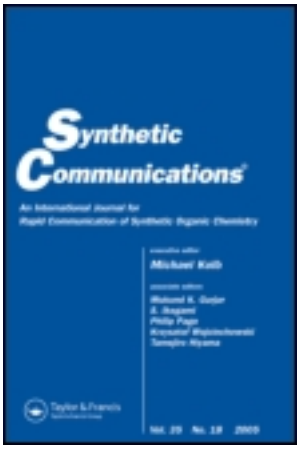

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Case of Pictet-Spengler Revisited: Application to the Synthesis of Dihydroisocoumarins

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Version of record first published: 28 Jul 2007.

To cite this article: N. Choukchou-Braham, B. Mostefa-Kara, N. Cheikh, M. A. Didi & D. Villemin (2005): A Case of Pictet-Spengler Revisited: Application to the Synthesis of Dihydroisocoumarins, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:2, 169-178

To link to this article: http://dx.doi.org/10.1081/SCC-200048399

Synthetic Communications®, 35: 169–178, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200048399

A Case of Pictet-Spengler Revisited: Application to the Synthesis of Dihydroisocoumarins

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Abstract: The reaction of Pictet-Spengler was revisited, and its modified conditions were applied to develop a general methodology toward the synthesis of dihydroisocoumarins containing a no-electron rich aromatic ring.

Keywords: Dihydroisocoumarins, benzylic alcohol, Pictet-Spengler reaction

INTRODUCTION

Among the different classes of natural products that have been studied for their biological activities, isocoumarins have received limited attention. Mellein (Fig. 1), an *Aspergillus Mellius* metabolite isolated by Nishikawa in 1933, is the first example in such a class known for presenting antibacterial activity.[1,2] Hydrangenol, an allergenic[3–6] natural product and AI-77-B,

Received in Poland October 25, 2004
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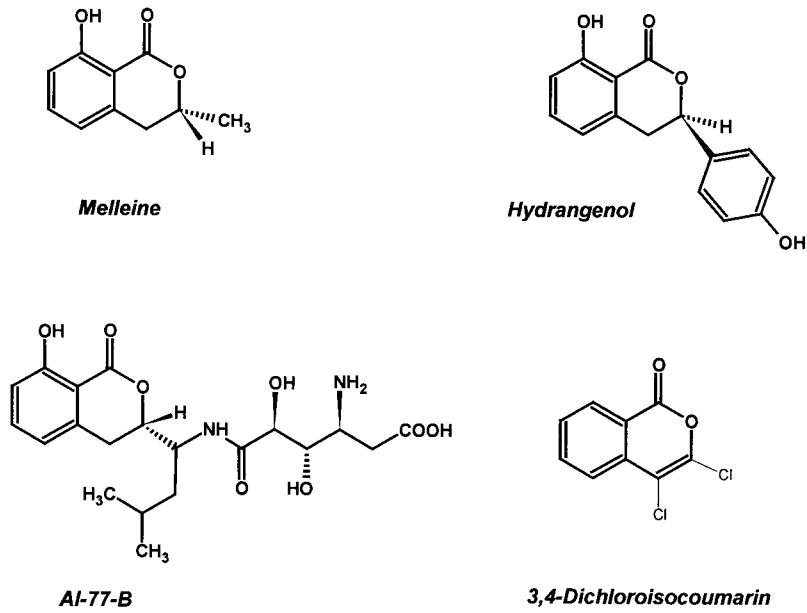


Figure 1. Dichloroisocoumarin and some examples of natural dihydroisocoumarins.

an isolate from *Bacillus Pumilus* with gastroprotective[7] effects, are other examples of isocoumarins that have been targeted for organic synthesis.[8–19] To the best of our knowledge, not enough attention has been devoted to the full investigation of the biological activity of this class of products.

During the course of our research aiming at developing novel antiallergenic and anti-inflammatory compounds, 3,4-dichloroisocoumarin (Fig. 1) attracted our attention. Although it is considered as a potent serine protease inhibitor with a wide range of activity, it exhibits none toward beta-lactamases.[20] Therefore, we decided to investigate the activity of different dihydroisocoumarins (DHICs) analogous to the dichloroisocoumarin.

