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Substituent dependent regioselective synthesis of pyranopyrandiones and 1,2-teraryls from 2*H*-pyran-2-ones☆

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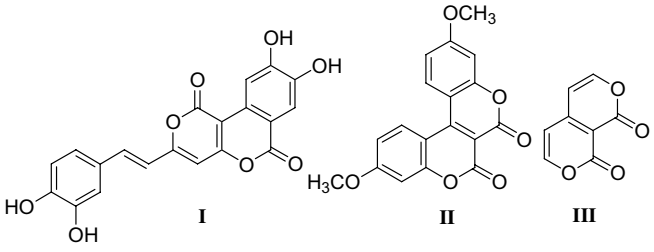
Abstract—The one-pot substituent-directed regioselective synthesis of 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **3** as the major and 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles **4** as the minor products has been delineated through ring transformation of suitably functionalized 2*H*-pyran-2-ones **1** with aryl acetones **2**. Under similar reaction conditions, 6-aryl-4-*sec*-amino-2*H*-pyran-2-ones **5** led, regioselectively, to 3,4-diaryl-2-methyl-6-*sec*-aminobenzonitriles **6**.

A literature survey on the chemistry of pyranopyrandiones and 1,2-teraryls revealed that compounds of both ring systems have been meagerly explored. The basic skeleton of pyranopyrandiones is present as a subunit in various natural and synthetic products, for example, **I** and **II**, of therapeutic importance and display anticancer[1,2] and antibacterial[3] activities. These compounds also exhibit photochemical[4] and luminescence properties.[5]



The natural product **I**, meshimakobnol, has been isolated from the fruit body of *Phellinus linteus* and possesses anticancer activity.[1] The synthetic pyranopyrandione **II** was obtained[3] from the reaction of 3-methoxyphenol and diethyl ethoxymethylenemalonate, albeit in poor yield.

The only structural commonality found in compounds of types **I** and **II** is the benzopyran moiety, but they differ in their site of fusion with the other pyranone ring.

The chemistry of pyrano[3,4-*c*]pyran-4,5-diones is largely unexplored. Except for MO calculations, that is, correlation of delocalization energy, π-bond order and π-charge density of 20 different theoretical pyranopyrandiones including pyrano[3,4-*c*]pyran-4,5-dione[6] **III**, no other additional information is available in the literature. This has inspired us to develop an innovative route for the construction of this class of compounds in order to explore their therapeutic potential.

The wide-ranging applications of 1,2-teraryls as liquid crystals,[7] laser dyes,[8] conducting polymers,[9] textile dye carriers,[10] and dihydroortate dehydrogenase inhibitors[11] have also prompted us to develop a regioselective synthesis of 1,2-teraryls.

Here, we report a one-pot regioselective synthesis of 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **3** and 3,4-diaryl-2-methyl-6-*sec*-aminobenzonitriles **6** via base-catalyzed ring transformation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1** and 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **5** with aryl acetones **2**. The precursors **1** used for the synthesis of pyrano[3,4-*c*]-4,5-diones **3** were prepared[12] via the reaction of aryl

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methyl ketones and methyl 3,3-dimethylthio-2-cyanoacrylate. The 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **5** were obtained[13] by refluxing a mixture of compounds **1** with various *sec*-amines in ethanol for 5 h. The precursor 2*H*-pyran-2-ones **1** are endowed with three electrophilic centres C2, C4 and C6 in which the latter is highly prone to nucleophilic attack due to the extended conjugation and the presence of an electron withdrawing cyano substituent at position 3 of the pyran ring while the C4 electrophilic centre is susceptible to soft nucleophiles. In this reaction, the carbanion formed from the aryl acetone acts as a nucleophile and preferentially attacks at C4 of the pyran ring to form, initially, a substitution product which undergoes cyclization under basic conditions to give pyrano[3,4-*c*]pyran-4,5-diones **3** as the major products. We have been able to isolate other minor compounds, characterized as the 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles **4** resulting from attack of the carbanion generated from the aryl acetone **2** at position C6 of the pyran ring with cyclization followed by ring opening (Scheme 1). The products with high R_f values were characterized as 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles **4** and those with low R_f values were characterized as 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **3**. Finally, their structures were confirmed by spectroscopic studies.

