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Polycondensed Heterocycles. X. A New Method For The Preparation of Pyrrolo[2,1-*c*][1,4]benzothiazepines by Intramolecular Mitsunobu Cyclisation.

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Abstract: A modified Mitsunobu reaction of 2-hydroxymethylpyrrole and suitable thiophenol derivatives lead to intermediates which can be easily elaborated and eventually cyclised to the title compounds. The cyclisation step consists of another Mitsunobu reaction variation by which an "activated" pyrrole is N-alkylated intramolecularly, under very mild conditions.

Keywords: benzothiazepines; cyclisation; Mitsunobu reactions; pyrroles.

Pyrrolo[2,1-*c*][1,4]benzothiazepines represent a class of compounds which are supposed to possess interesting biological properties, but are still largely unknown.[1-3] However, the lack of general methods for the preparation of such compounds does not allow a deep investigation of their biological properties to be performed, all existing methods suffering from excessive length and low overall yields. In addition to the already described procedures,[3] we present herein new synthetic methods to the title products, involving an intramolecular Mitsunobu dehydration reaction, as a final cyclisation step. The first synthetic pathway starts from the known aldehyde **1**[4] which was smoothly reduced to the corresponding alcohol **2** by using $NaBH_4$. After demethylation, achieved by means of sodium in *N,N*-dimethylacetamide, thiophenol **3** had to be immediately reacted without purification, because of its high sensitivity to air oxidation, thus leading to a very low yield of tricyclic **4** in the subsequent cyclisation using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP) (Scheme 1).[5] An additional drawback of this procedure is the redox nature of the Mitsunobu reaction which is responsible for a side oxidation of the thiol group, so partly preventing it from taking part in dehydration. Accordingly, the partial success of the final cyclisation does not render the overall procedure effective due to poor isolated yields and to the instabilty of the intermediates. Once more, the hitherto available procedures for the synthesis of tricyclics of type **4** utilizing a preformed N-alkylated pyrrole as the starting material with a C(11)-S(10) bond formation in the final cyclisation step proved to be unsatisfactory.

Aldehyde **1**, the starting material for the above reported synthetic pathway, was independently prepared by us using a Mitsunobu reaction modification starting from alcohol **5** and 2-pyrrolecarboxyaldehyde **6** by means of the highly reactive 1,1'-(azodicarbonyl)dipiperidine (ADDP) and tri-*n*-butylphosphine (TBP) dehydrating system (Scheme 2).

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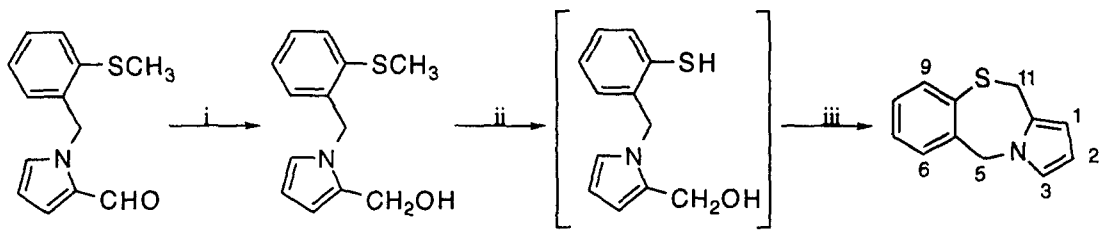
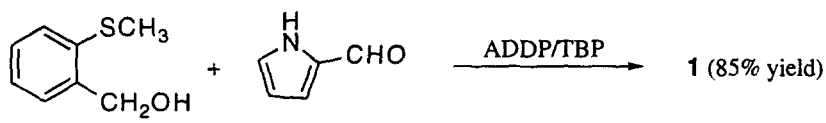
Scheme 1[a]



1 2 3 4

[a]*Reagents and conditions*: i) $NaBH_4$, 2-propanol, rt, 2 h, 92%; ii) Na, *N,N*-dimethylacetamide, 90°C, 8 h; iii) DIAD, TPP, THF, rt, 3 h, 30%.

