Acta Chemica Scandinavica B 35 (1981) 197–199

A Synthesis of the 2*H*-Benzo[*b*]thiocin System through [2+2] Cycloaddition

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Thiochroman-3-one has been prepared from *o*-nitrophenylacetic acid. Cycloaddition of dimethyl acetylenedicarboxylate to the pyrrolidine enamine of thiochroman-3-one, followed by electrocyclic ring opening of the cyclobutene system in the tricyclic adduct, yields 4,5-bis-methoxycarbonyl-3-(1-pyrrolidinyl)-2*H*-benzo[*b*]thiocin.

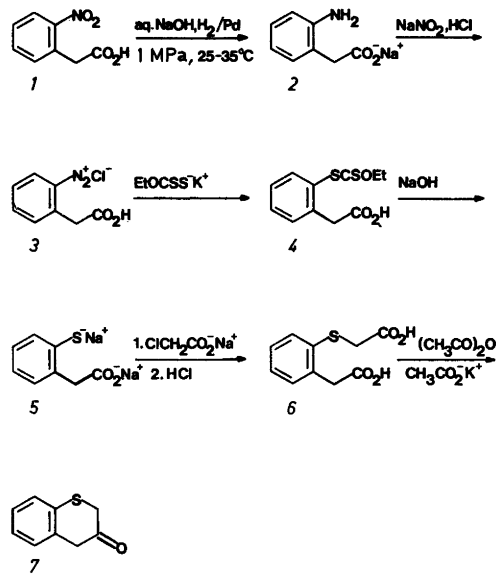
Compounds belonging to the title system are scarce. In the attempted methylation of 3-methylthiochroman-4-one,[1] an eight-membered ring compound was unexpectedly formed in high yield; in the authors' nomenclature, 6,8,8-trimethyl-6-(*o*-methylthiobenzoyl)-4-thiabenzocyclooctenone.

A straightforward approach to a compound with a saturated eight-membered ring would involve Friedel-Crafts cyclization of 5-phenylthiovaleryl chloride, but this reaction does not yield a monomeric ketone.[2] The corresponding cyclization of 4-phenylthiobutyric acid in polyphosphoric acid gives a high yield of seven-membered ring ketone.[3] We were unable to obtain monomeric products from 5-phenylthiovaleric acid in polyphosphoric acid.

A ring expansion which has been successfully employed with carbocyclic compounds consists in the [2+2] cycloaddition of an electrophilic triple bond to an enamine.[4–6] We have applied this reaction to the pyrrolidine enamine of thiochroman-3-one, which was allowed to react with dimethyl acetylenedicarboxylate. After electrocyclic ring opening, 4,5-bis-methoxycarbonyl-3-(1-pyrrolidinyl)-2*H*-benzo[*b*]thiocin was obtained. The structure of this eight-membered ring compound has been verified by single-crystal X-ray diffraction.[7]

Thiochroman-3-one has earlier been obtained through photo-isomerization of isothiochroman-4-one or from *o*-mercaptobenzoic acid in a multistep synthesis involving a Wolff rearrangement.[8] Since both of these routes were deemed impractical on a large scale, we have developed a new synthesis, which is illustrated in Scheme 1.

The starting material, *o*-nitrophenylacetic acid, was donated by AB Bofors Nobel Kemi, Sweden. Literature methods for its preparation exist.[9] Catalytic reduction with hydrogen using palladium on carbon was performed in alkaline solution, since



Scheme 1. Preparation of thiochroman-3-one.

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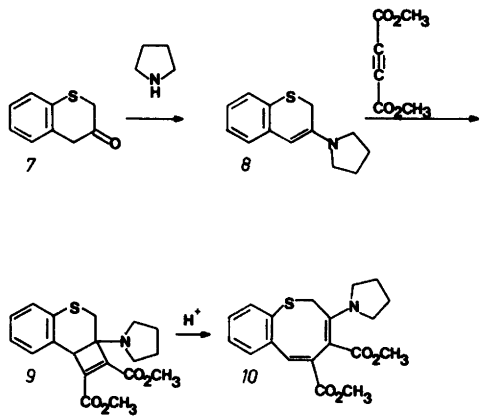

Scheme 2. Preparation of 4,5-bis-methoxycarbonyl-3-(1-pyrrolidinyl)-2*H*-benzo[*b*]thiocin.

o-aminophenylacetic acid easily cyclizes to oxindole,[10] whereas the anion is stable.

