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β-CYCLODEXTRIN CATALYSED ONE-POT SYNTHESIS OF ARYL BENZOTHIAZOLES FROM DIMETHYLACETALS IN AQUEOUS-PHASE

Ravi Lakkakula[a,b], Arnab Roy[a], Khagga Mukkanti[b] and Mendu Narender*[a]

[a]GVK Biosciences Private Limited, Plot No. 28 A, IDA Nacharam, Hyderabad – 500076.

[b]Jawaharlal Nehru Technological University, Kukatpally, Hyderabad-500085, India.

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***Corresponding Author**
Mendu Narender
GVK Biosciences Private Limited, Plot No. 28 A, IDA Nacharam, Hyderabad - 500076.

ABSTRACT

A facile synthetic protocol for 2-arylbenzothiazoles from dimethylacetals and 2-amino thiophenol by using β-cyclodextrin as a mild and efficient catalyst for the formation of inclusion complex in water at 50°C. The reactions using β-cyclodextrin were very fast and proceeds with good yields of the products.

KEYWORDS: Dimethyl acetals, thiophenol, β-cyclodextrin, supramolecular chemistry.

1. INTRODUCTION

Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements like nitrogen, sulphur and oxygen. Benzothiazoles are nitrogen and sulphur containing bicyclic heterocyclic scaffold with numerous applications. In 1887, 2-substituted benzothiazole was first synthesized by Hofmann*et. al*.[1] Especially 2-substituted benzothiazoles are of great interest due to their significant biological activities and various applications in the pharmaceutical chemistry and material sciences.[2-9] These derivatives of benzothiazole showed varied biological activities such as anticonvulsant,[10] antidiabetic,[11] anticancer,[12] antimicrobial,[13] antiviral,[14] antihelmintic,[15] antitubercular,[16] antimalarial,[17] analgesic,[18] fungicidal[19] and antiinflammtory.[20] Violatinctamine and Luciferin are some of the biologically active molecules bearing benzothiazole nucleus (**Fig. 1**). The Violatinctamine was isolated from the Kenyan tunicate *Cystodytes cf.* Violatinctus[21] and Luciferin (Figure 1) was isolated in 1949.[22]

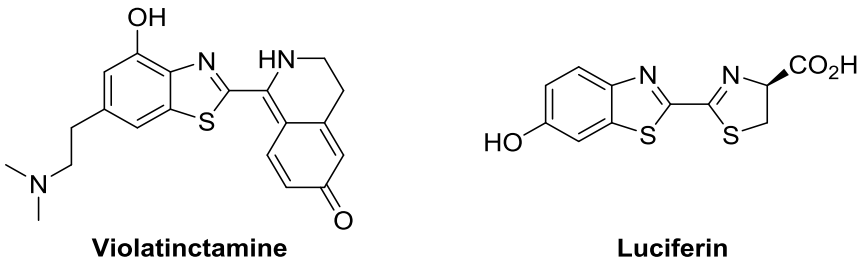
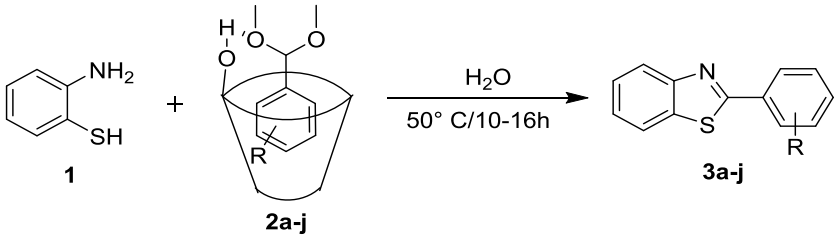


Figure 1: Some of the biologically active benzothiazole derivatives.

