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Note

Solvent-free synthesis of 2-alkyl and 2-alkenylbenzothiazoles from fatty acids under microwave irradiation

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Rapid and efficient condensation of 2-aminothiophenol with various fatty acids under microwave irradiation in solvent-free conditions with or without P_4S_{10} is carried out to afford the corresponding 2-substituted benzothiazoles. The one-pot synthesis is obtained in high purity, good yield of products and in short span of time in presence of catalyst under MW irradiation. The compounds are identified on the basis of IR, ^{1}H NMR and MS.

Keywords: Fatty acids, 2-alkylbenzothiazole, 2-alkenylbenzothiazole, phosphorous pentasulphide, microwave irradiation

The benzothiazole structural motifs may be found in numerous pharmaceutical agents with a diverse range of biological properties such as antitumour[1], antiviral[2], anticonvulsant[3], neuroprotective[4] and immunosuppressive properties[5]. They have also found applications in industry as antioxidants, vulcanization accelerators and as a dopant in a light-emitting organic electoluminesent device[6,7]. Several methods have been reported in the literature for the synthesis of 2-substituted benzothiazoles. The most common direct method is the condensation of 2-aminothiophenol with the substituted aromatic aldehydes[8] and carboxylic acids or its derivatives in polyphosphoric acids (PPA)[9], polyphosphate ester[10], or a mixture of methane sulphonic acid and phosphorus pentoxide[11]. Other methods include potassium ferricyanide cyclization of thiobenzanilides[12], reaction of α,α,α-trihalomethyl aromatic compounds with 2-aminothiophenol in PPA[13], palladium-catalyzed reaction of aryl halides with *o*-aminothiophenol in presence of carbon monoxide[14], reaction of 2,2′-dinitrodiphenyl disulphide with acid chlorides or with acid anhydrides in the presence of $TiCl_4$ / Sm (Ref. 15), and cerric ammonium nitrate mediated reaction of thiophenols and aromatic nitriles[16]. Some of these methods suffer from disadvantages such as long reaction times, limited availability of oxidant, toxicity of reagents and difficulties in product handling and isolation. However, there is still an interest in developing a clean, mild and efficient method to synthesize 2-substituted benzothiazoles.

Microwave-assisted reactions in solvent or solvent-free conditions have gained popularity because of rapid reaction rate, cleaner reactions and ease of manipulation[17]. Solvent-free organic synthesis using microwave irradiations (MW) and inorganic supports have attracted immense interest as environmentally benign methodologies[18]. Recently, some methods use MW heating for the synthesis of 2-substituted benzothiazoles such as condensation of ortho esters with 2-aminothiophenol using KFS clay[19], benzaloximes or aromatic aldehydes with 2-aminothiophenol using $Ca(OCl)_2$ / Al_2O_3 or MnO_2/SiO_2 (Ref. 20), reaction of aromatic and various short chain aliphatic carboxylic acids with 2-aminothiophenol[21], β-chlorocinnamaldehydes with 2-aminothiophenol using *p*-toluenesulfonic acid [22], and aromatic aldehydes with 2-aminothiophenol in an ionic liquid[23].

Eco-friendly microwave-assisted synthesis in general is likely to have a large impact on synthetic organic chemistry, compared to traditional processing of organic synthesis. Microwave enhanced chemistry saves significant time and very often improves yields. The present work is in continuation of the study on the derivatization of fatty acids[24-27] and keeping in view the synthetic practical applications of fatty acid derivatives, 2-alkyl and 2-alkenylbenzothiazoles from different types of fatty acids have been synthesized under MW irradiation. The synthesized compounds are a valuable addition to the lipid chemistry.

