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Versatile 2-Fluoroacrylic Building Blocks for the Synthesis of Fluorinated Heterocyclic Compounds

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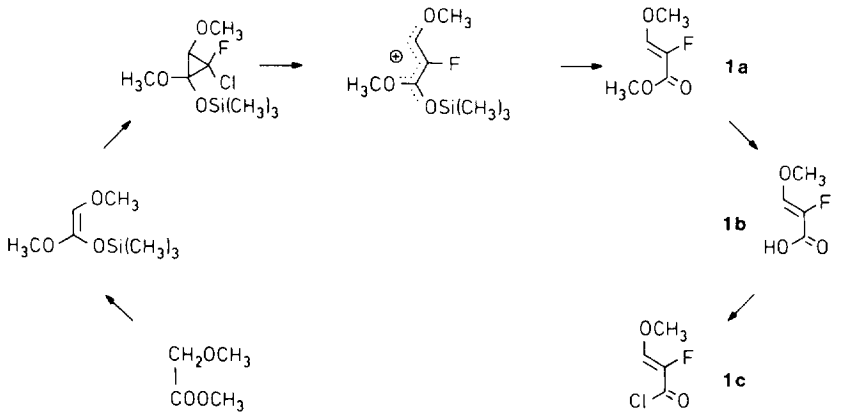
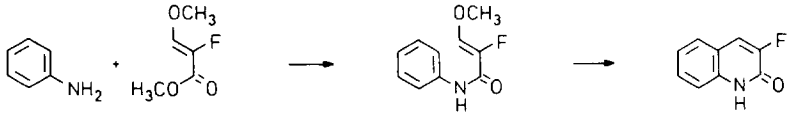
Abstract : The methyl ester of 2-fluoro-3-methoxyacrylic acid and the corresponding acyl chloride can be used for the efficacious synthesis of fluorine bearing pyrazolones, pyrimidines, coumarines and benzothiopyranones. Depending on the C_3F component and the conditions employed, the same cyclization partner (e.g., 2-aminothiophenol) may lead to two or even three different products.

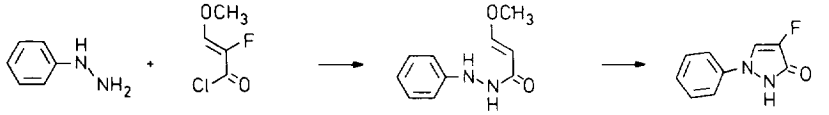
The cycloaddition between chlorofluorocarbenes and enethers provides halocyclopropanes which can be submitted to hydrolytic ring opening. [1] The 2-fluoroenals, -enones and -enesters thus obtained may serve as building blocks for the synthesis of fluorinated heterocycles [2 - 6]. In this respect, methyl 2-fluoro-3-methoxyacrylate (**1a**) [5] proved to be a particular versatile intermediate. It is readily prepared using the methyl methoxyacetate derived 1,2-dimethoxy-1-trimethylsilyloxyethene as the precursor. Initially formed as a 1 : 1 mixture of stereoisomers, it can be readily converted into the pure (*Z*) component under thiolate catalysis. The ester **1a** can be saponified and the resulting 2-fluoro-3-methoxyacrylic acid **1b** converted with thionyl chloride into the acyl chloride **1c**.



One application of methyl 2-fluoro-3-methoxyacrylate (**1a**) has already been described : its base promoted condensation with aniline followed by cyclization under strongly acidic conditions afforded 3-fluoro-2-quinolone [5]. We wish now to report further syntheses of fluorine bearing heterocycles involving the ester **1a**, the acid **1b** or the acyl chloride **1c**.

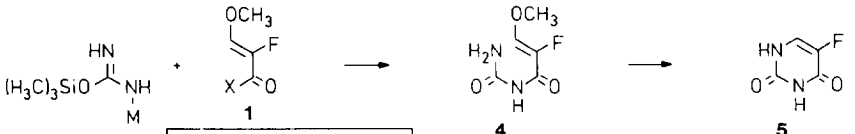


The acylation of phenylhydrazine with the chloride **1c** proceeded smoothly. Concentrated sulfuric acid was required to accomplish the ring closure of the intermediate **2** (78%). 1*H*-4-Fluoro-2-phenylpyrazol-5-one (**3**) was isolated with an over-all yield of 72%.



1c **2** **3**

While *O*-(trimehylsilyl)urea, even after activation by deprotonation with butyllithium reacted sluggishly with ester **1a** and gave the acylation product **4** with only poor yield (55%). The cyclization to 5-fluorouracil (**5**, 67%) occured upon treatment with sodium hydroxide. Previous syntheses of the potent anticancer drug 5-fluorouracil present hazards, using either fluoroacetic acid as the starting material [7] or elemental fluorine [8], if not trifluoromethyl hypofluorite (perfluoromethanol) [9], as the reagent.

