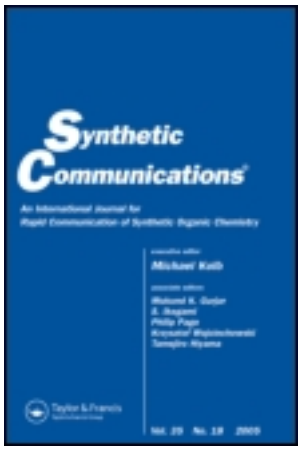


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Solvent-Free Synthesis of 2-Furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles Under Microwave Irradiation

Xicun Wang [a] , Zheng Li [a] , Zhengjun Quan [a] , Xinsheng Lu [a] & Ruhu Gou [a]
[a] College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, P.R. China
Published online: 19 Aug 2006.

To cite this article: Xicun Wang , Zheng Li , Zhengjun Quan , Xinsheng Lu & Ruhu Gou (2003) Solvent-Free Synthesis of 2-Furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles Under Microwave Irradiation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:16, 2891-2897, DOI: 10.1081/SCC-120022179

To link to this article: http://dx.doi.org/10.1081/SCC-120022179

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 16, pp. 2891–2897, 2003

Solvent-Free Synthesis of 2-Furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles Under Microwave Irradiation

Xicun Wang, Zheng Li,* Zhengjun Quan, Xinsheng Lu, and Ruhu Gou

College of Chemistry and Chemical Engineering,
Northwest Normal University,
Lanzhou, Gansu, P.R. China

ABSTRACT

A practical solvent-free method for the preparation of 2-furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles under microwave irradiation is described.

Key Words: Solvent-free; 1,3,4-Thiadiazole; Microwave irradiation.

*Correspondence: Zheng Li, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P.R. China; E-mail: lizheng@nwnu.edu.cn.

DOI: 10.1081/SCC-120022179 0039-7911 (Print); 1532-2432 (Online)

Substituted 1,3,4-thiadiazoles have attracted much attention due to their diverse biological activities, such as antimicrobial,[1] antibacterial,[2] anesthetic,[3] anticonvulsant,[4] cardiotonic,[5] antihypertensive,[6] anti-inflammatory[7] and antiulcer[8] activities. Meanwhile, aryloxyacetic acid derivatives have also been used as herbicides,[9] diuretics,[10] and plant-growth regulators.[11] In addition, benzofuran or aryl substituted furan derivatives also possess local anesthesia,[12] analgesic,[13] insect antifeedant,[14] cannabimimetic,[15] anti-arrhythmic and hypotensive,[16] anti-histaminic and anti-allergic,[17] reductase inhibitory,[18] estrogenic,[19] metallothioneinogenic[20] activities.

Based on the above facts, the species bearing all of 1,3,4-thiadiazole, aryloxyacetyl and furyl moieties in one molecular are possibly potential candidates of biologically active compounds. Consequently, there is a need to explore an expeditious, environmentally benign synthetic protocol to get a library of this kind of compounds.

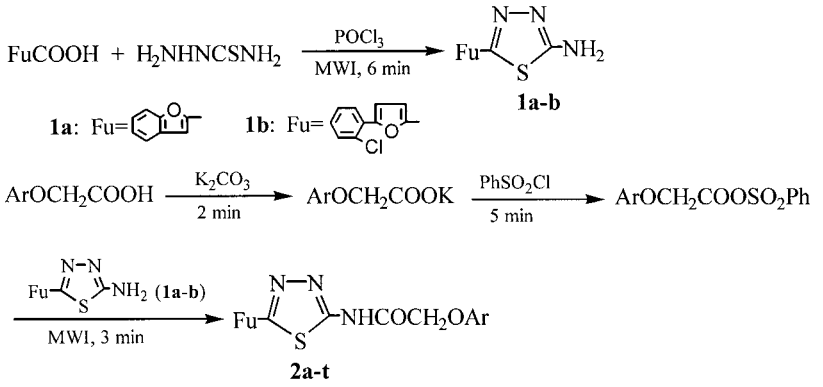
The development of solvent-free organic synthesis is of current interest because of the many advantages, such as reduced pollution, low cost, simplicity in process and handling, potential applications in combinatorial chemistry and chemical industry.[21]

Microwave energy has now developed into a useful technique for a variety of application in organic synthesis, especially for the solventless reactions[22] since the solvent-free MW-assisted reactions can provide an opportunity to work with open vessels thus avoiding the risk of high-pressure development and increasing the potential of such reaction to upscale.

