Tetrahedron Letters,Vol.29,No.37,pp 4685-4686,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ARYL RADICAL-INDUCED CYCLIZATION ROUTES TO FURO[2,3-b]BENZOFURANS. ABBREVIATED FORMAL SYNTHESES OF AFLATOXINS B_1 AND B_2

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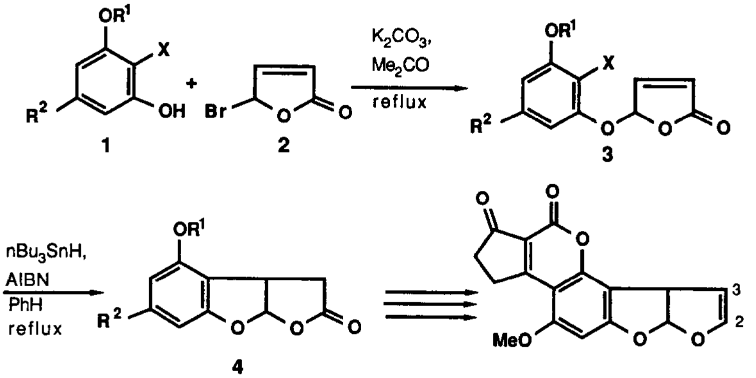
Summary: Radical-induced cyclization of butenolide ethers **3a-c** affords furobenzofurans **4a-c**; deprotection of **4c** gives **4d**, thus concluding formal total syntheses of aflatoxins B_1 (**5**) and B_2 (**6**).

Although conceptualization of free radical-mediated cyclizations has resulted in innovative syntheses of complex alicyclic systems,[1] the methodology and application of aryl radical-mediated annelations remain underdeveloped.[2] As an exploitation of our general method of radical-induced heteroring annelation,[2f] we report on the construction of the furobenzofuran ring system via radical ring closure, **3** → **4** and demonstrate its utility for the rapid assemblage of an intermediate **4d** used by Büchi in the first, highly instructive total synthesis of aflatoxin B_1 (**5**).[3] Our work illustrates the potential of radical chemistry for the synthesis of aflatoxin metabolites specifically[4] and aromatic natural products in general and emphasizes the advantage of the directed metalation tactic[5] for the regiospecific construction of requisite contiguously substituted aromatic precursors **1**.



5 Aflatoxin B_1
6 Aflatoxin B_2 (2,3-dihydro)

a : R^1 = Me, R^2 = H; **b**: R^1 = MOM, R^2 = H; **c**: R^1 = MOM, R^2 = OMe;
d : R^1 = H, R^2 = OMe

Condensation of the iodomethoxy phenol **1a** (X = I)[6a] with the bromo butenolide **2** (1.5 - 2 equiv)[7] afforded the ether **3a** (X = I) which when subjected to the nBu$_3$SnH radical-induced ring closure conditions[2f] furnished the tricyclic lactone **4a**.[8] Similarly, the analogous methoxymethoxy system **1b** (X = I)[6b] was converted into the ether **3b** (X = I) which cleanly led to the benzodifuran **4b**.[8] The aflatoxin B$_1$ (**5**) synthesis was initiated by coupling the substituted bromophenol **1c** (X = Br)[6c,9] with **2** to give **3c** (X = Br) which, upon nBu$_3$SnH-induced cyclization, provided compound **4c**.[8] Deprotection [9-BBN-Br (3 equiv)/CH$_2$Cl$_2$/-78°C (1 h) → 0°C (0.5 h)][10] furnished the phenol **4d**.[11] Since **4d** has been transformed into aflatoxin B$_1$ (**5**) and B$_2$,[3] our work constitutes a total synthesis of these toxic metabolites.

This work provides a new entry into the furo[2,3-b]benzofurans which is comparably efficient but considerably shorter than previously reported routes.[3,12] It is undoubtedly only an early indication of the utility of the radical-induced cyclization in aromatic natural product synthesis.[13,14]

References and Footnotes

[+] NATO Postdoctoral Fellow, 1987-88; [++] NSERC Undergraduate Summer Scholar, 1988.

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6. Prepared from a) 3-methoxymethoxyanisole: t-BuLi/TMEDA/Et$_2$0/-78°C; I$_2$; TFA/CH$_2$Cl$_2$/RT (63%); b) 1,3-dimethoxymethoxybenzene: t-BuLi/TMEDA/Et$_2$0/-78°C; I$_2$; TFA/CH$_2$Cl$_2$/RT (40%); c) 2-bromo-5-methoxyresorcinol (prepared according to the method used for the synthesis of 2-bromoresorcinol: Davis, T.L.; Harrington, V.F. J. Am. Chem. Soc., 1934, 56, 129): NaH/ClCH$_2$OMe/DMF (23%).
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8. **4a**: 42%, mp 124-126°C (EtOH), IR(CHCl$_3$) ν(max) 1791 cm^{-1}, NMR (CDCl$_3$) δ 2.98 (m, 2H), 4.21 (q, 1H, J = 6.4, 11.3 Hz), 6.50-6.59 (m, 3H); **4b**: 79%, mp 105-107°C (EtOH), IR(CHCl$_3$) ν(max) 1788 cm^{-1}, NMR (CDCl$_3$) δ 2.91-3.07 (m, 2H), 4.10-4.39 (m, 1H), 6.51 (d, 1H, J = 6.1 Hz); **4c**: 74%, mp 103-105°C (EtOH), IR(CHCl$_3$) ν(max) 1792 cm^{-1}, NMR (CDCl$_3$) δ 2.91-2.99 (m, 2H), 4.14-4.22 (m, 1H), 6.50 (d, 1H, J = 6.2 Hz).
9. Attempts to prepare **1c** (X = I) from 3,5-dimethoxymethoxyanisole by metalation resulted in the formation of a 2:1 inseparable mixture of 2- and 4-iodo isomers necessitating the use of the classical method.[6c]
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13. Yields are of chromatographically pure materials and are not optimized. All new compounds show analytical and spectral (IR, NMR, MS) data consistent with the structures shown.
14. We gratefully acknowledge NSERC and Merck Frosst Canada for financial support and S. Rafferty (NSERC Undergraduate Summer Scholar, 1986) for technical assistance.

(Received in USA 31 May 1988)