Synthesis of [1]Benzothieno[3,2-*d*]pyrimidines Substituted with Electron Donating Substituents on the Benzene Ring

Alexander J. Bridges and Hairong Zhou

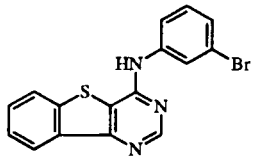
Department of Chemistry, Parke Davis Pharmaceutical Research, Division of the Warner-Lambert Company, 2800 Plymouth Rd, Ann Arbor, MI 48105, USA

Received July 5, 1996

Various 2-fluorobenzonitriles were converted to the corresponding 3-amino[1]benzothiophenecarboxylic acid esters, which in turn were annulated with formamidine or various equivalents to produce the desired tricyclic benzothienopyrimidines. Various methoxy and nitro/amino substituents were placed on the phenyl ring, requiring several different strategies to prepare the desired benzothiophenes. Several different pyrimidone annulations were also required. The use of an electron rich 2-bromobenzonitrile in a four-step one-pot low temperature lithiation sequence to produce highly electron-rich amino[1]benzothiophenecarboxylate esters is also described. The synthesis of 7-amino-8-fluoro[1]benzothieno[3,2-*d*]pyrimid-4(3*H*)-one was relatively straightforward, but synthesis of the corresponding 7-amino-8-protio analogue proved to be very difficult, and required several approaches before a successful one was found.

J. Heterocyclic Chem., **34**, 1163 (1997).

Introduction.



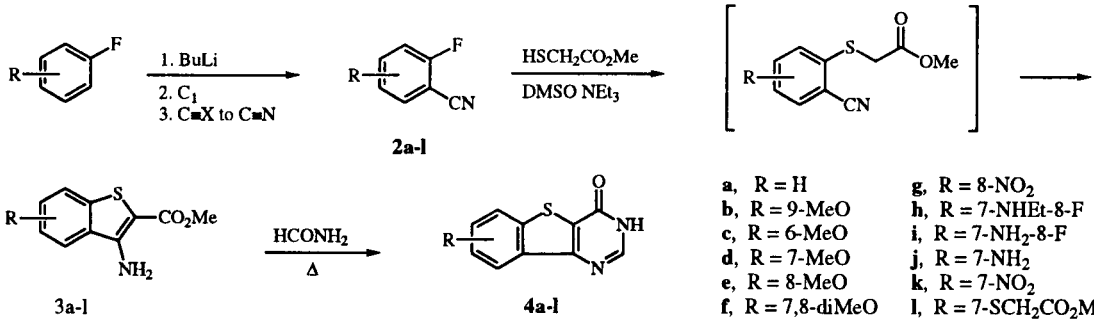
1

In connection with studies on inhibitors of the epidermal growth factor receptor tyrosine kinase, we wished to look at various tricyclic homologues of the basic 4-anilinopyrimidine pharmacophore [1,2]. One of the targets chosen was the [1]benzothieno[3,2-*d*]pyrimidine **1**, which proved to be a 1.6 n*M* IC_{50} inhibitor of tyrosine kinase, leading us to examine a series where we looked at the effects of electron donating substituents in the phenyl ring, because in the corresponding (bicyclic) quinazoline series such substituents were found to be optimal [3,4]. In this paper we report the successful syntheses of a number of 6- through 9-substituted [1]benzothieno[3,2-*d*]pyrimidones, which can be used as precursors for the desired inhibitors, which will be described elsewhere [5].

The general synthetic route used is shown in Scheme 1 using 2-fluorobenzonitriles **2** as starting materials. The intermediate 3-amino[1]benzothiophene-2-carboxylate esters **3** have been prepared by similar displacements from both 2-chloro [6] and 2-nitro [7] benzonitriles, and by reaction of a malonate anion with 3-chlorobenzoisoxazoles [8]. Nucleophilic displacement of an *ortho*-halobenzonitrile **2** with a thioglycollate anion, followed by spontaneous base induced aldol cyclization gives the 3-amino[1]benzothiophene-2-carboxylic acid ester **3**. This can be cyclized with a formate equivalent in a Niementowski synthesis [9] to give the desired tricyclic pyrimidones **4** [6,10-13]. We elected to use 2-fluorobenzonitriles in this route because a wide variety of substitution patterns are available by exploiting the directed metalation abilities of fluorine [14], and displacement of the *ortho*-fluorine atom from benzaldehydes by a thioglycollate ester has been shown to be an excellent method for preparation of [1]benzothiophenecarboxylate esters [15]. Initially we targeted methoxy substitution at the 6- through 9-positions, the 7,8-dimethoxy product, and amino/nitro substitution at the 7- and 8-positions. It was anticipated that electron donors on the benzene ring would sometimes cause

Scheme 1

General Synthesis of Benzo-substituted [1]Benzothienopyrimidones from Fluorobenzenes



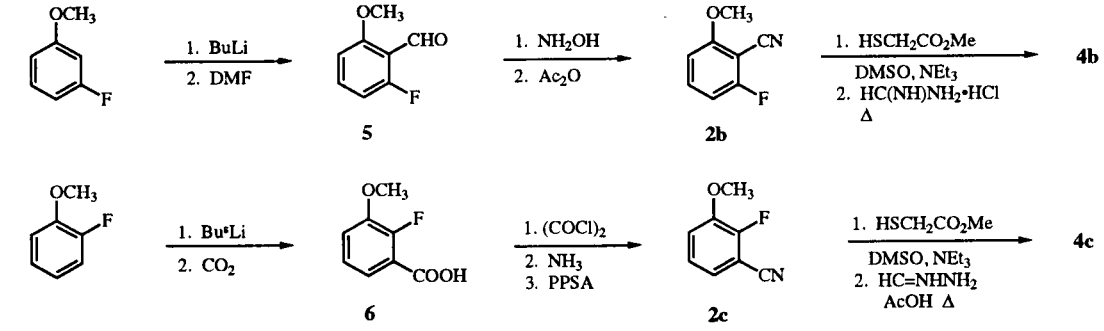
problems with displacement reactions due to their detrimental effects on the electrophilicity of the aromatic ring, thus masking electron donation by the use of a nitro group as a synthon for the amino group [10] and as an alternative, electrophilic introduction of a sulfur atom were utilized successfully to overcome these shortcomings.

Results.

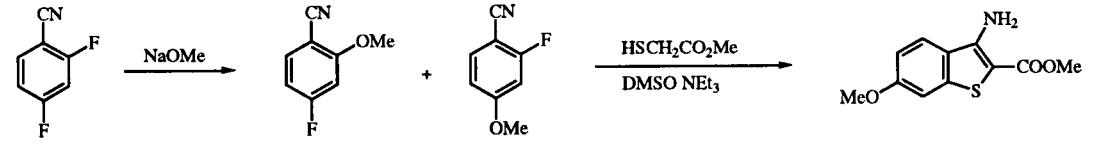
The first preparation examined was that of the unsubstituted [1]benzothienopyrimidone **4a**. Reaction of 2-fluorobenzonitrile **2a** with methyl thioglycollate and excess triethylamine in dimethyl sulfoxide at 100° gave a good yield of the desired methyl 3-amino[1]benzothiophene-2-carboxylate (**3a**) after a simple work up consisting of pouring into ice-water. Conversion to the corresponding tricyclic compound **4a** occured with equal ease, simply by heating in excess formamide at 175° for 2 hours, obtaining clean **4a** in an overall yield of 55% from **2a**.

Although a similar strategy could be adopted for the 7-methoxy compound **4d**, by lithiation-silylation at the 2-position of 3-fluoroanisole followed by lithiation-carbonylation at the 6-position [19], it was deemed much simpler to follow an alternative route. 2,4-Difluorobenzonitrile **7** was reacted with methanolic sodium methoxide to give a 1:1 mixture of the desired 2-fluoro-4-methoxybenzonitrile **2d** and the unwanted isomer **8**. Treatment of this crude mixture with thioglycollate and potassium *t*-butoxide displaced fluorine from both isomers, but **3d** could be crystallized from the mixture in overall 14% yield on the difluoride. Annulation with formamidine acetate gave **4d** in 81% yield.

