Synthesis of 2-Aryl and Coumarin Substituted Benzothiazole Derivatives

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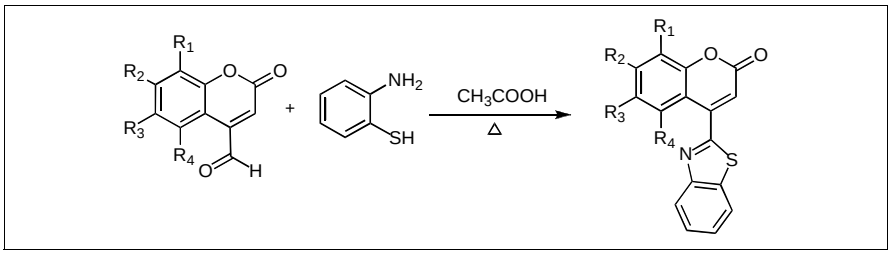

A facile and effective method for the synthesis of some benzothiazole derivatives is described. The method involves the action of aryl aldehyde and *o*-aminothiophenol in acetic acid resulting into *in situ* formation of the thiol substituted Schiff's base and its cyclization to 2-aryl benzothiazole upon prolonged heating.

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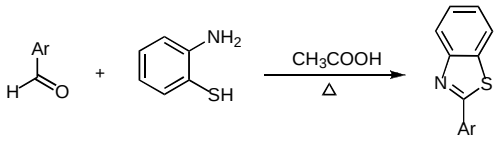
Benzothiazoles are heterocyclic compounds with multiple applications and they have been known from long ago to be biologically active, [1-3] their varied biological features are still of great scientific interest nowadays. They are widely found in bioorganic and medicinal chemistry with applications in drug discovery and have a very intensive antitumor [4-6], antiviral [7], anti-HIV [8], microbiological activity [9-10], for treatment of auto-immune and inflammatory diseases [11], in the prevention of solid organ transplant rejection epilepsy [12-14], amyotrophic lateral sclerosis [15] and analgesia [16].

Several research efforts towards the synthesis of substituted benzothiazoles have been used. The methods involve the oxidative cyclization of 2-thiobenzanilides to corresponding benzothiazoles. Hexacyanoferrate [17] and organic ammonium tribromide (OATB) [18] are some of the oxidizing agents of choice. In most of the cases the Schiff's base formed by heating the *o*-aminothiophenol and an aldehyde in appropriate solvent is isolated, followed by its oxidation to desired benzothiazole using $FeCl_3$ [19]. One more reagent, scandium triflate [20] which acts as an acid catalyst for cyclization and oxidation step is widely used. Microwave mediated one-pot synthesis of 2-arylbenzothiazoles from 2-aminothiophenol with aromatic aldehydes in an ionic liquid medium has been studied [21]. Literature survey has revealed the synthesis of benzoxazole and benzimidazole substituted on the 4-position of 2*H*-1-benzopyran-2-ones, but hardly any report on the synthesis of such 4-substituted benzothiazole has been cited [22].

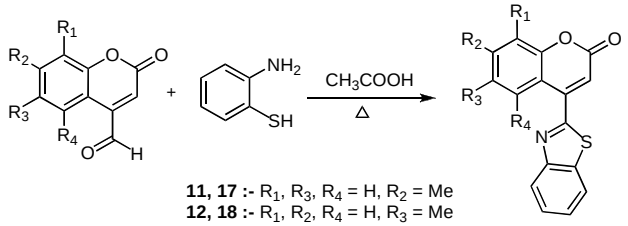
We in this paper have reported our finding on the synthesis of 2-arylbenzothiazole from 2-aminothiophenol and aryl aldehydes in high yields. For the synthesis of 2-arylbenzothiazoles (**6-10**)[23], the aryl aldehyde (**1-5**) and *o*-aminothiophenol were refluxed for 5 hours in acetic acid which acts as a solvent and catalyst (Scheme 1). The 2-aminothiophenol is first condensed with an aldehyde to give a thiol substituted Schiff's base which then cyclizes upon prolonged heating to give the benzothiazole derivative. The various substituted 2*H*-1-benzo/naphtha-pyran-2-ones-4-aldehydes (**11-16**) as depicted in Scheme 2 required for the synthesis has been prepared as per the method reported earlier and also some of them developed in our laboratory [24a-d]. These 2*H*-1-benzo/naphthopyran-2-ones-4-aldehydes (**11-16**) where reacted with *o*-amino-thiophenol in refluxing acetic acid to give 4-(2-benzo-thiazolyl)-2*H*-1-benzo/naphthopyran-2-ones (**17-22**).

