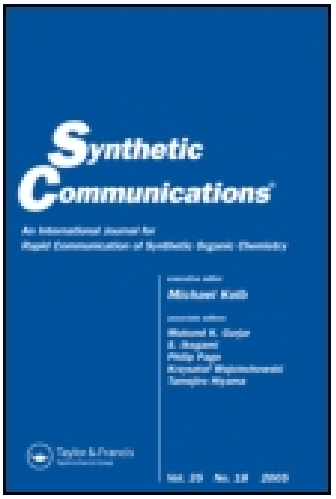

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Efficient and Convenient Protocol for the Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles Using $HClO_4$-SiO_2 as a Heterogeneous Recyclable Catalyst

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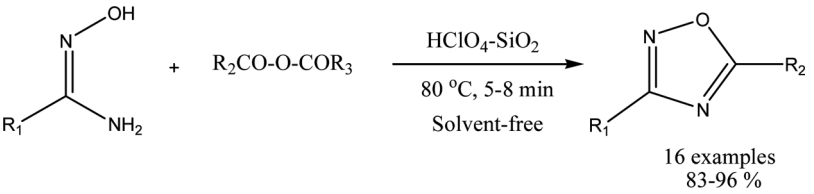
EFFICIENT AND CONVENIENT PROTOCOL FOR THE SYNTHESIS OF 3,5-DISUBSTITUTED 1,2,4-OXADIAZOLES USING $HClO_4$-SiO_2 AS A HETEROGENEOUS RECYCLABLE CATALYST

Ramu Tadikonda, Mangarao Nakka, Mahaboob Basha Gajula, Srinuvasarao Rayavarapu, Padma Rao Gollamudi, and Siddaiah Vidavalur

Department of Organic Chemistry and Foods, Drugs and Water, Andhra University, Visakhapatnam, India

GRAPHICAL ABSTRACT



Abstract *Silica-supported perchloric acid ($HClO_4$-SiO_2) was found to be a new, highly efficient, inexpensive, and reusable catalyst for a rapid and efficient synthesis of various 1,2,4-oxadiazoles with good to excellent yields under solvent-free conditions. The present methodology has been effectively utilized for the synthesis of oxolamine, an anti-inflammatory drug.*

Keywords Acid anhydrides; amidoxime; $HCLO_4$-SiO_2; 1,2,4-oxadiazole; reusable catalyst

INTRODUCTION

1,2,4-Oxadiazole scaffolds are known to possess significant biological activities, such as anti-inflammatory,[1] antiviral,[2] antirhinoviral,[3] and antitumor[4] activities. 1,2,4-Oxadiazoles are often used in drug discovery as hydrolysis-resisting bioisosteric replacements for ester or amide functionalities and are also used in the design of dipeptidomimetics as peptide building blocks. Moreover, the 1,2,4-oxadiazole motif can be found in several drugs and drug leads including the potent S1P1 agonist (**1**),[5] the metabotropic glutamate subtype 5 (mGlu5) receptor (**2**),[6] and muscarinic receptor[7] for the treatment of Alzheimer's disease. Generally, 1,2,4-oxadiazoles are synthesized by coupling of amidoximes with (i) activated carboxylic acid derivatives such as acid chlorides,[8] fluorides,[9] anhydrides,[10] or active ester;[11] and (ii) carboxylic acids in

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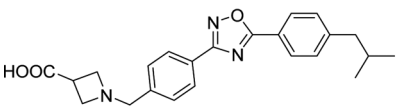
the presence of coupling reagents including dicyclohexylcarbodiimide (DCC),[10b,12] 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC),[8a,10a,13] 2-(dimethylamino) propyl chloride (DIC)/HOBt,[9] bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl),[10b] 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU),[14] or 1,1′-carbodiimidazole (CDI)[15] followed by cyclodehydration.[16] Other methods to obtain 1,2,4-oxadiazoles include reaction of amidoximes with aryl halides in the presence of palladium catalysts[17] or with aldehydes followed by oxidation.[18] However, these methods always suffered from the limitation of harsh conditions, tedious synthetic procedures, long reaction times, and expensive reagents or solvents. Therefore, developing a milder and general procedure to access 1,2,4-oxadiazoles is still highly desirable.



