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

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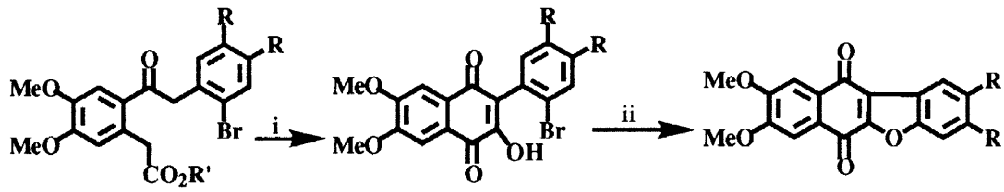
SUMMARY- Here we account the transformation of 2-[(2'-bromophenyl)acetyl]phenylacetic acids and 1-benzylisoquinolines into benzo[b]naphtho[2,3-d]furan-6,11-diones. Synthesis of benzo[b]naphtho[2,1-d]furans from 1-benzylisoquinolines is also described.

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 K_2CO_3 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**.



1 a: R=R'=H
b: R=H, R'=Me,
c: R=OMe; R'=H
d: R=OMe, R'=Me

2 a: R=H; b: R=OMe

3 a: R=H; b: R=OMe

Scheme 1: *Conditions: i) aq. NaOH, MeOH. ii) CuO, K_2CO_3, pyr.*

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

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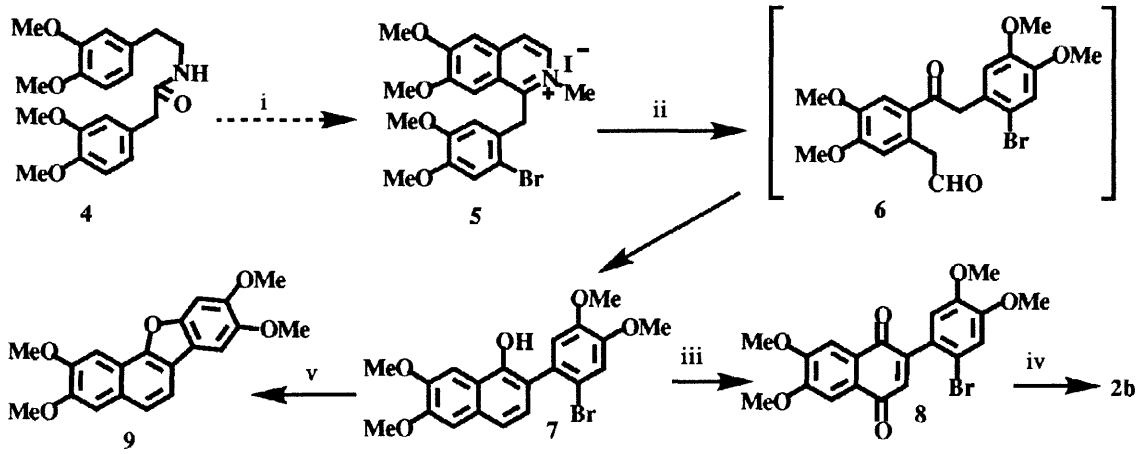
Ullman reaction conditions. The tranformation of **5** into **7** implies the opening of the nitrogen ring to give a ketoenamine, subsequent hydrolysis of the enamine group, and final intramolecular aldol condensation of the ketoaldehyde **6**.



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, MeOH:H_2O (8:2), 50°C. (v) CuO, K_2CO_3, pyr.*

Note that in the course of these syntheses via benzylisoquinolines, 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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7. 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, -OCH_3), 4.06 (s, 3H, -OCH_3), 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, -OCH_3), 4.02 (s, 3H, -OCH_3), 4.06 (s, 3H, -OCH_3), 4.07 (s, 3H, -OCH_3), 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, -OCH_3), 4.02 (s, 3H, -OCH_3), 4.04 (s, 3H, -OCH_3), 4.11 (s, 3H, -OCH_3), 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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