ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 3, pp. 679–682. © Pleiades Publishing, Ltd., 2015.

Synthesis of 2-(4-Aminophenyl)benzothiazoles Using MF Resin Supported H^+ under Solvent Free Conditions[1]

Yingjie Lei[a,b], Xinshi Wu[b], Guochun Zhang[a], and Cuiling Ai[a]

[a] *Shaanxi Key Laboratory of Comprehensive Utilization of Tailings Resources. Shaanxi, 726000, P.R. China*

[b] *Department of Chemistry and Chemical Engineering, Tianjin University of Technology, Tianjin, 300384, P.R. China*
e-mail: yingjlei@163.com

Received November 19, 2014

Abstract—A simple and convenient approach to 2-(4-aminophenyl)benzothiazole derivatives by condensation of *o*-aminothiophenol with (un)substituted *p*-aminobenzoic acid under the action of melamine formaldehyde resin (MFR) supported sulfuric acid under microwave irradiation (MW) and solvent-free conditions has been developed. Structures of the corresponding products were elucidated by IR, ^{1}H NMR spectra, and elemental analysis. The resin could be easily recovered and reused for subsequent reactions.

Keywords: 2-(4-aminophenyl)benzothiazole, nitrothiobenzanilidine, 1,3,4-oxadiazoles, IR, ^{1}H NMR spectra

DOI: 10.1134/S1070363215030251

INTRODUCTION

2-Arylbenzothiazoles are important moieties in medicinal chemistry. 2-(4-Aminophenyl)benzothiazoles and their analogues represent a novel class of antitumor agents [1, 2]. The methods for their synthesis presented in the literature can be divided into two main groups: Jacobson cyclization of substituted nitrothiobenzanilidine in presence of aqueous sodium hydroxide and potassium ferricyanide followed by reduction [3] and the other one is *o*-aminothiophenol condensation with the substituted aromatic aldehydes [4], carboxylic acids or their derivatives [5–7]. However, the above methods have drawbacks such as toxic reagents or solvents involved, high temperature, long reaction time, and some others.

Microwave irradiation has become the efficient method to simplify and improve organic reactions conditions. Solvent-free organic synthesis based on polymer-supported reagents have attracted attention due to minimization of environmental problems. For example, o-aminothiophenol reacted this way with orthoesters in the presence of KFS clay [8], benzaldoximes using alumina or silica gel [9, 10], or aromatic aldehydes in an ionic liquid [11]. Recently melamine formaldehyde resin (MFR) supported sulfuric acid was used as a dehydrating agent for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from carboxylic acids and hydrazides [12].

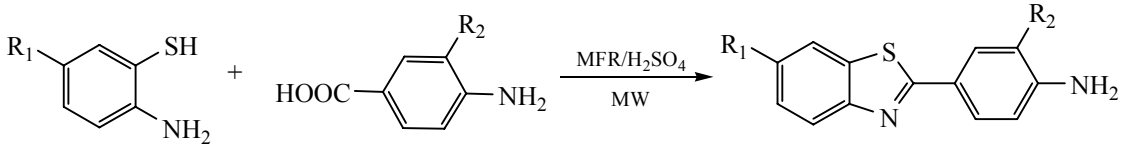
However, to the best of our knowledge, a versatile MW promoted solvent-free protocol for the synthesis of pharmacologically active 4-aminophenylbenzothiazoles by condensation of neat benzoic acid with o-aminothiophenol has not been reported. Herein is presented the catalytic effect of MFR supported sulfuric acid on the synthesis of antitumor agents, 2-(4-aminophenyl)benzothiazol (Scheme 1).

RESULTS AND DISCUSSION

The main objective of our research was development of a simple and rapid solvent free method for 2-(4-aminophenyl)benzothiazole under MW irradiation. The worked out optimum conditions were molar ratio of *p*-aminobenzoic acid to *o*-aminothiophenol 1 : 2, irradiation time 6–8 min and power level of MW set-up 900 W. The electronic nature of substituents on *p*-aminobenzoic acids had low effect on the reaction process, though additional studies are needed for supporting this statement.

[1] The text was submitted by the authors in English.

