RJC

RASĀYAN *J. Chem.*
Vol. 18 | No. 4 |1987-1992| October-December | 2025
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

$FeCl_3$-PROMOTED SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES FROM ARYLHYDRAZIDES AND ARYLIDENE MELDRUM'S ACIDS VIA OXIDATIVE BOND CLEAVAGE FOR SUSTAINABLE CHEMICAL PROCESSES

K. Satishkumar, Y. Kumari, B. Varaprasad, T. Meenakshi, Opio Boniface, L. Chinnari, V. Christopher and V. Siddaiah✉

Department of Chemistry, Andhra University, Visakhapatnam, 530003, Andhra Pradesh, India.
✉Corresponding author: sidduchem@gmail.com

ABSTRACT

A novel synthetic strategy for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles has been developed using $FeCl_3$ as a catalyst. Conveniently, several 1,3,4-oxadiazoles that are 2,5-disubstituted, both symmetrical and asymmetrical, can be produced in an efficient and adaptable fashion by condensation of arylhydrazides with arylidene Meldrum's acid *via* iron mediated oxidative cleavage of arylidene Meldrum's acid using DMSO as oxidant and solvent. This process is compatible with both aromatic and aliphatic arylidene Meldrum's acids. Other benefits of this process include good yields, high functional group tolerance, low cost of catalyst, and phasing out hazardous chemicals. This new synthetic route has significant potential for applications in drug development and material science and presents an environmentally benign alternative for producing heterocyclic compounds.

Keywords: $FeCl_3$ Catalyst**,** Arylhydrazides, Arylidene Meldrum's Acid, 1,3,4-Oxadiazoles, Oxidative Cleavage, Heterocyclic Synthesis

RASĀYAN *J. Chem.*, Vol. 18, No.4, 2025

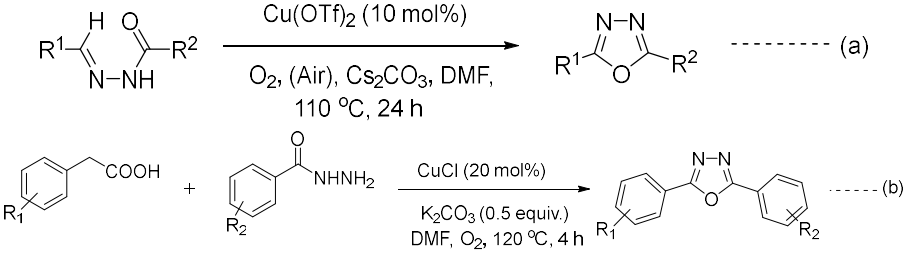
INTRODUCTION

1,3,4-Oxadiazoles represent a remarkable group of heterocyclic substances that possess significant focus in both pharmaceutical[1] and material sciences[2] because of their varied range of physiological processes as well as practical applications[3]. Their potential for therapeutic use spans antibacterial and antifungal effects[4], providing tools for combating infections. They also offer analgesic and anti-inflammatory properties[5], which are useful for pain management and reducing inflammation. Additionally, 1,3,4-oxadiazoles have demonstrated antiviral and anticancer activities[6], making them promising candidates for treating viral infections and various cancers. Their antihypertensive and anticonvulsant properties[7] contribute to managing high blood pressure and seizure disorders, while some derivatives show promise in anti-diabetic treatments. Notably, certain 1,3,4-oxadiazoles that are 2,5-disubstituted have shown promise in addressing complex conditions such as Alzheimer's disease[8] and obesity, indicating their versatility in treating neurodegenerative diseases and aiding in weight management. This broad applicability extends beyond the pharmaceutical realm into agriculture, where these compounds are employed as herbicides, insecticides, and plant protection agents[9]. In the realm of materials science, 1,3,4-oxadiazoles are utilized in advanced technologies. They are incorporated into organic light-emitting diodes (OLEDs),[10] where they contribute to efficient light emission; laser dyes, enhancing the performance of lasers; optical brighteners, improving the brightness of materials; and scintillators, which are used in radiation detection. The development of efficient synthetic methods to approach and modify 2,5-disubstituted 1,3,4-oxadiazoles is of paramount importance. Such advancements not only facilitate drug discovery and the development of new materials but also enable the exploration of novel applications, thereby expanding the utility and impact of these versatile compounds. In this context, various methods[11] have been developed in order to synthesize 1,3,4-oxadiazoles. S. Guin *et al.*[12] reported access to substituted 1,3,5-oxadiazoles by N-arylidene hydrazide imine C-H functionalization in the presence of Cu catalyst. Subsequently, Renhua Liu and his group[13] developed substituted oxadiazoles by dehydrogenatively cyclizing acylhydrazones with palladium catalysis. Moreover, L. Wang's coworkers[14]