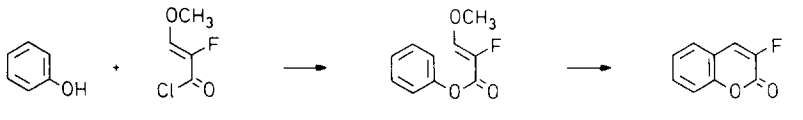


1

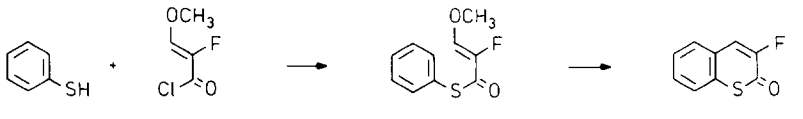
M = H, Li; X = H_3CO, Cl

4 **5**

The reaction of chloride **1b** with phenol gave the phenyl ester **6** and subsequent acid catalyzed cyclization the benzopyran **7**. Analogously, thiophenol was converted into the thioester **8** and the benzothianone **9**.

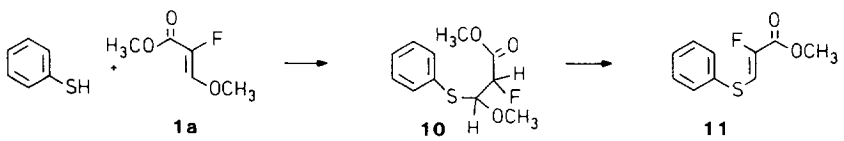


1c **6** **7**



1c **8** **9**

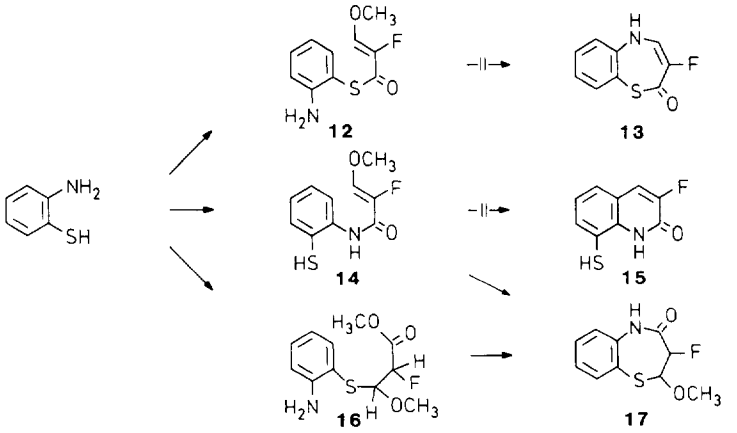
A different mode of interaction was observed with the ester **1a**. This time, the thiophenol underwent a 1,4-addition giving rise to the monothioacetal **10**. When this compound was heated in the presence of potassium hydrogen sulfate to 150 °C, methanol was eliminated and methyl 2-fluoro-3-(phenylthio)acrylate (**11**; *Z/E* 10 : 1; 77%) formed.



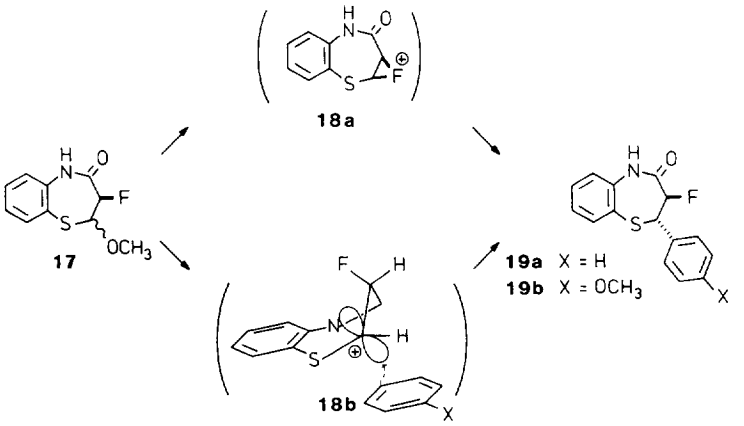
1a **10** **11**

At first sight, the bifunctional nucleophile 2-aminothiophenol should offer at least one additional reaction channel. Depending on the reaction conditions and the leaving group, the electrophilic building block (**1a** or **1c**)

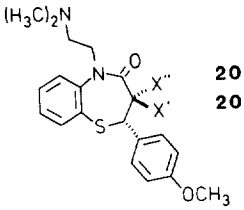
may undergo 1,2- or 1,4-addition (attack at the carbonyl group or at the vinologous β-position, respectively), as described above for thiophenol. Furthermore, the amino rather than the mercapto group may act as the nucleophilic site, again having an option on a 1,2- or 1,4-addition mode. Actually, whatever conditions are employed, always the same product, the seven-membered ring lactam **17** is formed. It may originate from the thioacetal precursor **16**, but also through the *o*-mercaptoanilide **14**. The latter intermediate may result from a direct intermolecular 1,2-addition of the amino moiety onto the ester **1a** or, more likely, by intramolecular 1,4-addition of the amino group onto a transient thioester **12**, a high energy species. In contrast, the final product, benzothiazepinone **17**, is thermodynamically particularly favorable.