Previous experience suggested that the thiophene annulation reaction would not work acceptably with a methoxy *para* to the fluorine atom [15]. Additionally, although **4e** should be available from 4-fluoroanisole, 2-fluoro-4,5-dimethoxybenzonitrile is not readily available. However, both 2-bromo-5-methoxy- and 2-bromo-4,5-dimethoxybenzonitrile, **9** and **10**, are readily available from analogous acids or aldehydes, so an umpolung approach to the sulfur introduction was examined. Although 2-lithiobenzonitriles are unstable at -78° [20], it was felt that they could probably be both generated by halogen-metal exchange and quenched with sulfur at lower temperatures where they would be stable. Therefore, halogen-metal exchange on bromide **10** was carried out with one equivalent of *n*-butyl lithium in ether at -110° for 5 minutes generating anion **11**. Sulfur was then added to the reaction mixture, to generate **12** *in situ*. The mixture was allowed to warm slowly to 25°, with an equivalent of ethyl bromoacetate being added [21] at -50°. On a small scale this gave **3f** in 79% yield from **10**, but on larger scales the yield was around 30%. This remarkable transformation consists of a transmetalation, a thiation, an alkylation and



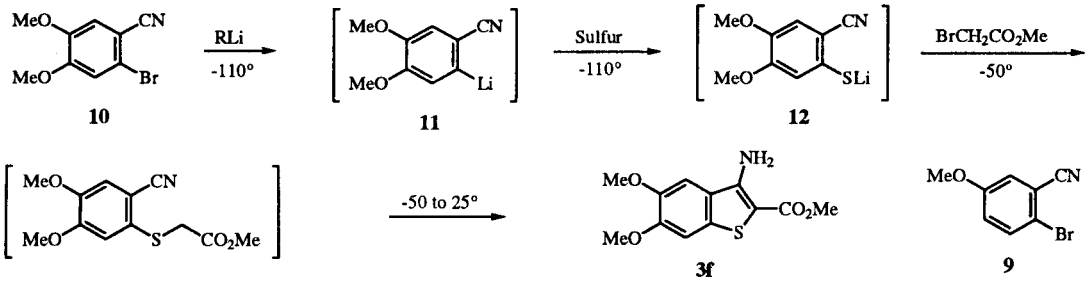
The 9- and 6-methoxy analogues, **4b** and **4c** were approached using 3- and 2-fluoroanisoles as starting materials. Directed lithiation-formylation of 3-fluoroanisole [14] between the two substituents gave the aldehyde **5**, which was converted to nitrile **2b** by oximation and dehydration with acetic anhydride [16] in 53% yield. Annulation of the thienyl ring gave **3b** in 83% yield, but formamide only gave **4b** in 22% yield. However, formamidine acetate fusion [17] of **3b** at 180° gave tricycle **4b** in 47% yield. In a similar fashion 2-fluoroanisole was selectively lithiated ortho to fluorine as described previously [14], and after carboxylation the corresponding acid **6** which was aminated quantitatively and dehydrated with phosphorus pentoxide/hexamethyl disiloxane [18] to give **2c** in 50% overall yield. Nitrile **2c** was annulated with thioglycollate to give aminoester **3c**, in 43% yield, and formamide gave tricycle **4c** in 56% yield. In this case formamidine acetate gave a considerably poorer result.



7 8 2d 3d

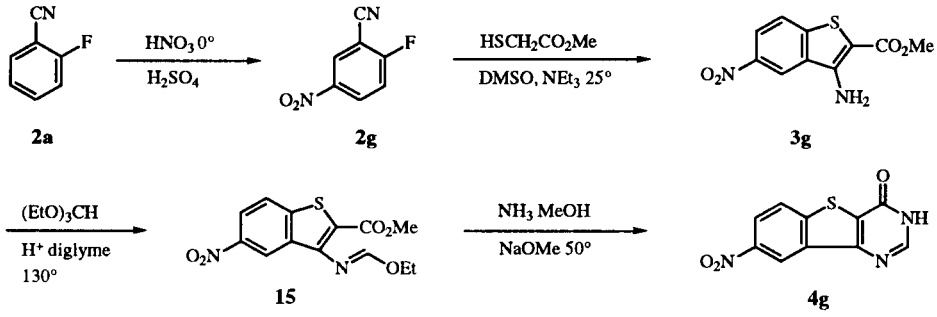
Scheme 2

One Pot anionic annulation of a thiophene onto a 2-bromobenzonitrile



an aza-Claisen Schmidt acylation all in one pot as shown in Scheme 2. Cyclization of **3f** with formamide went in acceptable yield to give **4f**. When the same sequence was carried out on 2-bromo-5-methoxybenzonitrile **9**, the anionic annulation only gave **3e** in 34% yield. The pyrimidone annulation to give **4e** was also very inefficient giving less than 10% yields with both formamide and formamidine hydrochloride.

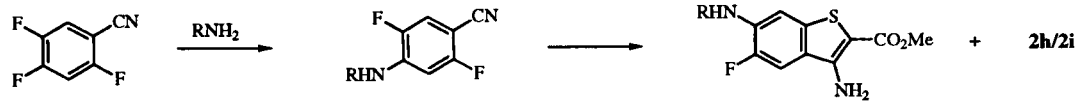
responding amide **13** with ammonia in a bomb did not go cleanly, although **13** did cyclize cleanly to the desired pyrimidone with ethyl orthoformate. Reaction of **3g** with dimethylformamide acetal gave the corresponding amidine **14**, but it did not cyclize to **4g** when treated with ammonia under mild conditions. Initial attempts to react **3g** with ethyl orthoacetate [13] to form the iminoether **15** were not very clean, but **15** could be obtained very



Some nitrogen substituents at the 7- and 8-positions of the ring were also examined. Use of 5-nitro-2-fluorobenzonitrile **2g**, obtained by nitration of **2a**, should lead to the 8-nitro derivative **4g**, which could then be converted *via* reduction and aminations to the 8-amino and 8-alkylamino substituted compounds. As the reductions and alkylations were done after the 4-anilino side chain had been introduced, they will be reported on elsewhere, but it has been shown that **4g** is a useful precursor for such compounds [22]. This sequence worked very well, as **2a** nitrates readily to form **2g** in 93% yield. Because the fluorine is now activated by both cyano and nitro, displacement in dimethyl sulfoxide with triethylamine is highly exothermic at rt, and gave analytically pure **3g** in quantitative yield. The first small scale cyclization of **3g** with formamide gave clean **4g** in 65% yield, but this result proved to be irreproducible, especially on scale-up, when rather impure product would be obtained in 20-50% yield, under a wide variety of conditions. Several alternatives to formamide were examined. Both formamidine hydrochloride and *O*-isopropyl formimidate hydrochloride gave similar results to formamide. Conversion of **3g** to the cor-

cleanly, in high yields if catalytic tosic acid in diglyme at 130°, combined with distilling out the ethanol byproduct, was used, but it was very susceptible to decomposition back to **3g**. When iminoether **15** was reacted with methanolic ammonia in a bomb at 50°, pyrimidone **4g** was formed, but even under rigorously anhydrous conditions variable amounts (15-30%) of starting amine **3g** were recovered. Acidifying the reaction, by adding ammonium chloride was ineffective, but basifying it by addition of one equivalent of sodium methoxide suppressed the reversion allowing the desired pyrimidone **4g** to be obtained in 91% yield containing 0-6% of **3g**.

