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SYNTHESIS OF ETHENYLBENZOTHIAZOLE DERIVATIVES

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Abstract: Ethenylbenzothiazoles were synthesized by the Horner-Emmons reaction of benzothiazolylmethylphosphonate with aldehydes under phase transfer catalytic conditions in 60-71% yields. Not only aromatic but also aliphatic aldehydes gave the desired products under these mild conditions in 66-71% yields.

It has been reported that the Horner-Emmons reaction of 2-benzothiazolylmethylphosphonate with aldehydes gave *trans*-2-ethenylbenzothizole derivatives,[1,2,3] which were also obtained by the aldol condensation of 2-methylbenzothiazole with aldehydes.[4,5] However, the conditions for the aromatic and conjugated aliphatic aldehydes requires harsh acidic conditions (at 150°C for a few hours in acetic anhydride) and the yields obtained for the ethenyl derivatives were less than 42%.[4] On the contrary, the basic aldol condensation has been reported to give improved yields.[5] Under these circumstances, we have examined the Horner-Emmons reaction of some aldehydes because the aldehydes employed

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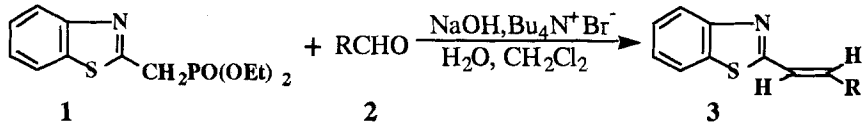
previously were restricted to aromatic,[5] conjugated aliphatic aldehydes[1,2,3] 4-dimethylaminobenzaldehyde[1] and 4-dimethylaminocinnamaldehyde.[1]

We wish to present here a simple and general procedure for the synthesis of ethenylbenzothiazoles by means of the Horner-Emmons reaction in the presence of a phase transfer catalyst without any anhydrous basic conditions (NaH in DME,[1] $NaNH_2$ in THF,[2] and DBU and LiCl in CH_2Cl_2[3]). The reaction sequence is shown in the **Scheme 1**.

An aqueous sodium hydroxide solution (50%) was added to a mixture of the phosphonate[6] (**1**) and the aldehyde (**2**) in the presence of a catalytic amount of tetrabutylammonium bromide. The mixture was vigorously stirred at room temperature for one hour (the phosphonate completely consumed, which was monitored by TLC). The products (**3**) were obtained by column chromatography on silica gel in 60-71% yields. The results are summarized in the **Table 1**.

The reaction proceeded smoothly under quite mild conditions (room temperature within one hour) without self-condensation of non-conjugated aliphatic aldehydes, and anhydrous conditions are not necessary. Furthermore, the phosphonate was easily obtained from commercially available 2-methylbenzothiazole in two steps; the chlorination of the methyl group by trichloroisocyanuric acid[7] and the Michaelis-Arbuzov reaction of obtained 2-chloromethylbenzothiazole.

A broad range of the aldehydes can be used such as aliphatic, aromatic and heterocyclic ones. Thus, the reaction could have a wide scope potentiality for the synthesis of ethenylbenzothiazole derivatives, which could be a useful precursor for many drugs.



1 2 3

Scheme 1

Table 1. Phase transfer catalytic Horner-Emmons reaction of diethoxylphosphorylmethylbenzothiazole with aldehydes

Compound	R	mp (°C)	Yield (%)
3a[a)]	ethyl	---	69
3b[b)]	propyl	31-32	61
3c[c,f,h)]	1E-propenyl	70-71	60
3d[d,g,i)]	phenyl	108-110	68
3e[d,g,j)]	3-pyridyl	109-111	71
3f[e,g,k)]	2-phenyl-E-ethenyl	116-117	66

b) colorless oil. b) colorless plates. c) pale yellow plates.

d) colorless needles. e) pale yellow needles.

f) recrystallized from hexane. g) recrystallized from hexane-diethyl ether.

h) Lit.[1] mp 72-73°C. i) Lit.[4] mp 112°C. j) Lit.[4] mp 113°C. k) Lit.[4] mp 120°C.

Experimental

All melting points are uncorrected. Proton magnetic resonance (^{1}H-NMR) spectra were recorded at 200 MHz on a Varian Gemini-200 spectrometer. Chemical shifts are quoted in δ value (ppm) with tetramethylsilane as the internal standard, and coupling constants (J) are given in Hz. The mass (MS) spectrum was recorded on a Hitachi M-80B spectrometer.