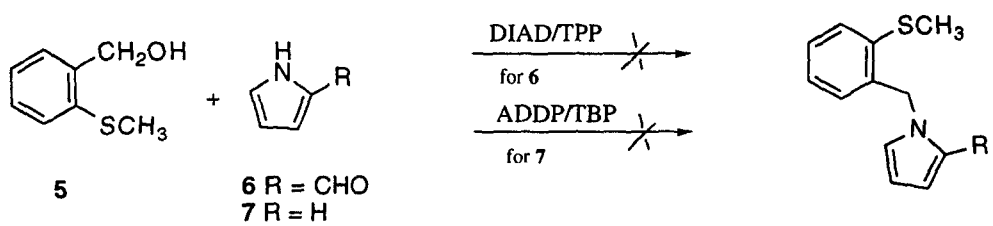
Scheme 2



5 6

Such a condensation was successful by virtue of both pyrrole NH proton acidity, a consequence of the presence of the electron withdrawing aldehyde carbonyl group, and to the effectiveness of the new dehydrating system, which is reported to be efficient even for weakly acidic proton (pKa up to 13).[6] In fact, no formation of condensation products could be detected using the classic Mitsunobu reagents, namely DIAD and TPP, in an attempt to obtain a similar condensation. On the other hand, the use of the more effective ADDP-TBP system does not succeed in N-alkylation "unactivated" pyrrole **7** (R = H, pKa = 17.5)[7] by alcohol **5** (Scheme 3).

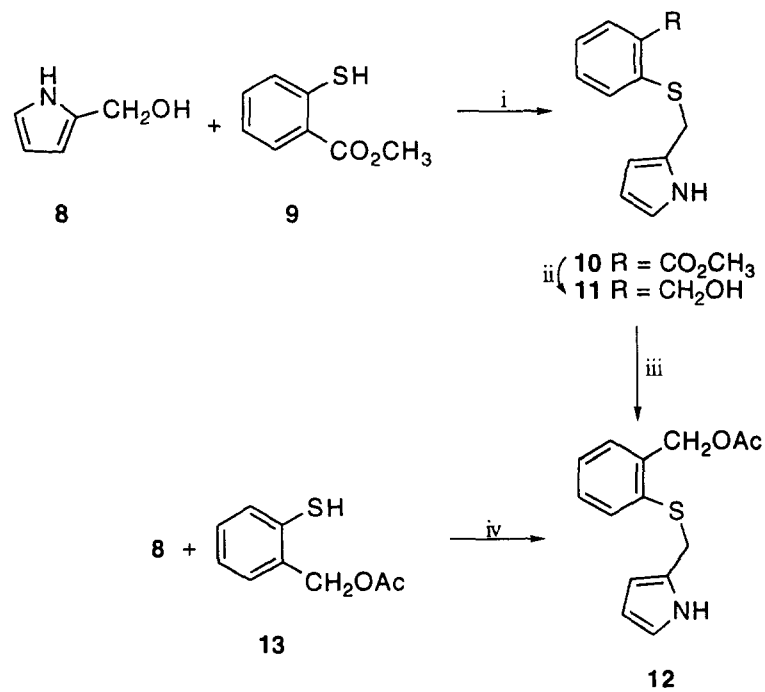
Scheme 3



5 **6** R = CHO
7 R = H

These results suggested an alternative synthetic route to the title compounds involving, contrary to the usual pathway, the formation of the C(5)-N(4) bond as the final step, provided an activating electron-withdrawing group was present at position 2 of the pyrrole ring. Thus, condensation of 2-hydroxymethylpyrrole **8**[8] (1 eq) and methyl thiosalicylate **9** (1 eq) under almost classic Mitsunobu conditions using TPP (1.2 eq) and DIAD (1.2 eq), following the procedure described by Volante,[5] led to sulfide **10**[9] (88% yield). LAH reduction of compound **10** followed by acetylation of intermediate alcohol **11** under standard conditions (Ac_2O, DMAP, pyridine) gave then compound **12**, in excellent yield. Furthermore, compound **12** could be directly obtained by condensation between alcohol **8** and thiosalicyl acetate **13**, in the same conditions as above (Scheme 4).

Scheme 4[a]

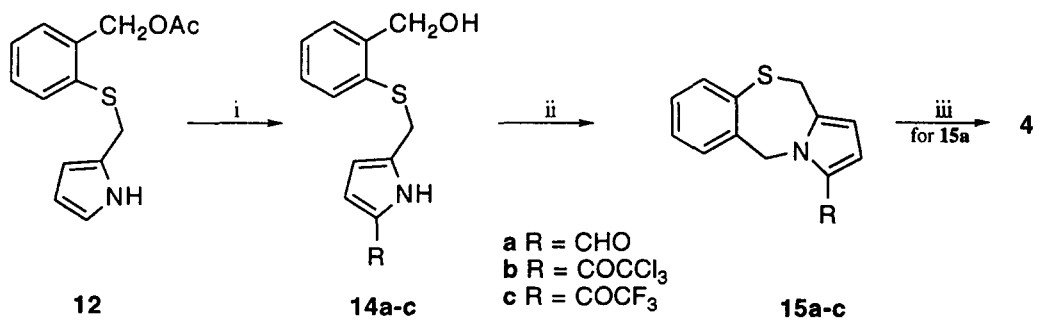


[a]*Reagents and conditions*: i) DIAD, TPP, THF, rt, 2 h, 88%; ii) LAH, Et_2O, 0°C, 15 min, 88%; iii) Ac_2O, DMAP, pyridine, 3 h, 92%; iv) DIAD, TPP, THF, 15 min, 83%.

