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SIMPLE AND EFFICIENT SYNTHESIS OF BENZOFURAN DERIVATIVES FROM TYROSOL

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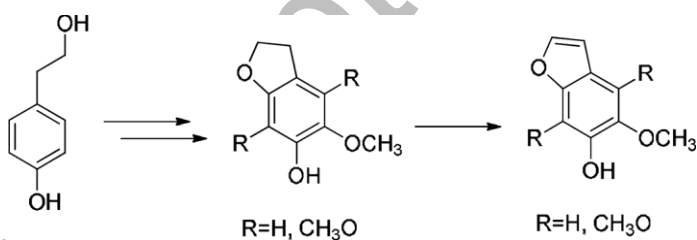
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Abstract

A convenient strategy for the preparation of compounds bearing the benzofuran skeleton starting from tyrosol, a phenol largely present in olive oil production waste, with no biological importance, is reported. A bromination/methoxylation sequence, already described for the synthetic transformation of natural occurring compounds, was exploited. Depending on the solvent used for the methoxylation reaction together with the presence of a 4-phenol moiety respect to the side chain, benzodihydrofurans or a benzofurans derivative can be obtained.



KEYWORDS: Benzofurans; polyphenols; antioxidants; heterocyclization

INTRODUCTION

In the last years we have largely investigated a method to oxyfunctionalize the aromatic ring of natural occurring compounds in order to enhance their biological activities.^[1] The method involves a methoxylation of an aromatic bromide, a reaction optimized by us and already reported.^[2] The bromination of activated aromatic rings can be performed by a number of methods,^[3] but we found the system NaBr/Oxone to be the most efficient and clean. In this way the bromination can be modulated to easily obtain the desired products. The most interesting example is the bromination of tyrosol (4-hydroxyphenethyl alcohol) which can be selectively transformed to the monobromo or dibromo derivatives, allowing to access to aromatic compounds with different degree of oxygenation.

The main example of the potentiality of this synthetic pathway for the preparation of compounds bearing the benzofuran skeleton is the easily and convenient transformation of tyrosol into hydroxytyrosol.^[4]

Other methods are reported in literature for etherification of aryl bromides, by catalysis of palladium using complex and costly ligands,^[5] or copper under conditions which extend our method,^[6] but our goal is to exploit this strategy to produce compounds with high value starting from waste of industry. Tyrosol is a polluting chemical, largely present in the waste of the olear industry, with no biological importance, meanwhile hydroxytyrosol is one of the strongest antioxidants in nature, with many potential uses in medicine, as integrator, in protective and anti-age creams, and more.^[7] By this methodology we were able to conveniently produce rare natural compounds.^[8] The advantage is to make those compounds available for biological investigations at low cost.

RESULTS AND DISCUSSION

In this work we describe a facile and straightforward synthesis of benzofuran derivatives starting from tyrosol using the bromination/methoxylation approach. The synthetic pathway for obtaining benzofuran and benzodihydrofuran derivatives is summarized in Scheme 1. Such as for the transformation of tyrosol into hydroxytyrosol, the aim of this work is to valorize an industrial waste.

The first step of the synthesis is a monobromination of tyrosol, which was performed as previously reported^[4] paying attention to the reaction conditions to avoid the further halogenation. In an improved procedure with respect to that previously reported by us,^[4] the methoxylation was performed in DMF at 100°C stirring overnight, but we observed that the reaction occurs also in eco-sustainable dimethylcarbonate (DMC) at lower temperature, namely 90°C.^[1]

Our purpose is always to use conditions with lower environmental impact, but in the first methoxylation step the use of DMC as solvent was not possible due to the competing carboxymethylation of the side chain and this was not compatible with further steps.

The second bromination was performed on the homovanillic alcohol protected as diacetate (**4**) to avoid its decomposition in the oxidative media.

Finally, the ring closure was obtained under the same conditions as the methoxylation.

The probable mechanism of the reaction involves an oxidative addition of the copper to

the aromatic ring. The primary alcohol of the side chain can act as competitive ligand for the metal leading to an intramolecular insertion after the reductive elimination. In this case the process is so favorable that it occurs at lower temperature.

