A Practical Synthesis of 2,3-Dihydro-2-benzofurancarboxylic Acid: A General Route to 2,3-Dihydrobenzofurans

Colin R. Edwards, Michael J. Readhead* and Neil J. Tweddle

Chemical Process Development, Reckitt and Colman plc, Dansom Lane, Hull, HU8 7DS, England

Received November 5, 1987

A practical synthesis of 2,3-dihydro-2-benzofurancarboxylic acid is reported in five steps and approximately 40% overall yield. The methodology offers a useful new route to 2-substituted-2,3-dihydrobenzofurans.

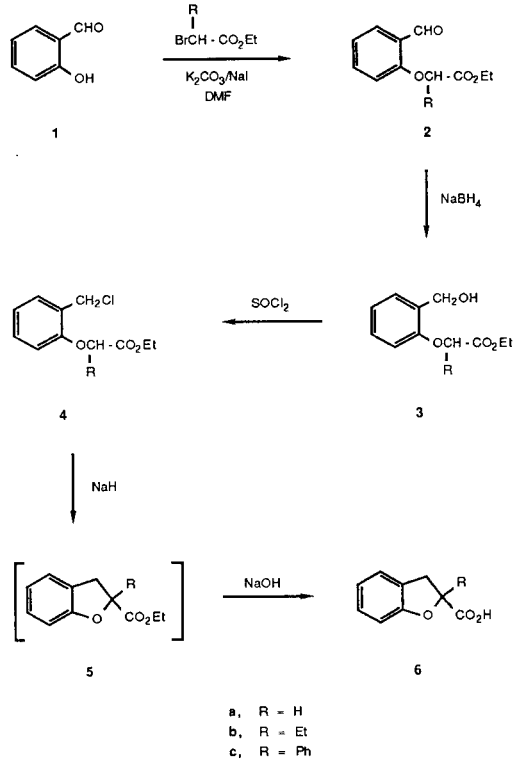
J. Heterocyclic Chem., **24**, 495 (1987).

During the course of our studies directed towards the discovery of novel therapeutic agents acting on α-adrenoreceptors we required a general synthetic route suitable for the production of 2,3-dihydro-2-benzofurancarboxylic acids **6** from milligram to kilogram quantities. Although a considerable amount of work has been reported on the synthesis of 2-alkyl-2,3-dihydrobenzofurans [1], fewer methods are available for the corresponding 2-carboxylic acids. These procedures [2-4] suffer from low yields or involve conditions which are unsuitable for scale-up. We have previously described [5] the use of some of these methods for the preparation of 2-(substituted)-dihydrobenzofurans. It was evident that a facile alternative route suitable for the large scale preparation of **6** was desirable. We therefore developed an improved route to **6** which was ideally suited for our purposes.

Ethyl 2-formylphenoxyacetate (**2a**) was prepared by a modification of the procedure of Bernstein *et al* [6] who isolated **2a** in low yield by condensing salicylaldehyde with ethyl bromoacetate in ethyl alcohol in the presence of sodium. We found that if the condensation was carried out in dimethylformamide using potassium carbonate as base the aldehyde **2a** was obtained in 82% yield. Reduction of the aldehyde **2a** with sodium borohydride gave the alcohol **3a** in quantitative yield. This optimum yield was achieved by adding pellets of sodium borohydride to a solution of the aldehyde in ethyl alcohol. Treatment of the alcohol **3a** with thionyl chloride gave the chloride **4a** in 78% yield.

The cyclisation of the chloride **4a** to a dihydrobenzofuran was the key step in the new synthesis. This was eventually achieved using sodium hydride in *N*-methyl-2-pyrrolidinone when a mixture of ester and acid was isolated. Hydrolysis with aqueous sodium hydroxide gave the acid **6a** in 68% yield from the chloride (overall yield >40%). Lower and inconsistent yields were obtained when the cyclisation was attempted in tetrahydrofuran or dimethylformamide.