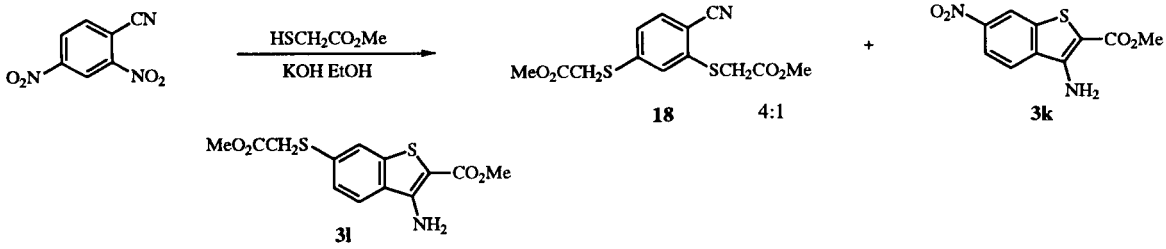
The initial approach to 7-amino substitution utilized 2,4-difluorobenzonitrile **7** in an analogous route to that adopted for the 7-methoxy compound. Simultaneously, we examined the 7-amino-8-fluoro substitution pattern, starting with 2,4,5-trifluorobenzonitrile **16** as it was felt that the extra fluorine would improve the chemistry of the route, as well as producing a differentially disubstituted phenyl ring. This proved to be relatively straightforward, but as discussed subsequently the sequence could not be made to work satisfactorily with difluoride **7**.



16 2h/2i 3h/3i

Reaction of **16** with ethylamine in dimethylformamide was highly exothermic, and gave exclusively the para displacement product, amine **2h** in 98% yield. Reaction with ammonia did not go smoothly in dimethylformamide, even in a bomb at 50°, but simply heating **16** with ammonia at 50° in a bomb gave **2i** quantitatively, with no trace of the unwanted regioisomer. Reaction of **2h** with sodium hydride and methyl thioglycollate in dimethyl sulfoxide for 10 minutes at 75°, followed by precipitation with water gave the desired benzothiophene **3h**, in about 50% yield, containing at least 30 mole% unreacted benzonitrile. This crude mixture could be cyclized to the desired tricycle **4h** in good yield with formamidine acetate, and most benzonitrile washed away by rinsing with chloroform or acetone. Reaction of **2i** with potassium *t*-butoxide and methyl thioglycollate in dimethyl sulfoxide at 75°, followed by precipitation with water gave the desired benzothiophene **3i**, usually quite cleanly in 38-48% yields. When the reason for the low yield was investigated, in this case also, the crude reaction mixtures always contained starting material, although in lesser amounts than the ethylamino case. A considerable effort was made with different bases, temperatures and stoichiometries to drive this reaction to completion, but none were successful, although some conditions did increase the amount of a minor byproduct of undetermined structure. This is very suggestive that this substitution pattern is right at the boundary for favorable electronics for the ring annulation. Fusing **3i** with formamidine acetate at 180° gave the desired tricycle **4i** in 73% yield.

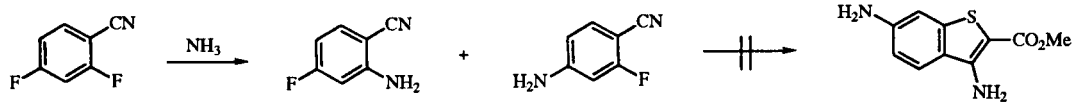
When the same reaction sequence was attempted with difluorobenzonitrile **7**, the first step went as expected and about an 11:9 ratio of undesired 2-displacement product **17** and **2j** were obtained after treatment with ammonia in a bomb. Treatment of **2j** with thioglycollate under a wide variety of conditions yielded no product at all. As some *N*-alkylated derivatives of **2j** would form a benzothiophene after forming an *N*-*t*-butoxycarbonyl derivative [22], the reaction of **2j** with di-*t*-butyl dicarbonate was examined, but conditions were not found to get more than minimal conversion to the desired *t*-Boc derivative. Additionally the Bocamino benzothiophenes examined did not undergo pyrimidone annulation in an acceptable manner, so this approach was abandoned.



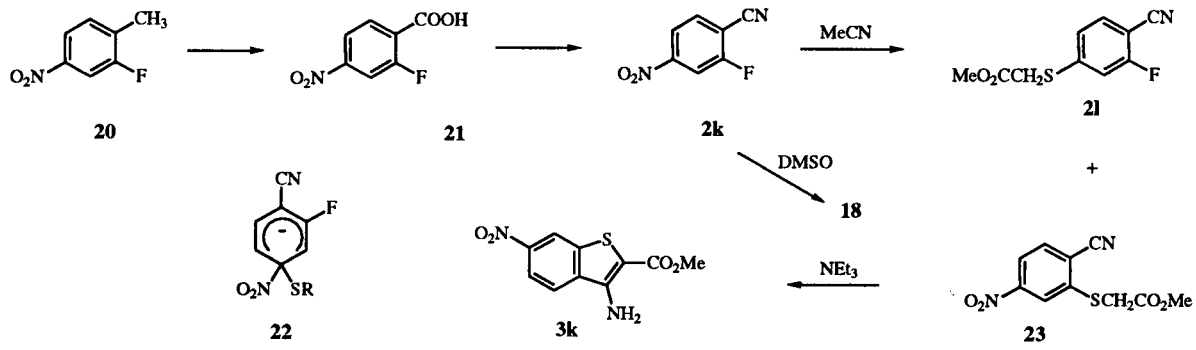
18 4:1 3k 3l

Displacement on 2,4-dinitrobenzonitrile with thioglycollate in ethanolic potassium hydroxide is reported to give the benzothiophene **3k** [11]. When we repeated that reaction under the literature conditions of slowly adding the base last, the products were the double displacement product **18**, and the desired benzothiophene in a 4:1 ratio. When the thiolate anion was preformed and added to the reaction mixture, the only products were **18** and its cyclization product **3l**.

In order to bias this system in favor of 2-displacement, the 2-fluoro derivative **2k** [23,24] was prepared by oxidation of toluene **20** to acid **21** [25], followed by conversion to nitrile **2k** as described previously for **2b**. Reaction of **2k** with one equivalent of thioglycollate in dimethyl sulfoxide under mildly basic conditions gave only **18** in moderate yield. This unexpected result was investigated by nmr experimentation, which showed that the initial



7 17 2i 3j



displacement was occurring exclusively at the 4-position, to form **2l**, a result not entirely consistent with the exclusive isolation of **18**. As we expected the fluorine displacement to be easier than nitro displacement, and as we did not expect the fluorine of **2l** to be activated enough to displace under our mild reaction conditions, this nmr result was puzzling, but both the large change in chemical shifts upon nitro (but not fluoro) displacement, and the retention of the characteristic F-H couplings in **2l** left no doubt as to its structure. It was surmised that the highly polar solvents used might favor a Reissert type intermediate **22**, rather than an electron transfer process which we assume to be the mechanism of fluoride displacement. Therefore we looked at this reaction in a series of less polar solvents using nmr, to see if this highly active system would still undergo reaction, and if the course of the reaction would be changed. No reaction occurred in chloroform or ethyl acetate, but in both acetone and acetonitrile a 1:1 mixture of **2l** and **23** were obtained. In the presence of excess triethylamine **23** spontaneously cyclized to **3k**. When this reaction was scaled up, the major product was **18**, but on running the reaction at low concentration **3k** was obtained in 47% yield after purification. Neither formamide nor formamidine acetate heated with **3k** under the usual conditions, led to appreciable pyrimidone annulation, but **4k** was produced in 36% yield when heated with formamidine acetate at 190° for 5 hours.

Conclusions.

A variety of electron rich benzo ring-substituted benzo[*b*]thieno[3,2-*d*]pyrimid-4(3*H*)-ones, or their nitro precursors have been prepared. Several different techniques had to be used to produce the α-cyano thioether intermediates, and the initial displacement-annulation proved to be at best partially effective if strong enough electron donors were present. Additionally, the second annulation often requires careful manipulation of conditions to produce acceptable yields. Activation of the 4-position, reduction of nitro substituents to amines, and biological activity of suitably substituted derivatives of these tricycles will be reported on elsewhere.

EXPERIMENTAL

3*H*-[1]Benzothieno[3,2-*d*]pyrimid-4-one **4a**.

Ethyl 3-Aminobenzothiophene-2-carboxylate **3a**.

