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An innovative synthesis of dibenzofurans through a carbanion-induced ring transformation reaction☆

Atul Goel,* Manish Dixit and Deepti Verma

Medicinal & Process Chemistry Division, Central Drug Research Institute, Lucknow 226001, India

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Abstract—An innovative route for the synthesis of substituted dibenzofurans has been delineated through a ring transformation reaction of suitably functionalized *2H*-pyran-2-ones by reaction with 7-methoxybenzofuran-3-one, in high yield. The novelty of the procedure lies in the creation of an aromatic ring from a 2*H*-pyran-2-one involving the $-COCH_2-$moiety of the substrate.

Substituted benzofurans, dibenzofurans and their structural isomers have attracted the attention of organic chemists for many years due to their occurrence in a wide variety of pharmaceutical and natural products possessing useful biological activities.[1] The majority of naturally occurring dibenzofurans such as penioflavin[2] **1**, corticin A[3] **2** and their derivatives[4] (Fig. 1) are biosynthesized as diverse secondary metabolites of lichens or of higher fungi. Some of the dibenzofurans, for example cannabifuran[5] **3** and ruscodibenzofuran[6] **4** and related compounds have been isolated from plants and possess diuretic and anti-inflammatory activity. Apart from its biological relevance, the chemistry of dibenzofurans is of significance due to the directing effect on ring functionalization of the furan oxygen.[7]

The intramolecular cyclization of the 2-phenoxybenzene diazonium salt reported by Graebe and Ullmann[8] is one of the oldest and the simplest methods known for the construction of the dibenzofuran skeleton. Other classical methods include the acid-catalyzed dehydration of 2,2′-dihydroxybiphenyls or their methyl ethers,[1b] photochemical cyclization of 2-phenoxyphenols,[9] and the thermal rearrangement of diquinones.[10] Despite various modifications of the reaction conditions, these cyclization reactions produce low yields of the desired compounds, which has restricted the applicability of these reactions.[11]

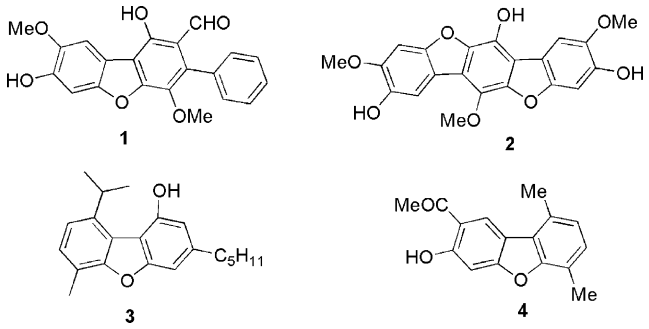

Figure 1. Naturally occurring dibenzofurans: penioflavin (**1**) and cortcin A (**2**) produced by the fungi *Penioflavin sanguinea* Bres. and *Corticum caerulum*, respectively, and cannabifuran (**3**) and ruscodibenzofuran (**4**) isolated from the plants *Cannabis sativa* L. and *Ruscus aculeatus* L., respectively.

Recent approaches to access this heterocyclic ring system include flash vacuum pyrolysis of 3-(2-furoyl)-cinnoline at high temperature,[12] gas-phase condensation of phenoxy radicals at moderately elevated temperature,[13] and the Diels–Alder type cycloaddition of 2-isopropenyl-3-methoxybenzofuran with DMAD.[14] More recently, the metal assisted benzannulation reaction[15] has received a great deal of attention for preparing diversely functionalized arenes and heteroarenes. Many examples of benzannulation using heterocycle-based chromium–carbene complexes and suitably functionalized alkynes have been reported in recent years.

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* Corresponding author. Fax: +91 522 2623405; e-mail: agoel13@yahoo.com

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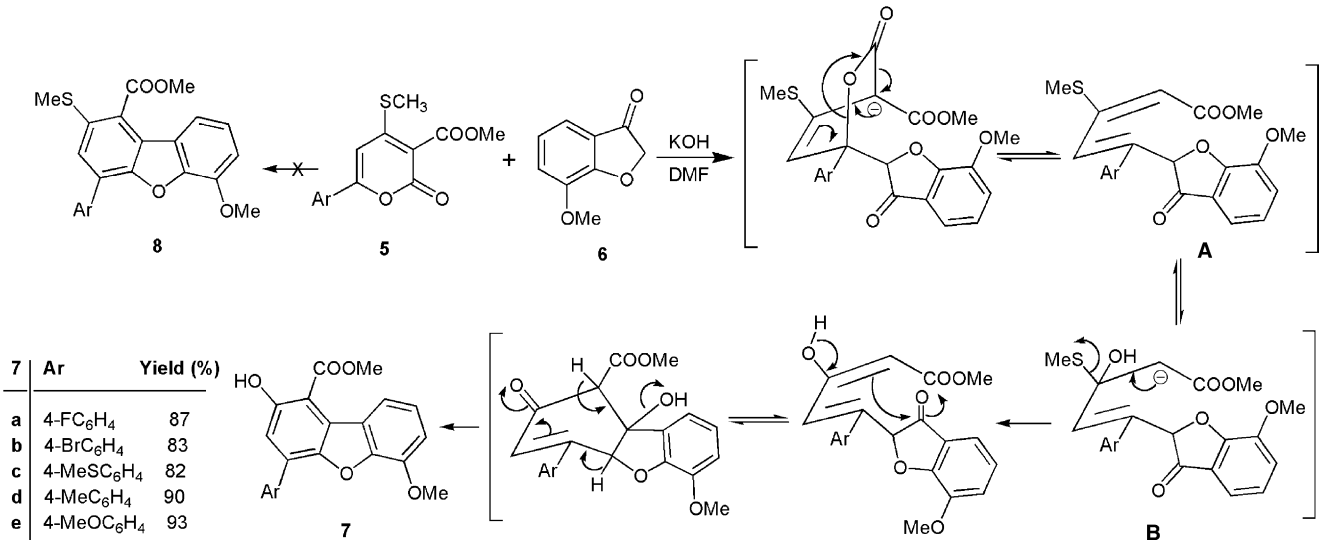