Results and Discussion

Considering that MW irradiations using commercial domestic ovens have been used to accelerate organic reactions, the high heating efficiency giving remarkable rate enhancement and dramatic reduction in reaction times and better yields, it appeared interesting to introduce benzothiazole moiety into fatty acids under microwave irradiation. The synthesis of 2-substituted benzothiazoles **3a-f** by condensation of 2-aminothiophenol **2** with various saturated and olefinic (internal and terminal) fatty

acids **1a-f** under MW and solvent free conditions in short time (**Scheme I**, path a) is now reported. The investigations showed that 2-aminothiophenol reacts equally well with different types of fatty acids. The yield of 2-substituted benzothiazoles was found to be moderate. In order to determine the optimum conditions for the synthesis of 2-alkyl and 2-alkenyl-benzothiazoles in faster and efficient ways, the effect of variation in the molar ratios of reagents and the irradiation time and power level of microwave set-up was investigated. After some experimentation, a set of conditions were found that generally provides 2-substituted benzothiazoles in moderate yields. The optimum conditions employed are that the molar ratio of fatty acids and 2-aminothiophenol is 1:1.2 and irradiation time and power level of microwave set up are 30 min and full power. Since the compounds were obtained in optimal yield, it was thought to carry out the reaction in presence of catalyst, with the aim to increase the yield. The reagent chosen was P_4S_{10} as it has been used for thionation and could be safely used under microwave irradiation[28]. Thus, when a mixture of fatty acids **1a-f** and 2-aminothiophenol **2** were irradiated with MW in presence of P_4S_{10}, it resulted in the formation of corresponding 2-substituted benzo-thiazoles **3a-f** (**Scheme I,** path b). The reaction proceeded efficiently and was completed within 3-4 min as compared to the reaction without catalyst. The use of P_4S_{10} as catalyst was found to be successful in terms of yield (**Table I**). The yield of both 2-alkyl and 2-alkenylbenzothiazoles did not depend on the length of fatty acid chain. The synthesized compounds were identified on the basis of IR, ^{1}H NMR and mass spectra. ^{1}H NMR spectra of 2-(heptadec-8-enyl)-benzothiazole **3d** showed characteristic signals of two sets of doublets at δ 7.96 and 7.83 and two sets of triplets at δ 7.44 and 7.34 for total four aromatic protons. A triplet for two hydrogens was observed at δ 3.11 for methylene protons alpha to thiazole moiety while a multiplet was observed at δ 1.88 for two hydrogens β to thiazole ring. The structure of **3d** was further supported by its mass spectral studies, which showed molecular ion peak at *m/z* 371 consistent with its molecular formula $C_{24}H_{37}NS$. Base peak appears at *m/z* 134. Detailed spectra of titled compounds are given in the experimental section.

