Convenient synthesis of 1,2-dihydroquinoline-3-carboxylic acid and 2*H*-1-benzothiopyran-3-carboxylic acid derivatives

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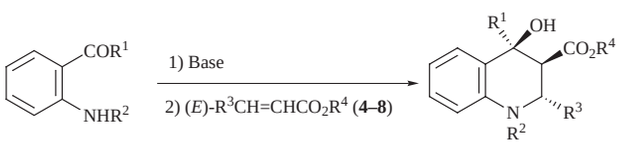
A new and efficient method for the preparation of 1,2-dihydroquinoline-3-carboxylic acid derivatives *via* a magnesium amide-induced sequential conjugate addition–aldol type condensation reaction between 2-(alkylamino)phenyl ketones and α,β-unsaturated carboxylic acid derivatives, followed by simple dehydration, is described. The method can be applied to the synthesis of 2*H*-1-benzothiopyran-3-carboxylic acid derivatives using 2-mercaptobenzophenone in place of 2-(alkylamino)phenyl ketones.

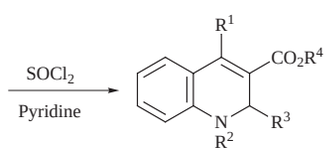
3-Quinolinecarboxylic acid derivatives are of well established importance in medicinal[1] and synthetic chemistry[2] and several efficient methods for their preparation have been reported.[3] 1,2-Dihydroquinoline derivatives have also received substantial attention due to their potential biological activities arising from their antioxidative properties,[4] as well as their usefulness as precursors of some other biologically active compounds.[5] However, there have been, so far, few reports on synthetic approaches to 1,2-dihydroquinoline-3-carboxylic acid derivatives. Qiang and Baine reported on the formation of these derivatives, in which the dihydroquinolines, formed *via* the thermal 6π electrocyclic rearrangement reaction of *N*-benzylidene-2-vinylanilines, were oxidized by air to give the corresponding quinoline derivatives.[6] Recently, the synthesis of *N*-phenylsulfonyl-1,2-dihydroquinoline-2,3-dicarboxylates utilizing activated acetylenedicarboxylates has been reported by Yavari and co-workers.[7] We have recently reported the one-pot synthesis of 4-amino-1,2-dihydroquinoline-3-carboxylates by the magnesium amide-induced tandem conjugate addition/enolate–nitrile coupling reaction between 2-(methylamino)-benzonitrile and α,β-unsaturated carboxylates.[8] As an extension of this earlier study we now wish to describe an efficient method for the general preparation of 1,2-dihydroquinoline-3-carboxylic acid derivatives based on the tandem conjugate addition/aldol-type reaction between 2-(alkylamino)phenyl ketones[9] and α,β-unsaturated carboxylic acid derivatives. This affords 4-hydroxy-1,2,3,4-tetrahydroquinoline-3-carboxylic acid derivatives, which are susceptible to subsequent dehydration using thionyl chloride. It is also described that a similar sequence with 2-mercaptobenzophenone in place of 2-(alkylamino)phenyl ketones affords 2*H*-1-benzothiopyran-3-carboxylic acid derivatives.[10,11] They are also of biological interest.[12]

The preparation of 1,2-dihydroquinoline-3-carboxylates **16**–**22** from 2-(alkylamino)phenyl ketones **1**–**3** and α,β-unsaturated carboxylates **4**–**8** was carried out according to Scheme 1. We first chose 2-(methylamino)benzophenone **1** and *tert*-butyl crotonate **4** as the model substrates, and investigated conditions which led to a satisfactory formation of the desired product, *tert*-butyl 4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate **9**. It was found that the reaction proceeded smoothly with magnesium bis(diisopropyl)amide (MBDA), generated *in situ* from 2 equiv. each of diisopropylamine and ethylmagnesium bromide, to afford **9** as the sole diastereomer in good isolated yield (Table 1, entry 1). Previously we had used 4 equiv. each of diisopropylamine and ethylmagnesium bromide for satisfactory formation of 4-amino-1,2-dihydroquinoline-3-carboxylates.[8] In the cases cited here this was not necessary. The amide anion of **1**, generated by the treatment with LDA in THF, was also treated with **4** to afford **9** but in much lower yield (entry 2). No more than a trace amount of **9** could be obtained by using NaH (entry 3). The bivalent magnesium ion may be responsible for the success of the present reaction sequence. The results obtained by using three *o*-aminophenyl ketones **1**–**3** and five α,β-unsaturated carboxylates **4**–**8** are summarized in Table 1. Each of the reactions with the carboxylates **4**–**7** gave only one of the possible four (two for **6**) diastereomers (**9**–**12**, **14** and **15**; entries 1, 4–6, 8 and 9). The *cis*-stereochemistry of these products at C-3 relative to C-4 was determined on the basis of their IR spectra, which showed absorptions assignable to the 3-ester carbonyls at rather decreased wavenumbers (1694–1704 cm^{-1}), attributable to the hydrogen bonding interactions between the ester carbonyls and 4-OH groups. The *trans*-stereochemistry of these products, excluding **6**, at C-2 relative to C-3 was established by the values of the coupling constants between 2-H and 3-H (9.0–11.8 Hz). In the case of using diethyl fumarate (**8**), the 2,3-dicarboxylate **13** was obtained as a mixture of two diastereomeric forms,



