Asian Journal of Chemistry Vol. 17, No. 2 (2005), 991–995

Microwave Assisted Synthesis of Ethyl 2,4-disubstituted thiazole-5-acetates for their Antioxidant Activity

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Synthesis of ethyl 3-aroylpropionates (**3–4**) has been conducted under microwave irradiation in open vessels and then brominated to ethyl 3-bromo-3-aroylpropionate (**5–6**). Ethyl 2,4-disubstituted thiazole-5-acetates (**8a–s**) have been synthesized by condensing thiourea/(un)substituted phenylthiourea (**7**) with bromo ester (**5–6**) under microwave irradiation using ethanol as the microwave energy transfer agent. The synthesized compounds have been tested *in-vitro* for their antioxidant activity.

Key Words: Synthesis, Substituted thiazole, Microwave, Antioxidant activity.

INTRODUCTION

Thiazole derivatives are important heterocyclic compounds used as therapeutic agents including analgesic and antiinflammatory activities[1–4]. Several thiazole acetic acids and esters were found to be very important inhibitors of inflammation[5–11].

The most general route to synthesize thiazole involves the cyclization of a reagent containing the C—C unit by a great variety of reactants bearing the N—C—S fragment of the ring and is still the most widely used method of synthesis of thiazoles[12]. These syntheses are typical examples of the bis-nucleophile plus bis-electrophile method of constructing heterocycles. The nitrogen and sulphur atoms of the N—C—S reagent act as nucleophilic centre and both the carbon atoms of the C—C reagent are electrophilic centres. Thioamides, thiourea and ammonium thiocarbamate are commonly used as N—C—S substrates and a halocarbonyl compound is a typical reagent.

There are several reports on the microwave assisted rate enhancement of organic reactions in high dielectric constant solvents such as DMF, water and DMSO[13, 14]. We report here a rapid and simple procedure for microwave assisted Hantzsch's synthesis of thiazole **(Scheme-1).** Thiourea and various aromatic thioureas (N—C—S unit) were reacted with ethyl 3-bromo-3-aroyl propionates (C—C unit) in ethanol under microwave irradiation to yield the title compounds.

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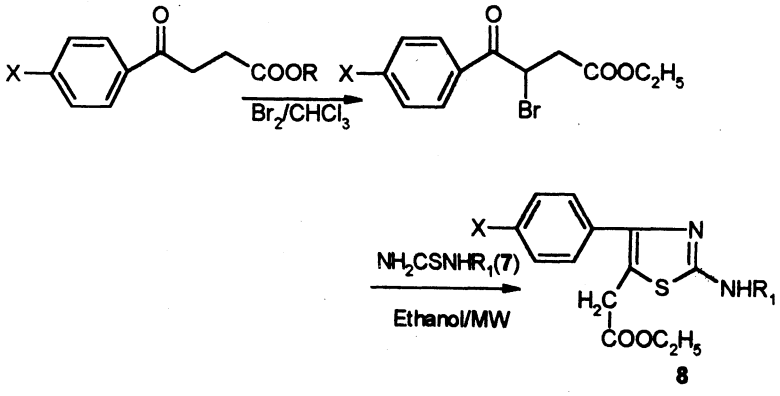
The reactions proceeded smoothly under reaction conditions and gave the desired products in good yield. One of the mechanisms that may contribute to NSAID's antiinflammatory activity include the reduction of super oxide radical; therefore, antioxidant activity of the newly synthesized compounds has been studied.



