Improved Selective Reduction of 3-Formylchromones Using Basic Alumina and 2-Propanol

Ramiro Araya-Maturana,[1,*] Jorge Heredia-Moya,[1] Hernán Pessoa-Mahana,[1] and Boris Weiss-López[2]

[1]Department of Organic and Physical Chemistry, Faculty of Chemical and Pharmaceutical Sciences, and [2]Department of Chemistry, Faculty of Sciences, University of Chile, Casilla, Santiago, Chile

ABSTRACT

Treatment of formylchromones, dissolved in 2-propanol with basic alumina at 75°C, selectively reduces the formyl group with good yields without any activation process of the alumina.

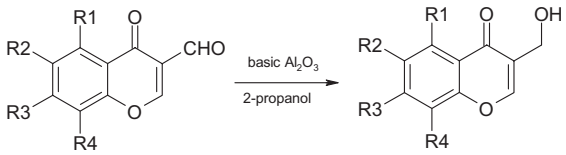
*Correspondence: Ramiro Araya-Maturana, Department of Organic and Physical Chemistry, Faculty of Chemical and Pharmaceutical Sciences University of Chile, Casilla, 233 Santiago 1, Chile; Fax: 56-2-6782868; E-mail: raraya@ciq.uchile.cl.

The remarkable biological activities of 4-oxo-4*H*-1-benzopyranes (chromones) prompted to several groups to synthesize a large variety of 2- or 3-substituted derivatives.[1–8] The Vilsmeir–Haack reaction of *o*-hydroxyacetophenones provides a facile entry into the field of chromones yielding 4-oxo-4*H*-1-benzopyran-3-carboxaldehydes (3-formylchromones),[9,10] a variety of 3-formylchromones has been described by this method.

An attractive way to synthesize 3-substituted chromone derivatives may be envisaged through selective functional group interconversion of the formyl group. The requisite of this strategy is to posses synthetic methods that allow the selective conversion of the aldehydic carbonyl group in the presence of the other two electropositive centers (namely C-2 and pyrone carbonyl carbon). Owing to the synthetic versatileness of hydroxy group that permits the use of alcohols as building blocks besides the reported antiallergic and antiasthma activities of 3-hydroxymethylchromone moiety[6,11] we decide to study the reduction of 3-formyl chromones. This reaction has been previously reported using different methods with variable yields. The first of them, described thirty years ago, utilized $NaBH_4$ and $AlCl_3$ to reduce selectively the formyl group of the parent compound 3-formyl chromone in very low yield.[9a] However, different authors have claimed that certain two substituted chromones underwent reduction of both aldehyde carbonyl and α,β-ethylenic group using sodium borohydride-aluminum chloride as well as sodium borohydride, DIBAL-H in tetrahydrofuran and sodium cyanoborohydride in the presence of acid, and are inert to Meerwein–Pondorf–Verley homogeneous conditions using aluminium isopropoxide.[12] Because of the difficulty in obtaining clean reduction of α,β-ethylenic aldehydes other methods have been reported. For instance, 2-propanol on dried woelm alumina has shown synthetic utility.[12] The yields obtained were about 50%. The drawbacks of this method, as pointed out by the authors, are the high temperature (400°C under vacuum) required for the alumina activation and the relatively large amount of alumina (3–5 g/mmol of carbonyl substrate) necessary for effective substrate reduction. Also has been described that the parent 3-formylchromone and the two derivatives 6-methyl and 6-chloro-3-formylchromone, when dissolved in CH_2Cl_2 and in contact with Brockman neutral alumina (dried at 120°C under vacuum), gives a mixture of at least six products one of them corresponding to 3-hydroxymethyl chromones with yields between 20–30%.[13]

As far as we know the best method reported at this time consists in the treatment of formyl chromones with diborane giving the corresponding 3-hydroxymethylchromone with high yield.[14] However, several significant advantages of the alumina supported 2-propanol, such as the low

Table 1. Results for the reduction of formylchromones.



Compound	Product	R^1	R^2	R^3	R^4	Isolated yield (%)
1a	2a	H	H	H	H	61
1b	2b	OH	H	H	H	50
1c	2c	H	OH	H	H	15
1d	2d	H	OMe	H	H	65

cost of the 2-propanol, easy product isolation, the selectivity for carbonyl reduction and the compatibility with many different types of functional groups make that this method remain as attractive alternative.

We had observed that basic alumina can satisfactorily replace the neutral dried alumina, without a previous drying process, in the reduction of the parent 3-formylchromone therefore eliminating the main drawback of this method. The yield is comparable to those with dried neutral alumina. In this communication we report the potential utility of 2-propanol/basic alumina for the selective reduction of carbonyl aldehyde group of certain formyl substituted chromones.

