Dialkyl 2*H*-1-benzothiopyran-2,3-dicarboxylates *via* intramolecular Wittig reaction

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Reaction of 3-mercaptobenzaldehyde (**1**) with dialkyl acetylenedicarboxylate in the presence of triphenylphosphine leads to the corresponding 2*H*-1-benzothiopyran 2,3-diesters.

Keywords: fused thiopyrans, Wittig reactions, acetylenic esters

The 2*H*-1-benzothiopyrans (thiochromenes) constitute a relatively unexplored class of heterocycles. Although not particularly common in nature, this class of sulfur-containing heterocycle is of synthetic and biological interest. 3,4-dihydro-2*H*-1-benzothiopyrans, more commonly known as thiochromans, exhibit anti inflammatory, antipyretic, anti-depressant and analgesic activities.[1]

A survey of the literature revealed that 2*H*-1-benzothiopyrans were prepared via the condensation of thiophenols with acyclic acid derivatives, followed by reduction and dehydration.[2] Arnoldi *et al*.[3] have obtained 2,3-disubstituted 2*H*-1-benzothiopyrans in moderate yields (40–50%) by reaction of 2-mercaptophenylmethyl triphenylphosphonium bromide with 2-haloketones in the presence of a base in refluxing toluene. More recently, Kobayashi *et al*.[4] have synthesised trisubstituted 2*H*-1-benzothiopyrans in moderate overall yields (46–65%) on the basis of our previous work using the system of triphenylphosphine and DMAD for the synthesis of coumarins and chromene derivatives.[5] It is expected that protonation of the products produced in a three component reaction between triphenylphosphine, dialkyl acetylenedicarboxylate and 2-mercaptobenzaldehyde leads to vinyl triphenylphosphonium salts which may undergo an intramolecular Wittig reaction to produce dialkyl 2*H*-1-benzothiopyran-2,3-dicarboxylates after cyclisation.

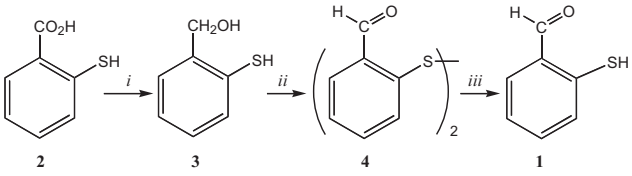
We now report a novel synthesis of dialkyl 2*H*-1-benzothiopyran-2,3-dicarboxylates starting with the readily available 2-mercaptobenzoic acid.

Reduction of 2-mercaptobenzoic acid (**2**) with lithium aluminum hydride in dry THF according to the procedure of Arnoldi and Carughi[3] results in 2-mercaptobenzyl alcohol (**3**) in 96% yield. This alcohol, usually obtained as a viscous oil but sometimes as a low-melting solid, is sufficiently pure (NMR) to be used in the following step. However, it is air sensitive and forms the corresponding disulfide at room temperature on work-up, if air is not excluded. (Scheme 1)

Oxidation of **3** with pyridinium chlorochromate (PCC)[7] in dichloromethane at room temperature afforded 2,2'-dithiodibenzaldehyde **4** in 53% yield.[8] Conversion of the disulfide **4** into the desired product **1** requires selective reduction of the disulfide function. Kasmai and Mischke[9] have found that the treatment of **4** with triphenylphosphine in a solvent system methanol, water and DMF (2:1:2) at room temperature gives the aldehyde **1** quantitatively. From this procedure 2-mercaptobenzaldehyde was obtained as a yellow oil in 80% yield after purification by chromatography.

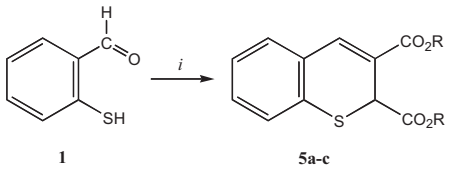
Treatment of 2-mercaptobenzaldehyde (**1**) with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine in dichloromethane at room temperature gave the corresponding 2,3-disubstituted 2*H*-1-benzothiopyrans **5a–c** in moderate yield (Scheme 2).

A plausible mechanism for the reaction is shown in Scheme 3.



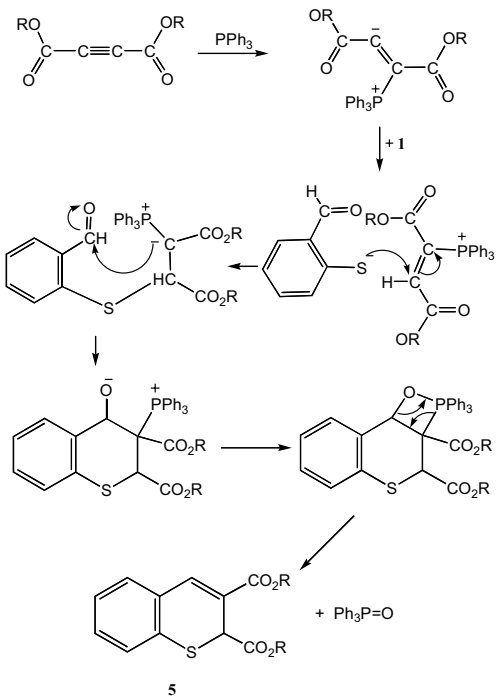
Reagents and conditions: *i, (a)* $LiAlH_4$/THF/r.t. *(b)* H^+, 95%; *ii*, PCC/CH_2Cl_2, r.t. 4h, 53%; *iii*, PPh_3, MeOH; H_2O/DMF, r.t. 30 min, 80%