1. R = H, X = H; 2. R = H, X = Cl; 3. R = C_2H_5, X = H;
4. R = C_2H_5, X = Cl; 5. X = H; 6. X = Cl

Scheme-1

RESULTS AND DISCUSSION

Ethyl 3-aroyl propionates (**3, 4**) were prepared in better yields by irradiating a mixture of 3-aroyl propionic acids (**1, 2**) concentrated sulphuric acid and ethanol in open glass containers using unmodified household microwave oven in 1.5 min. This procedure considerably reduces the longer reaction time (7 h of refluxing) usually encountered in traditional ester synthesis[15]. The acid is then brominated to 3-bromo-3-aroylpropionate (**5, 6**). The reaction of 3-bromo-3-aroylpropionate with thiourea and (un)substituted phenyl thiourea **7** in ethanol at reflux for 60–75 min resulted in the formation of thiazole acetates **8a–s** in 65–78% yield. The same reactions under microwave irradiation, however, provide the desired products expeditiously in 85–95% yield in 0.5–1.5 min. A pulsed technique is followed that entails irradiating the reaction mixture at a lower power for successive intervals of 30 s each time with a cooling period of 1 min. The reaction vessel was also covered with a funnel. This method is followed to avoid evaporation of ethanol, since the unmodified household microwave oven lacks the special attributes of commercial microwave reactors in terms of control of temperature and reflux condenser.

The generality of this approach has been demonstrated by the condensation of a variety of aromatic thioureas with halo ketones (**Scheme-1**). This reproducible microwave protocol, however, is much simpler and cleaner when compared to the conventional method in terms of enhanced reaction rates, higher yields and the ease of manipulation. The reaction is monitored on TLC using *n*-hexane/EtOAc (7 : 3 v/v) as a solvent system and the integrity of the product is confirmed by

the spectral data obtained. The IR spectra of the compounds displayed absorption between 3220–3190 cm^{-1} due to diaryl NH and 1735–1720 cm^{-1} due to ν(C=O) functions of ester. In the ^1H NMR spectra protons of methylene group flanked by thiazole and ester function, methylene and methyl protons of ethyl ester group have resonated as singlet, quartet and triplet in the region of δ 3.70–3.75, 4.1–4.25 and 1.26–1.30 respectively. The aromatic methyl protons of **8(d, e)** and **8(m, n)** have resonated singlet in the region of δ 2.30–2.35. The NH protons of para substituted aryl amino group at second position of thiazole have been noticed at δ 7.85–7.95 as a hump, whereas in the *o*-substituted compounds NH proton is merged with the aromatic protons, which were resonated in the region of δ 6.9–7.8. The mass spectra and ^{13}C NMR of some of the compounds also supported the spectra assigned to them.

TABLE-1
PHYSICAL DATA AND ANTI-OXIDANT ACTIVITY OF 2-AMINO SUBSTITUTED THIAZOLES

Sl. No.	Compd. No.	Substitutions		Irradiation time (min)	Yield (%)	m.p. (°C)	IC_{50} (μ mol)
		X	R_1				
1.	**8a**	H	H	0.5	93	166–167	NA
2.	**8b**	H	2-ClC_6H_4	1.0	95	94–95	670
3.	**8c**	H	3-ClC_6H_4	1.0	86	104–105	506
4.	**8d**	H	2-$CH_3C_6H_4$	1.0	92	120–121	828
5.	**8e**	H	4-$CH_3C_6H_4$	1.0	90	148–149	517
6.	**8f**	H	4-$COCH_3C_6H_4$	1.5	82	166–167	901
7.	**8g**	H	4-BrC_6H_4	1.0	89	116–117	446
8.	**8h**	H	2,4-$Cl_2C_6H_3$	1.0	90	71–72	381
9.	**8i**	Cl	H	0.5	91	155–156	NA
10.	**8j**	Cl	C_6H_5	1.0	85	110–111	510
11.	**8k**	Cl	2-ClC_6H_5	1.0	92	101–102	442
12.	**8l**	Cl	3-ClC_6H_4	1.0	87	112–113	577
13.	**8m**	Cl	2-$CH_3C_6H_4$	1.0	90	140–141	590
14.	**8n**	Cl	4-$CH_3C_6H_4$	1.0	86	148–149	427
15.	**8p**	Cl	4-$COCH_3C_6H_4$	1.5	88	144–145	845
16.	**8q**	Cl	4-BrC_6H_4	1.0	89	167–168	410
17.	**8r**	Cl	4-F	1.0	86	151–152	305
18.	**8s**	Cl	2,4-$Cl_2C_6H_3$	1.0	91	102–103	272
19.	Ascorbic acid						100