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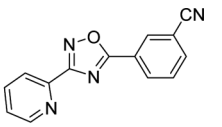
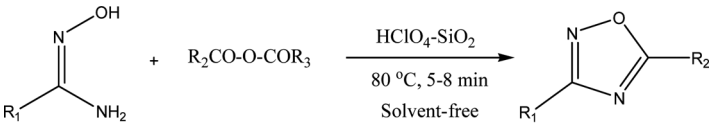


2

In recent years, heterogeneous catalysts have gained prominence because of environmental and economic considerations.[19] They have successfully been utilized in several organic transformations to minimize undesirable waste that causes environmental pollution. To the best of our knowledge, no report on the use of silica-supported perchloric acid ($HClO_4$-SiO_2) as a catalyst utilizing carboxylic acid anhydrides is known for the synthesis of 3,5-disubtituted 1,2,4-oxadiazoles. As a part of our ongoing research program[20] on the development of efficient and environmentally benign synthetic protocols for the synthesis of heterocycles, herein we report a simple and efficient one-pot method for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles from amidoximes and acid anhydrides using silica-supported perchloric acid ($HClO_4$-SiO_2) at 80 °C under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

Initially, a mixture of benzamidoxime (**3a**, 1.47 mmol) and acetic anhydride (**4a**, 1.77 mmol) was heated at 80 °C under solvent-free conditions in the presence of different catalysts such as activated SiO_2, $NaHSO_4$-SiO_2, *p*-toluenesulfonic acid (*p*-TSA)–SiO_2, amberlyst-15, and $HClO_4$-SiO_2 (5 mol% each) separately. Activated SiO_2, $NaHSO_4$-SiO_2, *p*-TSA-SiO_2, and amberlyst-15 catalyze the reaction to furnish the desired product **5a**, albeit in poor yields (Table 1, entries 3–6). To our delight, $HClO_4$-SiO_2 gave the desired 3,5-disubstituted 1,2,4-oxadiazole **5a** in 95% yield (Table 1, entry 9). Encouraged by this result, we then focused on optimizing the reaction



3 **4** **5**

Scheme 1. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles.

Table 1. Optimization of reaction conditions

Entry	Catalyst	Amount of catalyst (mol %)	Temperature (°C)	Time (min)	Yield (%)[a]
1	—	—	rt	300	15
2	—	—	80	120	40
3	Activated SiO_2	5	80	90	55
4	$NaHSO_4$-SiO_2	5	80	60	60
5	*p*-TSA-SiO_2	5	80	30	65
6	Amberlyst-15	5	80	3	68
7	$HClO_4$-SiO_2	5	Rt	180	25
8	$HClO_4$-SiO_2	5	50	20	79
9	$HClO_4$-SiO_2	5	80	5	95
10	$HClO_4$-SiO_2	5	100	5	90
11	$HClO_4$-SiO_2	5	120	5	85
12	$HClO_4$-SiO_2	10	80	5	87
13	$HClO_4$-SiO_2	1	80	30	80

[a]Isolated yield.

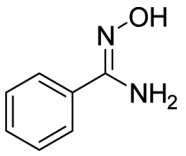
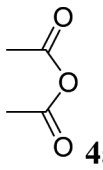
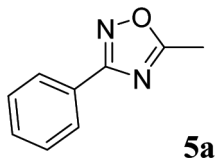
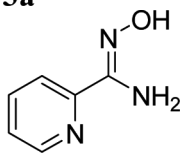
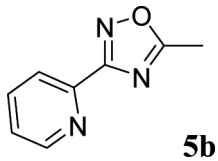
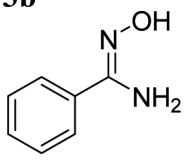
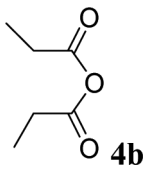
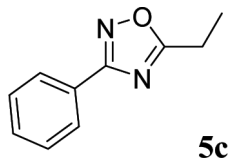
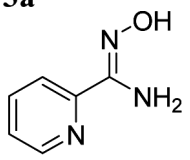
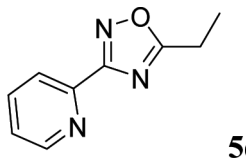
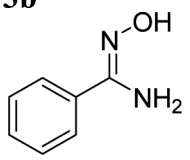
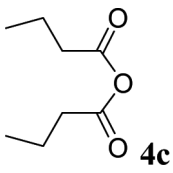
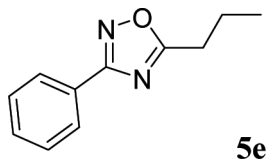
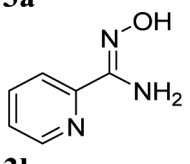
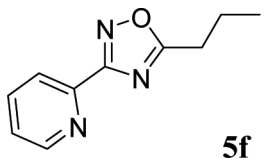
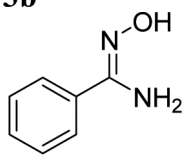
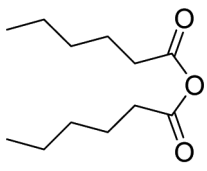
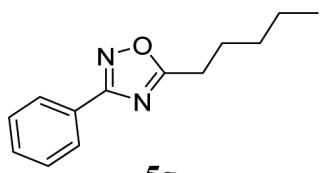
conditions. The $HClO_4$-SiO_2 loading was subsequently examined (Table 1, entries 9, 12, and 13), and it was found that 5 mol% of $HClO_4$-SiO_2 provides the maximum yield in the least time (Table 1, entry 9). We immediately undertook a study to examine the effects of temperature on this transformation (Table 1, entries 7, 8, 10, and 11). The results demonstrated that 80 °C appeared to be the optimum temperature for this transformation. Thus, the best yield, cleanest reaction, and most facile workup were achieved by employing 5 mol% of $HClO_4$-SiO_2 at 80 °C under solvent-free conditions (Table 1, entry 9).

