An expeditious synthesis of methyl 5-(2-amino 4-arylthiazolyl) acetates using microwave irradiation

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Abstract : 2,4,5-Trisubstituted thiazole derivatives can be prepared conveniently by condensation of methyl 3-bromo-3-aryl propionates with thiourea and (un)substituted phenyl thiourea under microwave irradiation in good yields. The structures of the newly synthesized compounds are characterized by spectral data and elemental analysis.

Keywords : Microwave irradiation, thiazole, thiourea.

Thiazole derivatives are reported to show a broad spectrum of biological activity, which includes antimicrobial¹, antidiabetic², analgesic and anti-inflammatory³ activities. The introduction of thiazole ring improved the activity as in meloxicam in the oxicam series of anti-inflammatory drugs⁴. Thiazoles are easily metabolized by routine biochemical reactions and are noncarcinogenic in nature⁵. In view of their safety and importance, there is a continuing interest in developing versatile synthetic routes. Generally, 2-aminothiazoles are synthesized by the condensation of a halo carbonyl compound with thiourea, known as Hantzsch synthesis⁶ and has a wide scope, permitting the synthesis of a variety of thiazole derivatives.

In this paper, we wish to report a novel synthesis of methyl 5-(2-amino 4-arylthiazolyl) acetates (**4a-r**) from methyl 3-bromo-3-arylpropionates (**2**) and (un)substituted phenyl thioureas (**3a-i**) (Scheme 1) by MORE chemistry⁹ using PEG-400 as a solvent. PEG-400 is miscible with water thereby simplifying the workup. Furthermore it is inexpensive and readily available in bulk quantities.

Results and discussion

The methyl 3-arylpropionates **1c-d** were prepared in better yields by irradiating a mixture of 3-arylpropionic acids **1a-b**, concentrated sulphuric acid and methanol in open glass containers using unmodified household microwave oven in 1.5 min. This procedure considerably reduces the longer reaction time (7 hours of refluxing¹⁰) usually encountered in traditional ester synthesis. The acid is then brominated to methyl 3-bromo-3-

arylpropionate **2a-b**. The reaction of 3-bromo-3-arylpropionate with (un)substituted phenyl thiourea **3a-i** in methanol at reflux resulted in the formation of thiazoles acetates **4a-i** and **4j-r** with 65–78% yield in 60–75 min. However, when the reaction was performed in PEG-400 in microwave oven the reaction time was reduced to 0.5–1.5 min and the yield rose to 85–95%. The reaction mixture was exposed to the microwave irradiation in an open vessel covered with stemless glass funnel at lower power (540 W). The long neck of glass vessel remains cool since glass is transparent to microwaves. A beaker of water was kept near the reaction vessel to serve as “heat sink” to provide fine control of the temperature of the reaction mixture¹¹.

We have also attempted the above reaction in PEG-200, ethylene glycol, diethylene glycol, DMSO, isopropyl alcohol and without any solvent (Table 1). The maximum yield of the desired product was obtained when the reaction was performed in PEG-400.

To test the generality of the reaction a variety of phenyl thioureas (**3a-i**) were condensed with bromo propionates in PEG-400 under microwave irradiation to form the corresponding methyl 4-aryl-2-arylamino thiazolyl acetates (Table 2). When two electron withdrawing groups were placed in phenyl thiourea **3** the yields of substituted thiazolyl acetates **4g-h** and **4p-q** were slightly less and the rate of reaction was also slower.

Table 1. Reaction of methyl 3-bromo-3-(4-chlorobenzoyl)propionate- with 2-chlorophenyl thiourea in various solvents under microwave irradiation for 1 min at 540 W

Entry	Solvent	Yield % (4b)
1.	PEG-400	92
2.	PEG-200	82
3.	Ethylene glycol	71
4.	Diethylene glycol	65
5)	Isopropyl alcohol ^d	80
6.	DMSO	74
7.	Without solvent	45

^aCarefully irradiated in long neck open vessel covered with stemless glass funnel to avoid the evaporation of IPA.

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) oven (900 W) equipped with a turntable was used for irradiation. The IR spectra were run on Shimadzu FT IR spectrophotometer in KBr pellets. ¹H NMR spectra were obtained using Jeol GSX-400 FT NMR 400 MHz in CDCl₃/DMSO-*d*₆ solvent using TMS as internal reference. Mass spectra were recorded by Jeol-JMS-300 spectrometer at 70 eV.