1 R^1=Ph, R^2=Me
2 R^1=Ph, R^2=Bn
3 R^1=Et, R^2=Me

9–15



16–22

4 R^3=Me, R^4=*t*-Bu
5 R^3=Ph, R^4=Et
6 R^3=H, R^4=*t*-Bu
7 R^3=2-furyl, R^4=*t*-Bu
8 R^3=CO_2Et, R^4=Et

9, **16** R^1=Ph, R^2=R^3=Me, R^4=*t*-Bu
10, **17** R^1=R^3=Ph, R^2=Me, R^4=Et
11, **18** R^1=Ph, R^2=Me, R^3=H, R^4=*t*-Bu
12, **19** R^1=Ph, R^2=Me, R^3=2-furyl, R^4=*t*-Bu
13, **20** R^1=Ph, R^2=Me, R^3=CO_2Et, R^4=Et
14, **21** R^1=Ph, R^2=Bn, R^3=Me, R^4=*t*-Bu
15, **22** R^1=Et, R^2=R^3=Me, R^4=*t*-Bu

Scheme 1

Table 1 Preparation of quinoline-3-carboxylic acid esters **9**–**15** and **16**–**22**

Entry	Aminophenyl ketone **1**–**3**	α,β-Unsaturated ester **4**–**8**	Base	Product **9**–**15** (Yield %)[a]	Product **16**–**22** (Yield %)[a]
1	**1**	**4**	MBDA	**9** (80)	**16** (89)
2	**1**	**4**	LDA	**9** (33)	—
3	**1**	**4**	NaH	**9** (0)	—
4	**1**	**5**	MBDA	**10** (67)	**17** (85)
5	**1**	**6**	MBDA	**11** (82)	**18**[c]
6	**1**	**7**	MBDA	**12** (52)	**19** (90)
7	**1**	**8**	MBDA	**13** (42)[b]	**20** (92)
8	**2**	**4**	MBDA	**14** (71)	**21** (94)
9	**3**	**4**	MBDA	**15** (36)	**22** (73)

[a] Isolated yields after purification by preparative TLC on SiO_2 or recrystallization. [b] A mixture of two diastereomers (*ca.* 60:40 by ^1H NMR) was obtained. The relative configuration of each diastereomer was not determined. [c] This product was too unstable to be isolated.

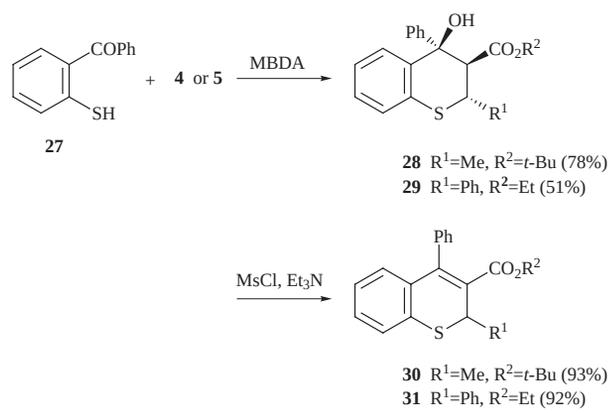
whose stereochemistries have not yet been determined (entry 7). Ethyl 2-(methylamino)phenyl ketone **3** could be used in the present reaction to give the corresponding product **15**, though the yield was rather lower, probably due to the competitive self condensation of **3** initiated by the deprotonation of the hydrogen α to the carbonyl group.

The subsequent dehydration of the hydroxytetrahydroquinolinecarboxylates **9**–**15** was performed with thionyl chloride in pyridine to give the corresponding 1,2-dihydroquinoline-3-carboxylates **16**, **17** and **19**–**22** in good yields; however, the dehydration of **11** under these conditions gave an intractable mixture of products. This is probably due to the instability of the corresponding dihydroquinoline derivative **18** under reaction and/or workup conditions. These results are also outlined in Scheme 1 and Table 1. Methanesulfonyl chloride also proved to be usable in this dehydration. However, the reaction proceeded more slowly than that using thionyl chloride, to give the desired dehydration products in somewhat diminished yields.

2,3-Dihydroquinoline-3-carbonitriles **25** and **26** could also be prepared by the tandem reaction between 2-(methylamino)-benzophenone **1** and α,β-unsaturated carbonitriles **23** and **24** in the presence of the magnesium amide under the same conditions as for the reaction with α,β-unsaturated carboxylates **4**–**8**. We found that the reaction was followed spontaneously by dehydration. Compounds **25** and **26** were formed in one pot in moderate-to-fair overall yields. These results are illustrated in Scheme 2.

