

Full Paper

A Handy and Solventless Direct Route to Primary 3-[3-Aryl)-1,2,4-oxadiazol-5-yl]propionamides Using Microwave Irradiation

Ricardo A.W. Neves Filho and Rajendra M. Srivastava *

Departamento de Química Fundamental, Universidade Federal de Pernambuco, 50.740-540 Recife, PE, Brazil

*Author to whom correspondence should be addressed, e-mail: rms_indu@yahoo.com

Received: 15 December 2005; in revised form: 24 March 2006 / Accepted: 5 May 2006 / Published: 9 May 2006

Abstract: A one-step, simple and straightforward synthesis of the title amides from the corresponding carboxylic acids, urea and imidazole under microwave irradiation is described.

Keywords: 1,2,4-Oxadiazoles, microwave irradiation, amides, spectroscopy, imidazole

Introduction

1,2,4 Oxadiazoles are well known compounds which exhibit diversified biological activities [1-4]. The work from our laboratory also cites other pharmacological properties previously reported by other researchers [5,6]. The analgesic and antiinflammatory effects of 5-methyl-3-phenyl-1,2,4-oxadiazole were discovered as early as in 1972 [7]. Incorporation of a carboxyl function into the C-5 side-chain of 1,2,4-oxadiazoles improves both analgesic and antiinflammatory properties [8]. Similar pharmacological properties have been displayed by carboxylic acid amides as well [9,10] and incorporation of a carboxylic acid derivative, like an amide, might result in different biological activity. For example, while lysergic acid is inactive, its *N,N*-diethylamide derivative (LSD) thoroughly changes the human behavior and causes psychic alterations and hallucinations at doses as low as 1mg/kg body weight [11]. Although the preparation of amides using conventional procedures is well documented [12,13], clean, fast and less cumbersome methods are less common. A literature search

did reveal some reports of the preparation of amides using microwave radiation [14a-d-18], but mostly dealing with secondary and tertiary amides. Two reports describe preparation of primary amides, one employing carboxylic acid, imidazole and urea [19] and the other using carboxylic acid, urea and pyridine [20]. On the other hand 1,2,4-oxadiazoles containing a primary amide function in their C-5 side-chain have drawn practically no attention. Two companies market 3-[3-phenyl-1,2,4-oxadiazol-5-yl]propionamide (**4a**, [21a,b]), but no experimental details are available. Because of the great significance of the amide functionality, we wished to develop a speedy, eco-friendly and solvent-free technique to obtain such compounds. Herein, we report the synthesis of six 3-[3-(aryl)-1,2,4-oxadiazol-5-yl]propionamides **4a-f** under solvent-free conditions employing an unmodified domestic microwave oven [22] (Scheme 1). The reactions are clean, the work-up is simple and the yields are relatively high (Table 1).

Scheme 1. Preparation of **4a-f** from **1a-f** and **2**.

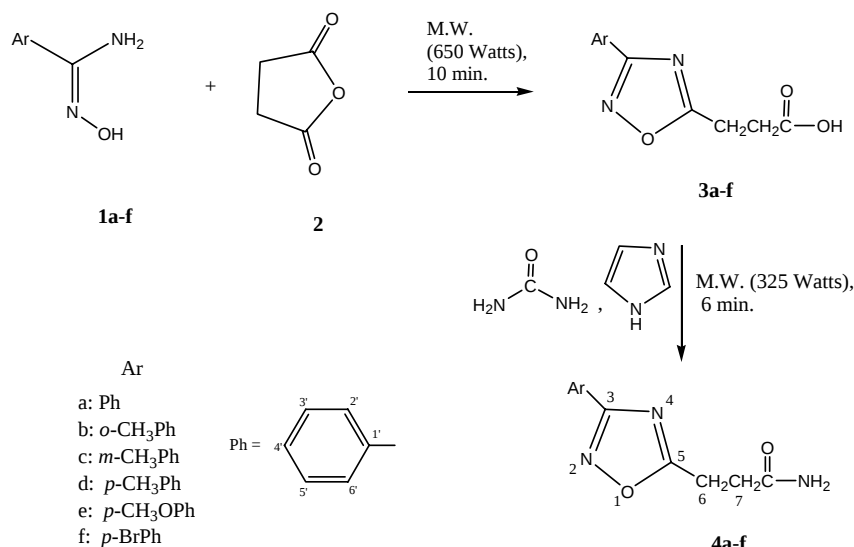


Table 1. Observed experimental results for the synthesis of **4a-f**.