Scheme 1



Reagents and conditions: *i,* PPh_3 , RO_2C-C_2-CO_2R/ CH_2Cl_2, -4° C, then R.T. 24h, 55-67%

Scheme 2



Scheme 3

Experimental

Melting points were determined with an electrothermal 9100 apparatus. IR spectra were recorded with a Philips PU 9800 FT-IR spectroscope. Mass spectra were recorded on a Finnigan-Mat 84300 mass spectrometer operating at an ionisation potential of 70 eV.

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Elemental analyses were performed using a Heraeus CHN–O–Rapid analyser. ^{1}H and ^{13}C NMR spectra were measured with a JEOL EX-90A spectrometer at 90 and 22.6 MHz respectively, recorded of samples in $CDCl_3$.

All solvents were freshly distilled. Deoxygenated solvents were prepared by bubbling N_2 through freshly distilled solvents for 20 min. THF and diethyl ether were dried by refluxing over benzophenone/Na. Pyridinium chlorochromate (PCC) was prepared by the published method.[7] 2-Mercaptobenzyl alcohol (**3**),[3] 2,2'-dithiodibenzaldehyde (**4**)[8] and 2-mercaptobenzaldehyde (**1**)[8] were prepared in 96%, 54% and 80% yields, respectively, according to the published procedures.

Synthesis of dialkyl 2H-1-benzothiopyran-2,3-dicarboxylates (**5a–c**)
To a magnetically stirred solution of triphenylphosphine (2 mmol, 0.524 g) and 2-mercaptobenzaldehyde (**1**) (2 mmol, 0.276 g) in CH_2Cl_2 (10 ml) at -4°C a solution of dialkyl acetylenedicarboxylate (2 mmol) in CH_2Cl_2 (6 ml) at was added dropwise over a period of 10 min. The reaction mixture was stirred at room temperature for 24 h and then cooled to 0°C, when most of the triphenylphosphine oxide formed in the reaction separated out and was removed. The product **5** was isolated as a yellow solution which was further purified by column chromatography using a mixture of hexane/ethyl acetate (4 : 1) as eluent.

Dimethyl 2H-1-benzothiopyran-2,3-dicarboxylate (**5a**): Yield 55%, yellow oil. (A melting point of 91–92°C has been reported for this compound,[10] but we were not able to solidify it.) ^{1}H NMR: δ 3.73 (s, 3H), 3.71 (s, 3H), 4.82 (s, 1H), 6.79–7.63 (m, 5H). ^{13}C NMR: δ 51.6 (OCH_3), 51.3 (OCH_3), 46.5 (CH), 125.1, 125.5, 126.7, 128.2, 128.8, 129.4, 136.5, 138.7 (ArC and C =CH), 163.8, 166.2 (C=O). MS: *m/z* (relative intensity) 266 (4.5), 265 (15), 204 (100%). Anal. Calc. for $C_{13}H_{12}O_4S$: C 59.08, H 4.58, S 12.13. Found: C 58.85, H 4.45, S 12.07%.

Diethyl 2H-1-benzothiopyran-2,3-dicarboxylate (**5b**): Yield 60%, pale yellow solid, m.p. 91–93°C. ^{1}H NMR: δ 1.23 (t, 3H), 1.15 (t, 3H), 4.14 (q, 2H), 4.25 (q, 2H), 4.37 (s, 1H), 6.81–7.66 (m, 4H). ^{13}C NMR: δ 13.7 (CH_3), 14.0 (CH_3), 38.6 (CH), 61.0 (O–CH_2), 61.4 (O–CH_2), 125.8, 126.4, 127.9, 128.6, 129.8, 130.3, 130.7, 137.7 (ArC and C=CH), 164.3,166.2 (C=O). MS: *m/z* (relative intensity) 292 (M^+, 26), 219 (100%). Anal. Calc. for $C_{15}H_{16}O_4S$: C, 61.64, H, 5.47; S, 10.94. Found C, 61.32, H, 5.35; S, 10.6%.

Di-t-butyl 2H-1-benzothiopyran-2,3-dicarboxylate (**5c**): Yield 67%, yellow oil. ^{1}H NMR δ 1.33 (s, 9H), 1.45(s, 9H), 4.42(s, 1H), 7.08–7.15 (m, 4H), 7.53 (s, 1H). ^{13}C NMR: δ: 20.8, 22.0 (t-Bu), 39.2 (CH), 80.4 (O–C), 123.2, 124.9, 125.5, 127.2, 129.2, 129.7, 130.2, 135.4 (Ar–C and C=CH), 162.5, 167.5 (CO). MS: *m/z* (relative intensity) 348 (M^+, 2), 191 (100), 57 (90%). Anal. Calc. for $C_{19}H_{24}O_4S$: C, 65.52; H, 6.98; S, 9.19. found: C, 64.67; H, 7.0; S, 9.12%.

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