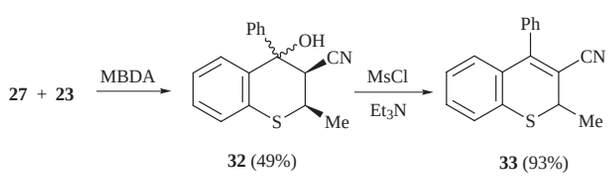
Scheme 2

Subsequently, we turned our attention to the extension of the present reaction sequence and envisaged that the replacement of the alkylamino group of the 2-(alkylamino)phenyl ketones by a hydroxy or mercapto group would be expected to afford the corresponding benzopyran or benzothiopyran derivatives. All attempts to obtain the expected benzopyran derivative from the reaction of 2-hydroxybenzophenone with *tert*-butyl crotonate **4** using various bases were unsuccessful. However, the treatment of 2-mercaptobenzophenone **27** with α,β-unsaturated carboxylates **4** and **5** in the presence of the (diisopropylamino)magnesium reagent resulted in the formation of the desired dihydrobenzothiopyran derivatives **28** and **29** in fair to good yields, as outlined in Scheme 3. Each of these products was obtained as a sole diastereomer, and the stereochemistry was established on the basis of considerations on its spectral data similar to those described for **9**–**15** (see Experimental).



Scheme 3

The dehydration step leading to benzothiopyran derivatives **28** and **29** was somewhat troublesome relative to that for the quinolinecarboxylates **16**–**22**. Application of thionyl chloride under conditions similar to those described above for **16**–**22** for dehydration of compound **28** resulted in a complex mixture of products. From this the desired product **30** was obtained only in 29% yield along with the corresponding sulfoxide of **28** in 31% yield. Dehydration of **28** was successfully achieved with methylsulfonyl chloride in the presence of triethylamine to give the desired product **30** in an almost quantitative yield. Compound **29** was also subjected to the dehydration with methylsulfonyl chloride under similar conditions to give the corresponding benzothiopyran derivative **31** almost quantitatively. Similarly, we were able to synthesize a 2*H*-1-benzopyran-3-carbonitrile derivative **33** as shown in Scheme 4. The dihydrobenzothiopyran-3-carbonitrile derivative **32** was obtained in moderate yield from 2-mercaptobenzophenone **27** and crotononitrile **23**. The stereochemistry of **32**, however, has not been established unambiguously. Although the coupling constant between 2-H and 3-H (J = 2.7 Hz) indicated that these two hydrogens are *cis*-orientated, the relative configuration at the 4-position is not clear from the spectral data obtained. Although we have no firm explanation at this point, the stereochemistry of **32**, different from those of **28** and **29**, may be attributed to the lower ability of a nitrile group to hydrogen bond, compared with that of the ester carbonyl group. Similar treatment of **32** with methyl-



Scheme 4

sulfonyl chloride and triethylamine led to the formation of compound **33** in an almost quantitative yield.

The results reported in this paper present a procedure that provides a rapid route for the preparation of 1,2-dihydroquinoline-3-carboxylic acid and 2*H*-1-benzothiopyran-3-carboxylic acid derivatives. The simplicity of the reactions and the ready availability of the starting materials make it attractive.

Experimental

The mps were recorded with a Laboratory Devices MEL-TEMP II melting point apparatus and are uncorrected. The IR spectra were determined using KBr disks (unless stated otherwise) with a Perkin-Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. *J* Values are given in Hz. Low-resolution mass spectra were recorded on a JEOL AUTO-MASS 20 spectrometer (Centre for Joint Research and Development, this University). Column chromatography was carried out on Merck Kieselgel 60 F_{254}. Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use. All reactions were carried out under argon.

Starting materials

2-(Methylamino)benzophenone **1** was prepared following the procedure reported by Couture *et al.*[13] 2-(Benzylamino)benzophenone **2** was prepared by the action of PhLi upon 2-(benzylamino)benzonitrile under conditions similar to those reported for the preparation of **1**.[13] **2**: mp 84–86 °C (hexane); ν_{max}/cm^{-1} 3356 and 1621; δ_H 4.51 (2H, d, *J* 5.8), 6.55 (1H, td, *J* 6.8 and 1.0), 6.74 (1H, d, *J* 8.4), 7.25–7.55 (10H, m), 7.62 (1H, dd, *J* 7.9 and 2.1) and 8.99 (1H, br s). Ethyl 2-(methylamino)phenyl ketone **3**[14] was prepared by the action of EtMgBr upon 2-(methylamino)benzonitrile under conditions similar to those reported for the preparation of 2-(benzylamino)phenyl ethyl ketone.[13] *tert*-Butyl 3-(2-furyl)propanoate **7** was prepared by the reaction of (*tert*-butoxycarbonylmethyl)triphenylphosphonium bromide with furan-2-carbaldehyde. **7**: bp 190 °C (bath temp)/13 mmHg; ν_{max}/cm^{-1} (neat) 1705, 1639 and 1153; δ_H 1.51 (9H, s), 6.25 (1H, d, *J* 16.0), 6.44 (1H, dd, *J* 3.6 and 1.8), 6.56 (1H, d, *J* 3.2), 7.33 (1H, d, *J* 16.0) and 7.44 (1H, d, *J* 1.8). 2-Mercaptobenzophenone **27**[10] was prepared by the action of PhLi upon 2-mercaptobenzoic acid. **27**: bp 190 °C (bath temp)/0.36 mmHg; ν_{max}/cm^{-1} (neat) 2550 and 1653; δ_H 4.21 (1H, s), 7.18 (1H, td, *J* 7.3 and 1.5), 7.25–7.5 (5H, m), 7.59 (1H, td, *J* 7.3 and 1.3) and 7.77 (2H, dd, *J* 7.3 and 1.3). All of the other chemicals used in this study were commercially available.

