A comparative study on the synthesis of 3'-aryl-3-methyl/2, 3-dimethylspiro[6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-5, 2'-(tetrahydro[1,3] thiazolane)]-4'-ones using microwave irradiation and conventional methods

Peesapati Venkateswarlu* and Nageswara Rao Vasireddy

Industrial Chemistry Laboratories, Centre for Environment, J.N.T. University, Hyderabad – 500 072, India

A convenient one pot synthesis of 3'-aryl-3-methyl/2,3-dimethylspiro[6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-5,2'-(tetrahydro[1,3]thiazolane)-4'-ones under microwave irradiation, as well as conventional methods, is described. Microwave irradiation has resulted in the reduction of time from hours to minutes. Antimicrobial activity of these compounds was studied and that some compounds gave positive results.

Keywords: benzocycloheptenones, imines, spirothiazolidines, antibacterials

There has been a growing interest in the use of microwave irradiation in organic synthesis during the past decade, since the first contribution by Gedye *et al.*[1] and Girguere *et al.*[2] in 1986. The number of publications and reviews that have advocated the advantages and the use of microwave irradiation over conventional technology have increased significantly.[3] Remarkable decreases in reaction time and, in some cases, cleaner reaction and better yields have made this technique widely applicable in organic synthesis.

The thiazole nucleus appears frequently in the structure of various natural products and biologically active compounds, notably thiamine (vitamin B), penicillins, antibiotics such as micrococcin,[4] cardiac and glycemic benefits of troglitazone[5] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids.[6] Numerous thiazolidine derivatives exhibit sedative,[7] anesthetic,[8] anticonvulsant,[9] antituberculous,[10] amebicidal[11] and fungicidal[12] activities.

The reaction of imines with mercaptoacetic acid or substituted mercaptoacetic acid is a convenient method for the synthesis of a wide variety of thiazolidine derivatives.[13,14] Prompted by these observations and in continuation of our work[15-17] on the synthesis of fused heterocyclic systems, we now wish to report the synthesis of new spirothiazolidine derivatives using microwave irradiation as well as by conventional methods. In this work the spirothiazolidines **2a–h** have been prepared using conventional methods and under microwave irradiation by condensing 3-methyl/2,3-dimethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one[18] (**1a,b**), an aromatic amine and mercaptoacetic acid without isolating the intermediate imines. Using microwave irradiation, reaction times are reduced from several hours to a few minutes. Both conventional and microwave methods gave moderate yields.

The structure of compound **2a** has been ascertained by an NMR study. In the NMR spectra of **2a** two complex multiplets were observed in the ranges of δ_H 2.68–2.76 and 2.85–2.95 which certainly arise from the methylene protons at the 6-position. The IR spectrum of **2a** exhibited absorption band at 1728 cm^{-1} due to the CO functional group. The M^+ peak in the mass spectrum at 357 further confirms the structure **2a.** In a similar manner compounds **2b–2h** were prepared and their structures determined.

Biological evaluation

All the compounds were screened for their antimicrobial activity at a concentration of 40 μg/well in agar media[19] using Doxycyclin in antibacterial and Nalidixic acid in antifungal activity as reference compounds. Compounds **2a**, **2c** and **2g** showed good activity in terms of diameter of the zone of inhibition (12 mm), while other compounds **2b** (10 mm), **2f** (7 mm), and **2h** (10 mm) showed moderate activity as compared with Doxycyclin (15 mm) against gram –ve bacterium *E. coli.* Compounds **2a** (10 mm), **2b** (8 mm), **2d** (5 mm), **2e** (13 mm), **2f** (7 mm), **2g** (8 mm) and **2h** (12 mm) showed moderate to good activity as compared with Doxycyclin (18 mm) against gram +ve bacterium *Bacillus Suffilis.* All the compounds were found ineffective against the fungus *Trichoderma* species.

