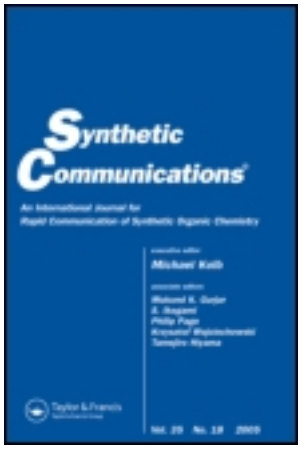

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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http://www.tandfonline.com/loi/lsyc20

One-Step Protection-Free Synthesis of 3-Aryl-5-hydroxyalkyl-1,2,4-oxadiazoles as Building Blocks

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Accepted author version posted online: 26 Mar 2013.Published online: 26 Jun 2013.

To cite this article: Ricardo A. W. Neves Filho, Diana C. B. da Silva-Alves, Janaína V. dos Anjos & Rajendra M. Srivastava (2013): One-Step Protection-Free Synthesis of 3-Aryl-5-hydroxyalkyl-1,2,4-oxadiazoles as Building Blocks, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:19, 2596-2602

To link to this article: http://dx.doi.org/10.1080/00397911.2012.724757

Synthetic Communications®, 43: 2596–2602, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.724757

ONE-STEP PROTECTION-FREE SYNTHESIS OF 3-ARYL-5-HYDROXYALKYL-1,2,4-OXADIAZOLES AS BUILDING BLOCKS

Ricardo A. W. Neves Filho, Diana C. B. da Silva-Alves, Janaína V. dos Anjos, and Rajendra M. Srivastava
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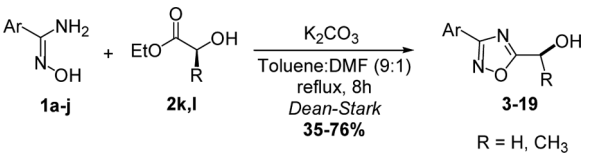
GRAPHICAL ABSTRACT



Abstract *A simple and straightforward synthesis of 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles is described. The reaction among arylamidoximes, ethyl glycolate or ethyl lactate, and potassium carbonate in refluxing toluene afforded the desired 1,2,4-oxadiazoles in moderate to good yields. The synthesis has been accomplished in a single step, avoiding protection–deprotection protocols.*

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Keywords Cyclodehydration; 1,2,4-oxadiazoles; thermal reaction

INTRODUCTION

1,2,4-Oxadiazole-containing compounds have been attracting great attention because of their applications in therapeutics and materials chemistry.[1–5] When employed as a pharmacophore, the 1,2,4-oxadiazole ring has been used as anti-inflammatory,[6] apoptosis inducing,[7] antimicrobial,[8,9] larvicidal,[10] and cytotoxic[11] agent, for example. In particular, 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles are noteworthy because they were widely employed as 5-lipoxygenase activating protein inhibitors;[12] *N*-type calcium channel antagonists;[13] inhibitors of stearoyl-coenzyme-A delta-9 desaturase;[14] stearoyl-CoA desaturase inhibitors for treatment of obesity, diabetes, and metabolism-related diseases;[15] and bombesin-2 (BB2) receptor antagonists for treating cancer and Alzheimer disease.[16] Furthermore, these compounds

Received July 10, 2012.
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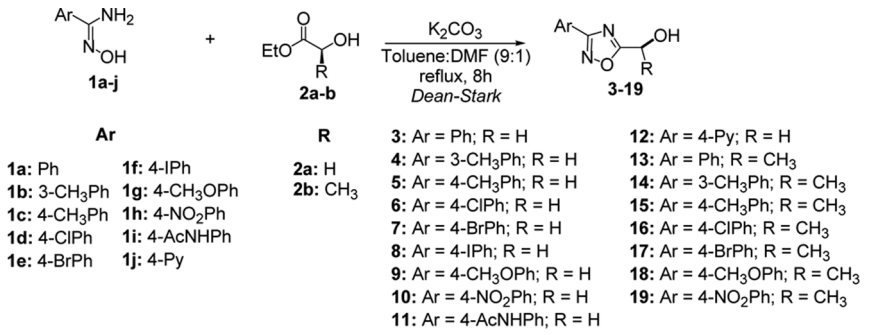


Scheme 1. Synthesis of oxadiazoles **3**–**19** from arylamidoximes **1a**–**j** and esters **2a**–**b**.

have also presented low toxicity (>800 mg/kg of body weight) and sedative action at doses as low as 50–75 mg/kg when injected in mice or rats intraperitoneally.[17] Moreover, other compounds containing the 3-aryl-5-hydroxymethyl-1,2,4-oxadiazole moiety have been employed as fungicides, pesticides,[18] and building blocks for synthesizing biologically active compounds.[19–23]

Because of the great importance of title compounds, there is a vast industrial interest in this class of oxadiazoles because some of them are commercially available, but in gram quantities.[24] Therefore, it would be nice to achieve their synthesis in a simple and cost-effective manner.

