A New Preparative Route to Substituted Dibenzofurans by Benzannulation Reaction. An Application to the Synthesis of Cannabifuran

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Received 10 July 2003

Abstract: A new regioselective pathway to substituted dibenzofuran derivatives is described here. According to this procedure substituted 1-acetoxy-3-alkoxycarbonyl dibenzofurans are obtained by treatment of 6-(2-methoxyaryl)-3-alkoxycarbonylhex-3-en-5-ynoic acids with acetic anhydride in the presence of sodium acetate. The latter acids are prepared from the easily available substituted *o*-iodo-anisoles by Sonogashira coupling with propargylic alcohol and Wittig reaction as the key steps. The described benzannulation reaction proceeds in regioselective fashion and a range of substituents are tolerated. Its synthetic utility is demonstrated by a new synthesis of cannabifuran, a naturally occurring dibenzofuran.

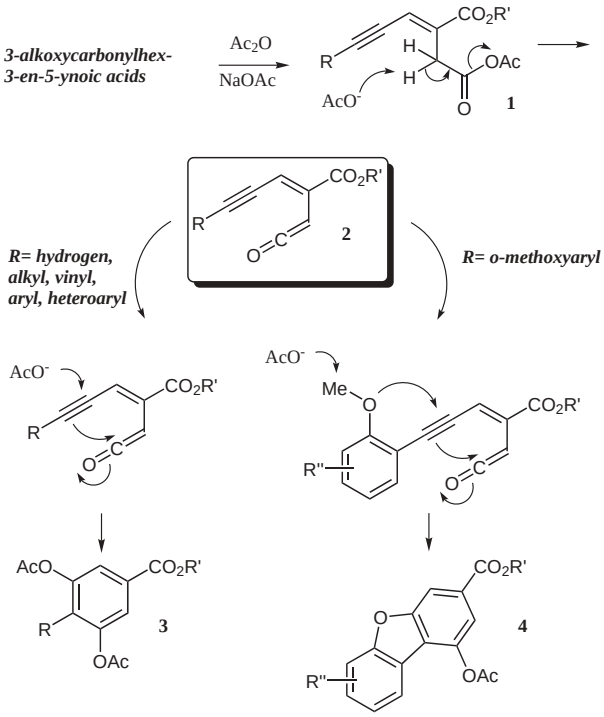
Key words: annulations, enynes, benzofurans, phenols, natural products

Fused aromatic heterocycles are attractive targets of organic synthesis because of their biological activities and their wide occurrence in nature.

In this context, the dibenzofuran system was found in several natural products[1] arising from plant and lichens reported to have phytoalexin,[1a–c] antifungal and antibiotic[1d–f] properties. These results have prompted the development of versatile and regioselective synthetic routes to benzofurans and dibenzofurans[2] with functional groups at specific positions.

Numerous methods for the preparation of dibenzofurans have been reported. The ring closure of substituted diaryl ethers,[3] the acid catalyzed intramolecular cyclization of hydroxylated biphenyls[4] and the direct functionalization of dibenzofuran framework[5] are the most employed strategies. However, the main restriction of these approaches lies in the harsh reaction conditions, the low yields, and the use of expensive catalysts. Therefore, an increasing number of milder approaches based on annulation[6] reactions have received growing attention.

We have successfully developed the benzannulation reaction of 3-alkoxycarbonyl-3,5-hexadienoic acids[7] and of 3-alkoxycarbonylhex-3-en-5-ynoic acids[8] to give the 4-substituted 3-hydroxy-benzoic acid derivatives and the 4-substituted 3,5-dihydroxybenzoic acid derivatives, respectively. We envisage that the latter process (Scheme 1) is suitable also for the preparation of dibenzofurans. Indeed, we found that the treatment of 3-alkoxycarbonylhex-3-en-5-ynoic acids with acetic anhydride and sodium acetate affords the phenolic derivatives **3**.