tert-Butyl (2*R**,3*R**,4*S**)-4-hydroxy-1,2-dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 9. Typical procedure for the preparation of tetrahydroquinolinecarboxylates 9–15

Diisopropylamine (2 mmol, 0.20 g) was added to a stirred solution of EtMgBr (2 mmol) in Et_2O (7 cm^3) at 0 °C, and the mixture was heated at reflux for 1 h. To the cooled (0 °C) turbid solution was added successively 2-(methylamino)benzophenone **1** (1.0 mmol, 0.20 g) and then *tert*-butyl crotonate **4** (2.0 mmol, 0.28 g). The resulting mixture was stirred for 2 h at the same temperature before it was quenched by adding aqueous saturated NH_4Cl. The organic layer was separated and the aqueous layer was extracted with Et_2O twice (20 cm^3 each). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel (1:5 EtOAc–hexane) to afford the *hydroxyquinolinecarboxylate* **9** (0.28 g, 80%) as a pale yellow solid: mp 92–94 °C (hexane) (Found: C, 74.8; H, 7.8; N, 4.0. $C_{22}H_{27}NO_3$ requires C, 74.75; H, 7.7; N 3.95%); ν_{max}/cm^{-1} 3463, 1698 and 1604; δ_H 1.01 (9H, s), 1.31 (3H, d, *J* 7.3), 3.02 (1H, d, *J* 11.1), 3.03 (3H, s), 3.83 (1H, dq, *J* 11.1 and 7.3), 4.39 (1H, s), 6.51 (1H, t, *J* 7.3), 6.57 (1H, dd, *J* 7.3 and 1.4), 7.42 (1H, d, *J* 7.3), 7.1–7.35 (4H, m) and 7.46 (2H, dd, *J* 8.1 and 1.4); *m*/*z* 353 (M$^+$, 8.8%), 320 (12), 264 (87) and 220 (100).

Ethyl (2*R,3*S**,4*R**)-4-hydroxy-1-methyl-2,4-diphenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 10.** A pale yellow solid; mp 90–93 °C (hexane) (Found: C, 77.4; H, 6.4; N, 3.8. $C_{25}H_{23}NO_3$ requires C, 77.5; H, 6.5; N, 3.6%); ν_{max}/cm^{-1} 3466, 1704 and 1604; δ_H 0.50 (3H, t, *J* 7.4), 2.79 (3H, s), 3.35–3.6 [3H, m including d (*J* 11.8) at 3.42], 4.59 (1H, s), 4.85 (1H, d, *J* 11.8), 6.56 (1H, t, *J* 7.4), 6.63 (1H, dd, *J* 7.4 and 1.6), 6.84 (1H, d, *J* 8.4), 7.15–7.4 (9H, m) and 7.47 (2H, d, *J* 6.9); *m*/*z* 387 (M$^+$, 1.8%), 254 (28) and 182 (100).

***tert*-Butyl *cis*-4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 11.** A pale yellow solid; mp 105–107 °C (hexane) (Found: C, 74.0; H, 7.7; N, 3.9. $C_{21}H_{25}NO_3$ requires C, 74.3; H, 7.4; N, 4.1%); ν_{max}/cm^{-1} 3419, 1698 and 1600; δ_H 1.21 (9H, s), 2.98 (3H, s), 3.2–3.3 (2H, m), 3.71 (1H, dd, *J* 12.1 and 10.6), 4.43 (1H, s), 6.57 (1H, td, *J* 7.9 and 1.1), 6.65 (1H, d, *J* 7.9), 6.87 (1H, dd, *J* 7.9 and 1.6), 7.15 (1H, td, *J* 7.9 and 1.6) and 7.2–7.45 (5H, m); *m*/*z* 339 (M$^+$, 28%), 283 (39), 264 (51) and 220 (100).

***tert*-Butyl (2*R**,3*S**,4*R**)-4-hydroxy-2-(2-furyl)-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 12.** A pale yellow solid; mp 176–178 °C (hexane) (Found: C, 74.1; H, 6.7; N, 3.45. $C_{25}H_{27}NO_4$ requires C, 74.05; H, 6.7; N, 3.45%); ν_{max}/cm^{-1} 3461, 1703 and 1606; δ_H 0.95 (9H, s), 2.84 (3H, s), 3.60 (1H, d, *J* 11.6), 4.71 (1H, s), 4.94 (1H, d, *J* 11.6), 6.3–6.35 (2H, m), 6.54 (1H, td, *J* 7.9 and 1.1), 6.63 (1H, dd, *J* 7.9 and 1.6), 6.79 (1H, d, *J* 7.9), 7.18 (1H, td, *J* 7.9 and 1.6), 7.25–7.4 (3H, m), 7.43 (1H, t, *J* 1.3) and 7.48 (2H, dd, *J* 7.9 and 1.6); *m*/*z* 405 (M$^+$, 3.6%), 330 (10) and 286 (100).