The most common method for the preparation of 1,2,4-oxadiazole ring-containing compounds is the acylation of amidoximes followed by cyclodehydration.[1,25,26] In addition, all known procedures achieving 3-aryl-5-hydroxymethyl-1,2,4-oxadiazoles from amidoximes and glycolic acid derivatives involve protection–deprotection protocols. This is done to avoid the acylation of OH moiety in ethyl glycolate or ethyl lactate.[17,20,27] Recently, it has been disclosed that the base-catalyzed thermal reaction between carboxylic acid esters and amidoximes furnishes 1,2,4-oxadiazoles.[28–30] Lately, our research group has successfully synthesized functionalized 1,2,4-oxadiazoles by reacting arylamidoximes and methyl levulinate in the presence of potassium carbonate under solvent-free microwave irradiation.[30] Although it is well established that transesterification is achieved by heating a carboxylic acid ester and an alcohol in the presence of a strong base, there is no report concerning this type of reaction by using a relatively weaker base such as potassium carbonate. In this article, we report the preparation of title compounds **3–19** by the reaction of arylamidoximes **1a–j** and ethyl glycolate **2a** in the presence of K_2CO_3 in refluxing toluene. We have also extended this method for synthesizing 3-aryl-5-(hydroxyeth-1-yl)-1,2,4-oxadiazoles **13–19** by employing *S*-ethyl lactate **2b** (Scheme 1). The literature does not report such syntheses.

RESULTS AND DISCUSSION

Initially, we tried the reaction of amidoxime **1a** and ethyl glycolate **2a** using toluene as a solvent, but the reaction did not proceed, possibly because of the poor miscibility of ester **2a** in this solvent. Therefore, we have used dimethylformamide

(DMF) as a cosolvent. Thus, a mixture of toluene–DMF (9:1) worked well for compounds **3–10** and **13–19**, but better yields were achieved for compounds **11** and **12** when we changed the ratio of toluene and DMF to 7:3. Water removal during the reaction by using a Dean–Stark apparatus helped to complete the reaction. It is noteworthy to find that using K_2CO_3 as a base results in better chemical yields compared to the use of Na_2CO_3. Expensive cesium carbonate can also be used for this end without any improvement either in the reaction time or yields. We have also investigated microwave (MW) irradiation for substrates **1a** and **2a**; the reaction completed in 10 min, but the yield (24%) was quite poor in comparison with the solution procedure. However, we have also observed the formation of a large quantity of 3,5-diphenyl-1,2,4-oxadiazole in the MW experiments, probably due to thermal homocoupling reaction of two arylamidoxime molecules.[31] After attaining the right conditions, we succeeded in synthesizing 17 different 1,2,4-oxadiazoles **3–19** containing a hydroxymethyl group attached to the C-5 side chain of the heterocyclic ring by the reaction of aryl amidoximes **1a–j** and ethyl glycolate **2a** or ethyl lactate **2b** (Table 1).

It can be noticed that electron-releasing as well as electron-removing groups at the *para* position of the phenyl ring do not influence the reaction. Although this procedure works well and appears promising, there is one limitation. For example, when amidoximes containing a nitrogen atom inside or outside the phenyl ring (e.g., **1i** and **1j**), were used, the yields were quite poor. Increasing the polarity of the solvent system (toluene–dimethylformamide, 7:3) improved the yields but to a lesser extent compared to other arylamidoximes without having a nitrogen atom (see Table 1).

To verify the application of our method in multigram synthesis, the reaction of **1a** with **2a** was performed at a 25 mmol scale with impressive results (the yield of the