http://doi.org/10.31788/RJC.2025.1849401

reported a protocol for the synthesis of 2,5-diaryl substituted 1,3,4-oxadiazoles from aryl tetrazoles and aldehydes in the presence of DTB. Recently, our team[15] has also developed copper-catalysed dual-oxidation synthesis of 2,5-disubstituted 1,3,4-oxadiazoles in a single pot using arylacetic acids and hydrazides. Beyond their success, these methodologies are unfortunately prone to several drawbacks, including severe response scenarios, harmful substances, a narrow range of substrates, and/or challenges with scaling. It is still very desirable to have broader and simpler processes for synthesizing 1,3,4-oxadiazoles derived from easily obtainable precursors. This has encouraged us to search for an easier and more efficient approach in line with SDG-12: *Responsible Consumption and Production*. Nevertheless, arylidene Meldrum's acids have been proved to be valuable reagents in the synthesis of complex organic molecules. They are more stable than aldehydes and are involved in the in situ generation of aldehydes[16] through the oxidative cleavage of the double bond by common oxidizing agents. Moreover, due to its potent reactivity, dimethyl sulfoxide serves as a significant reagent in chemical synthesis. This solvent can be easily purchased from commercial sources, is reasonably priced, has little toxicity, and is frequently utilized as an oxidant in popular organic transformations. Because of its sophisticated characteristics, DMSO is commonly used as an oxygen source[17] in organic transformations. As far as we are aware, there is no literature-based information on the synthesis of 1,3,4-oxadiazoles employing DMSO as an oxidant using hydrazides and arylidene Meldrum's acid. Based on the above facts, the author proposed a novel procedure for the production of 1,3,4-oxadiazoles that are 2,5-disubstituted. Hydrazides and arylidene Meldrum's acid through oxidative scission of the double bond by DMSO in the presence of $FeCl_3$ catalyst at 120 °C for 6 h (Scheme-1).

Previous Work



Present Work

EXPERIMENTAL

General Information

Without any purification, all reagents used were of commercial quality. The ^1H and ^{13}C NMR spectra of the synthesized compounds were recorded using a Bruker 400 MHz NMR spectrometer in $CDCl_3$ solution. TMS ($\delta = 0.00$) served as the internal standard for ^1H NMR, while the central lines of $CDCl_3$ ($\delta = 7.26$ for 1H and 77.00 ppm for ^{13}C) were used for ^{13}C NMR. Mass data were obtained through HRMS (High Resolution Mass Spectrometry) using electro spray ionization with a Bruker-Waters system. TLC was used to track reactions on aluminum plates coated with silica gel, F254 indicator, purchased from Merck, and spots were visualized under a UV lamp. Through the use of column chromatography, crude products were refined using 100–200 mesh silica gel and an eluent mixture of hexane and ethyl acetate. Arylhydrazides and arylidene Meldrum's acids were synthesized according to published procedures.

