A New and Concise Synthesis of 3-Aryl- and 3-Alkyl-1*H*-2-benzothiopyran-1-ones (Thioisocoumarins)

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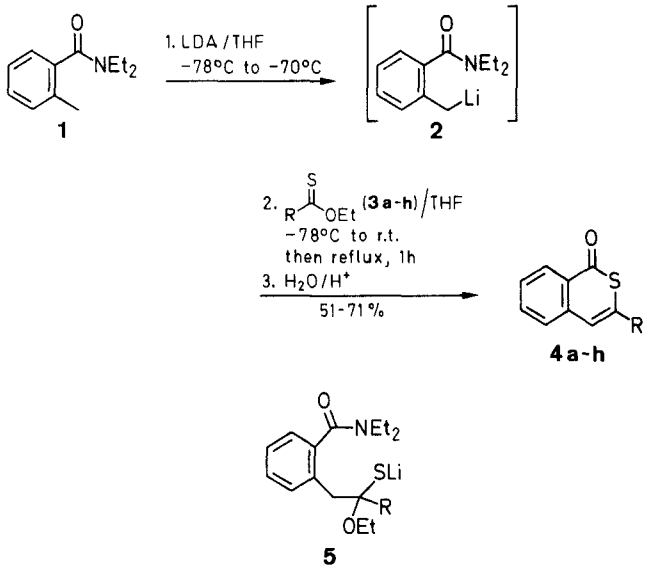
3-Aryl- and 3-alkyl-1*H*-2-benzothiopyran-1-ones are readily accessible by reaction of the lithiated *N,N*-diethyl-*o*-toluamide (*N,N*-diethyl-2-methylbenzenecarboxamide) with appropriate aromatic, heteroaromatic and aliphatic thioesters.

The 1*H*-2-benzothiopyran-1-one (thioisocoumarin) skeleton is a heterobicyclic system of rather simple structure, but paradoxically the methodologies devised for the elaboration of this framework are generally limited and not diversified. Indeed, the main synthetic route to such compounds is from the corresponding heterocyclic thiones present in the variable sulfuration products of methyl 2-(aroylmethyl)benzoates with phosphorus(V) sulfide. The obtention of the oxo compounds requires either treatment with potassium permanganate[1] or hydrogen peroxide in acetic acid,[2] or the acidic hydrolysis of their phenylhydrazono derivatives.[3] The only exception concerns the synthesis of 3-methylthio-4-cyanothioisocoumarin obtained by treatment of methyl 2-cyanomethylbenzoate[4] with carbon disulfide. However, the method is rather restrictive, especially with regard to the eventual introduction of various substituents in the six-membered heterocyclic moiety. We have developed a novel and effective synthetic approach to the 3-aryl and previously unknown 3-alkyl derivatives of this fused heterocyclic systems.

Our strategy consists in reacting *O*-ethyl thiocarboxylates **3a–h** with the lithium derivative **2** of *N,N*-diethyl-*o*-toluamide (**1**).

The *O*-ethyl thiocarboxylates **3a–g** are obtained by conversion of the appropriate nitriles into the corresponding ethyl imidate esters via Pinner reaction and by subsequent treatment with hydrogen sulfide.[5] The aliphatic *O*-ethyl thiocarboxylate **3h** is prepared from the carboxylic ester using the Lawesson's reagent in refluxing toluene.[6]

The anion of *N,N*-diethyl-*o*-toluamide (**2**) is generated with lithium diisopropylamide (LDA) in anhydrous tetrahydrofuran. This operation must be carried out at −78 °C to prevent self condensation of the lithiated species **2**. The addition of the appropriate thioesters is also effected at this temperature. The annulation reaction which gives rise to the desired fused heterocycles is induced by refluxing the reaction mixture in tetrahydrofuran. The 3-aryl-, 3-heteroaryl- and 3-alkyl-1*H*-2-benzothiopyran-1-ones **4a–h** are obtained in good yield by this method. It is likely that these heterocyclization reactions proceed via the intermediacy of species like **5** arising from the nucleophilic attack of the preformed benzylic carbanion **2** on the reactive thiocarbonyl group of **3a–h**. The cyclocondensation reaction is then the result of the attack of the sensitive *N,N*-diethylamido group by the transient sulfur anion.