Compound	ReactionTemp.(°C) ^a	Yield (%) ^b	R _f values ^c	M.p (° C) ^d
4a	130	73	0.22	175-176
4b	110	83	0.28	124-125
4c	117	85	0.26	122-123
4d	115	87	0.26	168-169
4e	110	84	0.19	174-175
4f	120	87	0.24	161-162

^a Temperature recorded by a Minipa model 350 infrared thermometer.

^b Chromatographically pure material.

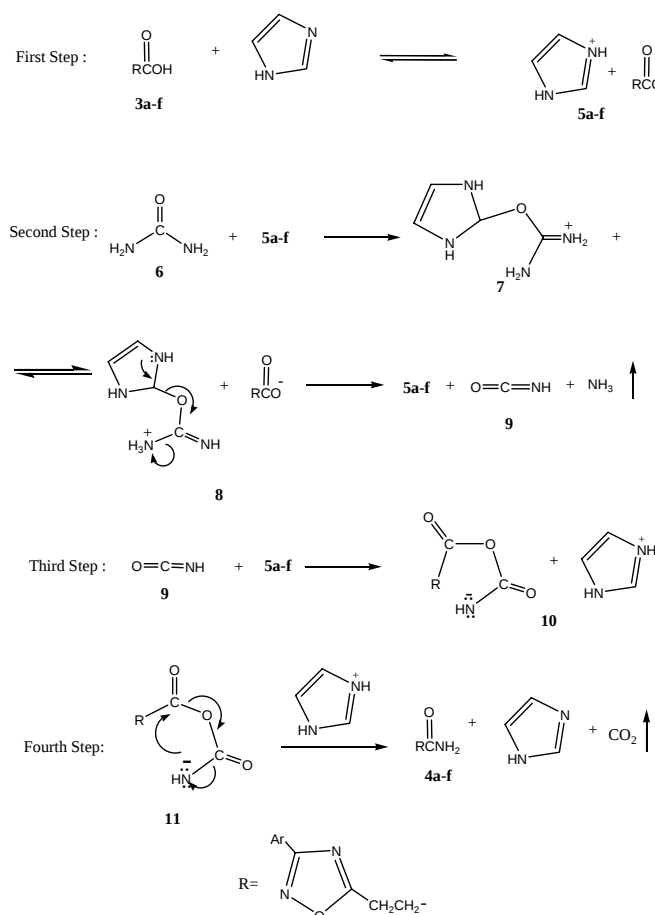
^c Solvent system: 5.0:4.5:0.5 benzene-ethyl acetate-methanol.

^d Crystallized from chloroform containing a little ethyl acetate.

Results and Discussion

Based upon previous suggestions concerning the reaction of a carboxylic acid and imidazole [14, 23], Khalafi-Nezhad *et al.* [19] proposed the formation of an imidazolium carboxylate salt, which absorbs microwave energy. The energy increase then causes the decomposition of urea followed by proton exchange with the imidazolium ion and subsequent formation of an ammonium carboxylate salt which furnishes an amide. Aside from this, the mechanism of primary amide formation from an acid, imidazole and urea has not been discussed. To us, the decomposition of the ammonium carboxylate salt at a relatively low temperature and in such a short time seems difficult. In order to know whether an ammonium salt of a carboxylic acid is responsible for the amide formation, we took readily available ammonium benzoate and subjected it to microwave irradiation under conditions similar to those described earlier. Ammonium benzoate remained unchanged as verified by TLC and the melting point of the crystals. This indicates that ammonium salts is not responsible for primary amide formation in such a reaction. Therefore, we postulate a different mechanism, in which the highly reactive iminoketene **9**, formed through reaction of urea with imidazolium ion, is the main agent in the transformation of the carboxylate into an amide: nucleophilic attack of the carboxylate on the iminoketene, followed by proton exchange with imidazolium ion results in **11** which, through a S_N1 reaction similar to the formation of acyl halides with $SOCl_2$, gives the amide. This mechanism is more logical and is being proposed here for the first time (Scheme 2).

Scheme 2. Mechanism of formation of primary amides **4a-f** from **3a-f** in the presence of imidazole and urea under microwave irradiation.



Conclusions

In summary, we have synthesized six primary amides **4a-f** in six minutes using microwave energy. A new mechanism of formation of these amides from an acid, imidazole and urea is being proposed for the first time.