To generate a small library of functionalized 1,2,4-oxadiazoles (**5**), we next utilized a variety of substrates to explore the synthetic scope and generality of this method under the optimal conditions (Table 2). Notably, a wide range of anhydrides (**4a**–**h**) and amidoximes (**3a** and **3b**) were well tolerated and proceeded smoothly under the optimized reaction conditions. All products obtained were characterized by spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

Next, we investigated the reusability of $HClO_4$-SiO_2. A mixture of benzamidoxime, acetic anhydride, and $HClO_4$-SiO_2 was stirred at 80 °C for 5 min. After the completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was diluted with dichloromethane (DCM, 5 mL) and the catalyst was separated by simple filtration. The recovered catalyst was activated and reused for three consecutive times with only slight variation in the yields of the products (93%, 92%, and 90%).

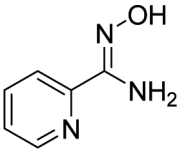
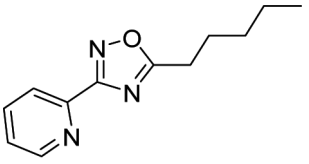
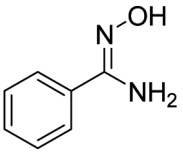
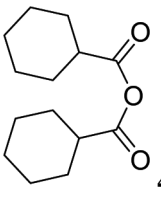
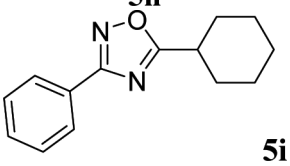
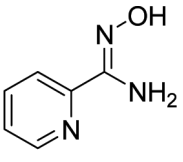
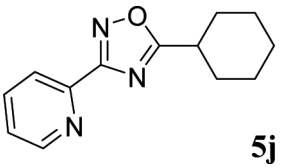
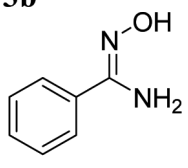
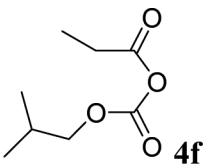
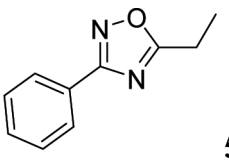
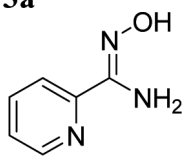
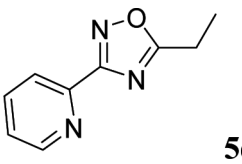
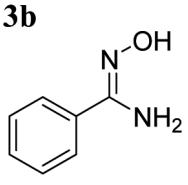
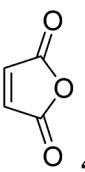
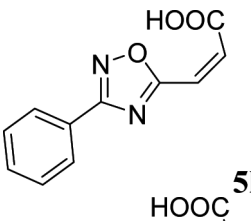
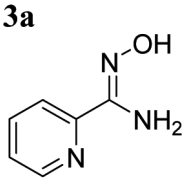
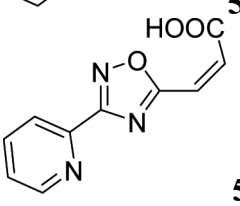
Substituted oxadiazoles are present in many important pharmaceutically active molecules. Although many of the compounds in Table 2 already display drug like attributes, we wanted to demonstrate the utility of this method through the synthesis of a pharmaceutically relevant molecule oxolamine, an anti-inflammatory drug. Thus, benzamidoxime (**3a**) was treated with 3-chloropropanoic anhydride in the presence of $HClO_4$-SiO_2 under solvent-free conditions to get compound **6**. Subsequently, it was treated with commercially available $Et_2NH \cdot HCl$ in the presence of K_2CO_3 under refluxing conditions to afford desired oxolamine (**7**) in 84% yield (Scheme 2).

