131.9, 130.6, 129.7, 129.1, 127.0, 125.7, 125.4, 123.6, 123.1, MS (ESI): *m/z* 301 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_9BrN_2O$: 300.9975, found 300.9971.

2-(3-Bromophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole (3h): Solid, m.p. 138-139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.7 Hz, 1H), 8.11- 8.06 (m, 2H), 7.70 (m, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.47-7.41 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.89, 162.6, 138.3, 134.9, 133.8, 131.9, 131.2, 130.7, 129.8, 127.7, 125.6, 125.4, 123.1, 121.4. MS (ESI): *m/z* 370 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_7Cl_2Br_2N_2O$ = 370.9173 $(M+H)^+$, Found 370.9152.

2-(3-Bromophenyl)-5-(2-nitrophenyl)-1, 3, 4-oxadiazole(3i): Solid, m.p. 187-188^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.01 (m, 3H), 7.87-7.73 (m, 2H), 7.63-7.48 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 161.2, 148.2, 133.6, 133.0, 132.4, 132.1, 131.6, 129.1, 127.1, 124.6, 123.2, 118.6. MS (ESI): *m/z* 347 $(M+H)^+$; HRMS (ESI) calcd for $C_{14}H_8BrN_3O_3$ = 347.13902 $(M+H)^+$, Found 347.13938.

2, 5-Bis(3-bromophenyl)-1,3,4-oxadiazole (3j): Solid, m.p. 101-102^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.7 Hz, 1H), 8.12-8.06 (m, 1H), 7.70 (m, 1H), 7.43 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 134.9, 130.7, 129.8, 125.5, 125.5, 123.2. MS (ESI): *m/z* 378 $(M+H)^+$; HRMS (ESI) $C_{14}H_8Br_2N_2O$: 378.0982. Found: 378.0977.

2-(4-Chlorophenyl)-5-(p-tolyl)-1,3,4-oxadiazole (3k): Solid, m.p. 137-138^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dt, *J* = 6.8, 3.3 Hz, 1H), 8.04 (d, *J* = 8.2 Hz, 2H), 7.58 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.53-7.38 (m, 1.6 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 162.7, 142.4, 133.0, 132.2, 131.2, 129.7, 127.0, 123.2, 120.9, 21.6. MS (ESI): *m/z* 271 $(M+H)^+$; HRMS (ESI) calcd for $C_{15}H_{11}ClN_2O$ = 271.0281 $(M+H)^+$, Found 271.0284.

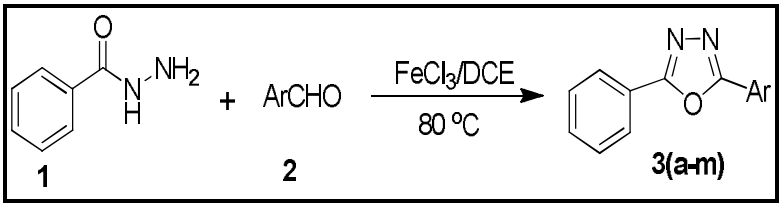
2-(3-Bromophenyl)-5-(naphthalen-1-yl)-1,3,4-oxadiazole (3l): Solid, m.p. 147-148^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 8.7 Hz, 1H), 8.33 (t, *J* = 1.7 Hz, 1H), 8.27 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.13 (m, 1H), 8.06 (m, 1H), 7.95 (m, 1H), 7.750-7.67 (m, 2H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 162.8, 134.7, 133.8, 132.8, 132.3, 130.7, 130.0, 129.8, 128.7, 128.5, 128.2, 126.8, 126.1, 125.7, 125.5, 124.8, 123.1, 120.1. MS (ESI): *m/z* 352 $(M+H)^+$; HRMS (ESI) calcd for $C_{18}H_{11}BrN_2O$ = 352.2490 $(M+H)^+$, Found 352.2493.

2-(4-Methoxyphenyl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (3m): Solid, m.p. 120-121^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.01 (m, 1H), 7.81 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.55 (dd, *J* = 5.0, 1.1 Hz, 1H),

7.19 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.07 – 6.98 (m, 1H), 3.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 162.3, 160.3, 129.8, 129.4, 128.6, 128.0, 125.3, 116.1, 114.4, 55.4. MS (ESI): *m/z* 259 $(M+H)^+$; HRMS (ESI) calcd for $C_{13}H_{10}N_2O_2S$ = 259.0590 $(M+H)^+$, Found 259.0594.

RESULTS AND DISCUSSION

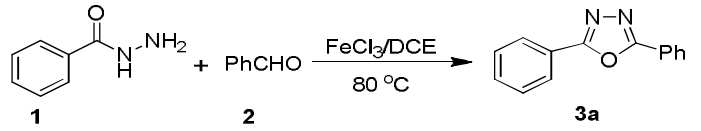
Following our interest on oxidative cyclization, we herein report a mild and effective method for the synthesis of 1, 3, 4-oxadiazoles using $FeCl_3$ as a novel reagent system (Scheme 1).



Scheme 1.Oxidative Cyclization of N-arylhydrazones.

