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An efficient approach to access 2,5-disubstituted 1,3,4-oxadiazoles by oxidation of 2-arenoxybenzaldehyde *N*-acyl hydrazones with molecular iodine

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An oxidative cyclization of 2-arenoxybenzaldehyde *N*-acyl hydrazones **3a–o** was employed to synthesize new 2,5-disubstituted 1,3,4-oxadiazole compounds **4a–d, 4f–i, 4k–n**. This method involves oxidative cyclization of 2-arenoxybenzaldehyde *N*-acyl hydrazones **3a–o** with molecular iodine mediated catalysis in which potassium carbonate served as a base. Characterization of all the synthesized novel compounds involved, proton and carbon NMR, mass spectrometry, and CHN elemental analysis. The synthesis of novel 2,5-disubstituted 1,3,4-oxadiazoles may display potential to provide pharmacologically important heterocyclic compounds.

Introduction

Recently, synthesis of 1,3,4-oxadiazole compounds has received a great deal of attention in organic chemistry which has occupied a significant position in material science because they are electron deficient and can transport electrons. For carboxylic acids, esters, and amides, 2,5-substituted 1,3,4-oxadiazoles are powerful bioisosteres. In fact, 1,3,4-oxadiazoles are privileged scaffolds in medicinal chemistry. 1,3,4-oxadiazole structure has been investigated to see that they have antibacterial,[1,2] anticonvulsant,[3,4] anti-allergic,[5] antifungal,[6,7] antiviral[8] and antidepressant properties.[9] Furthermore, 1,3,4-oxadiazole motifs are widely used in anticancer drug research.[10–15] Most of the drugs having 1,3,4-oxadiazole units such as Zibotentan, Raltegravir, Nesapidil, Furamizole, and Fenadiazole are presently used in the clinic. Structures are shown in Figure 1.

Accordingly, the formation of 1,3,4-oxadiazole moiety has become a primary area of interest for both synthetic and medicinal chemists. Synthetic procedures for them has been described in the literature. There are two conventional synthetic methodologies available. In one of these methods, 1,2-diacylhydrazines are dehydratively cyclized, with reagents like thionyl chloride, polyphosphoric acid, phosphorus oxytrichloride, and sulfuric acid.Another method is the oxidative

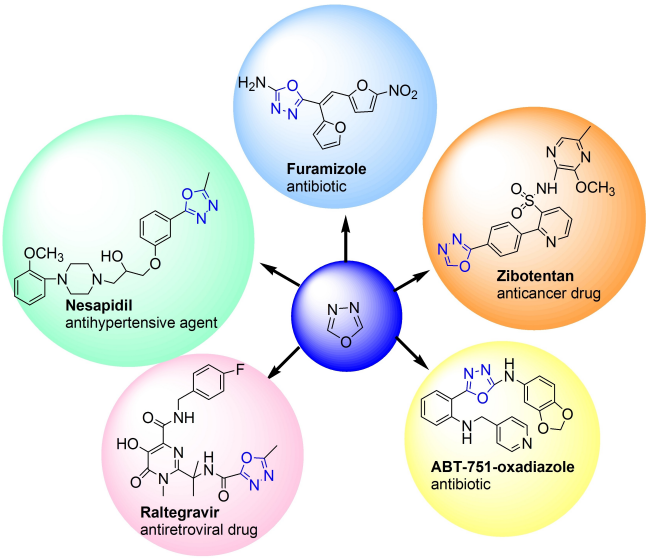

Figure 1. Representative examples of clinical drugs bearing 1,3,4-oxadiazole core.

cyclization of acyl hydrazones utilizing oxidants. Various oxidants such as $KMnO_4$,[16] chloramine T,[17] Br_2,[18] ceric ammonium nitrate (CAN),[19] HgO/I_2,[20] trichloroisocyanuric acid (TCCA),[21] and $Cu(OTf)_2$[22] are used in this oxidative cyclization method. Nevertheless, a considerable number of them show suffering from limitations, to name a few, substrate scope is limited, the medium is strongly alkaline or acidic, the reaction yield is low, reaction times are long, work-up procedures are complicated, yielding toxic metal waste and bring out scalability problems. A method which is facile, environmentally benign, and does not contain metallic compounds to synthesize these important heterocycles is therefore crucial. In recent years, 1,3,4-oxadiazoles have been seen in many publications employing an oxidative cyclization method catalyzed by I_2. For example, Chang and coworkers reported a highly efficient