To such an end, we felt a need to develop a general method that would lead to different DHICs from the same precursor and in considerable amounts whenever required. We report herein the synthesis of different DHICs through the application of modified Pictet-Spengler conditions.

RESULTS AND DISCUSSION

In our retrosynthetic analysis, we envisaged a conceptually appealing yet simple approach based on the Pictet-Spengler reaction conditions. Although

that reaction is a variant of the Mannich one and therefore uses an amine, we conjectured that it would also work when an alcohol is involved through probably a slightly different mechanism. Hence, the DHIC framework would arise from the alcohol **3a–f** through chloromethylation, followed by chromium oxidation (Fig. 2). It is noteworthy that the Pictet-Spengler reaction is reported to work only when the aromatic ring is electron-rich to promote the ring closing. In our case, we successfully tried it on a nonsubstituted ring and obtained good yields. On the other hand, conditions previously reported for the chloromethylation uses formaldehyde along with hydrochloric acid. In our case, we replaced the highly toxic formaldehyde by para-formaldehyde, which produced good yields as well.

Hence, treating aldehyde **4a–f** with benzyl Grignard produced the equivalent homobenzylic alcohol **3a–f** with excellent yields (Scheme 1). Subsequent chloromethylation using either formaldehyde solution in water or para-formaldehyde in acidic medium at a temperature between 50 and 60°C generated the corresponding isochromans **2a–f**. It is to be noted that only in the case of **3f** that dehydration producing stilbene occurred along with the right product. In all other cases, ring formation was faster than dehydration. Finally, oxidation using chromium trioxide[21,22] in aqueous acetic acid at room temperature afforded the DHICs **1a–f** with yields ranging from 66 to 82%. All compounds were identified by proton Nuclear Magnetic Resonance (NMR) and Fourier Transformed Infrared (FT-IR) spectroscopy.

CONCLUSION

We have shown that simple modification of the Pictet-Spengler conditions, mainly heating and substituting formaldehyde by its correspondent polymer, produces DHICs in good yields. Activation of the aromatic ring with an electron-donor group is not necessary in this case, and it is therefore possible to obtain a whole plethora of compounds in this manner. Work for the synthesis of potential protease inhibitors analogous to 3,4-dichloroisocoumarin is currently undergoing and will be communicated in due time.

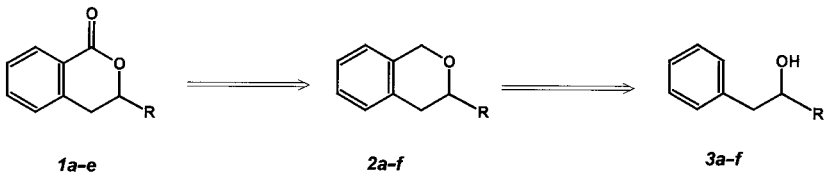
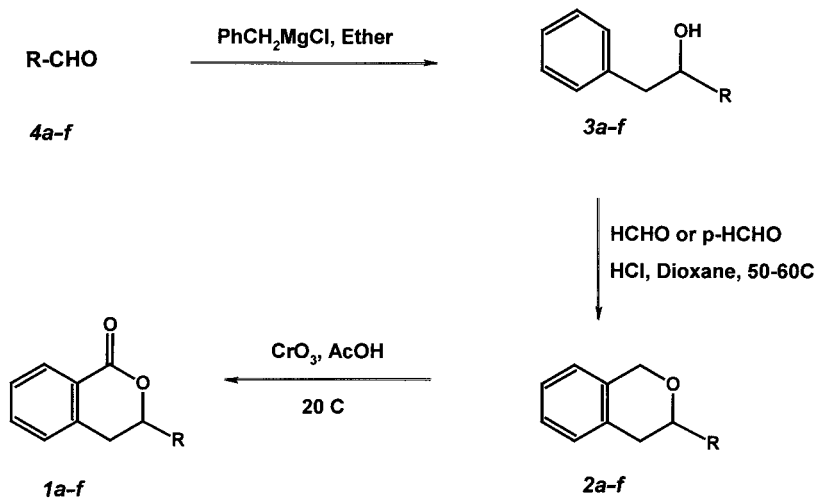


Figure 2. Retrosynthetic analysis of dihydroisocoumarins.