The thioacetal **17** was found to exist as a 1 : 1 *cis/trans* mixture. Nevertheless, the pure *trans* isomers **19a** (X = H; 92%) and **19b** (X = OCH_3; 91%; *o/p* ratio 1 : 3) were obtained, when thioacetal **17** was treated with concentrated sulfuric acid in the presence of benzene or anisole. Although fluoronium ions are still a controversial issue [10], it is tempting to rationalize the observed stereoselectivity with the intermediacy of a bridged species **18**. However, an open cation **18b** can equally well explain the results provided the fluorine atom accupies the quasiaxial position, in other words, the carbon-fluorine bond is perpendicular to the carbenium plane and parallel to the empty *p*-orbital . For steric reasons, the arene can only approach from the opposite side.



The *p*-anisyl derivative **19b** was purified by recrystallization and a 2-dimethylaminoethyl chain was attached to the nitrogen atom of the ring. The resulting final product **20b** (X' = F; X" = H; 86%) is structurally related to Diltiazem **20a** (X' = H; X" = $OCOCH_3$) [11], a very potent calcium channel blocker which is administered as a coronary dilator and, in particular, for the treatment of angina pectoris and hypertension.



20a X' = H, X" = $OCOCH_3$
20b X' = F, X" = H

EXPERIMENTAL

1. Generalities

Starting materials have been purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim), or Merck-Schuchardt (Hohenbrunn), unless literature sources or details of the preparation are given. *Butyllithium* was supplied by CheMetall, Frankfurt. All commercial reagents were used without further purification.

Air and moisture sensitive compounds were stored in Schlenk tubes or Schlenk burettes. They were protected by and handled under an atmosphere of 99.995% pure nitrogen.

Hexane was obtained anhydrous by careful azeotropic distillation, *tetrahydrofuran* and *diethyl ether* by distillation from sodium wire after the characteristic blue color of *in situ* generated sodium diphenyl ketyl was found to persist.

Ethereal extracts were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice methanol baths is consistently indicated as -75 °C and "room temperature" (22 - 26 °C) as 25 °C. *Melting ranges* (mp) are reproducible after resolidification, unless otherwise stated ("dec."), and are corrected using a calibration curve which was established with authentic standards. If no melting points are given, it means that all attempts to crystallize the liquid product have failed even at temperatures as low as -75°C. If reduced pressure is not specified, *boiling ranges* were determined under ordinary atmospheric conditions (720 ± 25 mmHg).

Silica gel (Merck Kieselgel 60) of 70 - 230 mesh (0.06 - 0.20 mm) particle size was used for *column chromatography*. The solid support was suspended in hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of the liquid was still some 3 - 5 cm above the silica layer, the dry powder obtained by absorption of the crude product mixture on 15 - 20 g silica gel and subsequent evaporation of the solvent was poured on top of the column.

Whenever reaction products were not isolated, their yields were determined by *gas chromatography* comparing their peak areas with that of an internal standard and correcting the ratios by calibration factors. The purity of distilled compounds was checked on at least two columns loaded with stationary phases of different polarity. Chromosorb G-AW of 80 - 100 and 60 - 80 mesh particle size was chosen as the support for packed analytical or preparative columns (2 or 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz was chosen as the material for coated, Grob type capillary columns (≥ 10 m long). The type of the stationary phase used is abbriviated as SP-2340 (cyanopropylsilicone) and SPB-5 (methylphenylsilicone). In the case of programmed temperature increase a rate of 10 °C/min was maintained.

Nuclear magnetic resonance spectra of hydrogen-1 nuclei in deuterochloroform solution were recorded of deuteriochloroform solutions (unless specified otherwise) at 250 MHz or, if marked by an asterisk, at 400 MHz and of fluorine-19 nuclei at 376 MHz. Chemical shifts δ refer to the signal of tetramethylsilane in the case of ^{1}H spectra and to α,α,α-trifluorotoluene in the case of ^{19}F spectra. Coupling constants (*J*) are measured in Hz. Abbreviations of coupling patterns : s (singlet), d (doublet), t (triplet), td (triplet of doublets) and m (multiplet).

Mass spectra were obtained at a 70 eV ionization potential maintaining a source temperature of 200 °C. Whenever no molecular peak was observed under standard conditions, chemical ionization ("c.i.") in an ammonia atmosphere at 100 °C source temperature was applied.

2. 2-Fluoro-3-methoxyacrylic Acid Derivatives

Methyl 2-fluoro-3-methoxyprop-2-enoate (1a) : The preparation starting with methyl methoxyacetate *via* the chlorofluorocarbene cycloadduct with (*Z*)-1,2-dimethoxy-1-(trimethylsilyloxy)ethene has been described previously [5]. The ester is initially obtained as a (*Z/E*) isomer mixture. However, it can be readily converted into the pure (*Z*) isomer by treating its 2 M solution in tetrahydrofuran with catalytic amounts (*e.g.*, 0.05 equivalents) of lithium thiophenolate.