Several methods were developed for the synthesis of 2-substituted benzothiazoles some of them includes condensation of 2-aminothiophenols with acid chlorides,[23] aldehydes,[24] acetophenone,[25] esters,[26] Jacobson's cyclization of thiobenzanilides[27] and carboxylicacids.[28] Among these methods condensation of 2-aminothiophenol with aldehydes was the most frequent method used. The different catalysts and reagents used in this condensation consists of Br_2-AcOH/$CHCl_3$,[29] PTSA,[30] H_2O,[31] SiO_2-H_2SO_4,[32] L-proline,[33] TMSCl/DMF,[34] I_2,[35] $Pd_2(dba)_3$/xantphos/ toluene,[36] nano-CeO_2/H_2O,[37] ABMs-$ZnBr_2$/toluene,[38] NaCN/DMF,[39] PCC,[40] SiO_2-CuNPs/CH_3OH,[41] NH_4Cl,[42] Glucose oxidase-peroxidase,[43] $BF_3 \cdot OEt_2$,[44] CAN/PEG,[45] PIFA/EtOH,[46] $Sc(OTf)_3$,[47] tBuOCl/CH_3CN,[48] CdSNPs,[49] $Yb(OTf)_3$,[50] Dowex 50W,[51] $FeCl_3$-Montmorillonite K-10,[52] H_2O_2/$Fe(NO_3)_3$,[53] ionic liquids/μw,[54] trichloro isocyanuric acid[55] and bakers' yeast/CH_2Cl_2.[56] In spite of wide exploration of this condensation some of the previously reported methods suffer from several drawbacks such as drastic reaction conditions, longer reaction times with poor yields, formation of unwanted side products. Other drawbacks includes use of toxic reagents and hazardous and volatile organic solvents like $CHCl_3$, CH_2Cl_2, toluene, $CH_3CN$and MeOH, use of expensive, toxic catalysts, excessive oxidative catalyst, also high temperatures and use of anhydrous solvents, inert atmosphere, longer reaction times, tedious work up and low yields in the presence of water. Thus, in view of these shortcomings, there was a need to develop a mild and eco-friendly synthetic methodology for these high value compounds by specially replacing use of organic solvents, most of which are flammable, toxic or carcinogenic. Recently organic reactions in aqueous media have acquired significance attention in organic synthesis as they overcome the harmful effects of organic solvents and are also environmentally benign.

Water is a non-expensive, non-toxic and most readily available reaction medium, making it an environmentally and economically attractive solvent.[57] However, the fundamental problem in performing reactions in water is that the most of the organic substrates are

hydrophobic and are insoluble in water. In the past few decades supramolecular reactivity has attracted tremendous interests.[58] The best approach appeared to be through supramolecular catalysis[59] by involving cyclodextrin inclusion complex formation with the substrate by non-covalent bonding as seen in enzymes.[60] In our efforts to develop biomimetic approaches through supramolecular catalysis[59] and also to overcome some of the drawbacks of the existing methodologies for synthesizing aryl benzothiazole derivatives, we have attempted for the first time the aqueous-phase synthesis of benzothiazole derivatives from dimethyl acetals by using readily available 2-amino thiophenol and β -cyclodextrin (β -CD) in water (**scheme 1**).



Scheme 1: Synthesis of 2-arylbenzothiazole.

Cyclodextrins, which are cyclic oligosaccharides with hydrophobic cavities, exert micro environmental effects leading to selective reactions. β-Cyclodextrin was one of the supramolecular hosts and has been introduced into the water-phase catalytic systems including reduction, oxidation, ring opening and hydrolysis.[61] This cyclic oligosaccharide composed of 6-8 glucopyranose units linked by glycosidic bonds.[62] They catalyze reactions involving supramolecular catalysis through non-covalent bonding.

Based on the above observation and in view of the efforts towards development of environmentally-benign, simple, mild and eco-friendly reaction protocol, we have decided to explore the potential of β-cyclodextrin as a catalyst for the synthesis of 2-arylbenzothiazoles.

MATERIALS AND METHODS

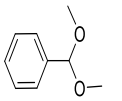
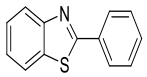
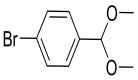
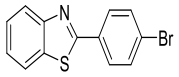
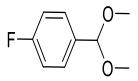
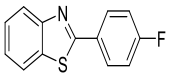
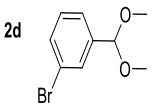
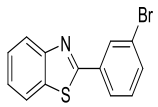
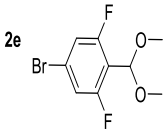
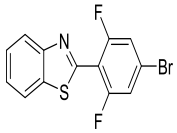
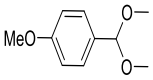
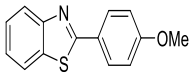
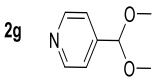
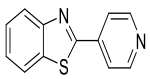
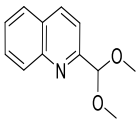
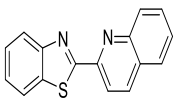
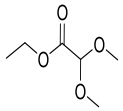
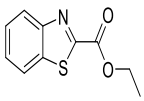
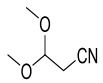
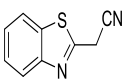
All chemicals and reagents used for the synthesis were obtained from commercial sources and were used without any further purification. Reactions were monitored by thin layer chromatography (TLC), performed on silica gel glass plates containing Merck TLC Silica Gel 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. 1HNMR spectra were recorded inAgilent-400 MHz instrument. 13CNMR spectra were recorded in Agilent-400 MHz Chemical shifts (δ) are reported in ppm downfield from TMS

internal standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electro thermal melting point apparatus (Buchi-M-565), and are uncorrected. The infra-red spectra were recorded as potassium bromide disk using Schimadzu-FT-IR spectrophotometer.