Scheme 1.

EXPERIMENTAL

The PMR spectra were recorded on a Bruker AC250 instrument using tetramethylsilane (TMS) as internal standard reference. Unless specified, $CDCl_3$ was used as the solvent of choice. Infrared spectra were recorded on a Jasco FT-IR 430 spectrometer in $CHCl_3$ with absorptions in cm^{-1}. Melting points (mp) were determined on a Buchi-Tottoli 510 with no correction. Flash chromatography was performed by using Kiesegel 40 to 63 μm silicagel. Tetrahydrofuran (THF) and diethylether were distilled on Na/benzophenone prior to use. Dioxane was dried on 4 Å molecular sieves prior to use.

Synthesis of Homobenzylic Alcohol (3a–f)

General Procedure

To a solution of benzylmagnesium chloride freshly prepared in ether (10 mL) from magnesium (0.6 g, 23.8 mmol) and benzyl chloride (3 g, 23.8 mmol) was added at 0°C to a solution of aldehyde **4a–f** (15.89 mmol) in ether (5 mL). After stirring for 2 hr at room temperature, the reaction mixture was quenched with saturated ammonium chloride. The two phases were separated, and the aqueous layer was extracted twice with ether. The combined organic layers were then washed once with brine and dried over $MgSO_4$. Filtration followed by concentration in vacuo produced the corresponding residue that was purified by flash chromatography.

(±)-1-Phenylpropan-2-ol (**3a**)

Obtained from acetaldehyde; viscous liquid; yield 93%; $R_f = 0.41$ (eluent: $AcOEt/C_6H_{12} = 10/90$); $C_9H_{12}O$; ^1H NMR δ: 1.25 (t, 3H, CH_3), 2.45–2.90 (m, 2H, $PhCH_2$), 3.45 (m, 1H, $PhCH_2CH$), 7.20 (m, 5H, Ph); IR: 3374 (O–H), 2965–2923 (C–H), 1448 (C=C_{ar}), 1081 (C–O).

(±)-1-Phenylpentan-2-ol (**3b**)

Obtained from butanal; viscous liquid; yield 86%; $R_f = 0.13$ (eluent: $AcOEt/C_6H_{12} = 10/90$); $C_{11}H_{16}O$; ^1H NMR δ: 0.94 (t, 3H, CH_3), 1.49 (m, 4H, –CH_2–), 2.42–2.90 (m, 2H, $PhCH_2$), 3.52 (m, 1H, $PhCH_2CH$), 7.28 (m, 5H,Ph); IR: 3464 (O–H), 3114 (C–H_{ar}), 1470–1554 (C=C_{ar}), 1109 (C–O–).

(±)-1-Phenylnonan-2-ol (**3c**)

Obtained from octanal; viscous liquid; yield 89%; $R_f = 0.37$ (eluent: $AcOEt/C_6H_{12} = 10/90$); $C_{15}H_{24}O$; ^1H NMR δ: 0.98 (t, 3H, CH_3), 1.37 (m, 12H, –CH_2), 2.39–2.78 (m, 2H, $PhCH_2$), 3.79 (m, 1H, $PhCH_2CH$), 7.31 (m, 5H,Ph); IR ($CHCl_3$): 3408 (O–H), 3126 (C–H_{ar}), 1475–1539 (C=C_{ar}), 1103 (C–O–).

(±)-1,2-Diphenylethanol (**3d**)

Obtained from benzaldehyde; white solid; mp 66°C; yield 77%; $R_f = 0.37$ (eluent: $AcOEt/C_6H_{12} = 20/80$); $C_{14}H_{14}O$; ^1H NMR δ: 2.65 (broad, 1H,O–H), 3.00 (m, 2H, $PhCH_2CH$); 4.89 (m, 1H, $PhCH_2CHPh$), 7.20–7.33 (m, 10H, 2Ph); IR: 3400 (O–H, broad), 3022–2924 (C=H_{ar}), 2862 (C–H_{al}), 1490–446 (C=C_{ar}), 1033 (C–O).

