Research Article

Microwave-Assisted Solution Phase Synthesis of Novel 2-{4-[2-(*N*-Methyl-2-pyridylamino)ethoxy]phenyl}-5-Substituted 1,3,4-Oxadiazole Library

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A new series of 2-{4-[2-(*N*-methyl-2-pyridylamino)ethoxy]phenyl}-5-substituted 1,3,4-oxadiazoles were synthesized by the oxidative cyclization of hydrazones derived from 4-[2-(methylpyridin-2-ylamino)ethoxy]benzaldehyde and aryl hydrazines using chloramine-T as an efficient catalyst. All steps were assisted by microwave irradiation. Microwave enables all these reactions to be simple, rapid, high yielding, and avoid chromatograph purification and led environmentally benign total synthesis of focused oxadiazole library. All the synthesized compounds were isolated in good yield and characterized by ¹H NMR, ¹³C NMR, and elemental analyses. The title compounds represent a novel class of biologically active heterocycles.

1. Introduction

1,3,4-Oxadiazoles are versatile lead compounds for designing potent bioactive agents. This interesting class of heterocyclic compounds shows broad spectrum of biological activities. Substituted 1,3,4-oxadiazoles have revealed antimicrobial [1], anti-inflammatory [2], antimycobacterial [3], analgesic [4], anticonvulsant [5], antihypoglycemic [6], and insecticidal properties [7]. Compounds possessing oxadiazole moieties show anticancer [8, 9] and tyrosinase inhibitory activities [10]. Oxadiazoles are used as fluorescent whiteners and also act as muscle relaxants [11].

Meanwhile, microwave-assisted organic synthesis is a rapidly growing field in organic chemistry [12–14]. In the early days, domestic microwaves were used with poor reproducibility. Moreover, accidents were common due to the lack of control. The introduction of dedicated equipment by CEM, milestone, biotage, plazmatronika, Anton Paar and domestic companies Shikoku Instrumentation, EYELA and so on allowing for the online monitoring of temperature, power and pressure had a large impact on the further

development of this research field [15]. In particular, the pharmaceutical industry requires the production of a higher number of novel chemical entities, which requires chemists to employ a number of resources to reduce the time for the production of compounds. In general, most organic reactions have been heated using traditional heat transfer equipment such as oil baths, sand baths, and heating jackets. These heating techniques are, however, rather slow, and a temperature gradient can develop within the sample. In addition, local overheating can lead to product, substrate, and reagent decomposition. Microwave radiation provides an alternate to conventional heating as it utilizes the ability of liquids or solids to transform electromagnetic energy into heat.

In our previous studies, we have synthesized 2-{4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl}-5-substituted 1,3,4-oxadiazoles which showed promising antimicrobial [1] as well as anticancer activities [8, 9]. Recently, we have reported microwave-assisted synthesis of the antihyperglycemic drug rosiglitazone [16]. In continuation to our work on the synthesis of biologically active heterocycles [17, 18], herewith, we are reporting as an efficient

SCHEME 1: Synthesis of 2-[4-[2-N-methyl-2-pyridylamino)ethoxy]phenyl]-5-substituted 1,3,4-oxadiazole library.

microwave-assisted synthesis of novel 2-[4-[2-(N-methyl-2-pyridylamino)ethoxy]phenyl]-5-substituted 1,3,4-oxadiazole library by using CEM Discover microwave synthesizer (Scheme 1).