Acknowledgments

The authors express their gratitude to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial assistance; one of us (R.A.W.N.F.) extends his thanks to CNPq for an undergraduate fellowship (August 2004 to present).

Experimental Section

General

Melting points were determined on an Electrothermal (Mel-Temp) apparatus (Model No. 1002D) and are uncorrected. All reactions were monitored by TLC analysis (TLC plates GF₂₅₄ Merck). IR spectra were measured with a IFS66 Bruker spectrometer employing KBr disks. ¹H-NMR spectra were recorded with a Varian Unity Plus 300 MHz spectrometer using SiMe₄ as an internal standard. All reactions were conducted in a Sanyo domestic microwave oven model EM-300B (220v/650W/2450 MHz).

General Synthetic Procedure

An appropriate arylamidoxime **1a-f** (1.0 mmol) was allowed to react with succinic anhydride (**2**, 1.1 mmol) in a domestic microwave oven following the procedure reported earlier to afford **3a-f** [22]. A mixture of an appropriate acid **3a-f** (1.0 mmol), imidazole (1.5 mmol) and urea (3.0 mmol) were well triturated and placed in a small glass test tube followed by irradiation for 6.0 min. in an unmodified domestic microwave oven (50% power) and then cooled. The solid was treated with ethyl acetate and filtered to remove the insoluble material. TLC analysis (elution with 5.0:4.5:0.5 benzene-ethyl acetate-methanol, followed by visualization under ultraviolet light) showed spots with R_f values ranging from 0.19-0.28. The product dissolved in ethyl acetate was applied to a thick-layer chromatographic plate and developed with the above-mentioned solvent mixture. Work-up furnished chromatographically pure primary amides **4a-f**. The main experimental details for each case are compiled in Table 1.

Spectral and Analytical Data of Compounds **4a-f**

3-[3-Phenyl-1,2,4-oxadiazol-5-yl]propionamide (4a): IR: ν 3500 (N-H, asym.), 3250 (N-H, sym.), 1693 (C=O) cm⁻¹; ¹H-NMR (CDCl₃): δ 2.86 (t, 2H, J = 7.2 Hz, CH₂-7), 3.31 (t, 2H, J = 7.2 Hz, CH₂-6), 5.45 and 5.66 (2bs, 2H, NH₂), 7.40–7.54 (m, 3H, arom.), 7.80–8.08 (m, 2H, arom.); Anal. calcd. for C₁₁H₁₁O₂N₃: C, 60.82, H, 5.10, N, 19.34. Found: C, 61.05, H, 5.51, N, 19.42.

3-[3-(*o*-Tolyl)-1,2,4-oxadiazol-5-yl]propionamide (**4b**): IR: ν 3436 (N-H, asymm.), 3250 (N-H, Symm), 1695 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 2.61 (s, 3H, CH_3), 2.86 (t, 2H, $J = 7.2\text{Hz}$, CH_2 -7), 3.31 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -6), 5.55 and 5.70 (2bs, 2H, NH_2), 7.29-7.41 (m, 3H, arom.), 7.94 (d, 1H, $J = 9.3\text{Hz}$, arom.); Anal. calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_3$: C, 62.33, H, 5.67, N, 18.17. Found: C, 62.22, H, 5.93, N, 18.56.

3-[3-(*m*-Tolyl)-1,2,4-oxadiazol-5-yl]propionamide (**4c**): IR: ν 3347 (N-H, asymm.), 3250 (N-H, symm.), 1694 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 2.42 (s, 3H, CH_3), 2.85 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -7), 3.30 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -6), 5.71 and 5.78 (2bs, 2H, NH_2), 7.26 -7.39 (m, 2H, arom.), 7.80-8.00 (m, 2H, arom.); Anal. calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_3$: C, 62.33, H, 5.67, N, 18.17. Found: C, 62.40, H, 5.71, N, 17.98.

3-[3-(*p*-Tolyl)-1,2,4-oxadiazol-5-yl]propionamide (**4d**): IR: ν 3323 (N-H, asymm.), 3250 (N-H, symm.), 1693 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 2.41 (s, 3H, CH_3), 2.85 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -7), 3.29 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -6), 5.46 and 5.70 (2bs, 2H, NH_2), 7.28 (d, 2H, $J = 7.2\text{ Hz}$, H-3' & H-5'), 7.93 (d, 2H, $J = 7.2\text{ Hz}$, H-2' & H-6'); Anal. calcd. for $\text{C}_{12}\text{H}_{13}\text{O}_2\text{N}_3$: C, 62.33, H, 5.67, N, 18.17. Found: C, 62.36, H, 5.69, N, 18.20.