(±)-1-(4′-Methoxyphenyl)-2-Phenylethanol (**3e**)

Obtained from 4-methoxy-benzaldehyde; white solid, mp 61°C; yield 91%; $R_f = 0.22$ (eluent: $AcOEt/C_6H_{12} = 20/80$); $C_{15}H_{16}O$; ^1H NMR δ: 1.85 (broad, 1H, OH), 2.99 (m, 2H, $PhCH_2CH$), 3.80 (s, 3H, OCH_3), 4.84 (m, 1H, $PhCH_2CH$), 6.85–7.33 (m, 9H, Ph); IR: 3283 (O–H, broad), 3020–2929 (C–H_{ar}), 2850 (C–H_{al}), 1509–1450 (C=C_{ar}), 1247 (C_{ar}–O–C), 1031 (C–O).

(±)-1-(4′-Chlorophenyl)-2-Phenylethanol (**3f**)

Obtained from 4-chloro-benzaldehyde; white solid; mp 59°C; yield 82%; $R_f = 0.32$ (eluent: $AcOEt/C_6H_{12} = 20/80$); $C_{14}H_{13}OCl$; ^1H NMR

δ: 2.75–2.90 (m, 2H, $PhCH_2CH$), 3.40 (broad, 1H, OH), 4.75 (m, 1H, $PhCH_2CH$), 7.10–7.30 (m, 9H, Ph); IR: 3413 (O–H, broad), 3000–2900 ($C-H_{ar}$), 2850 ($C-H_{al}$), 1483–1448 ($C-C_{ar}$), 1030 (C═O), 827 (C═Cl).

Synthesis of Isochromans 2a–f

General Procedure

Dry hydrogen chloride was bubbled for 2 hr at 50–60°C in a mixture of alcohol **3a–f** (4.44 mol), formaldehyde (0.85 g, 9.90 mmol) or para-formaldehyde (0.89 g) instead of and concentrated hydrochloric acid (0.53 g, 5.46 mmol) in dry dioxane (10 mL). After cooling down to room temperature, the mixture was poured into ice water, and the product was extracted three times with 25 mL of ether. The combined organic layers were then washed once with a 10% solution of $NaHCO_3$, water and then dried over calcium chloride. Filtration and concentration in vacuum produced then a residue that was purified by flash chromatography.

(±)-3-Methylisochroman (**2a**)

Prepared from (±)-1-phenylpropan-2-ol (**3b**); viscous liquid; yield 50%; $R_f = 0.60$ (eluent: $AcOEt/C_6H_{12} = 10/90$); $C_{10}H_{12}O$; ^1H NMR δ: 1.33 (d, 3H, CH_3), 2.74 (m, 2H, $PhCH_2$), 3.68 (m, 1H, $PhCH_2CH$), 4.85–5.24 (m, 2H,$PhCH_2O-$), 7.12 (m, 4H, Ph); IR: 3023 ($C-H_{ar}$), 2925–2890 ($C-H_{ar}$), 1110 (C–O–C), 1492–1604 ($C=C_{ar}$).

(±)-3-Propylisochroman (**2b**)

Prepared from (±)-1-phenylpentan-2-ol (**1b**); viscous liquid; yield 64 %; $R_f = 0.29$ (eluent:$AcOEt/C_6H_{12} = 10/90$); $C_{12}H_{16}O$; ^1H NMR δ: 0.98 (m, 3H, CH_3), 1.57 (m, 4H, $-CH_2-$), 2.74–2.94 (m, 2H, $PhCH_2$), 3.68 (m, 1H,$PhCH_2CH$), 4.82 (m, 3H, $PhCH_2-O$), 7.14–7.20 (m, 4H, Ph); IR: 3166 ($C-H_{ar}$), 2996 ($C-H_{ar}$), 1554 ($C=_{ar}$), 1101 (C–O–C).