General Protocol for the Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

Arylhydrazide (1), arylidene Meldrum's acid (2), $FeCl_3$ (10 mol%), and K_2CO_3 were dissolved in DMSO (2 mL) in a round-bottom flask fitted with a magnetic stirring bar. TLC was used to track the reaction's development during the six hours while the mixture was agitated at 120 °C. The reaction mixture was left to cool to room temperature after the reaction was accomplished, before separation with water and ethyl

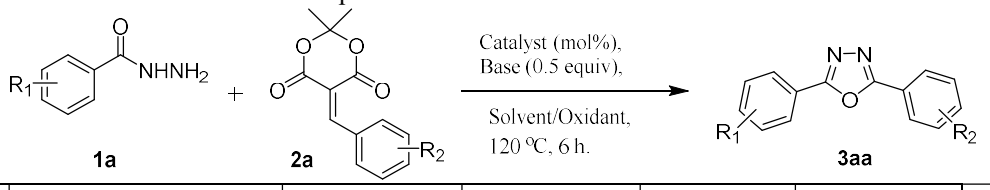
acetate. Over anhydrous Na_2SO_4, the organic layer was dried and was vacuum-extracted to yield the crude product. The crude product was refined to get the corresponding products using column chromatography with ethyl acetate and hexane as eluents on silica gel (100–200 mesh).

2,5-Diphenyl-1,3,4-oxadiazole (3aa)
White solid, yield: **3aa**-90% mp: 135-139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 – 8.15 (m, 4H), 7.59 – 7.55 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.75, 131.67, 129.17, 126.96, 123.95. HRMS-(ESI) (*m/z*): $(M+H)^+$ calcd. for $C_{14}H_{10}N_2O$ 223.0871 found 223.0856.

2-Phenyl-5-(*m*-tolyl)-1,3,4-oxadiazole (3ca)
White solid, yield: **3ca** - 86%, mp: 111-122 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 – 8.15 (m, 2H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.59 – 7.55 (m, 3H), 7.47-7.39 (d, *J* = 7.9 Hz, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.44, 139.09, 132.65, 131.81, 129.08, 127.55, 124.06, 123.88, 21.62. HRMS-(ESI) (*m/z*): $(M+H)^+$ calcd. for $C_{15}H_{12}N_2O$ 237.1028 found 237.1031.

RESULTS AND DISCUSSION

Table-1: Optimization of the Reaction Conditions[a]



Entry	Catalyst (mol%)	Oxidant	Base	Solvent	Temp (°C)	Yield %[b]
1	$FeCl_3$(10)	O_2	Cs_2CO_3	DMSO	120	70
2	$FeBr_3$(10)	O_2	Cs_2CO_3	DMSO	120	48
3	$FeCl_2$(10)	O_2	Cs_2CO_3	DMSO	120	42
4	$Fe(acac)_2$(10)	O_2	Cs_2CO_3	DMSO	120	40
5	CuCl(10)	O_2	Cs_2CO_3	DMSO	120	60
6	$FeCl_3$(10)	O_2	Cs_2CO_3	ACN	120	41
7	$FeCl_3$(10)	O_2	Cs_2CO_3	DMF	120	46
8	$FeCl_3$(10)	O_2	K_2CO_3	DMSO	120	88
9	$FeCl_3$(10)	O_2	$NaHCO_3$	DMSO	100	56
10	$FeCl_3$(10)	PIDA	K_2CO_3	DMSO	120	41
11	$FeCl_3$(10)	TBHP	K_2CO_3	DMSO	120	33
12	$FeCl_3$(10)	O_2	-	DMSO	120	NR
13	-	O_2	K_2CO_3	DMSO	120	NR
14	$FeCl_3$(20)	O_2	K_2CO_3	DMSO	120	85

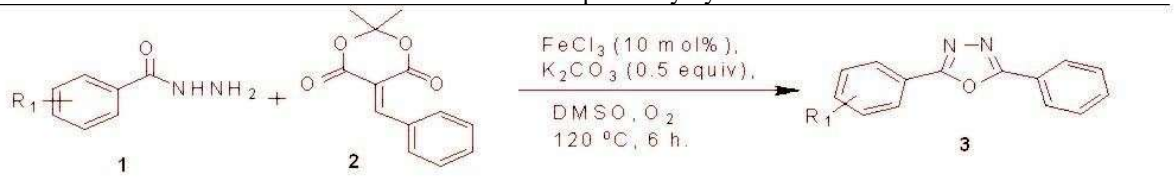
[a]Reaction conditions:3.1a (0.1 mmol), 3.2a (0.1 mmol), catalyst (10 mol %), base (0.5 equiv.), solvent (2 mL), 120 °C, under oxygen atmosphere, 6 h, [b]isolated yields, NR-no reaction.