Diethyl 4-hydroxy-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-2,3-dicarboxylate 13. A mixture of two diastereomers (*ca.* 2:1); a pale yellow oil; R_f 0.42 (1:5 EtOAc–hexane) (Found: C, 68.8; H, 6.8; N, 3.6. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.6; N, 3.65%); ν_{max}/cm^{-1} (neat) 3478, 1738, 1728 (sh) and 1605; δ_H 0.97 (1H, t, *J* 6.9), 1.00 (2H, t, *J* 6.9), 1.14 (1H, t, *J* 7.4), 1.28 (2H, t, *J* 6.9), 2.98 (1H, s), 3.06 (2H, s), 3.60 (0.67H, d, *J* 5.3), 3.68 (0.33H, d, *J* 7.4), 3.7–4.05 (3.32H, m), 4.06 (0.67H, d, *J* 5.3), 4.1–4.3 (1.35H, m), 4.45 (0.33H, d, *J* 7.4), 4.63 (0.33H, s), 6.6–6.8 (3H, m), 6.96 (0.33H, dd, *J* 7.4 and 1.6), 7.16 (0.33H, d, *J* 7.4 and 1.6) and 7.2–7.4 (5H, m); *m*/*z* 383 (M$^+$, 1.5%), 310 (18) and 105 (100).

***tert*-Butyl (2*R**,3*R**,4*S**)-1-benzyl-4-hydroxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 14.** A pale yellow solid; mp 137–139 °C (hexane) (Found: C, 78.0; H, 7.35; N, 3.05. $C_{28}H_{31}NO_3$ requires C, 78.3; H, 7.3; N, 3.25%); ν_{max}/cm^{-1} 3449, 1694 and 1603; δ_H 1.09 (9H, s), 1.22 (3H, d, *J* 6.3), 3.17 (1H, d, *J* 11.1), 4.06 (1H, dq, *J* 11.1 and 6.3), 4.49 (1H, s), 4.62 (1H, d, *J* 17.9), 4.66 (1H, d, *J* 17.9), 6.50 (1H, td, *J* 7.9 and 1.2), 6.56 (1H, d, *J* 7.9), 6.59 (1H, d, *J* 7.9), 7.03 (1H, td, *J* 7.9 and 1.2), 7.2–7.4 (8H, m) and 7.51 (2H, d, *J* 6.9); *m*/*z* 429 (M$^+$, 0.14%), 396 (18), 350 (21) and 91 (100).

***tert*-Butyl (2*R**,3*R**,4*S**)-4-ethyl-4-hydroxy-1,2-methyl-1,2,3,4-tetrahydroquinoline-3-carboxylate 15.** A pale yellow oil; R_f 0.36 (1:5 EtOAc–hexane) (Found: C, 70.6; H, 8.9; N, 4.4. $C_{18}H_{27}NO_3$ requires C, 70.8; H, 8.9; N, 4.6%); ν_{max}/cm^{-1} (neat) 3498, 1702 and 1604; δ_H 0.88 (3H, t, *J* 7.4), 1.31 (3H, d, *J* 6.3), 1.47 (9H, s), 1.74 (1H, dq, *J* 14.2 and 7.4), 2.30 (1H, dq, *J* 14.2 and 7.4), 2.70 (1H, d, *J* 9.0), 2.93 (3H, s), 3.6–3.75 (2H, m),

6.65–6.75 (2H, m), 7.17 (1H, dt, *J* 7.9 and 1.6), and 7.30 (1H, dd, *J* 7.9 and 1.6); *m*/*z* 305 (M^+, 24%), 187 (45) and 131 (100).

tert-Butyl 1,2-dimethyl-4-phenyl-1,2-dihydroquinoline-3-carboxylate 16. Typical procedure for the preparation of dihydroquinolinecarboxylates 16, 17 and 19–22

Thionyl chloride (0.60 mmol, 71 mg) was added to a stirred solution of the hydroxytetrahydroquinolinecarboxylate **9** (0.40 mmol, 0.15 g) in Et_2O (2 cm^3) containing pyridine (1.2 mmol, 96 mg) at 0 °C. After stirring for 5 min, 10% aqueous $NaHCO_3$ was added. The organic material was extracted with Et_2O three times (10 cm^3 each). The combined extracts were washed successively with 10% aqueous HCl, water and then brine, and dried (Na_2SO_4). After evaporation of the solvent the residue was purified by preparative TLC (1 : 5 EtOAc–hexane) to give the *1,2-dihydroquinolinecarboxylate* **16** (0.12 g, 89%) as a lemon-yellow solid; mp 106–108 °C (hexane) (Found: C, 78.8; H, 7.7; N, 4.05. $C_{22}H_{25}NO_2$ requires C, 78.8; H, 7.5; N, 4.2%); ν_{max}/cm^{-1} 1682 and 1618; δ_H 1.09 (9H, s), 1.20 (3H, d, *J* 6.3), 3.00 (3H, s), 4.42 (1H, q, *J* 6.3), 6.53 (1H, t, *J* 7.9), 6.57 (1H, d, *J* 7.9), 6.60 (1H, dd, *J* 7.9 and 1.6), 7.17 (1H, td, *J* 7.9 and 1.6) and 7.3–7.4 (5H, m); *m*/*z* 335 (M^+, 12%), 320 (87) and 264 (100).

