Research Article

Citric Acid Catalyzed Microwave Irradiated Solvent Free Synthesis of 2-Substituted Benzothiazole Derivatives from 2-Aminothiophenol and Aryl Aldehydes

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Abstract

A series of 2-aryl benzothiazole derivatives were synthesized by the condensation reaction of 2-aminothiophenol and aryl aldehyde in presence of catalytic amount of citric acid under microwave irradiation and solvent free conditions without metals or reactive stoichiometric oxidants in good yield. Clean reaction profiles, environmental familiar microwave technique, quick isolation of the products, excellent chemo selectivity are the wondrous features for this protocol.

Keywords: Citric acid, 2-aminothiophenol, 2-substituted benzothiazole, solvent-free conditions, MW

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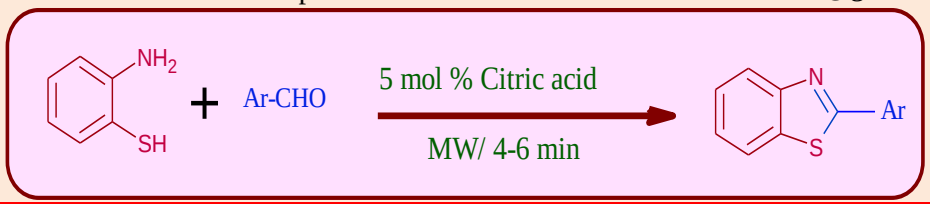


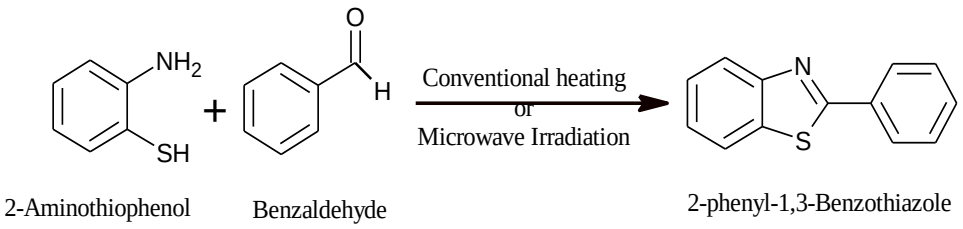
Introduction

Heterocyclic compounds are an important part of bioactive natural products, medicines, materials and other functional molecules like advanced materials including non-linear optics (NLO) [1], organic light-emitting diodes (OLED) [2] and liquid crystals [3]. Most of the heterocyclic compounds possess significant applications in material science such as dyestuff, brightening mediators, data storage, plastics, and analytical reagents.

Benzothiazoles derivatives are principle class of heterocyclic systems [4], which play a vital role in organic and bioorganic chemistry. The small and elementary benzothiazole nucleus whenever present in compounds involved in exploration planed at evaluating advanced products that possess striking biological activities. 2-Aryl benzothiazoles derivatives are biologically active class of heterocyclic compounds which make attractive and extensive affection [5]. Benzothiazole derivatives are known for their biological and pharmaceutical activities, such as antitumor [6], antimicrobial [7], antiglutamate/antiparkinson [8], broad spectrum Ca^{+2} channel antagonist [9], anticonvulsant [10], antiparasitic [11], anti-inflammatory [12], anti-stress ulcer [13], antibiotics [14], antiviral activities [15]. Due to the pharmaceutical intention of the benzothiazole key structure, only a few synthetic routes has been reported. Thus synthesis of benzothiazole systems is much interested, and considerable research has been moved towards those derivatives. The synthesis of benzothiazole are condensation by using several catalysts like CTAB/H_2O [16], Al_2O_3-Fe_2O_3 [17], $Pd(PPh_3)_4/K_2CO_3$ [18], DMSO/120 °C [19], ionic liquid 1-phenyl-3-methylimidazolium bromide [pmIm]Br [20], scandium triflate [21], silica gel [22], MnO_2/SiO_2 [23], molecular iodine [24], activated C [25], *p*-toluene sulphonic acid [26], SiO_2/graphite [27]. Yet, furthermost of these techniques suffers from several restricted access such as the necessity of extreme reaction circumstances (strong acids, high temperatures), prolonged reaction time, drawback of being limited to simply aromatic aldehydes, use of noxious and exclusive reagents/catalyst, use of hazardous solvents, low yields, formation of by-products and tedious work-up procedures. Recently in microwave assisted reaction have directed to an increasing demand for multifunctional resources for the reason that such synthetic paths exploiting harmful solvents and reagents and producing poisonous waste have become dispirited and there have been much exertions to improve harmless and environmentally-benevolent substitutions. Under microwave irradiation a synthesis of benzothiazole using some catalyst like p-TsOH [28], PEG-200/400 [29], SiO_2 [30], S_8/I_2 [4], anhydrous $CuSO_4/ZrOCl_2.8H_2O$ [31], Al_2O_3-V_2O_5 [32] has been employed. Herein, we report the efficient application of citric acid as catalyst seems to be an attractive approach for the synthesis of 2-substituted benzothiazoles by condensation of 2-aminothiphenol and aryl aldehyde. This green chemistry attitude was familiarized with the goal at

emerging cleaner courses through the proposal of progressive and ecologically caring chemical reactions [33-34]. Physical and chemical stability, no poisonousness, no corrosiveness, reusability, environmental friendly, short reaction period, immediate isolation of the products, remarkable yields and selectivity are main benefits of this procedure which make this method a smart and expedient methodology.