(*Z*)-2-Fluoro-3-methoxyprop-2-enoic acid (1b) : A 4.0 M aqueous solution (0.10 L) of sodium hydroxide was slowly added to methyl (*Z*)-2-fluoro-3-methoxyprop-2-enoate (**1a**; 34 g, 0.25 mol) in methanol (0.10 L). After 1 h at 25 °C, the mixture was washed with hexane (0.10 L), acidified with 2.0 M hydrochloric acid to pH 3, saturated with sodium chloride and extracted with diethyl ether (3 × 0.10 L). The combined organic layers were dried and evaporated. Recrystallization of the residue from a 1 : 1 (v/v) mixture of diethyl ether and hexane gave a white solid; 25 g (80%); mp 148 - 150 °C. - ^{1}H-NMR : δ 9.87 (1 H, s, broad), 7.03 (1 H, d, *J* 18.8), 3.95 (3 H, s). - MS : 120 (98%, M^{+}), 103 (99%), 89 (100%). - Analysis : calc. for $C_4H_5FO_3$ (120.08) C 40.01, H 4.20; found C 39.90, H 4.28%.

(*Z*)-2-Fluoro-3-methoxyprop-2-enoyl chloride (1c) : Thionyl chloride (30 mL, 49 g, 0.41 mol), in which (*Z*)-2-fluoro-3-methoxyprop-2-enoic acid (**1b**; 12 g, 0.10 mol) had been suspended, was heated under reflux for 2 h. The mixture was distilled, first to remove excess thionyl chloride (bp 75 - 80 °C) and, under reduced pressure, to collect product **1b**; 10.5 g (75%); bp 75 - 77 °C /10 mmHg. - ^{1}H-NMR*: δ 7.33 (1 H, d, *J* 16.9), 4.04 (3 H, s). - ^{19}F-NMR : δ 85.9 (d, *J* 16.9). - Analysis : calc. for $C_4H_4ClFO_2$ (138.60) C 34.68, H 2.91; found C 34.76, H 2.98%.

3. Reactions with Phenylhydrazine and Urea

(*Z*)-*N*-(2-Fluoro-3-methoxyprop-2-enoyl)-*N'*-phenylhydrazine (2) : Solutions of phenylhydrazine (7.0 g, 65 mmol) in diethyl ether (50 mL) and (*Z*)-2-fluoro-3-methoxyprop-2-enoyl chloride (3.1 g, 25 mmol) in diethyl ether (25 mL) were cooled to 0 °C and mixed. After 30 min at 25 °C, the precipitate formed was filtered and washed with diethyl ether (25 mL) and water (3 × 25 mL). Crystallization from acetone/hexane gave the product in form of colorless sheets; 4.1 g (78%); mp 132 - 134 °C. - ^{1}H-NMR : δ 7.8 (1 H, s, broad), 7.26 (2 H, symm. m), 7.94 (1 H, tt, *J* 7.1, 1.0), 6.90 (2 H, ddd, *J* 8.3, 2.0, 1.0), 6.88 (1 H, d, *J* 21.5), 6.09 (1 H, d, broad, *J* 3.6), 3.91 (3 H, s). - ^{19}F-NMR : δ 100.6 (d, *J* 21.5). - MS : 210 (89%, M^{+}), 179 (42%), 107 (100%). Analysis : calc. for $C_{10}H_{11}FN_2O_2$ (210.21) C 57.14, H 5.27; found C 57.26, H 5.24%.

4-Fluoro-1-phenyl-3-pyrazolone (3) : The acylhydrazine **2** (4.2 g, 20 mmol) was suspended in concentrated sulfuric acid (10 mL). After 30 min of stirring at 25 °C, the mixture was poured on ice. The precipitate obtained was collected by filtration, washed with water (3 × 25 mL) and dried. Recrystallization from chloroform gave yellowish prisms; 0.32 g (89%); 72% with respect to **1b**); mp 179 - 181 °C. - ^{1}H-NMR : δ 10.5 (1 H, s, broad), 7.57 (1 H, d, *J* 4.2), 7.4 (4 H, m), 7.2 (1 H, m). - ^{19}F-NMR : δ -122.3 (d, *J* 4.2). - MS : 178 (35%, M^{+}), 149 (15%), 104 (22%), 77 (100%). - Analysis : calc. for $C_9H_7FN_2O$ (178.17) C 60.67, H 3.96; found C 60.55, H 4.03%.

(*Z*)-*N*-(2-Fluoro-3-methoxyprop-2-enoyl)urea (4) : At 25 °C, methyllithium (40 mmol) in diethyl ether (25 mL) and, 30 min later, methyl (*Z*)-2-fluoro-3-methoxyprop-2-enoate (**1a**, 2.7 g, 20 mmol) were added to a solution of *O*-(trimethylsilyl)urea (5.3 g, 40 mmol) in tetrahydrofuran (20 mL). After 10 h at 25 °C, the mixture was neutralized with 2 M hydrochloric acid and extracted with ethyl acetate (5 × 20 mL). The organic phase was dried and evaporated. Recrystallization of the residue from acetone gave white needles; 2.0 g (55%); mp

199 - 201 °C. - ^{1}H-NMR : (D_3CCOCD_3) : δ 9.63 (1 H, s, broad), 7.85 (1 H, s, broad), 7.30 (1 H, d, *J* 20.5), 7.08 (1 H, s, broad), 3.94 (3 H, s). - MS : 162 (59, M^+), 147 (27%), 120 (39%), 103 (100%). - Analysis : calc. for $C_5H_7FN_2O_3$ (162.12) C 37.04, H 4.35; found C 37.24, H 4.40%.