3-[3-(4-Anisyl)-1,2,4-oxadiazol-5-yl]propionamide (**4e**): IR: ν 3339 (N-H, asymm.), 3250 (N-H, symm.), 1693 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): δ 2.85 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -7), 3.29 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -6), 3.87 (s, 3H, $\text{CH}_3\text{O-}$), 5.39 and 5.69 (2bs, 2H, NH_2), 6.78 (d, 2H, $J = 9.0\text{ Hz}$, H-3' & H-5', arom.), 7.99 (d, 2H, $J = 9.0\text{ Hz}$, H-2' & H-6', arom.); Anal. calcd for $\text{C}_{12}\text{H}_{13}\text{O}_3\text{N}_3$: C, 58.29, H, 5.30, N, 16.99. Found: C, 58.61, H, 5.41, N, 17.01.

3-[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]propionamide (**4f**): IR: ν 3350 (N-H, asymm.), 3250 (N-H, symm.), 1669 (C=O) cm^{-1} ; $^1\text{H-NMR}$ (DMSO-d_6): δ 2.68 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -7), 3.16 (t, 2H, $J = 7.2\text{ Hz}$, CH_2 -6), 6.85 and 7.49 (2bs, 2H, NH_2), 7.77 (d, 2H, $J = 8.4\text{ Hz}$, H-3' & H-5', arom.), 7.92 (d, 2H, $J = 8.4\text{ Hz}$, H-2' & H-6', arom.); Anal. calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{N}_3\text{Br}$: C, 44.62, H, 3.40, N, 14.19. Found: C, 44.81, H, 3.68, N, 14.00.

References and Notes

1. Clapp, L.B. In "Advances in Heterocyclic Chemistry"; Katritzky, A.R., Ed.; Academic Press: New York, **1976**; 20, pp. 65-116.
2. Clapp, L.B. In "Comprehensive Heterocyclic Chemistry"; Katritzky, A.R.; Rees, C.W., Eds.; Pergamon Press: Oxford, **1984**, 6, pp. 365-391.
3. Jochims, J.C. In "Comprehensive Heterocyclic Chemistry II"; Katritzky, A.R.; Rees, C.W.; Scriven, E.F.D., Eds.; Elsevier Science: Oxford, **1996**; 4, pp. 179-228.
4. Hemming, K. Recent developments in the synthesis, chemistry and applications of the fully unsaturated 1,2,4- oxadiazoles. *J. Chem. Res.* **2001**, 216, 209-216.
5. Antunes, R.; Batista, H.; Srivastava, R.M.; Thomas, G.; Araújo, C.C.; Longo, R.L.; Magalhães, H.; Leão, M.B.C.; Pavão, A.C. Synthesis, characterization and interaction mechanism of new oxadiazolo-phthalimides as peripheral analgesics. IV. *J. Mol. Struct.* **2003**, 600, 1-13.

