A route to a tetrabenzothiazole from Michael bis-addition compounds

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An efficient and practical synthesis of a tetrabenzothiazole has been developed by condensation of Michael bis-adducts with 2-aminothiophenol.

Keywords: tetrabenzothiazole, Michael addition, 2-aminothiophenol

The benzothiazole moiety is recognised to have an importance in compounds of interest in medicinal chemistry,[1-5] plant growth regulation[6] and in industrial applications.[7-10] The reported methods of benzothiazole synthesis involve two major routes: the condensation of 2-aminothiophenol with aldehydes,[11] carboxylic acids,[12] acid chlorides,[13] or esters[14] and by the cyclisation of thiobenzanilides.[15] Other general methods include microwave-mediated reaction of 2-aminothiophenol with β-chlorocinnamaldehydes,[16] palladium-catalysed Suzuki biaryl coupling of 2-bromobenzothiazole with arylboronic acids[17] and coupling of benzothiazoles with aryl bromides,[18] and the reaction between thiophenols and aromatic nitriles.[19]

The Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated esters and nitriles is one of the most useful carbon carbon bond forming reactions and has wide synthetic applications in organic synthesis.[20] This reaction is traditionally catalysed by strong bases that often lead to undesirable side reactions.[21] Thus, a number of milder reagents such as Al_2O_3, K_2CO_3, rhodium complex, ruthenium complex, clay-supported nickel bromide, quaternary ammonium salt, and N-phenyltris(dimethylamino)iminophosphorane immobilised on polystyrene resin at room-temperature ionic liquids have been developed over the past few years.[22-23] To the best of our knowledge the synthesis of tetra-benzothiazoles from Michael bis-adducts has not been reported previously.

In connection with our research programme directed toward the synthesis of novel benzothiazole derivatives, we describe the efficient synthesis of the tetra(benzothiazole) **(1)** from Michael bis-adducts (**2a–f**) with anhydrous potassium carbonate as the catalyst and tetrabutylammonium bromide(TBAB) as the phase-transfer catalyst. The results are reported in Table 1.

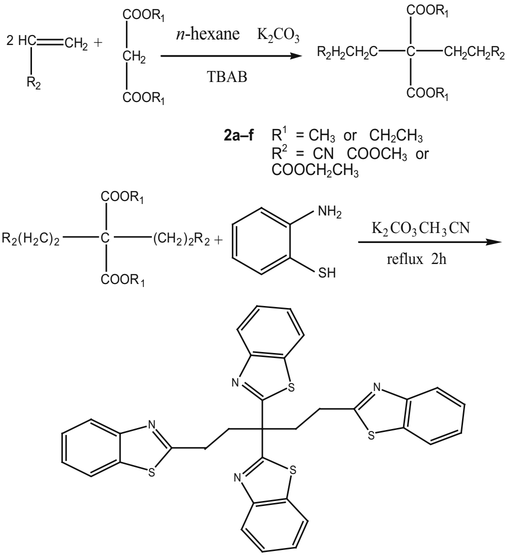
In conclusion, an efficient and practical synthesis of a tetrabenzothiazole has been developed by condensation of Michael bis-adducts with 2-aminothiophenol.

Experimental

Melting points were taken on a micro-apparatus (uncorrected). 1H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm are reported with TMS as the internal standard. Mass spectra were measured on a Finnigan MAT4510 instrument. IR spectra were obtained with a Perkin-Elmer 16 PC FT-IR spectrophotometer. Crystal structure determination was carried out on a Enraf-Nonius CAD-4 diffractometer.

Table 1 Synthesis of Michael bis-adducts

No.	R^1	R^2	Yield%
2a	Me	CN	92
2b	Me	COOMe	86
2c	Me	COOEt	82
2d	Et	CN	91
2e	Et	COOMe	85
2f	Et	COOEt	82



Scheme 1

General procedure for preparation of **2a**

Dimethyl malonate (50 mmol) was dissolved in n-hexane (20 mL), anhydrous potassium carbonate (100 mmol), tetrabutylammonium bromide (0.5 g) was added, then acrylonitrile (100 mmol) was slowly dropped into the mixture. The resulting mixture was refluxed for 12 h. 100 mL water was added to the mixture and the organic layer was dried with magnesium sulfate and the solvent was removed *in vacuo* to afford the crude compound. It was recrystallised from ethyl acetate (15 mL). Crystals of **(2a)** suitable for X-ray diffraction were obtained by slow evaporation of an alcohol solution.