(±)-3-Heptylisochroman (**2c**)

Prepared from (±)-1-phenylnonan-2-ol (**3c**); viscous liquid; yield 83%; $R_f = 0.43$ (eluent: $AcOEt/C_6H_{12} = 10/90$); $C_{16}H_{24}O$; ^1H NMR δ: 0.87 (t, 3H, CH_3), 1.29–1.88 (m, 12H, $-CH_2-$), 2.63 (m, 2H, $PhCH_2$), 3.68 (m, 1H, $PhCH_2CH$), 4.64–4.84 (m, 2H, $PhCH_2O-$), 7.07–7.36 (m,4H, Ph); IR: 3126 ($C-H_{ar}$), 2854 ($C-H_{ar}$), 1539 ($C=C_{ar}$), 1103 (C–O–C).

(±)-3-Phenylisochroman (**2d**)

Prepared from (±rpar;-1,2-diphenylethanol (**3d**); viscous liquid; yield 93%; $R_f = 0.59$ (eluent: $AcOEt/C_6H_{12} = 20/80$); $C_{15}H_{14}O$; ^1H NMR δ: 3.36 (m, 2H, $PhCH_2CH$), 3.69 (s, 2H, $PhCH_2O$), 5,03 (m, 1H, $PhCH_2CH$), 7.08–7.35 (m, 9H, 2Ph); IR: 3030–2936 (C–H_{ar}), 2860 (C–H_{al}), 1493–1447 (C═C_{ar}), 1206(C–O–C).

(±)-3-(4′-Methoxyphenyl) Isochroman (**2e**)

Prepared from (±)-1-(4′-methoxy-phenyl)-2-phenylethanol (**3e**); viscous liquid; yield 93%; $R_f = 0.53$ (eluent: $AcOEt/C_6H_{12} = 20/80$); $C_{16}H_{16}O_2$; ^1H NMR δ: 3.74 (m, 2H, $PhCH_2CH$), 3.83 (s, 3H, OCH_3), 4.42 (s, 2H, $PhCH_2O$–), 4.58–4.67 (m, 1H, $PhCH_2CH$), 7.23–7.58 (m, 8H, Ph); IR: 3010–2930 (C–H_{ar}), 2850 (C–H_{al}), 1504–1453 (C═C_{ar}), 1251 (C_{ar}–O–C), 1178 (C–O–C).

(±)-3-(4′-Chlorophenyl) Isochroman (**2f**)

Prepared from (±)-1-(4′-chloro-phenyl)-2-phenylethanol (**3f**); viscous liquid; yield 86%; $R_f = 0{,}60$ ($AcOEt/C_6H_{12} = 20/80$); $C_{15}H_{13}OCl$; ^1H NMR δ: 3.22-3.41 (m, 2H, $PhCH_2CH$), 3.68 (s, 2H, $PhCH_2O$–), 4.99 (m, 1H,$PhCH_2CH$), 7.03–7.28 (m, 8H, Ph); IR ($CHCl_3$): 3029–2950 (C–H_{ar}), 2841 (C–H_{al}), 1491–1447 (C═C_{ar}), 1207 (C–O–C), 822 (C–Cl).

Synthesis of 3,4-dihydroisocoumarins 1a–f

General Procedure

A mixture of CrO_3 (1.5 g, 15 mmol), water (2.5 mL) and glacial acetic acid (5 mL) were poured into a solution of isochroman **2a–f** (2.8 mmol) in glacial acetic acid (10 mL) while stirring. The mixture was then stirred for an additional 2 hr, followed by TLC before 10 mL of water was added. The product was extracted with chloroform twice, and the combined organic layers were washed with 10% Na_2CO_3. Drying over $MgSO_4$, filtration and concentration produced a residue that was purified by flash chromatography.

(±)-3-Methyl-3,4-dihydroisocoumarin (**1a**)

Obtained from (±)-3-methyl-isochroman (**2a**); viscous liquid; yield 82%; $R_f = 0.49$ ($AcOEt/C_6H_{12} = 10/90$); $C_{10}H_{10}O_2$; ^1H NMR δ: 1.51–1.53 (d, 3H, CH_3), 2.93 (m, 2H, $PhCH_2$), 4.64–4.72 (m, 1H, $PhCH_2CH$),

7.22–7.56 (m, 4H, Ph); IR: 3160 (C–H_{ar}), 2979 (C–H_{al}), 1718 (C=O), 1452–1604 (C=C_{ar}), 1116 (C–O–C).