In our continued intentions in the direction of synthesis of bioactive heterocyclic compounds by using microwave assisted [35], we report in this a modest and effective technique with cleaner protocols for the synthesis of benzothiazole using citric acid as a catalyst under microwave irradiation (**Scheme 1**).



Scheme 1: citric acid catalyzed synthesis of 2-Phenyl benzothiazole

Experimental

All the chemicals were purchased from Sigma Aldrich, Spectrochem and Thomas Baker. These chemicals were used without further purification. The reactions were carried out in dried glassware. Bruker AC NMR spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) was used for NMR spectra using $CDCl_3$ as solvent and chemical shifts (δ) are mentioned in parts per million (ppm) values and TMS as an internal reference as well as coupling constants are expressed in hertz (Hz). The microwave oven utilized for this work (800 W, 140 °C). Melting point apparatus with an open capillary was used for determination of melting point and were unchanged. Shimadzu QP2010 GCMS was used for recording mass spectra.

General procedure for the synthesis of 2-substituted benzothiazoles derivatives

Conventional Method

2-Aminothiophenol (1 mmol), aromatic aldehyde (1.2 mmol) and a catalytic amount of citric acid (5 mol %) were taken in 1 mL DMF solvent and thoroughly mixed in an open glass tube. The glass tube was placed in water bath for 120-150 min (Table 1). After complete conversion of the substrate as monitored by TLC (*n*-hexane: ethyl acetate, 1:4), the reaction mixture was extracted by using ethyl acetate and combined organic layers were dried over anhydrous Na_2SO_4. After evaporation of solvent, resulting solid was purified by recrystallization from EtOH to get desired product with high purity.

Microwave Irradiation

Aromatic aldehydes (1.2 mmol) and 2-aminothiophenol (1 mmol) and catalytic amount of 5 mol % citric acid were thoroughly mixed in an open glass tube and stirred for 15 minutes. Then the reaction mixture was kept in domestic microwave oven (800 watt) at optimized level 100% for 4-6 min with intermittent cooling after each 10 sec of irradiation. TLC was used for monitoring the progress of reaction (*n*-hexane: ethyl acetate, 1:4). At last reaction was cooled to room temperature and added water (20 mL). Afterword's, the procedure is similar to conventional method.

Spectral data of representative compounds

*2-Phenyl-1, 3-Benzothiazole (Table 3, entry **3a**)* M.P.110-112 °C;^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.04-8.11 (m, 3H, Benzothiazole-H_7, Ph-H_2, H_6), 7.85 (Benzothiazole-H_4), 7.51-7.54 (m, 3H, Ph-H_3, H_4, H_5), 7.41-7.43 (m, 2H, Benzothiazole-H_5, H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (Benzothiazole-C_2), 153.1 (Benzothiazole-C_{7a}), 134.9 (Ph-C_1), 134.2 (Benzothiazole-C_{3a}) 129.5 (Ph-C_3, C_5), 128.3 (Ph-C_4), 127.4 (Ph-C_2, C_6), 124.8 (Benzothiazole-C_5), 124.6 (Benzothiazole-C_6), 122.7 (Benzothiazole-C_7), 122.3 (Benzothiazole-C_7); IR (cm^{-1}): 3159, 1611, 1532, 1458, 1378, 1259, 1081, 889, 832, 785, 725; MS (EI): m/z 212.23 [M+1].

*2-(4-Methylphenyl)-1, 3-Benzothiazole (Table 3, entry **3b**)* M.P. 82-84°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.93-8.01 (m, 2H, Benzothiazole-H_7, H_4), 7.27-7.37 (m, 2H, Benzothiazole-H_5, H_6), 7.38-7.53 (m, 4H, Ph-H_2, H_6, H_3,

H_5), 2.29-2.33 (m, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (Benzothiazole-C_2), 153.2 (Benzothiazole-C_{7a}), 139.2 (Ph-C_4), 134.9 (Benzothiazole-C_{3a}), 128.9 (Ph-C_3, C_5), 127.9 (Ph-C_2, C_6), 127.5 (Ph-C_1), 124.7 (Benzothiazole-C_5), 123.2 (Benzothiazole-C_6), 122.1 (Benzothiazole-C_4), 118.9 (Benzothiazole-C_7), 21.2 (OCH_3); IR (cm^{-1}): 3091, 2955, 1659, 1579, 1537, 1259, 1222, 864, 797; MS (EI): m/z 225.12 [M+].

