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A one-pot efficient synthesis of highly functionalized 5,6-dihydronaphthalenes from 2*H*-pyran-2-one☆

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Abstract—A one-pot efficient synthesis of highly functionalized 5,6-dihydronaphthalenes has been delineated through carbanion-induced ring transformation of 2*H*-pyran-2-ones by 2-cyclohexenone.

The 1,2-dihydronaphthalene ring system is widely present in various natural products of therapeutic importance among which cannabisins **I**, isolated from the fruits of *Cannabis sativa*,[1] 6,7-dehydrosempervirol[2] **II**, isolated from the roots of *Salvia apiana* and negundin B[3] **III**, isolated from the roots of *Vitex negundo* are prominent. An extensive literature survey revealed that multi-step sequences[4] were needed to prepare highly functionalized 1,2-dihydronaphthalenes. This prompted us to develop an efficient, economical one-pot preparation of 5,6-dihydronaphthalenes without substitution in the reduced ring (Fig. 1).

Previously, compounds containing this ring system have been prepared by controlled reduction of naphthalene by Na or Li in liquid ammonia. The first step in this reduction is the formation of 1,4-dihydronaphthalene,[5–7] which isomerizes to 1,2-dihydronaphthalene[8,9] in the presence of a strong base. The demerit of this procedure is the difficulty in selective reduction of one of the fused rings of naphthalene as the reduction depends upon the type and position of any substituent attached to the ring. The presence of electron-releasing substituents in one of the naphthalene rings directs the reduction of the adjacent ring while electron-withdrawing substituents facilitate the reduction of the same ring. Another approach for the synthesis of this class of compounds is based on the reaction of 1-tetralone with organolithium or Grignard reagents to the alcohol followed by dehydration.[10,11] Similarly, 4-substituted 1-tetralones obtained by acid cyclization of 4-substituted-4-arylbutyric acids have also been transformed smoothly into 1,4-disubstituted, 1,2-dihydronaphthalenes.[12–14] Valkovich et al.[15] have reported a direct synthesis of 1,2-dihydronaphthalene by the pyrolysis of *trans*-1-phenyl-1,3-butadiene at 450 °C[16] as a major product together with *cis*-1-phenyl-1,3-butadiene as a minor constituent.

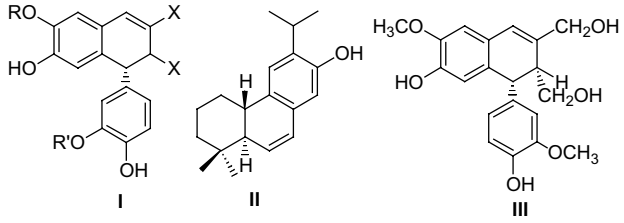

Figure 1. Naturally occurring dihydronaphthalenes.

Recently, compounds containing this ring system have been prepared either from the reaction of 7-oxabenzonorbornadiene or 7-azabenzonorbornadiene with alkenylzirconium reagents using $NiCl_2(PPh_3)_2$ and Zn powder as catalyst.[17]

Here, we report an efficient one-pot synthesis of highly functionalized 1,2-dihydronaphthalenes through ring transformation of 6-aryl-4-substituted-2*H*-pyran-2-ones **1a**–**k** by 2-cyclohexenone **2** in moderate yields. The precursors, 2*H*-pyran-2-ones **1a**–**g** were prepared[18] from

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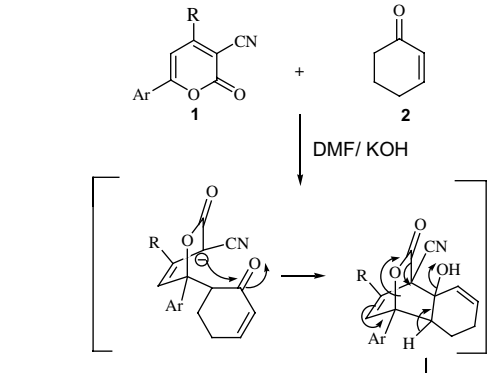
the reaction of methyl 2-cyano-3,3-di(methylthio)acrylate and an aryl methyl ketone, which on further reaction with a secondary amine yielded the corresponding 4-amino-6-aryl-2*H*-pyran-3-carbonitriles **1h–k**.