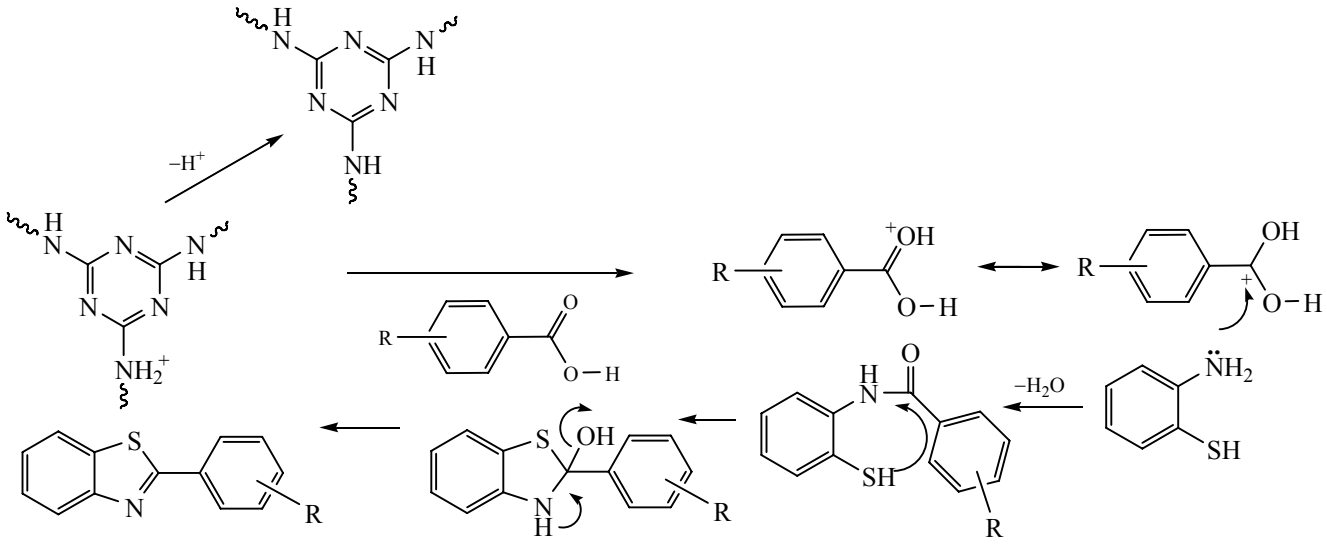
Scheme 1. Synthesis of 2-(4-aminophenyl)benzothiazoles



Ia–Id **IIa–IIe** **IIIa–IIIj**

I: R^1 = H (**a**), R^1 = CH_3 (**b**), R^1 = OCH_3 (**c**), R^1 = Et (**d**); **II**: R^2 = H (**a**), R^2 = CH_3 (**b**), R^2 = Cl (**c**), R^2 = Br (**d**), R^2 = I (**e**); **III**: R^1 = H; R^2 = H (**a**), R^1 = CH_3; R^2 = H (**b**), R^1 = OCH_3; R^2 = H (**c**), R^1 = Et; R^2 = H (**d**), R^1 = H; R^2 = CH_3 (**e**), R^1 = H; R^2 = Cl (**f**), R^1 = H; R^2 = Br (**g**), R^1 = H; R^2 = I (**h**), R^1 = Et; R^2 = CH_3 (**i**), R^1 = OCH_3; R^2 = CH_3 (**j**).

Scheme 2. The plausible mechanism of the reaction



Possibility of recycling the catalyst was studied in the reaction of *o*-aminothiophenol with *p*-aminobenzoic acid under the action of 30 mol % of MFR sulfuric acid. Upon completion of the reaction, ethanol was added for recovering the insoluble catalyst by filtration. The recovered resin was dried and reactivated by its treatment with sulphuric acid in diethyl ether solution. The catalyst was filtered off, rinsed with ether, and reused after drying at 75°C in an oven. Upon reactivation of catalyst could be recycled three times with the yield lowering from 87 to 80% after the third cycle.

Though a detailed study of the process is needed, a plausible mechanism of the reaction of substituted aminothiophenol with *p*-aminobenzoic acid can be expressed as follows (Scheme 2).

The MFR supported sulfuric acid facilitates the dehydration process in which the nucleophilic attack of the protonated carboxylic acid by the amine group leads to formation of the intermediate amide, followed by intramolecular condensation with –SH giving the benzothiazoles.