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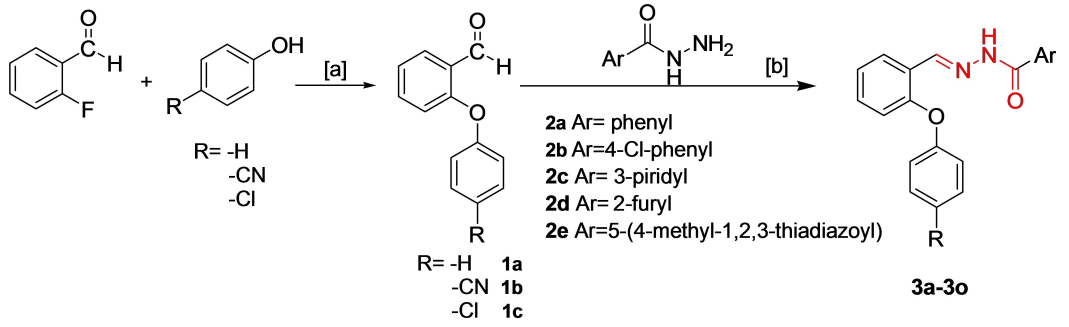
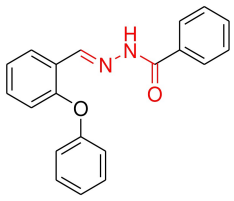
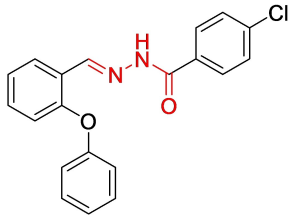
Table 1. Synthesis of *N*-acyl hydrazones.





3a 82%



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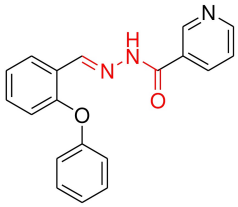
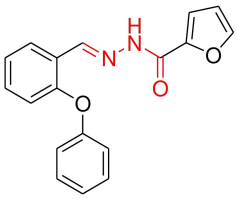


3c 92%



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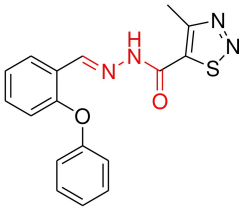

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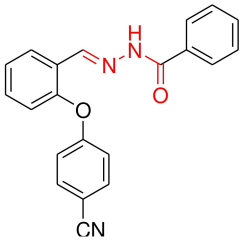
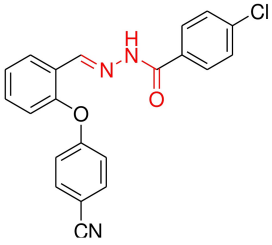
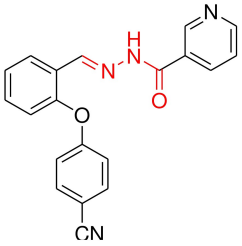


