

Microwave assisted synthesis of some new 2-substituted-1,4-benzothiazine derivatives

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Manuscript received 17 June 2008, revised 12 April 2010, accepted 12 April 2010

Abstract : The nitrogen and sulphur containing compounds are well known for their vital role in medicinal chemistry. Here, we report the synthesis of 2-hydrazido-1,4-benzothiazine (2) from 2-carbethoxy 1,4-benzothiazine-3-(1*H*)-one (1) and hydrazine hydrate which then treated with acetyl acetone, ethyl acetoacetate, cyanoethylacetate to give substituted 2-(benzothiazine-3-one-2-yl-oxo)-3,5-dimethyl pyrazole (2a), 1-(benzothiazine-3-one-2-yl-oxo)-3-methyl pyrazole-5-one (2b) and (1-benzothiazine-3-one-2-yl-oxo)-3-amino pyrazole-5-one (2c) respectively under microwave irradiation. Further, the reaction of 2 with phenyl isothiocyanate under microwave irradiation yielded 1-(benzothiazolyl-oxo)-4-phenyl thiosemicarbazide (2d) which was subsequently cyclised with conc. H₂SO₄ and dil. NaOH to give targeted 2-(benzothiazin-3-one-2-yl)-5-anilino-1,3,4-oxadiazole (2e) and 1-phenyl-2-[benzothiazine-3(1*H*)-one-2-yl]-5-mercapto-1,3,5-triazole (2f) respectively.

Keywords : 1,4-Benzothiazine, microwave synthesis, pyrazoles, oxadiazoles.

Introduction

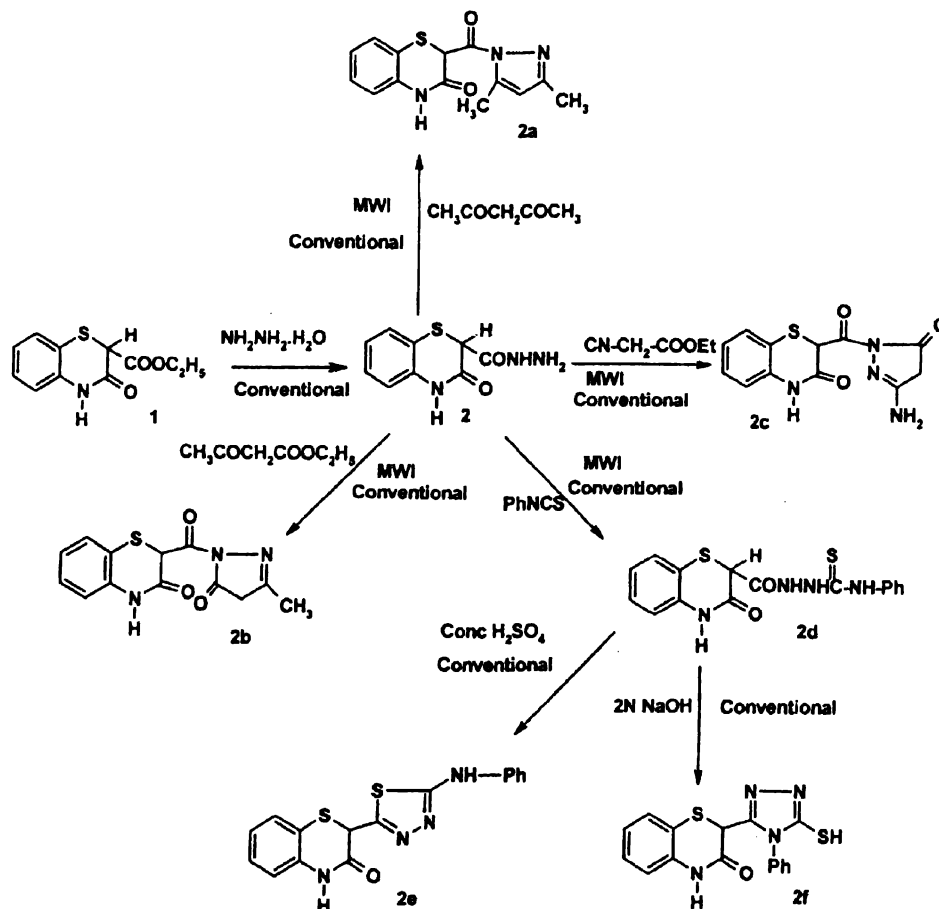
1,4-Benzothiazines possess various biological activities such as antitumor, anti-inflammatory, antidepressant, antibacterial etc. and several derivatives of them are in clinical use^{1,2}. The 1,4-benzothiazine are bicyclic compounds which are important in medicinal chemistry as therapeutic agents. Some of these compounds influence the growth hormone releasing system and antimicrobial activities^{3,4}. The 1,4-benzothiazine moiety is found in the molecules which have been tested on Aldose Reductase inhibition, Ca²⁺ antagonism, immunomodulating and anti-inflammatory activities⁵⁻⁷. 1,4-Benzothiazines resemble to phenothiazines which are well established antipsychotic drugs^{8,9}, in having a fold along the nitrogen-sulfur axis and can be anticipated to possess biological activities like phenothiazine. The basic unit present in mammalian red hair and feather is the 1,4-benzothiazine nucleus¹⁰. Luciferin and rafamycin are 1,4-benzothiazine derivatives, obtained by biosynthesis and are found to possess pharmacological activities¹¹. 1,4-Benzothiazines are known for their utility as dyestuffs¹², photographic developers¹³, ultraviolet light absorbers and antioxidants¹⁴. Semotiadil, a derivative of 1,4-benzothiazine has been