IR (KBr, cm^{-1}): 3155–3280 ν(NH), 1715–1735 ν(C=O); ^1H NMR, $CDCl_3$ δ : 7.85–7.95 (NH), 6.9–7.8 (Ar—H), 4.10–4.25 (CH_3, J = 7.00–7.13 Hz), 3.70–3.75 (CH_2), 1.20–1.30 (CH_2, J = 7.05–7.10 Hz) for **8a–8s** in addition to 2.30–2.35 (Ar—CH_3) for **8d, e** and **8m, n**, 2.5–2.55 ($COCH_3$) for **8f** and **8p**. NA = not active.

Antioxidant activity: Antioxidant activity (IC_{50}) was determined by reduction of diphenyl-2-picrylhydrazyl[16] (DPPH) in methanol (516 nm). Compounds **8h**, **8r** and **8s** showed good scavenging of DPPH free radical. 4-Chlorophenyl thiazole-5-acetates **8i–s** showed higher activity than 4-phenyl thiazole-5-acetates **8a–h**.

EXPERIMENTAL

Melting points are uncorrected and were recorded in liquid paraffin bath using open end capillaries. Thin layer chromatography was performed on silica gel G; a simple household microwave (BPL Sanyo India) over (900 W) equipped with a turntable was used for irradiation. The IR spectra were run on Shimadzu FTIR spectrophotometer in KBr pellets. ^1H NMR and ^{13}C NMR were obtained using Jeol GSX-400 FT NMR 400 MHz in $CDCl_3$/DMSO-d_6 solvent using TMS as internal reference. Mass spectra were recorded by Jeol-JMS-300 spectrometer at 70 eV. The compounds were analyzed for C, H and N analysis and the values were found within ±0.4% of the calculated values.

Ethyl 3-benzoyl propionate (3)

A mixture of 3-benzoyl propionic acid **1** (2 g), concentrated sulphuric acid (0.5 mL) and ethanol (10 mL) was taken in a conical flask and placed in a microwave oven. The conical flask was covered with stemless funnel to prevent excessive evaporation. A beaker containing water was placed near the reaction flask to serve as heating sink. The reaction mixture was irradiated at 200 W for 1.5 min. After that the reaction mixture was cooled to room temperature and poured into ice-cold water. The ester was then extracted into ether and washed with water and sodium bicarbonate solution. The ether layer was separated, dried over anhydrous sodium sulphate and distilled off to get ethyl ester as viscous oil **3** (yield 96%, lit.[15] 75%), whereas ethyl 3(4-chlorobenzoyl) propionate **4** was obtained as white solid. Yield 93%, m.p. 65–66°C.

Ethyl 3-bromo-3-benzoyl propionate (5)

Bromine (1.7 g 11 mmol) was added dropwise to a solution of ethyl 3-benzoyl propionate **3** (2.85 g, 10 mmol) in 20 mL hot chloroform with constant stirring. The reaction mixture was stirred for an additional 2 h. The reaction mixture was washed with water, dried over anhydrous sodium sulphate and then the solvent was removed to get the bromo ester **5** as viscous oil which was used as such for the next step (yield 84%), whereas an analytically pure sample of ethyl 3-bromo-3-(4-chloro phenyl)propionate **6** was obtained by crystallization from aqueous alcohol. Yield 80%, m.p. 77° C.

Ethyl 4-phenyl-2-(3-chlorophenyl amino)thiazole-5-acetate (8c)

A mixture of bromo ester **5** (1.4 g, 5 mmol) and 3-chloro phenylthiourea **7** (0.93 g, 5 mmol) in ethanol (10 mL) was irradiated in an unmodified microwave oven at 200 W for 1.0 min. On completion of the reaction the reaction mixture was cooled to room temperature and triturated with sodium carbonate solution. The triturated mixture was allowed to stand for 15 min to complete the separation

of the product and then filtered. The solid was washed with water, dried and crystallized from ethanol to afford pure thiazole acetates **8c** (86%, m.p. 104–105° C).