2. Results and Discussions

All the reactions were carried out in CEM Discover microwave apparatus. Acid hydrazides **3 (a–t)** were synthesized from corresponding acids by microwave irradiation for 20–50 min in the yield range 60–88%. Alcohol **6** was synthesized in 92% yield in 10 min at 140°C, which was converted to aldehyde **7** in 20 min at 100°C to yield 90%. Aldehyde **7** was converted to hydrazones **8 (a–t)** in 20–30 min to yield 70–85%. Hydrazones **8 (a–t)** were oxidatively cyclized

under microwave irradiation in 20–50 min to give title compounds **9 (a–t)**. Chloramine-T [19, 20] was used as an efficient reagent for the oxidative cyclization of aryl hydrazones **8 (a–t)** to give 1,3,4-oxadiazoles **9 (a–t)** in good yield and purity, without column purification in any stage (Table 1). However, by conventional method, the reaction takes 6–10 h heating and results in impure product due to side reactions, which needs column purification or further crystallization, and yields are generally low. Though there are several reagents for cycloaddition, chloramine-T is found to be effective reagent since it is mild, easy to handle, commercially available, nontoxic, and water tolerant. All the synthesized 1,3,4-oxadiazoles were characterized by ^1H NMR, ^{13}C NMR and elemental analyses. ^1H NMR of all the synthesized oxadiazoles showed singlet in the region δ 3.0–3.4 due to $-\text{NCH}_3$ group, and two triplets in the region δ

TABLE 1

Entry	Oxadiazole	Structure	Yield (%)	Melting point (°C)
1	9a		78	161-162
2	9b		76	122-124
3	9c		74	139-140
4	9d		79	142-144
5	9e		72	151-153
6	9f		70	118-120
7	9g		80	158-159
8	9h		81	152-153
9	9i		80	124-125
10	9j		78	158-160
11	9k		69	oily
12	9l		81	159-161
13	9m		73	182-184
14	9n		78	156-158
15	9o		70	oily
16	9p		74	143-145
17	9q		81	129-132
18	9r		79	100-101

TABLE 1: Continued.

Entry	Oxadiazole	Structure	Yield (%)	Melting point (°C)
19	9s		80	109–111
20	9t		77	155–158

3.9–4.2 and 4.1–4.4 are due to two methylene groups. The aromatic protons and other protons are observed in the expected region. ^{13}C NMR of all the synthesized oxadiazoles showed peaks in the expected region.

3. Conclusion

In conclusion, we have developed an efficient microwave-assisted method for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles. Chloramine-T was used as an efficient catalyst for cycloaddition under microwave irradiation. The method is quicker, high yielding, environment friendly, and cleaner chemistries. The isolated products are very pure and do not need any column purification. The method is very useful for combinatorial synthesis new libraries in drug discovery. The full paper and biological evaluation will be published elsewhere in future.

3.1. General Procedure for the Synthesis of Aroyl Hydrazines 3 (a–t). A solution of respective aromatic acid **1** (a–t) (0.5 g), ethanol (2 mL), and catalytic amount of conc. H_2SO_4 were inserted into CEM Discover microwave vessel, sealed and irradiated microwave at 100°C for 10–20 min. After the completion of the reaction by TLC (chloroform-ethyl acetate: 1 : 1), ethanol was removed and the product was extracted with dichloromethane, washed with dil. NaHCO_3 water and dried. Solvent was evaporated and the residue was dissolved in ethanol (2 mL), and 98% hydrazine hydrate (0.5 mL) was added. The mixture was irradiated at 120°C for 20–30 min. After the completion of the reaction by TLC (toluene/ethyl acetate/DEA, 7.5 : 2.5 : 1), the reaction mixture was cooled, and the solid formed was filtered and washed with chilled ethanol (1 mL) to get corresponding aroyl hydrazine **3** (a–t).

3.2. 2-(Methyl-pyridin-2-ylamino)ethanol 6. A mixture of 2-chloropyridine **4** (1.00 g, 8.81 mmol) and 2-(N-methyl-amino)ethanol **5** (1.33 g, 17.7 mmol) were introduced into a CEM discover vessel equipped with a magnetic stirrer. The vessel was sealed, and the reaction mixture was irradiated microwave (300 W) for 10 min at 140°C twice successively. The completion of the reaction was monitored by TLC (Toluene-ethyl acetate, 1 : 1). The reaction mass was cooled at room temperature, diluted with 2 mL water, and extracted into 10 mL ethyl acetate twice. The combined ethyl acetate layer was washed with water, saturated brine, dried over anhy. Na_2SO_4 and concentrated in vacuo to give **6** (1.23 g, 92%) as a pale yellow oil.