*2-(3-Methoxyphenyl)-1, 3-Benzothiazole (Table 3, entry **3c**)* M.P. 100-102°C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.08 (s, 1H, Benzothiazole-H_7), 7.49-7.52 (m, 1H, Benzothiazole-H_4, Ph-H_2), 7.67-7.69 (m, 2H, Benzothiazole-H7, Ph-H2), 7.39-7.44 (m, 3H, Ph-H_6, Benzothiazole-H_5, H_6), 7.29 (m, 1H, Ph-H_5), 7.20 (m,1H, Ph-H_4), 3.80 (s,3H,OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (Benzothiazole-C_2), 157.5 (Ph-C_3), 153.7 (Benzothiazole-C_{7a}), 134.3 (Benzothiazole-C_{3a}), 131.4 (Ph-C_1), 128.4 (Ph-C_5), 126.8 (Ph-C_6), 126.3 (Benzothiazole-C_6), 124.7 (Benzothiazole-C_5), 122.7 (Benzothiazole-C_4), 122.4 (Benzothiazole-C7), 114.6 (Ph-C4), 111.6 (Ph-C_2), 55.3 (OCH_3); IR (cm^{-1}): 3073, 1699, 1569, 1397, 1322, 1258, 1258, 897, 755, 727; MS (EI): *m/z* 241.38 [M^+].

*2-(4-Methoxyphenyl)-1, 3-Benzothiazole (Table 3, entry **3d**)* M.P. 100-102 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.94 (s, 1H, Benzothiazole-H_7), 7.83–7.88 (m, 3H, Benzothiazole-H_7, Ph-H_2, H_6), 7.47 (m, 1H, Benzothiazole-H_6), 7.22 (s, 1H, Benzothiazole-H_5), 7.17-7.19 (m, 2H, Ph-H_3, H_5), 3.83 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1 (Benzothiazole-C_2), 160.2 (Ph-C_4), 153.6 (Benzothiazole-C_{7a}), 134.3 (Benzothiazole-C_{3a}), 128.6 (Ph-C_2, C_6), 127.5 (Ph-C_1), 126.3 (Benzothiazole-C_6), 124.7 (Benzothiazole-C_5), 122.5 (Benzothiazole-C_7), 122.3 (Benzothiazole-C_4), 114.7 (Ph-C_3, C_5), 55.3 (OCH_3); IR (cm^{-1}): 3058, 1638, 1529, 1430, 1358, 1236, 1231, 856, 769, 723; MS (EI): *m/z* 241.26 [M^+].

*2-(2, 5-Dimethoxyphenyl)-1, 3-Benzothiazole (Table 3, entry **3e**)* M.P. 104-106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.91 (m, 1H, Benzothiazole-H_7), 7.42-7.44 (m, 2H, Benzothiazole-H_4, H_6), 7.39 (m, 1H, Benzothiazole-H_5), 7.35 (m, 1H, Ph-H_6,), 6.92-6.96 (m, 2H, Ph-H_3, H_4), 3.85 (Ph-$H_{2\text{-}OCH3}$), 3.68 (Ph-$H_{5\text{-}OCH3}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5 (Benzothiazole-C_2), 155.8 (Ph-C_2), 157.3 (Ph-C_5), 153.8 (Benzothiazole-C_{7a}), 134.3 (Benzothiazole-C_{3a}), 126.4 (Benzothiazole-C_6), 124.1 (Benzothiazole-C_5), 122.9 (Benzothiazole-$_{C7}$), 122.7 (Benzothiazole-C_4), 116.4 (Ph-C_1), 115.6 (Ph-C_4), 112.1 (Ph-C_3), 111.2 (Ph-C_6), 55.5 (Ph-C_2-OCH_3), 55.2 (Ph-C_5-OCH_3); IR (cm-1): 3144, 1648, 1591, 1474, 1393, 1179, 1062, 895, 833, 768, 732; MS (EI): *m/z* 271.23 [M^+].

*2- (4-Nitrophenyl)-1, 3-Benzothiazole (Table 3, entry **3f**)* M.P. 222-224°C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.33 (s, 1H, Benzothiazole-H_7), 7.91-7.97 (m, 3H, Benzothiazole-H_4, Ph-H_2, H_6), 8.29 (m, 2H, Ph-H_3, H_5), 7.56-7.59 (m, 2H, Benzothiazole-H_5, H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6 (Benzothiazole-C_2), 153.4 (Benzothiazole-C_{7a}), 140.3 (Ph-C_4), 134.4 (Benzothiazole-C_{3a}), 128.7 (Ph-C_2, C_6), 126.3 (Benzothiazole-C_6), 124.8 (Benzothiazole-C_5), 124.7 (Benzothiazole-C_5), 122.6 (Benzothiazole-C_7), 122.3 (Benzothiazole-C_4), 121.9 (Benzothiazole-C_1), 121.6 (Ph-C_1), 117.9 (Ph-C_3, C_5); IR (cm^{-1}): 3067, 1639, 1607, 1538, 1502, 1229, 1149, 891, 826, 778, 719; MS (EI): *m/z* 256.24 [M^+].