Experimental

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra are recorded on a FT-IR 1605 Perkin Elmer. Proton NMR in $CDCl_3$ on a Varian FT-80A spectrometer with TMS as internal standard. Mass spectra were taken on a VG-micromass 7070H mass spectrometer. TLC was run on silica gel G coated plates and iodine vapour as visualising agent.

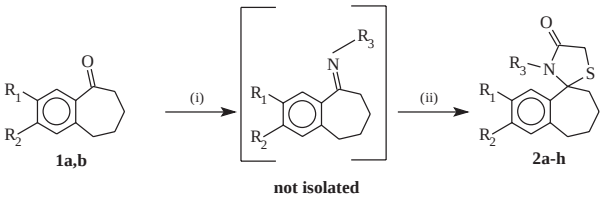
3'-Aryl-3-methyl/2,3-dimethylspiro[6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5,2'-(tetrahydro[1,3]thiazolane)]-4'-ones (2): General procedure: A: Microwave: A mixture of 3-methyl/2, 3-dimethyl 6,7,8,9-tetrahydrobenzocyclohepten-5-one (**1a,b**) (1 mmol), primary aromatic amine (1 mmol) and glacial acetic acid (0.05 ml) in dry ethanol (5 ml) were placed in an Erlenmeyer flask, covered with a watch glass and irradiated in the microwave oven for 7 minutes. On cooling the mixture, mercaptoacetic acid (1.5 mmol) was added and irradiation was continued for 6–8 minutes under the same conditions. After completion of the reaction (monitored by TLC), the mixture was dissolved in chloroform, washed with water and dried over anhydrous sodium sulfate. It was purified by preparative TLC using as eluent ethyl acetate / hexane / glacial acetic acid in the ratio 4 : 6 : 0.1.

B: conventional: A mixture of 3-methyl/2,3-dimethyl 6,7,8, 9-tetrahydrobenzocyclohepten-5-one (**1a,b**) (1 mmol), primary aromatic amine (1 mmol) and glacial acetic acid (0.05 ml) was refluxed in toluene for 3 h using a Dean–Stark apparatus and the water formed was removed azeotropically. On cooling the mixture, mercaptoacetic acid (1.5 mmol) was added, the reaction mixture was refluxed again for 15-18 hr and worked-up in the usual way. It was purified by preparative TLC using eluent as ethyl acetate / hexane / glacial acetic acid in the ratio 4 : 6 : 0.1.

2a: Yield: Microwave 61% (conventional 56%), viscous liquid, IR (neat): 1728 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.80–1.95 (2H, m, 7-CH_2), 2.02–2.18 (2H, m, 8-CH_2), 2.35 (3H, s, 11-CH_3), 2.50–2.60 (2H, m, 9-CH_2), 2.68–2.76 (1H, m, 6-CH), 2.85–2.95 (1H, m, 6-CH), 3.18 (2H, s, $COCH_2$) and 6.40–7.50 (7H, m, ArH); MS: *m/z* 357 (M^+). [Found: C, 66.80; H, 5.55; N, 3.83. $C_{20}H_{20}NClOS$ requires C, 67.22; H, 5.60; N, 3.92%].

2b: Yield: Microwave 62% (conventional 55%), m.p.64–66°C; IR (neat): 1708 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.78–1.90 (2H, m, 7-CH_2), 1.98–2.10 (2H, m, 8-CH_2), 2.22 (6H, s, 10,11-CH_3), 2.40–2.58 (2H, m, 9-CH_2), 2.65–2.78 (1H, m, 6-CH), 2.85–3.00 (1H, m, 6-CH), 3.20 (2H, s, $COCH_2$) and 6.20–7.40 (6H, m, ArH). [Found: C, 67.55; H, 5.86; N, 3.69. $C_{21}H_{22}NClOS$ requires C, 67.92; H, 5.92; N, 3.77%].