Scheme 1



1, 6 :- Ar = Ph
2, 7 :- Ar = 4-MePh
3, 8 :- Ar = 4-MeOPh
4, 9 :- Ar = 4-ClPh
5, 10:- Ar = 2-C_4H_3S

Scheme 2



11, 17 :- R_1, R_3, R_4 = H, R_2 = Me
12, 18 :- R_1, R_2, R_4 = H, R_3 = Me
13, 19 :- R_1-R_2 = benzo, R_3, R_4 = H
14, 20 :- R_2, R_4 = H, R_1, R_3 = Me
15, 21 :- R_1, R_4 = H, R_2, R_3 = Me
16, 22 :- R_1, R_3, R_4 = H, R_2 = OAc

EXERIMENTAL

^{1}H nmr(400 Mz) spectra were measured on Varian Mercury 400 AS (30° C) instrument using TMS as an internal standard. The ir spectra were recorded in KBr, on a Shimadzu FTIR-4200 spectrophotometer. Melting points are uncorrected and measured on a Büchi apparatus. The (un)substituted benzaldehydes required were purchased from Lancester Chemical company.

General Procedure for One-pot Syntheses of 2-Phenylbenzo[*d*]-thiazole (**6**).

Benzaldehyde **1** (0.583 g, 5.5 mmol) and *o*-aminothiophenol (0.625 g, 5 mmol) were taken in 7 ml of acetic acid and heated to reflux for 5 h. Reaction mixture was cooled to room temperature and decomposed over ice water mixture. The solid that separated was collected by filration, dried and crystallized from ethanol/water with some decolorizing carbon to obtain pure crystalline product **6**, 0.8 g (yield = 76 %, mp = 113-14 °C, lit.[23] mp = 114 °C).

For the synthesis of various coumarin substituted benzothiazoles **17-22**, the coumarin-4-carboxaldehyde **11-16** and *o*-aminothiophenol was refluxed in acetic acid as per the procedure given above. The spectroscopic data for (un)substituted 2-phenylbenzo[*d*]thiazole (**6-10**) and 4-(2-benzothiazolyl)-2*H*-1-benzo/naphthopyran-2-ones (**17-22**) are given below.

2-Phenylbenzo[*d*]thiazole (**6**).

The compound was obtained as colourless crystals from ethanol/water, (Yield = 76%, mp = 113-14 °C, lit.[23] mp = 114 °C), ir (KBr): 1478, 1362, 1252, 1125, 883 and 750 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 7.09-7.20 (m, 3H), 7.25-7.33 (m, 3H) 7.58 (t, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 8.03 (d, *J* = 7.5 Hz, 1H).

Anal. Calcd. for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.18; Found: C, 73.69; H, 4.42; N, 6.51; S, 15.35.

2-(4-Methylphenyl)benzo[*d*]thiazole (**7**).

The compound was obtained as pale yellow crystals from ethanol/water, (Yield = 80%, mp = 82-83 °C, lit.[23] mp = 83 °C), ir (KBr): 1475, 1365, 1241, 1130, 892 and 745 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 2.42 (s, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.98-8.05 (m, 3H).

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.45; H, 4.79; N, 6.34; S, 14.32.

2-(4-Methoxyphenyl)benzo[*d*]thiazole (**8**).

The compound was obtained as pale yellow crystals from ethanol, (Yield = 83%, mp = 201-02°C, lit.[23] mp = 202 °C), ir (KBr): 1476, 1368, 1262, 1142, 889 and 744 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 3.86 (s, 3H), 6.98 (d, J = 8.2 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 8.02-8.09 (m, 3H).