RESULTS AND DISCUSSION

In general, the reactions were carried out by the in situ formation of the β -cyclodextrin (β -CD) complex of the dimethylacetal (**2a-j**) in water at 50 °C, followed by the addition of 2-amino thiophenol (**1**); stirring at the same temperature gave the corresponding aryl benzothiazole (**3a-j**) in excellent yields (**Table 1**) and also do not generate any toxic waste products, no by-products have been detected. Here, the key role of cyclodextrin appears to activate benzaldehyde dimethyl acetal through hydrogen bonding and facilitating the hydrolysis. The hydrolysed product further reacted with 2-amino thiophenol to yield 2-arylbenzothiazoles.[63] These reactions were efficiently carried out with β-cyclodextrin (1 mmol of cyclodextrin per mmol of the substrate). The used cyclodextrin in the reaction can also be recovered and reused. β-Cyclodextrin was used as a catalyst since it is easily accessible and inexpensive among various cyclodextrins. To test our hypothesis a reaction was performed without β-cyclodextrin, no deprotection takes place and hence, no cyclization was observed. The yields were comparatively high for 4-methoxy-dimethylacetalbenzaldehyde and for dimethylacetal pyridine-4-aldehyde (**Table-1**). This is a step economy synthesis for aryl benzothiazoles from benzaldehyde dimethyl acetals.

Table 1: Substituted 2-arylbenzothiazole compounds (3a-j).

Entry	Substrate (1)	Substrate (2a-j)	Product (3a-j)	Time (h)	Yield (%)[a]	MP (°C)[b]	Lit mp (°C)
1		2a 	3a 	16`	66	112-113	110-111, Lit (60d)
2		2b 	3b 	16	68	130-132	128.7-129.9, Lit (60e)
3		2c 	3c 	16	65	103-104	101-102, Lit (63)
4		2d 	3d 	16	67	89-91	91-93, Lit (67)
5		2e 	3e 	16	70	129-131	New product
6		2f 	3f 	16	80	118-119	119-120, Lit (60d)
7		2g 	3g 	10	86	127-129	130-132, Lit (68)
8		2h 	3h 	16	65	186-187	185-186, Lit (65)
9		2i 	3i 	16	71	68-69	69-70, Lit (66)
10		2j 	3j 	16	78	100-102	103, Lit (64,a,b)

[a]Isolated yields; [b]melting point recorded on Buchi-M-565

We have demonstrated for the first time that arylbenzothiazoles formation can be promoted by β-cyclodextrin in water. Thus overcoming many of the drawbacks in the existing methodologies.

EXPERIMENTAL SECTION

General procedure for the synthesis of substituted 2-arylbenzothiozoles (3a-j)

β-Cyclodextrin (1 mmol) was dissolved in water (20 ml) at 50 ^{o}C. Then aryldimethylacetals (1 mmol, **2a-j**) dissolved in acetone (1 ml) and added drop wise, followed by 2-

aminothiophenol (1.2 mmol, **1**) and the resulting reaction mixture was stirred at 50°C until the reaction was complete (as monitored by TLC analysis) (Table 1). Then the reaction mixture was diluted with ethyl acetate and filtered. The separated organic layer from the filtrate was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to get crude product, which was further purified by flash column chromatography on silica-gel (60-120 mesh) using a mixture of petroleum ether and ethyl acetate as eluent to provide the corresponding pure products of substituted 2-arylbenzothiozoles, yield = 65-86% (**3a-j**). The aqueous layer was cooled to 5 °C to recover β-CD by filtration. The final structures of compounds were confirmed by consistent with previous literature reports.[53, 60d,e, 63, 64a,b, 65-67]

Spectral characterization data of compounds (3a-j)

2-Phenylbenzo[d]thiazole (3a)

White solid. Yield 66%; MP: 112-113 °C [110-111, Lit [60d]]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (q, *J* = 3.2, 2.8 Hz, 3H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.49 (p, *J* = 4.4 Hz, 4H), 7.38 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.12, 154.22, 135.14, 133.71, 131.02, 129.08, 127.63, 126.37, 125.25, 123.31, 121.68; FT-IR (KBr) ν_{max} **(**cm^{-1}): 3443.0, 3423.9, 3062.0, 2923.2, 1506.4, 1476.5, 1432.21, 1311.6, 1222.9, 962.5, 762.8, 729.1; MS (ESI): (*m/z*) 212 $[M+H]^+$; HRMS calcd for $C_{13}H_9NS$, 212.0456 $[M+H]^+$; found: 212.0525 $[M+H]^+$.