Methyl 3-(4-chlorobenzoyl)propionate (1c) : 3-(4-Chlorobenzoyl)propionic acid **1a** (2.1 g, 10 mmol), dry methanol (20 ml) and concentrated sulphuric acid (0.5 ml) were taken in a long neck conical flask covered with stemless funnel to avoid excessive evaporation. The resulting mixture was irradiated in a domestic microwave oven 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 **1c** was extracted into ether and washed with water, sodium bicarbonate solution and the ether layer was separated, dried and distilled off to get methyl 3-(4-chlorobenzoyl)propionate **1c** (m.p. 62–63 °C, 96%, lit.¹² m.p. 63 °C, 75%).

Methyl 3-bromo-3-(4-chlorobenzoyl)propionate (2a) : Methyl 3-(4-chlorobenzoyl)propionate **1c** (2.2 g, 10 mmol) was brominated in warm chloroform (20 ml) by addition of bromine (1.7 g, 11 mmol) dropwise with stirring over 30 min, stirring was continued for another 2 h. The reaction mixture was washed with water and then chloroform layer was dried over sodium sulphate and distilled to get methyl 3-bromo-3-(4-chlorobenzoyl)propionate **2a** as viscous oil which was used as such for the next step. Yield : 95% (Scheme 1).

Methyl 2-phenylamino-4-(4-chlorophenyl)thiazole-5-acetate (4a) : A slurry of bromo propionate **2a** (900 mg, 3 mmol) and phenyl thiourea **3a** (450 mg, 3 mmol) in PEG-400 (10 ml) was irradiated at 540 W for 1 min.

Table 2. Physical data of compounds

Compd.	Substituted thiazole		Time (min)	M.p. (°C)	Yield (%)	
	X	Y			MW	Conventional
4a	Cl	H	1.0	119–120	93	69
4b	Cl	2-Cl	0.5	97–98	92	73
4c	Cl	4-Br	1.0	147–148	89	65
4d	Cl	2-CH ₃	1.0	125–126	85	69
4e	Cl	4-CH ₃	1.0	152–153	91	71
4f	Cl	4-CH ₃ CO	1.5	160–161	95	73
4g	Cl	3-Cl-4-F	1.0	100–101	87	68
4h	Cl	2,4-Cl ₂	1.0	120–121	85	69
4i	Cl	3-CH ₃	1.0	122–123	89	65
4j	H	2-Cl	0.5	90–91	92	72
4k	H	4-Br	1.0	109–110	90	71
4l	H	2-CH ₃	1.0	121–122	92	78
4m	H	4-CH ₃	1.0	101–102	88	74
4n	H	4-CH ₃ CO	1.5	152–153	90	69
4p	H	3-Cl-4-F	1.0	110–111	81	68
4q	H	2,4-Cl ₂	1.0	102–103	86	65
4r	H	4-Cl	1.0	126–127	84	69

1a R = H, X = Cl; 1b R = H, X = H; 1c R = CH₃, X = Cl; 1d R = CH₃, X = H; 2a X = Cl; 2b X = H; 3a Y = H; 3b Y = 2-Cl; 3c Y = 4-Br; 3d Y = 2-CH₃; 3e Y = 4-CH₃; 3f Y = 4-COCH₃; 3g Y = 3-Cl-4-F; 3h Y = 2,4-Cl₂; 3i Y = 2-ClH₃

Scheme 1

Then the reaction mixture was cooled to room temperature, triturated with 10% sodium carbonate solution (50 ml), allowed to stand for 15 min and then filtered. The solid was washed with water, dried and crystallized from ethanol to yield thiazole-5-acetate **4a** (1 g, 93%) as white solid, m.p. 119–120 °C; $\gamma_{\max}$ 3280 (N–H), 1720 (>C=O, ester), 3025, 2912 and 2875 (CH₂ and CH₃), 1603, 1586 and 1480 (ArC=C) and 765 cm⁻¹ (Ar–Cl); δ 3.73 (2H, s, CH₂), 3.74 (3H, s, CH₃), 7.03 (1H, t, *J* 7.33 Hz, ArH_{4'}), 7.13 (2H, m, ArH_{3'} and ArH_{5'}), 7.24 (2H, m, ArH_{2'} and ArH_{6'}), 7.31 (2H, d, *J* 8.46 Hz, ArH_c and ArH_e), 7.49 (2H, d, *J* 8.47 Hz, ArH_b and ArH_f), 8.6 (1H, s, NH); MS (EI) *m/z* 358 (M⁺), 360 (M⁺ + 2) (Found : C, 60.30; H, 4.19; N, 7.81; S, 8.76. Calcd. for C₁₈H₅O₂N₂SCl : C, 60.25; H, 4.20; N, 7.80; S, 8.93%).