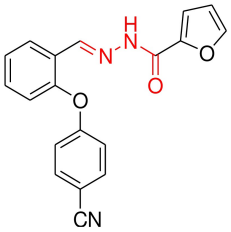
3f 80%



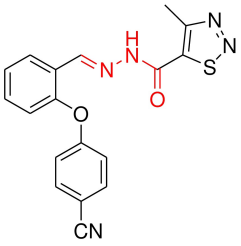
3g 88%



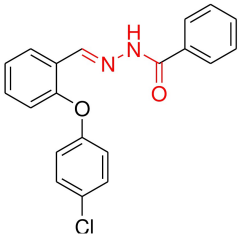
3h 90%



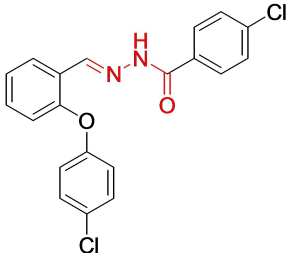
3i 85%



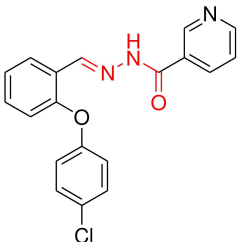
3j 95%



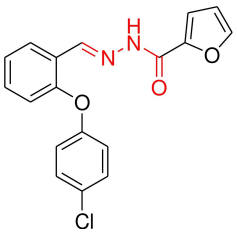
3k 80%



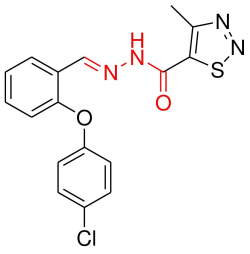
3l 91%



3m 87%



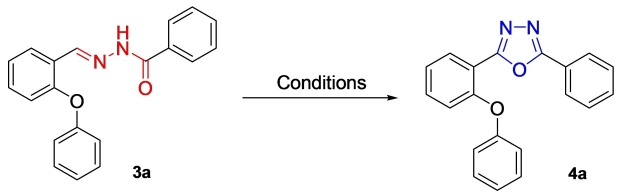
3n 80%



3o 94%

[a] K_2CO_3, DMF, 175 °C, 2 h. [b] Absolute ethanol, reflux, 2–5 h.

Table 2. Study of reaction conditions for the synthesis of 1,3,4-oxadiazole 4a from *N*-acyl hydrazone 3a[a]



Entry	I_2 (mol %)	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	10	K_2CO_3 (3)	DMSO	100	4	63
2	10	Na_2CO_3 (3)	DMSO	100	4	45
3	10	Cs_2CO_3 (3)	DMSO	100	4	50
4	10	$NaHCO_3$ (3)	DMSO	100	4	42
5	10	KOH (3)	DMSO	100	10	0
6	10	NEt_3 (3)	DMSO	100	10	0
7	5	K_2CO_3 (3)	DMSO	100	4	20
8	15	K_2CO_3 (3)	DMSO	100	4	79
9	20	K_2CO_3 (3)	DMSO	100	4	82
10	15	K_2CO_3 (2)	DMSO	100	4	65
11	15	K_2CO_3 (4)	DMSO	100	4	80
12	15	K_2CO_3 (6)	DMSO	100	4	77
13	15	K_2CO_3 (3)	DMSO	120	4	83
14	15	K_2CO_3 (3)	DMSO	150	4	79
15	**15**	**K_2CO_3 (3)**	**DMSO**	**120**	**8**	**90**
16	15	K_2CO_3 (3)	Toluene	110	4	0
17	15	K_2CO_3 (3)	CH_3CN	80	4	10
18	15	K_2CO_3 (3)	DMF	150	4	16

[a] Reaction conditions: **3a** (0.5 mmol) and solvent (2 mL). [b] Isolated yields.

formation of the oxidative C–O bond in which 1,3,4-oxadiazoles were synthesized from *N*-acyl hydrazones.[23] Patel and co-workers also enhanced an oxidative cyclization method via I_2/H_2O_2 to obtain 2,5-disubstituted 1,3,4-oxadiazoles.[24] In 2015, the group of Wu also established the synthesis of 1,3,4-oxadiazoles via an iodine catalyzed direct annulation of hydrazides.[25] Recently, Huang et al. reported a one-pot synthesis of 1,3,4-oxadiazoles along with the mediation of molecular iodine, the reaction continues with a cyclization and deacylation steps.[26] In these works, molecular iodine has been found as an efficient oxidant to carry out oxidative cyclization of *N*-acyl hydrazones owing to its low cost, environmental safety, low toxicity, and ease of experimental work.

To our ongoing efforts in the preparation of various heterocyclic pharmacological active motifs,[27–29] we herein synthesized new 2,5-disubstituted 1,3,4-oxadiazoles from their precursors *N*-acyl hydrazones with molecular iodine. However, to the best of our knowledge, molecular iodine-mediated oxidative cyclization for the synthesis of 2,5-disubstituted 1,3,4-oxadiazole compounds from 2-arenoxybenzaldehydes and various substituted hydrazides has not yet been reported. Herein, we choose 2-arenoxybenzaldehyde *N*-acyl hydrazone derivatives as the substrates to prepare 2,5-disubstituted 1,3,4-oxadiazoles in the presence of I_2 as the oxidant and K_2CO_3 as the base, therefore we achieved the compounds we desired in moderate to good yields.

