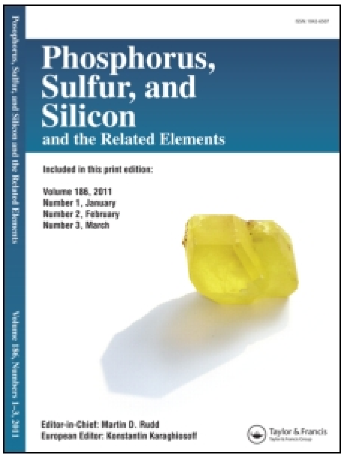


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Expeditious Synthesis of Thiadiazolo Benzodiazepines Under Conventional Method and Microwave Irradiation

J. Venu Madhav[a]; B. Rajitha[a]
[a] Department of Chemistry, National Institute of Technology, Warangal, India

To cite this Article Madhav, J. Venu and Rajitha, B.(2008) 'Expeditious Synthesis of Thiadiazolo Benzodiazepines Under Conventional Method and Microwave Irradiation', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 12, 2984 — 2989

To link to this Article: DOI: 10.1080/10426500802049670

URL: http://dx.doi.org/10.1080/10426500802049670

Phosphorus, Sulfur, and Silicon, 183:2984–2989, 2008
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500802049670

Taylor & Francis
Taylor & Francis Group

Expeditious Synthesis of Thiadiazolo Benzodiazepines Under Conventional Method and Microwave Irradiation

J. Venu Madhav and B. Rajitha
Department of Chemistry, National Institute of Technology,
Warangal, India

This article explores the use of sulfamic acid as an efficient catalyst for the one-pot synthesis of thiadiazolo 1, 5 benzodiazepines by using benzo[c][1,2,5]thiadiazole-4,5-diamine and various types of ketones in the presence of chloroform as a solvent under conventional methods and microwave irradiation. Our method is more advantageous than current methods. The catalyst (sulfamic acid) is cost effective, readily available and gives excellent yields with high purity. In comparison, the microwave irradiation method is equally as effective with a shorter reaction time and still maintaining high yields.

Keywords Benzodiazepine; benzo[c][1,2,5]thiadiazole-4,5-diamine; ketone; sulfamic acid

INTRODUCTION

Anthramycin, tomaymycin, and sibiromycin are found to be antitumor agents and antibiotics, which contain the benzodiazepine moiety.[1,2] In the literature, this moiety is extensively exploited as anti-HIV agents,[3] anti-inflammatory, analgesic, hypnotic and anti-depressive agent.[4] 1, 5 benzodiazepines are used as starting materials for the preparation of some fused ring benzodiazepine derivatives.[5–7] Due to their broad spectrum of biological activity, these compounds have received a great deal of attention in connection with their synthesis. Thiadiazolo benzodiazepines were not reported in the literature. In continuation of our studies on thiadiazolo heterocycles,[8] we have expedited synthesis of these new systems. Generally, benzodiazepines are synthesized by the condensation of *o*-phenylene diamines with α, β-unsaturated carbonyl compounds,[9] β-haloketones,[10]

Received 30 January 2008; accepted 12 March 2008.

Financial assistance from U.G.C (RGNF) Grant No: F.16-158/2006(SA-II) New Delhi is gratefully acknowledged.

Address correspondence to B. Rajitha, Department of Chemistry, National Institute of Technology, Warangal 506004, India. E-mail: rajitabhargavi@yahoo.com

or ketones.[11] Several methodologies have been reported in the literature for this condensation by using various types of reagents, including BF_3-etherate,[11] polyphosphoric acid-SiO_2,[12]$NaBH_4$, [13] $Yb(OTf)_3$, [14]and acetic acid under microwave conditions,[15] ionic liquids,[16] $SbCl_3$-Al_2O_3,[17] $YbCl_3$, [18]Zn[L-proline]$_2$,[19]$Ag_3PW_{12}O_{40}$,[20] and $MgO/POCl_3$.[21]Many of these methodologies, however, are associated with several shortcomings such as long-reaction conditions, low product yields and occurrence of several side products. Moreover, some of the reagents employed are expensive.

Recently, sulfamic acid has emerged as a good solid acid catalyst for some important organic transformations such as the synthesis of benzoxanthenes,[22] and oxazoles.[23] In continuation of our work on sulfamic acid, we wish to report here the synthesis of thiadiazolo benzodiazepines. Sulfamic acid is recyclable and easy to handle as a catalyst owing to its immiscibility with common organic solvents and it is a very stable crystalline solid, it is commercially available and is an inexpensive catalyst. The microwave irradiation accelerated synthesis is also emerging as a powerful tool in organic synthesis[24] due to short reaction times and increase of yields with high purity, and allow precise control of reaction parameters.