Table 1. Melting points and yields of compounds **3–19**

Compound	Ar	R	Yield (%)	M.p. (°C)	M.p. (°C) Lit.[31]
3	C_6H_5	H	69 (67)[a]	59–60	56–60
4	3-CH_3-C_6H_4	H	57	58–59	–
5	4-CH_3-C_6H_4	H	72	84–85	–
6	4-Cl-C_6H_4	H	70	93–94	95–96
7	4-Br-C_6H_4	H	73	94–95	–
8	4-I-C_6H_4	H	76	113–114	–
9	4-CH_3O-C_6H_4	H	68	155–156	158–159
10	4-NO_2-C_6H_4	H	56	124–125	–
11	4-AcNH-C_6H_4	H	22 (45)[b]	176–177	–
12	4-Pyridyl	H	5 (35)[b]	152–153	N.A.
13	C_6H_5	CH_3	70	Oil	–
14	3-CH_3-C_6H_4	CH_3	66	Oil	–
15	4-CH_3-C_6H_4	CH_3	72	Oil	–
16	4-Cl-C_6H_4	CH_3	68	75–76	–
17	4-Br-C_6H_4	CH_3	63	90–91	–
18	4-CH_3O-C_6H_4	CH_3	66	83–84	–
19	4-NO_2-C_6H_4	CH_3	51	151–152	–

[a]Experiment performed at 25 mmol scale.
[b]Yields in parenthesis indicates the use of 7:3 toluene:DMF (V/V) system during the reaction.

product **3** was 69%). These findings show that it could be possible to scale up the newly developed protocol at a much larger scale.

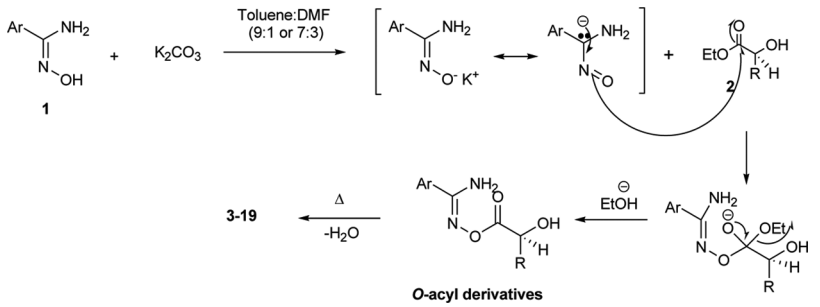
Next, we tried to perform the same reaction by using ethyl lactate. The method has worked well in all cases. We also observed total racemization of the products, as verified by optical rotation measurements.

Because the final products **13–19** have been found as racemic, it is obvious that potassium carbonate in refluxing toluene did the job. At the moment, it is not clear if optically active ethyl lactate suffered any racemization (partial or total) before reacting with arylamidoximes. Even if the optically active ester reacted as such with arylamidoximes to form the intermediates possessing an asymmetric carbon atom, the latter could undergo racemization before cyclization or after cyclization to provide inactive 5-(hydroxyeth-1-yl)-3-aryl-1,2,4-oxadiazoles **13–19**. It appears to us that it has been a gradual process from the beginning until the end of the reaction, although we cannot be sure about it.

We also employed the same reaction protocol employing thioglycolic acid methyl ester instead of **2**. In this reaction, we have observed the formation of a complex mixture of products and decomposition of the starting materials.

The key to success for the reaction between **1** and **2** is the quick formation of a resonance-stabilized anion at the oxygen atom of arylamidoxime in the presence of K_2CO_3, which consequently attacks the carbonyl carbon atom of the ester group followed by the ejection of the ethoxy group with the formation of *O*-acyl derivative of aryl amidoxime. The *O*-acyl derivative then cyclodehydrates to furnish the product (Scheme 2).

As observed, the unprotected –OH group of ethyl glycolate and ethyl lactate did not cause any significant difficulty in the reaction in the presence of K_2CO_3. Even if it has removed the proton from the –OH group, the oxygen atom would not be



Scheme 2. Mechanism of formation of 1,2,4-oxadiazoles **3**–**19** from compounds **1** and **2**.

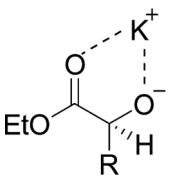


Figure 1. Complexation of potassium cation with negatively charged esters **2a** and **2b**.

able to stabilize the negative charge on it, although it would form a five-membered complex with potassium cation (Fig. 1). This unique situation could allow the reaction to proceed without protection of –OH in **2a** and **2b**, respectively.

In summary, we have developed a direct protection–deprotection-free approach for synthesizing 3-aryl-5-hydroxyalkyl-1,2,4-oxadiazoles (**3–19**). The base-mediated reaction between amidoximes **1a–j** and esters **2a** and **2b** furnished the desired products in good yields and presented a large scope of applications. This protocol has successfully been scaled up to 25 mmol quantity. Thus this procedure appears to be suitable for further applications at larger scales.

EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. Infrared (IR) spectra of the compounds were recorded on a Perkin-Elmer model 283 spectrometer employing KBr pellets. ^{1}H NMR spectra were obtained with a Varian 300-MHz instrument using tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were recorded on a Varian 75-MHz spectrometer. Elemental analysis was performed with a Carlo Erba instrument model E-1110. Optical rotations were recorded using a Jasco P2000 polarimeter. Thin-layer chromatography (TLC) was performed on plates coated with silica gel containing GF_{254} as fluorescent indicator. The solvent system for the development was $CHCl_3$–EtOAc (7:3).

Typical Experimental Procedure

In a round bottom flask equipped with a reflux condenser and a Dean–Stark trap, the suitable arylamidoxime **1a–j** (5 mmol) and carboxylic acid ethyl ester **2a** or **2b** (7.5 mmol) were dissolved in a mixture of toluene:DMF (9:1, v/v) (80 mL). Then, potassium carbonate (0.83 g, 6 mmol) was added. The contents were stirred under reflux for 8 h. The contents in the flask were diluted with ethyl acetate (40 mL) and water (40 mL). The phases were separated and the organic layer was washed with 1 M aqueous hydrochloric acid solution (40 mL), saturated $NaHCO_3$ solution (40 mL) and then with a saturated brine solution (40 mL). The resulting organic phase was dried over anhydrous sodium sulfate. Solvent removal under reduced pressure provided the crude product, which could be purified either by crystallization or by column chromatography.

5-Hydroxymethyl-3-phenyl-1,2,4-oxadiazole (3)

Colorless crystals (69%), crystallized from EtOAc and *n*-hexane, mp: 59–60 °C. (lit.[16]): 58–60 °C. IR (KBr): 3293, 2909, 1598 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.01 (bs, 1H), 4.5 (s, 2H), 7.43–7.53 (m, 3H), 8.02 (d, $J = 9.6$ Hz, 2H), ^{13}C NMR (75 MHz, $CDCl_3$): 56.3, 126.0, 127.3, 128.9, 131.5, 168, 178.5.

SUPPORTING INFORMATION

Full experimental details and spectroscopic data (^{1}H and ^{13}C NMR spectra) for compounds **3–19** can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

Our thanks go to the Brazilian National Research Council (CNPq) and Pernambuco State's Scientific and Research Foundation (FACEPE, PRONEX-0788-1.06/08 CNPq) for providing financial assistance. One of us (R. A. W. N. F.) is grateful to CNPq for a technician's fellowship.

