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Naphtho[2,3-*c*]furan-4,9-diones and related compounds: theoretically interesting and bioactive natural and synthetic products

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Dedicated to Associate Professor Dieter Wege on the occasion of his retirement

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Abbreviations: Ac, acetyl; AIBN, 2′-azobis(isobutyronitrile); Ar, aryl; Bn, benzyl; BOM, benzyloxymethyl; Bu^t, *tert*-butyl; CSA, camphor-10-sulfonic acid; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM, dichloromethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DiBAL-H, diisobutylaluminium hydride; DMAP, *N*,*N*-dimethyl-4-aminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; Et, ethyl; FVP, flash vacuum pyrolysis; HMDS, hexamethyldisilazide; IBF, isobenzofuran; LDA, lithium diisopropylamide; *m*CPBA, *meta*-chloroperbenzoic acid; Me, methyl; MTPACl, Mosher's acid chloride = 2-methoxy-2-(trifluoromethyl)phenylacetyl chloride; NBS, *N*-bromosuccinimide; *n*-Bu, 1-butyl; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; Ph, phenyl; PMB, *para*-methoxybenzyl; PMP, *para*-methoxyphenyl; Py, pyridyl or pyridine; TBAF, tetrabutylammonium fluoride; TBDPS, *tert*-butyldiphenylsilyl; TBS, *tert*-butyldimethylsilyl; *t*-Bu, *tert*-butyl; TEMPO, 2,2,6,6-tetramethylpiperidinyl 1-oxide; TFA, trifluoroacetic acid; TFPAA, trifluoroperacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; TMS, trimethylsilyl; TPAP, tetrapropylammonium perruthenate; Ts, tosyl = *para*-toluenesulfonyl.

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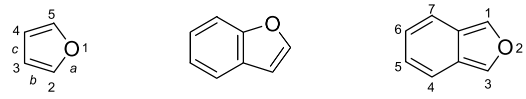
1. Introduction

The furan moiety (**1**) occurs widely in synthetic and natural products, either as a simple structural unit or as part of a more complex annulated system.[1–3] With regard to the latter, there are two possible points of fusion to the furan ring, a fact that has important ramifications for the stability of the systems resulting from fusion with aromatic nuclei. Fusion of a benzene ring at the *b*-bond, as in benzofuran (**2**) (Fig. 1), does not perturb the benzene nucleus and thus gives rise to stable compounds. Accordingly, a vast number of *b*-fused synthetic and natural products[1,4] exist. In contrast, fusion at the *c*-bond, as in isobenzofuran (IBF) (**3**), interrupts the benzene π-sextet, reducing the aromaticity and, correspondingly, the stability of the system. The number of known *c*-fused compounds is therefore much smaller.

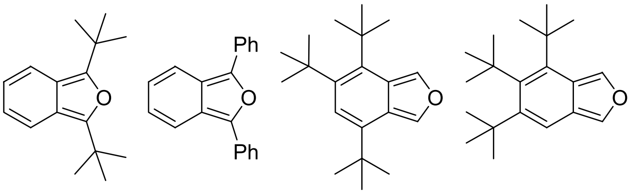


1 **2** **3**

Figure 1.

Compounds incorporating the IBF structural unit display a propensity to undergo addition across the 1,3-positions, generating the more stable benzenoid aromatic systems. Thus, while benzofuran (**2**) is a stable compound, IBF (**3**) has been isolated only at low temperature, and rapidly polymerises on warming to room temperature.[5–7]

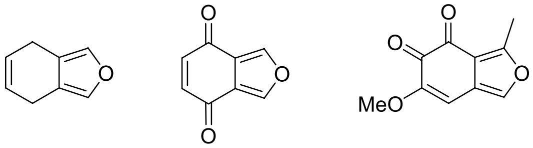
Stability can be imparted to the IBF moiety by incorporation of substituents into the 1- and 3-positions. Bulky substituents hinder the approach of reagents to the labile diene unit, thereby reducing the reactivity of the derivative. For example, 1,3-di-*t*-butylisobenzofuran (**4**)[8,9] (Fig. 2) is a crystalline solid, stable at room temperature over prolonged periods.[10] Aryl substituents also impart stability through conjugation. 1,3-Diphenylisobenzofuran (**5**), for example, is a commercially available, stable crystalline solid. The tri-*t*-butyl-substituted isobenzofurans **6** and **7**, although more open to attack at the 1,3-positions, are also stable at room temperature.[11,12] This is presumably due to the out-of-plane deformations induced by the bulky *o*-*t*-butyl groups, which reduce the π-conjugation, and thus the *o*-quinonedimethide (*o*-xylylenoid) character of the system.



4 **5** **6** **7**

Figure 2.

Partially hydrogenated derivatives and those with carbonyl substituents in the benzenoid ring also have increased stability. In these compounds, addition across the 1,3-positions does not generate the dramatic increase in resonance energy observed with the parent species. Consequently, stable examples of this structural type exist, including 4,7-dihydroisobenzofuran (**8**),[13–15] isobenzofuran-4,7-dione (**9**)[16–19] and the natural product, albidin (**10**) (Fig. 3).[20,21]

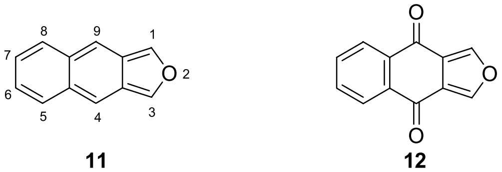


8 **9** **10**

Figure 3.

The chemistry of isobenzofurans has been the subject of several reviews[22–27] and continues to be an active area of research.

On the basis of structure-reactivity considerations, naphtho[2,3-*c*]furan (**11**) (Fig. 4) should be even more reactive than IBF[24] and, whilst having being generated in solution and trapped in situ,[28,29] is probably too reactive to be isolated under normal laboratory conditions.[30] Introduction of carbonyl groups into the 4- and 9-positions generates the naphtho[2,3-*c*]furan-4,9-dione (isofuranonaphthoquinone) ring system (**12**), removing the *o*-quinonedimethide character present in **11** and thereby stabilising the system (Fig. 4).



11 **12**

Figure 4.

It was the relationship of naphtho[2,3-*c*]furan-4,9-diones to naphtho[2,3-*c*]furan (**11**) that initially aroused the author's interest in this class of compounds. In particular, the natural products ventilone F and G, were originally formulated as **13** and **14**, comprising an IBF nucleus (Fig. 5).[31,32] As discussed below, it is likely that these structures are incorrect.[33]

The related naphtho[2,3-*c*]furan-4(9*H*)-ones, of which the parent compound **15** is unknown, comprise a relatively