*2-(2-Nitrophenyl)-1, 3-Benzothiazole (Table 3, entry **3g**)* M.P. 136-138 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.26-8.29 (m, 2H, Benzoxazole-H_7, Ph-H_3), 8.08 (m, 1H, Ph-H_6), 7.87-7.91 (m, 3H, Benzoxazole-H_4, Ph-H_4, H_5), 7.74 (m, 1H, Benzoxazole-H_5), 7.59 (m, 1H, Benzoxazole-H_6); ^{13}C NMR (75 MHz, CDCl3): δ 167.2 (Benzoxazole-C_2), 153.2 (Benzoxazole-C_{7a}), 148.1 (Ph-C_2), 134.7 (Benzoxazole-C_{3a}), 129.5 (Ph-C_4), 128.7 (Benzoxazole-C_4), 128.4 (Ph-C_3), 127.7 (Ph-C_6), 127.5 (Ph-C_5), 126.3 (Benzoxazole-C_6), 124.7 (Benzoxazole-C_5), 122.5 (Benzoxazole-C_7), 121.9 (Ph-C_1); IR (cm^{-1}): 3058, 1637, 1636, 1548, 1515, 1261, 1172, 872, 839, 743, 701; MS (EI): m/z 256.25 [M+].

*2- (4-Cynophenyl)-1, 3-Benzothiazole (Table 3, entry **3h**)* M.P. 164-166 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.29 (m, 1H, Benzoxazole-H_5), 7.92-7.97 (m, 4H, Ph-H_2, H_3, H_5, H_6), 7.81 (m, 1H, Benzoxazole-H_4), 7.61-7.56 (m, 2H, Benzoxazole-H_5, H_6); ^{13}C NMR (75 MHz, CDCl3): δ 166.7 (Benzoxazole-C_2), 153.1 (Benzoxazole-C_{7a}), 134.2 (Benzoxazole-C_{3a}), 132.9 (Ph-C_3,C_5), 127.6 (Ph-C_2, C_6), 126.8 (Ph-C_1) 126.3 (Benzoxazole-C_6), 124.5 (Benzoxazole-C_5), 122.5 (Benzoxazole-C_7), 122.9 (Benzoxazole-C_7) 122.1 (Benzoxazole-C_4), 118.1 (CN), 112.8 (Ph-C_4); IR (cm^{-1}): 3094, 2239, 1664, 1554, 1523, 1296, 1158, 851, 726; MS (EI): *m/z* 236.27 [M^+].

*2- (4-Hydroxyphenyl)-1, 3-Benzothiazole (Table 3, entry **3i**)* M.P. 228-230 °C; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 11.19 (s. 1H, OH), 7.92 (s, 1H, Benzothiazole-H_7), 7.81-7.86 (m, 3H, Benzothiazole-H_4, Ph-H_2, H_6), 7.41 (s, 1H, Benzothiazole-H_6) 7.29-7.32 (m, 3H, Benzothiazole-H_6, Ph-H_3, H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9 (Benzothiazole-C_2), 157.2 (Ph-C_4), 153.9 (Benzothiazole-C_{7a}), 134.3 (Benzothiazole-C_{3a}), 128.2 (Ph-C_2,C_6), 127.6

(Ph-C_1), 126.8 (Benzothiazole-C_5), 124.1 (Benzothiazole-C_5), 122.6 (Benzothiazole-C_7), 122.1 (Benzothiazole-C_4), 115.4 (Ph-C_3, C_5); IR (cm^{-1}): 3371, 3022, 1644, 1579, 1571, 1223, 892, 753, 719; MS (EI): m/z 227.09 [M+].

*2-(2-Hydroxyphenyl)-1, 3-Benzothiazole (Table 3, entry **3j**)* M.P. 130-132 °C; ^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm) 11.48 (s. 1H, OH), 7.88-7.92 (m, 2H, Benzothiazole-H_7, Ph-H_6), 7.85 (m, 1H, Benzothiazole-H_4), 7.65 (s, 1H, Benzothiazole-H_4), 7.40-7.43 (m, 2H, Benzothiazole-H_6, Ph- H_5, Benzothiazole-H_6), 7.28-7.31 (m, 3H, Benzothiazole-H_5, Ph-H_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9 (Benzothiazole-C_2), 157.6 (Ph-C_2), 153.7 (Benzothiazole-C_{7a}), 131.3 (Benzothiazole-C_{3a}), 128.2 (Ph-C_4), 128.6 (Ph-C_6), 126.7 (Benzothiazole-C_6), 124.7 (Benzothiazole-C_5), 122.6 (Benzothiazole-C_7), 122.1 (Benzothiazole-C_4), 119.1 (Ph-C_5), 117.4 (Ph-C_3), 116.5 (Ph-C_1); IR (cm^{-1}): 3348, 3158, 1651, 1540, 1509, 1262, 1138, 852, 839, 771, 716; MS (EI): *m/z* 211.39 [M^+].

*2-(4-Bromophenyl)-1, 3-Benzothiazole (Table 3, entry **3k**)* M.P.128-130°C;^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.12 (s, 1H, Benzothiazole-H_7), 7.84-7.88 (m, 3H, Benzothiazole-H_4, Ph-H_2, H_6), 7.72 (m, 2H, Ph-H_3, H_5), 7.40-7.42 (m, 2H, Benzothiazole-H_5, H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7 (Benzothiazole-C_2), 153.6 (Benzothiazole-C_{7a}), 134.5 (Benzothiazole-C_{3a}), 130.4 (Ph-C_3, C_5) 127.2 (Ph-C_2,C_6), 126.9 (Ph-C_1), 126.1 (Benzothiazole-C_6), 124.8 (Benzothiazole-C_5), 124.0 (Ph-C_4), 122.6 (Benzothiazole-C_7), 122.0 (Benzothiazole-C_4); IR (cm^{-1}): 3131, 1693, 1648, 1477, 1244, 1136, 859, 833, 759; MS (EI): *m/z* 289.44 [M^+].