In conclusion, we have worked out a simple and efficient solvent free synthesis of 2-(4-aminophenyl)-benzothiazole from aminothiophenol and amino benzoic acid promoted by MFR sulfuric acid under MW irradiation. The high yield method is environmentally friendly and simple which makes it favourable for the consequent biological evaluation.

EXPERIMENTAL

Materials and methods. All chemicals were purchased from commercial suppliers and used as received. Melting points were determined with an electrothermal micromelting point apparatus and uncorrected. NMR spectra were recorded on a JEOL JNM-ECA 400 spectrometer with tetramethylsilane internal standard. ESI mass spectra were measured by an ESI-LTQ MS spectrometer. Elemental analyses

were performed on a Perkin-Elmer Model 240 analytical apparatus. MW irradiation was performed in an unmodified Galanz WD 900M domestic microwave oven. All compounds were purified by thick layer chromatography using silica gel from Merck.

Preparation of MF-supported sulfuric acid. Polymer-supported reagent was prepared according to the previously reported method [12]. To a solution of melamine–formaldehyde resin (6 g) in 60mL of acetone commercial sulfuric acid (98%, 6 mL) was added dropwise over a period of 30 min at room temperature. The precipitate was filtered off and dried in vacuum.

Compounds IIIa–IIIg *(general procedure).* To a solution of *o*-aminothiophenol (**Ia–Id**, 5 mmol) and (un)substituted *p*-aminobenzoic acid (**IIa–IIe**, 10 mmol) in diethyl ether (10 mL) was added MFR-supported sulfuric acid (**IIIg**). The slurry was mixed thoroughly and the solvent was removed by rotary evaporation. The resulting solid was irradiated in a MW oven at 900 W for 6–8 min. On completion of the process, the reaction mixture was cooled down to room temperature and ethanol (20 mL) was added. The suspended resin was isolated by filtration and washed with diethyl ether. The filtrate was concentrated under reduced pressure and subjected to chromatography on silica gel to afford the products **IIIa–IIIj**.

4-Benzothiazol-2-yl phenylamine (IIIa). Yellow solid, 87%, mp 130–132°C; IR (KBr), ν, cm^{-1}: 3300, 3200, 1635, 1610, 830. ^{1}H NMR spectra spectra (DMSO-d_6), δ, ppm: 7.92 m (3H, Ar-H), 7.84 m (1H, Ar-H), 7.44 m (1H, Ar-H), 7.32 m (1H, Ar-H), 6.72 d (*J* = 4.2 Hz, 2H, Ar-H), 4.00 s (2H, NH_2). MS (ESI): *m/z* 226.05 (calculated), 227.05, [*M* + H]$^+$ (found). Calculated, %: 69.00; H 4.45; N 12.38. $C_{13}H_{10}N_2S$. Found, %: C 69.03; H 4.69; N 12.29.

4-(6-Methylbenzothiazol-2-yl)phenylamine (IIIb). Yellow solid; 86%; mp 180–182°C; IR (KBr), ν, cm^{-1}: 3302, 3199, 1636, 1610, 830. ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 7.85 m (3H, Ar-H), 7.63 s (Ar-H), 7.28 m (2H, Ar-H), 6.71 m (Ar-H), 4.00 s (2H, NH_2), 2.46 s (3H, CH_3). MS (ESI): *m/z* 240.07 (calculated), 241.08, [*M* + H]$^+$ (found). Calculated, %: C 69.97; H 5.03; N 11.66. $C_{14}H_{12}N_2S$. Found, %: C 69.84; H 5.01; N 11.70.

4-(6-Methoxy-benzothiazol-2-yl)-phenylamine (IIIc). Yellow solid, 88%; mp 174–176°C; IR(KBr), ν, cm^{-1}: 3300, 3200, 1635, 1607, 830. ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 7.85 s (Ar-H), 7.80 d (*J* = 4.8 Hz, 2H, Ar-H), 7.35 d (*J* = 2.4 Hz, Ar-H), 7.04 m (3H, Ar-H), 3.98 s (2H, NH_2), 3.85 s (3H, OCH_3). MS (ESI): *m/z* 256.07 (calculated), 257.08 [*M* + H]$^+$ (found). Calculated, %: C 65.60; H 4.72; N 10.93. $C_{14}H_{12}N_2OS$. Found, %: C 65.35; H 4.90; N 10.67.