2-(4-Bromophenyl) benzo[d]thiazole (3b)

White solid. Yield 68%; MP: 130-132 °C [128.7-129.9 Lit.[60e]]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.1 Hz, 1H), 7.98 – 7.95 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.54 – 7.48 (m, 1H), 7.40 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.7, 123.4, 125.5, 126.6, 129.0, 132.3, 132.6, 135.1, 154.2, 166.7; IR (KBr) ν_{max} (cm^{-1}): 3055.3, 1503.5, 1473.6, 1430.2, 1393.6, 1310.6, 1224.8, 1066.6, 1009.7, 966.3, 829.4, 754.2, 718.5. MS (ESI): (*m/z)* 291.96 $[M+H]^+$; HRMS calcd for $C_{13}H_8BrNS$, 291.9540 $[M+H]^+$; found: 291.9606 $[M+H]^+$.

2-(4-Fluorophenyl) benzo[d]thiazole (3c)

Pale yellow solid. Yield 65%, MP: 103-104 °C [101-102 Lit.[63]]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.04 (m, 1H), 7.91 (d, *J* = 8.0 Hz, 0H), 7.50 (t, *J* = 7.6 Hz, 0H), 7.41 (d, *J* = 7.6 Hz, 0H), 7.19 (t, *J* = 8.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$); δ 116.1, 116.4, 121.7, 123.3, 125.3, 126.5, 129.6, 129.7, 130.1, 135.2, 154.2, 163.3, 165.8, 166.8. IR (KBr) ν_{max}

(cm^{-1}): 3435.3, 1600.9, 1519.0, 1483.3, 1434.1, 1408.1, 1312.6, 1228.7, 1156.3, 1098.5, 966.3, 840.0, 810.4, 758.0; MS (ESI): (*m/z)* 230 $[M+H]^+$; HRMS calcd for $C_{13}H_8FNS$, 230.0361 $[M+H]^+$; found: 230.0431 $[M+H]^+$.

2-(3-Bromophenyl) benzo[d]thiazole (3d)

White solid. Yield 67%, MP: 89-91°C [91-93 Lit.[67]]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 1.9 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.53 – 7.45 (m, 1H), 7.37 (dt, *J* = 21.6, 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.17, 154.04, 135.55, 135.16, 133.83, 130.43, 126.60, 126.21, 125.62, 123.52, 123.25, 121.75; IR (KBr) ν_{max} (cm^{-1}): 3437.3, 1558.5, 1501.6, 1463.0, 1428.3, 1402.3, 1309.7, 1216.1, 1067.6, 975.0, 859.3, 783.1, 747.4; MS (ESI): (*m/z)* 291.9 $[M+H]^+$; HRMS calcd for $C_{13}H_8BrNS$, 291.9540 $[M+H]^+$, found: 291.9606 $[M+H]^+$.

2-(4-Bromo-2, 6-difluorophenyl) benzo[d]thiazole (3e)

Off white solid, Yield 70%; MP: 129-131; ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.2 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 161.5, 159.0, 158.9, 154.8, 153.0, 135.6, 26.5, 125.9, 124.3, 124.2, 124.1, 124.0, 121.3, 116.5, 116.2, 111.6, 111.5, 111.3, FT-IR (KBr) ν_{max} (cm^{-1}): 3070.8, 1604.8, 1555.6, 1454.3, 1410.9, 1311.6, 1311.6, 1191.0, 1082.1, 1035.8, 953.8, 851.8, 759.0, 731.0; MS (ESI): (*m/z*) 327.9 $[M+H]^+$; HRMS calcd for $C_{13}H_6BrF_2NS$, 327.9352 $[M+H]^+$, found: 327.9416 $[M+H]^+$.

2-(4-Methoxyphenyl) benzo[d]thiazole (3f)

White solid. Yield 80%; MP; 118-119°C [119-120 Lit.[60d]]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.6, 3.5 Hz, 3H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.04 – 6.96 (m, 2H), 3.89 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 114.4, 121.6, 122.9, 124.8, 126.3, 123.5, 129.2, 134.9, 154.3, 162.0, 167.9; IR (KBr) ν_{max} (cm^{-1}): 3445.0, 2929.0, 1600.9, 1519.0, 1481.3, 1434.1, 1307.7, 1256.6, 1223.8, 1171.8, 1112.9, 1025.2, 966.3, 831.3, 758.0, 729.1; MS (ESI): (*m/z*) 242 $[M+H]^+$; HRMS calcd for $C_{14}H_{11}NOS$, 242.0561 $[M+H]^+$; found: 242.0630 $[M+H]^+$.