Treatment of formyl chromones 1a–d dissolved in 2-propanol with basic alumina at 75°C, in about the same ratio reported for the neutral dried alumina, allowed to obtain the 3-hydroxymethyl chromones in good yields (50–60%), with the exception of compound 2C, because to the free phenolyc hydroxyl group, as shown in Table 1, this kind of compounds are the starting materials for the synthesis of a series of *bis*-3-hydroxymethylchromoniloxy derivatives that present a high anti-asthma activities.[15] Although this product is obtained in low yield (15%) this methodology remains as a feasible alternative because the synthesis of 2C has been only reported with 5% of yield.[11a] In Table 1 are summarized the results of reductions of 3-formylchromones.

EXPERIMENTAL

All melting points uncorrected were determined on a Kofler hot-stage apparatus. Infrared spectra were recorded on a FT-IR Bruker

IFS 55 spectrophotometer for KBr disc and wave numbers are reported in cm^{-1}. The ^1H and ^{13}C NMR spectra were performed on Bruker AVANCE DRX 300 spectrometer operating at 300.13 MHz (^1H) or 75.47 MHz (^{13}C). Measurements were carried out a probe temperature of 300K, using $CDCl_3$ containing tetramethylsilane (TMS) as internal standard. Microanalysis was performed using Fisons EA 1108 analyzer. Basic alumina used was Panreac Montplet & Esteban for column chromatography.

The formyl chromones used as substrates were synthesized through Vilsmeier–Haack reaction, their physical and spectroscopic properties are in accordance with the reported bibliography.

GENERAL PROCEDURE FOR PREPARATION OF 1A–D

The experimental conditions utilized were similar to the report in the literature.[9b] To a cooled dimethylformamide solution of *o*-hydroxyacetophenone, phosphorus oxychloride was added dropwise and then the ice bath was removed. The stirring reaction mixture was kept at 75°C overnight and then treated with ice-water to give the corresponding 3-formyl chromone derivative.

4-Oxo-4*H*-1-benzopyran-3-carboxaldehyde (1a). M.p. 149–151°C (Lit.[6] 151–152°C). ^1H NMR, δ ($CDCl_3$): 7.52 (ddd, 1H, $J_1 = 7.9$ Hz, $J_2 = 7.2$ Hz, $J_3 = 1.1$ Hz, 6-H), 7.56 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 1.1$ Hz, 8-H), 7.77 (ddd, 1H, $J_1 = 8.5$ Hz, $J_2 = 7.2$ Hz, $J_3 = 1.7$ Hz, 7-H), 8.32 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.7$ Hz, 5-H), 8.57(s, 1H, 2-H); 10.40 (s, 1H, CHO).

5-Hydroxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (1b).[16] M.p. 157°C. ^1H NMR, δ ($CDCl_3$): 6.91 (dd, 1H, $J_1 = 0.7$ Hz, $J_2 = 8.3$ Hz, 6-H), 6.99 (dd, 1H, $J_1 = 0.7$ Hz, $J_2 = 8.3$ Hz, 8-H), 7.61 (dd, 1H, $J_1 = J_2 = 8.3$ Hz, 7-H), 8.52 (s, 1, 2-H); 10.32 (s, 1H, CHO), 12.10 (s, 1H, OH).

6-Hydroxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (1c).[17] M.p. 235–238°C (dec.). ^1H NMR, δ ($CDCl_3$): 6.08 (s, 1H, OH), 7.30 (dd, 1H, $J_1 = 9.01$ Hz, $J_2 = 3.05$ Hz, 7-H), 7.48 (d, 1H, $J = 9.01$ Hz, 8-H), 7.69 (d, 1H, $J = 3.05$ Hz, 5-H), 8.55 (s, 1H, 2-H); 10.39 (s, 1H, CHO).

6-Methoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (1d). M.p. 163–165°C (Lit.[9b] 164–166°C). ^1H NMR, δ ($CDCl_3$): 3.93 (3H, s, OCH_3), 7.32 (dd, 1H, $J_1 = 9.2$ Hz, $J_2 = 3.0$ Hz, 7-H), 7.48 (1H, d, $J = 9.2$ Hz, 8-H), 7.66 (1H, d, $J = 3.0$ Hz, 5-H), 8.53 (1H, s, 2-H); 10.41 (1H, s, CHO).

GENERAL PROCEDURE FOR REDUCTION OF FORMYLCHROMONES

About 1 g of basic alumina and about 50 mg of the corresponding formyl chromone (5% of alumina weight) dissolved in 10 mL of 2-propanol were placed in a round-bottom flask containing a magnetic bar, the mixture is stirred for 4 h at 75°C. Vacuum filtration through celite, and rotatory evaporation of solvent give crude alcohols which may be purified by column chromatography using ethyl acetate/hexane 1:1 as eluent.