(±)-3-Propyl-3,4-dihydroisocoumarin (**1b**)

Obtained from (±)-3-propyl-isochroman (**2b**); viscous liquid; yield 81%; $R_f = 0.25$ (AcOEt/$C_6H_{12} = 10/90$); $C_{16}H_{22}O_2$; ^{1}H NMR δ: 0.96 (m, 3H, CH_3), 1.66 (m, 4H, $-CH_2-$), 2.94 (m, 2H, $PhCH_2$), 4.56 (m, 1H, $PhCH_2CH$), 7.20–7.58 (m, 3H, H_5, H_6 and H_7), 8.08 (m, 1H, H_8); IR: 3127 (C–H_{ar}), 1713 (C=O), 1519 (C=C_{ar}), 1112 (C–O–C).

(±)-3-Heptyl-3,4-dihydroisocoumarin (**1c**)

Obtained from (±)-3-heptylisochroman (**2c**); viscous liquid; yield 66%; $R_f = 0.29$ (AcOEt/$C_6H_{12} = 10/90$); $C_{16}H_{22}O_2$; ^{1}H NMR δ: 0.88 (t, 3H, CH_3), 1.28–1.88 (m, 12H, $-CH_2-$), 2.97 (m, 2H, $PhCH_2$), 4.48–4.55 (m, 1H, $PhCH_2CH$), 7.22–7.52 (m, 3H, H5, H6, H7), 8.10 (m, 1H, H8); IR: 3100 (C–H_{ar}), 2927–2856 (C–H_{al}), 1725 (C=O, 1459–1606 (C=C_{ar}), 1116 (C–O–C).

(±)-3-Phenyl-3,4-dihydroisocoumarin (**1d**)

Obtained from (±)-3-phenyl-isochromane (**2d**); viscous liquid; yield 77%; $R_f = 0.28$ (AcOEt/$C_6H_{12} = 20/80$); $C_{15}H_{12}O_2$; ^{1}H NMR δ: 3.28–3.39 (m, 2H, $PhCH_2CH$), 5.03 (m, 1H, $PhCH_2CH$), 7.20–7.38 (m, 9H, 2Ph); IR: 3062 (C–H_{ar}), 2925 (C–H_{al}), 1727 (C=O), 1452 (C=C_{ar}), 1112 (C–O–C)

(±)-3-(4′-Methoxyphenyl)-3,4-dihydroisocoumarin (**1e**)

Obtained from (±)-3-(4′-methoxyphenyl) isochroman (**2e**); white solid; mp 109; yield 80%; $R_f = 0.46$ (AcOEt/$C_6H_{12} = 20/80$); $C_{16}H_{14}O_3$; ^{1}H NMR δ: 3.88 (s, 3H, OCH_3), 3.96 (m, 2H, $PhCH_2CH$), 4.66 (m, 1H, $PhCH_2CH$), 6.84–7.96 (m, 8H, Ph); IR: 3000 (C–H_{ar}), 2890 (C–H_{al}), 1684 (C=O), 1513–1427 (C=C_{ar}), 1110(C–O–C).

(±)-3-(4′-Chlorophenyl)-3,4-dihydroisocoumarin (**1f**)

Obtained from (±)-3-(4′-chlorophenyl) isochroman (**2f**); white solid; mp 91, yield 78%; $R_f = 0.26$ (AcOEt/$C_6H_{12} = 20/80$); $C_{15}H_{11}O_2Cl$; ^{1}H NMR δ: 3.91 (m, 2H, $PhCH_2CH$), 4.62 (m, 1H, $PhCH_2CH$), 6.89–7.90 (m, 8H, Ph); IR: 3090 (C–H_{ar}), 2896 (C–H_{al}),1683 (C=O), 1424 (C=C_{ar}), 1091 (C–O–C), 808 (C–Cl).

ACKNOWLEDGMENTS

We thank the Comité Mixte d'Evaluation et de Prospective de Coopération Interuniversitaire Franco-Algérienne (CMEP) for its financial support (03MDU581).

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