With the aim at increasing the acidity of the pyrrole NH proton, compound **12** was formylated after Vilsmeier condition followed by an *in situ* deacetylation to **14a** adopting a prolonged hydrolytic work-up. Compound **14a** was eventually cyclised to 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine-3-carboxaldehyde **15a** by modified Mitsunobu reaction by means of the more reactive ADDP/TBP system,[6] in excellent yield. Similar results were obtained for compounds **14b** and **14c** prepared after acylation of **12** by trichloroacetyl chloride[10] or

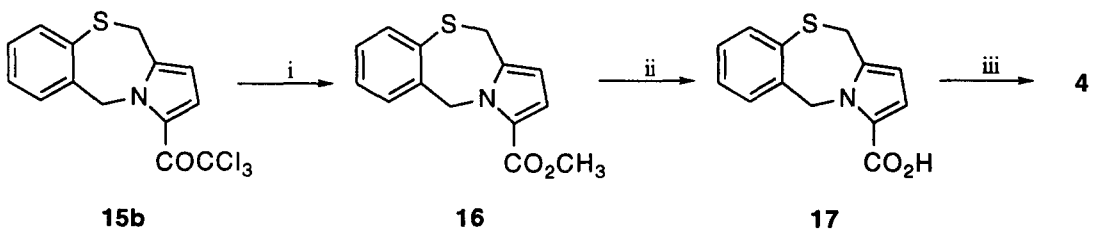
trifluoroacetic anhydride,[11] respectively, followed by an *in situ* hydrolysis of the intermediate esters, and subsequent cyclisation to **15b** and **15c** (Scheme 5). In an attempt to obtain the tricycle **4**, aldehyde **15a** was subjected to a decarbonylation reaction under different conditions, but it proved to be highly resistant even under harsh conditions (*i.e.* dil. H_2SO_4, 150°C, sealed tube). A 15% yield of tricycle **4** could only be isolated from **15a** by the use of 5% palladium on charcoal and mesitylene at reflux, following a procedure described by Anderson and co-workers.[12] Alternatively, ketone **15b** was transformed into the acid **17** by a two-step procedure using at first sodium methoxide in methanol to obtain the corresponding methyl ester **16**, then LiOH for the subsequent hydrolysis. Finally, decarboxylation of acid **17** in phenyl ether at 250°C gave a 58% yield of 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **4** (Scheme 6).

Scheme 5[a]



[a]*Reagents and conditions*: i) $POCl_3$/DMF or MeCOCl or TFAA then K_2CO_3; ii) ADDP, TBP, benzene/THF, rt, 3 h; iii) Pd/C, mesitylene, reflux, 3 h, 15%.

Scheme 6[a]



[a]*Reagents and conditions*: i) MeONa, MeOH, rt, 15 min, 80%; ii) $LiOH{\cdot}H_2O$, THF/MeOH/H_2O, reflux, 20 h, 85%; iii) Ph_2O, 250°C, 10 min, 58%.

No suitable conditions to transform the benzylic OH of compound **11** into an appropriate leaving group (*i.e.* halide, tosylate) to be subjected to intramolecular base catalyzed displacement by a virtual N-pyrrolyl anion were found. On the other hand, compound **10** proved to be very sensitive to bases (*i.e.* NaH/DMF, MeONa/MeOH, MeMgBr/ether) utilized in the attempt to generate a pyrrolyl anion, leading invariably to starting ester **9**, as the sole isolable degradation product. Such a behaviour could be tentatively explained by an increase of the electron density on the pyrrole nitrogen consequent to deprotonation. This would promote the formation of the electrophilic 1-azafulvene **18** (which would polymerize spontaneously),[13,14] with the elimination of the thiolate anion **19** (Scheme 7).

Aldehyde **15a**, ketones **15b,c** and acid **17** could best be envisaged as versatile intermediates to be elaborated into several potentially biologically active derivatives.[15]

In conclusion, we have herein described a short and efficient reaction sequence, which allows the preparation of numerous pyrrolobenzothiazepine derivatives, the biological evaluation of which are currently under scrutiny.