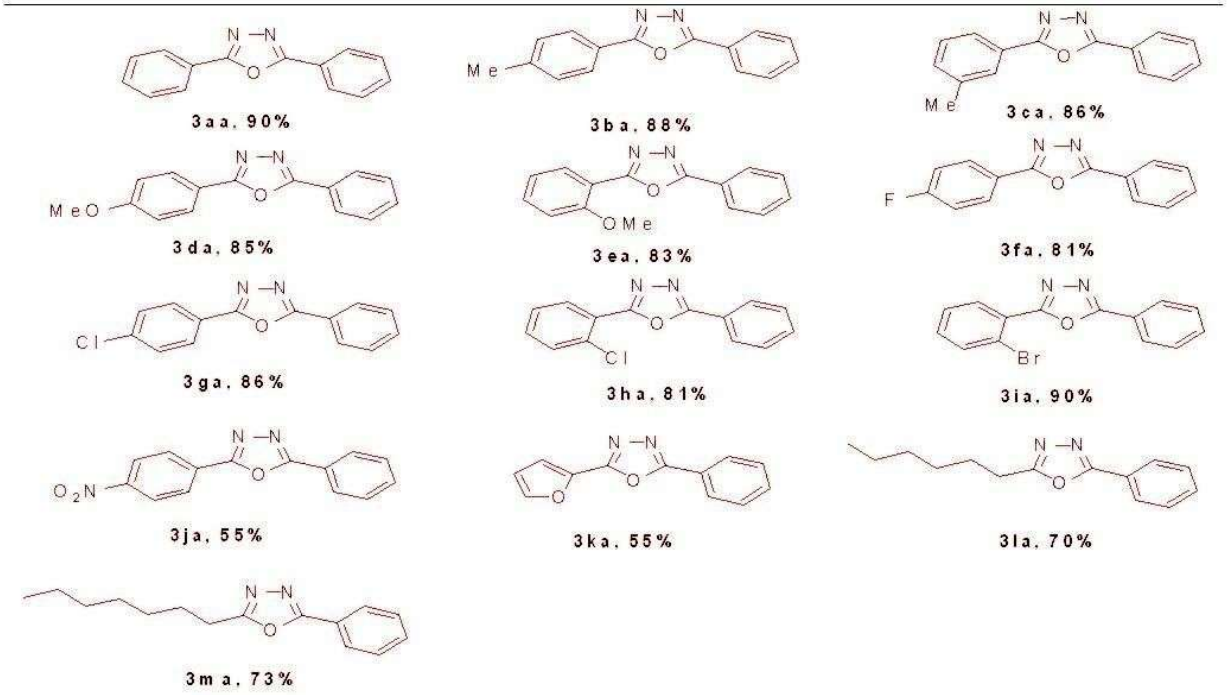
Initially, the author explored the study by using arylhydrazide (1a) and arylidene Meldrum's acid (2a) as key substrates to achieve the finest reaction conditions. In the first experiment, the reaction was carried out with $FeCl_3$ (10 mol %), Cs_2CO_3 (0.5 equiv), in DMSO (2 mL) at 120 °C for 6 h under an oxygen atmosphere. To his delight, the desired product 3aa was obtained with 70% yield (Table-1, entry 1). Next, to improve the yield of compound 3aa, several catalysts such as $FeBr_3$, $FeCl_2$, $Fe(acac)_2$, and CuCl were investigated. Among these, $FeCl_3$ was found to be the most effective catalyst (Table-1, entries 2-5). Then, a variety of solvents such as CAN and DMF were screened, but no significant improvement in the yield of 3aa was observed