In the cyclization of *o*-(carboxymethylthio)-phenylacetic acid, a mixture of thiochroman-3-one and its enol acetate is formed. The latter is hydrolyzed to thiochroman-3-one during the alkaline work-up (see the Experimental part) but might perhaps be isolated in a pure state if so desired, provided that the alkaline treatment is omitted.

In the [2+2] cycloaddition step, the tricyclic compound initially formed (Scheme 2) could not be isolated in a pure state, since chromatography on silica gel at room temperature brought about ring opening. Evidence for its existence was provided by the proton NMR spectrum of the crude reaction mixture. For comparison, the substituted cyclobutene resulting from dimethyl acetylenedicarboxylate and 2-dimethylamino-2-methylthiostyrene is isolable at room temperature, whereas the one from 2,2-bis(dimethylamino)styrene is not.[11]

EXPERIMENTAL

o-*(Carboxymethylthio)phenylacetic acid (6).* A solution of 543 g (3 mol) of *o*-nitrophenylacetic acid (*1*) in 3 l of 1 M sodium hydroxide in water was reduced in the presence of 10 g of 10 % palladium on charcoal (Engelhardt) at a hydrogen pressure of 1 MPa. Hydrogen uptake was complete in 2 h. After filtration from the catalyst, the solution was evaporated at reduced pressure to a volume of 1.5 l. If so desired, the evaporation may be completed to dryness, yielding a colourless salt, but in the present case, the solution was used directly in the following step.

To 500 ml of the above solution of sodium *o*-aminophenylacetate (1 mol), 75 g of sodium nitrite was added, and the resulting solution added to 250 ml of conc. hydrochloric acid and enough crushed ice to keep the temperature below 5 °C. The resulting diazonium solution was added in 15 min to a well-stirred solution of 240 g of potassium *O*-ethyl dithiocarbonate in 500 ml of water at 50 – 60 °C. The pH values was maintained above 8 by simultaneous addition of anhydrous sodium carbonate. After the copious nitrogen evolution had ceased, the solution was added to excess hydrochloric acid and ice. The dithiocarbonate acid was precipitated as a gummy mass which solidified when left overnight. The supernatant liquid was filtered off. The solid was dissolved in 2.5 l of 1 M sodium hydroxide in water, and the solution brought to boiling under nitrogen. In 4 h, 500 ml of evil-smelling distillate was collected and discarded. An aqueous solution of 113 g (1.2 mol) of chloroacetic acid, neutralized with cold aqueous sodium hydroxide, was added, and the solution was refluxed for 2 h. It was allowed to cool and added to excess hydrochloric acid and ice. The diacid was precipitated as a yellow, sandy material. It was filtered off, washed with cold water, and allowed to dry. Coloured by-products were removed through boiling with dichloromethane, which is a poor solvent for the acid. The purified acid weighed 203 g (0.9 mol, 90 % yield from *1*). M.p. 183 – 185 °C, ^{1}H NMR (270 MHz, CD_3COCD_3): δ 3.72 (2 H, s), 3.91 (2 H, s), 7.24 – 7.35 (3 H, m) and 7.57 – 7.60 (1 H, m). Anal. $C_{10}H_{10}O_4S$: C, H, S.