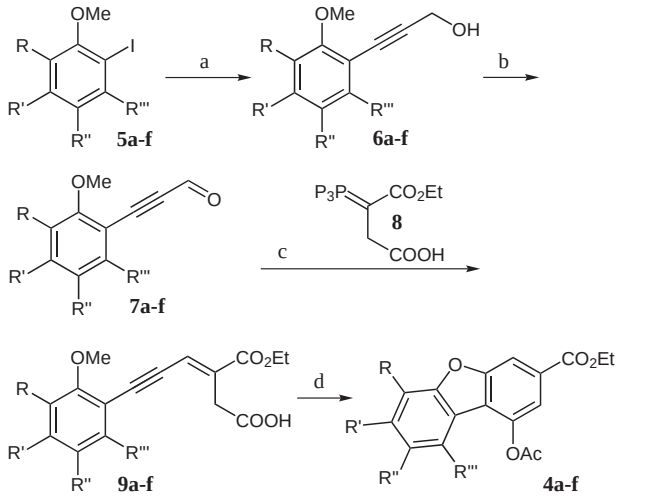


Scheme 1 Proposed pathways to 4-substituted 3,5-diacetoxybenzoates and 1-acetoxy-3-alkoxycarbonyl dibenzofurans.

This process probably involves the ynenylketene **2**, formed from mixed anhydride **1**, which may be cyclized through electrophilic attack and nucleophilic addition to the triple bond. If the substituent in position 6 of the ynoic acid shows the *o*-methoxyaryl framework, the phenolic oxygen acts as nucleophile and gives addition to the triple bond with concomitant evolution of methyl acetate. The products of the latter process are the 1-acetoxy-3-alkoxycarbonyl dibenzofurans **4a**–**f** where both the furan ring and the phenolic ring are building up by benzannulation reaction.

Herein is documented the efficiency of this synthetic route starting from a variety of 6-substituted-3-alkoxycarbonylhex-3-en-5-ynoic acids **9a**–**f**. These latter compounds were obtained in three steps from the easily available substituted *o*-iodoanisoles[9] **5a**–**f** (Scheme 2).

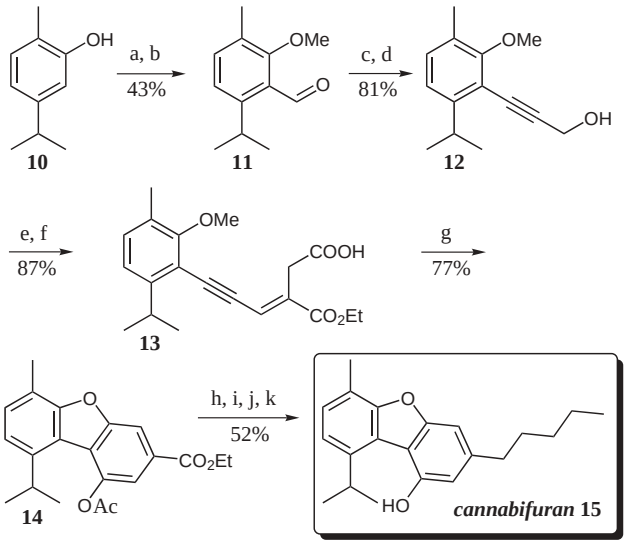
SYNLETT 2003, No. 13, pp 2005–2008
Advanced online publication: 08.10.2003
DOI: 10.1055/s-2003-42037; Art ID: G16603ST



Scheme 2 *Reagents and conditions:* a) Propargyl alcohol (2 equiv), Et_3N (3 equiv), CuI (0.01 equiv), $(Ph_3P)_2PdCl_2$ (0.01 equiv); b) MnO_2, CH_2Cl_2, 8 h at r.t.; c) **7a**–**f**, **8**, toluene/$CHCl_3$, r.t., 4 h; d) Ac_2O (10 equiv.) and NaOAc (2 equiv), hydroquinone (0.05 equiv), then heating 1 h at reflux.