Other compounds **4b–r** were synthesized in a similar manner using various phenyl thioureas.

4f ¹H NMR (CDCl₃) δ 2.56 (3H, s, COCH₃), 3.78 (3H, s, CH₃), 3.87 (2H, s, CH₂), 7.21 (2H, d, *J* 8.69 Hz, ArH_{2'} and ArH_{6'}), 7.34 (2H, d, *J* 8.24 Hz, ArH_c and ArH_e), 7.53 (2H, d, *J* 8.26 Hz, ArH_b and ArH_f), 7.83 (2H, d, *J* 8.70-Hz, ArH_{3'} and ArH_{5'}), 7.95 (1H, br, NH); **4h** δ 3.76 (3H, s, CH₃), 3.79 (2H, s, CH₂), 7.24 (1H, dd, *J* 2.3 and 8.87 Hz, ArH_{5'}), 7.38 (1H, s, ArH_{3'}), 7.40 (2H, d, *J* 8.51 Hz, ArH_c and ArH_e), 7.54 (2H, d, *J* 8.49 Hz, ArH_b and ArH_f), 8.15–8.24 (2H, m, ArH_{6'} and NH); MS : 426 (M⁺), 369 (100%), 332, 297, 262, 196, 181, 149, 137, 111, 102, 91; **4i** δ 2.24 (3H, s, Ar–CH₃), 3.73 (3H, s, CH₃), 3.77 (2H, s, CH₂), 6.79 (1H, s, ArH_{2'}), 6.85 (1H, d, *J* 7.56 Hz, ArH), 6.99 (1H, m, ArH), 7.13 (1H, t, *J* 7.70 Hz, ArH_{5'}), 7.30 (2H, d, *J* 8.52 Hz, ArH_c and ArH_e), 7.51 (2H, d, *J* 8.48 Hz, ArH_b and ArH_f), 8.75 (1H, br, NH); MS *m/z* 374 (M⁺ + 2), 372 (M⁺), 315/313, 278, 196, 181 (100%), 149, 137, 111, 102, 91; **4j** δ 3.76 (3H, s, CH₃), 3.7 (2H, s, CH₂), 6.95 (1H, t, *J* 7.52 Hz, ArH), 7.2–7.4 (5H, m, ArH), 7.65 (2H, d, *J* 8.15 Hz, ArH), 8.1 (1H, d, *J* 8.20 Hz, ArH); **4k** δ 3.73 (3H, s, CH₃), 3.75 (2H, s, CH₂), 7.16–7.24 (5H, m, ArH), 7.35 (2H, d, *J* 8.45 Hz, ArH_{3'} and ArH_{5'}), 7.51

(2H, d, *J* 8.43 Hz, ArH_{2'} and ArH_{6'}), 7.94 (1H, br, NH); MS *m/z* 404 (M⁺ + 2), 402 (M⁺), 345/343 (100%), 331/329, 264, 162, 147, 115, 103, 77; **4p** δ 3.75 (3H, s, CH₃), 3.76 (2H, s, CH₂), 6.80–6.90 (2H, m, ArH), 7.0 (1H, m, Hz, ArH), 7.28–7.31 (3H, m, ArH), 7.50–7.54 (2H, m, ArH), 9.4–9.7 (1H, br, NH); **4q** δ 3.76 (3H, s, CH₃), 3.83 (2H, s, CH₂), 7.23 (1H, dd, *J* 2.36 and 8.86 Hz, ArH_{5'}), 7.35–7.39 (2H, m, ArH and NH), 7.41–7.46 (2H, m, ArH), 7.58–7.61 (3H, m, ArH), 8.18 (1H, d, *J* 8.87 Hz, ArH_{6'}).

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