The C-6 position is highly electrophilic due to extended conjugation and the presence of an electron-withdrawing substituent at C-3 of the pyran ring. C-6 in 2-cyclohexenone **2** can form a carbanion and participates in the ring transformation by attacking C-6 of the pyranone ring (Scheme 1).

Thus an equimolar mixture of the 2*H*-pyran-2-one **1**, and 2-cyclohexenone **2** was stirred in the presence of powdered KOH in DMF at room temperature for 20 h, poured into ice water and neutralized with 10% HCl. The precipitate of the 4-aryl-2-substituted–5,6-dihydronaphthalene-1-carbonitrile **3** was filtered off and purified by column chromatography. The ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-ones **1a–g** with 2-cyclohexenone was not a clean reaction, possibly due to a side reaction at the C-4 electrophilic centre of the pyranone. The reactions of 4-amino-6-aryl-2*H*-pyran-3-carbonitriles **1h–k** with 2-cyclohexenone were smoother and cleaner. All the synthesized compounds were unambiguously characterized by spectroscopic and elemental analysis.[19] The ^{1}H NMR spectrum of **3a** showed a triplet at δ 3.10 and a multiplet at δ 2.33–2.43 due to the CH_2 protons. Both methine protons of the reduced ring resonated as multiplets at 6.03–6.08 and 6.36–6.41 ppm.

The reaction is possibly initiated by the attack of a carbanion generated in situ from 2-cyclohexenone at C-6 on the highly electrophilic C-6 centre of the pyran ring. Cyclization involving carbonyl of 2-cyclohexenone and C-3 of the pyran ring followed by ring opening provides



3	Ar	R	Yield(%)
a	C_6H_5	SCH_3	37
b	4-$CH_3C_6H_4$	SCH_3	38
c	4-$CH_3OC_6H_4$	SCH_3	35
d	4-BrC_6H_4	SCH_3	35
e	4-ClC_6H_4	SCH_3	40
f	4-FC_6H_4	SCH_3	41
g	2-thienyl	SCH_3	38
h	4-BrC_6H_4	1-piperidinyl	52
i	4-ClC_6H_4	1-piperidinyl	51
j	4-$CH_3OC_6H_4$	1-piperidinyl	48
k	2-thienyl	1-piperidinyl	50

Scheme 1.

4-aryl-2-substituted-5,6-dihydronaphthalene-1-carbonitriles **3**.

Our methodology provides an innovative route for an efficient one-pot synthesis of 4-aryl-2-substituted-5,6-dihydronaphthalene-1-carbonitriles, using very economical reagents. It also provides an option for functionalization of the reduced ring by starting from substituted 2-cyclohexenones. The work-up of the reaction is also very simple.

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19. Typical procedure for **3**: An equimolar mixture of 2*H*-pyran-2-one **1** (1 mmol), 2-cyclohexenone **2** (1 mmol) and powdered KOH (1.5 mmol) in dry DMF was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and neutralized with 10% HCl. The

