

New, Simple Total Syntheses of Benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones and Benzo[*b*]naphtho[2,1-*d*]furans

Elena Martínez, Luis Martínez, Juan C. Estévez, Ramón J. Estévez* and Luis Castedo

Departamento de Química Orgánica de la Universidad de Santiago and Unidad Asociada (C.S.I.C.),
15706 Santiago de Compostela, Spain

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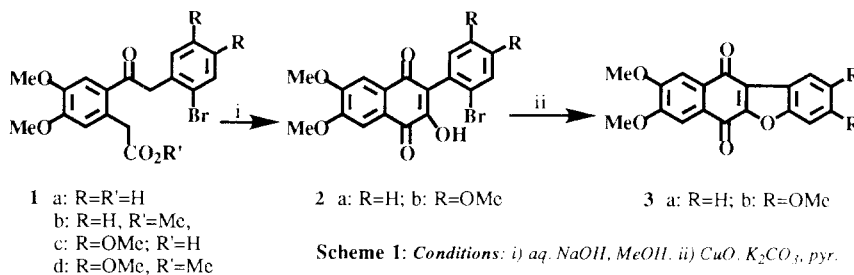
SUMMARY- Here we account the transformation of 2-[(2'-bromophenyl)acetyl]phenylacetic acids and 1-benzylisoquinolines into benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones. Synthesis of benzo[*b*]naphtho[2,1-*d*]furans from 1-benzylisoquinolines is also described.

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Benzo[*b*]furonaphthoquinones (**3**) are compounds that have recently become interesting synthetic targets due to the high activity shown in various biological tests.¹ This activity has been attributed to their possessing a 2-phenylnaphthalene-type structure in which the two ring systems are coplanar, a feature that is also present in other biologically and pharmacologically active compounds including the carcinogenic agent benzo[*a*]pyrene, the antineoplastic ellipticine and the anticoccidial WS5995A among others.² Benzo[*b*]furonaphthoquinones have previously been obtained by complex reaction sequences in only moderate yields.³ As a continuation of our work on naphthoquinone compounds,⁴ we have now developed novel, simple and efficient syntheses of compounds **3**.

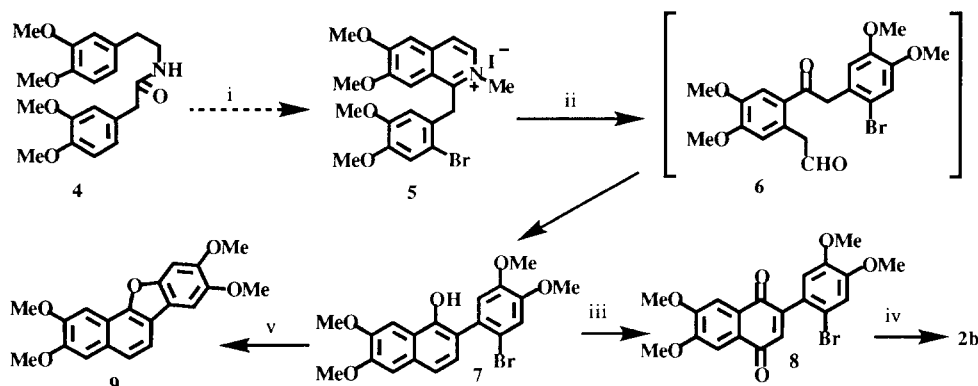
In a first synthesis, we started from ketoesters **1** and generated the furan ring by means of an intramolecular Ullman coupling reaction. Treatment of bromoketoester **1b**⁵ with aq. sodium hydroxide in refluxing methanol for 1 h. afforded bromoquinone **2a** in 95% yield by mixed Claisen condensation followed by oxidation of the cyclized product.

When **2a** was refluxed under argon for 13 hours with CuO and K₂CO₃ in dry pyridine,⁶ benzofuronaphthoquinone **3a**⁷ was obtained in 90% yield as a red solid of mp 282–284 °C (methanol). The generality of this strategy was corroborated by the analogous transformation of bromoketoester **1d**⁸ into tetramethoxylated benzofuronaphthoquinone **3b** via naphthoquinone **2b**.