Due to the ready availability of appropriately substituted 2-bromo esters this new synthesis offers general access to 2-substituted-2,3-dihydrobenzofurans. Further work is in progress to determine the scope and limitations of the procedure, but the methodology has allowed the preparation and evaluation of derivatives of **6** for biological activity, some of which have already been reported [5].



EXPERIMENTAL

Melting points were determined in a Buchi melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer 1310 spectrophotometer and nuclear magnetic resonance spectra on a Jeol FX90Q spectrometer using tetramethylsilane as internal standard. Elemental analysis was performed on a Carlo Erba 1106 elemental analyser.

Ethyl 2-Formylphenoxyacetate (**2a**).

To a stirred suspension of anhydrous potassium carbonate (304 g, 2.2 moles) and sodium iodide (60 g, 0.4 mole) in dry dimethylformamide (400 ml) was added dropwise salicylaldehyde (244.2 g, 2.0 moles). The reaction mixture was allowed to cool to 40° before the addition of ethyl bromoacetate (367.4 g, 2.2 moles). The mixture was stirred at room temperature for 20 hours and was then added to cold water (4 l). The resulting yellow

solid was collected by filtration, washed with water (4 x 1 l) and finally dried under vacuum at 30° over phosphorous pentoxide. The dried solid was washed with a mixture of diethyl ether and hexane (1:1, 3 x 400 ml) and finally dried for 18 hours under vacuum (0.05 mm) to give **2a** (341.1 g, 82%), mp 46-47° (lit [6], mp 45-46°).

Ethyl 2-Hydroxymethylphenoxyacetate (**3a**).

To a stirred solution of sodium ethoxide (1.55 g, 0.028 mole) in ethyl alcohol (800 ml) cooled to 0-5° with an ice-water bath was added **2a** (339 g, 1.63 moles). Sodium borohydride pellets (15.71 g, 0.43 mole) were added over 2 hours with the reaction temperature <8° during the addition. The mixture was stirred for 1.75 hours and was poured into dilute hydrochloric acid (4 l, 0.25 *N*). The aqueous mixture was extracted with dichloromethane (3 x 600 ml). The combined organic extracts were washed with saturated sodium chloride solution, dried (sodium sulphate) and the solvents removed *in vacuo* to give **3a** as an oil (342 g, 100%) which was sufficiently pure by spectroscopic analysis to be used directly in the next step. ^{1}H nmr (deuteriochloroform): 1.28 (t, 3H, J = 7 Hz, CH_3), 3.31 (S, 1H, OH), 4.24 (q, 2H, J = 7 Hz, CH_2), 4.68 (S, 2H, CH_2), 4.71 (S, 2H, CH_2), 6.7-7.4 (m, 4H, ArH); ir (neat): 3430 (OH), 1750 (C=O), 1600, 1590 cm^{-1}.

Ethyl 2-Chloromethylphenoxyacetate (**4a**).

A solution of **3a** (341.0 g, 1.62 moles) in dry dichloromethane (500 ml) was added over 45 minutes to a stirred solution of thionyl chloride (211.75 g, 1.78 moles) and pyridine (2.18 g, 0.028 mole) in dry dichloromethane (500 ml). The mixture was stirred under reflux for 1.5 hours. The cooled mixture was poured into water (2.4 l) and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 x 100 ml). The combined extracts were washed with saturated sodium bicarbonate solution (4 x 500 ml), saturated sodium chloride solution (500 ml) dried (sodium sulphate) and evaporated *in vacuo* to leave an oil (394.8 g) which was distilled at 114-122° (0.15 mm) to give **4a** (287.45 g, 78%) as an oil which slowly crystallised on standing, mp <25°; nmr (deuteriochloroform): 1.26 (t, 3H, J = 7 Hz, CH_3), 4.23 (q, 2H, J = 7 Hz, CH_2), 4.66 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 6.7-7.5 (m, 4H, ArH); ir (bromoform): 1750 (C=O), 1600, 1590 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}ClO_3$: C, 57.78; H, 5.73. Found: C, 57.55; H, 5.76.

2,3-Dihydro-2-benzofurancarboxylic Acid (**6a**).