5-Fluorouracil (5) : Under stirring, a suspension of the urea derivative **4** (3.2 g, 20 mmol) in 2 M aqueous sodium hydroxide (20 mL) was heated to 80 °C until, after some 60 min, a clear solution had formed. The mixture was neutralized with 2 M hydrochloric acid, saturated with sodium chloride and extracted with ethyl acetate (3 × 15 mL). After evaporation of the solvent, the residue was purified by chromatography on silica gel using ethyl acetate as the eluent; 1.8 g (67%); mp 279 - 281 °C (dec.; lit. [7] : mp 280 - 281 °C). - ^{1}H-NMR*: (D_3CSOCD_3) : δ 11.1 (2 H, s, broad); 7.71 (1 H, d, *J* 6.5). - ^{19}F-NMR : (D_3CSOCD_3) : δ 110.3 (d, *J* 6.5).

4. Reactions with Phenol and Thiophenol

Phenyl (*Z*)-2-fluoro-3-methoxyprop-2-enoate (6) : Pyridine (5.0 mL, 5.1 g, 65 mmol) was added to a solution of (*Z*)-2-fluoro-3-methoxyprop-2-enoyl chloride (3.1 g, 25 mmol) and phenol (2.4 g, 25 mmol) in diethyl ether (50 mL). After 1 h at 25 °C, the mixture was washed with 2 N hydrochloric acid (2 × 25 mL) and a saturated aqueous solution of sodium hydrogen carbonate (2 × 15 mL), dried and evaporated. Distillation of the residue under reduced pressure afforded a colorless liquid, which solidified upon standing; 3.7 g (94%); mp 42 - 43 °C; bp 109 - 110 °C/2 mmHg. - ^{1}H-NMR*: δ 7.4 (2 H, m), 7.3 (1 H, m), 7.2 (2 H, m), 7.11 (1 H, d, *J* 18.7), 3.97 (3 H, s). - ^{19}F-NMR : δ 95.6 (d, *J* 18.7). - MS 197 (20%, M^+ + 1), 196 (15%, M^+), 120 (3%), 103 (100%). - Analysis : calc. for $C_{10}H_9FO_3$ (196.18) C 61.23, H 4.62; found C 61.02, H 4.72%.

2*H*-3-Fluorobenzo[*b*]pyran-2-one (3-fluorocoumarine) (7) : Concentrated sulfuric acid (20 mL) was added to a solution of phenyl ester **6** (3.9 g, 20 mmol) in chloroform (20 mL). The mixture was stirred 30 min at 0 °C before being poured on crushed ice. The aqueous phase extracted with chloroform (2 × 15 mL) and the combined organic layers were washed with a saturated aqueous solution (25 mL) of sodium hydrogen carbonate. The solvent was evaporated and the residue crystallized from acetone/hexane; 2.8 g (90%); mp 146 - 148 °C (lit. [12] : mp 148 °C). - ^{1}H-NMR : δ 7.5 (2 H, m), 7.44 (1 H, d, *J* 8.5), 7.4 (2 H, m). - ^{19}F-NMR : δ -66.8 (d, *J* 8.5). - MS : 164 (M^+), 136 (29%), 108 (100%).

***S*-Phenyl (*Z*)-2-fluoro-3-methoxyprop-2-enethioate (8)** : (*Z*)-2-Fluoro-3-methoxyprop-2-enyl chloride (**1c**; 3.1 g, 25 mmol) was added to a solution of thiophenol (2.6 mL, 2.8 g, 25 mmol) and pyridine (5.0 mL, 50 mmol) in diethyl ether (50 mL). After 30 min at 25 °C, the mixture was poured into an aqueous solution of 1 N HCl (50 mL). The aqueous phase was extracted with diethyl ether (3 × 50 mL) and the organic phase washed with brine (2 × 50 mL). The solvent was evaporated and the residue crystallized from a 1 : 1 mixture of diethyl ether and hexane; 5.0 g (94%); mp 93 - 94 °C. - ^{1}H-NMR* : δ 7.4 (5 H, m), 6.89 (1 H, d, *J* 20.0), 3.94 (3 H, s). - ^{19}F-NMR : δ -93.7 (d, *J* 20.0). - MS : 212 (14%, M^+), 109 (11%). - Analysis : calc. for $C_{10}H_9FO_2S$ (212.24) C 56.59, H 4.27; found C 56.87, H 4.30%.