Anal. Calcd. for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.91; H, 4.47; N, 5.65; S, 13.42.

2-(4-Chlorophenyl)benzo[*d*]thiazole (**9**).

The compound was obtained as colourless crystals from ethanol, (Yield = 65%, mp = 115-16°C, lit.[23] mp = 116 °C), ir (KBr): 1470, 1375, 1245, 1133, 876 and 716 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 7.10 (d, J = 8.3 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 7.2 Hz, 1H).

Anal. Calcd. for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; Cl, 14.43; N, 5.70; S, 13.05. Found: C, 63.37; H, 3.15; Cl, 14.60; N, 5.49; S, 13.14.

2-(2-Thiophenyl)benzo[*d*]thiazole (**10**).

The compound was obtained as colourless crystals from ethanol/water, (Yield = 65%, mp = 97-98 °C, lit.[23]] mp = 98 °C), ir (KBr): 1450, 1356, 1262, 1146, 850 and 729 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 7.05-7.13 (m, 2H), 7.28 (d, J = 7.8 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H).

Anal. Calcd. for $C_{11}H_7NS_2$: C, 60.80; H, 3.25; N, 6.45; S, 29.51. Found: C, 60.98; H, 3.11; N, 6.60; S, 29.72.

4-(2-Benzothiazolyl)-7-methyl-2*H*-1-benzopyran-2-one (**17**).

The compound was obtained as colourless crystals from ethanol, (Yield = 76%, mp = 162-63), ms: m/z = 293, 294 (M^+, M^{+1}); ir (KBr): 2923, 1726, 1622, 1481, 1382, 1267, 1188, 1110, 879, 817 and 723 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 2.50 (s, 3H), 6.83 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H).

Anal. Calcd. for $C_{17}H_{11}NO_2S$: C, 69.61; H, 3.78; N, 4.77; S, 10.93. Found: C, 69.49; H, 3.83; N, 4.62; S, 10.85.

4-(2-Benzothiazolyl)-6-methyl-2*H*-1-benzopyran-2-one (**18**).

The compound was obtained as colourless crystals from ethanol, (Yield = 80%, mp = 153-55), ir (KBr): 3064, 2920, 1728, 1564, 1483, 1423, 1315, 1261, 1178, 1107, 952, 858 and 727 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 2.45 (s, 3H), 6.85 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.38 (s, 1H).

Anal. Calcd. for $C_{17}H_{11}NO_2S$: C, 69.61; H, 3.78; N, 4.77; S, 10.93. Found: C, 69.52; H, 3.68; N, 4.64; S, 10.80.

4-(2-Benzothiazolyl)-2*H*-1-naphtho[1,2-*b*]pyran-2-one (**19**).

The compound was obtained as pale yellow crystals from ethanol, (Yield = 86%, mp = 149-50), ir (KBr): 3060, 1732, 1631, 1589, 1554, 1481, 1375, 1267, 1151, 1020, 925, 852 and 750 cm^{-1}; ^{1}H nmr ($CDCl_3$): 6.97 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.68 (t, J = 7.7 Hz, 2H), 7.76 (d, J = 8.0 Hz, 1H), 7.91 (dd, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.63 (dd, 2H).

Anal. Calcd. for $C_{20}H_{11}NO_2S$: C, 72.93; H, 3.37; N, 4.25; S, 9.73. Found: C, 72.82; H, 3.48; N, 4.11; S, 9.60.

4-(2-Benzothiazolyl)-6,8-dimethyl-2*H*-1-benzopyran-2-one (**20**).

The compound was obtained as colourless crystals from ethanol, (Yield = 82%, mp = 173-75), ir (KBr): 3068, 2920, 1720, 1602, 1568, 1483, 1458, 1388, 1261, 1172, 1018, 954, 856 and 761cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 2.41 (s, 3H), 2.45 (s, 3H), 6.83 (s, 1H), 7.29 (s, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.15 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H).

Anal. Calcd. for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.23; H, 4.12; N, 4.39; S, 10.33.

4-(2-Benzothiazolyl)-6,7-dimethyl-2*H*-1-benzopyran-2-one (**21**).