In continuation of ongoing program to synthesize biologically active compounds and develop benign and rapid strategy for organic transformation under solventless conditions using microwave irradiation and the interest in green chemistry theme with growing emphasis on pollution prevention, we have explored an expeditious solvent-free route to prepare 2-furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles under microwave irradiation.

The required 2-amino-5-furyl-1,3,4-thiadiazoles (**1a–b**) are prepared by the reaction of benzo-2-furancarboxylic acid or 5-(2-chlorophenyl)-2-furancarboxylic acid with thiosemicarbazide in the presence of the same equivalent of phosphorus oxychloride under microwave irradiation. In contrast, the conventional heating method have to use much more excess of phosphorus oxychloride both as dehydrant and solvent, and the mixture have to reflux for many hours before the product is afforded in good yield.[23]

Aryloxyacetic acid is ground with equivalent of potassium cabonate in a motar until the acid disappeared and potassium aryloxyacetate formed



Scheme 1.

according to TLC analysis. Then equivalent of phenylsulfonyl chloride is added and the mixture is ground again until a viscous paste is observed and a mixed anhydride formed. After that, 2-amino-5-furyl-1,3,4-thiadiazole is added, and the mixture is irradiated in a microwave oven until all paste solidified. The completion of the reaction is monitored by TLC using ethyl acetate and petroleum oil (3:2) as eluent. The product, 2-furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles (**2a–t**), those are of acceptable purity for most purpose, are given in excellent yield only by washing the resulting solid using distilled water. If greater purity is required, the product can be recrystallized from acetic acid and water (Sch. 1). In order to compare the difference between microwave and traditional method, the same reactions for compound **2a–t** are designed to proceed in the solution of acetonitrile and reflux for four hours, but no any products are isolated.

The characterization of compounds **2a–t** is based on their IR (KBr), ^{1}H NMR, and elemental analyses. The IR spectra exhibit a characteristic strong absorption at 1699–1723 cm^{-1} for carbonyl. The ^{1}H NMR spectral data of **2a–t** in d_6-dimethylsulfoxide show peaks at 13.07–13.26 (NH) and 4.86 4.93 ppm (CH_2). All data of elemental analysis are good agreement with the structure proposed. The yield and melting point of **2a–t** are summarized in the Table 1.

In conclusion, we have found an efficient protocol for the preparation of title compounds by solvent-free MW-assisted reaction. This strategy can also be readily suitable for the preparation of the libraries of various substituted 1,3,4-thiadiazoles.

Table 1. Solvent-free preparation of 2-furyl-5-aryloxyacetylamido-1,3,4-thiadiazoles under MWI.

Product	Substrate	Ar	M.p. (°C)	Yield[a] (%)
2a	**1a**	C_6H_5	216–217	88
2b	**1a**	2-$CH_3C_6H_4$	246–247	85
2c	**1a**	3-$CH_3C_6H_4$	258–259	90
2d	**1a**	4-$CH_3C_6H_4$	260–261	86
2e	**1a**	4-$CH_3OC_6H_4$	269–270	91
2f	**1a**	2-ClC_6H_4	239–240	88
2g	**1a**	4-ClC_6H_4	272–273	90
2h	**1a**	2,4-$Cl_2C_6H_3$	315–316	87
2i	**1a**	2-Naphthyl	266–267	89
2j	**1a**	4-$O_2NC_6H_4$	251–252	88
2k	**1b**	C_6H_5	201–202	86
2l	**1b**	4-$CH_3OC_6H_4$	234–235	87
2m	**1b**	2-ClC_6H_4	200–201	85
2n	**1b**	4-ClC_6H_4	260–261	91
2o	**1b**	2,4-$Cl_2C_6H_3$	190–191	84
2p	**1b**	2-Naphthyl	216–217	91
2q	**1b**	4-$O_2NC_6H_4$	277–278	88
2r	**1b**	3-$O_2NC_6H_4$	269–270	85
2s	**1b**	2-$O_2NC_6H_4$	213–214	88
2t	**1b**	1-Naphthyl	260–261	92

[a]Yields refer to the isolated products.

EXPERIMENTAL

Infrared spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^{1}H NMR spectra on a FT-80A instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario El Elemental Analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting points were observed in an open capillary tube and uncorrected. Aryloxyacetic acids,[24] benzo-2-furan-carboxylic acid[25] and 5-(2-chlorophenyl)-2-furancarboxylic acid[26] were prepared according to literature procedures. Phenylsulfonyl chloride and phosphorus oxychloride were commercially available and used as received.

