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An efficient synthesis of 4,5-dihydronaphtho[2,1-*b*]furan through a novel ring transformation of 2*H*-pyran-2-one☆

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Abstract—An innovative route for the synthesis of substituted naphtho[2,1-*b*]furan has been delineated through a ring transformation reaction of suitably functionalized 2*H*-pyran-2-ones by reaction with 6,7-dihydro-5*H*-benzofuran-4-one, in good yield.

Benzofuran and naphthofuran nuclei are key structural motifs found in a large number of biologically important natural products, mainly belonging to the sesquiterpene and arylquinone classes.[1] Many of the natural naphthofurans such as (±)-laevigatin[2] (**I**), (+)-heritol[3] (**II**) and balsaminone[4] A (**III**) possess interesting pharmacological and cytotoxic properties (Fig. 1). Several synthetic compounds bearing this ring skeleton are associated with diverse biological activities such as antifungal,[5] antibacterial,[6] antiviral,[7] β-adrenolytic,[8] antitumor,[9] and anthelmintic.[10] The nitro derivatives of naphtho[2,1-*b*]furans have been extensively studied for their mutagenic activities, for example 7-methoxy-2-nitronaphtho[2,1-*b*]furan is one of the strongest mutagens described for mammalian cells.[11] The wide pharmacological potential of these bioactive moieties has attracted many organic and medicinal chemists to develop efficient routes for their syntheses.

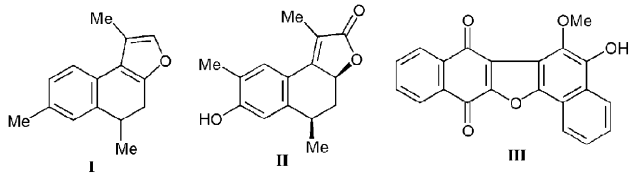

Figure 1. Examples of natural products bearing naphthofuran skeleton.

Numerous synthetic methodologies for the synthesis of naphtho[2,1-*b*]furans have been reported in the literature.[12] Among them, the reaction of a 1-substituted-2-naphthol with various reagents such as chloroacetone, a chloroacetate ester or phenacyl bromide is the simplest approach to prepare 1,2-substituted-naphtho[2,1-*b*]furans. However, the application of these procedures limits the scope of derivatization simply because of the need for functionalized naphthols, which are not always easily available. Recently the metal assisted Dötz benzannulation reaction[13] has received a great deal of attention for preparing diversely functionalized arenes and heteroarenes. Many examples of benzannulation using an array of α,β-unsaturated chromium–carbene complexes and suitably functionalized alkynes have been reported in recent years. Unfortunately the scope of these reactions suffers due to the difficulty in obtaining suitably functionalized organometallic reagents and low yields of final compound due to the formation of undesired byproducts. The wide-ranging applications of naphtho[2,1-*b*]furans and limitations of existing procedures prompted us to develop an efficient route to their synthesis that could offer flexibility of substituent variations in their molecular architecture.

In addition, most of the existing procedures afford 1- or 2-substituted naphthofurans. Herein, we report an elegant route for preparing 1,2-unsubstituted naphtho-[2,1-*b*]furans through carbanion-induced ring transformation of 2*H*-pyran-2-ones with cyclic ketones in good yields, which has the flexibility of introducing electron donor or acceptor substituents on the aromatic rings.