2-(Pyridin-4-yl) benzo[d]thiazole (3g)

Yellow solid. Yield 86%; MP:127-129 °C [130-132 Lit.[68]]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, *J* = 5.2 Hz, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.96 (q, *J* = 3.5, 2.1 Hz, 3H), 7.51 (dt, *J* = 35.1, 7.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 121.2, 121.6, 121.9, 123.9, 126.2, 126.8,

135.2, 140.5, 150.8, 154.0, 165.1; IR (KBr) ν_{max} (cm^{-1}): 3447.9, 2925.1, 2853.8, 1742.7, 1593.2, 1476.5, 1409.0, 1314.5, 1252.8, 1214.2, 1161.2, 977.9, 823.6, 758.0, 728.1; MS (ESI): (*m/z)* 213 $[M+H]^+$; HRMS calcd for $C_{12}H_8N_2S$, 213.0408 $[M+H]^+$; found: 213.0482 $[M+H]^+$.

2-(Benzo[d]thiazol-2-yl) quinoline (3h)

Yellow solid. Yield 65%; MP: 186-187 °C [185-186 Lit.[65]]; ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.85 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.76 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.58 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.54 – 7.49 (m, 1H), 7.43 (td, *J* = 7.6, 7.1, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.93, 154.45, 151.40, 136.81, 129.99, 129.06, 127.71, 126.13, 123.86, 122.09, 118.41; IR (KBr) ν_{max} (cm^{-1}): 3445.9, 3052.4, 2925.1, 2853.8, 1592.3, 1558.5, 1501.6, 1427.3, 1323.2, 1116.8, 993.3, 936.4, 835.2, 755.1, 726.2; MS (ESI): (*m/z*) 263 $[M+H]^+$; HRMS calcd for $C_{16}H_{10}N_2S$, 263.0565 $[M+H]^+$, found: 263.0634 $[M+H]^+$.

Ethyl benzo[d]thiazole-2-carboxylate (3i)

White solid. Yield 71%; MP: 68-69 °C [69-70 Lit.[66]]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 - 1.58 (m, 3H) 4.56 (q, *J*=7.34 Hz, 2H) 7.48 - 7.65 (m, 2 H) 7.98 (d, *J*=7.83 Hz, 1 H) 8.26 (d, *J*=8.31 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.98, 62.75, 121.74, 125.12, 126.73, 127.19, 136.40, 152.83, 158.16, 160.25; IR (KBr) ν_{max} (cm^{-1}): 3064.46, 3001.36, 2720.83, 1941.38, 1794.61, 1749.64, 1552.33, 1498.96, 1361.08, 1316.84, 1227.48, 1097.92, 1013.65, 854.76, 723.60; MS (ESI): (*m/z*) 208 $[M+H]^+$; HRMS calcd for $C_{10}H_9NO_2S$, 208.0354 $[M+H]^+$; found: 208.0417 $[M+H]^+$.

2-(benzo[d]thiazol-2-yl) acetonitrile (3j)

White solid. Yield 78%; MP: 100-102 °C [103 Lit.[64a,b]]; ^1H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 2 H) 7.41 - 7.46 (m, 1 H) 7.50 - 7.55 (m, 1 H) 7.90 (d, *J*=7.83 Hz, 1 H) 8.05 (d, *J*=7.82 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 22.89, 114.84, 121.44, 122.99, 125.60, 126.35, 135.13, 152.45, 158.10; IR (KBr) ν_{max} (cm^{-1}): 3061.52, 2920.83, 2618.24, 2277.96, 2251.95, 1918.31, 1798.16, 1628.32, 1556.12, 1513.31, 1433.42, 1382.34, 1307.50, 1239.94, 1109.93, 1058.60, 903.97, 762.32; MS (ESI): (*m/z*) 175 $[M+H]^+$; HRMS calcd for $C_9H_6N_2S$, 174.0252 $[M+H]^+$; found: 175.0317 $[M+H]^+$.

CONCLUSION

In conclusion, we have described an efficient and convenient approach to 2-arylbenzo thiazoles (**3a-j**) by using β-cyclodextrin as catalyst. Their structures were established on the basis of IR, ^{1}HNMR, ^{13}CNMR, mass spectral analysis data.

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