Preparation of 2-Amino-5-(benzo-2-furyl)-1,3,4-thiadiazole (1a)

The mixture of 0.81 g (5.0 mmol) of benzo-2-furancarboxylic acid, 0.50 g (5.5 mmol) of thiosemicarbazide and 0.2 mL of $POCl_3$ was irradiated in a microwave oven (490 W) for 6 min. The completion of the reaction was monitored by TLC. The resulting mixture was poured into ice water (30 mL) and centralized with aqueous solution of NaOH (3 M) until the PH = 9–10. Then the suspension was filtered and the solid was recrystallized from DMF–C_2H_5OH to give product **1a**. Yield: 95%. m.p.: 278–279°C. ^{1}H NMR (80 MHz, DMSO-d_6): δ 6.31 (2H, s, NH_2, exchangeable with D_2O), 7.0–8.0 (5H, m, Ar-H&Fu-H). IR (KBr, ν, cm^{-1}): 3415, 3281 (N-H), 1631 (C=N), 1504, 1347, 1250, 1066 cm^{-1} (1,3,4-thiadiazole nucleus). Anal. calcd. for $C_{10}H_7N_3OS$: C, 55.29; H, 3.25; N, 19.34. Found: C, 55.12; H, 3.16; N, 19.23.

2-Amino-5-(5′-(2″-chlorophenyl)-2′-furyl)-1,3,4-thiadiazole (**1b**) was prepared according to the similar procedure using 5-(2-chlorophenyl)-2-furancarboxylic acid instead of benzo-2-furancarboxylic acid. Yield: 92%. m.p.: 203–204°C. ^{1}H NMR (80 MHz, DMSO-d_6): δ 6.36 (2H, s, NH_2, exchangeable with D_2O), 7.1–8.1 (6H, m, Ar-H&Fu-H). IR (KBr, ν, cm^{-1}): 3420 (N-H), 1628 (C=N), 1510, 1350, 1246, 1057 cm^{-1} (1,3,4-thiadiazole nucleus). Anal. calcd. for $C_{12}H_8ClN_3OS$: C, 51.90; H, 32.90; N, 15.13. Found: C, 52.01; H, 2.96; N, 15.21.

General Procedure for Preparation of 2a–t

The mixture of aryloxyacetic acid (1.0 mmol) and anhydrous K_2CO_3 (1.0 mmol) was ground in a motar for 2 min, then phenylsulfonyl chloride (1.0 mmol) was added, and the mixture was further ground for 5 min until a paste was obtained. After 2-amino-5-furyl-1,3,4-thiadiazole (1.0 mmol) was added, the resulting mixture was irradiated in a microwave oven (350 W) for 3 min until the solidification of the paste was observed. The completion of reaction was monitored by TLC using ethyl acetate and petroleum oil (3:2) as eluent. Then the resulting solid was washed with distilled water (10 mL) and compound **2** was afforded as a solid. The analytic sample was obtained by recrystallizing from AcOH-H_2O (4:1). The data for representative compound are given below: **2e**: ^{1}H NMR (80 MHz, DMSO-d_6): δ 13.13 (1H, s, NH), 7.0–8.2 (10H, m, Ar-H&Fu-H), 4.86 (2H, s, CH_2), 3.82 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3287 (N-H), 1702 (C=O), 1499, 1350, 1247, 1071 (N=C-S-C=N). MS: m/z, 381 (M^+).

Anal. calcd. for $C_{19}H_{15}N_3O_4S$: C, 59.83; H, 3.96; N, 11.02. Found: C, 59.98; H, 4.03; N, 11.12. **2p**: ^{1}H NMR (80 MHz, DMSO-d_6): δ 13.13 (1H, s, NH), 6.9–8.2 (13H, m, Ar-H&Fu-H), 4.87 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3166 (N-H), 1701 (C=O), 1498, 1360, 1246, 1079 (N=C-S-C=N). MS: m/z, 461 (M^+). Anal. calcd. for $C_{24}H_{16}N_3O_3SCl$: C, 62.40; H, 3.49; N, 9.10. Found: C, 62.61; H, 3.56; N, 9.21.

ACKNOWLEDGMENT

The authors thank the Scientific and Technological Innovation Engineering of Northwest Normal University (NWNU-KJCXGC-02-08), Natural Science Foundation of Gansu Province (ZS021-A25-006-Z), Environmental Protection Foundation of Gansu Province (GH2002-16) and Youth Foundation of Northwest Normal University for the financial support of this work.