The compound was obtained as colourless crystals from ethanol, (Yield = 77%, mp = 194-96), ir (KBr): 3060, 1724, 1622, 1587, 1485, 1454, 1369, 1271, 1222, 1161, 1085, 850 and 754 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 2.31 (s, 3H), 2.38 (s, 3H), 6.79 (s, 1H), 7.20 (s, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.33 (s, 1H).

Anal. Calcd. for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.19; H, 4.09; N, 4.72; S, 10.25.

4-(2-Benzothiazolyl)-7-acetoxy-2*H*-1-benzopyran-2-one (**22**).

The compound was obtained as colourless crystals from ethanol, (Yield = 70%, mp = 179-80), ir (KBr): 3070, 1735, 1616, 1558, 1481, 1379, 1315, 1265, 1202, 1010, 854 and 759 cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.38 (s, 3H), 6.87 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.81 (d, J = 8.0 Hz, 1H).

Anal. Calcd. for $C_{18}H_{11}NO_4S$: C, 64.09; H, 3.29; N, 4.15; S, 9.50. Found: C, 64.15; H, 3.20; N, 4.01; S, 9.67.

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REFERENCES

[1] M. Lácová, J. Chovancová, O. Hýblová and S. Varkonda, *Chem. Pap*., **45**, 411 (1991).

[2] I. Chulák, V. Sutorius and V. Sekerka, *Chem. Pap*., **44**, 131 (1990).

[3] E. Kashiyama, I. Hutchinson, M. S. Chua, S. F. Stinson, L. R. Phillips, G. Kaur, E. A. Sausville, T. D. Bradshaw, A. D. Westwell and M. F. Stevens, *J Med Chem*., **42**(**20**), 4172 (1999).

[4a] T. D. Bradshaw, S. Wrigley, D. F. Shi, R. J. Schultz, K. D. Paull and M. F. Stevens, *Br J Cancer*., **77**(**5**), 745 (1998); [b] D. F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fichtner and M. F. Stevens, *J Med Chem*., **39**(**17**), 3375 (1996).

[5a] T. D. Bradshaw, M. S. Chua, H. L. Browne, V. Trapani, E. A. Sausville, M. F. G. Stevens, *Br. J. Cancer*., **86**, 1348 (2002); [b] I. Hutchinson, M. S. Chua, H. L. Browne, V. Trapani, T. D. Bradshaw, A. D. Westwell and M. F. Stevens, *J Med Chem*., **44**(**9**), 1446 (2001); [c] M. F. Stevens, C. J. McCall, P. Lelieveld, P. Alexander, A. Richter and D. E. Davies, *J. Med. Chem*., **37**(**11**), 1689 (1994).

[6a] I. Hutchinson, S. A. Jennings, B. R. Vishnuvajjala., A. D. Westwell and M. F. G.. Stevens, *J. Med. Chem*., ***45***, 744 (2002); [b] T. D. Bradshaw, M. F. Stevens and A. D. Westwell, *Curr Med Chem*., **8**(**2**), 203 (2001); [c] M. S. Chua, D. F. Shi, S. Wrigley, T. D. Bradshaw, I. Hutchinson, P. N. Shaw, D. A. Barrett, L. A. Stanley and M. F. Stevens, *J. Med. Chem*., **42**(**3**), 381 (1999).

[7] A. D. Borthwick, D. E. Davies, P. F. Ertl, A. M. Exall, T. M. Haley, G. J. Hart, D. L. Jackson, N. R. Parry, A. Patikis, N. Trivedi, G.. G.. Weingarten, J. M. Woolven, *J. Med. Chem*., **46**(**21**), 4428 (2003).

[8] S. R. Nagarajan, G.. A. De Crescenzo, D. P. Getman, H. Lu, J. A. Sikorski, J. L. Walker, J. J. McDonald, K. A. Houseman, G. P. Kocan, N. Kishore, P. P. Mehta, C. L. Funkes-Shippy and L. Blystone, *Eur. J. Med. Chem*., **11**, 4769 (2003).