*2-(4-Chlorophenyl)-1, 3-Benzothiazole (Table 3, entry **3l**)* M.P.112-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.03 (s, 1H, Benzothiazole-H_7), 7.79-7.85 (m, 3H, Benzothiazole-H_4, Ph-H_2, H_6), 7.71 (m, 2H, Ph-H_3, H_5), 7.35-7.38 (m, 2H, Benzothiazole-H_5, H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3 (Benzothiazole-C_2), 153.3 (Benzothiazole-C_{7a}), 135.4 (Ph-C_4), 134.2 (Benzothiazole-C_{3a}), 132.9 (Ph-C_1), 130.9 (Ph-C_3, C_5) 128.2 (Ph-C_2, C_6), 126.3 (Benzothiazole-C_6), 124.6 (Benzothiazole-C_5), 122.5 (Benzothiazole-C_7), 121.8 (Benzothiazole-C_4); IR (cm^{-1}): 3126, 1685, 1643, 1242, 1178, 842, 822, 726; MS (EI): *m/z* 245.33 [M^+].

*2-(2-Furan-2-yl)-1, 3-Benzothiazole (Table 3, entry **3m**)* M.P. 100-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.06 (m, 1H, Benzothiazole-H_4), 7.98 (m, 1H, Furanyl-H_5), 7.84-7.86 (m, 1H, Benzothiazole-H_7), 7.33-7.35 (m, 2H, Benzothiazole-H_5, H_6), 7.15 (m, 1H, Furanyl-H_3), 6.76 (m, 1H, Furanyl-H_4) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5 (Benzothiazole-C_2), 153.2 (Benzothiazole-C_{7a}), 149.3 (Furanyl-C_2), 144.9 (Furanyl-C_5), 133.5 (Benzothiazole-C_{3a}), 126.3 (Benzothiazole-C_6), 124.3 (Benzothiazole-C_5), 122.9 (Benzothiazole-C_7), 122.2(Benzothiazole-C_4), 113.3 (Furanyl-C_3), 112.9 (Furanyl-C_4); IR (cm^{-1}): 3012, 1684, 1353, 1284, 1180, 1038, 876, 812, 748, 726; MS (EI): *m/z* 201.13 [M^+].

*2-(2-Thiophen-2-yl)-1, 3-Benzothiazole (Table 3, entry **3n**)* M.P. 96-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.89 (m, 1H, Benzothiazole-H_4), 7.78 (m, 1H, Benzothiazole-H_7), 7.58 (m, 1H, Thionyl-H_5), 7.53 (m, 1H, Thionyl-H_3), 7.31-7.35 (m, 2H, Benzothiazole-H_5, H_6), 7.09 (m, 1H, Thionyl-H_4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (Benzothiazole-C_2), 151.5 (Benzothiazole-C_{7a}), 140.4 (Thionyl-C_2), 134.1 (Benzothiazole-C_{3a}), 130.9 (Thionyl-C_5), 130.2 (Thionyl-C_3), 128.2 (Thionyl-C_4), 124.7 (benoxazole-C_5), 122.9 (Benzothiazole-C_7), 122.2(Benzothiazole-C_4); IR (cm^{-1}): 3137, 1682, 1362, 1248, 1159, 1031, 869, 848, 762, 722; MS (EI): *m/z* 217.13 [M^+].

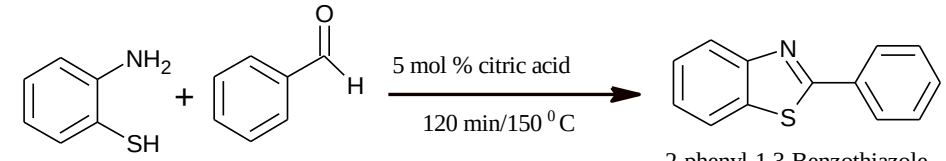
*2-(Anthracen-9-yl)-1, 3-Benzothiazole (Table 3, entry **3o**)* M.P. 210-212 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.73 (s, 1H, Anthranyl-H_{10})8.41-8.45 (m, 4H, Anthranyl-H_1, H_4, H_5, H_8), 8.22 (m, 1H, Benzothiazole-H_4),7.87-7.92 (m, 2H, Benzothiazole-H_5, H_7), 7.70 (m, 2H, Anthranyl-H_2, H_7), 7.53-7.57 (m, 3H, Anthranyl-H_3, H_6, Benzothazole-H_6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7 (Benzothiazole-C_2), 153.2 (Benzothiazole-C_{7a}), 134.4 (Benzothazole-C_{3a}), 130.9 (Anthranyl-C_9), 130.5 (Anthranyl-C_{4a}, C_{10a}), 130.2 (Anthranyl-C_{9a}, C_{8a}), 128.7 (Anthranyl-C_4, C_5), 128.3 (Anthranyl-C_2, C_7, C_{10}), 126.8 (Anthranyl-C_1, C_8), 126.9 (benoxazole-C_6), 124.7 (Benzothiazole-C_5), 122.6 (Benzothiazole-C_4), IR (cm^{-1}): 3162, 1656, 1636, 1626, 1572, 1531, 1499, 1387, 1232, 1094, 879, 869, 756, 755; MS (EI): *m/z* 311.23 [M^+].