2*H*-3-Fluorobenzothiin-2-one (9) : A stirred mixture of the thioester **8** (4.2 g, 20 mmol) in chloroform (20 mL) and concentrated sulfuric acid (20 mL) was heated for 1 h to 60 °C. The product was isolated as described for the benzopyranone **7** and crystallized from acetone/hexane; 3.0 g (83%); mp113 - 114 °C. - ^{1}H-NMR* : δ 7.59 (1 H, d, *J* 7.8), 7.5 (1 H, d, *J* 15.4), 7.5 (2 H, m), 7.43 (1 H, symm. m). - ^{19}F-NMR : δ -63.4 (d, *J* 15.4). - MS : 181 (98%, M^+ +1), 180 (100%, M^+), 152 (99%), 107 (40%). Analysis : calc. for C_9H_5FOS (180.20) C 59.99, H 2.80; found C 60.06, H 2.96%.

Methyl (*Z*)-2-fluoro-3-methoxy-3-(phenylthio)propionate (10) : A catalytic amount of potassium *tert*-butoxide (0.2 g, 2 mmol) was added to a solution of thiophenol (5.1 mL, 5.5 g, 50 mmol) and methyl (*Z*)-2-fluoro-3-methoxyprop-2-enoate (**1a**; 6.7 g, 50 mmol) in diethyl ether (25 mL). After 15 h at 25 °C, the mixture was washed with water, dried and evaporated. Distillation afforded a colorless, viscous liquid; 4.8 g (89%); bp 132 - 134 °C/3 mmHg; two diastereoisomers in the ratio of 3 : 1 (according to nmr spectroscopy). - ^{1}H-NMR : δ 7.5 (2 H, m), 7.3 (3 H, m), 5.0 (1.25 H, m), 4.92 (0.75 H, dd, *J* 48.0, 4.8), 3.83 (0.75 H, s), 3.81 (2.25 H, s), 3.57 (0.75 H, s), 3.54 (2.25 H, s). - ^{19}F-NMR : δ -130.4 (0.75 F, dd, *J* 48.0, 18.5), -132.6 (0.25 F, *J* 50.0, 19.7). - MS : 262 (100%, $M^+ + NH_4$), 244 (19%, M^+), 213 (82%). - Analysis : calc. for $C_{11}H_{13}FO_3S$ (244.28) C 54.08, H 5.36; found C 53.93, H 5.26%.

Methyl 2-fluoro-3-(phenylthio)prop-2-enoate (11) : Thioacetal **10** (6.1 g, 25 mmol) was heated in the presence of potassium hydrogen sulfate (0.5 g) and under reduced pressure (11 mmHg) 2 h at 150 °C. Upon subsequent distillation, a colorless liquid was collected; 4.1 g (77%); bp 104 - 105 °C/20 mmHg; (*Z*/*E*) ratio 10 : 1 (according to nmr). - ^{1}H-NMR : δ 7.5 (2 H, m), 7.4 (3 H, m), 7.09 (0.9 H, d, *J* 31.8), 6.98 (0.1 H, d, *J* 17.0), 3.93 (0.1 × 3 H, s), 3.83 (0.9 × 3 H, s). - MS : 212 (100%, M^+), 181 (13%), 153 (34%). - Analysis : calc. for $C_{10}H_9FO_2S$ (212.24) C 56.59, H 4.27; C 56.60, H 4.40%.

5. Reactions with 2-Aminothiophenol

Methyl (*Z*)-3-(2-aminophenyl)thio-2-fluoro-3-methoxypropanoate (16) : At 0 °C, butyllithium (30 mmol) in hexane (18 mL) and methyl (*Z*)-2-fluoro-3-methoxyprop-2-enoate (**1a**; 4.0 g, 30 mmol) were consecutively added to a solution of 2-aminothiophenol (7.5 g, 60 mmol) in tetrahydrofuran (0.10 mL). After 1 h at 25 °C, water was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with 1 M aqueous sodium hydroxide (2 × 25 mL) and brine (2 × 50 mL) before being dried. A viscous residue was left behind upon evaporation of the volatiles. After purification by chromatography on silica gel, using a 1 : 4 mixture of ethyl acetate and hexane as the eluent, a yellowish oil was collected which, according to nmr, was a 3 : 2 mixture of diastereoisomers; 6.9 g (88%). - ^{1}H-NMR : δ 7.43 (0.60 H, dd, *J* 7.5, 1.5), 7.39 (0.40 H, dd, *J* 7.5, 1.5), 7.2 (1 H, m), 6.7 (2 H, m), 5.04 (0.60 H, dd, *J* 47.0, 3.5), 4.93 (0.40 H, dd, *J* 26.1, 5.0), 4.91 (0.60 H, dd, *J* 22.5, 3.5), 4.81 (0.40 H, dd, *J* 8.5, 5.0), 3.82 (1.8 H, s), 3.81 (1.2 H, s), 3.55 (1.8 H, s), 3.54 (1.2 H, s). - ^{19}F-NMR : δ 135.9 (0.4 F, dd, *J* 47.0, 22.5), 128.0 (0.6 F, symm. m). - MS : 259 (19%, M^+), 239 (24%), 238 (24%), 136 (100%). - Analysis : calc. for $C_{11}H_{14}FNO_3S$ (259.30) C 50.95, H 5.44; found C 51.20, H 5.46%.