2-Fluorobenzonitrile (0.61 g, 5 mmoles), ethyl thioglycollate (0.60 g, 5 mmoles) and triethylamine (1.52 g, 15 mmoles) were stirred in dimethyl sulfoxide (5 ml) at 100° under nitrogen for 3 hours. The reaction mixture was poured onto ice-water (50 ml), and the solid was collected by suction filtration, rinsed with water, and air dried to give ethyl 3-aminobenzothiophene-2 carboxylate [7] (0.78 g, 70%) as a gray-brown solid; ^{1}H nmr (DMSO-d_6): δ 8.14 (1 H, d, J = 7.7 Hz), 7.88 (1 H, d, J = 8.1 Hz), 7.50 (1 H, dt, J_d = 1.2 Hz, J_t = 7.5 Hz), 7.39 (1 H, dt, J_d = 1.2 Hz, J_t = 7.6 Hz), 7.17 (2 H, brs), 4.26 (2 H, q, J = 7.1 Hz), 1.29 (3 H, t, J = 7.1 Hz).

3*H*-[1]Benzothieno[3,2-*d*]pyrimid-4-one **4a**.

Ethyl 3-aminobenzothiophene-2-carboxylate (764 mg, 3.45 mmoles) was heated in formamide (2 ml) under nitrogen at 140° for 2 hours, and at 180° for 20 hours. The solution was allowed to cool to 25°, and the slurry was diluted with ethanol (5 ml). The solid was collected by suction filtration, rinsed with ethanol (2 x 5 ml), and air dried to give 3*H*-[1]benzothieno[3,2-*d*]-pyrimid-4-one [11] (0.55 g, 79%) as a highly crystalline dark brown solid; ^{1}H nmr (DMSO-d_6): δ 12.85 (1 H, brs), 8.35 (1 H, s), 8.16 (1 H, d, J = 7.3 Hz), 7.67 (1 H, dt, J_d = 1.6 Hz, J_t = 7.5 Hz), 7.59 (1 H, dt, J_d = 1.2 Hz, J_t = 7.5 Hz).

9-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4b.**

2-Fluoro-6-methoxybenzaldoxime.

Hydroxylamine hydrochloride (334 mg, 4.76 mmoles) was added in portions to a solution of sodium bicarbonate (395 mg, 4.7 mmoles) in water (10 ml) at 25°. To this solution was added dropwise a mixture of 2-fluoro-6-methoxybenzaldehyde (725 mg, 4.7 mmoles) and ethanol (10 ml). The resulting mixture was stirred at 25° for 2 hours. The precipitate was collected by filtration and dried in a vacuum oven at 50° overnight to give 2-fluoro-6-methoxybenzaldoxime (720 mg, 89%); ^{1}H nmr (DMSO-d_6): δ 11.44, (1 H, s), 8.16 (1 H, s), 7.40, (1 H, m) 6.85~6.95 (2 H, m), 3.84 (3 H, s).

2-Fluoro-6-methoxybenzonitrile **2b**.

A solution of 2-fluoro-6-methoxybenzaldoxime (714 mg, 4.2 mmoles) in acetic anhydride (3.6 ml) was heated at reflux for 4 hours. The reaction was cooled to 25° and the volatile materials were removed to give a beige solid, which was dried at 50° in a

vacuum oven to give 2-fluoro-6-methoxybenzonitrile (635 mg, 84%); ^{1}H nmr (DMSO-d_6): δ 7.8-7.7 (1 H, m), 7.14-7.07 (2 H, m), 3.95 (3 H, s).

Methyl 3-Amino-4-methoxy[1]benzothiophene-2-carboxylate **3b**.

Methyl thioglycollate (0.18 ml, 1.9 mmoles) was added dropwise to a suspension of hexane-washed sodium hydride (60% oil suspension, 176 mg, 4.4 mmoles) in dimethyl sulfoxide (5 ml), while stirring under nitrogen at 25°. When gas evolution ceased, 2-fluoro-6-methoxybenzonitrile (266 mg, 1.76 mmoles) in dimethyl sulfoxide (5 ml) was added in one portion. After 3 hours, the reaction mixture was poured onto ice-water, and the beige precipitate was collected by suction filtration, rinsed with water and air dried to give methyl 3-amino-4-methoxybenzothiophene-2-carboxylate (345 mg, 83%); ^{1}H nmr (DMSO-d_6): δ 7.44-7.37 (2 H, m), 7.00, (2 H, brs), 6.90 (1 H, d, J = 7.7 Hz), 3.95 (3 H, s), 3.76 (3 H, s).

9-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4b**.

A mixture of methyl 3-amino-4-methoxybenzothiophene-2-carboxylate (202 mg, 0.85 mmole) and formamide (2 ml) was heated at 135° for 1 hour and then the temperature was raised to 190°. After 8 hours the reaction was cooled and the black solid was collected by filtration and air dried to give 9-methoxy-3*H*-benzothieno[3,2-*d*]pyrimid-4-one (45 mg, 23%), mp 312-313.0°: ^{1}H nmr (DMSO-d_6): δ 12.0 (1 H, brs), 8.31 (1 H, s), 7.70-7.55 (2 H, m), 7.10 (1 H, d, J = 7.7 Hz), 3.97 (3 H, s); ms: (CI) 233 (100, MH^+), 232 (28, M^+).

Anal. Calcd. for $C_{11}H_8N_2O_2S \cdot 0.15H_2O$: C, 56.23; H, 3.56; N, 11.93. Found: C, 56.22; H, 3.52; N, 12.03.

6-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4c**.

2-Fluoro-3-methoxybenzamide.

Catalytic dimethylformamide was added to a solution of 2-fluoro-3-methoxybenzonic acid [14] (710 mg, 4.2 mmoles) and oxalyl chloride (0.4 ml, 4.6 mmoles) in dichloromethane (20 ml), stirred under nitrogen at 25°. Gas evolution was observed for 3.5 hours after which ammonia was bubbled through the reaction solution for 5 minutes. A white solid formed immediately. After 20 minutes the solid was filtered and rinsed with dichloromethane. The filtrates were concentrated under reduced pressure to give 2-fluoro-3-methoxybenzamide (650 mg, quantitative) as a light yellow solid; ^{1}H nmr (DMSO-d_6): δ 7.67 (1 H, brs), 7.57 (1 H, brs), 7.2 (1 H, dt, J_d = 2.0 Hz, J_t = 7.8 Hz), 7.13-7.05 (2 H, m), 3.80 (3 H, s).

2-Fluoro-3-methoxybenzonitrile **2c**.

A mixture of 2-fluoro-3-methoxybenzamide (650 mg, 4.2 mmoles) and a preformed solution of phosphorus pentoxide/hexamethyl disiloxane [18] in *ortho*-dichlorobenzene (20 ml) was heated under nitrogen at 100° for 4 hours. When cooled to rt, the reaction solution was poured onto a plug of silica gel (30 g) followed by washing with sufficient hexane, and chloroform, then with 5% methanol/chloroform (3 x 200 ml). The 5% methanol washes were collected and concentrated under reduced pressure to give 2-fluoro-3-methoxybenzonitrile (350 mg, 53%) as a light brown solid; ^{1}H nmr (DMSO-d_6): δ 7.58 (1 H, dt, J_d = 1.4 Hz, J_t = 8.5 Hz), 7.43-7.32 (2 H, m) 3.90 (3 H, s).

Methyl 3-Amino-7-methoxy[1]benzothiophene-2-carboxylate **3c**.

This compound was made by the same procedure as **3b**, and was isolated as a yellow solid in 43% yield, mp 193.0-194.5°; ^{1}H nmr (DMSO-d_6): δ 7.67 (1 H, d, J = 8.1 Hz), 7.32 (1 H, t, J = 7.8 Hz), 7.09 (2 H, brs), 7.03 (1 H, d, J = 7.8 Hz), 3.88 (3 H, s), 3.72 (3 H, s); ms: (CI) 238 (71, MH^+), 237 (92, M^+) 206 (100, M-OCH_3^+).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.84; H, 4.66; N, 5.81.

6-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one.