Because the range of available ketoacids **1** is restricted by limitations of the Friedel-Crafts acylation reactions by which they are obtained, we also developed an alternative but closely related route to benzofuronaphthoquinones **3** via readily available 1-benzylisoquinolines.⁹ Bromination of papaverine and methylation of bromopapaverine gave *N*-methyl-1-bromobenzylisoquinolinium iodide **5**,¹⁰ which was refluxed in an aq. NaOH methanolic solution to afford 2-phenyl-1-naphthol **7** in 45% yield, via ketoaldehyde **6**. Subsequent oxidation of **7** with Fremy's salt furnished phenylnaphthoquinone **8** in 80% yield. Finally, heating compound **8** with methanolic aqueous NaOH gave hydroxyphenylnaphthoquinone **2b** in almost quantitative yield. Bromophenylnaphthol **7** was also easily transformed into benzonaphthofuran **9** when subjected to the above

Ullman reaction conditions. The transformation of **5** into **7** implies the opening of the nitrogen ring to give a ketoenamine, subsequent hydrolysis of the enamine group, and final intramolecular aldol condensation of the ketoaldehyde **6**.



Scheme 2: Conditions: (i) a) POCl_3 , CH_3CN ; b) Br_2 , AcOH ; c) MeI , acetone. (ii) NaOH , MeOH , reflux. (iii) Fremy's salt, K_2HPO_4 , acetone. (iv) NaOH , $\text{MeOH}:\text{H}_2\text{O}$ (8:2), 50°C . (v) CuO , K_2CO_3 , pyr.

Note that in the course of these syntheses via benzyloisoquinolines, the regiospecific transfer of a phenylacetyl group from the nitrogen atom of phenylethylamide **4** to the desired ortho position in **6** is effected by a three-step sequence that includes a Bischler-Napieralski cyclization. This constitutes a way of acylating aromatic rings that is less dependent on the electronic properties of substituents than is Friedel-Crafts acylation.

Work is in progress to establish the scope of this route to benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones and to study its extension to other tetracyclic compounds of pharmacological interest,² such as dibenzo[*c,h*]chroman-6-ones, dibenzo[*c,g*]chroman-5,7,12-triones and benzo[*b*]fluoren-11-ones.

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- All new compounds gave satisfactory analytical and spectroscopic data. Selected spectroscopic data for **compound 3a**: IR (ν , cm^{-1} , KBr), 1665 (C=O); ^1H NMR (δ , ppm), 4.05 (s, 3H, -OCH₃), 4.06 (s, 3H, -OCH₃), 7.45-7.69 (m, 3H, 3xAr-H), 7.63 (s, 1H, Ar-H), 7.64 (s, 1H, Ar-H), 8.25 (m, 1H, Ar-H); MS, m/z (%), 308 (M^+ , 100), 237 (13), 194 (13). **Compound 3b**: IR (ν , cm^{-1} , KBr), 1665 (C=O); ^1H NMR (δ , ppm), 3.99 (s, 3H, -OCH₃), 4.02 (s, 3H, -OCH₃), 4.06 (s, 3H, -OCH₃), 4.07 (s, 3H, -OCH₃), 7.12 (s, 1H, Ar-H), 7.58 (s, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H); MS, m/z (%), 368 (M^+ , 100), 325 (13), 69 (18). **Compound 9**: ^1H NMR (δ , ppm), 4.00 (s, 3H, -OCH₃), 4.02 (s, 3H, -OCH₃), 4.04 (s, 3H, -OCH₃), 4.11 (s, 3H, -OCH₃), 7.24 (s, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 7.39 (s, 1H, Ar-H), 7.59 (d, $J=8.4$ Hz, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 7.76 (d, $J=8.4$ Hz, 1H, Ar-H); MS, m/z (%), 338 (M^+ , 100), 323 (34).
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