separated solid was filtered, washed with water and dried. The crude product was purified by silica gel column chromatography using 1% ethyl acetate in hexane as an eluent to afford **3** in moderate yield. Compound **3a**: Yield 37%; mp 78–80 °C; IR (KBr) ν 2213 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.33–2.43 (m, 2H, CH_2), 2.54 (s, 3H, SCH_3), 3.10 (t, J = 8.2 Hz, 2H, CH_2), 6.03–6.08 (m, 1H, CH), 6.36–6.41 (m, 1H, CH), 7.03 (s, 1H, ArH), 7.28–7.32 (m, 2H, ArH), 7.40–7.46 (m, 3H, ArH); MS (FAB) 278 (M^++1). Anal. Calcd for $C_{18}H_{15}NS$: C, 77.94; H, 5.45; N, 5.05. Found: C, 77.71; H, 5.40; N, 4.93. Compound **3b**: Yield 38%; mp 102–104 °C; IR (KBr) ν 2214 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.32–2.38 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 3.07 (t, J = 8.2 Hz, 2H, CH_2), 6.02–6.09 (m, 1H, CH), 6.39–6.44 (m, 1H, CH), 7.02 (s, 1H, ArH), 7.17–7.28 (m, 4H, ArH); MS (FAB) 292 (M^++1). Anal. Calcd for $C_{19}H_{17}NS$: C, 78.31; H, 5.88; N, 4.81. Found: C, 78.60; H, 5.93; N, 4.49. Compound **3c**: Yield 35%; mp 122–124 °C; IR (KBr) ν 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.36–2.41 (m, 2H, CH_2), 2.54 (s, 3H, SCH_3), 3.07 (t, J = 8.2 Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 6.03–6.08 (m, 1H, CH), 6.40–6.45 (m, 1H, CH), 6.99 (s, 1H, ArH), 7.00 (d, J = 8.8 Hz, 2H, ArH), 7.24 (d, J = 8.8 Hz, 2H, ArH); MS (FAB) 308 (M^++1). Anal. Calcd for $C_{19}H_{17}NOS$: C, 74.23; H, 5.57; N, 4.56. Found: C, 74.62; H, 5.74; N, 4.34. Compound **3d**: Yield 35%; mp 126–128 °C; IR (KBr) ν 2218 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.36–2.42 (m, 2H, CH_2), 2.54 (s, 3H, SCH_3), 3.08 (t, J = 8.3 Hz, 2H, CH_2), 6.05–6.09 (m, 1H, CH), 6.31–6.36 (m, 1H, CH), 6.98 (s, 1H, ArH), 7.18 (d, J = 8.3 Hz, 2H, ArH), 7.58 (d, J = 8.3 Hz, 2H, ArH); MS (FAB) 358, 356 (M^++1), 357, 355 (M^+). Anal. Calcd for $C_{18}H_{14}BrNS$: C, 60.68; H, 3.96; N, 3.93. Found: C, 60.28; H, 3.86; N, 4.25. Compound **3e**: Yield 40%; mp 128–130 °C; IR (KBr) ν 2221 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.33–2.42 (m, 2H, CH_2), 2.54 (s, 3H, SCH_3), 3.08 (t, J = 8.2 Hz, 2H, CH_2), 6.03–6.12 (m, 1H, CH), 6.31–6.36 (m, 1H, CH), 6.99 (s, 1H, ArH), 7.24 (d, J = 8.8 Hz, 2H, ArH), 7.48 (d, J = 8.8 Hz, 2H, ArH); MS (FAB) 312, 314 (M^++1), 311, 313 (M^+) Anal. Calcd for $C_{18}H_{14}ClNS$: C, 69.33; H, 4.53; N, 4.49. Found: C, 69.29; H, 4.66; N, 4.20. Compound **3f**: Yield 41%; mp 104–106 °C; IR (KBr) ν 2219 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.33–2.42 (m, 2H, CH_2), 2.54 (s, 3H, SCH_3), 3.08 (t, J = 8.1 Hz, 2H, CH_2), 6.03–6.13 (m, 1H, CH), 6.31–6.36 (m, 