Result and Discussion

A model reaction of 2-aminothiophenol and benzaldehyde were investigated for various conditions under both thermal heating and microwave irradiation at different power of microwave oven with or without catalytic amount of citric acid (entries 1 to 16, **Table 1**). To achieve optimized condition like temperature for conventional heating and best power level for microwave irradiation reaction. Initially reaction carried out with or without catalyst under

conventional heating at various temperatures in different solvent provides 15-75 % yield (Table 1). Then reaction rate and yields increases with increasing concentration of citric acid. The quantitative study of this protocol has been taken at 0 to 6 mol % of citric acid for model reaction. After rapid conversion of crude product, reaction had been optimized for 5 mol % for 2-aminothiophenol and benzaldehyde. Our investigated optimized results were summarized in Table 1. The optimization clearly suggested that conventional heating temperature 150 °C and multimode microwave irradiation at full power were used with the catalytic amount of 5 mol % of citric acid (**Table 2**, entry 8). Furthermore the ratio of 2-aminothiophenol to aryl aldehyde is important for the yield of this resultant condensed crude product. The influence of the ratio of benzaldehyde with 2-aminothiophenol 1:1.2, high yields of product was achieved (**Table 3**). After optimization of the experimental protocol, we resulting these cases to other substrates by using certain aryl aldehydes.

Table 1 Optimized condition for synthesis of 2-Phenyl benzothiazole by conventional method

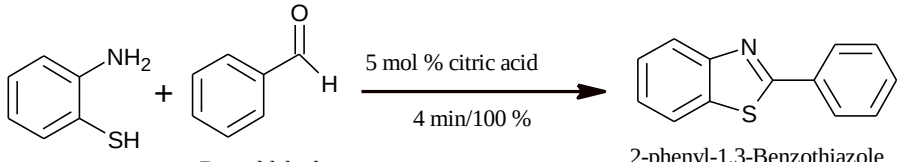


2-Aminothiophenol (1) + Benzaldehyde (2a) → 2-phenyl-1,3-Benzothiazole (3a)

Entries	Citric acid (mol %)	Solvent	Temprature (°C)	Time (min)	Yield (%)
1	0.1	DMF	150	120	15
2	0.2	DMF	150	120	26
3	0.3	DMF	150	120	42
4	0.4	DMF	150	120	59
5	0.5	DMF	150	120	75
6	0.5	Dioxane	150	120	52
7	0.5	Toluene	150	120	55
8	0.5	CH_3CN	150	120	48
9	0.6	DMF	150	120	75

Reaction condition: 2-Aminothiophenol (1 mmol), Benzaldehyde (1.2 mmol) and citric acid under conventional method.
[a] Isolated yields

Table 2 Optimized condition for synthesis of 2-Phenyl benzothiazole by microwave irradiation



2-Aminothiophenol (1) + Benzaldehyde (2a) → 2-phenyl-1,3-Benzothiazole (3a)

Entries	Power of MW oven (%)	Citric acid (mol %)	Time (min)	Yield[a] (%)
1	100	0	4	12
2	100	1	4	43
3	100	2	4	51
4	100	3	4	59
5	100	4	4	68
6	40	5	4	72
7	70	5	4	82
8	100	5	4	93
9	100	6	4	93

Reaction condition: 1 (1 mmol), 2a (1.2 mmol) and catalyst under Microwave Irradiation.
[a] Isolated Yield.

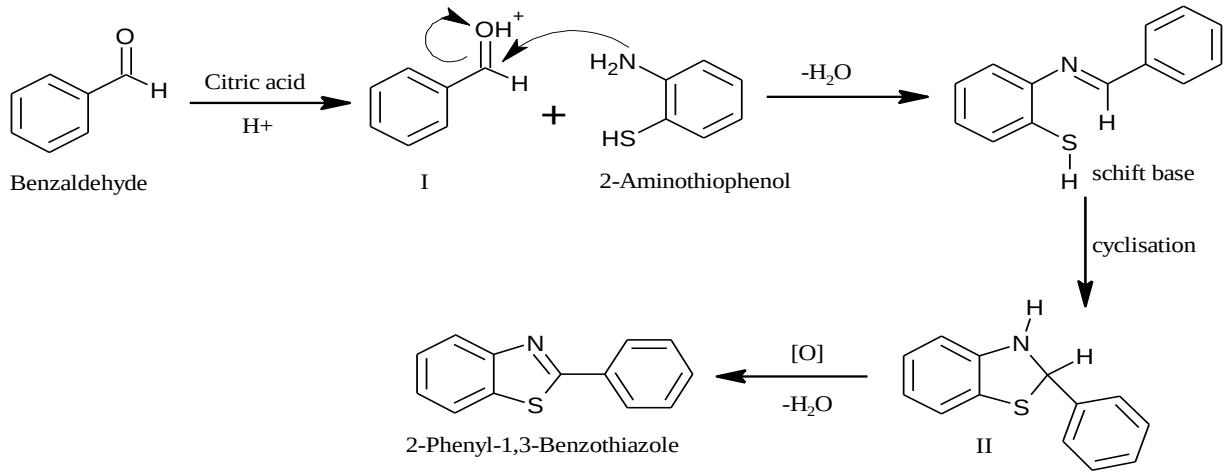
Table 3 Optimization of ratio of 2-aminothiophenol & benzaldehyde ratio for model reaction under both conventional method and microwave irradiation[a]