The reaction was carried out in DMC and good yield of the benzodihydrofuran derivative was obtained. In more drastic conditions (DMF, 120°C, 8 hrs) the reaction shifted towards the benzofuran derivative **9**. This occurs only when a para free phenol moiety with respect to the side chain is present. Although the mechanism at the basis of the process is still under investigation a way to produce **6** or **9** selectively is now available.

Compounds **7** and **8** were obtained by methylation and demethylation of **6** respectively. **10** was produced from **9** by methylation meanwhile the demethylation reaction led to a complex mixture of products, due to the liability of catechol compound.

By this pathway, a number of variously substituted benzodihydrofurans and benzofurans can be synthesised starting from tyrosol. An example is reported in Scheme 2 for compounds **15** and **16** with a fully oxygenated aromatic ring. In the methoxylation of **14** the two bromines were substituted by the ethanolic chain and the methoxy group respectively. The ring closure was complete before the methoxylation step since the monobrominated dihydrobenzofuran can be isolated.

BIOLOGICAL ASSAYS

The biological activity of **6**, **7**, **8**, **9**, **10**, **15Ac**, **16Ac**, **18** was assessed by measuring their ability to induce cytotoxicity by inhibiting cell metabolism and cell death by apoptosis in a monocytoid cell line U937. Toxicity of the drugs was evaluated by inhibition of cell metabolic activity, measured by reduction of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium) to formazan, using a commercial colorimetric as previously described.^[9] The results were expressed as the drug concentration required to inhibit 50 % of the metabolic activity (CC50). Apoptosis was expressed as percentage of hypodiploid nuclei following staining with Propidium iodide (PI), and evaluation through cytofluorimetric analysis.^{[1][0]} The results in Table 1, show that the compounds used at the concentration of 250 μM , variably induced in vitro cell death by apoptosis in U937 cells. In particular the compound **8**, was the most efficacious in inducing 71% of hypodiploid nuclei, while **9** and **15Ac** induced 10% and 19% hypodiploid nuclei respectively. However **8**, **9** and **15Ac**, were between 25 and 200 times less active than the chemotherapeutic drug etoposide, SN38 used as reference control. On the other side all the tested compounds did not highly inhibit the metabolic activity in U937 cells, showing IC50 between 1000 and 500 μM , except **8** that exhibited IC50 of 253 μM . Taken together these data indicated that these compounds were less toxic in vitro in comparison with SN38 (IC50 14 μM), nevertheless their pro apoptotic activity was lower than the reference compound. Therefore this class of molecules could be lead compounds to be undergoing further modification aimed to increase their specific activity.

CONCLUSIONS

In this work a synthetic pathway to obtain bicyclic oxygenated compounds from tyrosol is reported. In DMC and controlling reaction times benzodihydrofurans can be selectively obtained. Their dehydrogenated derivatives can be produced using DMF as the solvent and prolonging the reaction time.

All polyoxygenated compounds easily prepared by the reported methodology were investigated for their potential biological properties.

EXPERIMENTAL

General Procedures.

Bromination reaction. In a 50 mL round bottom flask equipped with magnetic stirring 1 mmol of substrate and 1 mmol of NaBr (102 mg) were dissolved in 7.5 mL of acetone. A solution of 900 mg of oxone in 7.5 mL of water was slowly added under stirring until completion of reaction (monitoring by TLC). 3 mL of saturated solution of sodium thiosulfate in water were then added. Acetone was evaporated under vacuum and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layer was washed with brine (3 x 15 mL) and dried with anhydrous sodium sulfate and the solvent evaporated under vacuum. Normally the product was utilized for the further reactions without any other purification.

The same procedure was used to obtain the dibrominated analog, increasing the equivalents of NaBr and oxone.

Methoxylation reaction. In a 25 mL round bottom flask an excess of complex solution was prepared dissolving in DMF (or DMC) 168 mg of CuBr and 10 mL of 25% w solution of CH₃ONa in methanol. After few minutes under stirring the mixture became blue. This solution was added in small portions to a solution of substrate (1 mmol) in DMF or DMC (2 mL) heated at the appropriate temperature (90°C for DMC and 100°C for DMF). The reaction was monitored by TLC, at the end the mixture was cooled in an ice bath and acidified with a 2M HCl solution. Methanol was evaporated under reduced pressure and the residue extracted with Et₂OAc (3 x 20 mL), washed with brine (3 x 15 mL), dried with anhydrous Na₂SO₄ and the solvent evaporated under vacuum. The crude was purified by flash chromatography (hexane/Et₂OAc 4:1).