Keywords: Naphtho[2,1-*b*]furan; 2*H*-pyran-2-one; 5*H*-benzofuran-4-one; Ring transformation reaction.
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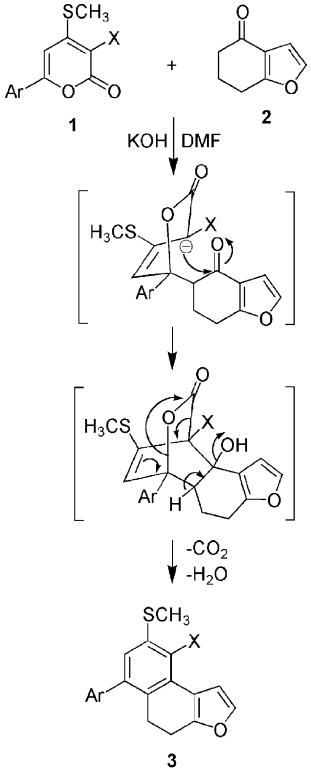
The 2*H*-pyran-2-ones **1** used as parent precursors were conveniently prepared by the reaction of methyl 2-carbomethoxy/cyano-3,3-dimethylthio-acrylate with acetophenone in high yield as described earlier.[14] The other starting material **2** was prepared by the reaction of 1,3-cyclohexanedione and an aqueous solution of chloroacetaldehyde in the presence of a base.[15] Our approach to variously substituted naphtho[2,1-*b*]furans involved stirring an equimolar mixture of the 2*H*-pyran-2-one **1**, 6,7-dihydro-5*H*-benzofuran-4-one **2**, and powdered KOH in dry DMF at room temperature for 24–30 h as shown in Scheme 1. The unique features of 2*H*-pyran-2-one **1** is the presence of three electrophilic centres; C2, C4, and C6 in which the latter is highly susceptible to nucleophiles due to the extended conjugation and the presence of the electron withdrawing substituent at position 3 of the pyran ring. The beauty of the reaction lies in the conversion of the lactone ring into an aromatic ring involving the $-C(O)CH_2-$ unit of the cyclic ketone **2**, in the presence of a base. This is a unique methodology for C–C bond forming reactions and may be applicable to the synthesis of various natural products possessing a naphtho[2,1-*b*] furan ring skeleton.



3	Ar	X	Yield (%)
a	C_6H_5	COOMe	68
b	4-ClC_6H_4	COOMe	64
c	4-FC_6H_4	COOMe	69
d	4-BrC_6H_4	COOMe	71
e	3,4-$Cl_2C_6H_3$	COOMe	68
f	2-thienyl	COOMe	63
g	4-ClC_6H_4	CN	54
h	4-BrC_6H_4	CN	59
i	4-$CH_3C_6H_4$	CN	48
j	4-$OCH_3C_6H_4$	CN	51

Scheme 1.

The mechanism, depicted in Scheme 1, implies that the reaction is initiated by attack of the carbanion generated in situ from 6,7-dihydro-5*H*-benzofuran-4-one **2** at position C-6 of the pyran-2-one, followed by cyclization involving the carbonyl group and C-3 of the pyran ring to form a bicyclic intermediate. Decarboxylation and dehydration then lead to naphthofurans **3a–j** in good yields. All the compounds synthesized were characterized by elemental and spectroscopic analyses.[16]

In summary, this methodology provides a one-pot efficient synthesis of diversely functionalized naphtho[2,1-*b*]furans 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.

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16. Typical procedure: A mixture of 3-carbomethoxy-4-methylsulfanyl-6-phenyl-2*H*-pyran-2-one (0.276 g, 1 mmol), 6,7-dihydro-5*H*-benzofuran-4-one (0.14 g, 1 mmol), and powdered KOH (84 mg, 1.5 mmol) in dry DMF (10 ml) was stirred at room temperature for 24 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 hexane as eluent. **3a**: Mp: 123–124 °C; MS (FAB): *m*/*z* 351 $(M + 1)^+$; IR (KBr) 1720 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.75–2.79 (m, 2H, CH_2), 2.86–2.92 (m, 2H, CH_2), 3.99 (s, 3H, OCH_3), 6.44 (d, 1H, $J = 2.0$ Hz, OCH=C*H*), 7.11 (s, 1H, ArH), 7.26–7.32 (m, 3H, ArH, and OC*H*=CH), 7.40–7.45 (m, 3H, ArH); Anal. calcd for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18%. Found: C, 72.08; H, 5.23%. **3g**: Mp: 181–182 °C; MS (FAB): *m*/*z* 352 $(M + 1)^+$; IR (KBr) 2228 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3H, SCH_3), 2.74–2.84 (m, 4H, $2CH_2$), 6.84 (s, 1H, ArH), 7.15 (d, 2H, $J = 8.6$ Hz, ArH), 7.33 (d, 1H, $J = 2.0$ Hz, OCH=C*H*), 7.36–7.41 (m, 3H, ArH, and OC*H*=CH); Anal. calcd for $C_{20}H_{14}ClNOS$: C, 68.27; H, 4.01; N, 3.98%. Found: C, 68.18; H, 4.23; N, 4.06%.