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Carbanion induced, base-catalyzed, synthesis of highly functionalized 8-aryl-3,4-dihydro-2(1*H*)-naphthalenones from 2*H*-pyran-2-ones†

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Abstract—A general and efficient synthesis of 8-aryl-5-methoxycarbonyl-6-methylsulfanyl-3,4-dihydro-2(1*H*)-naphthalenones **4a–i** and 8-aryl-5-cyano-6-*sec*-amino-3,4-dihydro-2(1*H*)-naphthalenones **4l–r** has been delineated from the acid hydrolysis of 8-aryl-5-methoxycarbonyl-6-methylsulfanyl-3,4-dihydro-2(1*H*)-naphthalenone-(2,2-dimethyltrimethylene)ketals **3a–i** and 8-aryl-5-cyano-6-*sec*-amino-3,4-dihydro-2(1*H*)-naphthalenone-(2,2-dimethyltrimethylene) ketals **3l–r**, obtained from the reaction of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl-2*H*-pyran-2-ones **1a–i** and 3-cyano-6-aryl-4-*sec*-amino-2*H*-pyran-2-ones **1l–r** with 1,4-cyclohexanedione mono-(2,2-dimethyltrimethylene)ketal **2**.

3,4-Dihydro-2(1*H*)-naphthalenone being an integral part of many natural products such as adrenocorticoids and progestins has been used as an important precursor for the synthesis of a wide range of compounds including steroids,[1] heterocycles[2] and pharmaceuticals.[3] 3,4-Dihydro-2(1*H*)-naphthalenone is quite expensive[4] compared to 3,4-dihydro-1(2*H*)-naphthalenone because of its multistep and difficult synthesis, and this leads to the need to develop an efficient and economical short synthesis of polyfunctionalized 2-naphthalenones.

Among various approaches known for the synthesis of 3,4-dihydro-2(1*H*)-naphthalenone,[5,6] reductive transformation of suitably functionalized 2-methoxynaphthalene derivatives is most common. These substrates have been synthesized[7,8] by a Friedel–Crafts reaction of the appropriate arylacetyl chloride with ethylene in poor yields. The 1-alkyl and 1-aryl derivatives of 2(1*H*)-naphthalenone have been obtained[9] by hydroboration of 1-alkyl or 1-aryl-3,4-dihydronaphthalene followed by chromic acid oxidation. Pd(II)-catalyzed hydrolysis of dioxolane acetal/ketal of 2(1*H*)-naphthalenone[10] in moist acetonitrile or acetone yielded 1-aryl-3,4-dihydro-2(1*H*)-naphthalenone. It was also synthesized[11] by 1,2-carbonyl transposition of 1-naphthalenone as well as oxidation[12] of 6-methoxy-1-methyl-3,4-dihydronaphthalene with peroxyacetimidic acid as the preferred oxidant and also by ion-exchange resin mediated hydrolytic cleavage of 1-aryl-1,2-epoxides.[13] Rh(II) acetate-catalyzed cyclization of α-diazoketones[14] and radical mediated cyclization[15] of δ-aryl-β-dicarbonyl compounds also yielded 3,4-dihydro-2(1*H*)-naphthalenones. It has also been obtained[16] either by acid hydrolysis of epoxy amides derived from 1-naphthalenone or by reductive cyclization of 5-(4-methoxyphenyl)-2-hexanone[17] followed by dehydrogenation and subsequent reduction. Recently, compounds with this ring system have been synthesized[18] either through carbopalladation of aryl nitriles or $InCl_3$ promoted rearrangement[19] of epoxides, derived from 3,4-dihydronaphthalene. A concise synthesis of 1-substituted-2(1*H*)-naphthalenones[20] has been recently reported by selective dehydration of 1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene.

Our approach to the synthesis of 3,4-dihydro-2(1*H*)-naphthalenones **4** is based on carbanion induced reaction of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl--2*H*-pyran-2-ones **1a-k** and 6-aryl-3-cyano-4-*sec*-amino-2*H*-pyran-2-ones **1l–r** with 1,4-cyclohexanedione mono-(2,2-dimethyl trimethylene)ketal **2**. These reactions yield 8-aryl-5-methoxycarbonyl-6-methylsulfanyl-3,4-dihydro-2(1*H*)-naphthalenone-(2,2-dimethyltrimethylene)-ketals **3a–k** and the corresponding nitriles **3l–r**. The ketals **3** on acid hydrolysis with formic acid yielded exclusively **4a–i** and **4l–r** (Scheme 1). This process

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provides a simple general route for the synthesis of diverse 8-aryl-3,4-dihydro-2(1*H*)-naphthalenones with the possibility of introducing different substituents at positions 5, 6 and 8.

The mechanism of this reaction can be rationalized by initial attack of the carbanion generated from **2** by alkali in DMF at position 6 of the pyran ring of **1**. The reaction proceeds with ring opening followed by decarboxylation and condensation–cyclization involving the keto functionality and C-3 of the pyran ring leading to **3**. Compounds **3** might also arise through inverse electron demand Diels–Alder cycloaddition of the enolate to the 2*H*-pyran-2-one **1** but this mechanism is less likely on the basis of previous precedent[21] and the mild reaction conditions used. The structure of one of the ketals, **3i** was confirmed by X-ray diffraction. The acid-hydrolysis of ketals **3** with formic acid (98%) at room temperature provided the title compounds **4** in moderate to good yields.[22]

Our initial attempts to prepare 8-aryl-3,4-dihydro-2(1*H*)-naphthalenone **4** in a one-pot process from the reaction of **1** and 1,4-cyclohexanedione in an equimolar ratio failed and starting materials were recovered.