RESULTS AND DISCUSSION

We portray here a new method for the synthesis of thiadiazolo benzodiazepines by the condensation of benzo[c][1,2,5]thiadiazole-4,5-diamine[25] with cyclic and acyclic ketones in the presence of sulfamic acid in chloroform, irradiated in a domestic microwave oven at 300 W level for 4–6 min at an interval of 30s. This furnished the expected products in good yields. Correspondingly, the reaction was carried out through a conventional method by stirring at 55°C for 2–5 h and afforded identical products. The results are summarized in Table I. A comparison of these two methods suggests that the microwave method is highly advantageous over the conventional method. The spectroscopic characterization and elemental analyses are shown in Tables II and III.

EXPERIMENTAL

All the melting points were uncorrected. The progress of the reaction was monitored by TLC. IR spectra (KBr) were recorded on Shimadzu FTIR model 8010 spectrometer and the ^1H NMR spectra on Varian Gemini 200 MHz spectrometer using TMS as internal standard. The

TABLE I Sulfamic Acid Catalyzed Synthesis of Thiadiazolo 1,5-Benzodiazepine Derivatives

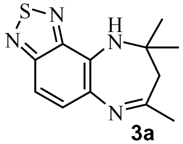
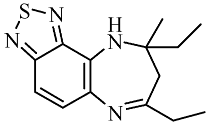
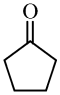
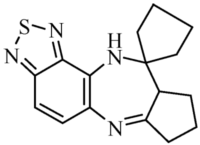
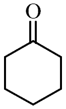
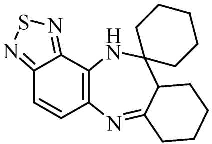
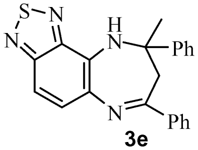
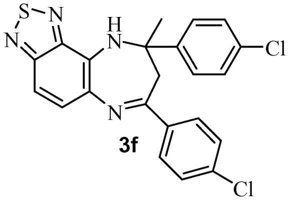
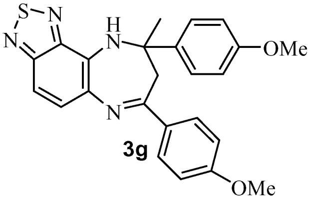
			Method A		Method B		
Entry	Ketone	Product	Time (min)	Yield (%)	Time (h)	Yield (%)	Mp (°C)
1	CH_3COCH_3	 **3a**	4	86	2	81	110
2	$CH_3COCH_2CH_3$	 **3b**	4.5	81	3.5	78	125
3		 **3c**	5	80	3	75	80
4		 **3d**	4.5	85	4	78	150
5	CH_3COPh	 **3e**	5.5	77	4	75	82
6	p-C!PhCH_3COPh	 **3f**	4.5	85	3.5	80	178
7	p-CH_3OCH_3COPh	 **3g**	6	72	5	70	85

TABLE II IR (Cm^{-1}), ^{1}H NMR (δ ppm) and Mass of the Compounds

Compd.	NH-str	C=N-str	^{1}H NMR ($CDCl_3$)	MS (EI): m/z (M^+)
3a	3345	1610	δ 1.85(s, 6H), 2.65(s, 2H), 2.91(s, 3H), 5.30(br s, 1H), 7.45(d, 1H), 7.63(d, 1H)	246
3b	3379	1610	δ 1.34(t, 3H), 1.51(t, 3H), 1.75(q, 2H), 2.35(m, 2H), 2.55(s, 3H), 2.95(q, 2H), 5.10(br s, 1H), 7.60(d, 1H), 7.75(d, 1H)	274
3c	3380	1630	δ 2.12 – 2.81(m, 12H), 3.03(m, 2H), 3.15(t, 1H), 5.10(s, 1H), 7.65(d, 1H), 7.71(d, 1H)	298
3d	3370	1635	δ 1.50 – 2.35(m, 16H), 2.70(t, 1H), 2.91(t, 2H), 5.31(s, 1H), 7.60-7.80(m, 2H)	326
3e	3365	1630	δ 1.91(s, 3H), 3.29(d, 1H), 3.45 (d, 1H), 5.45 (s, 1H), 7.15–7.71 (m, 12H)	370
3f	3388	1637	δ 1.87(s, 3H), 3.07(d, 1H), 3.50 (d, 1H), 5.85 (s, 1H), 7.15–7.65 (m, 10H)	439
3g	3380	1610	δ 1.85(s, 3H), 3.10–3.25(m, 2H), 3.91(s, 3H), 4.05(s, 3H), 5.31(s, 1H), 6.90–7.75(m, 10H)	430

elemental (C, H, N) microanalyses were performed on a Carlo Erba model EA1108. Mass spectra were recorded on a JEOL JMS D-300 Spectrometer.

