COMMUNICATION

A novel protocol for the synthesis of furo[2,3-*b*]benzofurans and dihydrofuro[2,3-*b*]benzofurans

Mukund G. Kulkarni *,† and Ravindra M. Rasne

Department of Chemistry, University of Pune, Pune 411 007, India

A Wittig olefination–Claisen rearrangement approach has been successfully applied to develop a novel protocol for the synthesis of the dihydrofuro[2,3-*b*]benzofuran and furo[2,3-*b*]benzofuran ring systems.

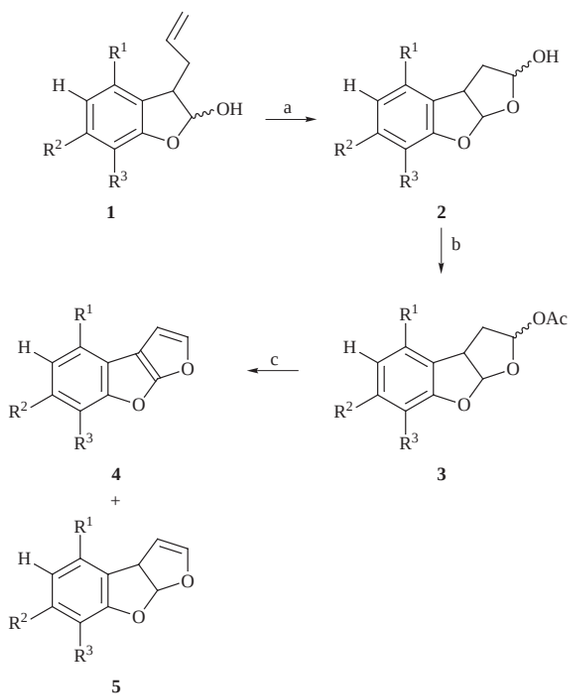
Introduction

The furo[2,3-*b*]benzofuran ring system occurs in several mold toxins like aflatoxin [1]-B_1, -B_2, -G_1, -G_2 and their metabolites like aflatoxin-M_1 and -M_2, sterigmatocystin [2] and versicorolin A [2] in the form of its di- or tetra-hydro derivatives. Several methods have been reported [3] for the construction of the di- and tetrahydrofuro[2,3-*b*]benzofurans, but synthesis of the furo[2,3-*b*]-benzofuran ring system as such has not been reported so far. We describe herein a simple and general protocol for the construction of the dihydrofuro[2,3-*b*]benzofuran ring system *via* a Wittig olefination–Claisen rearrangement approach.[4–7] Along with the dihydro compound we report the formation of the hitherto unknown furo[2,3-*b*]benzofurans.

Discussion

The lactols **1a**–**e** [7] on oxidative cleavage of the olefin with osmium tetroxide–sodium metaperiodate, gave the aldehydes **2a**–**e** [8] in moderate yields (Scheme 1). These aldehydes gave complex ^{1}H NMR spectra and from these spectra it was difficult to ascertain the number of forms that they existed in. It has been reported [9] that similar aldehydes exist as 5- and 6-membered lactols along with the open chain form with the tricyclic 5-membered lactol predominating. However treatment of compounds **2a**–**e** with acetic anhydride–sodium acetate produced a diastereomeric mixture of the lactol acetates **3a**–**e** [8] in near quantitative yields. Subjecting these acetates to pyrolysis at 450 °C under a nitrogen atmosphere, gave two compounds in each case. From the spectral data, the minor compounds obtained in 18–21% yield showed a bright fluorescence under UV light. The spectral data and elemental analyses of these compounds showed them to be the furo[2,3-*b*]benzofurans **4a**–**e**. The major compounds obtained in 54–61% yield were found to be the dihydrofuro[2,3-*b*]benzofurans **5a**–**e**. Apparently, the dihydrofuro[2,3-*b*]benzofurans undergo partial dehydrogenation under the reaction conditions to furnish the furo[2,3-*b*]-benzofurans.

The protocol described here is a simple, short and efficient route for the construction of furo[2,3-*b*]benzofurans and dihydrofuro[2,3-*b*]benzofurans. Application of this methodology to the total synthesis of aflatoxins is in progress.



