Organic Phosphorus Compounds. Part 3 [1]. Synthesis of 5-Fluorosubstituted Benzothiazolylbenzylphosphonates

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The regio specific synthesis of 5-fluorobenzothiazoles **14** has been accomplished by using difluorothiobenzanilides **13** as a key intermediate. Through this method, 5-fluorosubstituted fostedil **3** and its derivatives were synthesized and evaluated coronary vasodilator activity.

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Introduction of fluorine into organic molecules is becoming more important every day, especially in the field of biologically active compounds. The van der Waals radius of fluorine closely resembles hydrogen, so fluorine is a sterically less requiring substituent. The high carbon-fluorine bond energy renders the substituent relatively resistant to metabolic transformation. Because of these properties, fluorine has been extensively utilized in medicinal chemistry to influence the metabolism, bioactivity, and physical properties of pharmaceuticals [2].

Fostedil is a new calcium antagonist we have discovered [3,4]. Its structure is totally different from that of conventional calcium antagonists. Clinical studies of fostedil had already disclosed that a major metabolite of fostedil found in urine is the compound **2** (formed by hydroxylation of the 5-position of the benzothiazole ring of fostedil) [5]. We were interested in how the activity of fostedil would change after the introduction of fluorine into this compound. We expected that the duration of action of fostedil would be extended if a fluorine atom were placed into the 5-position of benzothiazole ring, thus suppressing its metabolism. Therefore, we synthesized the compounds **3** and assessed its coronary vasodilator action and the duration of this action.

There are many methods for synthesis of benzothiazole derivatives. The most frequently used method is that of Jacobson [6], which involves oxidation of thiobenzanilide **4** by potassium hexacyanoferrate to yield 2-phenylbenzothiazole **5** (Scheme I). When 5-fluorobenzothiazole **8** is synthesized by this method, 7-fluorobenzothiazole **7** is formed as a by-product. Roe *et al.* reported [7] a regiospecific method for synthesis of 5-fluorobenzothiazole. With this method, thiobenz-2-bromo-5-fluoroanilide **9** is transformed into a benzyne intermediate using potassium amide in liquid ammonia, and then the ring is closed regioselectively. However, since liquid ammonia and potassium are difficult to handle, it is not easy to synthesize with this method a sufficiently large amount of a compound to assess its pharmacological profile. Furthermore, since the starting material 2-bromo-5-fluoroaniline for this method is not commercially available, those who want to use this method have to synthesize it themselves.

We have recently developed a regiospecific method to introduce fluorine into the 5-position of the benzothiazole ring. Using this method, we have introduced a fluorine atom into fostedil **1** and assessed the coronary vasodilator effect of this compound. Scheme II shows the new procedure of 5-fluorobenzothiazole synthesis we recently

Scheme I

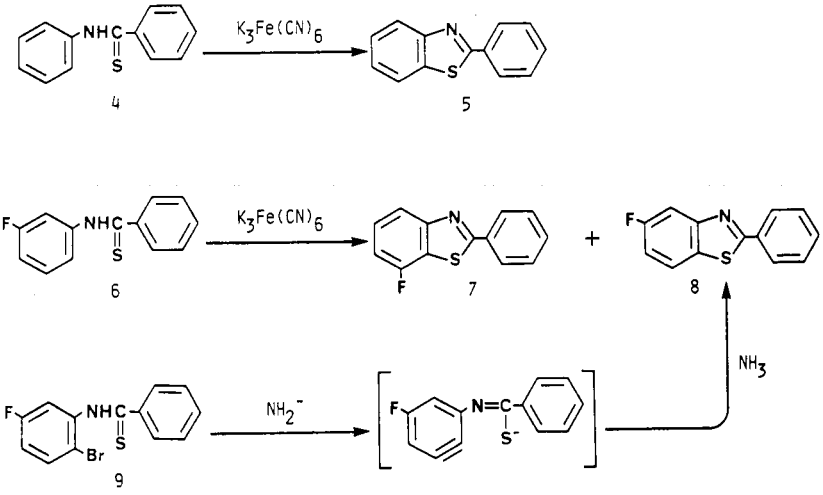
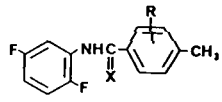