The required arylhydrazides were prepared from the corresponding esters and hydrazine hydrate. In a preliminary experiment, *N*-benzoyl-*N'*-benzylidenehydrazine, derived from benzhydrazine and benzaldehyde in dichloroethane (DCE) was treated with 10 mol% $FeCl_3$ at 25^{0}C to achieve the cyclization, but to our surprise, there was no formation of the required product even after prolonged reaction time (6 h) under same conditions (entries a-b, Table 1). These unsuccessful attempts led us to explore the addition of additives to accomplish the transformation. To our delight, addition of a catalytic amount of $FeCl_3$ to the reaction mixture at 80^{0}C led to the formation of new spot on TLC, which was confirmed as 2, 5-disubstituted 1, 3, 4-oxadiazole (entry c, Table 1). The above result indicates that the addition of $FeCl_3$ is crucial to achieve the desired product. To increase the conversion, the temperature was elevated to 100^{0}C, but there was no significant improvement in yield (entry d).

Table 1.Optimization of reaction conditions.

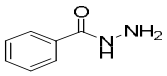
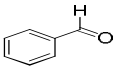
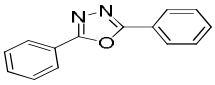
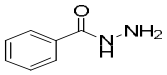
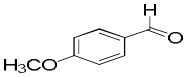
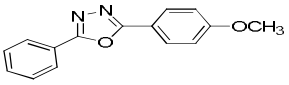
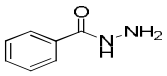
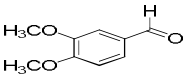
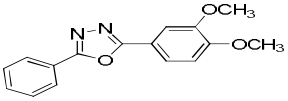
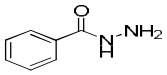
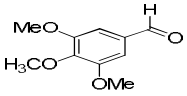
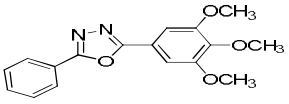
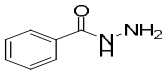
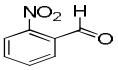
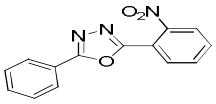
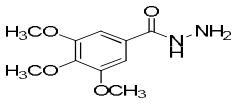
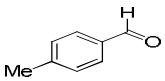
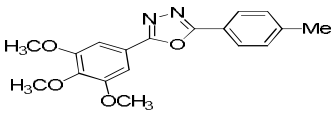
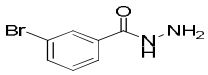
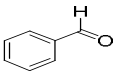
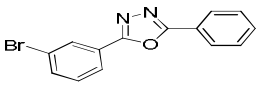
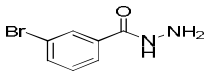
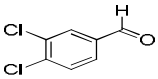
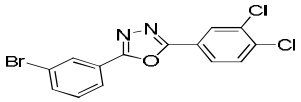
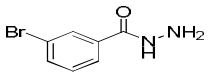
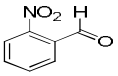
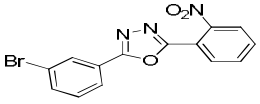
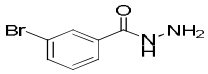
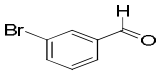
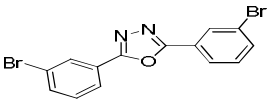
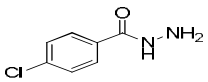
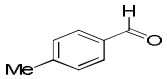
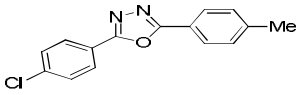
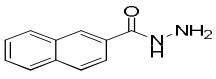
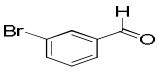
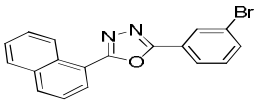
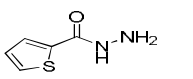
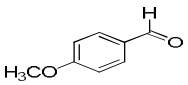
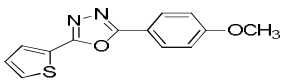


Entry	Reagents	mol%	Temp (°C)	Yield (%)
a	$FeCl_3$/DCE	10	25	0
b	$FeCl_3$/DCE	10	25 (6h)	0
c	$FeCl_3$/DCE	10	80	90
d	$FeCl_3$/DCE	10	100	90

[a]Reaction was faster at 80 °C and complete within 2h.

The above results encouraged us to examine the substrate scope with respect to various aldehydes and aryl hydrazides (Table 2). The substituent's present on aromatic ring of the aldehyde had shown some effect on the outcome of the reaction. For instance, benzaldehyde gave the desired product in 90% yield (entry a, Table 2), whereas the presence of electron-rich substituent like methoxy- or electron-deficient substituent such as nitro group on aromatic ring (entries b, c, d & e, Table 2) resulted relatively in lower yield. The scope of the reaction was further extended to different hydrazides.