Experimental Section

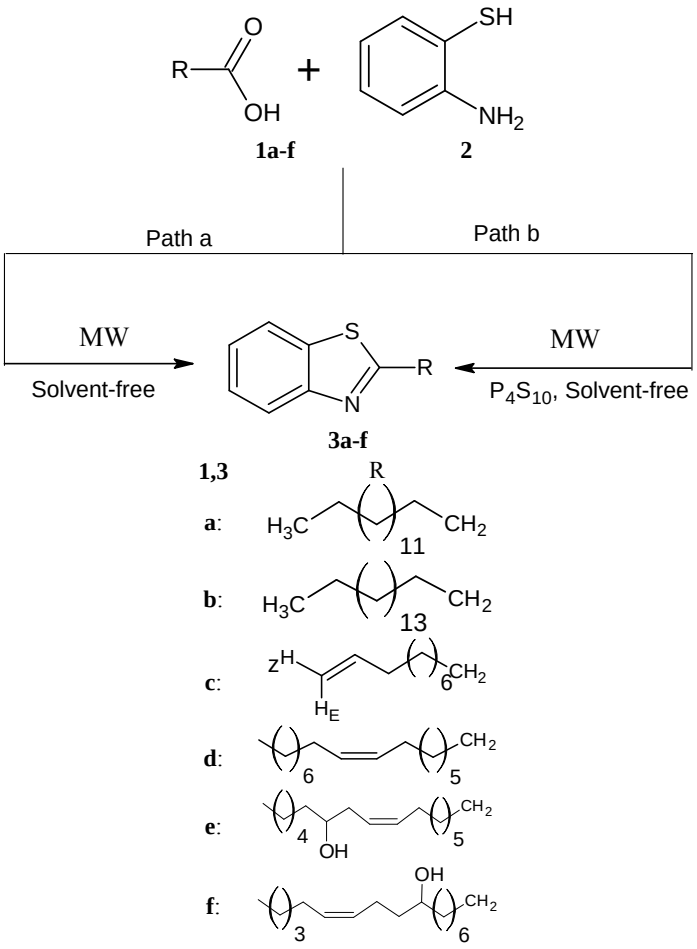
Undec-10-enoic and (*Z*)-octadec-9-enoic acids were obtained commercially from Fluka Chemicals (Switzerland). (9*Z*, 12*R*)-12-Hydroxyoctadec-9-enoic (ricinoleic) and (9*R*, 12*Z*)-9-hydroxyoctadec-12-enoic (isoricinoleic) acids were isolated from the natural sources *i.e.* from *Ricinus communis* and *Wrightia tinctoria* seed oils respectively following Gunstone's partition method[29]. 2-Aminothiophenol (99+%) was purchased from Sigma-Aldrich (Germany). Generally LR grade solvents were employed for extraction purpose and when required solvents were dried and distilled before use. Homogeneity of the product was observed on TLC. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-300 instrument. The chemical shifts were given in the δ scale, in ppm downfield from TMS. Coupling constants were expressed in Hz. Mass spectra were obtained on a Jeol SX-102 (FAB) spectrometer. IR spectra were obtained on Shimadzu 8201 PC FT-IR using KBr pellets. The MW irradiations were carried out using an unmodified domestic oven (LG, Model MC-808WAR, 1.35 KW, 2450MHz).

General procedure for the preparation of 2-substituted benzothiazoles in microwave-assisted, solvent-free conditions

A mixture of fatty acid (2.5 mmoles) and 2-aminothiophenol (3 mmoles) was placed in a beaker and subjected to MW irradiation using a domestic microwave oven and irradiated (multimode, full power) for appropriate time (**Table I**). After cooling, the product was extracted with diethyl ether (2×30 mL).The combined organic layer were washed with saturated solution of $NaHCO_3$ (2×10 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure to give the crude product. The product was purified by column chromatography over silica gel (hexane:diethyl ether, 4:1, v/v).

General procedure for the preparation of 2-substituted benzothiazoles in presence of P_4S_{10} under microwave, solvent-free conditions

A mixture of fatty acid (2.5 mmoles), 2-aminothiophenol (3 mmoles) and P_4S_{10} (1 mmole) was placed in a beaker and subjected to MW irradiation using a domestic microwave oven and irradiated (multimode, full power) for appropriate time (**Table I**). After cooling, the product was extracted with Et_2O (2×30 mL).The combined organic layer were washed with saturated solution of $NaHCO_3$ (2×10 mL), dried over anhyd. Na_2SO_4 and evaporated under reduced pressure to leave the crude product.



Scheme I — Synthesis of 2-substituted benzothiazoles with and without catalyst under solvent-free microwave irradiation

Table I — Reaction conditions and yield of 2-substituted benzothiazoles

Compd	Microwave Equipment	Power (%)		Time taken (min)		Yield (%)	
		Without catalyst	With P_4S_{10}	Without catalyst	With P_4S_{10}	Without catalyst	With P_4S_{10}
3a	Multimode	100	60	28	3	65	82
3b	Multimode	100	60	28	3	63	82
3c	Multimode	100	60	30	4	61	85
3d	Multimode	100	60	30	4	62	83
3e	Multimode	100	60	30	4	60	81
3f	Multimode	100	60	30	4	60	80

The product was purified by column chromatography over silica gel (hexane: diethyl ether, 4:1, v/v).