Ethyl 1-methyl-2,4-diphenyl-1,2-dihydroquinoline-3-carboxylate 17. A lemon-yellow solid; mp 139–142 °C (hexane) (Found: C, 80.4; H, 6.3; N, 3.6. $C_{25}H_{23}NO_2$ requires C, 80.65; H, 6.5; N, 3.9%); ν_{max}/cm^{-1} 1688 and 1627; δ_H 0.76 (3H, t, *J* 6.9), 2.89 (3H, s), 3.7–3.9 (2H, m), 5.54 (1H, s), 6.48 (1H, d, *J* 7.9), 6.52 (1H, t, *J* 7.9), 6.65 (1H, dd, *J* 7.9 and 1.6), 7.16 (1H, td, *J* 7.9 and 1.6) and 7.2–7.4 (10H, m); *m*/*z* 369 (M^+, 7.8%) and 292 (100).

***tert*-Butyl 2-(2-furyl)-1-methyl-4-phenyl-1,2-dihydroquinoline-3-carboxylate 19.** A lemon-yellow solid; mp 170–171 °C (hexane) (Found: C, 77.2; H, 6.45; N, 3.65. $C_{25}H_{25}NO_3$ requires C, 77.5; H, 6.5; N, 3.6%); ν_{max}/cm^{-1} 1690 and 1626; δ_H 1.07 (9H, s), 3.07 (3H, s), 5.50 (1H, s), 6.13 (1H, d, *J* 3.2), 6.21 (1H, dd, *J* 3.2 and 1.1), 6.5–6.6 (2H, m), 6.66 (1H, dd, *J* 7.9 and 1.6), 7.16 (1H, td, *J* 7.9 and 1.6), 7.30 (1H, dd, *J* 3.2 and 2.6) and 7.3–7.4 (5H, m); *m*/*z* 387 (M^+, 0.11%) and 271 (100).

Diethyl 1-methyl-4-phenyl-1,2-dihydroquinoline-2,3-dicarboxylate 20. A lemon-yellow oil; R_f 0.27 (1 : 5 EtOAc–hexane) (Found: C, 72.55; H, 6.4; N, 4.1. $C_{22}H_{23}NO_4$ requires C, 72.3; H, 6.35; N, 3.8%); ν_{max}/cm^{-1} (neat) 1737 and 1688; δ_H 0.87 (3H, t, *J* 7.4), 1.19 (3H, t, *J* 6.9), 3.19 (3H, s), 3.93 (2H, m), 4.11 (2H, m), 5.17 (1H, s), 6.57 (1H, t, *J* 7.9), 6.67 (1H, dd, *J* 7.9 and 1.6), 6.70 (1H, d, *J* 7.9), 7.22 (1H, td, *J* 7.9 and 1.6) and 7.25–7.4 (5H, m); *m*/*z* 365 (M^+, 0.20%) and 292 (100).

***tert*-Butyl 1-benzyl-2-methyl-4-phenyl-1,2-dihydroquinoline-3-carboxylate 21.** A lemon-yellow solid; mp 106–107 °C (hexane) (Found: C, 81.4; H, 7.0; N, 3.35. $C_{28}H_{29}NO_2$ requires C, 81.7; H, 7.1; N, 3.4%); ν_{max}/cm^{-1} 1683 and 1619; δ_H 1.09 (9H, t), 1.23 (3H, d, *J* 6.5), 4.49 (1H, q, *J* 6.5), 4.50 (1H, d, *J* 15.9), 4.63 (1H, d, *J* 15.9), 6.50 (1H, t, *J* 7.9), 6.56 (1H, d, *J* 7.9), 6.63 (1H, d, *J* 7.9 and 1.6), 7.05 (1H, td, *J* 7.9 and 1.6) and 7.25–7.45 (10H, m); *m*/*z* 411 (M^+, 0.48%), 396 (9.1), 340 (25) and 91 (100).

***tert*-Butyl 4-ethyl-1,2-dimethyl-1,2-dihydroquinoline-3-carboxylate 22.** A lemon-yellow oil; R_f 0.65 (1 : 5 EtOAc–hexane) (Found: C, 75.3; H, 8.9; N, 5.1. $C_{18}H_{25}NO_2$ requires C, 75.2; H, 8.8; N, 4.9%); ν_{max}/cm^{-1} (neat) 1702, 1641 and 1611; δ_H 1.01 (3H, d, *J* 6.3), 1.16 (3H, t, *J* 7.3), 1.55 (9H, s), 2.85–2.95 (5H, m including s at 2.90), 4.27 (1H, q, *J* 6.3), 6.55 (1H, d, *J* 8.4), 6.72 (1H, td, *J* 8.4 and 1.1), 7.20 (1H, td, *J* 8.4 and 1.1) and 7.38 (1H, dd, *J* 8.4 and 1.1); *m*/*z* 287 (M^+, 0.42%), 272 (36) and 216 (100).