Table 1

Benzanilides and Thiobenzanilides



Compound	X	R	Mp (°C)	Recrystallization Solvent	Yield (%)
12a	O	H	109.5-110.0	cyclohexane	88
12b	O	2-F	144.0-145.0	cyclohexane	63
12c	O	3-F	132.0-133.0	cyclohexane	86
12d	O	2-NO_2	156.0-157.0	benzene	80
12e	O	3-NO_2	126.5-127.5	cyclohexane-ethyl acetate	91
13a	S	H	120.0-121.0	cyclohexane	78
13b	S	2-F	152.0-153.0	cyclohexane	quant
13c	S	3-F	135.0-138.0	cyclohexane-ethyl acetate	78
13d	S	2-NO_2	161.0-162.0	cyclohexane-ethyl acetate	57
13e	S	3-NO_2	152.0-153.0	cyclohexane-ethyl acetate	66

Table 2

Cyclization of Thioamide **13a** with Base

Entry	Base	Solvent	Reaction Temp (°C)	Reaction Time (hours)	Yield (%)
1	NaOMe (1 eq)	MeOH	reflux	1.5	no reaction
2	NaOMe (1 eq)	NMP [a]	140	1.5	- [b]
3	*t*-BuOK (1 eq)	NMP	140	1.5	trace
4	*t*-BuOK (1 eq)	DMF [c]	140	1.5	88
5	*t*-BuOK (1 eq)	HMPA [d]	140	0.5	88

[a] *N*-Methylpyrrolidone. [b] Fluorine atom was substituted with methoxy group. [c] *N,N*-Dimethylformamide. [d] Hexamethylphospholictriamide.

Table 3

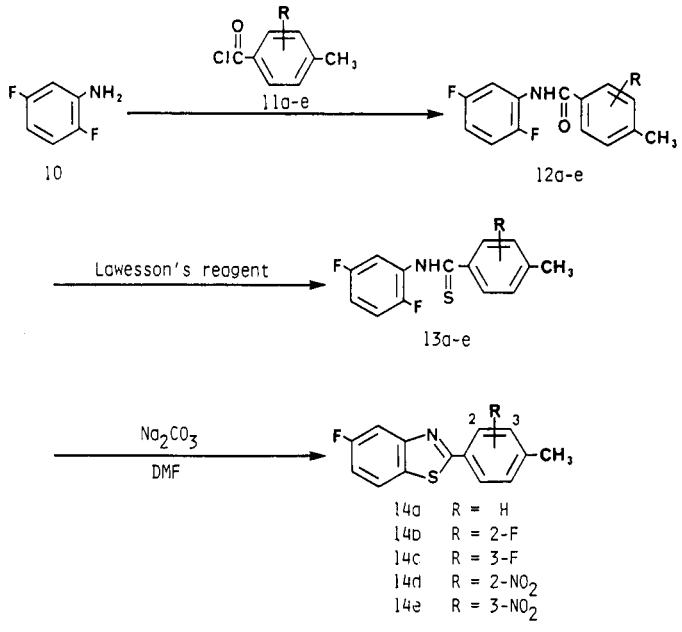
Cyclization of Thioamide **13e** with Base

Entry	Base	Solvent	Reaction Temp (°C)	Reaction Time (hours)	Yield (%)
1	*t*-BuOK (1 eq)	DMF	140	1.5	38
2	NaH (1.5 eq)	DMF	140	1.5	18
3	Na_2CO_3 (1 eq)	DMF	140	1.5	94
4	Na_2CO_3 (2 eq)	DMF	140	1.5	72
5	Na_2CO_3 (2 eq)	HMPA	140	0.5	- [a]