4-(6-Ethyl-benzothiazol-2-yl)-phenylamine (IIId). Yellow solid, 83%; mp 153–155°C; IR (KBr), ν, cm^{-1}: 3306, 3198, 1634, 1609, 830.^{1}H NMR spectra (DMSO-d_6), δ, ppm: 7.86 m (3H, Ar-H), 7.65 d (*J* = 0.4 Hz, Ar-H), 7.25 d (*J* = 7.6 Hz, Ar-H), 6.80 d (*J* = 4.8 Hz, 2H, Ar-H), 3.98 s (2H, NH_2) 2.76 (q, 2H, CH_2), 1.29 t (3H, CH_3). MS (ESI): *m/z* 254.09 (calculated), 255.09 [*M* + H]$^+$ (found). Calculated, %: 70.83; H 5.55; N 11.01. $C_{15}H_{14}N_2S$. Found, %: C 70.62; H 5.30; N 10.90.

4-Benzothiazol-2-yl-2-methyl-phenylamine (IIIe). Yellow solid, 85%; mp 145–147°C; IR(KBr), ν, cm^{-1}: 3304, 3205, 1637, 1614, 830.^{1}H NMR spectra (DMSO-d_6), δ, ppm: 7.99 m (Ar-H), 7.83 m (2H, Ar-H), 7.75 d (*J* = 8.0 Hz, Ar-H), 7.43 d (*J* = 8.0 Hz, Ar-H), 7.31 d (*J* = 8.0 Hz, Ar-H), 6.71 d (*J* = 8.0 Hz, Ar-H), 3.94 s (2H, NH_2), 2.23 s (3H, CH_3). MS (ESI): *m/z* 240.07 (calculated), 241.07 [*M* + H]$^+$ (found). Calculated, %: 69.97; H 5.03; N 11.66. $C_{14}H_{12}N_2S$. Found, %: C 69.83; H 5.03; N 11.72.

4-Benzothiazol-2-yl-2-chlorophenylamine (IIIf). White solid, 83%; mp 185–187°C; IR (KBr), ν, cm^{-1}: 3450, 3295, 1627, 1474, 1224, 750. ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 8.09 m (Ar-H), 8.03 m (Ar-H), 7.85 d (*J* = 8.0 Hz, Ar-H), 7.79 d (*J* = 8.0 Hz, Ar-H), 7.53 d (*J* = 8.0 Hz, Ar-H), 7.37 d (*J* = 8.0 Hz, Ar-H), 6.81 d (*J* = 8.0 Hz, Ar-H), 4.44(s, 2H, NH_2). MS (ESI): *m/z* 260.02 (calculated), 259.02 [*M* – H]$^-$, 261.02, [*M* – H + 2] (found). Calculated, %: 59.88; H 3.48; N 10.74. $C_{13}H_9ClN_2S$. Found, %: C 59.80; H 3.53; N 10.68.

4-Benzothiazol-2-yl-2-bromophenylamine (IIIg). White solid, 81%; mp 162–164°C; IR (KBr), ν, cm^{-1}: 3440, 3291, 1625, 1476, 1320, 1225, 754; ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 8.05 m (2H, Ar-H), 7.95 d (*J* = 8.0 Hz, Ar-H), 7.78 d (*J* = 8.0 Hz, Ar-H), 7.50 d (*J* = 8.0 Hz, Ar-H), 7.39 d (*J* = 8.0 Hz, Ar-H), 6.91 d (*J* = 8.0 Hz, Ar-H), 6.14 s (2H, NH_2). MS (ESI): *m/z* 305.19 (calculated), 304.19, [*M* – H]$^-$, 306.18, [*M* – H + 2] (found). Calculated, %: 51.16; H 2.97; N 9.18. $C_{13}H_9BrN_2S$. Found, %: C 51.08; H 3.03; N 9.22%.

4-Benzothiazol-2-yl-2-iodophenylamine (IIIh). Yellow solid, 84%; mp 165–167°C; IR (KBr), ν, cm^{-1}:

3424, 3285, 1627, 1584, 1224, 753; ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 8.19 m (Ar-H), 8.05 m (Ar-H), 7.94 d (J = 8.0 Hz, Ar-H), 7.79 d (J = 8.0 Hz, Ar-H), 7.49 d (J = 8.0 Hz, Ar-H), 7.38 d (J = 8.0 Hz, Ar-H), 6.86 d (J = 8.0 Hz, Ar-H), 5, 98 s (2H, NH_2). MS (ESI): *m/z* 351.95 (calculated), 352.96 $[M + H]^+$ (found). Calculated, %: 44.33; H 2.58; N 7.95. $C_{13}H_9IN_2S$. Found, %: C 44.38; H 2.52; N 7.90.