2-(Pentadecyl)-benzothiazole, 3a: Light yellow oily liquid. IR (KBr): 2928, 2857, 1588, 1459, 728, 672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (1H, d, *J* = 8.1 Hz, Ar-*H*), 7.84 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.45 (1H, t, *J* = 8.1 Hz, Ar-*H*), 7.34 (1H, t, *J* = 8.0 Hz, Ar-*H*), 3.11 (2H, t, *J* = 7.6 Hz, CH_2 α to thiazole ring), 1.88 (2H, m, -CH_2 β to thiazole ring), 1.29 (24H, brs, chain CH_2), 0.88 (3H, dist.t, CH_3); MS: *m/z* (%) 345 (M^+, 11.5), 162 (8.6), 148 (12.5), 134 (100). Anal. Found C, 76.54; H, 10.19; N, 4.01; S, 9.26. $C_{22}H_{35}NS$ requires C, 76.52; H, 10.14; N, 4.06; S, 9.28%.

2-(Heptadecyl)-benzothiazole, 3b: Pale yellow oily liquid. IR (KBr): 2928, 2857, 1588, 1459, 728, 672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (1H, d, *J* = 8.1 Hz, Ar-*H*), 7.84 (1H, d, *J* = 7.8 Hz, Ar-*H*), 7.45 (1H, t, *J* = 8.1 Hz, Ar-*H*), 7.34 (1H, t, *J* = 8.0 Hz, Ar-*H*),

3.11(2H, t, J = 7.6 Hz, CH_2 α to thiazole ring), 1.96 (2H, m, -CH_2 β to thiazole ring), 1.38 (28H, br.s, chain CH_2), 0.88 (3H, dist.t, CH_3); MS: *m/z* (%) 373 (M^+, 11.2), 162 (9.2), 148 (12.6), 134 (100). Anal. Found C, 77.18; H, 10.49; N, 3.70; S, 8.63. $C_{24}H_{39}NS$ requires C, 77.21; H, 10.46; N, 3.75; S, 8.58%.

2-(Dec-9-enyl)-benzothiazole, 3c: Colourless oily liquid. IR (KBr): 2927, 2855, 1592, 1439, 728, 672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (1H, d, J = 8.0 Hz, Ar-*H*), 7.84 (1H, d, J = 7.6 Hz, Ar-*H*), 7.44 (1H, t, J = 8.4 Hz, Ar-*H*), 7.34 (1H, t, J = 8.0 Hz, Ar-*H*), 5.82 (1H, tdd, $J_{H-^8CH_2}$ = 6.6 Hz, J_{H-H_Z} = 10.2 Hz, J_{H-H_E} = 17.1 Hz, CH_2=C*H*-), 5.02 (1H, dd, J_{H_Z-H} = 10.2 Hz, $J_{H_Z-H_E}$ = 3.6 Hz, H_ZC=CH-), 4.90 (1H, dd, J_{H_E-H} = 17.1 Hz, $J_{H_E-H_Z}$ = 3.6 Hz, H_EC=CH-), 3.11 (2H, t, J = 7.6 Hz, CH_2 α to thiazole ring), 2.03(2H, m, -CH_2-CH=CH_2), 1.88 (2H, m, -CH_2 β to thiazole ring), 1.33 (10H, br.s, chain CH_2); MS: *m/z* (%) 273 (M^+, 10.8), 246 (23.6), 162 (12.5), 148 (12.8), 139 (10.1), 134 (100). Anal. Found C, 74.62; H, 8.38; N, 5.20; S, 11.80. $C_{17}H_{23}NS$ requires C, 74.73; H, 8.42; N, 5.13; S, 11.72%.