1,2-Dimethyl-4-phenyl-1,2-dihydroquinoline-3-carbonitrile 25

2-(Methylamino)benzophenone **1** (0.21 g, 1.0 mmol) was treated with but-2-enenitrile **23** (0.13 g, 2.0 mmol) in the presence of the magnesium amide, prepared from Pr^i_2NH (2 mmol) and EtMgBr (2 mmol), under conditions similar to those described for the preparation of the tetrahydroquinolinecarboxylate **9** to give the *dihydroquinolinecarbonitrile* **25** (0.12 g, 48%) as a lemon-yellow solid; mp 115–117 °C (hexane) (Found: C, 83.15; H, 6.3; N, 10.7. $C_{18}H_{16}N_2$ requires C, 83.05; H, 6.2; N, 10.75%); ν_{max}/cm^{-1} 2201 and 1616; δ_H 1.30 (3H, d, *J* 6.3), 3.00 (3H, s), 4.24 (1H, q, *J* 6.3), 6.55–6.65 (2H, m), 6.78 (1H, dd, *J* 7.9 and 1.6), 7.23 (1H, td, *J* 7.9 and 1.6) and 7.3–7.5 (5H, m); *m*/*z* 260 (M^+, 33%) and 246 (100).

1-Methyl-2,4-diphenyl-1,2-dihydroquinoline-3-carbonitrile 26

This compound was prepared by a procedure similar to that described above for the preparation of **25**. A lemon-yellow oil; R_f 0.26 (1 : 5 EtOAc–hexane) (Found: C, 85.4; H, 5.6; N, 8.8. $C_{23}H_{18}NO_2$ requires C, 85.7; H, 5.6; N, 8.7%); ν_{max}/cm^{-1} (neat) 2206 and 1612; δ_H 2.88 (3H, s), 5.22 (1H, s), 6.55–6.65 (2H, m), 6.78 (1H, dd, *J* 7.9 and 1.6), 7.24 (1H, td, *J* 7.9 and 1.6) and 7.3–7.5 (10H, m); *m*/*z* 322 (M^+, 4.5%) and 245 (100).

tert-Butyl (2*R**,3*R**,4*S**)-4-hydroxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-1-benzothiopyran-3-carboxylate 28

To a cooled (0 °C) turbid solution of the magnesium amide, prepared *in situ* by treating EtMgBr (1.7 mmol) with Pr^i_2NH (0.17 g, 1.7 mmol) in Et_2O (7.1 cm^3) as described above, was added dropwise a solution of the mercapto ketone **27** (0.18 g, 0.84 mmol) in Et_2O (2 cm^3). After 5 min *tert*-butyl crotonate (0.24 g, 1.7 mmol) was added, and the mixture was stirred at the same temperature for 3 h before it was worked up in a manner similar to that described for the preparation of the tetrahydroquinoline derivative **9**. Purification by preparative TLC on silica gel (1 : 5 EtOAc–hexane) afforded the *dihydrobenzothiopyrancarboxylate* **28** (0.23 g, 78%) as a white solid; mp 123–125 °C (hexane) (Found: C, 70.9; H, 6.9; S, 9.1. $C_{21}H_{24}O_3S$ requires C, 70.75; H, 6.8; S, 9.0%); ν_{max}/cm^{-1} 3480 and 1694; δ_H 1.10 (9H, s), 1.36 (3H, d, *J* 6.9), 3.16 (1H, d, *J* 11.2), 4.07 (1H, dq, *J* 11.2 and 6.9), 4.75 (1H, s), 6.72 (1H, dd, *J* 6.9 and 1.5), 6.8–6.9 (1H, m), 7.07 (1H, ddd, *J* 7.9, 6.9 and 1.5), 7.12 (1H, dd, *J* 7.9 and 1.5), 7.2–7.4 (3H, m) and 7.35–7.45 (2H, m); *m*/*z* 356 (M^+, 1.6%) and 237 (100).

Ethyl (2*R**,3*S**,4*R**)-4-hydroxy-2,4-diphenyl-3,4-dihydro-2*H*-1-benzothiopyran-3-carboxylate 29

This compound was prepared by a procedure similar to that described above for the preparation of **28**. A white solid; mp 134–136 °C (hexane) (Found: C, 73.75; H, 5.7; S, 8.3. $C_{24}H_{22}O_3S$ requires C, 73.8; H, 5.7; S, 8.2%); ν_{max}/cm^{-1} 3461 and 1712; δ_H 0.50 (3H, t, *J* 7.3), 3.45 (2H, q, *J* 7.3), 3.78 (1H, d, *J* 11.6), 4.84 (1H, s), 5.13 (1H, d, *J* 11.6), 6.80 (1H, d, *J* 6.9), 6.85–6.95 (1H, m), 7.1–7.2 (2H, m), 7.25–7.25 (5H, m), 7.4–7.5 (3H, m) and 7.45–7.55 (2H, m); *m*/*z* 390 (M^+, 1.9%), 299 (97) and 213 (100).