3-Fluoro-2,3-dihydro-2-methoxy-1,5-benzothiazepin-4(5*H*)-one (17) : The crude ester **16** (6.4 g, 25 mmol), described above, was used without further purification. After having been dissolved in anhydrous dichloromethane (0.15 L), it was treated with trimethylaluminum (60 mmol) in heptane (2.0 M, 30 mL) at 0 °C for 1 h. The mixture was vigorously shaken with 2 M hydrochloric acid (0.20 L), the organic layer separated and the aqueous phase extracted with dichloromethane (3 × 50 mL). After drying and treatment with charcoal (20 g), the organic solvents were evaporated. The residue was triturated with anhydrous diethyl ether to give a white solid; 4.6 g (68% with respect to acrylate **1a**); mp 182 - 198 °C (dec.); two diastereomers in the ratio of 2 : 1 (according to nmr). - ^{1}H-NMR : δ 8.75 (0.65 H, s, broad), 8.67 (0.35 H, s, broad), 7.66 (0.65 H, dd, *J* 7.5, 1.3), 7.55 (0.35 H, dd, *J* 7.5, 1.3), 7.45 (0.67 H, td, *J* 7.5, 1.3), 7.35 (0.33 H, td, *J* 7.5, 1.3), 7.2 (2 H, m), 5.47 (0.35 H, dd, *J* 17.6, 3.1), 5.30 (0.35 H, dd, *J* 49.0, 3.1), 5.09 (0.65 H, dd, *J* 16.5, 7.7), 4.82 (0.67 H, dd, *J* 48.5, 7.7), 3.59 (0.33 × 3 H, s), 3.55 (0.65 × 3 H, s). - ^{19}F-NMR : δ -128.5 (0.65 F, dd, *J* 48.5, 17.6), -132.8 (0.35 F, dd, *J* 49.0, 16.5). - MS : 227 (34%, M^+), 207 (12%), 151 (99%), 123 (81%), 96 (100%). - Analysis : calc. for $C_{10}H_{10}FNO_2S$ (227.26) C 52.85, H 4.44; found C 52.56, H 4.21%.

***trans*-3-Fluoro-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (19a)** : Under stirring, concentrated sulfuric acid (2.0 mL) was added dropwise, in the course of 10 min, to a suspension of the cyclic thioacetal **17** (4.5 g, 20 mmol) in benzene (40 mL). The mixture was allowed to stand 30 min at 25 °C before it was diluted with ethyl acetate (0.10 L) and washed with water (2 × 25 mL), a saturated aqueous solution of sodium hydrogen carbonate (25 mL) and brine (50 mL) was crystallized from toluene to afforded colorless prisms; 5.0 g (92%); mp 230 - 231 °C (dec.). - ^{1}H-NMR : δ 8.6 (1 H, s, broad), 7.74 (1 H, dd, *J* 7.5, 1.5), 7.50 (1 H, td, *J* 7.5, 1.5), 7.3 (7 H, m), 5.06 (1 H, dd, *J* 48.0, 9.8), 4.70 (1 H, dd, *J* 16.0, 9.8). - ^{19}F-NMR : δ -121.5 (ddd, *J* 48.0, 16.0, 2.2). - MS : 273 (27%, M^+), 253 (32%), 215 (20%), 152 (100%). Analysis : calc. for $C_{15}H_{12}FNOS$ (273.33) C 65.91, H 4.42; found C 66.01, H 4.45%.

***trans*-3-Fluoro-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (19b)** : In a strictly analogous reaction using anisole instead of benzene, a 1 : 3 mixture of *ortho* and *para* isomers were obtained; 5.5 g (91%). Recrystallization from toluene allowed to isolate the pure *para* isomer. - ^{1}H-NMR : δ 8.6 (1 H, s, broad), 7.74 (1 H, dm, *J* 7.5), 7.49 (1 H, ddd, *J* 7.5, 7.0, 1.5), 7.3 (2 H, m), 7.25 (2 H, d, *J* 8.7), 6.89 (2 H, d, *J* 8.7), 5.00 (1 H, dd, *J* 48.0, 9.7), 4.69 (1 H, dd, *J* 16.2, 9.7), 3.81 (3 H, s). - ^{19}F-NMR : δ -121.0 (ddd, *J* 48.0, 16.2, 2.0). - MS : 303 (46%, M^+), 283 (33%), 250 (10%), 152 (100%). - Analysis : calc. for $C_{16}H_{14}FNO_2S$ (303.36) C 63.35, H 4.65; found C 63.52, H 4.88%.

A small sample of the *ortho* isomer was separated from the mother liquor by chromatography on silica gel; mp 180 - 182 °C. - ^{1}H-NMR : δ 8.75 (1 H, s, broad), 7.60 (1 H, dd, *J* 7.5, 7.4), 7.45 (1 H, td, *J* 7.5, 1.4), 7.3 (2 H, m), 7.2 (2 H, m), 6.9 (2 H, m), 5.33 (1 H, dd, *J* 47.5, 10.0), 5.19 (1 H, dd, *J* 15.8, 10.0). - ^{19}F-NMR : δ -122.4 (dd, *J* 47.5, 15.8). - MS : 303 (48%, M^+), 283 (22%), 152 (83%), 109 (98%), 91 (100%).