^1H NMR (CDCl_3): δ 3.05 (3H, s, NCH_3), 3.70 (2H, t, $J = 5.2$ Hz, CH_2CH_2), 3.84 (2H, t, $J = 5.2$ Hz, CH_2CH_2), 5.29 (1H, bs, OH, exchanges with D_2O), 6.52–6.58 (2H, m, ArH), 7.44–7.49 (1H, m, ArH), 8.39 (1H, d, $J = 4.2$ Hz, ArH); ^{13}C NMR (CDCl_3): δ 37.6, 49.7, 66.4, 111.5, 114.8, 137.4, 147.8, 158.2; IR (KBr pellet, cm^{-1}): ν 3069, 2961, 1764, 1667, 1485; Anal. Calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$: C, 63.13, H, 7.95, N, 18.41%. Found: C, 63.20, H, 7.85, N, 18.33%.

3.3. 4-[2-(Methyl-pyridin-2-ylamino)ethoxy]benzaldehyde 7. A mixture of **9** (1.00 g, 6.66 mmol), 4-fluorobenzaldehyde (827 mg, 6.61 mmol), KOH powder (1.10 g, 19.6 mmol), and tetrabutylammonium hydrogen sulphate (TBAHS) (220 mg, 0.650 mmol) in water (1 mL) and toluene (3 mL) was introduced into a CEM Discover microwave vessel equipped with a magnetic stirrer. The vessel was sealed, and the mixture was irradiated by microwave for 20 min at 85 – 100°C . The completion of the reaction was monitored by TLC (Toluene-Ethylacetate, 1 : 1). The reaction mass was cooled and diluted with 5 mL water and extracted into 25 mL toluene twice. The combined toluene layer was washed with water, dried over anhy. Na_2SO_4 , and concentrated under vacuo to give aldehyde **7** (1.53 g, 90%) as a pale yellow oil.

^1H NMR (CDCl_3): δ 3.05 (3H, s, NCH_3), 4.01 (2H, t, $J = 5.6$ Hz, CH_2CH_2), 4.27 (2H, t, $J = 5.6$ Hz, CH_2CH_2), 6.52–6.58 (2H, m, ArH), 6.99 (2H, d, $J = 8.6$ Hz, ArH), 7.45 (1H, m, ArH), 7.80 (2H, d, $J = 8.6$ Hz, ArH), 8.15 (1H, d, $J = 4.0$ Hz, ArH), 9.83 (1H, s, CHO); ^{13}C NMR (CDCl_3): δ 37.3, 48.6, 66.0, 105.1, 111.3, 114.1, 129.2, 131.3, 136.5, 147.0, 157.3, 163.0, 190.1; Anal. Calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}$: C, 63.13, H, 7.95, N, 18.41%. Found: C, 63.20, H, 7.85, N, 18.33%.

3.4. General Procedure for the Synthesis of Aroyl Hydrazones 8 (a–t). An equimolar mixture of aroyl hydrazine **3** (a–t) and 4-[2-(methyl-pyridin-2-ylamino)ethoxy]benzaldehyde **7** in isopropyl alcohol (4 mL) were inserted into CEM microwave vessel and irradiated for 20–50 min at 100°C . The progress of the reaction was monitored by TLC (Chloroform-ethyl acetate, 1 : 1). After the completion of the reaction, the mass was cooled and the solid formed was filtered to give aroyl hydrazones **8** (a–t) to yield 70–90%, which were directly used for next stage.