The same procedure as in the preparation of **4b** was used. The desired product was isolated as a dark brown solid in 56% yield, mp >320°; ^{1}H nmr (DMSO-d_6): δ 8.29 (1 H, s), 7.78 (1 H, d, J = 7.3 Hz), 7.52 (1 H, t, J = 7.8 Hz), 7.21 (1 H, d, J = 7.6 Hz), 3.97 (3 H, s); ms: (CI) 233 (100, MH^+), 232 (37, M^+); hrms: (CI) Calcd. for $C_{11}H_8N_2O_2S \cdot H^+$: 233.0385. Found: 233.0374.

Anal. Calcd. for $C_{11}H_8N_2O_2S \cdot 0.05H_2O$: C, 56.66; H, 3.50; N, 12.02. Found: C, 56.37; H, 3.11; N, 12.36.

7-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4d**.

Methyl 3-amino-6-methoxy[1]benzothiophene-2-carboxylate **3d**.

A solution of 2,4-difluorobenzonitrile (1.39 g, 10 mmoles) and sodium methoxide (1.08 g, 20 mmoles) in methanol (20 ml) was refluxed with stirring under nitrogen for 48 hours. On cooling, the mixture was diluted with water (25 ml) and extracted with ether (3 x 10 ml). The combined extracts were washed with water (3 x 10 ml) saturated brine (10 ml) and dried (magnesium sulfate). The solvent was removed under reduced pressure to give an undefined 5:4 mixture of 2-fluoro-4-methoxybenzonitrile **2d** and 4-fluoro-2-methoxybenzonitrile **8** (1.20 g, 72% combined yield) which was used directly in the next reaction. This mixture in dimethyl sulfoxide (2 ml) was added to a preformed solution of potassium *t*-butoxide (1.68 g, 15 mmoles) and methyl thioglycollate (1.06 g, 10 mmoles) in dimethyl sulfoxide (10 ml), stirred under nitrogen at 25°. After 2 minutes the now warm reddish-brown solution was heated to 60° for 5 minutes, and was then poured into vigorously stirred ice-water (50 ml). A sticky, yellow solid formed and after 15 minutes it was collected by Buchner filtration, rinsed with water and air dried. The resulting solid (1.12 g) was recrystallized from chloroform to give, after multiple recrystalizations of the mother liquors, methyl 3-amino-6-methoxy[1]benzothiophene-2-carboxylate **3d** (335 mg, 14% based on the difluoride **7**). The analytical sample (methanol) had mp 163.5-165°; ^{1}H nmr (DMSO-d_6): δ 8.02 (1 H, d, J = 8.8 Hz), 7.38 (1 H, d, J = 2.2 Hz), 7.12 (2 H, brs), 7.00 (1 H, dd, J = 8.9, 2.2 Hz), 3.83 (3 H, s), 3.76 (3 H, s); ms: (CI) 238 (86, MH^+), 237 (65, M^+), 206 (100, M - OCH_3^+).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.54; H, 4.59; N, 5.63.

7-Methoxy-3*H*-benzothieno[3,2-*d*]pyrimid-4-one **4d**.

A stirred solid mixture of methyl 3-amino-6-methoxybenzothiophene-2-carboxylate (288 mg, 1.2 mmoles) and formamidine acetate (624 mg, 6.0 mmoles) was heated rapidly under nitrogen to 175°, and kept at that temperature for 10 minutes. On cooling, the solid residue was mixed with water (5 ml) and sonicated. The solid was collected by Buchner filtration, rinsed with water (2 x 5 ml), chloroform (5 ml) and dried *in vacuo* at 75° to give 7-methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4d** (227 mg, 81%) as a fawn solid, mp 325-326°; ^{1}H nmr (DMSO-d_6): δ 12.75 (1 H, brs), 8.30 (1 H, s), 8.10 (1 H, d, J = 8.8 Hz), 7.74 (1 H, d, J = 2.5 Hz), 7.19 (1 H, dd, J = 8.8, 2.2 Hz), 3.89 (3 H, s); ms: (CI) 233 (100, MH^+), 232 (26, M^+).

Anal. Calcd. for $C_{11}H_8N_2O_2S$: C, 56.89; H, 3.47; N, 12.06. Found: C, 56.55; H, 3.51; N, 12.02.

8-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4e**.

Methyl 3-Amino-5-methoxy[1]benzothiophene-2-carboxylate **3e**.

n-Butyllithium (0.46 ml, 1.0 mmole) was added dropwise to a solution of 2-bromo-5-methoxybenzonitrile [26] (218 mg, 1.0 mmole) in dry ethyl ether (5 ml) stirred under nitrogen at -110°. After 5 minutes resublimed sulfur (64 mg, 2.0 mmoles) was added to the light yellow solution and the resulting mixture was allowed to warm up slowly to -50° when methyl bromoacetate (0.12 ml, 1.2 mmoles) was added. The reaction mixture was then warmed up to 25° and quenched by addition of dilute hydrochloric acid (0.1 *M*, 10 ml). The undissolved yellow solid was collected by filtration and dried. The mother liquors were concentrated down and purified by preparative tlc, eluting with 1% methanol/chloroform. The product was combined with the previous solid to give methyl 3-amino-5-methoxy[1]benzothiophene-2-carboxylate (82 mg, 35%) as a yellow solid, mp 149-150°; ^{1}H nmr (DMSO-d_6): δ 7.68 (1 H, d, J = 2.4 Hz), 7.65 (1 H, d, J = 8.9 Hz), 7.10-7.06 (3 H, m), 3.77 (3 H, s), 3.72 (3 H, s); ms: (CI) 238 (56, MH^+), 237 (62, M^+), 206 (100, M - OCH_3^+).

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; N, 5.90. Found: C, 55.46; H, 4.71; N, 5.85.

8-Methoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4e**.

A mixture of methyl 3-amino-5-methoxy[1]benzothiophene-2-carboxylate (78 mg, 0.33 mmole) and formamidine acetate (175 mg, 1.68 mmoles) was heated at 180° for 5 minutes and cooled to 25°. The reaction mixture was treated with dilute aqueous sodium carbonate solution and extracted with chloroform. The combined organic extracts were washed with water, saturated brine and dried (sodium sulfate). Removal of the solvent gave a brown solid which was a mixture of **3e** and **4e**, which were separated by preparative tlc eluting with 2% methanol/chloroform to give 8-methoxy-3*H*-[1]benzothieno-[3,2-*d*]pyrimid-4-one (7.5 mg, 10%); mp 287-288°; ^{1}H nmr (DMSO-d_6): δ 12.77 (1 H, brs), 8.27 (1 H, s), 7.99 (1 H, d, J = 8.8 Hz), 7.53 (1 H, t, J = 7.8 Hz), 7.40 (1 H, d, J = 7.8 Hz), 3.84 (3 H, s); ms: (CI) 233 (100, MH^+), 232 (32, M^+).

Anal. Calcd. for $C_{11}H_8N_2O_2S \cdot 0.4H_2O$: C, 55.17; H, 3.70; N, 11.70. Found: C, 55.41; H, 3.55; N, 11.34.

7,8-Dimethoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4f**.

2-Bromo-4,5-dimethoxybenzaldoxime.

This compound was prepared from 2-bromo-4,5-dimethoxybenzaldehyde as described above for **2b** in 90% yield; ^{1}H nmr (DMSO-d_6): δ 11.38 (1 H, s), 8.15 (1H, s), 7.42 (1 H, s), 7.23 (1 H, s), 3.75 (3 H, s), 3.72 (3 H, s).

2-Bromo-4,5-dimethoxybenzonitrile **10**.

This compound was prepared from 2-bromo-4,5-dimethoxybenzaldoxime as described above for compound **2b** in 100% yield; ^{1}H nmr (DMSO-d_6): δ 7.44 (1 H, s), 7.34 (1 H, s), 3.81 (3 H, s), 3.28 (3 H, s).