used as an anti-hypertensive and anti-anginal drug¹⁵. These multifarious applications of 1,4-benzothiazines and our previous success in the synthesis of heterocyclic compounds^{16,17}, have prompted us to synthesize new 1,4-benzothiazines bearing heteroaryl pharmacophores.

Microwave irradiation has been used for varieties of applications in organic synthesis^{19,20}. The classical approach^{21,22} for synthesis involved refluxing for several hours in presence of solvent, which result in generation of aqueous and organic wastes. However, the method reported by microwave is quite satisfactory in term of reaction time and yield.

Results and discussion

The starting 2-carbethoxy 1,4-benzothiazine-3-(1*H*)-one (1) has been prepared by reported method¹⁵. The strategy employed for the synthesis involved the reaction of 2-carbethoxy-1,4-benzothiazine-3-(1*H*)-one (1) with hydrazine hydrate to give 2-hydrazidobenzothiazine-3(1*H*)-one (2) as a key intermediate and confirmed on the basis of PMR spectrum which showed a singlet at δ 9.2 for -NH and singlet at δ 3.3 for the -CH confirms the formation of desired compound. Further, a typical experimen-



Scheme 1

tal procedure involved the mixing of 2-hydrazidobenzothiazine-3(1H)-one (2) with acetyl acetone in an open glass container without solvent followed by the irradiation of reaction mixture in a microwave oven at power output of 520 W for an appropriate time (monitored by TLC, Table 1) to afford 2-(benzothiazine-3-one-2-yl-oxo)-

3,5-dimethyl pyrazole (2a), whereas by conventional method it requires 3 h. Similarly, compound 2 was reacted with ethyl acetoacetate to afford the 1-(benzothiazine-3-one-2-yl-oxo)-3-methyl pyrazole-5-one (2b), whereas by conventional method it requires 7 h while 2 on reaction with ethyl cyanoacetate under microwave irradiation afforded the 1-(benzothiazine-3-one-2-yl-oxo)-3-amino pyrazole-5-one (2c). The 2a and 2b showed singlet at δ 2.1 and 2.2 respectively for the methyl proton along with others, which indicates the desired results. Obviously, 2c also showed singlet at δ 2.5 for the methylene protons. Similarly, 1-(benzothiazinyl-oxo)-4-phenyl thiosemicarbazide (2d) has been synthesized from compound 2 and phenyl isothiocyanate under microwave irradiation. Further, 2d was subsequently cyclised in presence of conc. H_2SO_4 and 2 N NaOH to furnish 2-(benzothiazine-3-one-2-yl)-5-anilino-1,3,4-oxadiazole (2e) and 1-phenyl-2-[benzothiazine-3(1H)-one-2-yl]-5-mercapto-1,3,5-triazole