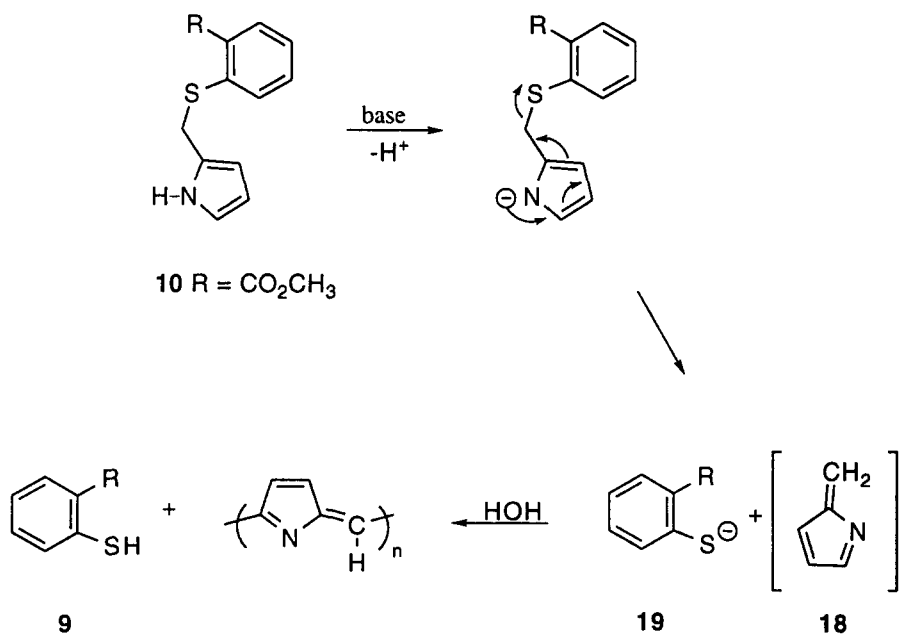
Experimental

Where necessary, solvents were dried and purified according to the recommended procedures.[16] Extracts were dried over Na_2SO_4 and solvents were removed under reduced pressure. Melting points were determined using an Electrothermal 8103 capillary apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 398 using KBr discs and nuclear magnetic resonance spectra were taken on a Bruker 200 instrument. The chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectral data were determined by direct insertion at 70 eV with a VG70 spectrometer. Flash chromatography separations were performed using Merck 230-400 mesh silica gel as the solid phase. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. All reactions were carried out in an argon atmosphere.

1-[2-(Methylthio)benzyl]pyrrole-2-carboxaldehyde **1**.

2-Methylthiobenzylalcohol **5** (1.09 g, 7 mmol), freshly distilled tri-*n*-butylphosphine (2.22 g, 11 mmol) and, pirrole-2-carboxaldehyde **6** (1.04 g, 11 mmol) were successively dissolved in dry benzene (20 ml) with stirring at 0°C, and solid ADDP (2.77 g, 11 mmol) was added to the solution. After 10 minutes, the reaction mixture was brought to room temperature and the stirring was continued for 48 hours. The solvent was removed and the resulting residue was triturated with diethyl ether:hexane, 1:1 (8 ml). Solid dihydro-ADDP which separated out was filtered off and the residue, obtained after evaporation of the solvent from the filtrate, was chromatographed on silica (benzene) to afford pure **1** as a solid (1.4 g, 85%), with physical and chemical data identical to those reported in ref. 4; mp 54° (light petroleum), Lit.[4] mp 53-54°.

Scheme 7



1-[2-(Methylthio)benzyl]-1*H*-pyrrole-2-methanol **2**.

To a stirred suspension of $NaBH_4$ (0.14 g, 3.6 mmol) in 2-propanol (10 ml) was added dropwise a solution of aldehyde **1** (0.42 g, 1.8 mmol) in 2-propanol (10 ml). The mixture was stirred at room temperature. for 2 hours. Removal of the solvent gave a white semi-solid which was stirred in water (20 ml) for 15 minutes, then extracted with dichloromethane. The organic layer was evaporated to dryness to give compound **2** as a solid (0.13 g, 92%); mp 68° (light petroleum); IR (nujol): υ cm^{-1}, 3380 (b OH); ^1H NMR ($CDCl_3$): δ 7.26 (d, 2 H, J = 4.0 Hz), 7.07 (m, 1 H), 6.64 (m, 1 H), 6.59 (m, 1 H), 6.19 (m, 1 H), 6.13 (t, 1 H, J = 3.0 Hz), 5.24 (s, 2 H), 4.52 (d, 2 H, J = 4.9 Hz), 2.49 (s, 3 H), 1.38 (bs, 1 H, exchangeable).

Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.79; H, 6.35; N, 5.91.

1-(2-Mercaptobenzyl)-1*H*-pyrrole-2-methanol **3**.