Methyl 3-Amino-5,6-dimethoxy[1]benzothiophene-2-carboxylate **3f**.

n-Butyllithium (0.39 ml, 0.85 mmole) was added dropwise to a solution of 2-bromo-4,5-dimethoxybenzonitrile (206 mg, 0.85 mmole) in anhydrous ethyl ether (5 ml) stirred under nitrogen at -110°. After 5 minutes, resublimed sulfur (27 mg, 0.84 mmole) was added to the reaction solution and the temperature was allowed to warm up slowly to -50° when methyl bromoacetate (0.10 ml, 1.03 mmoles) was added dropwise. The reaction was allowed to gradually warm up to 25° and was quenched with water and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were washed with water, saturated brine, and dried (magnesium sulfate). Concentration under reduced pressure gave methyl 3-amino-5,6-dimethoxy[1]benzothiophene-2-carboxylate (180 mg, 79%) as a yellow solid, mp 222.5-223.5°; ^{1}H nmr (DMSO-d_6): δ 7.69 (1 H, s), 7.36 (1 H, s), 7.07 (2 H, brs), 3.83 (3 H, s), 3.82 (3 H, s), 3.75 (3 H, s); ms (CI) 268 (53, MH^+), 267 (83, M^+), 236 (100, M - OCH_3^+).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.29; H, 4.90; N, 5.24. Found: C, 53.58; H, 4.91; N, 5.11.

7,8-Dimethoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4f**.

Methyl 3-Amino-5,6-dimethoxy[1]benzothiophene-2-carboxylate (124 mg, 0.46 mmole) was converted into 7,8-dimethoxy-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one (100 mg, 83%) using the same procedure as described above for **4b**, mp 300° dec; ^{1}H nmr (DMSO-d_6): δ 8.23 (1 H, s), 7.67 (1 H, s), 7.56 (1 H, s), 3.84 (3 H, s), 3.84 (3 H, s); ms: (CI) 263 (100, MH^+), 262 (41, M^+).

Anal. Calcd. for $C_{12}H_{10}N_2O_3S \cdot 0.25H_2O$: C, 54.02; H, 3.97; N, 10.50. Found: C, 54.02; H, 3.88; N, 10.51.

8-Nitro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4g**.

2-Fluoro-5-nitrobenzonitrile **2g**.

A mixture of concentrated nitric and sulfuric acids (1:1, 120 ml) was added dropwise over 1 hour to a solution of 2-fluorobenzonitrile (48.44 g, 0.4 mole) in sulfuric acid (200 ml), stirred under nitrogen at 0°. After a further 2 hours at 0°, the reaction mixture was poured slowly into stirred ice-water (1.2 l). After 1 hour, the pale yellow solid was collected by Buchner filtration, rinsed with water (4 x 100 ml), and air dried to give 2-fluoro-5-nitrobenzonitrile (62.79 g, 95%) as a pale yellow solid (**IRRITANT**); ^{1}H nmr (chloroform-d): δ 8.56 (1 H, dd, J = 5.5, 2.8 Hz), 8.51 (1 H, ddd, J = 9.1, 4.4, 2.8 Hz), 7.44 (1 H, dd, J = 9.0, 7.8 Hz).

Methyl 3-Amino-5-nitro[1]benzothiophene-2-carboxylate **3g**.

Methyl thioglycollate (29.29 g, 276 mmoles) was added over 3 minutes to a two phase mixture of triethylamine (80 ml, 0.55 mole) and 2-fluoro-5-nitrobenzonitrile (45.91 g, 276 mmoles) in dimethyl sulfoxide (250 ml), stirred under nitrogen at 25°. The solution rapidly darkened to a deep red-brown, there was a considerable exotherm, and the mixture became monophasic. After 30 minutes an orange-red ppt appeared. After 2 hours, the reaction mixture was poured into stirred ice-water (1.5 l), and the solid was collected by Buchner filtration, rinsed with water (4 x 100 ml), and dried in a vacuum oven at 60° to give methyl 3-amino-5-nitro-[1]benzothiophene-2-carboxylate (68.44 g, 98%) as a bright orange-red crystalline solid; ^{1}H nmr (DMSO-d_6): δ 9.23 (1 H, d, J = 2.1 Hz), 8.28 (1 H, dd, J = 8.8, 2.2 Hz), 8.11 (1 H, d, J = 8.8 Hz), 7.47 (2 H, brs), 3.34 (3 H, s); ms: (CI) 253 (100, MH^+), 252 (52, M^+).

Anal. Calcd. for $C_{10}H_8N_2O_4S$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.69; H, 3.17; N, 11.13.

Methyl 3,*N*-(*O*-Ethylformimidoyl)-5-nitro[1]benzothiophene-2-carboxylate **15**.

A slurry of methyl 3-amino-5-nitrobenzothiophene-2-carboxylate (25.22 g, 0.10 mole) and tosic acid monohydrate (0.38 g, 2 mmoles) in diglyme (50 ml) and triethyl orthoformate (30.66 g, 0.20 mole) was heated to 140°, with stirring under nitrogen, and volatile products were distilled out through a 15 cm Vigreux column and a short path stillhead at ~80°. When distillation ceased, the reddish solution was heated to 185°, causing further liquid to distill over at ~100°. When this distillation ceased, the reaction mixture was allowed to cool, and at 100° triethylamine (0.5 ml) was added, and the reaction mixture was allowed to crystallize at 25° overnight. The solid was collected by Buchner filtration, rinsed with methanol (2 x 50 ml), and briefly vacuum oven dried at 50° to give methyl 3,*N*-(*O*-ethylformimidoyl)-5-nitro[1]benzothiophene-2-carboxylate (28.94 g, 95%) as light yellow needles, which were very prone to hydrolysis; ^{1}H nmr (DMSO-d_6): δ 8.46 (1 H, d, J = 2.0 Hz), 8.33 (1 H, dd, J = 8.9, 2.3 Hz), 8.27 (1 H, d, J = 8.8 Hz), 8.16 (1 H, brs), 4.45 (2 H, brq, J = 7 Hz), 3.82 (3 H, s), 1.40 (3 H, brt, J = 7 Hz).

8-Nitro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4g**.

Methyl 3,*N*-(*O*-ethylformimidoyl)-5-nitrobenzothiophene-2-carboxylate (122.8, 398 mmoles containing 4% of **2g**) and sodium methoxide (21.5 g, 0.40 mole) in saturated ammoniacal methanol (1.3 l) was sealed in a stainless steel bomb and stirred at 25° for 1 hour and then heated to 60° for 20 hours, and allowed to cool to 20°. The thick yellow slurry was rinsed out of the bomb with further methanol (0.4 l), and acetic acid (24 g, 0.4 mole) and water (1 l) were added to the stirred slurry, which was then heated to reflux. The mixture was vigorously sparged with nitrogen, and reduced in volume to about 1.8 l. Ice (1.2 l) was then added and the reaction mixture was filtered. The precipitate was rinsed with methanol and dried in a vacuum oven to give 8-nitro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one (92.36 g, 91% corrected yield, containing 6.5% of **2g**). The analytical sample from methoxyethanol had mp >340°; ^{1}H nmr (DMSO-d_6): δ 13.10 (1 H, brs), 8.92 (1 H, s), 8.50-8.44 (3 H, m); ms: (CI) 248 (100, MH^+), 247 (15, M^+).

Anal. Calcd. for $C_{10}H_5N_3O_3S$: C, 48.58; H, 2.04; N, 17.00. Found: C, 48.54; H, 2.14; N, 16.71.

7-Ethylamino-8-fluoro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4h**.

4-Ethylamino-2,5-difluorobenzonitrile **2h**.

Ethylamine was bubbled for 5 minutes through a stirred solution of 2,4,5-trifluorobenzonitrile (943 mg, 6 mmoles) in dimethyl formamide (3 ml). There was an immediate exotherm, and a gelatinous precipitate. The mixture was capped and stirred at 25° for 2 hours and was then poured into dilute sodium hydroxide solution (0.2 M, 20 ml) and stirred at 0° for 30 minutes. The solid was collected by Buchner filtration, rinsed with water (2 x 10 ml) and air dried to give 4-ethylamino-2,5-difluorobenzonitrile (1.076 g, 98%) as a pale yellow solid mp 75.5-77°; ^{1}H nmr (DMSO-d_6): δ 7.56 (1 H, dd, J = 11.7, 6.1 Hz), 6.98 (1 H, brt, J = 5.6 Hz), 6.73 (1 H, dd, J = 12.3, 7.2 Hz), 3.18 (2 H, dq, J_d = 5.6 Hz, J_q = 7.3 Hz), 1.13 (3 H, t, J = 7.3 Hz); ms: (CI) 183 (100, MH^+), 182 (21, M^+).