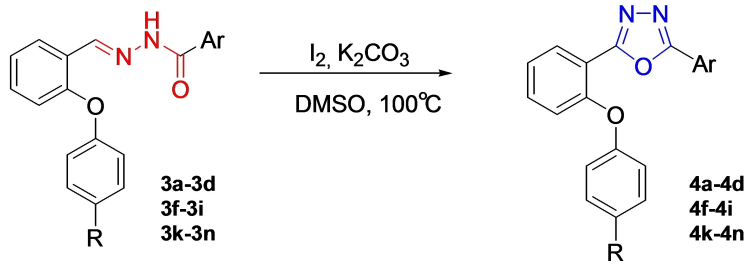
Results and Discussion

A series of 2-arenoxybenzaldehyde *N*-acyl hydrazine compounds **3a–o** were prepared, as to how we can proceed in their oxidative cyclization. The synthesis was started by nucleophilic aromatic substitution (S_NAr) reaction to obtain substituted 2-arenoxybenzaldehydes **1a–c.**[30] To prepare these compounds, 2-fluorobenzaldehyde underwent the S_NAr reaction with phenol derivatives to give the corresponding 2-arenoxybenzaldehydes **1a–c** in the presence of K_2CO_3 in DMF. Then these aldehydes **1a–c** were reacted with various substituted hydrazides **2a–e** in ethanol in reflux conditions to synthesize *N*-acyl hydrazones **3a–o** with high yields.[31] The desired *N*-acyl hydrazone **3a–o** series were obtained using the general procedures outlined in Table 1.

Then, *N*-acyl hydrazone **3a** was selected as a model substrate for oxidative cyclization reaction. Initially, *N*-acyl hydrazone **3a** (0.5 mmol) was treated with 10 mol% I_2 and K_2CO_3 (3 equiv) in dimethyl sulfoxide (2 mL) at 100 °C, affording **4a** at 63% isolated yield (Table 2, entry 1). The optimal conditions were found by testing various bases like K_2CO_3, Na_2CO_3, Cs_2CO_3, $NaHCO_3$, KOH, and NEt_3 (Table 2, entries 1–6). As a result, potassium carbonate led to the best conversion for compound **4a** (Table 2, entry 1) at 63% yield. Other bases presented either low efficiency or no reactivity. With the organic base NEt_3, no product was observed (Table 2, entry 6). When we finished choosing the suitable base, we then turned to the adequate quantity of molecular iodine needed in the reaction. We first used 10 mol% of molecular iodine, leading to a 63% yield of the desired compound, 4a (Table 2, entry 1). When increasing the amount of iodine to 15 mol%, the reaction yield was significantly increased to 79% (Table 2, entry 8). Increasing the amount of iodine to 20 mol% led to a slight improvement of the product yield (Table 2, entry 9). Moreover, the amount of K_2CO_3 was investigated. Conducting the reaction at 2.0 equivalent of potassium carbonate led to a decrease in the reaction yield (65%) (Table 2, entry 10). Whereas the yield was slightly increased when 4.0 equivalent of K_2CO_3 was employed (Table 2, entry 11). We have reviewed the use of potassium carbonate and found that the highest yield was obtained when 3.0 mol% of it was employed in the reaction, yielding **4a** at 79% yield (Table 2, entry 8). Attempts to improve the reaction yield of compound **4a** led to the consideration of different solvents, including acetonitrile, toluene, and dimethylformamide (Table 2, entries 16–18) but none of them proved useful in terms of effectivity and suitability as compared with dimethyl sulfoxide. We therefore found that dimethyl sulfoxide served as a very effective solvent. We also used different temperatures to see if the reaction yield is improved, and found that 120 °C was decided to be an optimum temperature. Reaction time was also another parameter we tested, and we found that 8 hours of reaction time resulted in an improvement of reaction yield for compound 4a (90%) (Table 2, entry 15).

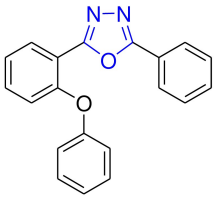
Thus having the above-optimized conditions in hand, the method was subsequently applied to *N*-acyl hydrazone **3a-o** series to examine the scope of the cyclization reaction. A series of new 2,5-disubstituted 1,3,4-oxadiazoles **4a–d, 4f–i, 4k–n**

Table 3. The substrate scope of oxidative cyclization for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **4a–d, 4f–i, 4k–n.**