Entries	Aryl aldehyde	Reaction time (min)	Yield[b] (%)
1	1.0	120 (4)	59 (84)
2	1.1	120 (4)	68 (89)
3	1.2	120 (4)	75 (93)
4	1.5	120 (4)	75 (93)

Reaction condition: 1 (1 mmol), 2a and catalyst (5 mol %) under conventional heating and microwave irradiation.
[a]The reaction time and yield under microwave irradiation condition are shown in the parenthesis.
[b]Isolated Yield.

The reaction was applied to wide varieties of aromatic aldehydes as shown in **Table 4**. Our method achieved a selection of functionalized benzothiazoles with a high level of functional group endurance with both electron-withdrawing and electron-donating groups and the grouping of a corresponding synthesizer and a microwave reactor allowable to rapidly prepare a collection of highly objective benzothiazoles with the exclusive product and no aberration in the yield. The reaction was applied to a variety of aromatic aldehydes as shown in Table 4. It was found that both aldehydes bearing electron-donating substituent's (entries 6-13, Table 4) as well as electron-withdrawing (entries 2-5, Table 4) substituent's gave desired benzothiazoles in excellent and an electron donating substituent like 4-OCH_3 and 4-CH_3 have high yield while electron poor derivatives like 4-Cl have low yield due to high electro negativity. Hetero aromatic aldehyde also undergoes this reaction giving anticipated product in lower yields (entries 13-14, Table 4). Noteworthy in short time, all of these reaction proceeded with pure product which was purified by recrystallization. The reaction path is reasonably ecological because of this course would not have the requirement for the expenditure of solvent as reaction media and reaction becomes quite eco-friendly. Several aldehydes delivered the corresponding medicinally precious 2-substituted benzothiazole derivatives in good to excellent yields.

The possible sequence of events of citric acid catalyzed synthesis of 2-Phenyl benzothiazole from 2-aminophenol and benzaldehyde is exposed in the subsequent mechanism (**Scheme 2**). Initially citric acid promoted electrophilic attack on carbonyl oxygen to form intermediate (I). Amino group of 2-aminothiophenol have nucleophilic attack on it to form intermediate (II) and loses a water molecule to form Schiff's base which underwent cyclization and subsequent air oxidation to form the desired product.

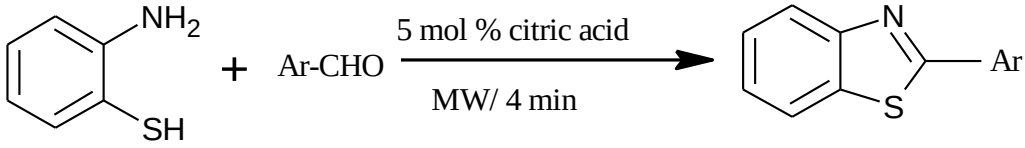


Scheme 2 Plausible mechanistic pathway for the synthesis of 3a

In this framework, researcher tested the reusability of catalyst for the large-scale operation and industrial point of view in production of 3a as shown in **Figure 1**. In the beginning, typical model reaction was accomplished as earlier mentioned technique. After the completion of reaction, catalyst was detached from reaction mixture by simple filtration, washed several times by ethyl acetate and was recycled for same reaction up to two periods with good to outstanding yield of desired product (92-81%). Further, typical reaction can be reiterated for two periods (4th & 5th)

which offered the anticipated product in poorer yields (74-66%). Consequently, this protocol is prepared cherished for three cycles (1st & 3rd).

Table 4 Synthesis of 2-Arylbenzothiazole by citric acid catalyzed reaction of 2-aminothiophenol and aryl aldehydes under conventional heating and microwave irradiation condition[a]