To a stirred solution of **4a** (285 g, 1.25 moles) in *N*-methyl-2-pyrrolidinone (1300 ml) cooled to 0-10° in an ice-water bath was added sodium hydride (59.84 g, 60% dispersion in mineral oil, 1.45 moles) in ten portions over 3 hours. The reaction was allowed to attain room temperature and stirred for a further 16 hours. Methyl alcohol (25 ml) was cautiously added and the mixture was poured into dilute hydrochloric acid (2 l, 0.25 *N*). The mixture was extracted with diethyl ether (4 x 500 ml). The combined organic extracts were washed with saturated sodium chloride and the solvents removed *in vacuo* to give an oil. The oil was treated with 2*N* aqueous sodium hydroxide (2324 ml) and heated under reflux for 2 hours. The cooled mixture was washed with petroleum ether (500 ml, bp 40-60°) and the aqueous phase acidified to *p*H 2 with concentrated hydrochloric acid. The acidic mixture was extracted with diethyl ether. The combined organic extracts were washed with saturated aqueous sodium chloride, dried (sodium sulphate) and evaporated *in vacuo* to give a pale yellow solid. Recrystallisation from toluene afforded **6a** as a white crystalline solid (129.2 g, 68%), mp 116-118°, (lit [7], mp 117.2-118.0°).

Using the procedure described above the following compounds were also prepared from the appropriate 2-bromoester.

2,3-Dihydro-2-ethylbenzofurancarboxylic Acid (**6b**).

This compound had mp 99-101°; nmr (deuteriochloroform): 1.03 (t, 3H, J = 7.5 Hz, CH_3), 1.77-2.34 (m, 2H, CH_2), 3.18 (d, 1H, J = 16 Hz, 3-H), 3.59 (d, 1H, J = 16 Hz, 3-H), 6.76-6.95 (m, 2H, ArH), 7.05-7.23 (m, 2H, ArH), 11.29 (s, 1H, COOH deuterium oxide exchangeable); ir (bromoform): 3000 (OH), 1715 (C=O), 1590 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.49.

2,3-Dihydro-2-phenylbenzofurancarboxylic Acid (**6c**).

This compound had mp 131-133°; nmr (deuteriochloroform): 3.52 (d, 1H, J = 17 Hz, 3-H), 4.12 (d, 1H, J = 17 Hz, 3-H), 6.74-7.76 (m, 9H, ArH), 11.05 (s, 1H, COOH, deuterium oxide exchangeable); ir (bromoform): 3000, 1705, 1590 cm^{-1}.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.04; H, 4.98.

Acknowledgement.

We gratefully thank Linda Bentley and Jill Roelich for technical assistance, Frank Hampson, Rosina Hearfield and Neil Hyde for the nmr spectra and microanalysis, and Mrs. Ginette Gray for the typing of this manuscript.

REFERENCES AND NOTES

[1] P. Cagniant and D. Cagniant, "Advances in Heterocyclic Chemistry", Vol 18, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, NY, 1975, p 338.

[2] D. M. Bowen, J. I. DeGraw, Jr., V. R. Shah and W. A. Bonner, *J. Med. Chem.*, **6**, 314 (1963).

[3] W. F. Hoffman, O. W. Woltersdorf, Jr., F. C. Novello, E. J. Cragoe, Jr., J. P. Springer, L. S. Watson and G. M. Fonelli, Jr., *J. Med. Chem.*, **24**, 865 (1981).

[4] B. Libis and E. Habicht, *Angew. Chem.*, **10**, 748 (1971).

[5] C. B. Chapleo, P. L. Myers, R. C. M. Butler, J. A. Davis, J. C. Doxey, S. D. Higgins, M. Myers, A. G. Roach, C. F. C. Smith, M. R. Stillings and A. P. Welbourn, *J. Med. Chem.*, **27**, 570 (1984).

[6] J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, *J. Am. Chem. Soc.*, **73**, 906 (1951).

[7] S. A. Harrison and D. Aelony, *J. Org. Chem.*, **27**, 331 (1962).