1H, CH), 6.98 (s, 1H, ArH), 7.09–7.19 (m, 2H, ArH), 7.56–7.61 (m, 2H, ArH); MS (FAB) 296 (M^++1). Anal. Calcd for $C_{18}H_{14}FNS$: C, 73.19; H, 4.78; N, 4.74. Found: C, 72.86; H, 4.70; N, 4.85. Compound **3g**: Yield 38%; mp 84–86 °C; IR (KBr) ν 2212 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 2.33–2.43 (m, 2H, CH_2), 2.55 (s, 3H, SCH_3), 3.07 (t, J = 8.2 Hz, 2H, CH_2), 6.11–6.16 (m, 1H, CH), 6.72–6.73 (m, 1H, CH), 7.08–7.13 (m, 2H, ArH), 7.14 (s, 1H, ArH), 7.41–7.44 (m, 1H, ArH); MS (FAB) 284 (M^++1). Anal. Calcd for $C_{16}H_{13}NS_2$: C, 67.81; H, 4.62; N, 4.94. Found: C, 67.74; H, 5.00; N, 4.77. Compound **3h**: Yield 52%; mp 138–140 °C; IR (KBr) ν 2210 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.59–1.60 (m, 2H, CH_2), 1.73–1.84 (m, 4H, CH_2), 2.29–2.39 (m, 2H, CH_2), 3.05 (t, J = 8.3 Hz, 2H, CH_2), 3.11–3.16 (m, 4H, NCH_2), 5.92–6.01 (m, 1H, CH), 6.28–6.32 (m, 1H, CH), 6.68 (s, 1H, ArH), 7.17 (d, J = 8.4 Hz, 2H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH); MS (FAB) 393, 395 (M^++1), 392, 394 (M^+) Anal. Calcd for $C_{22}H_{21}BrN_2$: C, 67.18; H, 5.38; N, 7.12. Found: C, 67.33; H, 5.32; N, 6.70. Compound **3i**: Yield 51%; mp 132–134 °C; IR (KBr) ν 2216 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.56–1.61 (m, 2H, CH_2), 1.75–1.78 (m, 4H, CH_2), 2.29–2.39 (m, 2H, CH_2), 3.05 (t, J = 8.3 Hz, 2H, CH_2), 3.11–3.16 (m, 4H, NCH_2), 5.94–6.01 (m, 1H, CH), 6.28–6.33 (m, 1H, CH), 6.68 (s, 1H, ArH), 7.23 (d, J = 8.3 Hz, 2H, ArH), 7.40 (d, J = 8.3 Hz, 2H, ArH); MS (FAB) 349, 351 (M^++1), 348, 350 (M^+) Anal. Calcd for $C_{22}H_{21}ClN_2$: C, 75.74; H, 6.07; N, 8.03. Found: C, 75.51; H, 6.37; N, 7.94. Compound **3j**: Yield 48%; mp 102–104 °C; IR (KBr) ν 2215 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.58–1.60 (m, 2H, CH_2), 1.76–1.78 (m, 4H, CH_2), 2.28–2.38 (m, 2H, CH_2), 3.04 (t, J = 8.3 Hz, 2H, CH_2), 3.10–3.15 (m, 4H, NCH_2), 3.86 (s, 3H, OCH_3), 5.90–5.99 (m, 1H, CH), 6.37–6.42 (m, 1H, CH), 6.71 (s, 1H, ArH), 6.96 (d, J = 8.4 Hz, 2H, ArH), 7.23 (d, J = 8.4 Hz, 2H, ArH); MS (FAB) 345 (M^++1). Anal. Calcd for $C_{23}H_{24}N_2O$: C, 80.20; H, 7.02; N, 8.13. Found: C, 80.00; H, 7.39; N, 8.04. Compound **3k**: Yield 50%; mp 134–136 °C; IR (KBr) ν 2216 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.56–1.64 (m, 2H, CH_2), 1.73–1.84 (m, 4H, CH_2), 2.33–2.39 (m, 2H, CH_2), 3.04 (t, J = 8.2 Hz, 2H, CH_2), 3.11–3.16 (m, 4H, NCH_2), 5.98–6.07 (m, 1H, CH), 6.64–6.69 (m, 1H, CH), 6.84 (s, 1H, ArH), 7.05–7.13 (m, 2H, ArH), 7.37–7.40 (m, 1H, ArH); MS (FAB) 321 (M^++1). Anal. Calcd for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74. Found: C, 75.39; H, 6.42; N, 8.64.