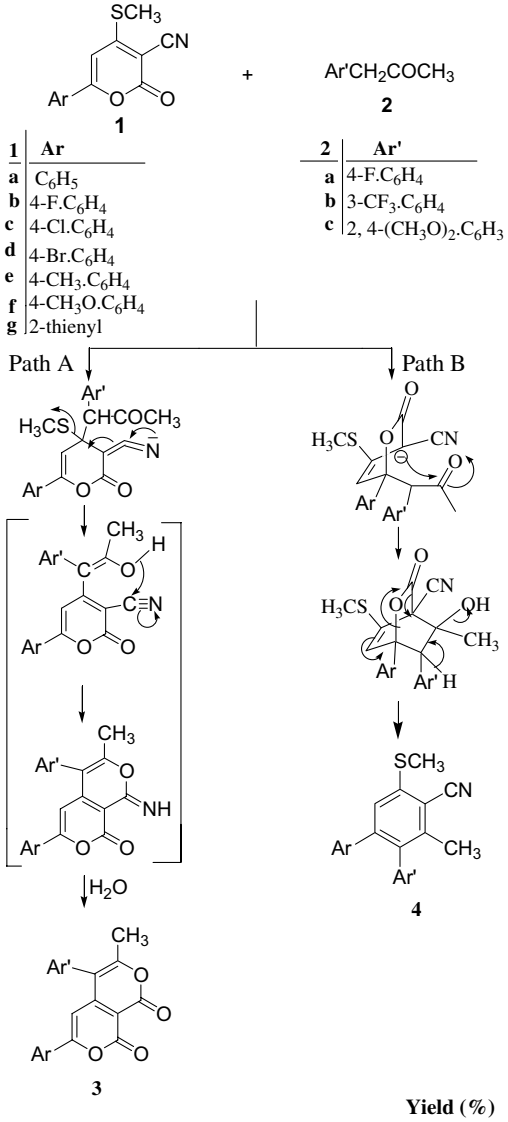
The poor yields and numerous commercial applications of 1,2-teraryls prompted us to develop a regioselective synthesis. The objective was achieved simply by changing the methylsulfanyl substituent, which is a good leaving group, at position 4 of the pyran ring **1** and replacing it with a *sec*-amino group. The substituent changed the electrophilicity of the C4 and C6 positions of the pyran ring resulting in the observed regioselectivity.

Thus, an equimolar mixture of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitrile **5**, aryl acetone **2** and powdered KOH in dry DMF was stirred for 24 h at room temperature and thereafter poured onto ice water with vigorous stirring. Neutralization of the alkaline aqueous solution with 10% HCl provided a precipitate which was filtered, washed with water and finally dried under vacuum. The crude product was purified by silica gel column chromatography (Scheme 2).

The ^{1}H NMR spectrum of **3l** showed two singlets at δ 2.15 and 6.00 for the CH_3 and aromatic methine protons, respectively. The IR spectrum showed two carbonyl peaks at 1707 and 1772 cm^{-1}. In the ^{1}H NMR spectrum of **4l**, three singlets at δ 2.29, 2.60 and 6.71 were attributed to CH_3, SCH_3 and the aromatic methine protons, respectively. The IR spectrum of **4l** showed the presence of a characteristic CN peak at 2211 cm^{-1}.

All the compounds synthesized were characterized by spectroscopic and elemental analyses. Data for representative compounds are included.[14]

A plausible mechanism involved in the formation of products **3** and **4** is depicted in Scheme 1. The first step in the formation of **3** is the attack of the carbanion formed from the aryl acetone in situ at position 4 of



1	Ar
a	C_6H_5
b	4-F.C_6H_4
c	4-Cl.C_6H_4
d	4-Br.C_6H_4
e	4-CH_3.C_6H_4
f	4-CH_3O.C_6H_4
g	2-thienyl

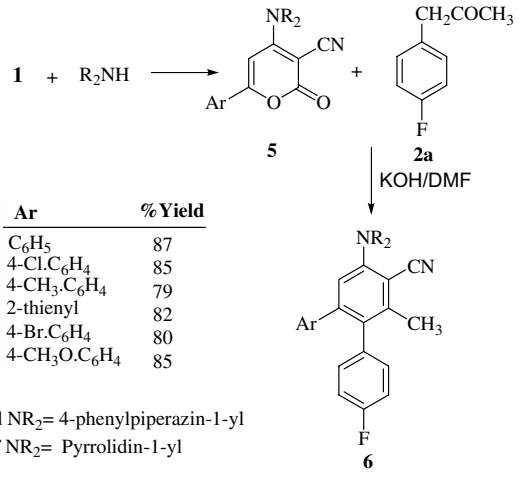
2	Ar'
a	4-F.C_6H_4
b	3-CF_3.C_6H_4
c	2, 4-$(CH_3O)_2$.C_6H_3