3.5. General Procedure for the Synthesis of 2-{4-[2-(N-Methyl-2-pyridylamino)ethoxy]phenyl}-5-Substituted 1,3,4-Oxadiazoles Typical Procedure 9g. A mixture of aroyl hydrazone **8g** (0.102 g, 0.25 mmol) and Chloramine-T. $3\text{H}_2\text{O}$ (0.82 g, 0.29 mmol) in ethanol (1 mL) were introduced into CEM

vessel and irradiated at 80–100°C for 20 min. The progress of the reaction was monitored by TLC. After the completion of the reaction, ethanol was removed, and residue was extracted with chloroform, washed with water, and dried. Chloroform was removed, and the residue was crystallized from ethanol to give **9g** as white solid (0.081 g, 80%), mp. 158–159°C. ¹H NMR (CDCl₃, 400 MHz): δ 3.16 (s, 3H, NCH₃), 4.03 (2H, t, *J* = 5.5 Hz, CH₂CH₂), 4.28 (2H, t, *J* = 5.5 Hz, CH₂CH₂), 6.52–6.59 (2H, m, ArH), 7.03 (2H, d, *J* = 8.6 Hz, ArH), 7.45–7.51 (3H, m, ArH), 8.02–8.07 (4H, m, ArH), 8.17 (1H, d, *J* = 4.8 Hz, ArH). ¹³C NMR (CDCl₃, 100 MHz): δ 37.9, 49.4, 66.6, 105.7, 111.9, 115.0 (2C), 116.2, 122.58, 128.0 (2C), 128.7 (2C), 129.4 (2C), 137.3, 137.7, 147.9, 158.2, 161.8, 163.3, 164.7.