tert-Butyl 2-methyl-4-phenyl-2*H*-1-benzothiopyran-3-carboxylate 30

To a stirred solution of **28** (0.18 g, 0.5 mmol) in CH_2Cl_2 (2.5 cm^3) containing Et_3N (0.12 g, 1.2 mmol) at 0 °C under argon was added dropwise MsCl (69 mg, 0.6 mmol). The mixture was stirred for 4 h at the same temperature before it was worked up in a manner similar to that described for the preparation of the dihydroquinoline derivatives **16** to give the *benzothiopyrancarboxylate* **30** (0.16 g, 93%) as a white solid: mp 86–88 °C (hexane) (Found: C, 74.5; H, 6.55; S, 9.5. $C_{21}H_{24}O_3S$ requires C, 74.5; H, 6.55; S, 9.5%); ν_{max}/cm^{-1} 1683; δ_H 1.13 (9H, s), 1.49 (3H, d, *J* 6.8), 3.86 (1H, q, *J* 6.8), 6.75 (1H, dd, *J* 7.4 and 1.6), 6.97 (1H, td, *J* 7.4 and 1.6), 7.1–7.2 (2H, m) and 7.3–7.4 (5H, m); *m*/*z* 338 (M^+, 6.2%) and 267 (100).

Dehydration of 28 with $SOCl_2$

In the same way as **9**, compound **28** (67 mg, 0.19 mmol) was treated with $SOCl_2$ to give **30** (18 mg, 29%), along with 3-*tert*-butoxycarbonyl-4-hydroxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-λ^4-benzothiopyran-1-oxide (21 mg, 31%) as a white solid: mp 158–160 °C (hexane–Et_2O) (Found: C, 67.7; H, 6.6. $C_{21}H_{24}O_4S$ requires C, 67.8; H, 6.5%); ν_{max}/cm^{-1} 3381 and 1692; δ_H 1.32 (3H, d, *J* 6.4), 1.38 (9H, s), 2.93 (1H, d, *J* 11.6), 3.25 (1H, s), 3.53 (1H, dq, *J* 11.6 and 6.4), 6.95–7.15 (3H, m), 7.2–7.35 (5H, m) and 7.45 (1H, d, *J* 8.2).

Ethyl 2,4-diphenyl-2*H*-1-benzothiopyran-3-carboxylate 31

This compound was prepared by a procedure similar to that described above for the preparation of **30**. A pale yellow oil; R_f 0.44 (1 : 5 AcOEt–hexane) (Found: C, 77.6; H, 5.4. $C_{24}H_{20}O_2S$ requires C, 77.4; H, 5.4%); ν_{max}/cm^{-1} (neat) 1695; δ_H 0.79 (3H, t, *J* 7.0), 3.84 (2H, q, *J* 7.0), 5.13 (1H, s), 6.84 (1H, dd, *J* 7.7 and 1.3), 6.97 (1H, td, *J* 7.7 and 1.3) and 7.05–7.45 (12H, m); *m*/*z* 372 (M^+, 12%) and 221 (100).

(2*R**,3*S**,4*R**)-4-Hydroxy-2-methyl-4-phenyl-3,4-dihydro-2*H*-1-benzothiopyran-3-carbonitrile 32

This compound was prepared by a procedure similar to that described above for the preparation of **28**. A white solid; mp 163–165 °C (hexane) (Found: C, 72.6; H, 5.3; N, 5.0; S, 11.1. $C_{17}H_{15}NOS$ requires C, 72.6; H, 5.4; N, 5.0; S, 11.4%); ν_{max}/cm^{-1} 3396 and 2252; δ_H 1.38 (3H, d, *J* 6.8), 2.95 (1H, s), 3.23 (1H, qd, *J* 6.8 and 2.7), 3.47 (1H, d, *J* 2.7) and 7.1–7.8 (9H, m); *m*/*z* 281 (M^+, 12%) and 213 (100).

2-Methyl-4-phenyl-2*H*-1-benzothiopyran-3-carbonitrile 33

This compound was prepared by a procedure similar to that described above for the preparation of **30**. A white solid; mp 138.5–140.5 °C (hexane) (Found: C, 77.6; H, 5.0; N, 5.2. $C_{17}H_{13}NS$ requires C, 77.5; H, 5.0; N, 5.3%); ν_{max}/cm^{-1} 2203; δ_H 1.57 (3H, d, *J* 6.9), 3.80 (1H, q, *J* 6.9), 6.89 (1H, dd, *J* 7.7 and 1.3), 7.05 (1H, td, *J* 7.7 and 1.3), 7.2–7.35 (3H, m), 7.39 (1H, dd, *J* 7.7 and 1.3) and 7.4–7.5 (3H, m); *m*/*z* 263 (M^+, 19%) and 248 (100).

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