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A New Approach to 2-Aryl-7-Alkoxy-Benzofurans: Synthesis of Ailanthoidol, a Natural Neolignan

Claudio Fuganti, Stefano Serra*

Dipartimento di Chimica del Politecnico,
Centro CNR per la Chimica delle Sostanze Organiche Naturali,
Via Mancinelli 7, 20131 Milano, Italy

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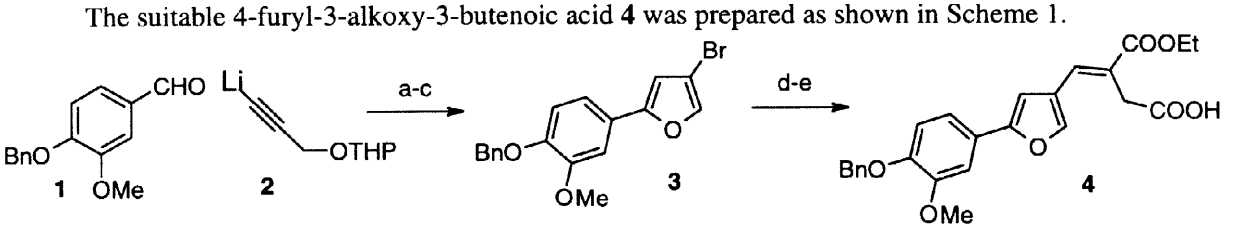
Abstract: A general method of synthesis of 2-aryl-7-alkoxy-benzofurans is described using a benzoannulation reaction as key step. The usefulness of this approach is shown in the new synthesis of ailanthoidol, a benzofuranoid neolignan isolated from the tree *Zanthoxylum ailanthoides*.

Keywords: Annulation, Benzofurans, Lignans, Natural Products

Lignans and neolignans[1] are important targets for organic synthesis due to the wide variety of biologically active products which are members of these classes. In spite of the abundance of chemical structures found, most of the syntheses[2] that have been carried out depend in fact upon a limited number of key reactions which have been used to build up the basic carbon skeleton. The syntheses of benzofuran neolignans[2, 3] have tended to follow biomimetic routes which always construct the substituted furan ring starting from two aromatic units. Recently we have developed a method of benzoannulation which allows the building up of biaryls[4] or ring fused heterocycles[5] starting from aromatic or heteroaromatic aldehydes and involving a mild base promoted cyclization reaction of 3-alkoxy-6-aryl-3,5-hexadienoic acids or 4-heteroaryl-3-alkoxy-3-butenoic acids respectively. In order to investigate the validity of our method for the synthesis of natural products we decided to prepare 2-aryl-7-alkoxy benzofurans, which are common frameworks in neolignans, starting from 3-formyl-5-aryl furans and build the fused aromatic rings using this kind of reaction. Herein we report this alternative pathway for the synthesis of ailanthoidol **6** which is a benzofuranoid neolignan recently isolated[6] from the tree *Zanthoxylum Ailanthoides* and showing the title structure.

The suitable 4-furyl-3-alkoxy-3-butenoic acid **4** was prepared as shown in Scheme 1.



Scheme 1

a) **2** + **1** then MnO_2, $CHCl_3$, r.t; b) PPTS, EtOH; c) HBr 10%, toluene; d) BuLi, THF, -78°C, 30 min. then dry DMF; e) triphenyl-(α-carbethoxy-β-carboxyethyl)phosphonium betaine, benzene, r.t. 6 h.

The aldehyde **1**[7] was condensed with the lithium salt of protected propyn-ol **2** to give the related carbinol in almost quantitative yield. The latter was converted into the 3-bromofuran **3** using a reported procedure [8] consisting in the oxidation of propargylic carbinol, selective deprotection of tetrahydropyranyl