[a] Complex mixture.

studied. The starting material is 2,5-difluoroaniline **10**, which is commercially available. This was transformed into benzanilide **12** by the routine method, and then into thiobenzanilide **13** using Lawesson's reagents. Table 1 shows benzanilides and thiobenzanilides obtained by this method. Intramolecular nucleophilic substitution of the fluorine with sulfur of thiobenzanilide **13** was studied. First, compound **13a** was dissolved in methanol and refluxed in the presence of sodium methoxide. However, no reaction occurred. When the same procedure was carried out in *N*-methylpyrrolidone instead of methanol and at the temperature of 150°, the fluorine was replaced with methoxy anion. When ring closure was attempted using potassium *t*-butoxide as a base, thiazole **14a** was obtained although the yield was low. The same procedure was repeated in various solvents, to find that the use of HMPA or DMF as a solvent leads to a high yield of ring closure (Table 2). Ring closure of the nitro-substituted derivative **13e** failed under the same conditions, because of a decomposition reaction. The ring closure of **13e** in DMF was further examined with various base. Results are shown in Table 3. The best result was obtained when one equivalent

Scheme II



of sodium carbonate is used as a base. In compounds **13a** through **13e**, ring closure occurred with a high yield under these conditions as shown in Table 3. This method, involving treatment of the thiobenz-2-fluoroanilide with sodium carbonate in DMF, proved to be an effective technique for the synthesis of benzothiazole. The thus obtained compound **14a-e** were brominated with NBS and then condensed with triethyl phosphite to yield the compounds **3a-e** as shown in Scheme III and Table 3.

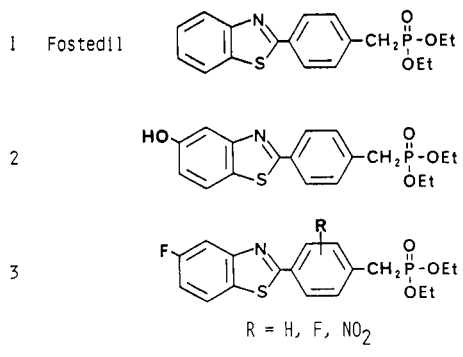


Figure I

The compounds **3a-3e** were intravenously injected into dogs (0.3 mg/kg) to assess their coronary vasodilator action. The coronary vasodilator activity of **3a, 3c, 3d** and **3e** were comparable or slightly more effective than that of fostedil. The compound **3a** was given to dogs (30 mg/kg) orally, then blood was sampled several times to determine the level of the compound in the blood. The time course of the blood level of the compound **3a** was quite similar to that of fostedil; that is, the duration of action was not improved by introduction of a fluorine atom into fostedil.

EXPERIMENTAL

Melting points were taken on a capillary melting point apparatus (Yamato MR-21) and were uncorrected. The structures of all compounds were supported by their ir (Shimazu IR-440) and

Scheme III

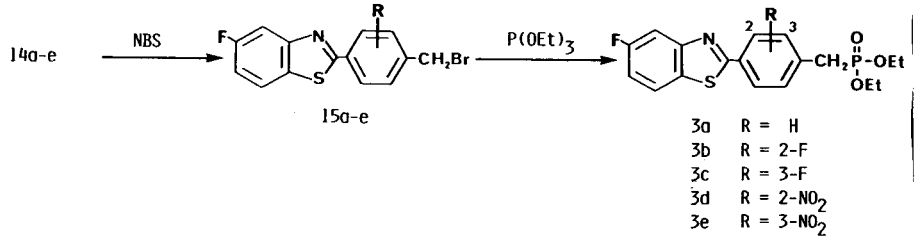
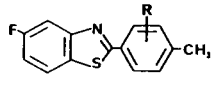


Table 4

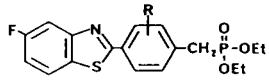
5-Fluoro-2-substituted Phenyl Benzothiazoles