To a solution of alcohol **2** (2.3 g, 1 mmol) in *N,N*-dimethylacetamide (20 ml) were added small pieces of sodium (1 g, 0.043 mol) and the mixture was stirred at 90°C for 8 hours. After cooling to room temperature the mixture was poured onto crushed ice and the resulting solution was filtered and washed with diethyl ether (2 x 20 ml). The aqueous solution was then made acidic (pH ~3) by addition of concentrated hydrochloric acid at 0°C. Diethyl

ether extraction gave almost pure **3** as an oil which was used without purification in the subsequent step; IR (neat): υ cm^{-1}, 3390 (b OH), 2590 (SH); ^1H NMR ($CDCl_3$): δ 6.80-7.45 (m, 3 H), 6.60 (m, 2 H), 6.30 (m, 1 H), 6.10 (m, 1 H), 5.42 (s, 2 H), 4.49 (d, 2 H, J = 4.7 Hz), 3.40 (s, 1 H, exchangeable), 1.40 (m, 1 H, exchangeable).

Cyclisation reaction to 5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzothiazepine **4**.

To a stirred and cooled (0° C) solution of Ph_3P (2.6 g, 10 mmol) in dry tetrahydrofuran (25 ml) was added dropwise diisopropyl azodicarboxylate (2 g, 10 mmol). After 30 minutes a solution of crude compound **3** (1.1 g, 5 mmol) in the same solvent (10 ml) was added slowly. The mixture was stirred for 1 hour at 0°C and then for 3 hours at room temperature. Removal of the solvent left a residue which was taken up in diethyl ether (5 ml). The insoluble material was filtered off and the oily residue obtained after evaporation of the solvent was chromatographed on silica (benzene:cyclohexane, 1:2) to give pure **4** (0.3 g, 30%), with physical and chemical data identical to those reported in ref. 3; mp 88-89° (light petroleum). Lit.[3] mp 86-88°.

2-[(2-Methoxycarbonylphenyl)thiomethyl]-1*H*-pyrrole **10**.

To a stirred and cooled (0° C) solution of TPP (5.4 g, 20.6 mmol) in dry tetrahydrofuran (20 ml) was added dropwise DIAD (4.16 g, 20.6 mmol). After 30 minutes a solution of 2-hydroxymethylpyrrole **8** (1 g, 10.3 mmol) and methyl thiosalicylate **9** (1.7 g, 10.1 mmol) in the same solvent (15 ml) was added slowly. The mixture was stirred for 30 minutes at 0°C and then for 2 hours at room temperature. Removal of the solvent left a residue, which was taken up in diethyl ether (5 ml). The insoluble material was filtered off and the oily residue obtained after evaporation of the solvent was chromatographed on silica (ethyl acetate:light petroleum, 1:5) to give pure **10** as a solid (2.2 g, 88%); mp 108-110° (diethyl ether); IR (nujol): υ cm^{-1}, 1730 (C=O); ^1H NMR ($CDCl_3$): δ 8.42 (bs, 1 H), 7.95 (d, 1 H, J = 6.4 Hz), 7.35 (m, 2 H), 7.12 (m, 1 H), 6.70 (m, 1 H), 6.15 (m, 2 H), 4.20 (s, 2 H), 3.89 (s, 3 H)

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.29; H, 5.35; N, 5.41.

2-[(2-Hydroxymethylphenyl)thiomethyl]-1*H*-pyrrole **11**.

To a cooled (0° C) solution of ester **10** (0.9 g, 3.6 mmol) in dry diethyl ether (15 ml) was added dropwise a suspension of LAH (0.28 g, 7.3 mmol) in the same solvent (10 ml). After 15 minutes, the unreacted LAH was cautiously quenched with water and a few drops of 15% sulfuric acid. The mixture was then extracted with ethyl acetate and the organic layer was evaporated to dryness to give compound **11** as a solid (0.7 g, 88%); mp 66-67° (benzene:cyclohexane); IR (nujol): υ cm^{-1}, 3390 (b OH); ^1H NMR ($CDCl_3$): δ 8.30 (bs, 1 H), 7.20-7.50 (m, 4 H), 6.65 (m, 1 H), 6.07 (m, 1 H), 5.95 (m, 1 H), 4.68 (d, 2 H, J = 5.5 Hz), 4.10 (s, 2 H), 1.95 (bs, 1 H, exchangeable).

Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 66.02; H, 5.95; N, 6.38.

2-[(2-Acetoxymethylphenyl)thiomethyl]-1*H*-pyrrole **12**.

Starting from **11**.

The alcohol **11** (1.09 g, 5 mmol) was dissolved in dry pyridine (15 ml) containing acetic anhydride (2 ml, 21 mmol) and 4-(dimethylamino)pyridine (10 mg). After completion of the reaction (tlc), the volatile materials were evaporated off and the product was purified by chromatography (ethyl acetate:light petroleum, 1:6). Compound **12** was obtained as a thick oil (1.2 g, 92%); IR (nujol): υ cm^{-1}, 1695 (C=O); ^1H NMR ($CDCl_3$): δ 8.35 (bs, 1 H), 7.20-7.50 (m, 4 H), 6.70 (m, 1 H), 6.08 (m, 1 H), 6.00 (m, 1 H), 5.23 (s, 2 H), 4.15 (s, 2 H), 2.13 (s, 3 H).