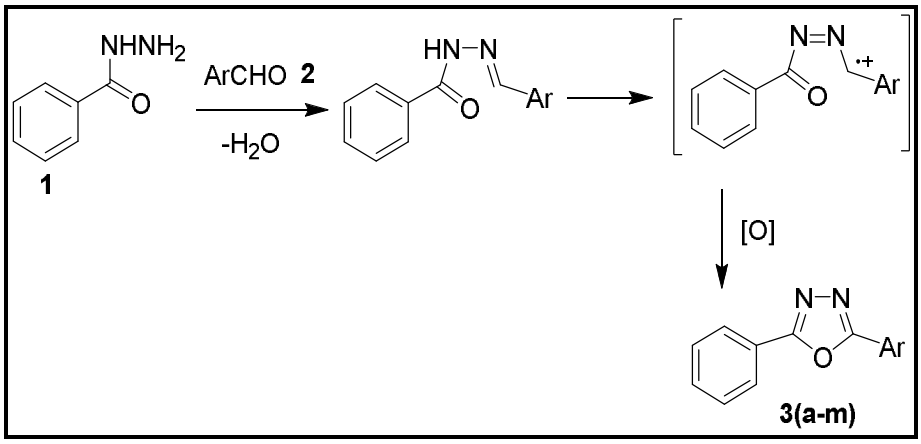
Table 2. Preparation of 1, 3, 4-oxadiazoles through an oxidative cyclization.

Entry	Hydrazide	Aldehyde	Product (3)[a]	Time (h)	Yield (%)[b]
a				2	90
b				2	78
c				2	76
d				2	72
e				2	69
f				2	80
g				2	78
h				2	75
i				2	69
j				2	78
k				2	79
l				2	70
m				2	61

[a]All products were characterized by NMR, IR and mass spectrometry.
[b]Yield refers to pure products after chromatography.

Similarly, the presence of halogen on aromatic ring of benzhydrazide slightly decreased the yield (entries g-k, Table 2). A sterically hindered 2-naphthohydrazide resulted in comparatively lower yield (entry l, Table 2). Interestingly, the reaction was also successful with heteroaromatic hydrazide, i.e. thiophene-2-carbohydrazide (entry m, Table 2).

A plausible reaction mechanism is proposed in Scheme 2. It is known that acyl hydrazide reacts with aldehyde to generate the acyl hydrazone as shown in Scheme 2. A subsequent cyclization of acyl hydrazone with concurrent aromatization would give the desired 2, 5-disubstituted 1, 3, 4-oxadiazole (Scheme 2).



Scheme 2.A plausible reaction pathway.

In summary, we have developed a one-pot strategy for the synthesis of 1, 3, 4-oxadiazioles using a combination of $FeCl_3$ at ambient temperature. This one-pot procedure proved to be quite general and worked well with a wide variety of aryl and heterocyclic aldehydes and variety of acylhydrazides. The advantage of this method lies in the simplicity of experimental procedure and the ready accessibility of the reagents, which render this an experimentally attractive method for the preparation of unsymmetrical 1, 3, 4-oxadiazoles.

CONCLUSIONS

In conclusion, we have demonstrated an efficient method for the synthesis of 2, 5-disubstituted 1, 3, 4-oxadiazoles. The present strategy provides a rapid access to highly substituted derivatives with high structural diversity in a single step process. These scaffolds find application in drug discovery.

REFERENCES

[1]. Robert E. Buntrock, Review of Heterocyclic Chemistry, 5th Edition, *J. Chem. Educ.*, **2012**, 89, 11, 1349-1350.
[2]. E. Brown, Ring Nitrogen and Key Biomolecules, *Kluwer Academic Press*.**1998.**
[3]. Yasuhiko Shirota, Organic materials for electronic and optoelectronic devices, *J. Mater. Chem.*, **2000,** 10, 1.
[4]. Zhong Jin, Imidazole, oxazole and thiazole alkaloids**,** *Nat. Prod.*, **2006**, *23*, 464-496.
[5]. Andrea Pace, Paola Pierro. The new era of 1, 2, 4-oxadiazoles. 2009, 7, 4337-4348.
[6]. Harish Rajak, Murali Dhar Karya, Pradeep Mishra, Biologically active 2,5-disubstituted-1,3,4 Oxadiazoles, *I. J. Pharma. Sci. Nano.*, **2009**, 2, 390-406.
[7]. N. D. James, J. W. Growcott, *Drugs Future*, **2009**, *34*, 624-634.
[8]. C. Dobrota, C. Paraschivescu, I. Dumitru, M. Matache, I. Baciu, L. Ruta, Convenient preparation of unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles promoted by Dess–Martin reagent, *Tetrahedron Lett.* **2009**, 50, 1886-1888.

[9]. O. Cyrous, A. Kangani, David E. Kelleya, W. Billy Day, One pot direct synthesis of oxazolines, benzoxazoles, and oxadiazoles from carboxylic acids using the Deoxo-Fluor reagent, *Tetrahedron Lett*. **2006**, 47, 6497–6499.
[10]. V. Padmavathi, G. Sudhakar Reddy, A. V. Nagendra Mohan, K. Mahesh, Synthesis of symmetrical and unsymmetrical 1,3,4-oxadiazoles and their interconversion to 1,3,4-thiadiazoles and 1,2,4-triazoles, **2008**, 17, 48-60.