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References

- [1] S. L. Gaonkar, K. M. Lokanatha Rai, and B. Prabhuswamy, "Synthesis and antimicrobial studies of a new series of 2-{4-phenyl}-5-substituted-1,3,4-oxadiazoles," *European Journal of Medicinal Chemistry*, vol. 41, no. 7, pp. 841–846, 2006.
- [2] M. M. Burbuliene, V. Jakubkiene, G. Mekuskiene, E. Udrenaitė, R. Smicius, and P. Vainilavicius, "Synthesis and anti-inflammatory activity of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1,3,4-oxadiazole-2-thiones," *Il Farmaco*, vol. 59, no. 10, pp. 767–774, 2004.
- [3] F. Macaev, G. Rusu, S. Pogrebnoi et al., "Synthesis of novel 5-aryl-2-thio-1,3,4-oxadiazoles and the study of their structure-anti-mycobacterial activities," *Bioorganic and Medicinal Chemistry*, vol. 13, no. 16, pp. 4842–4850, 2005.
- [4] M. Amir and K. Shikha, "Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino) phenyl]acetic acid derivatives," *European Journal of Medicinal Chemistry*, vol. 39, no. 6, pp. 535–545, 2004.
- [5] A. Zarghi, S. A. Tabatabai, M. Faizi et al., "Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1,3,4-oxadiazoles," *Bioorganic & Medicinal Chemistry Letters*, vol. 15, no. 7, pp. 1863–1865, 2005.
- [6] M. I. Husain, A. Kumar, and R. C. Srivastava, "Synthesis of N-(2-Naphthyloxyacetyl)thiosemicarbazides and 2-arylamino-5-(2-naphthyloxymethyl)-1,3,4-thiadiazoles/oxadiazoles as oral hypoglycemic agents," *Current Science*, vol. 55, pp. 644–646, 1986.
- [7] X. Zheng, Z. Li, Y. Wang et al., "Syntheses and insecticidal activities of novel 2,5-disubstituted 1,3,4-oxadiazoles," *Journal of Fluorine Chemistry*, vol. 123, no. 2, pp. 163–169, 2003.
- [8] A. Kumar, S. S. D'Souza, S. L. Gaonkar, K. M. Lokanatha Rai, and B. P. Salimath, "Growth inhibition and induction of apoptosis in MCF-7 breast cancer cells by a new series of substituted-1,3,4-oxadiazole derivatives," *Investigational New Drugs*, vol. 26, no. 5, pp. 425–435, 2008.
- [9] A. Kumar, S. S. D'Souza, S. R. Mysore Nagaraj, S. L. Gaonkar, K. M. Lokanatha Rai, and B. P. Salimath, "Antiangiogenic and antiproliferative effects of substituted-1,3,4-oxadiazole derivatives is mediated by down regulation of VEGF and inhibition of translocation of HIF-1α in Ehrlich ascites tumor cells," *Cancer Chemotherapy and Pharmacology*, vol. 64, no. 6, pp. 1221–1233, 2009.
- [10] M. T. H. Khan, M. I. Choudhary, K. M. Khan, M. Rani, and A. Rahman, "Structure-activity relationships of tyrosinase inhibitory combinatorial library of 2,5-disubstituted-1,3,4-oxadiazole analogues," *Bioorganic and Medicinal Chemistry*, vol. 13, no. 10, pp. 3385–3395, 2005.
- [11] J. Hill, "Comprehensive Heterocyclic Chemistry by A. R. Katritzky, Pergamon Press, Oxford, UK," vol. 4, p. 427, 1994.
- [12] P. Lidström, J. Tierney, B. Wathey, and J. Westman, "Microwave assisted organic synthesis—a review," *Tetrahedron*, vol. 57, no. 45, pp. 9225–9283, 2001.
- [13] A. De La Hoz, Á. Díaz-Ortiz, and A. Moreno, "Microwaves in organic synthesis: thermal and non-thermal microwave effects," *Chemical Society Reviews*, vol. 34, no. 2, pp. 164–178, 2005.
- [14] D. Dallinger and C. O. Kappe, "Microwave-assisted synthesis in water as solvent," *Chemical Reviews*, vol. 107, no. 6, pp. 2563–2591, 2007.
- [15] K. T. J. Loones, B. U. W. Maes, G. Rombouts, S. Hostyn, and D. Gaston, "Microwave-assisted organic synthesis: scale-up of palladium-catalyzed aminations using single-mode and multi-mode microwave equipment," *Tetrahedron*, vol. 61, no. 43, pp. 10338–10348, 2005.
- [16] S. L. Gaonkar and H. Shimizu, "Microwave-assisted synthesis of the antihyperglycemic drug rosiglitazone," *Tetrahedron*, vol. 66, no. 18, pp. 3314–3317, 2010.
- [17] S. L. Gaonkar, K. M. Lokanatha Rai, and B. Prabhuswamy, "Synthesis of novel 3-[5-ethyl-2-(2-phenoxy-ethyl)-pyridin]-5-substituted isoxazoline libraries via 1,3-dipolar cycloaddition and evaluation of antimicrobial activities," *Medicinal Chemistry Research*, vol. 15, no. 7-8, pp. 407–417, 2007.
- [18] S. L. Gaonkar, K. M. Lokanatha Rai, and S. N. Shetty, "Microwave-assisted synthesis and evaluation of anti-inflammatory activity of new series of N-substituted 2-butyl-5-chloro-3H-imidazole-4-carbaldehyde derivatives," *Medicinal Chemistry Research*, vol. 18, no. 3, pp. 221–230, 2009.
- [19] S. L. Gaonkar and K. M. Lokanatha Rai, "A new method for the generation of azoalkenes from ketohydrazones and its application to the synthesis of tetrahydropyridazine derivatives," *Tetrahedron Letters*, vol. 46, no. 35, pp. 5969–5970, 2005.
- [20] S. L. Gaonkar and K. M. Lokanatha Rai, "A new method for the generation of α-nitrosoolefins from ketooximes and its application to the synthesis of 5,6-dihydro-4H-1,2-oxazine derivatives," *Journal of Heterocyclic Chemistry*, vol. 42, no. 5, pp. 877–881, 2005.