* Correspondence. E-mail: vpeesapati@yahoo.com



a) $R_1 = CH_3$, $R_2 = H$, R_3 = 2-chlorophenyl
b) $R_1 = R_2 = CH_3$, R_3 = 2-chlorophenyl
c) $R_1 = CH_3$, $R_2 = H$, R_3 = 4-chlorophenyl
d) $R_1 = R_2 = CH_3$, R_3 = 4-chlorophenyl
e) $R_1 = CH_3$, $R_2 = H$, R_3 = 4-bromophenyl
f) $R_1 = R_2 = CH_3$, R_3 = 4-bromophenyl
g) $R_1 = CH_3$, $R_2 = H$, R_3 = 1-naphthyl
h) $R_1 = R_2 = CH_3$, R_3 = 1-naphthyl

Reagents :

(i) R_3NH_2 & AcOH
(ii) mercaptoacetic acid

Scheme 1

2c: Yield: Microwave 63% (conventional 58%); m.p.90–92°C; IR (neat): 1671 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.85–1.95 (2H, m, 7-CH_2), 1.95–2.15 (2H, m, 8-CH_2), 2.30–2.48 (5H, m, 11-CH_3 & 9-CH_2), 2.60–2.78 (1H, m, 6-CH), 2.85–3.00 (1H, m, 6-CH), 3.30 (2H, s, $COCH_2$) and 6.40–7.40 (7H, m, ArH). [Found: C, 66.75; H, 5.52; N, 3.87. $C_{20}H_{20}NClOS$ requires C, 67.22; H, 5.60; N, 3.92%].

2d: Yield: Microwave 65% (conventional 60%), m.p.108–110°C; IR (neat): 1693 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.80–1.90 (2H, m, 7-CH_2), 2.00–2.35 (8H, m, 10,11-CH_3 & 8-CH_2), 2.45–2.60 (2H, m, 9-CH_2), 2.65–2.75 (1H, m, 6-CH), 2.80–2.90 (1H, m, 6-CH), 3.20 (2H, s, $COCH_2$) and 6.35–7.60 (6H, m, ArH). [Found: C, 67.83; H, 5.90; N, 3.66. $C_{21}H_{22}NClOS$ requires C, 67.92; H, 5.92; N, 3.77%].

2e: Yield: Microwave 67% (conventional 58%), m.p.95–97°C; IR (neat): 1684 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.80–1.95 (2H, m, 7-CH_2), 2.05–2.18 (2H, m, 8-CH_2), 2.35 (3H, s, 11-CH_3), 2.50–2.60 (2H, m, 9-CH_2), 2.68–2.78 (1H, m, 6-CH), 2.85–2.95 (1H, m, 6-CH), 3.18 (2H, s, $COCH_2$) and 6.45–7.50 (7H, m, ArH). [Found: C, 59.62; H, 4.85; N, 3.37. $C_{20}H_{20}NBrOS$ requires C, 59.70; H, 4.97; N, 3.48%].

2f: Yield: Microwave 65% (conventional 60%), m.p.118–120°C; IR (neat): 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.78–1.88 (2H, m, 7-CH_2), 2.00–2.15 (2H, m, 8-CH_2), 2.25 (6H, s, 10,11-CH_3), 2.45–2.55 (2H, m, 9-CH_2), 2.65–2.75 (1H, m, 6-CH), 2.85–2.95 (1H, m, 6-CH), 3.20 (2H, s, $COCH_2$) and 6.30–7.40 (6H, m, ArH). [Found: C, 60.44; H, 5.16; N, 3.28. $C_{21}H_{22}NBrOS$ requires C, 60.57; H, 5.28; N, 3.36%].

2g: Yield: Microwave 57% (conventional 50%), m.p.62–64°C; IR (neat): 1714 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.80–1.95 (2H, m, 7-CH_2), 2.05–2.20 (2H, m, 8-CH_2), 2.38 (3H, s, 11-CH_3), 2.52–2.62 (2H, m, 9-CH_2), 2.68–2.78 (1H, m, 6-CH), 2.88–2.98 (1H, m, 6-CH), 3.20 (2H, s, $COCH_2$) and 6.50–7.60 (10H, m, ArH). [Found: C, 77.14; H, 6.07; N, 3.66. $C_{24}H_{23}NOS$ requires C, 77.21; H, 6.16; N, 3.75%].