Anal. Calcd. for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38. Found: C, 59.3; H, 4.48; 15.42.

Methyl 3-Amino-6-ethylamino-5-fluoro[1]benzothiophene-2-carboxylate **3h**.

Methyl thioglycollate (0.40 ml, 4.4 mmoles) was added dropwise to a hexane-washed suspension of sodium hydride (60% oil suspension, 249 mg, 6.25 mmoles) in dimethyl sulfoxide (10 ml), stirred under nitrogen at 25°. When gas evolution diminished, 4-ethylamino-2,5-difluorobenzonitrile (729 mg, 4.0 mmoles) was added in one portion, and after 10 minutes the mixture was heated to 75° for 10 minutes. The reaction mixture was poured into stirred ice-water (50 ml) and after 30 minutes the solid was collected by Buchner filtration, rinsed with water (2 x 10 ml) and dried *in vacuo* at 60° to give methyl 3-amino-6-ethylamino-5-fluoro[1]benzothiophene-2-carboxylate (674 mg, 52%) as a beige solid containing 22 mol% of **2h**. The analytical sample from methanol had mp 149.5-151°; ^{1}H nmr (DMSO-d_6): δ 7.79 (1 H, d, J = 12.5 Hz), 6.97 (2 H, brs), 6.95 (1 H, d, J = 8.1 Hz), 6.03 (1 H, dt, J_d = 2.0 Hz, J_t = 6.4 Hz), 3.72 (3 H, s), 3.16 (2 H, pentet, J = 7 Hz), 1.18 (3 H, t, J = 7.0 Hz); ms: (CI) 268 (100, M^+).

Anal. Calcd. for $C_{12}H_{13}FN_2O_2S$: C, 53.76; H, 4.88 N, 10.44. Found: C, 53.86; H, 4.96; 10.46.

7-Ethylamino-8-fluoro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4h**.

Methyl 3-amino-6-ethylamino-5-fluoro[1]benzothiophene-2-carboxylate (740 mg, 2.76 mmoles) and formamidinium acetate (1.56 g, 15 mmoles) were heated rapidly to 180° under nitrogen and kept at that temperature for 10 minutes. The mixture was cooled, and then treated vortically with water (10 ml). The solid was collected by Buchner filtration, rinsed with water (10 ml) and chloroform (2 x 10 ml) and dried in a vacuum oven at 50° to give 7-ethylamino-8-fluoro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one (672 mg, 83%), containing 6 mol% of starting material. The analytical sample from methoxyethanol had mp >325°; ^{1}H nmr (DMSO-d_6): δ 8.23 (1 H, s), 7.72 (1 H, d, J = 11.5 Hz), 7.30 (1 H, d, J = 7.8 Hz), 6.26 (1 H, brt, J = 5.6 Hz), 3.22 (2 H, dq, J_d = 5.6 Hz, J_t = 7.1 Hz), 1.21 (3 H, t, J = 7.1 Hz); ms: (CI) 264 (100, MH^+), 263 (82, M^+).

Anal. Calcd. for $C_{12}H_{10}FN_3OS$: C, 54.74; H, 3.83 N, 15.96. Found: C, 54.59; H, 3.76; 15.86.

7-Amino-8-fluoro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4i**.

4-Amino-2,5-difluorobenzonitrile **2i**.

A mixture of 2,4,5-trifluorobenzonitrile (1.571 g, 10 mmoles) and liquid ammonia (3 ml) was sealed in a 50 ml stainless steel pressure bomb, and heated to 60° for 4.5 hours. The bomb was cooled to 0°, and the excess gas was cautiously vented. The residual pale yellow solid was scraped out of the bomb, and extracted with ether (50 ml). The slurry was filtered, and the filtrate was rigorously evaporated under reduced pressure to give 4-amino-2,5-difluorobenzonitrile (1.536 g, quantitative) as a white crystalline solid, mp 36.5-38.5°; ^{1}H nmr (DMSO-d_6): δ 7.56 (1 H, dd, J = 11.0, 6.1 Hz), 6.66 (2 H, brs), 6.62 (1 H, dd, J = 11.6, 7.3 Hz); ms: (CI) 155 (100 MH+), 154 (17, M+).

Anal. Calcd. for $C_7H_4F_2N_2$: C, 54.55; H, 2.62; N, 18.18. Found: C, 54.59; H, 2.66; N, 18.34.

Methyl 3,6-Diamino-5-fluoro[1]benzothiophene-2-carboxylate **3i**.

4-Amino-2,5-difluorobenzonitrile (154 mg, 1.0 mmole) was added in one portion to a solution of methyl thioglycollate (150 µl, 1.65 mmoles) and potassium *t*-butoxide (177 mg, 1.58 mmoles) in dimethyl sulfoxide (2 ml), stirred under nitrogen at 25°. The reaction mixture was heated to 75° for 15 minutes and then poured into stirred water (10 ml). After 15 minutes the solid

was collected by Buchner filtration, rinsed with water (2 x 5 ml) and air dried to give methyl 3,6-diamino-5-fluoro[1]benzothiophene-2-carboxylate (92 mg, 38%) as a pale beige solid, mp 168-169.5°; ^{1}H nmr (DMSO-d_6): δ 7.80 (1 H, d, J = 12.2 Hz), 6.98 (2 H, brs), 6.95 (1 H, d, J = 8.1 Hz), 5.77 (2 H, brs), 3.72 (3 H, s); ms: (CI) 241 (65, MH^+), 240 (89, M^+), 209 (100, M - OCH_3^+).

Anal. Calcd. for $C_{10}H_9FN_2O_2S$: C, 49.99 H, 3.78 N, 11.66. Found: C, 49.93; H, 3.69; 11.61.

7-Amino-8-fluoro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4i**.

Methyl 3,6-Diamino-5-fluoro[1]benzothiophene-2-carboxylate (110 mg, 0.46 mmole) and formamidine acetate (0.52 g, 5 mmoles) were heated rapidly with stirring to 185°, under nitrogen. After 5 minutes at 185°, the reaction mixture was allowed to cool and was then suspended in water (5 ml) and sonicated. The solid was collected by Buchner filtration, rinsed with water (5 ml), and suspended in chloroform (20 ml) with sonication. The solid was again collected by Buchner filtration and dried *in vacuo* at 60° to give 7-amino-8-fluoro-3*H*-[1]benzothieno-[3,2-*d*]pyrimid-4-one (73 mg, 67%) as a brown solid. The analytical sample from methoxyethanol/methanol had mp >340°; ^{1}H nmr (DMSO-d_6): δ 8.23 (1 H, s), 7.73 (1 H, d, J = 11.2 Hz), 7.27 (1 H, d, J = 7.8 Hz), 5.99 (2 H, brs); ms: (CI) 236 (100 MH+), 235 (35, M+).

Anal. Calcd. for $C_{10}H_6FN_3OS \cdot 0.2CH_4O$: C, 50.69; H, 2.84 N, 17.39. Found: C, 50.55; H, 2.63; N, 17.12.

7-Nitro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4k**.

2-Fluoro-4-nitrobenzoic Acid [25].

To a solution of sodium dichromate (3.87 g, 13 mmoles) in acetic acid (20 ml) was added 2-fluoro-4-nitrotoluene (1.55 g, 10 mmoles) in portions, followed by dropwise addition of concentrated sulfuric acid (10 g). A strong exotherm was observed (100°) and the color changed from orange to green. The reaction was heated at 90° for 1 hour and cooled to 25°. The reaction mixture was dissolved in water (30 ml) and white crystals formed upon cooling at 0°. The white solid was collected by filtration washed with cold water and dried to give 2-fluoro-4-nitrobenzoic acid (0.99 g, 53%); ^{1}H nmr (DMSO-d_6): δ 8.16 (1 H, dd, J = 10.0, 2.0 Hz), 8.10-8.03 (2 H, m).