Table 2. $HClO_4$-SiO_2-catalyzed synthesis of 3,5-disubstituted 1,2,4-oxadiazoles

Entry	Amidoxime (**3**)	Anhydride (**4**)	Product (**5**)	Time (min)	Yield (%)[a]
1	 **3a**	 **4a**	 **5a**	5	95
2	 **3b**	**4a**	 **5b**	5	95
3	 **3a**	 **4b**	 **5c**	5	95
4	 **3b**	**4b**	 **5d**	6	94
5	 **3a**	 **4c**	 **5e**	5	95
6	 **3b**	**4c**	 **5f**	5	94
7	 **3a**	 **4d**	 **5g**	4	96

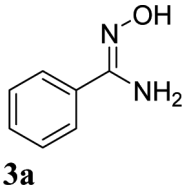
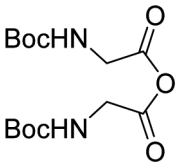
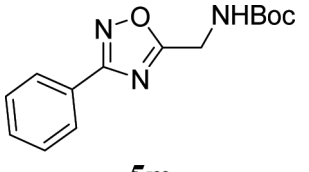
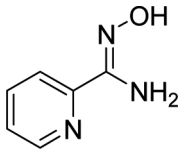
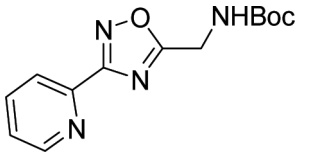
(*Continued*)

Table 2. Continued

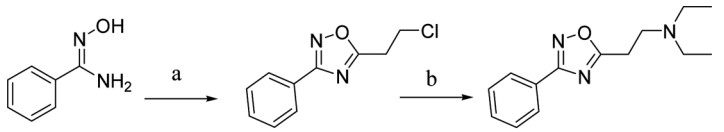
Entry	Amidoxime (**3**)	Anhydride (**4**)	Product (**5**)	Time (min)	Yield (%)[a]
8	 **3b**	**4d**	 **5h**	5	95
9	 **3a**	 **4e**	 **5i**	6	96
10	 **3b**	**4e**	 **5j**	5	95
11	 **3a**	 **4f**	 **5c**	7	92
12	 **3b**	**4f**	 **5d**	7	93
13	 **3a**	 **4g**	 **5k**	8	86
14	 **3b**	**4g**	 **5l**	8	83

(*Continued*)

Table 2. Continued

Entry	Amidoxime (**3**)	Anhydride (**4**)	Product (**5**)	Time (min)	Yield (%)[a]
15	 **3a**	 **4h**	 **5m**	7	91
16	 **3b**	**4h**	 **5n**	8	90

[a]Isolated yield.



3a **6** **7**

Scheme 2. Reagents and conditions: (a) 3-chloropropanoic anhydride, $HClO_4$-SiO_2, solvent-free, 80 °C, 8 min; (b) K_2CO_3, KI, CH_3CN, $Et_2NH.HCl$, reflux, 3 h.

The advantage of this method over previous methods could be established while comparing the results obtained with acetic anhydride as well as with hexanoic anhydride. For instance under the reaction condition with benzaldehyde and with ammonium acetate and nitroethane in acetic acid under reflux conditions to afford 5-methyl-3-phenyl-1,2,4-oxadiazole (**5a**) the reported yield is 50%,[21] whereas the same product could be obtained in 95% yield within 5 min under the method described on this report. On the other hand, the reaction of benzamidoxime with hexanoic anhydride in water under reflux conditions resulted in 53% yield of the 5-pentyl-3-phenyl-1,2,4-oxadiazole (**5g**) in 12 h,[22] whereas the present method affords 96% yield of the corresponding product in 4 min.

EXPERIMENTAL

General Experimental Procedure for 5-Methyl-3-phenyl 1,2,4-oxadiazole (Table 2, 5a)

A mixture of benzamidoxime (1.47 mmol), acetic anhydride (1.77 mmol), and $HClO_4$-SiO_2 (5 mol%) was stirred at 80 °C for the specified time (Table 2). After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and diluted with DCM, and the catalyst was allowed to settle down.