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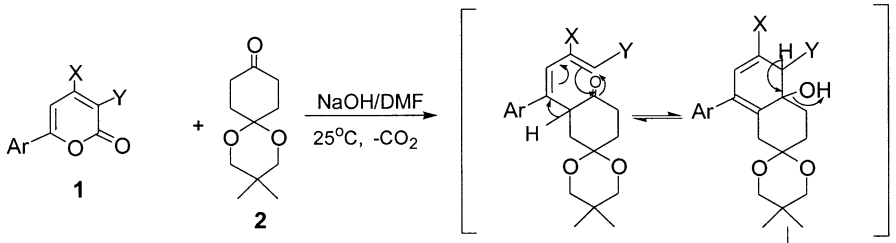
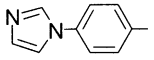
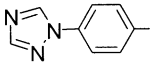
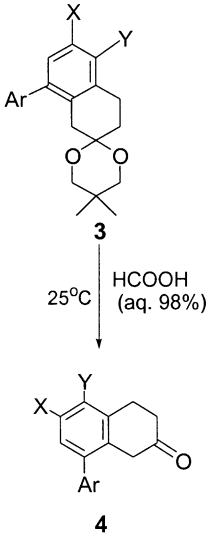


1,3,4	Ar	X	Y	Yield (%) 3	4
a	4-FC_6H_4	SMe	COOMe	45	68
b	4-ClC_6H_4	SMe	COOMe	49	80
c	4-$CH_3C_6H_4$	SMe	COOMe	52	82
d	4-$OCH_3C_6H_4$	SMe	COOMe	54	75
e	3-Cl,4-FC_6H_3	SMe	COOMe	48	70
f	3.4-$Cl_2C_6H_3$	SMe	COOMe	44	68
g	2-thienyl	SMe	COOMe	54	85
h		SMe	COOMe	58	65
i		SMe	COOMe	56	68
j	2-furyl	SMe	COOMe	48	-
k	4-pyridyl	SMe	COOMe	51	-
l	C_6H_5		CN	60	70
m	4-$O_2NC_6H_4$		CN	55	72
n	1-naphthyl	$(CH_3)_2N$–	CN	62	82
o	1-naphthyl		CN	57	85
p	1-naphthyl		CN	61	84
q	1-naphthyl		CN	55	85
r	2-naphthyl		CN	60	86



Scheme 1.

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22. Typical procedure for **3r**: A mixture of 3-cyano-4-(pyrrolidin-1-yl)-6-(2-naphthyl)-2*H*-pyran-2-one, **1r** (0.5 g, 1.58 mmol) and 1,4-cyclohexanedione mono-(2,2-dimethyl trimethylene)ketal (0.30 g, 1.58 mmol) and powdered KOH (0.22 g, 3.95 mmol) in dry DMF (10 ml) was stirred at room temperature for 40 h. After completion of the reaction, the mixture was poured into ice water with vigorous stirring and neutralized with 10% HCl. The crude product obtained was filtered, washed with water and finally purified on a silica gel column using $CHCl_3$:hexane (1:1) as eluent. The white crystalline solid obtained was characterized spectroscopically, yield 60%; mp 194°C; IR (KBr) ν 2195 cm^{-1} (CN); MS (m/z) 452 (M^+); NMR ($CDCl_3$) δ 0.85 (s, 3H, CH_3); 0.93 (s, 3H, CH_3); 1.94–2.0 (m, 4H, $2CH_2$); 2.17–2.23 (t, $J=6.8$ Hz, 2H, CH_2); 2.76 (s, 2H, CH_2); 3.04–3.08 (t, $J=6.8$ Hz, 2H, CH_2); 3.33 (d, $J=11.4$ Hz, 2H, CH_2); 3.36–3.61 (m, 6H, $3CH_2$); 6.52 (s, 1H, ArH); 7.37–7.56 (m, 3H, naphthyl); 7.73 (s, 1H, naphthyl); 7.82–7.89 (m, 3H, naphthyl).
Typical procedure for **4r**: A solution of **3r** (0.19 g, 0.4 mmol) in 98% aq. formic acid (5 ml) was stirred at room temperature for 12 h. At the end of the reaction, formic acid was distilled off under reduced pressure. The residue thus obtained was washed with water (15 ml) and extracted with chloroform (30 ml). The extract was evaporated under reduced pressure and the crude product obtained was purified on a silica gel column using chloroform as eluent, yield 0.13 g (86%), mp 206°C; IR (KBr) ν 2202 (CN); 1715 cm^{-1} (CO); MS (m/z) 366 (M^+); NMR ($CDCl_3$) δ 1.98–2.05 (m, 4H, $2CH_2$); 2.57 (t, $J=6.7$ Hz, 2H, CH_2); 3.29–3.39 (m, 4H, $2CH_2$); 3.60–3.67 (m, 4H, $2CH_2$); 6.59 (s, 1H, ArH); 7.30–7.35 (m, 2H, naphthyl); 7.50–7.56 (m, 2H, naphthyl); 7.69 (s, 1H, naphthyl); 7.82–7.96 (m, 3H, naphthyl).