Reductions via Boranes: A New, Convenient Method for the Preparation of 3-Substituted Esters and Thioesters of 3,4-Dihydrocoumarin

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Reductions of various *O*-ethyl coumarin-3-carboxylates and *O*-ethyl coumarin-3-thioncarboxylates with diborane, borane dimethyl sulfide, 9-borabicyclo[3.3.1]nonane, and bis[*t*-butylthio]ethane-diborane lead to the corresponding 3,4-dihydro derivatives with good yields.

Ethyl 3,4-dihydrocoumarin-3-carboxylates are synthetic intermediates which can be prepared by the condensation of phenolic Mannich bases, or of their methiodides, with the sodium derivative of ethyl malonate or with ethyl ethoxymagnesium malonate[1,2,3].

In the course of our search for a facile route to these derivatives, we undertook a systematic investigation of the reduction of various 3-substituted esters and thioesters of coumarin with nucleophilic and electrophilic hydrides, the point of interest being the behaviour of the ethylenic 3,4-double bond and of the ester, thioester, and lactone groups towards these reagents.

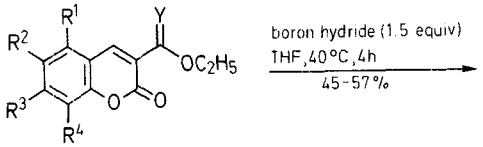
Table 1. *O*-Ethyl Coumarin-3-carboxylates and -thiocarboxylates **1a–f**

Compound	Yield [%]	m.p. [°C][a]	Molecular Formula or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}][b]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][c]
1a	78	94°	94°[5,8]	3080–2980, 1745, 1705	1.42 (t, 3H, CH_2CH_3); 4.42 (q, 2H, OCH_2CH_3); 7.2–7.8 (m, 4H$_{arom}$); 8.2 (s, 1H, —CH=)
1b	84	92°	$C_{12}H_{10}O_3S$ (234.3)	3050–2950, 1735, 1600	1.5 (t, 3H, CH_2CH_3); 4.7 (q, 1H, OCH_2CH_3); 7.1–7.8 (m, 4H$_{arom}$); 8.3 (s, 1H, —CH=)
1c	80	155°	$C_{14}H_{14}O_6$ (278.3)	3020–2920, 1760–1700	1.38 (t, 3H, CH_2CH_3); 3.86–3.9 (2s, 6H, OCH_3); 4.4 (q, 2H, OCH_2CH_3); 6.2–6.4 (m, 2H$_{arom}$); 8.8 (s, 1H, —CH=)
1d	82	160°	$C_{14}H_{14}O_5S$ (294.3)	3000–2900, 1750–1600	1.5 (t, 3H, CH_2CH_3); 3.86–3.9 (2s, 6H, OCH_3); 4.7 (q, 2H, OCH_2CH_3); 6.3–6.7 (m, 2H$_{arom}$); 8.2 (s, 1H, —CH=)
1e	89	88°	88°[9]	3050–3000, 1740, 1700	1.4 (t, 3H, CH_2CH_3); 4.0 (s, 3H, OCH_3); 4.42 (q, 2H, OCH_2CH_3); 7.1–7.3 (m, 3H$_{arom}$)
1f	76	114°	114°[10]	3100–3000, 1740–1700	1.5 (t, 3H, CH_2CH_3); 4.5 (q, 2H, OCH_2CH_3); 7.2–8.3 (m, 6H$_{arom}$); 8.8 (s, 1H, —CH=)

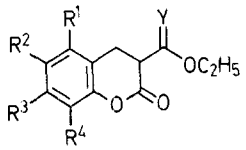
[a] Recrystallised from 8/1/1 ethanol/tetrahydrofuran/water.
[b] Perkin-Elmer 177 Infrared spectrometer.
[c] Varian T60 N.M.R. spectrometer.

The starting coumarins **1a–f** are easily prepared in excellent yields by the Knoevenagel reaction[4,5] of appropriate salicylaldehydes with diethyl malonate or with diethyl thionomalonate[6] (Table I).

Previous work showed that the reduction of 3-ethoxycarbonyl coumarins with sodium borohydride did not lead to the desired derivatives: 2′-hydoxybenzyl malonic esters were obtained[7]. We now report a new, convenient method for the preparation of 3-substituted esters and thioesters of 3,4-dihydrocoumarins via boranes. When representative 3-substituted esters and thionesters of coumarin **1a–f** were reduced with diborane (BH_3), borane/dimethyl sulfide (BMS), 9-borabicyclo[3.3.1]nonane (9-BBN), and bis [*t*-butylthio]ethane-diborane (BTED), the corresponding 3,4-dihydro derivatives **2a–f** were obtained with good yields in all experiments (Table 2).



1a-f



2a-f

1,2	R^1	R^2	R^3	R^4	Y
a	H	H	H	H	O
b	H	H	H	H	S
c	OCH_3	H	OCH_3	H	O
d	OCH_3	H	OCH_3	H	S
e	H	H	H	OCH_3	O
f			H	H	O

All reactions were carried out at 40°C for 4 h under anhydrous conditions using titrated solutions of borane in anhydrous tetrahydrofuran. Table 2 shows the various hydroborating agents used, the yields and melting points of the products obtained. These were purified by column chromatography on silica gel followed by recrystallisation from an ethyl acetate/ligroin mixture.