Table 1. Yields and reaction condition used for microwave-assisted synthesis

Entry	Conditions	Microwave method		Conventional method	
		Reaction time	Yield (%)	Reaction time (h)	Yield (%)
2a	-	2 min	85	5	76
2b	-	1 min	81	3	79
2c	AcOH	3 min	89	7	61
2d	-	30 s	90	2	68
2e	-	-	-	4	60
2f	-	-	-	4	65

(2f) respectively and confirmed on the basis of the spectroscopic data.

Experimental

All the chemicals have been purchased from Aldrich and used as received. The melting points were taken in open capillary and are uncorrected. IR spectra were recorded on Shimadzu IR-470 spectrophotometer using KBr pellets and proton NMR spectra recorded on 400 MHz spectrometer with tetra-methyl silane as an internal standard in DMSO- d_6 . Microwave irradiation (MWI) has been conducted in a Samsung M197DN (2450 MHz, 1500 W). All the reactions were carried out in an open glass container. The average bulk temperature at the end of reaction was measured by inserting a thermometer in the glass container.

General procedure :

2-Carbethoxy 1,4-benzothiazine-3-(1H)-one (1) :

2-Carbethoxy 1,4-benzothiazine-3-(1H)-one was prepared by reported method¹⁸; m.p. 140 °C (lit. m.p. 144 °C); IR (KBr) : 3056, 1728, 1674 cm^{-1} ; PMR (DMSO- d_6) : δ 2.0 (3H, t, -OCH₂CH₃), 4.01 (2H, q, -OCH₂CH₃), 4.51 (1H, s, -CH), 7.24-7.59 (4H, m, Ar-H) 10.33 (1H, s, -NH).

2-Hydrazidobenzothiazine-3(1H) one (2) :

A mixture of (1) 2-carbethoxy 1,4-benzothiazine-3-(1H)-one (5 mmol) and hydrazine hydrate (5 mmol), methanol (20 ml) was refluxed on the water bath for 7-8 h. The solid separated out was cooled to 0-5 °C and was filtered washed with water and recrystallized from ethanol; m.p. 160 °C; IR (KBr) : 3186, 2923, 1694, 1665 cm^{-1} ; PMR (DMSO- d_6) : δ 9.20 (1H, s, -NH), 6.84-7.5 (4H, m, Ar-H), 4.41 (2H, s, -NH₂), 3.3 (1H, s, -CH), 2.9 (1H, s, -NH-NH₂); M⁺ 222.

2-(Benzothiazine-3-one-2-yl-oxo)-3,5-dimethyl pyrazole (2a) :

A mixture of (2) 2-hydrazidobenzothiazine-3(1H)-one (1 mmol) and acetyl acetone (1 mmol) was irradiated in MW for 1 min interval at 130 °C (monitored by TLC). The crude product was recrystallized from methanol. Yield (85%); m.p. above 300 °C; IR (KBr) : 3402, 2923, 1710 cm^{-1} ; PMR (DMSO- d_6) : δ 2.45 (6H, s, -CH₃), 2.1 (1H, s, -CH), 3.5 (1H, br.s, -NH), 7.0-7.5 (4H, m, Ar-H), 6.8 (1H, s, Ar-H); M⁺ 320.

1-(Benzothiazine-3-one-2-yl-oxo)-3-methyl pyrazole-5-one (2b) :

A mixture of (2) 2-hydrazidobenzothiazine-3(1H)-one (1 mmol) and ethyl acetoacetate (1 mmol) and was irradiated in MW for 3 min interval at 130 °C (monitored by TLC). The crude product was recrystallized from methanol. Yield (81%); m.p. above 300 °C; IR (KBr) : 3315, 2935, 1678, 1665, 1595, 1403 cm^{-1} ; PMR (DMSO- d_6) : δ 2.2 (3H, s, -CH₃), 3.4 (1H, br.s, -NH), 2.32 (1H, s, -CH), 6.7-7.4 (4H, m, Ar-H), 2.2 (2H, s, -CH₂); M⁺ 305.