REFERENCES

1. Mamolo, M.; Vio, L.; Banfi, E. Farmaco **1996**, *51*, 71.
2. Kidwai, M.; Misra, P.; Kumar, R.; Saxena, R.K.; Gupta, R.; Bradoo, S. Monatsh. Chem. **1998**, *129*, 961.
3. Mazzone, G.; Pignatello, R.; Mazzone, S.; Panico, A.; Pennisi, G. Farmaco **1993**, *48*, 1207.
4. Chufan, E.E.; Pedregosa, J.C.; Badini, O.N.; Bruno-Blanch, L. Farmaco **1999**, *54*, 838.
5. Nomoto, Y.; Takai, H; Hirata, T.; Teranishi, M.; Ohno, T.; Kubo, K. Chem. Pharm. Bull. **1991**, *39*, 86.
6. Vio, L.; Mamolo, M.G.; Laneve, A. Farmaco **1989**, *44*, 165.
7. Amir, M.; Oberoi, A.; Alam, S. Indian J. Chem. Sect. B **1999**, *38*, 237.
8. Nishino, C.; Sato, F.; Uetake, T.; Fukunish, H.; Kojima, N. US5912258 **1999**; Chem. Abstr. *131*, 31943.
9. Shi, Y.N.; Lu, Y.C.; Fang, J.X.; Hua, Y.L. Chem. J. Chin. Univ. (Chinese) **1995**, *16*, 1710; Chem. Abstr. *124*, 316654.
10. Kitagawa, M.; Yamamoto, K.; Katakura, S.; Kanno, H.; Yamada, K. Chem. Pharm. Bull. **1991**, *39*, 2681.
11. Jain, P.K.; Srirastara, S.K. J. Indian Chem. Soc. **1992**, *69*, 402.
12. Mukhanova, T.I.; Granik, V.G.; Denisov, A.V.; Trubitsina, T.K.; Shvarts, G.Ya.; Mashkovskii, M.D. Pharm. Chem. J. (Engl. Transl.) **1994**, *28* (12), 893–897.

13. Burch, H.A.; Write, R.E.; Wright, G.C.; Goldenberg, M.M. J. Pharm. Sci. **1980**, *69*, 107.
14. Morimoto, M.; Urakawa, M.; Fujitaka, T.; Komai, K. Biosci. Biotechnol. Biochem. **1999**, *63* (5), 840.
15. Mechoulam, R.; Breuer, A.; Jaerbe, T.U.C.; Hiltunen, A.J.; Glaser, R. J. Med. Chem. **1990**, *33* (3), 1037.
16. Ragab, F.A.; Tawfeek, H. Eur. J. Med. Chem. Chim. Ther. **1987**, *22*, 265.
17. Takeuchi, N.; Kasama, T.; Ikeda, R.; Shimizu, K.; Hatakeyama, K. Chem. Pharm. Bull. **1984**, *32* (6), 2249.
18. Ishibashi, K.; Nakajima, K.; Sugioka, Y.; Sugiyama, M.; Hamada, T. Bioorg. Med. Chem. Lett. **1998**, *8* (6), 561.
19. Diwani, H.I.E.; Abu-Bakr, S.M.; Hishmat, O.H.; Arbid, M.S. Indian J. Chem. Sect. B **1993**, *32* (4), 494.
20. Rott, G.M.; Shevchenko, L.I.; Smoryzanova, O.A.; Savina, E.P.; Deeva, V.S.; Skvortsov, V.G.; Trofimov, F.A. Pharm. Chem. J. (Engl. Transl.) **1998**, *32* (2), 652.
21. (a) Metzger, J.O. Angew. Chem., Int. Ed. 1998, *37*, 2975; (b) Tanaka, K.; Toda, F. Chem. Rev. **2000**, *100*, 1025; (c) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. Synthesis **1998**,1213; (d) Varma, R.S. Green Chem. **1999**, *1*, 43; (e) Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.L.; Petit, A. Tetrahedron **1999**, *55*, 10851.
22. (a) Varma, R.S.; Kumar, D. Synth. Commun. **1999**, *29* (8), 1333; (b) Olsson, R.; Hansen, H.C.; Andersson, C.-M. Tetrahedron Lett. **2000**, *41* (41), 7947; (c) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. Synthesis **1998**, (9), 1213.
23. Wasfy, A.A. F.; Nassar, S.A.; Eissa, A. M. F. Indian J. Chem. Sect. B **1996**, *35* (11), 1218.
24. Li, Y.J.; Dai, Y.J.; Chen, J.C. Chem. J. Chin. Univ. (Chinese) **1988**, *9*, 584; Chem. Abstr. *110*: 74986h.
25. Farrar, M.W.; Levinl, R.J. Am. Chem. Soc. **1950**, *72*, 4433.
26. Krutosikova, A.; Kovac, J.; Sykova, V. Collection Czecholov. Chem. Commun. **1974**, *39*, 1892.

Received in Japan December 9, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016