2-Aminothiophenol 1 | Aryl aldehyde 2a-2q | 2-Aryl-1,3-Benzothiazole 3a-3q

Entry	Aryl aldehyde (2)	Time (min)	Product (3)	Yield[c] (%)	M.P. (°C)
1	Benzaldehyde	35 (4)	3a	75 (93)	110-112 [36]
2	4-Methybenzaldehyde	35 (4)	3b	72 (92)	82-84 [36]
3	3-MethoxyBenzaldehyde	40 (4)	3c	74 (92)	100-102 [37]
4	4-MethoxyBenzaldehyde	40 (4)	3d	72 (90)	118-120 [36]
5	2,5-Dimethoxybenzaldehyde	40 (4)	3e	68 (94)	104-106 [38]
6	4-Nitrobenzaldehyde	40 (4)	3f	68 (93)	222-224 [36]
7	2-Nitrobenzaldehyde	40 (4)	3g	77 (93)	136-138 [37]
8	4-Cynobenzaldehyde	55 (5)	3h	63 (89)	164-166 [39]
9	4-Hydroxybenzaldehyde	60 (5)	3i	59 (84)	228-230 [40]
10	2-Hydroxybenzaldehyde	60 (5)	3j	52 (85)	130-132 [40]
11	4-Bromobenzaldehyde	60 (5)	3k	56 (85)	128-130 [41]
12	4-Chlorobenzaldehyde	60 (5)	3l	65 (91)	112-114 [36]
13	2-Furfural	70 (6)	3m	62 (85)	100-102 [42]
14	2-Formylthiophene	70 (6)	3n	59 (87)	96-98 [42]
15	9-Anthraldehyde	80 (6)	3o	67 (85)	210-212 [43]

Reaction condition: 1 (1 mmol), 2a-2q (1.2 mmol) and 0.5 % citric acid under conventional heating and microwave irradiation.
[a] The reaction times and yields under microwave irradiation condition are shown in parenthesis.
[b] Products were characterized by their physical properties, comparison with authentic sample and by their spectral (^{1}H-NMR, ^{13}C-NMR, IR, MS) analysis.
[c] Isolated Yield.

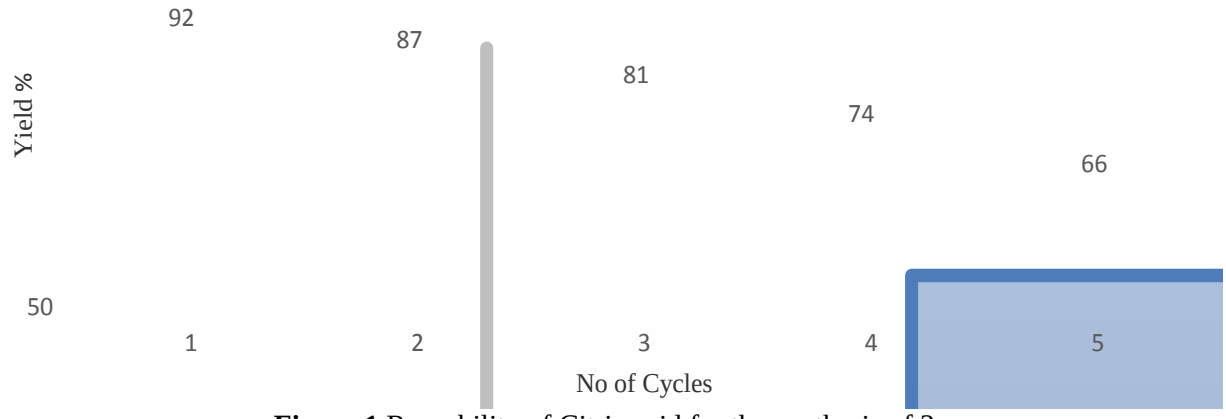


Figure 1 Reusability of Citric acid for the synthesis of 3a

In assessment with additional catalysts, the benefits of Citric acid exposed for analogous reaction of 2-Phenyl-benzothiazole from 2-aminothiophenol and benzaldehyde (**Table 5**). We observed that citric acid is extremely

dynamic catalyst for synthesis of 2-substituted benzothiazole derivatives at solvent free circumstances through both conventional heating and microwave irradiated condensation of aromatic aldehyde with 2-aminophenol.

Table 5 Comparison of citric acid with variety of other catalysts for the synthesis of 1a

Sr. No.	Catalyst used	Amount of catalyst	Temp (°C)	Time	Yield (%)
1	Citric acid	5 mol %	140°C	4 min	93
2	SiO_2-PTSA	10 mol %	150°C	10 min	90 [28]
3	PEG-200/400	2.0 g	120°C	15 min	89 [29]
4	silica gel	10 mol %	120°C	10 min	90 [30]
5	S_8/I_2	10 mol %	150°C	15 min	80 [31]
6	an $CuSO_4/ZrOCl_2.8H_2O$	10 mol %	150°C	3 min	80 [32]
7	Al_2O_3-V_2O_5	10 mol %	120°C	12 min	90 [33]
8	CTBA	5 mol %	100°C	8 hr	89 [16]
9	Al_2O_3-Fe_2O_3	5 mol %	60°C	12 min	89 [17]
10	Molecular I_2	10 mol %	60°C	60 min	88 [24]

Conclusion

In summary, we have described a simple and an entirely green procedure for the synthesis of 2-substituted benzothiazole by using Citric acid under conventional heating and microwave irradiation technique. It was found that microwave irradiation method is superior to conventional method. This protocol is suitable for large scale synthesis providing a valuable synthetic tool for industrial applications. The remarkable features of the procedure are mild reaction circumstances, enhanced reaction rates, clean reaction profiles, operational and experimental simplicity, greener reaction profile and avoidance of poisonous solvent and use of easily presented, commercial and eco-friendly catalyst.

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