Dimethyl bis(2-cyanoethyl) malonate **2a**: (92%):[24] M.p. 147–149 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, relative to TMS) δ: 3.83 (s, 6H, O–CH_3), 2.47 (t, 4H, –CH_2–CN), 2.26(t, 4H,-C-CH_2). Elemental analysis: Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.88; N, 11.76. Found: C, 55.52; H, 5.86; N, 11.72.

1,3,3,5 Tetramethyl pentane-1,3,3,5-tetra carboxylate **2b** (86%):[25] M.p. 54–56 °C (54–57 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, relative to TMS) δ: 3.74 (s, 6H, –C–COO–CH_3), 3.61 (s, 6H, –CH_2–COO–CH_3), 2.34 (t, 4H, CH_2–COO), 2.19(t, 4H, –C–CH_2). Elemental analysis: Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.32; H, 6.58. Found: C, 51.25; H, 6.62.

3,3-Dimethyl 1,5-diethyl pentane-1,3,3,5-tetra carboxylate **2c** (82%): M.p. 45–47 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, relative to TMS) δ: 4.22 (s, 6H, –C–COO–CH_3), 3.89 (q, 4H, –COO–CH_2–), 2.42 (t, 4H, –CH_2–COO–), 2.31 (t, 4H,–C–CH_2–), 1.3 (t, 6H, –COO–CH_2–CH_3) Elemental analysis: Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.22; H, 7.23; Found: C, 54.13; H, 7.31;

Diethyl bis(2–cyanoethyl) malonate **2d** (91%):[26] M.p. 62–64 °C (62 °C). ^{1}H NMR ($CDCl_3$, 500 MHz, relative to TMS) δ: 4.27 (s, 2H, CH_2), 6.53 (q, 1H, Ar), 6.61 (d, 1H, Ar), 7.15 (q, 1H, Ar). Elemental analysis: Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.65; H, 6.77; N, 10.53. Found: C, 58.50; H, 6.82; N, 10.46.

3,3-Diethyl-1,5-dimethyl pentane-1,3,3,5-tetra carboxylate **2e** (85%):[20] M.p. 52–54 °C. ^{1}H NMR (CDCl3, 500 MHz, relative to TMS) δ: 4.1(q, 4H, O–CH_2–), 3.6(s, 6H,O–CH_3), 2.3 (t, 4H, –CH_2–COO–), 2.2(t, 4H,–C–CH_2–), 1.2(t, 6H, –COO–CH_2–CH_3). Elemental analysis: Anal. Calcd for $C_{15}H_{24}O_8$: C, 54.22; H, 7.23. Found: C, 54.16; H, 7.32;

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1,3,3,5 Tetraethyl pentane–1,3,3,5–tetracarboxylate **2f** *(82%)*:[27] 140–142 °C (138–149 °C) ^1H NMR (CDCl3, 500 MHz, relative to TMS) δ: 4.03 (q, 4H, O–CH_2–), 3.6(q, 4H,O–CH_2), 2.3 (t, 4H, –CH_2–COO–), 2.2(t, 4H,–C–CH_2–), 1.32 (t, 6H, –C–COO–CH_2–CH_3), 1.23 (t, 6H, –CH_2–COO–CH_2–CH_3). Elemental analysis: Anal. Calcd for $C_{17}H_{28}O_8$: C, 56.67; H, 7.78. Found: C, 56.60; H, 7.82;

The Michael bis-addition compound (**2a**) was subjected to single crystal X-ray crystallography and intensity data were collected 293(2) K on the Enraf-Nonius CAD-4 diffractometer and use graphite monochromatic MoKα radiation (λ = 0.71073 Å). The structure was solved directly using the SHELXL-97 program[28] and refined with the SHELXL-97 program.[29] The molecular structure is shown in Fig. 1. Selected crystal data and structure refinement details are presented in Table 2. Selected bond distances and angles are listed in Table 3.[24]