4-(6-Ethyl-benzothiazol-2-yl)-2-methylphenyl-amine (IIIi). Brown solid, 81%; mp 171–173°C; IR (KBr), ν, cm^{-1}: 3306, 3198, 1634, 1609, 830. ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 7.84 m (3H, Ar-H), 7.65 d (J = 0.4 Hz, Ar-H), 7.25 m (2H, Ar-H), 6.70 d (J = 4.8 Hz, 2H, Ar-H), 3.92 s (2H, NH_2), 2.76 q (2H, CH_2), 2.22 s (3H, CH_3), 1.29 t (3H, CH_3). MS (ESI): *m/z* 268.10 (calculated), 269.10, $[M + H]^+$ (found). Calculated, %: 71.61; H 6.01; N 10.44. $C_{16}H_{16}N_2S$. Found, %: C 72.01; H 6.35; N 10.52.

4-(6-Methoxy-benzothiazol-2-yl)-2-methylphenyl-amine (IIIj). Yellow solid, 87%; mp 150–152°C; IR (KBr), ν, cm^{-1}: 3300, 3200, 1635, 1610, 830. ^{1}H NMR spectra (DMSO-d_6), δ, ppm: 7.87 d (J = 8.8 Hz, Ar-H), 7.77 d (J = 2.0 Hz, Ar-H), 7.69 d (J = 6.0 Hz, Ar-H), 7.30 d (J = 2.8 Hz, Ar-H), 7.03 m (2H, Ar-H), 3.93 s (2H, NH_2), 3.84 s (3H, OCH_3), 2.22 s (3H, CH_3). MS (ESI): *m/z* 270.08 (calculated), 271.08, $[M + H]^+$ (found). Calculated, %: 66.64; H 5.22; N 10.36. $C_{15}H_{14}N_2OS$. Found, %: C 66.58; H 5.38; N 10, 47.

ACKNOWLEDGMENTS

The authors are thankful to the Shaanxi Key Laboratory of Comprehensive Utilization of Tailings Resources (Shangluo University) for financial assistance under major research (grants nos. 2014SKY-WK005 and 2014SKY-WK008).

REFERENCES

1. Bradshaw, T.D., Shi, D.F., Schultz, R.J., Paull, K.D., Kelland, L., Wilson, A., Garner, C. Fiebig, H.H., Wrigley, S., and Stevens, M.F., *Br. J. Cancer*, 1998, vol. 78(4), pp. 421–429.
2. Hutchinson, I., Jennings, S.A., Vishnuvajjala, B.R., Westwell, A.D., and Stevens, M.F., *J. Med. Chem.*, 2002, vol. 45(3), pp. 744–747.
3. Hutchinson, I., Stevens, M.F., and Westwell, A.D., *Tetrahedron Lett*., 2000, vol. 41(3), pp. 425–428.
4. Deligeorgiev, T.G., *Dyes and Pigments*, 1990, vol. 12(4), pp. 243–248.
5. Stevens, M.F.G., McCall, J.C., and Lelieveld, P., WO9506469, 1995.
6. Kanaoka, Y., Hamada, T., and Yonemitsu, O., *Chem. Pharm. Bull*., 1970, vol. 18(3), pp. 587–590.
7. Boger, D.L., *J. Org. Chem*., 1978, vol. 43(11), pp. 2296–2297.
8. Villemin, D., Hammadi, M., and Martin, B., *Synth. Commun.,* 1996, vol. 26(15), pp. 2895–2899.
9. Bougrin, K., Loupy, A., and Soufiaoui, M., *Tetrahedron*, 1998, vol. 54(28), pp. 8055–8064.
10. Kodomari, M., Tamaru, T., and Aoyama, T., *Synth. Comm*., 2004, vol. 34(16), pp. 3029–3036.
11. Rann, B.C., Jana, R., and Dey, S.S., *Chem. Lett.*, 2004, vol. 33(3), pp. 274–275.
12. Yingjie, L., Shuying, L., and Hao, L., *Asian J. Chem,,* 2013, vol. 18, pp. 10454–10456.