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.59; H, 5.65; N, 5.61.

Starting from **13**.

To a stirred and cooled (0° C) solution of TPP (4.6 g, 17.5 mmol) in dry tetrahydrofuran (20 ml), was added dropwise DIAD (3.55 g, 17.6 mmol). After 30 minutes a solution of 2-hydroxymethylpyrrole **8** (0.85 g, 8.8 mmol) and thiosalicyl acetate **13**[9] (1.6 g, 8.8 mmol) in the same solvent (15 ml) was added slowly. The mixture was stirred for 15 minutes at room temperature. Removal of the solvent left a residue, which was taken up in diethyl ether (5 ml). The insoluble material was filtered off and the oily residue obtained after evaporation of the solvent was chromatographed (ethyl acetate:light petroleum, 1:6) to give pure **12** (1.9 g, 83%).

Thiosalicyl acetate **13**.

Thiosalicyl alcohol (1.4 g, 0.01 mol) was added to a mixture of sodium ethoxide (0.68 g, 0.01 mol) in dry THF (20 ml). After 10 minutes Ac_2O (1 ml, 0.01 mol) was added dropwise at 0°C. The mixture was stirred for 3 hours at 0°C. Removal of the solvent left a residue which was chromatographed on silica (ethyl acetate:light petroleum, 1:8) to give compound **13** as an oil (1.36 g, 75%); IR (neat): υ cm^{-1}, 2590 (SH), 1740 (C=O); ^1H NMR ($CDCl_3$): δ 7.25 (m, 2 H), 7.15 (m, 2 H), 5.15 (s, 2 H), 3.50 (s, 1 H), 2.10 (s, 3 H).

Anal. Calcd. for $C_9H_{10}O_2S$: C, 59.32; H, 5.53. Found: C, 59.39; H, 5.65.

5-[(2-Hydroxymethylphenyl)thiomethyl]-1*H*-pyrrole-2-carboxyaldehyde **14a**.

To a mixture of *N,N*-dimethylformamide (0.108 ml, 1.4 mmol) and 1,2-dichloroethane (0.5 ml) cooled at 0-5°C was added phosphorus oxychloride (0.13 ml, 1.4 mmol). The mixture was left for 30 minutes at room temperature and then a solution of compound **12** (0.36 g, 1.38 mmol) in 1,2-dichloroethane (0.5 ml) was added dropwise at 0°C. After 30 minutes stirring at room temperature, solid calcium carbonate (0.53 g, 5.3 mmol) was added and the mixture was warmed to 30-40°C for 15 minutes. After cooling to 0°C, a solution of potassium carbonate (0.97 g, 7 mmol) in water (2 ml) was added and the stirring was continued for 1.5 hours. Removal of volatiles left a residue which was taken up in ethyl acetate and the resulting solution was washed with water to neutrality. Evaporation of the solvent left a solid which was purified by chromatography (ethyl acetate:light petroleum, 2:5) to give pure **14a** as white crystals (0.29 g, 85%); mp 108-109° (benzene); IR (nujol): υ cm^{-1},

3370 (b OH), 1665 (C=O); ^{1}H NMR ($CDCl_3$): δ 10.20 (bs, 1 H), 9.32 (s, 1 H), 7.15-7.45 (m, 4 H), 6.85 (m, 1 H), 6.09 (m, 1 H), 4.75 (d, 2 H, J = 5.0 Hz), 4.15 (s, 2 H), 2.60 (bs, 1 H, exchangeable).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 62.89; H, 5.25; N, 5.50.

2-[(2-Hydroxymethylphenyl)thiomethyl]-5-trichloroacetyl-1*H*-pyrrole **14b**.

Trichloroacetyl chloride (0.15 ml, 1.4 mmol) was added at 0°C to dry benzene (4 ml). A cooled solution of compound **12** (0.3 g, 1.15 mmol) in dry benzene (4 ml) was then added slowly. After stirring for 2 hours at 0°C, the solution was partly concentrated and subsequently added at 0°C to potassium carbonate (0.14 g, 1 mmol) dissolved in water (2 ml) and methanol (1 ml) and stirring was continued for 1 hour. Removal of the solvent left a residue which was extracted into ethyl acetate and the resulting solution was washed with water to neutrality. Compoud **14b** was obtained, after chomatography (ethyl acetate:light petroleum, 1:3) as a low-melting pale yellow solid (0.35 g, 83%); IR (nujol): υ cm^{-1}, 3370 (b OH), 1730 (C=O); ^{1}H NMR ($CDCl_3$): δ 10.35 (bs, 1 H), 7.10-7.50 (m, 5 H), 6.10 (m, 1 H), 4.80 (s, 2 H), 4.15 (s, 2 H), 2.45 (bs, 1 H, exchangeable).