3, 4	R	3, 4	R
a	Ph	**e**	1,3-benzodioxol-5-yl
b	4-MeC_6H_4	**f**	2-thienyl
c	4-$MeOC_6H_4$	**g**	Me
d	4-ClC_6H_4	**h**	*c*-C_6H_{11}

Table. 3-Aryl- and 3-Alkyl-1*H*-2-benzothiopyran-1-ones **4a–h** Prepared

Product	Yield (%)	mp[a] (°C)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr) ν (cm^{-1}) C=O	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J(Hz)	MS (70 eV)[d] m/z (%)
4a	71	93–94	93[1]	1632	7.24–7.71 (m, 9H, H_{arom}, H_{vinyl}), 8.29 (d, 1H, J = 7.8, H_{peri})	238 (M^+, 100), 210 (69), 178 (27), 153 (6)
4b	69	115–116	116.5[1]	1626	2.4 (s, 3H, CH_3), 7.21–7.72 (m, 8H, H_{arom}, H_{vinyl}), 8.29 (d, 1H, J = 7.1, H_{peri})	252 (M^+, 100), 224 (57), 209 (25), 177 (13)
4c	65	116	117–121[1]	1640	3.8 (s, 3H, OCH_3), 7.20–7.66 (m, 8H, H_{arom}, H_{vinyl}), 8.28 (d, 1H, J = 7.3, H_{peri})	268 (M^+, 100), 240 (13), 225 (41), 197 (21), 165 (15)
4d	60	144–145	$C_{15}H_9ClOS$ (272.7)	1625	7.25–7.34 (m, 8H, H_{arom}, H_{vinyl}), 8.29 (d, 1H, J = 7.3, H_{peri})	274 (M^+, 35), 272 (M^+, 100), 246 (23), 244 (62), 208 (38), 176 (14)
4e	64	142	$C_{16}H_{10}O_3S$ (282.2)	1620	6.02 (s, 2H, OCH_2O), 6.80–7.71 (m, 7H, H_{arom}, H_{vinyl}), 8.28 (d, 1H, J = 6.8, H_{peri})	282 (M^+, 100), 254 (28), 240 (29), 208 (15)
4f	59	85	$C_{13}H_8OS_2$ (244.2)	1630	7.10–7.70 (m, 7H, H_{phenyl}, $H_{thiophene}$), 8.25 (d, 1H, J = 6.8, H_{peri})	244 (M^+, 100), 216 (53), 184 (18), 171 (41)
4g	51	49–50	$C_{10}H_8OS$ (176.2)	1638	2.38 (d, 3H, J = 1.1, CH_3), 6.94 (br s, 1H, H_{vinyl}), 7.34–7.73 (m, 3H_{arom}), 8.25 (d, 1H, J = 7.5, H_{peri})	176 (M^+, 100), 147 (86), 115 (9), 89 (14)
4h	61	45	$C_{15}H_{16}OS$ (244.4)	1635	1.27–2.79 (m, 11$H_{cyclohexyl}$), 6.97 (s, 1H, H_{vinyl}), 7.28–7.68 (m, 3H_{arom}), 8.25 (d, 1H, J = 7.4, H_{peri})	244 (M^+, 100), 211 (46), 173 (51), 115 (89)

[a] Uncorrected, measured with a Reichert-Termopan.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.21, Cl ±0.10, O ±0.24, S ±0.25.
[c] Recorded on a Bruker WP80 spectrometer.
[d] Obtained on a Riber 10-10 spectrometer.

In conclusion, the reaction of aromatic and heteroaromatic thioesters with the carbanion of *N,N*-diethyl-*o*-toluamide (**1**) offers a new synthetic approach to 3-aryl- and 3-alkyl-1*H*-2-benzothiopyran-1-ones **4**. This strategy has already been applied to the elaboration of arylisoquinolones[7] and hydroxyisoquinolines[8] by reaction of the carbanion **2** with imines and nitriles, respectively. The reactions described herein are an illustration of the versatility of aromatic and aliphatic thiocarboxylates in the elaboration of five,[9] six[10] and seven-membered[11] rings.

The aromatic, heteroaromatic and aliphatic *O*-ethyl thiocarboxylates **3a–h** were prepared according to literature procedures.[6,9,10]

3-Aryl and 3-Alkyl-1*H*-2-benzothiopyran-1-ones 4a–h; General Procedure:

A solution of LDA is prepared at −78 °C by addition of BuLi in hexane (1.6 M, 6.3 mmol) to *i*-Pr_2NH (1.7 mL, 10 mmol) in THF (20 mL). The mixture is stirred under Ar for 30 min and a solution of *N,N*-diethyl-*o*-toluamide (**1**; 1.91 g, 10 mmol) in THF (5 mL) is added dropwise at such a rate as to maintain the internal temperature below −70 °C. To the resulting dark purple solution the appropriate thioester **3** (11 mmol) dissolved in THF (5 mL) is added over a period of 5 min. The mixture is allowed to warm to r.t. and then gently heated under reflux for 1 h. After cooling, dilute HCl (50 mL) is added. The aqueous layer is extracted with EtOAc (2 × 25 mL). The combined organic layers are washed with brine (50 mL), dried ($MgSO_4$) and evaporated *in vacuo* to yield the crude condensed products which are recrystallized from abs. EtOH to give **4a–f**.

The cyclocondensation compounds **4g, h** are purified by column chromatography on silica gel using EtOAc/hexane (40:60) as eluent and by recrystallization from hexane/toluene.

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