2-(Heptadec-8-enyl)-benzothiazole, 3d: Light yellow oily liquid. IR (KBr): 2927, 2856, 1592, 1458, 728, 674 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (1H, d, J = 8.4 Hz, Ar-*H*), 7.83 (1H, d, J = 7.6 Hz, Ar-*H*), 7.40 (1H, t, J = 8.4 Hz, Ar-*H*), 7.31 (1H, t, J = 8.4 Hz, Ar-*H*), 5.34 (2H, m, -C*H*=C*H*-), 3.11 (2H, t, J = 7.6 Hz, -CH_2 α to thiazole ring), 2.01 (4H, m, -CH_2-CH=CH-CH_2-), 1.88 (2H, m, -CH_2 β to thiazole ring), 1.29 (20H, br.s, chain CH_2), 0.88 (3H, dist.t, CH_3); MS: *m/z* (%) 371 (M^+, 6.9), 258 (10.8), 162 (12.5), 148 (13.5), 134 (100). Anal. Found: C, 77.57; H, 10.01; N, 3.71; S, 8.71. $C_{24}H_{37}NS$ requires C, 77.63; H, 9.97; N, 3.77; S, 8.63%.

2-[(8*Z*,11*R*)-11-Hydroxyheptadec-8-enyl]-benzothiazole, 3e: Light brown viscous liquid. IR (KBr) : 2928, 2857, 1588, 1459, 728, 672 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96(1H, d, J = 8.0 Hz, Ar-*H*), 7.84 (1H, d, J = 8.0 Hz, Ar-*H*), 7.44 (1H, t, J = 7.2 Hz, Ar-*H*), 7.34 (1H, t, J = 7.2 Hz, Ar-*H*), 5.46 (2H, m, -C*H*=C*H*-), 3.88 (1H, m, -C*H*-OH), 3.11 (2H, t, J = 7.6Hz, -CH_2 α to thiazole ring), 2.42 (1H, m, -CH-O*H*), 2.01 (4H, m, -CH_2-CH=CH-CH_2-), 1.88 (2H, m, -CH_2 β to thiazole ring), 1.29 (18H, br.s, chain CH_2), 0.88 (3H, dist.t, CH_3); MS: *m/z* (%) 387 (M^+, 10.8), 302 (16.8), 162 (12.5), 148 (13.2), 134 (100). Anal. Found: C, 74.34; H, 9.50; N, 3.65; S, 8.32. $C_{24}H_{37}ONS$ requires C, 74.42; H, 9.56; N, 3.61; S, 8.27%.

2-[(8*R*,11*Z*)-8-Hydroxyheptadec-11-enyl]-benzothiazole, 3f: Brown coloured viscous liquid. IR (KBr): 2929, 2857, 1586, 1522, 1458, 728, 674 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (1H, d, J = 8.4 Hz, Ar-*H*), 7.84 (1H, d, J = 8.4 Hz, Ar-*H*), 7.44 (1H, t, J = 7.2 Hz, Ar-*H*), 7.34 (1H, t, J = 7.2 Hz, Ar-*H*), 5.34 (2H, m, -C*H*=C*H*-), 2.29 (1H, m, -CH-O*H*), 4.08 (1H, m, -C*H*-OH), 3.11 (2H, t, J = 7.2 Hz -CH_2 α to thiazole ring), 2.03 (4H, m, -CH_2-CH=CH-CH_2-), 1.88 (2H, m, -CH_2 β to thiazole ring), 1.44 (18H, br.s, chain CH_2), 0.98 (3H, dist.t, CH_3); MS: *m/z* (%) 387 (M^+, 9.2), 262 (14.5), 162 (12.4), 148 (11.8), 134 (100). Anal. Found: C, 74.38; H, 9.47; N, 3.66; S, 8.30. $C_{24}H_{37}ONS$ requires C, 74.42; H, 9.56; N, 3.61; S, 8.27%.

Conclusion

Herein has been presented clean and rapid synthesis of 2-substituted benzothiazoles from saturated and olefinic (internal and terminal) fatty acids and 2-aminothiophenol without solvent under MW. The use of P_4S_{10} in catalytic amount has provided the product in good yield.

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