1 2 3 4 5

Compound	R^1	R^2	R^3
1a–**5a**	H	H	OCH_3
1b–**5b**	H	OCH_3	H
1c–**5c**	H	OCH_3	OCH_3
1d–**5d**	NO_2	H	H
1e–**5e**	OCH_3	OCH_3	H

Scheme 1 *Reagents and conditions*: a, Cat. OsO_4, 2.2 equiv. $NaIO_4$, THF–H_2O (2:1), RT, 5 h (78–87%); b, 1.2 equiv. NaOAc, acetic anhydride, RT, 3 h, (87–94%); c, toluene, 450 °C (18–21% and 54–61%).

Experimental

General

All solvents were distilled and dried before use. Wittig salt was stored and used under argon. Dry THF was freshly prepared by distilling over benzophenone and sodium, under argon. Silica gel (100–200 mesh) was used for column chromatography. UV Spectra were recorded on a Perkin-Elmer Lambda 3B UV/VIS spectrophotometer. IR Spectra were recorded on a Perkin-Elmer model 1600 series FTIR instrument. ^{1}H and ^{13}C NMR spectra (δ/ppm, $SiMe_4$ as internal standard) in $CDCl_3$were recorded, on a JEOL FX90Q, Bruker AC 200 and Bruker AMX 500 spectrometers. *J* Values are given in Hz. Mass spectra were recorded at an ionization energy of 70 eV on a Finnigan MAT-1020 automated GC–MS instrument and mass values are expressed as *m*/*z* values. Elemental analyses were obtained on a HOSLI semi-automatic C, H analyzer. All melting and boiling points are uncorrected and were obtained with a paraffin oil bath.

General procedure for pyrolysis

The dihydrofuro[2,3-*b*]benzofurans **4a**–**e** and furo[2,3-*b*]benzofurans **5a**–**e** were prepared as follows. A solution of tetrahydrofuro[2,3-*b*]benzofuran-2-yl acetate **3** (5.3 mmol) in toluene (20

† E-Mail: mgkul@chem.unipune.ernet.in

cm^3) was pyrolysed, under a nitrogen atmosphere, in a short-contact continuous-flow system at 450 °C. The gaseous reaction mixture was cooled with dry ice–acetone and concentrated under reduced pressure. The crude product was chromatographed on silica gel (2–5% EtOAc in hexane eluent) to afford furo[2,3-*b*]benzofuran **4** and dihydrofuro[2,3-*b*]benzofuran **5**.

7-Methoxyfuro[2,3-*b*]benzofuran 4a. Colourless oil 19%, bp 67–70 °C/2.20 Torr (Found: C, 70.41; H, 4.39. $C_{11}H_8O_3$ requires C, 70.21; H, 4.29%); λ_{max}(methanol)/nm 204 (ε 108 300), 229 (ε 35 400); ν_{max}(film)/cm^{-1} 1621, 1591, 1486, 1435, 1341, 1279; δ_H(90 MHz, $CDCl_3$) 4.00 (3 H, s, ArOCH_3), 6.80 (1 H, d, *J* 2.57, -O-CH=C*H*-), 6.88 (1 H, m, Ar-*H*), 7.07–7.34 (2 H, m, 2 × Ar-*H*), 7.64 (1 H, d, *J* 2.57, -O-C*H*=CH-); *m*/*z* (EI) 188 (M^+, 0%), 162 (30), 148 (100), 133 (53), 119 (22), 105 (57), 91 (22), 77 (50), 63 (13).

6-Methoxyfuro[2,3-*b*]benzofuran 4b. Colourless oil 20%, bp 67–70 °C/2.20 Torr (Found: C, 70.05; H, 4.44. $C_{11}H_8O_3$ requires C, 70.21; H, 4.29%); λ_{max}(methanol)/nm 206 (ε 11 400), 233 (ε 37 900); ν_{max}(film)/cm^{-1} 1621, 1592, 1534, 1491, 1438, 1311; δ_H(90 MHz, $CDCl_3$) 3.88 (3 H, s, Ar-O-CH_3), 6.73–7.24 (2 H, m, -O-C*H*=C*H*-), 7.51–7.70 (3 H, m, Ar-*H*); *m*/*z* (EI) 188 (M^+, 0%), 148 (100), 133 (100), 105 (39), 89 (16), 77 (49), 63 (18).