Thiochroman-3-one (7). A mixture of 118 g (0.52 mol) of *6*, 450 ml of acetic anhydride, and 75 g of dry potassium acetate was slowly heated until carbon dioxide began to evolve (65 – 70 °C) and kept at this temperature until the gas evolution ceased. It was then gently refluxed for 1 h. A solution of 60 g of sodium hydroxide in 50 ml of water was slowly added to the cold reaction mixture, followed by a reflux period of 1 h. If the alkali treatment is omitted, the enol acetate of *7* will be present in the ratio 1:2 with the desired product, according to ^{1}H NMR analysis. After dilution with water, the mixture was extracted with dichloromethane. The organic phase was washed with water and saturated sodium chloride solution and dried over sodium sulfate. Evaporation and distillation gave a yellow oil, 60.4 g (70 %), b.p. 83 °C (0.4 mmHg), ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.27 (2 H, s), 3.67 (2 H, s), 7.09 – 7.25 (3 H, m) and 7.39 – 7.42 (1 H, m). The enol acetate of *7* gave three additional peaks in the ^{1}H NMR spectrum at δ 2.18, 3.58, and 6.30, respectively, with the integral ratio 3:2:1.

The ^{1}H NMR spectrum of *7* is in accordance with that reported by Lumma.[8] We have assigned the δ

3.27 singlet to the SCH_2CO methylene group through a hydrolysis of the *tert*-butyldimethylsilyl enol ether of *7* in DCl/D_2O; the signal was unchanged contrary to the other methylene signal. The silyl enol ether was prepared according to Untch.[12]

3-(1-Pyrrolidinyl)-2H-thiochromene (8). To a mixture of 25 g (0.152 mol) of 7 and 80 ml of benzene, 11 g (0.155 mol) of pyrrolidine was added. Water was azeotropically removed in a Dean-Stark trap. After completeness, 3 – 4 h, the solvent was removed under reduced pressure, and the residue set to a crystalline mass. Recrystallization from dichloromethane/ether gave 28.3 g (85 %), m.p. 87 – 93 °C, ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.92 (4 H, m), 3.28 (4 H, m), 3.50 (2 H, s), 5.20 (1 H, s) and 6.80 – 7.16 (4 H, m). The enamine deteriorates upon keeping, and no satisfactory elemental analysis was obtained.

4,5-Bis-methoxycarbonyl-3-(1-pyrrolidinyl)-2H-benzo[b]thiocin (10). A solution of 21.7 g (0.100 mol) of *8* in 120 ml of toluene was deoxygenated with nitrogen and cooled to 0 °C. Dimethyl acetylenedicarboxylate, 15 g (0.106 mol), in 15 ml of toluene was added dropwise during 1 h. The reaction mixture was stirred at 0 °C for 1 h and left for 24 h at room temperature. The solvent was removed at reduced pressure, the temperature not exceeding 60 °C. The residue was dissolved in 30 ml of acetic acid, and about 50 mg of *p*-toluenesulfonic acid was added. The product crystallized upon standing. The crystals were filtered off and washed with a little acetic acid. The yield was 22 g (60 %), m.p. 186 °C, ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.53 (2 H, m), 1.85 (2 H, m), 2.60 (2 H, m), 3.47 (1 H, d, *J* 12.4 Hz), 3.54 (3 H, s), 3.67 (2 H, m), 3.79 (3 H, s), 4.00 (1 H, d, *J* 12.4 Hz), 7.02 – 7.12 (2 H, m), 7.19 – 7.30 (2 H, m) and 7.66 (1 H, s). MS: M^+ 359.1168. Calc. for $C_{19}H_{21}NO_4S$, 359.1191. Fragments: *m/e* 359 (24.1), 327 (23.4), 326 (100), 300 (39.8), 171 (21.6), and 96 (16.5).

A ^{1}H NMR spectrum of the reaction mixture after removal of the toluene contained additional signals at δ 2.98 (1 H, d, *J* 13.2 Hz), 3.26 (1 H, d, *J* 13.2 Hz), 3.63 (3 H, s), 3.84 (3 H, s), and 4.11 (1 H, s). These are ascribed to the tricyclic adduct *9*, but attempted separation on a silica gel column brought about rearrangement to *10* as judged from NMR spectroscopy.

Acknowledgements. We wish to express our sincere thanks to AB Bofors Nobel Kemi, Karlskoga, Sweden, for a generous gift of *o*-nitrophenylacetic acid, and to AB Hässle, Mölndal, Sweden, for the use of their high-pressure hydrogenation equipment.

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Received October 22, 1980.