Sonogashira coupling[10] of **5a**–**f** with propargylic alcohol afforded alcohols **6a**–**f**, which were smoothly oxidized with MnO_2 to the corresponding aldehydes **7a**–**f** in quantitative yields. The following Wittig reaction with triphenyl-(α-ethoxycarbonyl-β-carboxyethyl)phosphonium ylide **8**[11] gave regioselectively[12] the suitable 6-(*o*-methoxyaryl)-3-alkoxycarbonylhex-3-en-5-ynoic acids **9a**–**f** in yields ranging from 80% to 89% (Table 1). The conversion of **9a**–**f** into benzannulated dibenzofurans was established by treatment[13] of the latter acids with an excess of acetic anhydride (10 equiv) in presence of sodium acetate (2 equiv) and hydroquinone (0.05 equiv) heating at reflux for one hour. The 1-acetoxy-3-alkoxycarbonyl dibenzofurans **4a**–**f** were obtained regioselectively in very good yields (87–97%). The examination of the substitution pattern of the aromatic ring of the acids **9a**–**f** shows the flexibility of this synthetic method: alkoxy, alkyl, nitro, carboxyalkyl, halo and aryl groups were unaffected under the reaction conditions.

In view of these results we decided to test our method in the synthesis of natural dibenzofurans and we selected as our target the minor cannabis constituent cannabifuran[1h] **15** (Scheme 3). The latter compound was previously prepared by a variety of methods including acid catalyzed intramolecular cyclization of biphenyls,[4c,d] transformation of the natural cannabidiol in the dibenzofuran[14] framework and cycloaddition or benzannulation of benzofuran derivatives.[6c,f,g] In this work we propose a different synthetic approach in which both the furan ring and one aromatic ring are formed in a single annulation step. Retrosynthetic analysis suggests that the acid **13** should yield 1-acetoxy-3-ethoxycarbonyl-6-methyl-9-isopropyl dibenzofuran **14** that shows the right functionalization for conversion to cannabifuran.



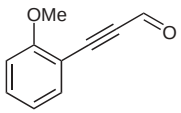
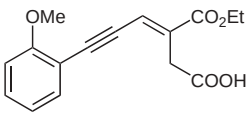
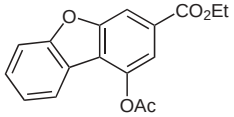
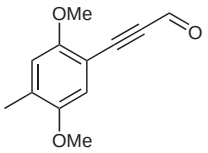
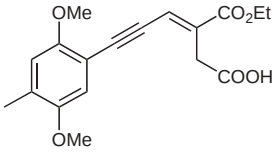
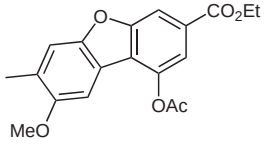
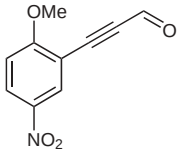
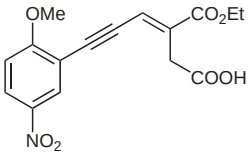
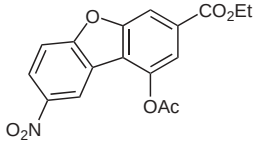
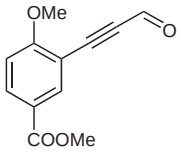
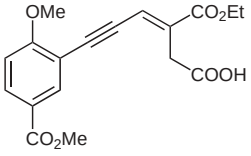
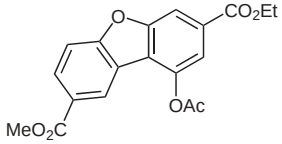
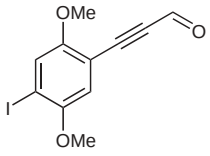
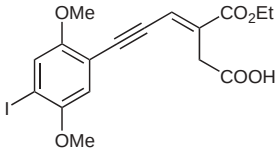
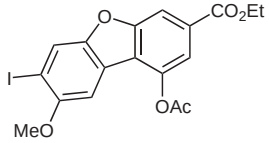
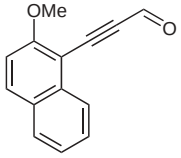
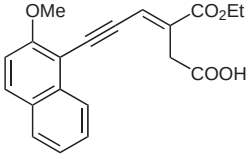
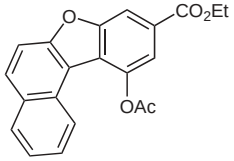
Scheme 3 *Reagents and conditions:* a) Hexamethylenetetramine, glycerol, H_3BO_3, paraformaldehyde; b) K_2CO_3, Me_2SO_4, acetone, reflux, 6 h; c) Ph_3P, CBr_4, Zn, CH_2Cl_2; d) BuLi (2 equiv), then formaldehyde; e) MnO_2, $CHCl_3$, reflux, 5 h; f) **8**, toluene, r.t., 3 h; g) Ac_2O (10 equiv), NaOAc (2 equiv), hydroquinone (0.05 equiv), then heating 1 h at reflux; h) $LiAlH_4$, THF; i) DDQ, dioxane, r.t., 24 h; j) BuLi, THF; k) Pd/C, EtOH, H_2, 3 atm, HCl cat., 2 d.