6,7-Dimethoxyfuro[2,3-*b*]benzofuran 4c. White solid 21%, mp 76–79 °C (Found: C, 65.88; H, 4.71. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.62%); λ_{max}(methanol)/nm 210 (ε 126 400), 243 (ε 40 800); ν_{max}(Nujol mull)/cm^{-1} 1621, 1499, 1423, 1321, 1283; δ_H(90 MHz, $CDCl_3$) 3.98 (3 H, s, Ar-O-CH_3), 4.20 (3 H, s, Ar-O-CH_3), 6.79 (1 H, d, *J* 2.31, -O-CH=C*H*-), 7.00 (1 H, d, *J* 9.00, Ar-*H*), 7.28 (1 H, d, *J* 9.00, Ar-*H*), 7.64 (1 H, d, *J* 2.31, -O-C*H*=CH-); *m*/*z* (EI) 218 (M^+, 0%), 178 (64), 163 (29), 148 (10), 135 (32), 120 (16), 92 (8), 77 (21).

4-Nitrofuro[2,3-*b*]benzofuran 4d. White solid 20%, mp 102–104 °C (Found: C, 58.99; H, 2.55. $C_{10}H_5O_4N$ requires C, 59.12; H, 2.48%); λ_{max}(methanol)/nm 238 (ε 132 000), 283 (ε 37 500); ν_{max}(Nujol mull)/cm^{-1} 1618, 1593, 1506, 1461, 1352, 1265; δ_H(90 MHz, $CDCl_3$) 7.00 (1 H, d, *J* 1.8, -O-CH=C*H*-), 7.68 (1 H, d, *J* 10.38, Ar-*H*), 7.87 (1 H, d, *J* 1.8, -O-C*H*=CH-), 8.36 (1 H, dd, *J* 10.28, 2.31, Ar-*H*), 8.65 (1 H, d, *J* 2.31, Ar-*H*); *m*/*z* (EI) 202 (M^+, 0%), 163 (100), 133 (30), 117 (40), 105 (8), 89 (72), 77 (9), 63 (20).

4,6-Dimethoxyfuro[2,3-*b*]benzofuran 4e. Colourless oil 20%, bp 78–81 °C/2.20 Torr (Found: C, 66.25; H, 4.85. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.62%); λ_{max}(methanol)/nm 213 (ε 12 900), 248 (ε 43 400); ν_{max}(film)/cm^{-1} 1616, 1498, 1459, 1376, 1275; δ_H(90 MHz, $CDCl_3$) 3.80 (3 H, s, Ar-O-CH_3), 3.90 (3 H, s, Ar-O-CH_3), 6.38 (1 H, d, *J* 2.57, -O-CH=C*H*-), 6.77 (1 H, d, *J* 10.28, Ar-*H*), 6.78 (1 H, d, *J* 2.13, Ar-*H*), 7.50 (1 H, d, *J* 2.57, -O-C*H*=CH-); *m*/*z* (EI) 218 (M^+, 0%), 178 (100), 163 (69), 148 (12), 135 (19), 120 (6), 92 (2).

3a,8a-Dihydro-7-methoxyfuro[2,3-*b*]benzofuran 5a. Colourless oil 61%, bp 80–83 °C/2.20 Torr (Found: C, 69.53; H, 5.39. $C_{11}H_{10}O_3$ requires C, 69.46; H, 5.30%); ν_{max}(film)/cm^{-1} 1616, 1489, 1459; δ_H(90 MHz, $CDCl_3$) 3.92 (3 H, s, Ar-O-CH_3), 4.7 (1 H, br d, *J* 7.71, Ar-C*H*-CH-), 5.31 (1 H, unresolved t, -O-C*H*-O-), 6.67 (1 H, unresolved, t, -O-CH=C*H*-), 6.77–7.00 (4 H, m, 3 × Ar-*H*, -O-C*H*=CH-); *m*/*z* (EI) 190 (M^+, 100%), 161 (96), 147 (31), 131 (7), 91 (7), 77 (5).