Then the reaction mixture was filtered and washed with DCM, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ and water. The obtained organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get crude compound **5a**, which was further purified by column chromatography on silica gel using hexane/EtOAc as eluents.

Mp 35–37 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.63 (s, 3H), 7.50–7.57 (m, 3H), 7.98–8.00 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.8, 126.3, 126.8, 129.0, 131.2, 167.6, 177.2; LC-MS: m/z 161 $[M+H]^+$. Anal. calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.09; N, 17.45.

CONCLUSIONS

In summary, we have developed a simple, efficient, and ecofriendly method for the synthesis of 3,5-diubstituted 1,2,4-oxadiazoles using $HClO_4$-SiO_2. The protocol uses amidoximes and acid anhydrides as starting materials, and the corresponding products were obtained in fair to excellent yields at 80 °C under solvent-free conditions. The $HClO_4$-SiO_2 catalyst was reused for three consecutive times with only a slight variation in yields of the products. The present methodology has been effectively utilized for the synthesis of oxolamine, an anti-inflammatory drug.

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SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra can be accessed on the publisher's website.

REFERENCES

1. Nicoaides, D. N.; Fylaktakidou, K. C.; Litinas, K. E.; Hadjipavlou-Litina, D. Synthesis and biological evaluation of several coumarin-4-carboxamidoxime and 3-(coumarin-4-yl)-1,2,4-oxadiazole derivatives. *Eur. J. Med. Chem.* **1998**, *33*, 715.
2. Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Parkes, K. E. B.; Thomas, G. J. Pyrimidine nucleosides. WO Patent 9706178, February 20, 1997.
3. Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. Oxadiazoles as ester bioisosteric replacements in compounds related to disoxaril: Antirhinovirus activity. *J. Med. Chem.* **1994**, *37*, 2421.