General procedure for preparation of **1**

Michael bis-adducts **2a–f** (50 mmol) were dissolved in acetonitrile (50 mL) and anhydrous potassium carbonate (50 mmol), and 2-aminothiophenol (200 mmol) was added. The resulting mixture was refluxed for 2 h. The solvent was removed *in vacuo* to afford the crude tetrabenzothiazole **(1)**. Then **(1)** was recrystallised with acetonitrile to afford the pure tetrabenzothiazole (**1**) suitable for structure determination.

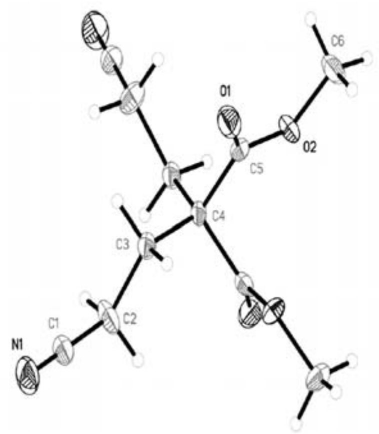

Fig. 1 An ORTEP plot of compound (**2a**) drawn 50% probability level.

Table 2 Crystal data and structure refinement for $C_{11}H_{14}N_2O_4$

Empirical formula	$C_{11}H_{14}N_2O_4$
Formula weight	238.24
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C 2/c
Unit cell dimensions	13.071(3) Å α = 90°
	8.5060(17) Å β = 90.55(3)°
	10.914(2) Å γ = 90°
Volume	1213.4(4) Å3
Z	8
Absorption correction	Semi-empirical
F(000)	504
Absorption coefficient	6.604 mm^{-1}
Theta range for data collection	2.86 to 25.15°
Reflections collected	1140
Independent reflections	1091 [R(int) = 0.3655]
Data/restraints/parameters	1091/78/860
Final R indices [$I > 2\sigma(I)$]	$R^1 = 0.0649$, $wR^2 = 0.1681$
	$R^1 = 0.0784$, $wR^2 = 0.1803$
Goodness of fit on *F*2	1.012
Largest diff. Peak and hole	0.213 and -0.237 e. Å-3

Table 3 Selected bond distances (Å) and angles (°) for compound (**2a**)

N1 C1 1.152(4)	C2 C3 1.535(4)
C1 C2 1.475(4)	C3 C4 1.544(3)
O1 C5 1.178(3)	C4 C5 1.535(3)
O2 C5 1.340(3)	C4 C5 1.535(3)
O2 C6 1.443(3)	C4 C3 1.544(3)
O2 C6 1.443(3)	C2 H2A 0.9700
N1 C1 C2 179.4(3)	C2 C3 C4 112.0(2)
C5 O2 C6 116.4(2)	C1 C2 C3 110.3(3)
C5 C4 C5 106.1(2)	C5 C4 C3 108.88(13)
O1 C5 O2 125.1(2)	C3 C4 C3 113.9(3)
O1 C5 C4 125.9(2)	O2 C5 C4 109.00(18)

3,3- Bisbenzothiazolyl-1,5-pentamethylene-2,2'-bisbenzothiazole **1**: (89%): M.p. 164–166 °C. IR (cm-1): 3377, 3062, 1614, 1468, 1441, 1303, 1240, 1095, 1020, 968. ^1H NMR ($CDCl_3$, 500 MHz, relative to TMS) δ: 4.27 (s, 2H, CH_2), 6.53 (q, 1H, Ar), 6.61 (d, 1H, Ar), 7.15 (q, 1H, Ar). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 76.7, 77.0, 77.3, 115.2, 118.2, 118.7, 131.6, 136.8, 148.6. Elemental analysis: Anal. Calcd for $C_{33}H_{24}N_4S_4$: C, 65.56; H, 3.97; N, 9.27. Found: C, 65.60; H, 3.90; N, 9.28%.

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