Compound	R	Method	Mp (°C)	Recrystallization Solvent	Yield (%)
14a	H	A	120.0-122.0	cyclohexane	88
14b	2-F	A	153.0-154.5	*n*-hexane	77
14c	3-F	A	127.0-129.0	cyclohexane	95
14d	2-NO_2	B	159.0-161.0	cyclohexane	63
14e	3-NO_2	B	190.0-191.5	cyclohexane-ethyl acetate	98

Table 5

5-Fluorobenzothiazolylbenzylphosphonates



Compound	R	Mp (°C)	Recrystallization Solvent	Yield (%)
3a	H	130.5-131.5	*n*-hexane	79
3b	2-F	127.0-128.0	*n*-hexane	44
3c	3-F	100.0-101.0	cyclohexane	37
3d	2-NO_2	131.0-132.0	cyclohexane	35
3e	3-NO_2	126.0-126.5	cyclohexane-ethyl acetate	33

60 and 100 MHz ^1H nmr (Hitachi R-24A and Nihon Denshi PS-100) spectra. All compounds were analyzed for C, H and N and the results were within 0.4% of the calculated theoretical values. No attempt was made to maximize the yields.

2',5'-Difluoro-4-methylbenzanilide (**12a**).

A mixture of 26.4 g (0.194 mole) of *p*-toluic acid, 90.1 g (0.757 mole) of thionyl chloride, a catalytic amount of *N,N*-dimethylformamide was refluxed for 3 hours and evaporated *in vacuo*. The residue was dissolved in 30 ml of tetrahydrofuran and added dropwise to a solution of 25.0 g (0.194 mole) of 2,5-difluoroaniline in 160 ml of pyridine at 5-10°. The mixture was stirred at room temperature for 2 hours and poured into 1.3 l of water. The precipitate was collected by filtration, washed with water, dried, and recrystallized from cyclohexane to give 42.1 g (88%) of **12a** as colorless leaflets, mp 109.5-110.0°; pmr (deuteriochloroform): 100 MHz, 2.45 (s, 3H, CH_3), 6.6-7.2 (m, 2H, aromatic H), 7.28 (d, 2H, aromatic H), 7.75 (d, 2H, aromatic H), 7.9-8.2 (bs, 1H, NHCO), 8.2-8.4 (m, 1H, aromatic H).

Anal. Calcd. for $C_{14}H_{11}F_2NO$: C, 68.01; H, 4.48; N, 5.67. Found: C, 67.78; H, 4.57; N, 5.75.

2',5'-Difluoro-(4-methyl)thiobenzanilide (**13a**).

A mixture of 36.7 g (0.148 mole) of **12a** and 35.9 g (88.8 mmoles) of Lawesson's Reagent in 175 ml of toluene was refluxed for 2 hours. The reaction mixture was concentrated to about one half of its initial volume and cooled in an ice bath. The precipitate was collected by filtration and washed with a small amount of benzene to give 30.5 g (78%) of **13a**. The product was recrystallized from cyclohexane to give yellow needles, mp 120.0-121.0°; pmr (deuteriochloroform): 100 MHz, 2.43 (s, 3H, CH_3), 6.8-7.4 (m, 4H, aromatic H), 7.75 (d, 2H, aromatic H), 8.6-8.9 (m, 1H, aromatic H), 8.9-9.2 (m, 1H, NHCS).

Anal. Calcd. for $C_{14}H_{11}F_2NS$: C, 63.86; H, 4.21; N, 5.32. Found: C, 63.66; H, 4.35; N, 5.50.

5-Fluoro-2-(4-methylphenyl)benzothiazole (**14a**).

[Method A].