4. Chimirri, A.; Grasso, S.; Montforte, A. M.; Rao, A.; Zappala, M. Synthesis and antitumor activity evaluation of δ2–1,2,4-oxadiazoline derivatives. *Farmaco* **1996**, *51*, 125.
5. Li, Z.; Chen, W.; Hale, J. J.; Lynch, C. L.; Mills, S. G.; Hadju, R.; Keohane, C. A.; Rosenbach, M. J.; Milligan, J. A.; Shei, G. J.; Chrebet, G.; Parent, S. A.; Bergstrom, J.; Card, D.; Forrest, M.; Quackenbush, E. J.; Wickham, L. A.; Vargas, H.; Evans, R. M.; Rosen, H.; Mandala, S. Discovery of potent 3,5-diphenyl-1,2,4-oxadiazole sphingosine-1-phosphate-1 ($S1P_1$) receptor agonists with exceptional selectivity against $S1P_2$ and $S1P_3$. *J. Med. Chem.* **2005**, *48*, 6169.
6. Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P. Discovery of novel heteroarylazoles that are metabotropic glutamate subtype 5 receptor antagonists with anxiolytic activity. *J. Med. Chem.* **2004**, *47*, 4645.
7. Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. Synthesis and biological activity of 1,2,4-oxadiazole derivatives: Highly potent and efficacious agonists for cortical muscarinic receptors. *J. Med. Chem.* **1990**, *33*, 2690.
8. (a) Rice, K. D.; Nuss, J. M. An improved synthesis of 1,2,4-oxadiazoles on solid support. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 753; (b) Meyer, E.; Joussef, A. C.; Gallardo, H. Synthesis of new 1,2,4- and 1,3,4-oxadiazole derivatives. *Synthesis* **2003**, *6*, 899.
9. Sams, C. K.; Lau, J. Solid-phase synthesis of 1,2,4-oxadiazoles. *Tetrahedron Lett.* **1999**, *40*, 9359.
10. (a) Liang, G. B.; Feng, D. D. An improved oxadiazole synthesis using peptide coupling reagents. *Tetrahedron Lett.* **1996**, *37*, 6627; (b) Borg, S.; Estenne Bouhtou, G.; Luthman, K.; Csoregh, I.; Hesselink, W.; Hacksell, U. Synthesis of 1,2,4-oxadiazole, 1,3,4-oxadiazole, and 1,2,4-triazole-derived dipeptidomimetics. *J. Org. Chem.* **1995**, *60*, 3112.
11. Buchanan, J. L.; Vu, C. B.; Merry, T. J.; Corpuz, E. G.; Pradeepan, S. G.; Mani, U. N.; Yang, M.; Plake, H. R.; Varkhedkar, V. M.; Lynch, B. A.; MacNeil, I. A.; Loiacono, K. A.; Tiong, C. L.; Holt, D. A. Structure–activity relationships of a novel class of SRC SH2 inhibitors. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2359.
12. Braga, A. L.; Ludtke, D. S.; Alberto, E. E.; Dornelles, L.; Filho, W. A. S.; Corbellini, V. A.; Rosa, D. M.; Schwab, R. S. One-pot synthesis of chiral *N*-protected α-amino acid-derived 1,2,4-oxadiazoles. *Synthesis* **2004**, *10*, 1589.
13. Rudolph, J.; Theis, H.; Hanke, R.; Endermann, R.; Johannsen, L.; Geschke, F. U. *seco*-Cyclothialidines: New concise synthesis, inhibitory activity toward bacterial and human DNA topoisomerases, and antibacterial properties. *J. Med. Chem.* **2004**, *44*, 619.
14. Poulain, R. F.; Tartar, A. L.; Deprez, B. P. Parallel synthesis of 1,2,4-oxadiazoles from carboxylic acids using an improved, uronium-based, activation. *Tetrahedron Lett.* **2001**, *42*, 1495.
15. Deegan, T. L.; Nitz, T. J.; Cebzanov, D.; Pufko, D. E.; Porco, J. A. Parallel synthesis of 1,2,4-oxadiazoles using CDI activation. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 209.
16. Grant, D.; Dahl, R.; Cosford, N. D. Rapid multistep synthesis of 1,2,4-oxadiazoles in a single continuous microreactor sequence. *J. Org. Chem.* **2008**, *73*, 7219.
17. Young, J. R.; DeVita, R. J. Novel synthesis of oxadiazoles via palladium catalysis. *Tetrahedron Lett.* **1998**, *39*, 3931.
18. Srivastava, R. M.; de Almeida Lima, A.; Viana, O. S.; da Costa Silva, M. J.; Catanho, M. T. J. A.; de Morais, J. O. F. Anti-inflammatory property of 3-aryl-5-(n-propyl)-1,2,4-oxadiazoles and antimicrobial property of 3-aryl-5-(n-propyl)-4,5-dihydro-1,2,4-oxadiazoles: Their syntheses and spectroscopic studies. *Bioorg. Med. Chem.* **2003**, *11*, 1821.
19. (a) Samajdar, S.; Becker, F. R.; Naik, P. K. Surface-mediated highly efficient regio-selective nitration of aromatic compounds by bismuth nitrate. *Tetrahedron Lett.* **2000**, *41*, 8017; (b) Bahulayan, D.; Narayan, G.; Sreekumar, V.; Lalithambika, M. Natural

bentonite clay/dilute HNO_3 (40%): A mild, efficient, and reusable catalyst/reagent system for selective mononitration and benzylic oxidations. *Synth. Commun.* **2002**, *32*, 3565; (c) Srinivas, K. V. N. S.; Das, B. An efficient one-pot synthesis of pyrano- and furoquinolines employing two reusable solid acids as heterogeneous catalysts. *Synlett* **2004**, *10*, 1715.

20. (a) Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, C. V. An efficient one-pot synthesis of polyhydroquinoline derivatives via Hantzsch condensation using a heterogeneous catalyst under solvent-free conditions. *Arkivoc* **2006**, *2*, 201; (b) Maheswara, M.; Siddaiah, V.; Damu, G. L. V.; Rao, Y. K.; Rao, C. V. A solvent-free synthesis of coumarins via Pechmann condensation using heterogeneous catalyst. *J. Mol. Catal. A: Chem.* **2006**, *255*, 49; (c) Siddaiah, V.; Basha, G. M.; Padma Rao, G.; Viplava Prasad, U.; Suryachendra Rao, R. PEG-mediated catalyst-free synthesis of 1,4-dihydropyridines and polyhydroquinoline derivatives. *Synth. Commun.* **2012**, *42*, 627.
21. Young, T. E.; Beidler, W. T. Direct synthesis of 5-methyl-3-aryl-1,2,4-oxadiazoles from aryl aldehydes, nitroethane, and ammonium acetate. *J. Org. Chem.* **1985**, *50*, 1182.
22. Kaboudin, B.; Malekzadeh, L. Organic reactions in water: An efficient method for the synthesis of 1,2,4-oxadiazoles in water. *Tetrahedron Lett.* **2011**, *52*, 6424.