Methylation reaction. 1 mmol of substrate was dissolved in 7 mL of acetone, 3 mmol of K₂CO₃ and 2 mmol of dimethyl sulfate were added for every phenol moiety. The mixture was stirred overnight at r.t. The reaction was quenched with a 10% solution of NH₄OH in water (5 mL) then acetone was removed under vacuum. The residue was dissolved with Et₂OAc and washed with a 2M solution of HCl in water until acidity. The product was obtained in substantially quantitative yield.

Demethylation reaction. BBr₃ (4.5 mL) was added to 1 mmol of substrate dissolved in dichloromethane (7 mL) at -20°C. After the reaction was complete, monitoring it by TLC, the mixture was quenched with water. The crude was extracted with diethyl ether (3 x 10 mL), the organic layers was washed with brine (3 x 5 mL) and dried with anhydrous

Na₂SO₄. After evaporation of the solvent under vacuum the product was obtained pure enough to be used for further reactions.

In example compounds **8** and **10** were synthesized through a sequence of reaction as above.

2,3-Dihydro-benzofuran-5,6-diol (8). Light brown solid, 74%. M.p. 107.2-109°C. IR (CHCl₃, cm⁻¹): 3210, 1615, 1275, 840. ¹H -NMR D₆-DMSO (ppm): 6.92 (1H, s, ArH), 6.72 (1H, s, ArH), 4.86 (3H, s, OCH₃), 3.67 (2H, t, *J*=7.3 Hz, CH₂O), 2.79 (2H, t, *J*=7.3 Hz, CH₂Ar). ¹³C -NMR D₆-DMSO (ppm): 144.6, 144.5, 128.6, 118.7, 117.3, 112.1, 61.4, 38.2. Analysis, calc. for C₈H₈O₃: C 63.15, H 5.30; found C 63.12, H 5.27.

5,6-Dimethoxy-benzofuran (10). White solid, 35%. M.p. 54.5-56.5°C. ¹H -NMR (ppm): 7.50 (1H, d, *J*=1.9 Hz, C=CH-O), 7.04 (1H, s, ArH), 7.00 (1H, s, ArH), 6.64 (1H, d, *J*=1.9 Hz, C=CH), 3.89 (3H, s, OCH₃). ¹³C -NMR (ppm): 149.5, 147.8, 146.4, 143.8, 119.0, 106.4, 102.2, 95.2, 56.2, 56.0. Analysis, calc. for C₁₀H₁₀O₃: C 67.41, H 5.66; found: C 67.42, H 5.64.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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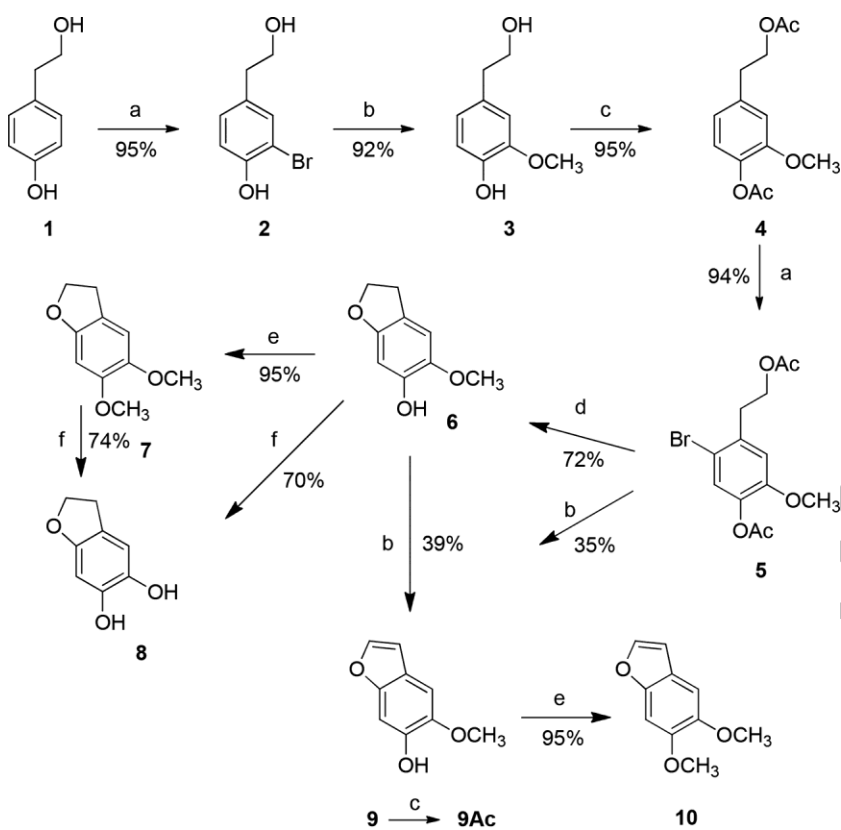
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Table 1. a) Apoptosis was evaluated in U937 cells as a percentage of hypodiploid nuclei by flow cytometry analysis after 24 h of incubation. b) MACC50 is the metabolic activity cytotoxic inhibitory concentration 50%, evaluated in the U937 cell line by MTS assay