IR (cm^{-1}, KBr): 3220, 1731, 1600, 1549, 738. ^1H NMR (300 MHz, $CDCl_3$) δ : 1.2 (3H, t, J = 7.0 Hz, CH_3), 3.7 (2H, s, CH_2), 4.13 (2H, q, J = 7.05 Hz, CH_2), 7.0–7.8 (9H, m, aromatic), 9.5–9.7 (1H, hump, NH). ^{13}C NMR (300 MHz, DMSO-d_6) δ : 14.0 (C_9, CH_3), 32.1 (C_6, CH_2), 60.8 (C_8, CH_2), 113.8 (C_5), 115.2 (C_6), 116.1 (C_2), 120.6 (C_4), 127.7 (C_d), 128.1 (C_b and C_f), 128.4 (C_c and C_e), 130.4 (C_5), 133.3 (C_3), 134.6 (C_6), 142.4 (C_1), 147.6 (C_4), 160.6 (C_2), 170.1 (>C=O). MS (m/z): 374 ($M^+ + 2$), 372 (M^+), 229, 182, 147, 135, 103, 77, 63.

ACKNOWLEDGEMENTS

The authors are thankful to Prof. B.G. Shivananda, Principal, Al-Ameen College of Pharmacy, Bangalore for providing facilities and to Dr. G. Bagavant for his support.

REFERENCES

1. J.F. Armond, E.J. Edgard, D. Frederic, J.M. Claude and C. Erwin, Int Patent, 200101860 (2001); *Chem. Abstr.*, **134**, 17851 (2001).
2. V. Paola, G. Athina, I. Matteo, B. Bernadetta, P. Graziella, C.A. Cabras and P.L. Colla, *Bio. Org. Med. Chem.*, **11**, 4785 (2003).
3. B.S. Holla, K.V. Malini, B.S. Rao, B.K. Sarojini and N.S.E. Kumari, *Eur. J. Med. Chem.*, **38**, 313 (2003).
4. B. Tjeed, J. Vallugarda and R.Emound, *J. Med. Chem.*, **45**, 3813 (2002).
5. A.M. Abdelal, M. Gineinam, M. Tayel and A. Tanatawy, *Sci. Pharma*, **21** (1993).
6. S.S. Pawan, *Bioorg. Med. Chem.*, **7**, 24 (1999).
7. S.A. Patil and G. Bagavant, *J. Indian Chem. Soc.*, **71**, 205 (1994).
8. E. Bansal, V.K. Srivastava and A. Kumar, *Indian J. Chem., Sec. B*, **39B**, 357 (2000).
9. A.R. Maarouf, M.K. Qoot, N. Boulatara and A.R. El-Naddaf, *Alexandria J. Pharma Sci.*, **15**, 77 (2001).
10. W. Hepwarth, B.B. Newbold, D.S. Platt and G.J. Stacey, *Nature*, **22**, 582 (1969).
11. A. Mursean, M. Coman, M. Kori and L. Smithi, *Clujul Med.*, **59**, 262 (1986); *Chem. Abstr.*, **106**, 149101 (1987).
12. J. Metzger, in: Kevin, T. Potts (Eds.), Comprehensive Heterocyclic Chemistry, (Pergamon Press, New York, Vol. 6, p. 294 (1984).
13. A.K. Bose, M.S. Manhas, M. Gosh, V.S.R. Shah, S.S.K. Tabey and Z.U. Lipkkowaska, *Heterocycles*, **30**, 741 (1990).
14. S. Antonia, L. Sonia, A. Francesca, A. Enrico, G. Marina and D. Michele, *Eur. J. Med. Chem.*, **34**, 1003 (1990).
15. C. Sanche-Moreno, J. Larranri and F. Saura-Calixto, *J. Sci. Food Agric.*, **79**, 1301 (1999).

(*Received*: 19 June 2004; *Accepted*: 24 December 2004) AJC-4039