[a]Reaction Conditions
1 (0.1 mmol), **2** (0.1 mmol), $FeCl_3$ (10 mol%), K_2CO_3 (0.5 equiv), DMSO (2.0 mL) at 120 °C, under an oxygen atmosphere, 6-8 h, [b]isolated yields. After acquiring the ideal reaction conditions, the substrate inclusivity of this transformation was then evaluated. As manifested in Table-2, substituted arylhydrazides

reacted with arylidene Meldrum's acid and provided corresponding compounds in good to excellent yields. Simple arylhydrazide (**1a)** reacted with arylidene Meldrum's acid (**2a)** effortlessly to produce the intended product **3aa** in 90% yield. Arylhydrazides with groups that donate electrons, like 4-Me, 3-Me, 4-OMe, and 2-OMe, participated in the reaction readily and produced respective products in good yields (**3ba-3ea**). The optimal conditions were also tolerated with halogenated (4-Cl, 2-Cl, 2-Br, 4-F) substrates (3fa-3ia), which provide opportunities for further functionalization. Importantly, hydrazide with a strong electron-withdrawing group like 4-NO_2 was found to be a suitable coupling partner, generating desired product 3ja in 55% yield.

Table-2: Substrates Scope of Arylhydrazides[a]





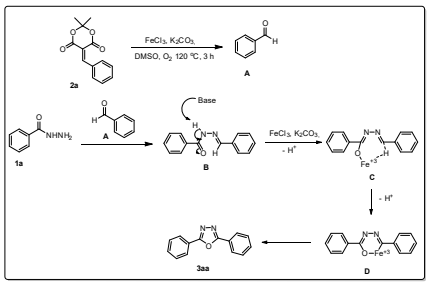
[a]Reaction conditions:3.1a (0.1 mmol), 3.2a (0.1 mmol), catalyst (10 mol %), base (0.5 equiv.), solvent (2 mL), 120 °C, under oxygen atmosphere, 6 h, [b]isolated yields, NR-no reaction.

Pleasingly, hydrazide containing a heterocyclic group could be reacted with arylidene Meldrum's acid 2a and provided the corresponding oxadiazole in 55% yield (3ka). It is noteworthy to mention that hydrazides containing alkyl substituents also reacted favorably, producing the desired compounds in good yields (3la and 3ma).

Based on the earlier research literature,[18-20,] the plausible reaction mechanism is discussed in Scheme-3. Initially, aldehyde (A) is formed from arylidene Meldrum's acid (2a) *via* oxidative cleavage of the carbon-carbon double bond under optimized conditions. Then, aldehyde (A) is condensed with arylhydrazide (1a) to yield B in the presence of base and $FeCl_3$. Finally, 3aa is formed from B *via* oxidative cyclization.

CONCLUSION

In conclusion, an oxidative breakage of the carbon-carbon double bond has been developed as a straightforward and novel technique for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. The $FeCl_3$-catalyzed synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from arylhydrazides and arylidene Meldrum's acids offers a green and efficient method for the preparation of heterocyclic compounds.



Plausible Mechanism

The usage of mild conditions and a catalytic approach supports SDG-12 (*Responsible Consumption and Production*) by minimizing the use of hazardous reagents and reducing waste. The broad applicability of this reaction holds promise for drug development and material science, contributing to SDG-3 (*Good Health and Well-Being*) through the creation of bioactive compounds. Overall, this sustainable synthetic method presents a significant advancement in both chemical innovation and environmental sustainability.

ACKNOWLEDGMENTS

The authors thank SERB DST (Department of Science and Technology), New Delhi, for funding through project EEQ/2021/000168.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-12: Responsible Consumption and Production* All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

V. Siddaiah https://orcid.org/0000-0002-7190-7932
K. Satishkumar http://orchid.org/0009-0008-1251-1410
Y. Kumari http://orchid.org/0009-0005-2652-9986
B. Varaprasad http://orchid.org/0000-0002-4324-7201
T. Meenakshi http://orchid.org/0009-0002-8222-0498
Opio Boniface http://orchid.org/0009-0006-0805-0899
L. Chinnari http://orchid.org/0009-0007-1146-2656
V. Christopher https://orcid.org/0000-0002-6829-3124