1-(Benzothiazine-3-one-2-yl-oxo)-3-amino pyrazole-5-one (2c) :

A mixture of (2) 2-hydrazidobenzothiazine-3(1H)-one (1 mmol) and ethyl cyanoacetate (1 mmol) was irradiated in MW for 2 min interval at 130 °C (monitored by TLC). The product was washed with water and recrystallized from methanol. Yield (89%); m.p. above 300 °C; IR (KBr) : 3458, 3150, 2923, 1678, 1602, 1475, 1309, 1246, 918, 817, 762 cm^{-1} ; PMR (DMSO- d_6) : δ 2.54 (2H, s, -CH₂), 3.5 (2H, br.s, -NH₂), 5.2 (1H, s, -CH), 6.4-8.3 (4H, m, Ar-H), 10.8 (1H, s, -NH); M⁺ 288.

1-(Benzothiazinyl-oxo)-4-phenyl thiosemicarbazide (2d) :

A mixture of (2) 2-hydrazidobenzothiazine-3(1H)-one (1 mmol) and phenyl isothiocyanate (1 mmol) was irradiated in MW for 30 s at 80 °C (monitored by TLC). The product was washed with water and recrystallized from methanol. Yield (90%); m.p. 112 °C; IR (KBr) : 3222, 2924, 1679 cm^{-1} ; PMR (DMSO- d_6) : δ 2.51 (1H, s, -NH), 9.9 (1H, s, -NH), 10.4 (1H, s, -NH), 2.6 (1H, s, -NH), 6.9-7.80 (9H, m, Ar-H), 3.33 (1H, s, -CH); M⁺ 357.

All these compounds 2a, 2b, 2c and 2d also synthesized by conventional method using methanol as a solvent but process found to be more lengthy.

2-(Benzothiazine-3-one-2-yl)-5-anilino-1,3,4-oxadiazole (2e) :

A mixture of (2d) (1 mmol) 1-(benzothiazinyl-oxo)-4-phenyl thiosemicarbazide was added in small portions to conc. H₂SO₄ (5 ml) at 0 °C. The mixture was kept stirring for 4 h. It has been allowed to stand overnight at room temperature and then poured into crushed ice and neutralized with 10% liq. ammonia till pH was neutral.

The solid separated was filtered, washed with ice-cold water and recrystallized from ethanol. Yield (60%); m.p. above 300 °C; IR (KBr) : 3321, 3261, 2930, 1675, 1610, 1540, 1415, 1320 cm^{-1} ; PMR ($\text{DMSO}-d_6$) : δ 3.3 (1H, s, -NH), 5.7 (1H, s, -NH), 6.9–7.6 (9H, m, Ar-H); M^+ 340.

1-Phenyl-2-[benzothiazine-3(1H)-one-2-yl]-5-mercapto-1,3,5-triazole (2f) :

Mixtures of (2d) (1 mmol) 1-(benzothiazinyl-oxo)-4-phenyl thiosemicarbazide and 2 N sodium hydroxide (10 ml), methanol (10 ml) were refluxed on the water bath for 4 h. The reaction mixture was concentrated to 1/3 of its volume and cooled. The solution was cooled and acidified with dil. HCl. The precipitated solid was filtered, washed with water and recrystallised from ethanol. Yield (65%); m.p. above 300 °C; IR (KBr) : 2520, 2924, 1665 cm^{-1} ; PMR ($\text{DMSO}-d_6$) : δ 3.58 (1H, s, -CH), 2.1 (1H, s, -SH), 6.90–7.98 (9H, m, Ar-H); M^+ 312.

Conclusion :

In conclusion, we have synthesized 2-substituted-1,4-benzothiazine by eco-friendly microwave irradiation method. The simple operation, inexpensive reagents, high yield and significantly very short time are some unique features of present method. This is one of the economical and attractive methods for the synthesis of desired compounds.

Acknowledgement

The authors thank Institute of Science, Mumbai, and Indian Institute of Science, Bangalore for spectral analysis and UGC, New Delhi for providing grant to Chemistry Department, Shivaji University, Kolhapur under SAP.

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