Table 2. *O*-Ethyl 3,4-Dihydrocoumarin-3-carboxylates and -thiocarboxylates **2a–f**

Product	Hydroborating agent	Yield [%]	m.p.[a] [°C]	Molecular Formula or Lit. m.p. [°C]
2a	BH_3	54	53°	53°[1,2]
	9-BBN	57		
	BMS	45		
	BTED	45		
2b	9-BBN	55	oil	$C_{12}H_{12}O_3S$ (236.3)
2c	9-BBN	55	100°	$C_{14}H_{16}O_6$ (280.3)
2d	9-BBN	55	122°	$C_{14}H_{16}O_5S$ (296.3)
2e	9-BBN	45	88°	$C_{13}H_{14}O_5$ (250.3)
2f	9-BBN	52	115°	114–115°[3]

[a] Recrystallised from ethyl acetate/ligroin.

Table 3. Selected N.M.R. Data for Compounds **2a–f**

Product	^{1}H-N.M.R. ($CDCl_3$/TMS)[a] δ [ppm]		^{13}C-N.M.R. ($CDCl_3$/TMS)[b] δ [ppm]	
	H-3[c]	H-4a, H-4b[c]	C-3	C-4
2a	3.75 (q, 1H)	3.0–3.6 (oct, 2H)	46.04	26.95
2b	3.95 (q, 1H)	3.0–3.75 (oct, 2H)	55.14	30.07
2c	4.0 (q, 1H)	3.0–3.6 (oct, 2H)	46.0	20.8
2d	4.0 (q, 1H)	3.0–3.6 (oct, 2H)	55.48	23.78
2e	3.7 (q, 1H)	2.95–3.6 (oct, 2H)	45.85	27.06
2f	3.8 (q, 1H)	3.25–3.8 (oct, 2H)	45.76	23.45

[a] Varian EM90 N.M.R. spectrometer.
[b] Varian CFT20 N.M.R. spectrometer.
[c] For all products: $J_{4a,4b} = 15$ Hz; $J_{3,4a} = 8$ Hz, $J_{3,4b} = 7$ Hz.

The structures of derivatives **2a–f** were determined by microanalysis (C ± 0,21%, H ± 0,32%), by I.R. ($\nu_{C=O}$: 1725 cm^{-1} and 1755 cm^{-1} attribuable to saturated lactone and ester groups) and by N.M.R. spectrocopy. Table 3 shows the ^{1}H-N.M.R. and ^{13}C-N.M.R. data of the reduced part of the 3,4-dihydrocoumarins.

This study indicates that it is now possible to reduce the double bond of a molecule in a convenient fashion and with an acceptable regioselectivity in the presence of ester or thioester and lactone groups, with yields of 45–57%.

O-Ethyl Coumarin-3-thiocarboxylate (1b); Typical Procedure:
A magnetically stirred solution of redistilled salicylaldehyde (1.22 g, 10 mmol) and diethyl monothionmalonate[7] (1.83 g, 11 mmol) in anhydrous ethanol (50 ml) containing dry piperidine (5 drops) is heated to reflux for 1 h and left to cool overnight. The product is filtered off, washed with ethanol (5 ml) and recrystallised from ethanol/tetrahydrofuran/water (8/1/1); yield: 1.95 g (84%); m.p. 92°C.

3-Ethoxycarbonyl-3,4-dihydrocoumarin (2a); Typical Procedure:
All glass equipment is dried at 100°C overnight and assembled in a stream of nitrogen. The boranes were commercially available: BH_3, 9-BBN, BMS (Aldrich), and BTED (Expansia). Their tetrahydrofuran solutions were titrated by a standard procedure[11]. A solution of 9-BBN (30 ml, 15 mmol) in dry tetrahydrofuran (distilled from benzophenone ketyl) is added dropwise with a syringe via a septum inlet to a magnetically stirred solution, cooled to 0°C, of 3-ethoxycarbonylcoumarin (**1a**; 2.18 g, 10 mmol) in anhydrous tetrahydrofuran (25 ml), in a flask connected to a mercury bubbler. The reaction mixture is left to come to room temperature and is then heated to 40°C. When T.L.C. (ligroin/ethyl acetate: 85/15) shows the reaction to be finished (~4 h), the mixture is cooled to 0°C and acidified by cautious dropwise addition of hydrochloric acid (10% v/v). After decantation, the aqueous phase is extracted with ether (3 × 25 ml). The combined tetrahydrofuran and ether solutions are washed with water (2 × 5 ml) and dried with sodium sulfate. Solvents are removed in vacuum and the product, purified by column chromatography on silica gel (ligroin/ethyl acetate, 9/1) is recrystallised from ligroin/ethyl acetate; yield: 1.25 g (57%); m.p. 53°C.

Reductions with Other Boranes:
Reductions using titrated solutions of BH_3, BMS, and BTED in anhydrous tetrahydrofuran are carried out as above. Products and yields are given in Table 1.

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