3-(Hydroxymethyl)-4-oxo-4*H*-1-benzopyrane (2a). M.p. 109–110°C (Lit.[6] 108–110°C). ^{1}H NMR, δ ($CDCl_3$): 3.00 (t, 1H, $J = 6.3$ Hz, $CH_2O\underline{H}$), 4.59 (dd, 2H, $J_1 = 6.3$ Hz, $J_2 = 0.7$ Hz, $C\underline{H}_2OH$), 7.43 (ddd, 1H, $J_1 = 7.9$ Hz, $J_2 = 7.3$ Hz, $J_3 = 1.0$ Hz, 6-H), 7.48 (1H, d, $J = 8.6$ Hz, 8-H), 7.70 (ddd, 1H, $J_1 = 8.6$ Hz, $J_2 = 6.9$ Hz, $J_3 = 1.6$ Hz, 7-H), 7.95 (t, 1H, $J = 0.7$ Hz, 2-H), 8.24 (dd, 1H, $J_1 = 7.9$ Hz, $J_2 = 1.6$ Hz, 5-H).

5-Hydroxy-3-(hydroxymethyl)-4-oxo-4*H*-1-benzopyrane (2b). M.p. 102–104°C. ^{1}H NMR, δ ($CDCl_3$): 4.58 (s, 2H, $C\underline{H}_2OH$), 5.12 (t, 1H, $J = 0.8$ Hz, $CH_2O\underline{H}$), 6.82 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 0.9$ Hz, 6-H), 6.92 (1H, dd, $J_1 = 8.4$ Hz, $J_2 = 0.8$ Hz, 8-H), 7.55 (dd, 1H, $J_1 = J_2 = 8.4$ Hz, 7-H); 7.94 (t, 1H, $J = 0.8$ Hz, 2-H), 12.25 (s, 1H, 5-H).

^{13}C NMR, δ ($CDCl_3$): 58.3, 107.5, 111.15, 111.8, 122.09, 136.07, 154.0, 157.2, 160.98, 183.0. IR: 3415, 1651, 1271. Anal. calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 61.93; H, 4.28.

6-Hydroxy-3-(hydroxymethyl)-4-oxo-4*H*-1-benzopyrane (2c). M.p. 217–219°C (Lit.[11] 215–218.5°C). ^{1}H NMR, δ (DMSO-d_6): 4.42 (d, 2H, $J = 4.5$ Hz, $C\underline{H}_2OH$), 5.17 (t, 1H, $J = 4.5$ Hz, $CH_2O\underline{H}$), 7.29 (dd, 1H, $J_1 = 2.5$ Hz, $J_2 = 8.9$ Hz, 7-H); 7.39 (d, 1H, $J = 2.5$ Hz, 5-H), 7.58 (d, 1H, $J = 9$ Hz, 8-H), 8.22 (s, 1H, 2-H), 10.08 (s, 1H, 6-OH).

3-(Hydroxymethyl)-6-methoxy-4-oxo-4*H*-1-benzopyrane (2d). M.p. 151–152°C (Lit.[6] 150–153.5°C). ^{1}H NMR, δ ($CDCl_3$): 2.99 (t, 1H, $J = 6.5$ Hz, $CH_2O\underline{H}$), 3.91 (s, 3H, OCH3), 4.59 (d, 2H, $J = 5.6$ Hz, $C\underline{H}_2OH$), 7.29 (dd, 1H, $J_1 = 9.3$ Hz, $J_2 = 3.0$ Hz, 7-H), 7.42 (d, 1H, $J = 9.2$ Hz, 8-H), 7.57 (d, 1H, $J = 2.9$ Hz, 5-H), 7.93 (s, 1H, 2-H).