7	Ar	Yield (%)
a	4-FC_6H_4	87
b	4-BrC_6H_4	83
c	4-$MeSC_6H_4$	82
d	4-MeC_6H_4	90
e	4-$MeOC_6H_4$	93

Scheme 1.

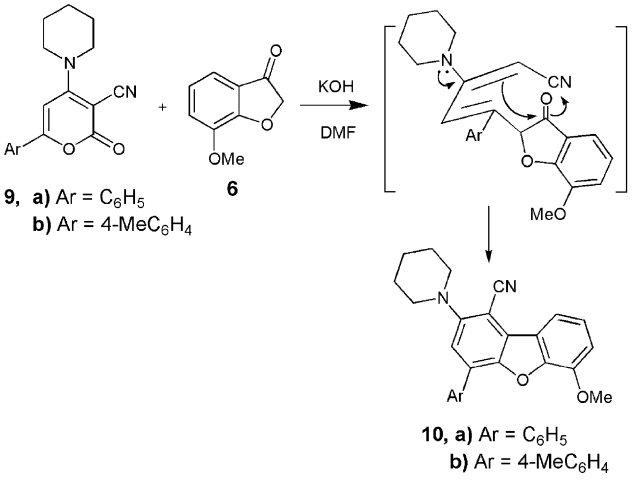
Unfortunately, the scope of these procedures suffers due to the difficulty in obtaining suitably functionalized organometallic reagents, high temperature reaction conditions and a low yield of final compound. The chemical and pharmacological potentials of substituted dibenzofurans and the limitations of existing procedures prompted us to develop an expeditious route to their synthesis that could offer flexibility in the substituents on their molecular frame.

Herein, we report an elegant route for preparing dibenzofurans through carbanion-induced ring transformation of 2*H*-pyran-2-ones with benzofuran-3-one in high yields, which has the flexibility of introducing electron donor or acceptor substituents on the aromatic rings.

The 2*H*-pyran-2-ones **5** used as parent precursors were conveniently prepared in high yield by the reaction of methyl 2-carbomethoxy-3,3-dimethylthio-acrylate with acetophenone as described earlier.[16] The unique feature of 2*H*-pyran-2-ones **5** is the presence of three electrophilic centres at C-2, C-4 and C-6 in which the latter two are susceptible to nucleophiles due to the extended conjugation and the presence of the electron withdrawing substituent at position 3 of the pyran ring. Our approach to diversely substituted dibenzofurans involved stirring an equimolar mixture of 2*H*-pyran-2-one **5**, benzofuran-3-one **6** and powdered KOH in dry DMF under an inert atmosphere at ambient temperature for 4–6 h as shown in Scheme 1. It is interesting to note that the reaction of 6-aryl-3-carbomethoxy-4-methylsulfanyl-2*H*-pyran-2-ones (**5a**–**e**) with 7-methoxybenzofuran-3-one afforded 2-hydroxy-6-methoxy-4-aryl-dibenzofuran-1-carboxylic acid methyl esters (**7a**–**e**) instead of the corresponding 2-methylsulfanyl derivatives (**8**).

The mechanism, depicted in Scheme 1, implies that the reaction is initiated by attack of the carbanion generated in situ from benzofuran-3-one **6** at position C-6 of the 2*H*-pyran-2-one, followed by decarboxylation to form diene intermediate **A**. The C-3 position of the diene **A** is electrophilic in nature and hydroxide may attack at this position to form intermediate **B**, followed by elimination of methyl mercaptan and intramolecular cyclization involving the carbonyl group of benzofuran-3-one and C-2 of the diene, followed by aromatization to yield **7a**–**e** in high yields.