3/4	Ar	Ar'	Yield (%) 3	4
a	C_6H_5	4-F.C_6H_4	60	19
b	C_6H_5	3-CF_3.C_6H_4	73	9
c	C_6H_5	2,4-$(CH_3O)_2$.C_6H_3	73	11
d	4-F.C_6H_4	4-F.C_6H_4	70	21
e	4-Cl.C_6H_4	4-F.C_6H_4	73	16
f	4-Cl.C_6H_4	3-CF_3.C_6H_4	64	21
g	4-Br.C_6H_4	3-CF_3.C_6H_4	71	16
h	4-Br.C_6H_4	4-F.C_6H_4	68	18
i	4-CH_3.C_6H_4	4-F.C_6H_4	71	18
j	4-CH_3O.C_6H_4	4-F.C_6H_4	60	21
k	4-CH_3O.C_6H_4	3-CF_3.C_6H_4	69	13
l	2-thienyl	4-F.C_6H_4	75	15

Scheme 1.

the pyran ring with formation of a substitution product as an intermediate, which undergoes cyclization involving the CN group and enolic OH under basic conditions followed by hydrolysis to yield **3** as the major product. The absence of nitrogen in microanalyses was consistent with the assigned structure.

In the case of the formation of **4**, the carbanion attacks at C6 of the pyran ring with cyclization followed by ring



6	Ar	%Yield
a	C_6H_5	87
b	4-Cl.C_6H_4	85
c	4-CH_3.C_6H_4	79
d	2-thienyl	82
e	4-Br.C_6H_4	80
f	4-CH_3O.C_6H_4	85

6a-d NR_2= 4-phenylpiperazin-1-yl
6e, f NR_2= Pyrrolidin-1-yl

Scheme 2.

opening condensation–cyclization involving the CO functionality and C3 of the pyran ring to yield 1,2-teraryls **4** as minor products. Changing the SCH_3 substituent to a *sec*-amino group exclusively yielded 3,4-diaryl-2-methyl-6-*sec*-aminobenzonitriles **6**.

Our procedure provides an easy access to the synthesis of 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **3** in 60–75% yields and 1,2-teraryls **4** in 9–21% yields, in one step, using very simple reagents. A change of substituent from SCH_3 to a *sec*-amino group in **1** exclusively provided amino substituted 1,2-teraryls **6**. The work-up for this reaction is very simple and the synthesis is very economical.

Acknowledgements

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14. (a) General procedure for the synthesis of 1,7-diaryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **3** and 3,4-diaryl-2-methyl-6-methylsulfanylbenzonitriles **4**: A mixture of **1** (1 mmol), aryl acetone **2** (1 mmol) and KOH (84 mg 1.5 mmol) in dry DMF (10 mL) was stirred for 24 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring and then neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and finally purified on a silica gel column using 0.5% and 5% ethyl acetate in hexane as eluent for **4** and **3**, respectively. (**3l**) Yield 75%; mp >250 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.15 (s, 3H, CH_3), 6.0 (s, 1H, ArH), 7.06–7.13 (m, 1H, ArH), 7.20–7.26 (m, 4H, ArH), 7.44–7.46 (m, 1H, ArH), 7.54–7.62 (m, 1H, ArH); IR (KBr) 1707 and 1772 cm^{-1} (CO); MS *m*/*z* 355 (M^++1); $C_{19}H_{11}FO_4S$ (354.04) Calcd: C, 64.40; H, 3.13. Found: C, 64.46; H, 3.17. (**4l**) Yield 15%; mp 150–152 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.29 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 6.71 (s, 1H, ArH), 6.84–6.88 (m, 1H, ArH), 7.03–7.07 (m, 4H, ArH), 7.21–7.24 (m, 1H, ArH), 7.33 (s, 1H, ArH); IR (KBr) 2211 cm^{-1} (CN); MS *m*/*z* 339 (M^+); $C_{19}H_{14}FNS_2$ (339.06) Calcd: C, 67.23; H, 4.16; N, 4.13. Found: C, 67.26; H, 4.19; N, 4.10. (b) General procedure for the synthesis of 3,4-diaryl-2-methyl-6-*sec*-aminobenzonitriles **6**: A mixture of **5** (1 mmol), aryl acetone **2** (1 mmol) and KOH (84 mg, 1.5 mmol) in dry DMF (10 mL) was stirred for 24 h at room temperature. The reaction mixture was poured onto crushed ice with vigorous stirring and neutralized with 10% HCl. The precipitate obtained was filtered, washed with water and finally purified on a silica gel column using 0.5% ethyl acetate in hexane as eluent. **6e**: Yield 80%; mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.01 (s, 4H, CH_2), 2.29 (s, 3H, CH_3), 3.64 (br s, 4H, NCH_2), 6.49 (s, 1H, ArH), 6.85–7.00 (m, 6H, ArH), 7.27 (d, J = 7.9 Hz, 2H, ArH); IR (KBr) 2201 cm^{-1} (CN); MS *m*/*z* 435 (M^++1); $C_{24}H_{20}BrFN_2$ (434.08) Calcd: C, 66.22; H, 4.63; N, 6.43. Found: C, 66.26; H, 4.59; N, 6.50.