A solution of 2',5'-difluoro-(4-methyl)thiobenzanilide (**13a**) (18.9 g, 71.8 mmoles) in 40 ml of *N,N*-dimethylformamide was added dropwise with stirring to a suspension of potassium *t*-butoxide (8.1 g, 71.8 mmoles) in 50 ml of *N,N*-dimethylformamide at 0°. The resulting mixture was heated and stirred at 140-150° for 3.5 hours. After cooling to room temperature, the reaction mixture was poured into 1 l of water. The precipitate was collected by filtration, washed with water, and dried to give 17.1 g (98%) of 5-fluoro-2-(4-methylphenyl)benzothiazole (**14a**). The product was recrystallized from *n*-hexane to give colorless prisms, mp 120.0-122.0°; pmr (deuteriochloroform): 100 MHz, 2.42 (s, 3H, CH_3), 7.0-7.4 (m, 3H, aromatic H), 7.6-8.0 (m, 4H, aromatic H).

Anal. Calcd. for $C_{14}H_{10}FNS$: C, 69.11; H, 4.14; N, 5.76. Found: C, 69.31; H, 3.89; N, 5.75.

Diethyl 4-(5-Fluorobenzothiazol-2-yl)benzylphosphonate (**3a**).

A mixture of 27.1 g (0.111 mole) of **14a**, 19.8 g (0.111 mole) of *N*-bromosuccinimide, and a catalytic amount of 2,2'-azobisisobutyronitrile in 420 ml of carbon tetrachloride was refluxed for 2 hours. The hot reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting slurry was filtered to give 27.4 g of the crude solids of 2-(4-bromomethylphenyl)-5-fluorobenzothiazole (**15a**). The crude **15a** was purified by column chromatography (silicagel, cyclohexane-ethyl acetate (20:1) as eluant) and recrystallized from cyclohexane-ethyl acetate to give colorless crystals, mp 139.0-141.0°. A mixture of 27.4 g of crude **14a** and 38.1 g (0.230 mole) of triethyl phosphite was stirred at 140-150° for 0.5 hours. After cooling to 60-70°, the reaction mixture was poured into 250 ml of *n*-hexane. The resulting mixture was allowed to cool to room temperature. The precipitate was collected by filtration, washed with cyclohexane, and purified *via* column chromatography using silicagel and eluting with ethyl acetate to give colorless powder. Recrystallization from *n*-hexane gave 25.4 g (60%) of **3a** as colorless needles, mp 130.0-132.0°; pmr (deuteriochloroform): 60 MHz, 1.25 (t, 6H, CH_3), 3.19 (d, 2H, CH_2P), 3.7-4.3 (m, 4H, OCH_2), 6.9-8.2 (m, 7H, aromatic H).

Anal. Calcd. for $C_{18}H_{19}FNO_3PS$: C, 56.99; H, 5.05; N, 3.69. Found: C, 57.22; H, 4.88; N, 3.68.

5-Fluoro-2-(4-methyl-3-nitrophenyl)benzothiazole (**14e**).

[Method B]

A mixture of 12.3 g (39.9 mmoles) of 2',5'-difluoro-4-methyl-3-nitrothiobenzanilide (**13e**) and 2.1 g (20.0 mmoles) of sodium carbonate in 65 ml of DMF was stirred at 140-150° for 1.5 hours. After cooling to room temperature, the reaction mixture was poured into 500 ml of water. The precipitate was collected by filtration, washed with water, and dried to give 11.3 g (98%) of **14e**. The product was recrystallized from ethyl acetate-cyclohexane to give colorless needles, mp 190.0-191.5°; pmr (deuteriochloroform): 300 MHz, 2.67 (s, 1H, CH_3), 7.20 (td, 1H, aromatic H), 7.47 (d, 1H, aromatic H), 7.74 (dd, 1H, aromatic H), 7.83 (dd, 1H, aromatic H), 8.17 (dd, 1H, aromatic H), 8.63 (d, 1H, aromatic H).

Anal. Calcd. for $C_{14}H_9FN_2O_2S$: C, 58.33; H, 3.15; N, 9.72. Found: C, 58.41; H, 3.19; N, 9.77.

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