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REFERENCES

1. Ellis, G.P. *Chromones*, *Chromanones*, chapter XII, *Hydroxychromones* 633–689; chapter XIII *Alkoxychromones*, 691–748; Chapter XIV *Halochromones*, 749–777.
2. Ellis, G.P.; Becket, G.J.P.; Shaw, D.; Wilson, H.K. Benzopyrones. 14. Synthesis and antiallergic properties of some *N*-tetrazolilcarboxamides and related compounds. J. Med. Chem. **1978**, *21* (11), 1120–1126.
3. Davidson, D.N.; Kaye, P.T. Chromone studies. Part 2. An efficient synthesis of *N*,*N*-dimethylchromone-2-carboxamides. Synthetic Commun. **1990**, *20* (5), 727–732.
4. Refat, H.M. Heterocyclic synthesis with nitriles: synthesis of some new chromone and flavone and its utilization for the synthesis of potentially antitumorigenic policyclic chromones and flavones. Synthetic Commun. **1999**, *29* (9), 1429–1436.
5. Saengchantara, S.T.; Wallace, T.W. Conjugate addition to 3-(*p*-tolylsulphinyl)chromone: a route to 2-substituted chromones and chiral 2-substituted chroman-4-ones. Tetrahedron **1990**, *46* (18) 6553–6564.
6. Klutchko, S.; Cohen, M.P.; Shavel, J., Jr.; von Strandtmann, M. Heterocyclic synthesis with *b*-ketosulfoxides IV. Synthesis of 3-substituted chromones. J. Heterocyclic Chem. **1974**, *11*, 183–188.
7. Enders, D.; Geibel, G.; Osborne, S. Diastereo- and enantioselective total synthesis of stigmatellin A. Chem. Eur. J. **2000**, *6* (8), 1302–1309.
8. Harvey, R.G.; Hahn, J.-T.; Bukowska, M.; Jackson, H. A new chromone and flavone synthesis and its utilization for the synthesis of potentially antitumorigenic policyclic chromones and flavones. J. Org. Chem. **1990**, *55* (25), 6161–6166.
9. (a) Nohara, A.; Umetani, T.; Sanno, Y. A facile síntesis of chromone-3-carboxaldehyde, chromone-3-carboxylic acid, and 3-hydroxymethylchromone. Tetrahedron Lett. **1973**, (22), 1995–1998; (b) Nohara, A.; Umetani, T.; Sanno, Y. A Studies on antianapylactic agents–I. A facile synthesis of 4-oxo-4H-1-benzopyran-3-carboxaldehydes by Vilsmeier reagents. Tetrahedron **1974**, *30*, 3553–3561.
10. Rajanna, K.C.; Solomon, F.; Ali, M.M.; Saiprakash, P.K. Kinetics and mechanism of Vilsmeier–Haack síntesis of 3-formyl chromones derived from *o*-hydroxy aryl alkyl ketones: a structure reactivity study. Tetrahedron **1996**, *52* (10), 3669–3682.
11. (a) von Strandtmann, M.; Shavel, J., Jr.; Klutchko, S.; Cohen, M.P. 3-(Hydroxymethyl)chromones. US Appl. **1974**, *3*, 798, 240; (b)

Herzig David, J.; Schumann, P.R.; Kusner, E.J.; Robichaud, L.; Giles, R.E.; Dubnick, B.; von Strandtmann, M.; Klutchko, S.; Cohen, M.P.; Shavel, J. Jr. The search for specific inhibitors of immediate hypersensitivity reactions. The activity of some chromones in various laboratory models. Monogr. Physiol. Soc. Philadelphia **1977**, *1*(Inmunopharmacology), 103–124.

12. (a) Posner, G.H.; Runquist, A.W.; Chapdelaine, M.J. Organic reactions at alumina surfaces, 6. isopropyl alcohol and diisopropylcarbinol on dehydrated alumina as reagents for very selective carbonyl reductions. J. Org. Chem. **1977**, *42*, 1202–1208; (b) Posner, G.H. Organic reactions at alumina surfaces. Angew. Chem. Int. Ed. Engl. **1978**, *17*, 487–496.
13. Ghosh, C.K.; Bhattacharyya, S. Benzopyrans: part 40—Alumina mediated transformations of 4-oxo-4H-1-benzopyran-3-carbaldehyde, -3-carboxylic acid and their 2-methyl homologues. Indian J. Chem. Sect. B **1999**, *38* (2), 166–172.
14. Ghosch, C.K.; Bhattacharyya, S. Benzopyrans: part 36–A simple synthesis of 3-hydroxymethylchromone. Indian J. Chem. Sect. B **1997**, *36* (3), 267–268.
15. Aries, R. Substances derives de la Chromone. FR. Appl. **1975**, 2,239,467.
16. (a) Polyakov, V.K.; Shevtsova, R.G.; Tsukerman, S.V. Dipole moments of chromone-3-aldehydes. Zh. Obshch. Khim. **1979**, *49* (7), 1560–1563; (b) Kononenko, L.V.; Shevtsova, R.G.; Polyakov, V.K.; Tsukerman, S.V.; Bezuglyi, V.D. Polarographic study of substituted chromone-3-aldehydes. Zh. Obshch. Khim. **1979**, *49* (12), 2693–2698.
17. Fitton, A.; Frost, J.; Suschitzky, H.; Houghton, P. Conversion of 3-formylchromones into pyrrole and thiophene derivatives. Synthesis **1977**, (2), 133–135.