[9] I. Yildiz-Oren, I. Yalcin, E. Aki-Sener and N. Ucarturk, *Eur. J. Med. Chem*., **39**(**3**), 291 (2004).

[10] A. Latrofa, M. Franco, A. Lopedota, A. Rosato, D. Carone and C. Vitali *Fermaco*, **60**(**4**), 291 (2005).

[11] J. Das, R. V. Moquin, C. Liu, A. M. Doweyko, H. F. Defex, Q. Fang, S. Pang, S. Pitt, D. R. Shan, G. L. Schieven and J. Wityac, *Bioorg. Med. Chem. Lett*., **13**, 2587 (2003).

[12] S. J. Hays, M. J. Rice, D. F. Ortwine, G. Johnson, R. D. Schwarz, D. K. Boyd, L. F. Copeland, M. G. Vartanian and P. A. Boxer, *J. Pharm. Sci*., **83**, 1425 (1994).

[13] P. Jimonet, F. Audiau, M. Barreau, J. C. Blanchard, A. Boireau, Y. Bour, M. A. Coleno, A. Doble, G. Doerflinger, C. D. Huu, M. H. Donat, J. M. Duchesne, P. Ganil, C. Gueremy, E. Honore, B. Just, R. Kerphirique, S. Gontier, P. Hubert, P. M. Laduron, J. Le Blevec, M. Meunier, J. M. Miquet, C. Nemecek, M. Pasquet, J. P. Pratt, J. Ratuad, M. Reibud, J. M. Stutzman and S. Mignani, *J. Med. Chem*., **42**, 2828 (1999).

[14] Y. He, A. Benz, T. Fu, M. Wang, D. F. Covey, C. F. Zorumski and S. Mennerick, *Neuropharmacology*, **42**, 199 (2002).

[15] G. Bensimon, L. Lacomblez. and V. Mienenger, *New Engl. J. Med*., **35**, 295 (1994).

[16] C. Y. Jeong, J. Choi and M. Ha Yoon, *Eur. J. Pharmacol*., **502**(**3**), 205 (2004).

[17a] H. Schwartz, *Nath Appl*., 6, 607, 039, (1966); *Chem. Abstr*., **Vol #**, abstract # (year); [b] A. Osuka, Y. Uno, H. Horiuchi and H. Suzuki, *Synthesis*, 145 (1984); [c] H. Saikachi and T. Hisono, *Chem. Pharm. Bull*., **8**, 51 (1960); [d] S. H. Compare and T. Hisano, *Chem. Pharm. Bull*., **7**, 716 (1959).

[18] F. M. Moghaddam, H. Z. Boeini, *Synlett*, **10**, 1612 (2005).

[19] L. Racane, V. Tralic-Kulenovic, D. W. Boykin and G. Karminski-Zamola, *Molecules*, **8**, 342 (2003).

[20a] T. Itoh, K. Nagata, H. Ishikawa and A. Ohsawa, *Heterocycles*, **63**, 2769 (2004); [b] T. Itoh, K. Nagata, H. Ishikawa and A. Ohsawa, *Heterocycles*, **62**, 197 (2004); [c] T. Itoh, K. Nagata, H. Ishikawa and A. Ohsawa, *Heterocycles*, **52**, 1037 (2000).

[21] B. C. Ranu, R. Jana and S. S. Dey, *Chem. Lett*., **33**, 274 (2004).

[22] D. N. Nicolaides, K. C. Fylaktakidou, K. E. Litinas, G. K. Papageorgios and D. I. Hadjipaviou-litina, *J. Heterocycl. Chem*., **35**, 619 (1998).

[23] V. I. Cohen, *J. Heterocycl. Chem*., **16**, 13 (1979).

[24a] S. D. Joshi and R. N. Usgaonkar, *Indian J. of Chem. Sec. B*, **21**, 399 (1982); [b] K. Ito and J. Maruyama, *Chem. Pharm. Bull*., **34**(**1**) 390 (1986); [c] U. C. Mashelkar and A. A. Audi, *Journal of Indian Council of Chemists*, **18**(**1**), 37 (2001); [d] K. Ito and N. Kaoru, *J. Heterocycl. Chem*. **25**, 511 (1988).