Compound	Conc. (μM)	% hypodiploid nuclei(a)	MACC50 (μM)(b)
6	250	5	818
7	250	4	> 1000
8	250	71	253
9	250	10	744
10	250	7	737
15Ac	250	19	557
16Ac	250	4	> 1000
18	250	9	803
SN38	10	80	14

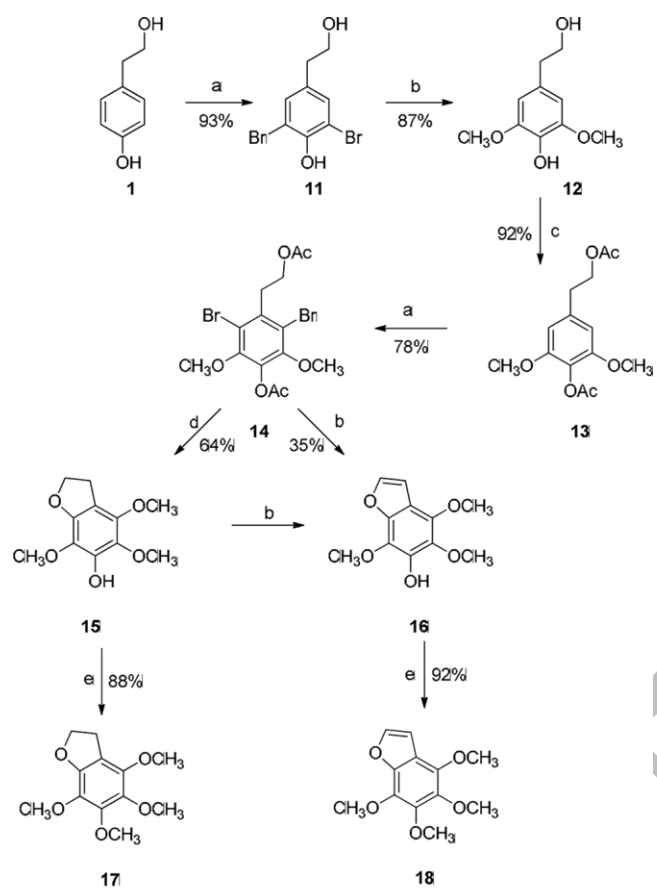
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Scheme 1. Synthesis of dioxygenated benzofuran derivatives



a) NaBr, oxone, H₂O, acetone, r.t.; b) CuBr, CH₃ONa, DMF, 120°C;
 c) Ac₂O, Py; d) CuBr, CH₃ONa, DMC, 90°C; e) Na₂CO₃, acetone, Me₂SO₄
 f) BBr₃, CH₂Cl₂, -20°C

Scheme 2. Synthesis of tetraoxygenated benzofuran derivatives



a) NaBr, oxone, H₂O, acetone, r.t.; b) CuBr, CH₃ONa, DMF, 120°C;
 c) Ac₂O, Py; d) CuBr, CH₃ONa, DMC, 90°C; e) Na₂CO₃, acetone, Me₂SO₄