2h: Yield: Microwave 59% (conventional 53%), m.p.82–84°C; IR (neat): 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ_H 1.90–2.05 (2H, m, 7-CH_2), 2.20–2.30 (8H, m, 10,11-CH_3 & 8-CH_2), 2.40–2.50 (2H, m, 9-CH_2), 2.65–2.75 (1H, m, 6-CH), 2.82–2.92 (1H, m, 6-CH), 3.20 (2H, s, $COCH_2$) and 6.20–7.40 (9H, m, ArH). [Found: C, 77.47; H, 6.34; N, 3.52. $C_{25}H_{25}NOS$ requires C, 77.51; H, 6.45; N, 3.61%].

One of the authors (VN Rao) is thankful to the UGC, New Delhi for the award of the Junior Research Fellowship.

Received 23 December 2003, accepted 9 February 2004
Paper 03/2268

References

1 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera and J. Rousell, *Tetrahedron Lett.*, 1986, **27,** 279.
2 R.J. Giguere, T.L. Bray, S.M. Duncan and G. Majetich, *Tetrahedron Lett.*, 1986, **27,** 4945.
3 R.A. Abramovitch, *Org. Prep. Proc. Int.*, 1991, **23,** 685; S. Caddick, *Tetrahedron.*, 1995, **51,** 10403; C.R. Strauss and R.W. Trainor, *Aust. J. Chem.*, 1995, **48,** 1665; S. Deshayes, M. Liagre, A. Loupy, J. –L. Luche and A. Petit, *Tetrahedron.*, 1999, **55,** 10851.
4 M.N.G. James and K.J. Watson, *J. Chem. Soc.*, 1966, 1361.
5 M.N. Ghazzi, J.E. Perez, T.K. Antonucci, J.H. Driscoll, S.M. Huang and B.W. Faja, *Diabetes.*, 1997, **46,** 433.
6 U. Schmidt, R. Utz, A. Lieberknecht, H. Griesser, B. Potzolli, J. Bahr, K. Wagner and P. Fischer, *Synthesis.*, 1987, 233.
7 W.J. Doran and H.A. Shoule, *J. Org. Chem.*, 1939, **3,** 193.
8 A.R. Surrey, *J. Am. Chem. Soc.*, 1949, **71,** 3354.
9 H.D. Troutman and L.M. Long, *J. Am. Chem. Soc.*, 1948, **70,** 3436.
10 N.P. Buu-Hoi, N.D. Xuong and F. Binon, *J. Chem. Soc.*, 1956, 716.
11 A.R. Surrey and R.A. Cutler, *J. Am. Chem. Soc.*, 1954, **76,** 578.
12 J. Kinugawa and H. Nagase, *Yakugaku Zasshi.*, 1966, **86,** 101.
13 J.J. Modha, J.M. Parmar, N.J. Datta and H.H. Parekh, *Ind. J. Chem.*, 2002, **41B,** 2694.
14 B. Goel, T. Ram, R. Tyagi, E. Bansal, A. Kumar, D. Mukherjee and J.N. Sinha, *Eur. J. Med. Chem.*, 1999, **34,** 265.
15 V. Peesapati and S.C. Venkata, *Ind. J. Chem.*, 2003, **42B,** 616.
16 V. Peesapati, P. Sreelakshmi and K. Anuradha, *J. Chem. Res. (S).*, 2001, 372.
17 V. Peesapati, K. Anuradha and S. Suresh Babu, *J. Chem. Res. (S).*, 2000, 496.
18 S.G. Sen Gupta and Parimal Krishna Sen, *Sci. Cult.*, Calcutta, 1992, **28,** 343; L.F. Somerville and C.F.H. Allen, *Org. Synth.*, 1943, **2,** 81; Jr. R.C. Gilmore and W.J. Horton, *J. Am. Chem. Soc.*, 1951, **73,** 1411.
19 C. Kvanagh, *Anal. Microbial*, Academic Press, New York, 1963.