Therefore, we designed the synthesis of **13** starting from the commercially available carvacrol **10**. The latter phenol was submitted to regioselective Duff formylation[15] and the resulting substituted salicylaldehyde was protected by transformation in its ether **11** by methylation with dimethyl sulphate. The following formyl–ethynyl conversion[16] was performed by chain extension of the aldehyde by one carbon to form the corresponding dibromoolefin. This was treated with two equivalents of BuLi to give the related lithium acetylide. The reaction of the latter salt with formaldehyde gave propyn-ol **12**,[17] which was submitted to the MnO_2 oxidation–Wittig homologation procedure described above to afford the desired acid **13**.

As expected, treatment of **13** with acetic anhydride in the presence of sodium acetate and hydroquinone gave dibenzofuran **14** as a single regioisomer. It is noteworthy that though the yield of the latter conversion was good (77%) it was not quite complete as reported for compound **4a**–**f**. We assume that the intermediate ynenylketene should be close to the bulky isopropyl group to achieve the adequate conformation for the annulation process. According to our explanation the above mentioned reaction was not effected by the activating or deactivating effect of the substituents on the aromatic ring (compounds **4a**–**f**) and was faintly depressed by the steric hindrance of the groups placed in position *ortho* to the ethynyl group (compound **14**).

Finally, we converted the dibenzofuran **14** in the cannabifuran **15** by modification of some reported procedures.[6g]

Table 1 Synthesis of Acids **9** and Dibenzofurans **4** from Aldehydes **7** (Scheme 2)

Entry	Aldehydes **7**	Acids **9**	Wittig (yields, %)[a]	Dibenzofuran **4**	Benzannulation (yields, %)[a]
a			**89**		**92**
b			**87**		**97**
c			**89**		**93**
d			**85**		**95**
e			**80**		**89**
f			**88**		**87**

[a] After chromatography and/or crystallization.

Reduction of **14** with $LiAlH_4$ followed by the DDQ oxidation[18] of the resulting benzyl alcohol gave directly the corresponding 1-hydroxy-3-formyl dibenzofuran without protection–deprotection manipulation of phenolic hydroxyl group. The following treatment with BuLi and hydrogenolysis of the resulting carbinol gave the title compound in good yield (52% over four steps).

In conclusion, we have described a new preparative method to 1-acetoxy-3-alkoxycarbonyl dibenzofurans starting from substituted *o*-iodoanisoles. Our approach is efficient, experimentally simple and the starting materials are easily available. This route shows some advantages over the classical processes as demonstrated in the synthesis of the natural dibenzofuran cannabifuran.

Acknowledgment

We thank MURST for partial financial support.

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(9) 2-Iodoanisole **5a** is commercially available. The substituted 2-iodoanisoles **5b**, **5c** and **5e** were prepared from 1,4-dimethoxy-3-methylbenzene, *p*-nitroanisole and hydroquinone dimethyl ether, respectively by halogenation according to the following references: (a) Lucht, B. L.; Mao, S. S. H.; Tilley, T. D. *J. Am. Chem. Soc.* **1998**, *120*, 4354. (b) Robinson, G. M. *J. Chem. Soc.* **1916**, *109*, 1078. (c) Wariishi, K.; Morishima, S.-I.; Inagaki, Y. *Org. Proc. Res. Dev.* **2003**, *7*, 98; respectively. (d) The substituted 2-iodoanisoles **5d** and **5f** were prepared from *p*-hydroxybenzoic acid and β-naphthol respectively, by halogenation followed by methylation with Me_2SO_4/K_2CO_3 in dry acetone. The above mentioned halogenation reaction was performed according to: Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287.