Anal. Calcd. for $C_{14}H_{12}Cl_3NO_2S$: C, 46.11; H, 3.32; N, 3.84. Found: C, 46.02; H, 3.25; N, 3.60.

2-[(2-Hydroxymethylphenyl)thiomethyl]-5-trifluoroacetyl-1*H*-pyrrole **14c**.

This compound was prepared by applying the same procedure described for compound **14b**, but using trifluoroacetic anhydride as the acylating agent. Compound **14c** was obtained as a white solid in 80% yield; mp 95° (benzene:cyclohexane); IR (nujol): υ cm^{-1}, 3365 (b OH), 1735 (C=O); ^{1}H NMR ($CDCl_3$): δ 10.30 (bs, 1 H), 7.15-7.45 (m, 4 H), 7.05 (m, 1 H), 6.15 (m, 1 H), 4.80 (s, 2 H), 4.15 (s, 2 H), 2.30 (bs, 1 H, exchangeable).

Anal. Calcd. for $C_{14}H_{12}F_3NO_2S$: C, 53.33; H, 3.84; N, 4.44. Found: C, 53.09; H, 3.63; N, 4.28.

General procedure for the preparation of compounds **15a-c**.

An alcohol **14a-c** (2 mmol) and TBP (3 mmol) were successively dissolved in a mixture of dry benzene (30 ml) and dry THF (20 ml) with stirring at 0°C, and solid ADDP (3 mmol) was added in portions to the solution. After 3 hours stirring at room temperature, the volatiles were evaporated. Diethyl ether (10 ml) was added to the semisolid residue and any resulting solid was filtered off. Removal of the solvent gave a semisolid residue which was purified by column chromatography (ethyl acetate:light petroleum, 1:8). Recrystallization from cyclohexane yielded white crystals (chemical and physical data of compounds **15a-c** are collected in Table I).

Methyl 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine-3-carboxylate **16**.

Freshly prepared sodium methoxide (37.5 mg, 0.7 mmole) was added in portions to a stirred and cooled (0°C) solution of compound **15b** (0.2 g, 0.58 mmole) in dry methanol (2 ml). The solution was allowed to reach room temperature and stirred for 15 minutes. The solvent was evaporated and the resulting residue was extracted into diethyl ether. Removal of the solvent left a solid which was recrystallized to give pure ester **16** as a white solid (30 mg, 80%); mp 154-155° (cyclohexane); IR (nujol): υ cm^{-1}. 1735 (C=O); ^1H NMR ($CDCl_3$): δ 7.35 (d, 1 H, J = 7.0 Hz), 6.95-7.15 (m, 3 H), 6.82 (d, 1H, J = 4.0 Hz), 6.05 (d, 1 H, J =4.0 Hz), 5.76 (s, 2 H), 4.30 (s, 2 H), 3.80 (s, 3 H).

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.70; H, 4.92; N, 5.12.

Table I. Physical and chemical data for compounds **15a-c**.

Compd	Mp °C	Yield %	Recryst. Solvent[a]	I.R. (υ cm^{-1})	Molecular Formula and Analysis %. Calcd./Found	^1H NMR ($CDCl_3$)	ms:m/z (M^+)
15a	162-164	85	A	1660	$C_{13}H_{11}NOS$ C 68.10 H 4.84 N 6.11 C 68.01 H 4.79 N 6.00	9.47 (s, 1 H), 7.38 (d, 1 H, J = 6.6 Hz), 7.05-7.14 (m, 3 H), 6.83 (d, 1 H, J = 4.0 Hz), 6.14 (d, 1 H, J = 4.0 Hz), 5.82 (s, 2 H), 4.30 (s, 2 H)	229
15b	153-154	80	A	1740	$C_{14}H_{10}Cl_3NOS$ C 48.51 H 2.91 N 4.04 C 48.40 H 2.99 N 3.95	7.48 (d, 1 H, J = 7.1 Hz), 7.10 (m, 3 H), 7.05 (d, 1 H, J = 4.1 Hz), 6.19 (d, 1 H, J = 4.1 Hz), 5.84 (s, 2 H), 4.30 (s, 2 H)	346
15c	169-170	76	A	1745	$C_{14}H_{10}F_3NOS$ C 56.56 H 3.39 N 4.71 C 56.71 H 3.59 N 4.50	7.48 (d, 1 H, J = 7.0 Hz), 7.10 (m, 4 H), 6.19 (d, 1 H, J = 4.0 Hz), 5.84 (s, 2 H), 4.30 (s, 2 H)	297

[a] A = cyclohexane

5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzothiazepine-3-carboxylic acid **17**.