2-Fluoro-4-nitrobenzamide **2l**.

To a mixture of 2-fluoro-4-nitrobenzoic acid (0.98 g, 5.3 mmoles) and oxalyl chloride (0.48 ml, 5.5 mmoles) in dichloromethane (25 ml), stirred under nitrogen at 25°, was added 3 drops of dimethyl formamide. **Gas evolution!** The solid slowly dissolved and after 4 hours the volatile material was removed under reduced pressure. Saturated aqueous ammonia (5 ml) was added to the residue and the mixture was stirred for 10 minutes. The solid was extracted with chloroform.(3 x 20 ml). The combined organic layer was washed with water, saturated brine and dried (magnesium sulfate). The solvent was removed under reduced pressure to give 2-fluoro-4-nitrobenzamide (0.83 g, 85%) as a light yellow solid; ^{1}H nmr (DMSO-d_6): δ 8.15 (1 H, dd, J = 10.0, 2.2 Hz), 8.06 (1 H, dd, J = 8.5, 2.2 Hz), 8.02 (1 H, brs), 7.88 (1 H, brs), 7.81 (1 H, dd, J = 8.3, 7.0 Hz).

2-Fluoro-4-nitrobenzonitrile **2k**.

A mixture of 2-fluoro-4-nitrobenzamide (0.83 g, 4.6 mmoles) and phosphorus pentoxide/hexamethyldisiloxane in 1,2-dichloroethane [18] (20 ml) was heated under nitrogen at 100° for 4 hours. Upon cooling the solution was poured onto a plug of silica gel and washed with hexane (200 ml) followed by 5% methanol/chloroform (400 ml). The methanol/chloroform washes were collected and concentrated under reduced pressure to give 2-fluoro-4-nitrobenzonitrile (0.71 g, 95%) as a beige solid; ^{1}H nmr (DMSO-d_6): δ 8.46 (1 H, dd, J = 9.5, 2.0 Hz), 8.37-8.22 (2 H, m).

Methyl 3-Amino-6-nitro[1]benzothiophene-2-carboxylate **3k**.

Methyl thioglycollate (0.08 ml, 0.85 mmole) was added to a solution of 2-fluoro-4-nitrobenzonitrile (145 mg, 0.87 mmole) and triethylamine (0.14 ml, 1.0 mmole) in acetonitrile (20 ml) stirred under nitrogen at 25°. After 3 hours further triethylamine (0.28 ml, 2.0 mmoles) was added to the solution, which was stirred at 25° for a further 16 hours. The solvent was removed under reduced pressure to give a brown residue, which upon trituration with chloroform precipitated methyl 3-amino-6-nitro[1]benzothiophene-2-carboxylate (103 mg, 54%) as a red brown solid, mp 228.5-229.5° (lit [7] 229-231°); ^{1}H nmr (DMSO-d_6): δ 8.87 (1 H, d, J = 2.0 Hz), 8.32 (1 H, d, J = 9.0 Hz), 8.15 (1 H, dd, J = 8.8, 2.0 Hz), 7.26 (2 H, br), 3.77 (3 H, s); ms: (CI) 253 (100, MH^+), 252 (52, M^+).

7-Nitro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one **4k**.

A mixture of methyl 3-amino-6-nitro[1]benzothiophene-2-carboxylate (20 mg, 0.08 mmole) and formamidine acetate (59 mg, 0.57 mmole) was heated at 190° for 5 hours and cooled to 25°. The reaction residue was triturated with water and 7-nitro-3*H*-[1]benzothieno[3,2-*d*]pyrimid-4-one (7 mg, 36%) was obtained by Buchner filtration as a dark brown solid, mp >320°; ^{1}H nmr (DMSO-d_6): δ 9.21 (1 H, d, J = 1.7 Hz), 8.39 (1 H, d, J = 8.5 Hz), 8.38 (1 H, s), 8.32 (1 H, dd, J = 8.8, 2.0 Hz); ms: (CI) 248 (100, MH^+), 247 (30, M^+).

Anal. Calcd. for $C_{10}H_5N_3O_3S$: C, 48.58, H, 2.04; N, 17.00. Found: C, 48.19; H, 2.09; N, 16.77.

REFERENCES AND NOTES

[1] G. W. Rewcastle, B. D. Palmer, A. J. Bridges, H. D. H. Showalter, L. Sun, J. M. Nelson, A. McMichael, A. J. Kraker, D. W. Fry and W. A. Denny, *J. Med. Chem.*, **39** 918 (1996).

[2] A. J. Bridges, *Expert Opinions in Therapeutic Patents*, **5**, 1245 (1995).

[3] A. J. Bridges, H. Zhou, D. R. Cody, G. W. Rewcastle, A. McMichael, H. D. H. Showalter, D. W. Fry, A. J. Kraker and W. A. Denny, *J. Med. Chem.*, **39**, 267 (1996).

[4] J. R. Woodburn, A. J. Barker, A. E. Wakeling, S. A. Cartlidge, D. H. Davies and B. E. Valcaccia, *Proceedings of the 86th AACR Annual Meeting*, Abstract 2665 (1996).

[5] A. J. Bridges, A. D. Sercel, H. D. H. Showalter, H. Zhou, A. MacMichael and D. W. Fry, manuscript in preparation.

[6] G. G. De Angelis and H.-J. E. Hess, US Patent 3,706,747 (1972); *Chem. Abstr.*, **78**, 72187 (1973). US Patent 3,755,583 (1973); *Chem. Abstr.*, **79**, 11564 (1973).

[7] J. R. Beck, *J. Org.Chem.*, **37**, 3224 (1972).

[8] D. E. L. Carrington, K. Clarke and R. M. Scrowston, *J. Chem. Soc. (C)*, 3903 (1971).

[9] V. Niementowski, *J. Prakt. Chem.*, **51**, 564 (1895).

[10] M. Robba, P. Touzot and R. M. Riquelme, *Tetrahedron Letters*, 4549 (1972).

[11] J. R. Beck and J. A. Yahner, *J. Org. Chem.*, **38**, 2450 (1973).

[12] M. Robba, P. Touzot and H. El-Kashef, *J. Heterocyclic Chem.*, **17**, 1923 (1980).

[13] F. El-Telbany, and R. O. Hutchins, *J. Heterocyclic Chem.*, **22**, 401 (1985).

[14] A. J. Bridges, A. Lee, E. M. Maduakor and C. E. Schwartz, *Tetrahedron Letters*, **33**, 7495 (1992).

[15] A. J. Bridges, A. Lee, E. M. Maduakor and C. E. Schwartz, *Tetrahedron Letters*, **33**, 7499 (1992).

[16] J. H. Hunt, *Chem. Ind.*, 1873 (1961).

[17] E. C. Taylor and W. A. Ehrhart, *J. Am.. Chem. Soc.*, **82**, 3138 (1960).

[18] M. Yokoyama, S. Yoshida and S. Imamoto, *Synthesis*, 591 (1982).

[19] R. J. Mills, N. J. Taylor and V. Snieckus, *J. Org. Chem.*, **54**, 4372 (1989).

[20] T. D. Krizan and J. C. Martin, *J. Am. Chem. Soc.*, **105**, 6155 (1983).

[21] S. Gronowitz, M. Herslof, R. Svenson, G. Bondesson and O. Magnusson, *Acta Pharm. Suec.*, **15**, 368 (1978).

[22] H. Zhou and A. J. Bridges, unpublished results.

[23] J. F. Bunnett, E. W. Garbisch and K. M. Pruitt, *J. Am. Chem. Soc.*,**79**, 385 (1957).

[24] B. A. Bolto and J. Miller, *Aust. J. Chem.*, **9**, 74 (1956).

[25] A. L. Jackman, P. R. Marsham, T. J. Thornton, J. A. M. Bishop, B. M. O'Connor, L. R. Hughes, A. H. Calvert and T. R. Jones, *J. Med. Chem.*, **33**, 3067 (1990).

[26] A. P. Thomas, D. A. Roberts and D. A. Thomason, *Bioorg. Med. Chem. Letters*, **4**, 2615 (1994).