In order to confirm the reaction pathway, we further exploited the reaction by replacing the methylsulfanyl group at position C-4 in 2*H*-pyran-2-one **5** with piperidine so that the electrophilicity at the C-3 position was reduced such that attack by the hydroxide at position C-3 on the diene intermediate **A** could not occur. Thus reaction of 2-oxo-4-(piperidin-1-yl)-6-phenyl-2*H*-pyran-3-carbonitrile (**9a**) with 7-methoxybenzofuran-3-one was carried out as shown in Scheme 2. As expected, we characterized the isolated compound as 6-methoxy-2-(piperidin-1-yl)-4-phenyldibenzofuran-1-carbonitrile (**10a**) in moderate yield. The reaction was further confirmed by preparing another derivative (**10b**) using the same strategy. The beauty of the reaction lies in the transformation of an aromatic ring by creating a C–C



Scheme 2.

bond through the reaction of a 2*H*-pyran-2-one involving the $-COCH_2$-unit of the benzofuran-3-one under mild reaction conditions. All the compounds synthesized were characterized by elemental and spectroscopic analyses.[17]

In summary, this methodology provides an innovative synthesis of diversely functionalized dibenzofurans in high yields. The potential of the procedure lies in the creation of C–C bonds through carbanion-induced ring transformation of 2*H*-pyran-2-ones in a single step from easily accessible precursors.

Acknowledgements

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17. *Typical procedure*: a mixture of 3-carbomethoxy-4-methylsulfanyl-6-aryl-*2H*-pyran-2-one (1 mmol), 7-methoxybenzofuran-3-one (0.17 g, 1 mmol) and powdered KOH (84 mg, 1.5 mmol) in dry DMF (6 mL) was stirred at room temperature for 4–6 h. After completion of reaction, the mixture was poured onto crushed ice with vigorous stirring, then neutralized with 10% HCl. The precipitate thus obtained was filtered off, washed with water, dried and purified by silica gel column chromatography using 2% ethyl acetate in hexane as eluent.
4-(4-Fluorophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester (**7a**): mp: 214–215 °C; FABMS: *m/z* 367 (M^++1); IR (KBr) 1653 (CO), 3436 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ 4.02 (s, 3H, OCH_3), 4.19 (s, 3H, $COOCH_3$), 7.02 (d, 2H, J = 8.0 Hz, ArH), 7.22–7.28 (m, 3H, ArH), 7.86–7.94 (m, 3H, ArH), 11.29 (s, 1H, OH); Anal. Calcd for $C_{21}H_{15}FO_5$: C, 68.85; H, 4.13. Found: C, 68.91; H, 4.16.
4-(4-Bromophenyl)-2-hydroxy-6-methoxy-dibenzofuran-1-carboxylic acid methyl ester (**7b**): mp: 226–227 °C; FABMS: *m/z* 427 (M^++1); IR (KBr) 1654 (CO), 3428 cm^{-1} (OH); ^1H NMR (200 MHz, $CDCl_3$): δ 4.03 (s, 3H, OCH_3), 4.20 (s, 3H, $COOCH_3$), 7.03 (d, 1H, J = 8.0 Hz, ArH), 7.23–7.26 (m, 2H, ArH), 7.68 (d, 2H, J = 8.6 Hz, ArH), 7.80 (d, 2H, J = 8.6 Hz, ArH), 7.98 (d, 1H, J = 8.0 Hz, ArH), 11.29 (s, 1H, OH); Anal. Calcd for $C_{21}H_{15}BrO_5$: C, 59.04; H, 3.54. Found: C, 59.17; H, 3.68.
6-Methoxy-4-phenyl-2-piperidin-1-yl-dibenzofuran-1-carbonitrile (**10a**): mp: 198–200 °C; FABMS: *m/z* 383 (M^++1); IR (KBr) 2211 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 1.60–1.70 (m, 2H, CH_2), 1.81–1.92 (m, 4H, $2CH_2$), 3.22–3.28 (m, 4H, $2CH_2$), 4.04 (s, 3H, OCH_3), 7.06 (d, 1H, J = 8.0 Hz, ArH), 7.24 (s, 1H, ArH), 7.30–7.39 (m, 1H, ArH), 7.40–7.60 (m, 3H, ArH), 7.86–7.91 (m, 2H, ArH), 8.06 (d, 1H, J = 8.0 Hz, ArH); Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.73; H, 5.86; N, 7.28.
6-Methoxy-2-piperidin-1-yl-4-p-tolyl-dibenzofuran-1-carbonitrile (**10b**): mp: 150–151 °C; FABMS: *m/z* 397 (M^++1); IR (KBr) 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 1.58–1.68 (m, 2H, CH_2), 1.81–1.91 (m, 4H, $2CH_2$), 2.45 (s, 3H, CH_3), 3.22–3.27 (m, 4H, $2CH_2$), 4.04 (s, 3H, OCH_3), 7.06 (d, 1H, J = 8.0 Hz, ArH), 7.23 (s, 1H, ArH), 7.30–7.34 (m, 1H, ArH), 7.36 (d, 2H, J = 8.0 Hz, ArH), 7.80 (d, 2H, J = 8.0 Hz, ArH), 8.06 (d, 1H, J = 8.0 Hz, ArH); Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.81; H, 6.13; N, 7.14.