To a solution of ester **16** (0.26 g, 1.0 mmole) in THF (1 ml), methanol (1 ml) and water (0.5 ml) was added lithium hydroxyde monohydrate (50 mg, 1.2 mmole) portionwise. The mixture was refluxed for 20 hours, then

partly concentrated and diluted with water. The solution was washed with diethyl ether, then acidified with 2N HCl at 0°C to give a solid which was filtered, washed with water and thoroughly air-dried before recrystallization. Acid **17** was obtained as a white solid (0.21 g, 85%); mp 204-206° (dec.) (toluene:ethyl acetate); IR (nujol): υ cm^{-1}, 3350 (b OH), 1645 (C=O); ^1H NMR (DMSO): δ 7.20 (d, 1 H, *J* = 7.0 Hz), 6.85-7.15 (m, 3 H), 6.72 (d, 1 H, *J* = 4.0 Hz), 6.10 (d, 1 H, *J* = 4.0 Hz), 5.78 (s, 2 H), 4.50 (s, 2 H).

Anal. Calcd. for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71. Found: C, 63.49; H, 4.61; N, 5.48.

5*H*,11*H*-Pyrrolo[2,1-*c*][1,4]benzothiazepine **4**.

Starting from **15a**.

A mixture of 3-formyl-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **15a** (1 g, 4.4 mmole) and 5% palladium on charcoal (0.15 g) in mesitylene (10 ml) was refluxed for 3 hours. The mixture was then cooled to room temperature, diluted with dichloromethane (30 ml), filtered through Celite, and the catalyst was washed on the filter with several portions of dichloromethane. The organic solutions were combined and evaporated. The residue obtained was chromatographed (benzene:cyclohexane, 1:1) to give pure **4** as a white solid (0.13 g, 15%).

Starting from **17**.

A suspension of acid **17** (1 g, 4.1 mmole) in diphenyl ether (10 ml) was heated at 250°C for 10 minutes. The solvent was evaporated and the resulting residue was chromatographed (benzene:cyclohexane, 1:1) to give pure **4** (0.47 g, 58%).

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References and Notes

1. Garofalo, A.; Corelli, F.; Campiani, G.; Bechelli, S.; Becherucci, C.; Tafi, A.; Nacci, V. *Med. Chem. Res.*, **1994**, *4*, 385-395.
2. Garofalo, A.; Campiani, G.; Ciani, S. M.; Fiorini, I.; Nacci, V. *Tetrahedron*, **1996**, *52*, 7745-7754 and references cited therein.
3. Garofalo, A.; Nacci, V.; Corelli, F.; Campiani, G.; *Heterocycles*, **1990**, *31*, 1291-1300.
4. Nacci, V.; Garofalo, A.; Fiorini, I. *J. Heterocyclic Chem.*, **1986**, *23*, 769-773.
5. Volante, R. P. *Tetrahedron Lett.*, **1981**, *22*, 3119-3122.
6. Tsunoda, T.; Yamamiya, Y.; Itô S. *Tetrahedron Lett.*, **1993**, 34, 1639-1642.
7. Yagil, G. *Tetrahedon*, **1967**, *23*, 2855-2861.

8. Silverstein, R. M.; Ryskiewicz, E. E.; Chaikin, S.W. *J. Am. Chem. Soc.*, **1954**, *76*, 4485-4486. Since this compound polymerizes very easily, it must be utilized as soon as it has been prepared.
9. In such a reaction, any excess of thiol resulted in the formation of the corresponding disulfide which was very difficult to remove by chromatography.
10. Harbuck, J. W.; Rapoport, H. *J. Org. Chem.*, **1972**, *37*, 3618-3622.
11. Cooper, W. D. *J. Org. Chem.*, **1958**, *23*, 1382.
12. Demopoulos, B. J.; Anderson, H. J.; Loader, C. E.; Faber, K. *Can. J. Chem.*, **1983**, *61*, 2415-2422.
13. Meyers, f.; Adant, C.; Bredas J. L. *J. Am. Chem. Soc.*, **1991**, *113*, 3715-3719.
14. Abell, A. D.; Litten, J. C. *Tetrahedron Lett.*, **1992**, *33*, 3005-3008.
15. For related biologically active compounds: Effland, R. C.; Davis, L. *J. Heterocyclic Chem.*, **1985**, *22*, 1071-1075.
16. Perrin, D. D.; Armarego, W. L. F. *"Purification of Laboratory Chemicals"*, 3rd Edition, Pergamon Press. Oxford, 1988.