REFERENCES

1. A. Hassan, A.H. Khan, F. Saleem, H. Ahmad, and K.M. Khan, *Expert Opinion on Therapeutic Patents,* **32**, 969(2022), https://doi.org/10.1080/13543776.2022.2116312
2. N. Abd Alrazzak, *Materials Science and Engineering*, **454**, 012096 (2018), https://doi:10.1088/1757-899X/454/1/012096
3. M. Luczynski and A. Kudelko, *Applied Sciences***,** **12**, 3756(2022), https://doi.org/10.3390/app12083756
4. M.Y. Wani, A. Ahmad, R.A. Shiekh, K.J. Al-Ghamdi and A.J. sobral, *Bioorganic and Medicinal Chemistry*, **23**, 4172(2015), https://doi.org/10.1016/j.bmc.2015.06.053
5. A. Almasirad, Z. Mousavi, M. Tajik, M.J. Assarzadeh and A. Shafiee, *Daru Journal of Pharmaceutical Sciences*, **22**, 1(2014), https://doi.org/10.1186/2008-2231-22-22

6. C.E. Stecoza, G.M. Nitulescu, C. Draghici, M.T. Caproiu, O.T. Olaru, M. Bostan and M. Mihaila, *Pharmaceuticals* **14**, 438(2021), https://doi.org/10.3390/ph14050438
7. B. Rubina, K. Garima, K. Ravi and D. Manni, *Indian Journal of Pharmaceutical Education and Research*, **53**, 2019, https://doi.org/10.5530/ijper.53.2s.44
8. D.K. Waiker, A. Verma, N. Akilesh Singh, A. Roy, H. Dilnashin, V. Tiwari, S.K. Trigun, S.P. Singh, S. Krishnamurthy and P. Luna, *ACS Chemical Neuroscience*, **14**, 2217(2023), https://doi.org/10.1021/acschemneuro.3c00245
9. W.G. Duan, X.R. Li, Q.J. Mo, J.X. Huang, B. Cen and F.H. Lei, *International Journal of Biological Macromolecules*, **180**, 539(2021).
10. A. Paun, N.D. Hadade, C.C. Paraschivescu and M. Matache, *Journal of Materials Chemistry C*, **37**, 8596(2016), https://doi.org/10.1039/C6TC03003C
11. K.D. Patel, S.M., Prajapati, S.N., Panchal, and H.D. Patel, *Synthetic Communications*, **44**, 1859(2014), https://doi.org/10.1080/00397911.2013.879901
12. S. Guin, T. Ghosh, S.K. Rout, A. Banerjee and B. K. Patel, *Organic Letters*, **13**, 5976(2011), https://doi.org/10.1021/ol202409r
13. Jiang. Q, Qi. X, Zhang. C, J.I. X, Li. J and R. Liu, *Organic Chemistry Frontiers*, **5**, 386(2018), https://doi.org/10.1039/C7QO00749C
14. L. Wang, J. Cao, Q. Chen and M. He, *The Journal of Organic Chemistry*, **80**, 4743(2015), https://doi.org/10.1021/acs.joc.5b00207
15. C. Lekkala, V. Bodala, K. Yettula, B.k. Karasala, R.L. Podugu and S. Vidavalur, *ACS omega*, **31**, 27157(2022), https://doi.org/10.1021/acsomega.2c01586
16. M. Suresh, A. Kumari and R.B. Singh, *Tetrahedron*, **75**, 130573(2019), https://doi.org/10.1016/j.tet.2019.130573
17. Y.F. Liang, K. Wu, S. Song, X. Li, X. Huang, and N. Jiao, *Tetrahedron Letters*, **56**, 653(2015), https://doi.org/10.1021/ol5037387
18. A.K. Yadav and L.D. Yadav, *Tetrahedron Letters*, **55**, 2065(2014), https://doi.org/10.1016/j.tetlet.2014.02.022
19. Y. Wang, S. Mu, X. Li and Q. Song, *Chinese Chemical Letters*, **33**, 1511(2022), https://doi.org/10.1016/j.cclet.2021.08.089
20. A.V. Aksenov, V. Khamraev, N.A. Aksenov, N.K. Kirilov, D.A. Domenyuk, V.A. Zelensky and M. Rubin, *RSC Advances*, **12**, 6636(2019), https://doi.org/10.1039/C9RA00976K

[RJC-9401/2025]