3a,8a-Dihydro-6-methoxyfuro[2,3-*b*]benzofuran 5b. Colourless oil 59%, bp 77–80 °C/2.20 Torr (Found: C, 69.41; H, 5.37. $C_{11}H_{10}O_3$ requires C, 69.46; H, 5.30%); ν_{max}(film)/cm^{-1} 1618, 1496, 1455; δ_H(90 MHz, $CDCl_3$) 3.77 (3 H, s, Ar-O-CH_3), 4.60 (1 H, br d, *J* 7.71, Ar-C*H*-CH-), 5.21 (1 H, unresolved t, -O-C*H*-O-), 6.38–6.64 (3 H, m, -OC*H*=C*H*-, Ar-*H*), 6.75 (1 H, d, *J* 7.71, Ar-*H*), 7.14 (1 H, d, *J* 7.71, Ar-*H*); *m*/*z* (EI) 190 (M^+, 92%), 175 (28), 161 (100), 146 (16), 118 (22), 102 (7), 91 (9), 77 (97).

3a,8a-Dihydro-6,7-dimethoxyfuro[2,3-*b*]benzofuran 5c. White solid 54%, mp 90–92 °C (Found: C, 65.61; H, 5.34. $C_{12}H_{12}O_4$ requires C, 65.44; H, 5.49%); ν_{max}(Nujol mull)/cm^{-1} 1618, 1495; δ_H(90 MHz, $CDCl_3$) 3.90 (3 H, s, Ar-O-CH_3), 4.11 (3 H, s, Ar-O-CH_3), 4.61 (1 H, br d, *J* 9.00, Ar-C*H*-CH-), 5.30 (1 H, unresolved t, -O-C*H*O-), 6.50–6.64 (2 H, m, -O-C*H*=C*H*-), 6.88 (1 H, t, *J* 9.0, 2 × Ar-*H*); *m*/*z* (EI) 220 (M^+, 100%), 205 (38), 191 (51), 177 (27), 162 (7), 147 (9), 134 (8), 121 (3), 106 (10), 77 (12).

3a,8a-Dihydro-4-nitrofuro[2,3-*b*]benzofuran 5d. Yellow solid 60%, mp 122–124 °C (Found: C, 58.67; H, 3.37. $C_{10}H_7O_4N$ requires C, 58.54; H, 3.45%); ν_{max}(Nujol mull)/cm^{-1} 1618, 1460; δ_H(90 MHz, $CDCl_3$) 4.67 (1 H, br d, *J* 7.71, Ar-C*H*-CH-), 5.34 (1 H, t, *J* 2.57, -O-C*H*-O-), 6.59 (1 H, t, *J* 2.57, -O-CH=C*H*-), 6.80–7.17 (2 H, m, 2 × Ar-H), 8.12–8.36 (2 H, m, Ar-*H*, -O-C*H*=CH-); *m*/*z* (EI) 205 (M^+, 100%), 188 (13), 176 (18), 159 (13), 130 (32), 102 (17), 77 (12), 63 (4).

3a,8a-Dihydro-4,6-dimethoxyfuro[2,3-*b*]benzofuran 5e. White solid 61%, mp 96–98 °C (Found: C, 65.56; H, 5.33. $C_{12}H_{12}O_4$ requires C, 65.44; H, 5.49%); ν_{max}(Nujol mull)/cm^{-1} 1613, 1453; δ_H(90 MHz, $CDCl_3$) 3.75 (3 H, s, Ar-O-CH_3), 3.82 (3 H, s, Ar-O-CH_3), 4.59 (1 H, br d, *J* 6.42, Ar-C*H*-CH-), 5.37 (1 H, unresolved t, -O-C*H*-O-), 6.00–6.27 (2 H, m, Ar-*H*, -O-CH=C*H*-), 6.50 (1 H, m, -O-C*H*=CH-), 6.76 (1 H, d, *J* 7.7, Ar-*H*); *m*/*z* (EI) 220 (M^+, 100%), 191 (88), 177 (18), 147 (9), 89 (6), 77 (4).

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