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(13) Acids **9a**–**f** (50 mmol) were dissolved in acetic anhydride (48 mL, 0.5 mol). To this solution, anhyd sodium acetate (8.2 g, 0.1 mol) and hydroquinone (275 mg, 2.5 mmol) were added in one portion. The obtained heterogeneous mixture was heated at reflux for 1 h under a nitrogen atmosphere. After cooling to r.t., the acetic anhydride was removed in vacuo and the residue was treated with ethyl acetate (250 mL) and water (100 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography and crystallization to give phenol derivatives **4a**–**f**.

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(17) All new compounds were fully characterized. Selected analytical data:
12: Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.15; H, 8.35. Bp 150 °C/0.5 mmHg. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (6 H, d, *J* = 6.9 Hz), 2.23 (3 H, s), 2.50–2.85 (1 H, bs), 3.38 (1 H, m), 3.86 (3 H, s), 4.58 (2 H, s), 6.93 (1 H, d, *J* = 8.0 Hz), 7.10 (1 H, d, *J* = 8.0 Hz). EI-MS: *m/z* = 219 (M^+ + 1), 218 (M^+), 203, 187, 172, 159, 141, 128, 115, 105, 91, 77. FT-IR (film): ν = 813, 1029, 1077, 1237, 1273, 1405, 1459, 1481, 1571, 2225, 2929, 3407 cm^{-1}.
13: Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.60; H, 7.10. Mp 59–60 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (6 H, d, *J* = 6.9 Hz), 1.31 (3 H, t, *J* = 7.1 Hz), 2.24 (3 H, s), 3.34 (1 H, m), 3.77 (2 H, s), 3.83 (3 H, s), 4.26 (2 H, q, *J* = 7.1 Hz), 6.95 (1 H, d, *J* = 8.0 Hz), 7.15 (1 H, d, *J* = 8.0 Hz), 7.15 (1 H, s). EI-MS: *m/z* = 345 (M^+ + 1), 344 (M^+), 316, 300, 285, 270, 255, 239, 225, 209, 195, 173, 165, 152, 128, 115, 97. FT-IR (nujol): ν = 762, 1031, 1093, 1212, 1265, 1376, 1459, 1619, 1699, 1719, 2193 cm^{-1}.
14: Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.10; H, 6.25. Mp 113–114 °C (isopropyl ether). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (6 H, d, *J* = 6.9 Hz), 1.42 (3 H, t, *J* = 7.2 Hz), 2.45 (3 H, s), 2.54 (3 H, s), 3.99 (1 H, m), 4.42 (2 H, q, *J* = 7.2 Hz), 7.19 (1 H, d, *J* = 7.7 Hz), 7.30 (1 H, d, *J* = 7.7 Hz), 7.75 (1 H, d, *J* = 1.2 Hz), 8.16 (1 H, d, *J* = 1.2 Hz). EI-MS: *m/z* = 355 (M^+ + 1), 354 (M^+), 312, 297, 283, 267, 255, 239, 224, 205, 195, 178, 165, 152, 139, 128, 115, 102, 89. FT-IR(nujol): ν = 770, 1065, 1195, 1229, 1310, 1368, 1411, 1463, 1510, 1571, 1712, 1771 cm^{-1}.
Cannabifuran 15: Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.00; H, 8.45. Mp 79–80 °C (hexane). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (3 H, t, *J* = 6.6 Hz), 1.34 (6 H, d, *J* = 6.8 Hz), 1.20–1.46 (4 H, m), 1.55–1.81 (2 H, m), 2.53 (3 H, s), 2.66 (2 H, t, *J* = 7.5 Hz), 4.41 (1 H, m), 5.55 (1 H, bs), 6.46 (1 H, s), 7.01 (1 H, s), 7.17 (2 H, m). EI-MS: *m/z* = 311 (M^+ + 1), 310 (M^+), 295, 281, 267, 254, 238, 225, 211, 191, 178, 165, 152, 139, 119, 105, 89. FT-IR (nujol): ν = 760, 815, 1048, 1061, 1219, 1252, 1426, 1514, 1588, 1618, 1635, 3500 cm^{-1}.

(18) Becker, H.-D.; Björk, A.; Adler, E. *J. Org. Chem.* **1980**, *45*, 1596.