REFERENCES

1. Jakopin, Z.; Dolenc, M. S. *Curr. Org. Chem.* **2008**, *12*, 850–898.
2. Tiwari, S. B.; Kohli, D. V. *Med. Chem. Res.* **2008**, *17*, 386–398.
3. Lankau, H. J.; Unverferth, K.; Grunwald, C.; Hartenhauer, H.; Heinecke, K.; Bernoster, K.; Dost, R.; Egerland, U.; Rundfeldt, C. *Eur. J. Med. Chem.* **2007**, *42*, 873–879.
4. Gallardo, H.; Cristiano, R.; Vieira, A. A.; Neves Filho, R. A. W.; Srivastava, R. M.; Bechtold, I. H. *Liq. Cryst.* **2008**, *35*, 857–863.
5. Gallardo, H.; Cristiano, R.; Vieira, A. A.; Neves Filho, R. A. W.; Srivastava, R. M. *Synthesis* **2008**, 605–609.
6. Ispikoudi, M.; Amvrazis, M.; Kontogiorgis, C.; Koumbis, A. E.; Litinas, K. E.; Hadjipavlou-Litina, D.; Fylaktakidou, K. C. *Eur J. Med. Chem.* **2010**, *45*, 5635–5645.
7. Ziedan, N. I.; Stefanelli, F.; Fogli, S.; Westwell, A. D. *Eur J. Med. Chem.* **2010**, *45*, 4523–4530.
8. Rai, N. P.; Narayanaswamy, V. K.; Govender, T.; Manuprasad, B. K.; Shashikanth, S.; Arunachalam, P. N. *Eur J. Med. Chem.* **2010**, *45*, 2677–2682.
9. Tka, N.; Hassine, N. B. *Synth. Commun.* **2010**, *40*, 3168–3176.
10. Neves Filho, R. A. W.; Silva, C. A.; Silva, C. S.; Brustein, V. P.; Navarro, D. M. A. F.; dos Santos, F. A.; Alves, L. C.; Cavalcanti, M. G. S.; Srivastava, R. M.; Carneiro-Da-Cunha, M. G. *Chem. Pharm. Bull.* **2009**, *57*, 819–825.
11. dos Anjos, J. V.; Neves Filho, R. A. W.; Nascimento, S. C.; Srivastava, R. M.; Melo, S. J.; Sinou, D. *Eur. J. Med. Chem.* **2009**, *44*, 3571–3576.
12. Chu, L.; Li, B.; Ogawa, A. K.; Ok, H. O.; Ondeyka, D. L.; Patel, M.; Sisco, R.; Ujjainwalla, F.; Xu, J. PCT Int. Appl. 2007, WO patent 2007120574 A2; *Chem. Abstr.* **2007**, *147*, 486423.
13. Hobbs, C. J.; Lynch, R.; Mellor, S. L.; Radford, F.; Gilbert, J. C.; Stokes, S.; Glen, A.; Fuimana, A.; Earnshaw, C. G.; Lars, J. S.; Dean, K. E. S. PCT Int. Appl. 2006, WO patent 2006030211 A2; *Chem. Abstr.* **2006**, *144*, 390924.
14. Li, C. S.; Ramtohul, Y. K. PCT Int. Appl. 2007, WO patent 2007143824 A1; *Chem. Abstr.* **2007**, *148*, 78875.
15. Taniguchi, T.; Miyata, K.; Kubo, O. PCT Int. Appl. 2008, WO patent 2008044767 A1; *Chem. Abstr.* **2008**, *148*, 42912.
16. Galley, G.; Kitas, E. A.; Jakob-Roetne, R. PCT Int. Appl. 2006, WO patent 2006005486 A1; *Chem. Abstr.* **2006**, *144*, 128869.
17. Palazzo, G.; Silvestrini, B. *Boll. Chim. Farm.* **1962**, *101*, 251–253.
18. Oh, C. H.; Dong, H. G.; Lee, J. S.; Lee, S. C.; Hong, J. H.; Cho, J. H. *Arch. Pharm.* **2003**, *336*, 567–572.
19. Rhee, J. K.; Im, W. B.; Cho, C. H.; Choi, S. H.; Lee, T. H. PCT Int. Appl. 2005, WO patent 2005058886 A1; *Chem. Abstr.* **2005**, *143*, 97343.
20. Fyfe, M.; Gardner, L.; King-Underwood, J.; Procter, M.; Rasamison, C.; Schofield, K.; Thomas, G. H. PCT Int. Appl. 2005, WO patent 2005061489 A1; *Chem. Abstr.* **2005**, *143*, 115543.

21. Aldous, D. J.; Smith, G. F.; Astles, P. C.; Pickett, S. D.; McLay, I. M.; Stuttle, K. A. J.; Ratcliffe, A. J. PCT Int. Appl. 1997, WO patent 9703967 A1; *Chem. Abstr.* **1997**, *126*, 212048.
22. Palazzo, G.; Baiocchi, L.; Picconi, G. *J. Heterocycl. Chem.* **1979**, *16*, 1469–1475.
23. Kuduk, S. D.; Bock, M. G.; Feng, D.-M.; Wai, J. M.-C. U. S. Pat. Appl. Publ. 2004, US 20040063761 A1; Chem. Abstr. **2004**, *140*, 303540.
24. UkrOrgSynthesis Building Blocks, Alinda Chemical Ltd. Building Blocks, ChemBridge Building Block Library, AKos Building Blocks Product List, and Bio-Farma Product List.
25. Braga, V. M. L.; Melo, S. J.; Srivastava, R. M.; Falcão, E. P. S. *J. Braz. Chem. Soc.* **2004**, *15*, 603–607.
26. Melo, S. J.; Sobral, A. D.; Lopes, H. L.; Srivastava, R. M. *J. Braz. Chem. Soc.* **1998**, *9*, 465–468.
27. Palazzo, G. US 3270028, 1966; Chem. Abstr. **1966**, *65*, 108075.
28. Amarasinghe, K. K. D.; Maier, M. B.; Srivastava, A.; Gray, J. L. *Tetrahedron Lett.* **2006**, *47*, 3629–3631.
29. Du, W.; Truong, Q.; Qi, H. B.; Guo, Y.; Chobanian, H. R.; Hagmann, W. K.; Hale, J. J. *Tetrahedron Lett.* **2007**, *48*, 2231–2235.
30. de Freitas, J. J. R.; Freitas, J. C. R.; da Silva, L. P.; de Freitas, J. R.; Kimura, G. Y. V.; Srivastava, R. M. *Tetrahedron Lett.* **2007**, *48*, 6195–6198.
31. Leite, L. F. C. C.; Srivastava, R. M.; Cavalcanti, A. P. *Bull. Soc. Chim. Belg.* **1989**, *98*, 203–210.