Chlorination of 2-Methylbenzothiazole[6]: Powdered trichloroisocyanuric acid (2.70 g, 16 mmol) was added to a solution of 2-methylbenzothiazole (5.22 g, 35 mmol) in dichloromethane, and the mixture was heated under reflux for 5 hours. After cooling to room temperature, the precipitated solid was removed by suction and washed with dichloromethane. The filtrate and the washing were evaporated and the residue was subjected to a silica gel column chromatography. Elution with hexane-dichloromethane (1:1; v/v) gave firstly 2-dichloromethylbenzothiazole (0.40 g, 5%) as colorless prisms, mp 70-72°C (Lit.[8] mp 72-73°C) and secondary 2-chloromethylbenzothiazole (3.26 g, 51%) as colorless prisms, mp 35-36°C (Lit.[9] mp 34°C).

2-Diethoxyphosphorylmethylbenzothiazole[6] (**1**): A mixture of 2-chloromethylbenzothiazole (0.94 g, 5.14 mmol) and triethylphosphite (1.0 ml) was heated at 150 °C for 2 hours. The volatiles were removed under reduced pressure using a vacuum pump. The residue was subjected to a silica gel column chromatography. Elution with dichloromethane-methanol (98:2; v/v) gave the product as pale yellow oil (1.30 g, 89%).

General Procedure for the Horner-Emmons Reaction of Benzothiazolylmethylphosphonate (**1**) with Aldehydes: The aldehyde (**2**, 0.25 mmol), 2-diethoxyphosphorylmethylbenzothiazole (**1**, 0.20 mmol) and tetrabutylammonium

bromide (0.025 mmol) were dissolved in dichloromethane (1.0 ml). An aqueous sodium hydroxide solution (50%, 0.3 ml) was added thereto, and the mixture was vigorously stirred at room temperature for 1 hour. The mixture was diluted with dichloromethane (20 ml). The dichloromethane solution was washed with water, dried over magnesium sulfate and evaporated. The residue was subjected to silica gel column chromatography. Elution with dichloromethane gave **3a-3f**.

2-(1E-Butenyl)benzothiazole (**3a**)[10]

Yield: 26 mg (69%). ^{1}H-NMR ($CDCl_3$): 7.94 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.5-7.3 (m, 2H), 6.9-6.7 (m, 2H), 2.5-2.3 (m, 2H), 1.16 (t, J = 7.3 Hz, 3H).

2-(1E-Pentenyl)benzothiazole (**3b**)

Yield: 24 mg (61%). ^{1}H-NMR ($CDCl_3$): 7.95 (d, J = 7.8 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.5-7.3 (m, 2H), 6.9-6.7 (m, 2H), 2.4-2.2 (m, 2H), 1.7-1.4 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H). MS m/z: 203.0755 (Calcd for $C_{12}H_{13}NS$: 203.0769).

2-(1E,3E-Pentadienyl)benzothiazole (**3c**)[1]

Yield: 24 mg (60%). ^{1}H-NMR ($CDCl_3$): 7.94 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.5-7.3 (m, 2H), 7.13 (dd, J = 10.4 and 15.7 Hz, 1H), 6.73 (d, J = 15.7 Hz, 1H), 6.9-6.7 (m, 1H), 6.7-6.5 (m, 1H), 1.88 (d, J = 6.6 Hz, 3H).

2-(2-Phenyl-E-ethenyl)benzothiazole (**3d**)[4]

Yield: 32 mg (68%). ^{1}H-NMR ($CDCl_3$): 8.01 (d, J = 7.7 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.7-7.3 (m, 9H).

2-[2-(3-Pyridyl-E-ethenyl)]benzothiazole (**3e**)[4]

Yield: 34 mg (71%). ^{1}H-NMR ($CDCl_3$): 8.81 (d, J = 3.1 Hz, 1H), 8.59 (dd, J = 1.6 and 4.8 Hz, 1H), 8.03 (d, J = 8.1 Hz, 1H), 8.0-7.9 (m, 2H), 7.6-7.3 (m, 5H).

2-(4-Phenyl-1E,3E-butadienyl)benzothiazole (**3f**)[4]

Yield: 35 mg (66%). ^{1}H-NMR ($CDCl_3$): 7.98 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.6-7.3 (m, 7H), 7.1-6.8 (m, 4H).

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