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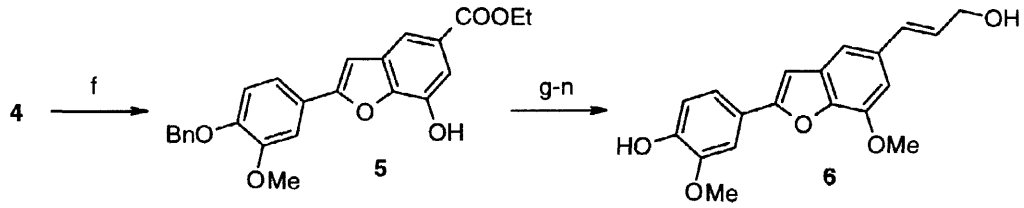
ether and acid-catalyzed cyclization to give **3**[9] in 45% overall yield. Regioselective lithiation at the 3-position of the furan ring was obtained through treatment of **3** with 1 eq. of BuLi at –78°C in THF and the quenching with an excess of dry DMF gives the related 3-formyl-furan in about 70% yield. Then, by conversion of the latter aldehyde, 4-furyl-3-alkoxycarbonyl-3-butenoic acid **4** was obtained by Wittig reaction using triphenyl-(α-carbethoxy-β-carboxyethyl)phosphonium betaine in benzene solution.[10]

Treatment of **4** in THF solution with $ClCO_2Et$ (1 eq.) followed by dropwise addition of Et_3N gave the mixed anhydride which smoothly cyclized in a excess of base (2 eq.) allowing the quantitative conversion into the benzofuran **5** (Scheme 2) in a few minutes and at room temperature.[11]



Scheme2

f) $ClCO_2Et$ 1 eq., Et_3N 2 eq.; g) CH_2N_2/CH_2Cl_2; h) $LiAlH_4$ /THF; i) $DMSO/(CF_3CO)_2$, Et_3N, -70°C; l) $Ph_3PCHCO_2Et/CHCl_3$, 50°C, 1h; m) MeOH/cyclohexene, Pd/C 10% reflux 30 min.; n) $LiAlH_4$/THF.

Conversion of **5** to the title compound **6** was carried out through unexceptional functional group interconversion. The phenolic group was methylated and the ethyl ester transformed in the aldehyde by reduction and Swern oxidation. Wittig reaction provides the whole framework of the target molecule. Selective removal of the benzylic group[12] followed by reduction of the ester gives ailanthoidol **6** in 40% overall yield, spectroscopically identical to the natural product.[6]

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[9] This compound was identified by the following analysis: ^1H NMR (250 MHz, $CDCl_3$) δ 3.95 (3H, s), 5.18 (2H, s), 6.57 (1H,s), 6.90 (1H, d, J=8.5Hz), 7.05-7.20 (2H, m), 7.25-7.50 (6H, m); EI-MS *m/z* 360 (M^+, 10), 269 (M^+-Bz, 14), 131 (10), 102 (15), 91 (100); FT-IR (nujol): ν (cm^{-1}) 795, 921, 1273, 1502, 1605.

[10] For the preparation and use of this betaine see: Hudson, R. F.; Chopard, P. A.; *Helv. Chim. Acta*, **1963**, *46*, 2178. The compound **4** was obtained in 75% yield upon chromatographic column and identified by the following analysis: ^1H NMR (250 MHz, CD_3SOCD_3) δ 1.25 (3H, t, J=7Hz), 3.58 (2H, s), 3.84 (3H, s), 4.18 (2H, q, J=7Hz), 5.11 (2H, s), 7.05-7.50 (9H, m), 7.55 (1H, s), 8.13 (1H, s); EI-MS *m/z* 436 (M^+, 76), 392 (M^+-H_2O, 21), 345 (M^+-Bz, 100), 301 (23), 197 (15), 91 (22); FT-IR (nujol): ν (cm^{-1}) 792, 1501, 1650, 1703

[11]Work up with HCl 5%, extraction with AcOEt and purification of the obtained crude product on silica gel column give **5** in 95% yield; ^1H NMR (250 MHz, CD_3SOCD_3) δ 1.35 (3H, t, J=7Hz), 3.89 (3H, s), 4.32 (2H, q, J=7Hz), 5.15 (2H, s), 7.20 (1H, d, J=9Hz), 7.30-7.55 (9H, m), 7.72 (1H, s), 10.50 (1H, bs); EI-MS *m/z* 418 (M^+, 37), 373 (M^+-OEt, 5), 327 (M^+-Bz, 100), 91 (63); FT-IR (nujol): ν (cm^{-1}) 799, 1511, 1681, 3307

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