6. Srivastava, R.M.; Morais, L.P.F.; Catanho, M.T.J.A.; Souza, G.M.L.; Seabra, G.M.; Simas, A.M.; Rodriguez, M.A.L. Synthesis and antiinflammatory activity of 3-aryl-5-isopropyl-1,2,4-oxadiazoles. *Heterocycl. Commun.* **2000**, *6*, 41-48.
7. Dahlgren, S.E.; Dalhamn, T. Antiinflammatory action of phenyl-methyl-oxadiazole (pmo) - experimental study on guinea-pig trachea. *Acta Pharmacol. Toxicol.* **1972**, *31*, 193-202.
8. Afiatpour, P.; Srivastava, R.M.; de Oliveira, M.L.; Barreiro, E.J. Analgesic and antiinflammatory effects of 3-[3-(phenyl)-1,2,4-oxadiazol-5-yl] propionic acid. *Braz. J. Med. Biol. Res.* **1994**, *27*, 1403-1406.
9. Glushkov, V.A.; Anikina, L.V.; Vikharev, Y.B.; Stryapunina, O.G.; Shklyayev, Y.V.; Tolstikov, A.G. Synthesis and antiinflammatory activity of N-[2-(p-hydroxyphenyl)-1,1-dialkylethyl]- α -dialkylamino acetamides. *Pharm. Chem. J.* **2004**, *38*, 86-89.
10. Sladowska, H.; Sieklucka-Dziuba, M.; Rajtar, G.; Sadowski, M.; Kleinrok, Z. Investigations on the synthesis and pharmacological properties of amides of 7-methyl-3-phenyl-1-[2-hydroxy-3-(4-phenyl-1-piperazinyl)propyl]-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-5-carboxylic acid. *Il Farmaco*, **1999**, *54*, 773-779.
11. Sanders-Bush, E.; Mayer, S.E. In "Goodman & Gilman's" *The Pharmacological Basis of Therapeutics*, 10th International Edition; Hardman, J.G.; Linbird, L.E., Eds.; McGraw-Hill: New York, **2001**; pp. 284-285.
12. Benz, G. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**; *6*, pp. 381-418.
13. Smith, M.B.; March, J. *March's Advanced Organic Chemistry. Reactions, Mechanisms and Structure, Fifth Edition*; John Wiley & Sons: New York, **2001**; pp. 506-513.
14. a) Baldwin, B.W.; Hirose, T.; Wang, Z.-H. Improved microwave oven synthesis of amides and imides promoted by imidazole; convenient transport agent preparation. *Chem. Commun.* **1996**, 2669-2670; b) Vasquez-Tato, M.P. Microwave-mediated synthesis of amides. *Synlett*, **1993**, 506 ; c) Gelens, E.; Smeets, L.; Sliedregt, L.A.J.M.; van Steen, B.J.; Kruse, C.G.; Leurs, R.; Orru, R.V.A. An atom efficient and solvent-free synthesis of structurally diverse amides using microwaves. *Tetrahedron Lett.* **2005**, *45*, 3751-3754; d) Gorelski, C.; Krlej, A.; Steffens, C.; Ritter, H. Microwave-assisted single-step synthesis of various (meth)acrylamides and poly(meth)acrylamides directly from (meth)acrylic acid and amines. *Macromol. Rapid Commun.* **2004**, *25*, 513-516.
15. Varma, R.S.; Naicker, K.P. Solvent-free synthesis of amides from non-enolizable esters and amines using microwave irradiation. *Tetrahedron Lett.* **1999**, *40*, 6177-6180.
16. Chen, J.J.; Deshpande, S.V. Rapid synthesis of alpha-ketoamides using microwave irradiation-simultaneous cooling method. *Tetrahedron Lett.* **2003**, *44*, 8873-8876.
17. Perreux, L.; Loupy, A.; Volatron, F. Solvent-free preparation of amides from acids and primary amines under microwave irradiation. *Tetrahedron* **2002**, *58*, 2155-2162, and references cited therein.
18. Sauer, D.R.; Kalvin, D.; Phelan, K.M. Microwave-assisted synthesis utilizing supported reagents: a rapid and efficient acylation procedure. *Org. Lett.* **2003**, *5*, 4721-4724.

19. Khalafi-Nezhad, A.; Mokhtari, B.; Rad, M.N.S. Direct preparation of primary amides from carboxylic acids and urea using imidazole under microwave irradiation. *Tetrahedron Lett.* **2003**, *44*, 7325-7328.
20. Pasha, M.A.; Jayashankara, V.P. Synthesis of amides from carboxylic acids and urea in the presence of pyridine under microwave irradiation. *J. Ind. Chem. Soc.* **2005**, *82*, 675-676.
21. a) InterBioScreen Ltd., P.O. Box 218, Moscow, Russia, publication date: Mar. 15, 2005;
b) ChemBridge Corporation, 16981 Via Tazon, Suite G, San Diego, CA, 92127, U.S.A. ChemBridge Screening Library, publication date: Jan. 12, 2005.
22. We have taken precautions to ensure that the results are reproducible. We first determined the region inside the microwave oven where the heating was the maximum using water samples and recording the temperatures with an infrared thermometer. After doing this, we repeated the reaction and got the same results. In our opinion, the reactions can be repeated easily without any problem by any chemist.
23. Rault, P.; Pilard, J.; Touaux, B.; Texier-Boullet, F.; Hamelin, J. Rapid generation of amines by microwave irradiation of ureas dispersed on clay. *Synlett* **1994**, 935-936.
24. Srivastava, R.M.; Seabra, G.M. Preparation and reactions of 3-[3-(aryl)-1,2,4-oxadiazol-5-yl] propionic acids. *J. Braz. Chem. Soc.* **1997**, *8*, 397-405.

Sample availability: Please contact the authors.