General Procedure

Method-A (Microwave Irradiation)

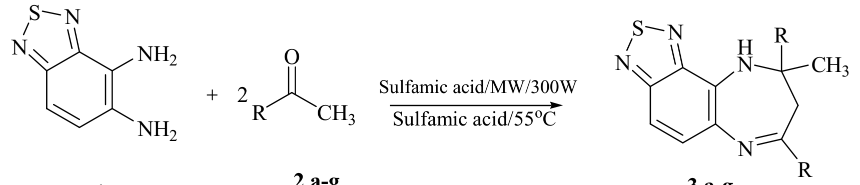
To a mixture of benzo[c][1,2,5]thiadiazole-4,5-diamine (0.6 m mol), ketone (1.2m mol) in chloroform (3 ml) was added sulfamic acid (0.02 m mol) and the reaction was irradiated in microwave oven (BPL, 800 model) at 300 W power level for the appropriate time (Table I). Completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature, and the solvent was evaporated under vacuum on a rotary evaporator. Water (5 ml) was added to reaction mixture and extracted with EtOAc (4 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (1:7) as eluent to afford the thiadiazolo benzodiazepine.

TABLE III C, H, N, S Analysis of the Compounds

		Cal (found) (%)			
Compd.	Molecular Formula	C	H	N	S
	$C_{12}H_{14}N_4S$	58.51 (58.47)	5.73 (5.77)	22.74 (22.70)	13.02 (13.07)
3b	$C_{14}H_{18}N_4S$	61.28 (61.24)	6.61 (6.64)	20.42 (20.38)	11.69 (11.65)
3c	$C_{16}H_{18}N_4S$	64.40 (64.42)	6.08 (6.06)	18.78 (18.74)	10.75 (10.71)
3d	$C_{18}H_{22}N_4S$	66.22 (66.25)	6.79 (6.82)	17.16 (17.19)	9.82 (9.80)
3e	$C_{22}H_{18}N_4S$	71.32 (71.27)	4.90 (4.94)	15.12 (15.17)	8.66 (8.62)
3f	$C_{22}H_{16}Cl_2N_4S$	60.14 (60.11)	3.67 (3.62)	12.75 (12.72)	7.30 (7.32)
3g	$C_{24}H_{22}N_4O_2S$	66.96 (66.97)	5.15 (5.11)	13.01 (13.05)	7.45 (7.49)

Method-B (Conventional Method)

To a mixture of benzo[c][1,2,5]thiadiazole-4,5-diamine (0.6 m mol), ketone (1.2m mol) in chloroform (10 ml) in a round-bottomed flask (50 ml) was added sulfamic acid (0.02 m mol) and the mixture was stirred at 55°C for appropriate time (Table I). After completion of the reaction (TLC), contents were cooled to room temperature, the solvent was evaporated under vacuum on a rotary evaporator. Water (5 ml) was added to the reaction mixture and extracted with EtOAc (4 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel using ethyl acetate-hexane (1:7) as eluent to give the thiadiazolo benzodiazepine.



1 **2 a-g** **3 a-g**

SCHEME 1

REFERENCES

[1] Rang, H. P., In *Pharmacology*, 5th ed. (Churchill Livingstone, 2003).

[2] (a) L. H. Strenbach, *J. Med. Chem.*, **22**, 1 (1979); (b) W. Leimgruber, V.Stefanovic, F. Schenker, A. Karr, and J. Berger, *J. Am. Chem. Soc.*, **87,** 5791 (1965);(c) W. Leimgruber, A. D. Batcho, and F. Schenker, *J. Am. Chem. Soc.*, **87,** 5793 (1965).

[3] (a) M. J. Kukla, H. J. Breslin, C. J. Diamond, P. P. Grous, C. Y. Ho, M. Mirands, J.D. Rodgers, R. G. Sherrill, E. De Clercq, R. Pauwels, K. Andries, L. J. Moens, M. A. C.