***trans*-3-Fluoro-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (20b) hydrochloride** : A mixture of the benzothiazepinone **19b** (3.0 g, 10 mmol), 1-chloro-2-(dimethylamino)ethane hydrochloride (1.4 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in *N,N*-dimethylformamide (20 mL) was stirred 2 h at 80 °C. Water (50 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (2 × 25 mL) and evaporated to dryness. The residue was taken up in methanol (10 mL) and treated with a slight excess (approx. 12 mmol) of an ethereal solution (approx. 2 M) of hydrogen chloride. Upon further addition of diethyl ether (50 mL), the hydrochloride precipitated completely. Recrystallization from methanol and diethyl ether afforded

white needles; 3.5 g (85%); mp 246 - 248 °C. - ^{1}H-NMR : δ 12.9 (1 H, s, broad), 7.70 (1 H, dd, *J* 7.5, 1.1), 7.64 (1 H, td, *J* 7.5, 1.1), 7.55 (1 H, dd, *J* 7.5, 1.1), 7.39 (1 H, td, *J* 7.5, 1.1), 7.12 (2 H, d, *J* 9.0), 6.85 (2 H, d, *J* 9.0), 4.90 (1 H, dd, *J* 48.5, 10.0), 4.7 (1 H, m), 4.50 (1 H, dd, *J* 15.8, 10.0), 4.4 (1 H, m), 3.8 (3 H, s), 3.4 (1 H, m), 3.2 (1 H, m), 2.96 (3 H, s, broad), 2.82 (3 H, s, broad). - ^{19}F-NMR : δ -122.0 (dd, *J* 48.5, 15.8). - MS : 374 (8%, M^+ *-Cl*), 167 (11%), 136 (26%), 109 (100%). - Analysis : calc. for $C_{20}H_{24}ClFN_2O_2S$ (410.94) C 58.46, H 5.89; found C 58.26, H 5.87%.

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References

1 Bessière, Y.; Savary, D.N.H.; Schlosser, M.; *Helv. Chim. Acta* **60** (1970),1739.
2 Schlosser, M.; *J. Fluorine Chem.* **54** (1991), 192.
3 Shi, G.-q.; Schlosser, M.; *J. Fluorine Chem.* **58** (1992), 135.
4 Shi, G.-q.; Schlosser, M.; *Tetrahedron* **49** (1993), 1445.
5 Shi, G.-q.; Takagishi, S.; Schlosser, M.; *Tetrahedron* **50** (1994), 1129. - In this article, acrylate **1a** is erroneously named methyl 2-fluoro-3-methoxy-2-*but*enoate.
6 Ghosh, S.N.; Schlosser, M.; *J. Fluorine Chem.* **67** (1994), 53.
7 Duschinsky, R.; Pleven, E.; Heidelberger, C.; *J. Am. Chem. Soc.* **79** (1957), 4559.
8 Cech, D.; Holy, A.; *Collect. Czech. Chem. Commun.* **41** (1976), 3335; Hillers, S.; Lazdin, A.; Veinbergs, A.; Snikeris, D.; Knunyants, I.L.; German, L.S.; Kazmina, N.B.; *US Pat.* 3'846'429 (applied 22 Sept. 1971, issued 5 Nov. 1974); *Chem. Abstr.* **83** (1975), 97'346s; Nakamura, J.; Takeuchi, T.; Sakuma, K.; Tomioko, H.; (to Mitsui Toatsu Chem.), *Jpn. Kokai Tokkyo Koho* 78'144'584 (applied 20 May 1977, issued 15 Dec. 1978); *Chem. Abstr.* **91** (1979), 20'535k; Kobayashi, Y.; Kumadaki, I.; Nakazato, A.; *Tetrahedron Lett.* **21** (1980), 4605; Haas, A.; Kortmann, D.; *Chem. Ber.* **114** (1981), 1176; see also an indirect method : Lal, G.S.; Pastore, W.; Pesaresi, R.; *J. Org. Chem.* **1995**, *60*, 7340 - 7342.
9 Robins, M.J.; Naik, S.R.; *J. Am. Chem. Soc.* **93** (1971), 5277.
10 Nguyen, V.; Cheng, X.-h.; Morton, T.H.; *J. Am. Chem. Soc.* **114** (1992), 7127; see also : Matsuda, H.; Hamatani, T.; Matsubara, S.; Schlosser, M.; *Tetrahedron* **44** (1988), 2865.
11 Nagao, T.; Sato, M.; Nakajima, H.; *Chem. Pharm. Bull.* **21** (1973), 92; see also : Godfraind, T.; Miller, R.; Wibo, M.; *Pharmacol. Rev.* **38** (1986), 321; *Chem. Abstr.* **106** (1987), 95382v; Floyd, D.M.; Moquin, R.V.; Atwal, K.S.; Ahmed, S.Z.; Spergel, S.H.; Gougoutas, J.Z.; Maley, M.F.; *J. Org. Chem.* **55** (1990), 5572; Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; *Tetrahedron Lett.* **32** (1991), 3519.
12 Bergmann, E.D.; Shahak, I.; *J. Chem. Soc.* **1961**, 4033.

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