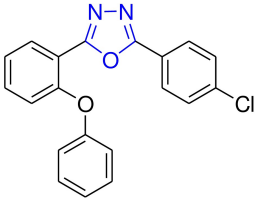


3a-3d
3f-3i
3k-3n

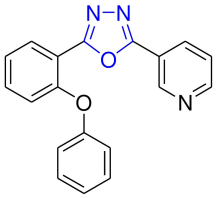
4a-4d
4f-4i
4k-4n



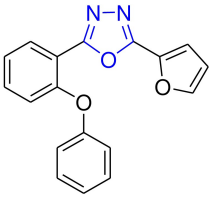
4a 90%



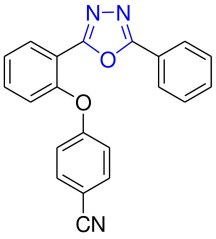
4b 72%



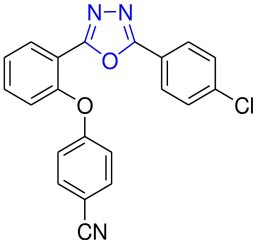
4c 81%



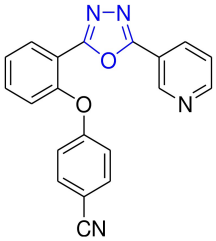
4d 86%



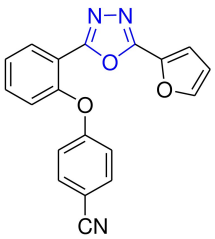
4f 88%



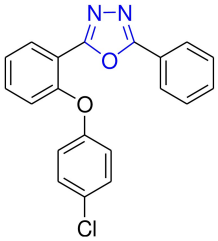
4g 84%



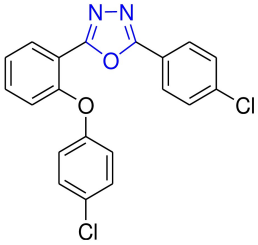
4h 87%



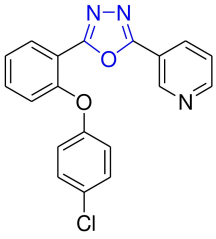
4i 92%



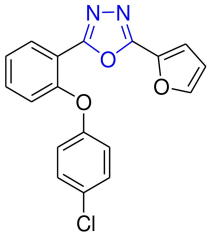
4k 91%



4l 70%



4m 72%



4n 89%

was successfully achieved with reaction yields of good to high values (Table 3). On the other hand, products were not observed under these optimized conditions, when *N*-acyl hydrazones where Ar group is 5-(4-methyl-1,2,3-thiadiazoyl) **3e, 3j, and 3o** were used as a substrate. Low yields and too many by-products were formed. Spectral and analytical characterization of all the structures were performed with FTIR, proton and carbon NMR, mass spectrometry, and CHN elemental analysis. All the synthesized *N*-acyl hydrazones **3a–o** show characteristic IR absorption peaks. The IR spectra of *N*-acyl hydrazones showed mainly stretching bands at 3100–3200 cm^{-1} assigned to -NH groups, at 1640–1650 cm^{-1} assigned to C=O groups, and at 1550–1600 cm^{-1} assigned to C=N groups, respectively. Successful formation of *N*-acyl hydrazones **3a–o** had a singlet, in the ^{1}H NMR spectra, for the NH group in the range of $\delta = 11.9–12.07$ ppm and a signal for the =CH group at $\delta = 8.39–9.05$ ppm were the characteristic signals. When ^{13}C NMR spectra are examined, carbons belonging to the C=O group in the range of 163–156 ppm and carbons belonging to the C=N group in the range of 161–154 ppm are seen. Because we spotted all these peaks in the respective spectra, the accuracy of these structures were validated. In the

case of 2,5-substituted 1,3,4-oxadiazoles, above mentioned IR and ^{1}HNMR spectra were missing that confirm the cyclization of *N*-acyl hydrazones and formation of the products with 1,3,4-oxadiazole skeleton.

2,5-disubstituted 1,3,4-oxadiazole series **4a–d, 4f–i, 4k–n** were synthesized using the general procedure outlined in Table 3.

Conclusion

In conclusion, we have described a molecular iodine-mediated C–O formation that is quite efficient and convenient. The condensation of 2-arenoxybenzaldehydes with substituted hydrazides led to the formation of *N*-acyl hydrazones, which are precursors of a series of novel 2,5-disubstituted 1,3,4-oxadiazoles. The oxidative cyclization method applied in this study is environmentally friendly because no metallic catalysts nor harmful solvents were used. The catalytic entity was molecular iodine and the base used was potassium carbonate. This protocol addresses the preparation of new 2,5-disubstituted 1,3,4-oxadiazoles from their precursors *N*-acyl hydrazones and it is believed that they will have enhanced biological and pharmaceutical activities.

Supporting Information Summary

Supplementary information section contains the experimental procedures, characterization details for all the compounds, and proton and carbon NMR spectral copies for all the compounds.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: *N*-acylhydrazones · oxidative cyclization · 1,3,4-oxadiazoles · molecular iodine

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