Janssen, and P. A. J. Janssen, *J. Med. Chem.*, **34,** 3187 (1991); (b) K. A. Parker and C. A. Coburn, *J. Org. Chem.*, **57,** 97 (1992).

[4] (a) H. Schutz, *Benzodiazepines* (Springer, Heidelberg, 1982); (b) R. Smalley, K. In *Comprehensive Organic Chemistry*; D. Barton, W. D. Ollis, Eds. (Pergamon, Oxford, 1979), Vol. 4, p. 600; (c) J. K. Landquist, In C*omprehensive Heterocyclic Chemistry*, A. R. Kartritzky and C. W. Rees, Eds. (Pergamon: Oxford, 1984), Vol. **1,** p. 166, 170; (d) L. O. Randall and B. Kappel, In *Benzodiazepines*, S. Garattini, E. Mussini, and L. O. Randall, Eds. (Raven Press, New York, 1973), p. 27.

[5] M. Essaber, A. Baouid, A. Hasnaoui, A. Benharreb, and J. P. Lavergne, *Synth. Commun.*, **28,** 4097 (2000).

[6] A. M. EI-Sayed, H. Abdel-Ghany, and A. M. M. EI-Saghier, *Synth.Commun.*,**29,** 3561 (1999).

[7] K. V. V. Reddy, P. S. Rao, and D. Ashok, *Synth.Commun.*, **30,** 1825 (2000).

[8] (a) G. V. Panakala Rao, B. Rajitha, Y. Thirupathi Reddy, P. Narsimha Reddy, and V. Naveen Kumar, *Phosphorus, Sulfur, and Silicon.*, **180,** 2119 **(**2005); (b) P. Narsimha Reddy, Y. Thirupathi Reddy, M. Kanakalingeswara Rao, and B. Rajitha, *Heterocycl.Commun.* **9,** 647 (2003).

[9] P. Stahlhofen and W. Ried, *Chem.Ber.*, **90,** 815 (1957).

[10] W. Ried and E. Torinus, *Chem.Ber.*, **92,** 2902**(**1959).

[11] J. A. L. Herbert and H. Suschitzky, *J. Chem. Soc., Perkin Trans.* **I,** 2657 (1974**).**

[12] D. I. Jung, T. W. Choi, Y. Y. Kim, I. S. Kim, Y. M. Park, Y. G. Lee, and D. H. Jung, *Synth.Commun.*, **29,** 1941 (1999).

[13] H. R. Morales, A. Bulbarela, and R. Contreras, *Heterocycles*. **24,** 135 (1986).

[14] M. Curini, F. Epifanio, M. C. Marcotullio, and O. Rosati, *Tetrahedron Lett.* **42,** 3193 (2001).

[15] M. Pozarentzi, J. S. Stephanatou, and C. A. Tsoleridis, *Tetrahedron Lett.*, **43,** 1755 (2002).

[16] D. V. Jarikote, S. A. Siddiqui, R. Rajagopal, T. Daniel, R. J. Lahoti, and K. V. Srinivasan, *Tetrahedron Lett.*,**44,**1835 (2003).

[17] B. A. Ganai, Satish Kumar, C. S. Andotra, and K. K. Kapoor, *Synth.Commun.*, **36,** 803(2006).

[18] J. Wu, F. Xu, Z. Zhou, and Q. Shen, *Synth.Commun.*, **36,** 457 (2006).

[19] V. Srivamurugan, K. Deepa, M. Palanichamy, and V. Murugesan, *Synth.Commun.*, **34,**3833 (2004).

[20] J. S. Yadav, B. V. Reddy, S. Praveenkumar, K. Nagaiah, N. Lingaiah, and P. S. Saiprasad, *Synthesis.*, **6,** 901 (2004).

[21] M. S. Balakrishna, and B. Kaboudin, *Tetrahedron Lett.*, **42,** 1127 (2001).

[22] B. Rajitha, B. Sunil Kumar, Y. Thirupathi Reddy, P. Narsimha Reddy, and N. Sreenivasulu,*Tetrahedron Lett.*, **46,** 8691 (2005).

[23] J. Venu Madhav, V. Naveen Kumar, and B. Rajitha, *Synth. Commun.*, **38,** 1799 (2008).

[24] S. Caddick, *Tetrahedron*, **51,** 10403 (1995).

[25] A. P. Komin and M. Carmack, *J. Heterocycl. Chem.*, **14,** 829 (1975).