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A substituent-controlled general approach to access arylated pyran-2-ones and pyrano[3,4-*c*]pyran-1,8-diones☆

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Abstract—2*H*-Pyran-2-ones are useful precursors for the synthesis of various aromatic and heterocyclic compounds. In this Letter, we describe substituent-controlled direct access to functionalized 4-(2-oxo-1,2-diarylethyl)-5,6-diaryl-pyran-2-ones by stirring a mixture of 3-cyano-5,6-diaryl-2*H*-pyran-2-ones and functionalized deoxybenzoins through an unusual decyanation reaction. Under similar reaction conditions, the reactions of 3-carbomethoxy-5,6-diaryl-2*H*-pyran-2-ones with either substituted acetophenones or deoxybenzoins led to the synthesis of pyrano[3,4-*c*]pyran-1,8-diones in excellent yields.

Functionalized pyran-2-ones and their fused pyranopyrandione scaffolds are key structural motifs found in a large number of biologically important natural products.[1] In addition, 2*H*-pyran-2-ones are useful synthetic intermediates for the synthesis of a variety of aromatic hydrocarbons and heterocyclic compounds.[2] Various natural products having pyran-2-one ring systems have displayed interesting biological activities.[3,4] Such an example is the natural product meshimakobnol (**I**) which has been isolated from the fruit body of *Phellinus linteus* and possesses anticancer activity (Fig. 1).[3] Radicinin (**II**) has been isolated from *Stemphylium radicinum* and showed inhibitory properties against the growth of several gram-positive bacteria.[5]

Further, interesting photochemical,[6] fluorescence and luminescence properties,[7] and molecular orbital calculations, correlation of delocalization energies, π-bond order and π-charge density of different theoretical pyranopyrandiones[8] have been reported for similar molecular scaffolds. Recently, Knaus and co-workers designed and synthesized a series of arylated pyran-2-ones and evaluated them for cyclooxygenase-2 (COX-2) inhibitory activity.[9] One of the compounds, 3,4,6-triphenyl-2-pyrone **III**, was found to be a potent and selective COX-2 inhibitor with an IC_{50} of 0.02 μM.

Despite the plethora of synthetic processes[10] for the synthesis of 2*H*-pyran-2-ones, less attention has been paid

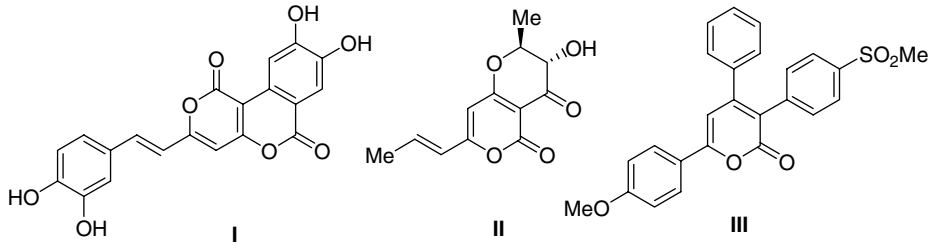

Figure 1. Structures of natural and synthetic 2*H*-pyran-2-ones.

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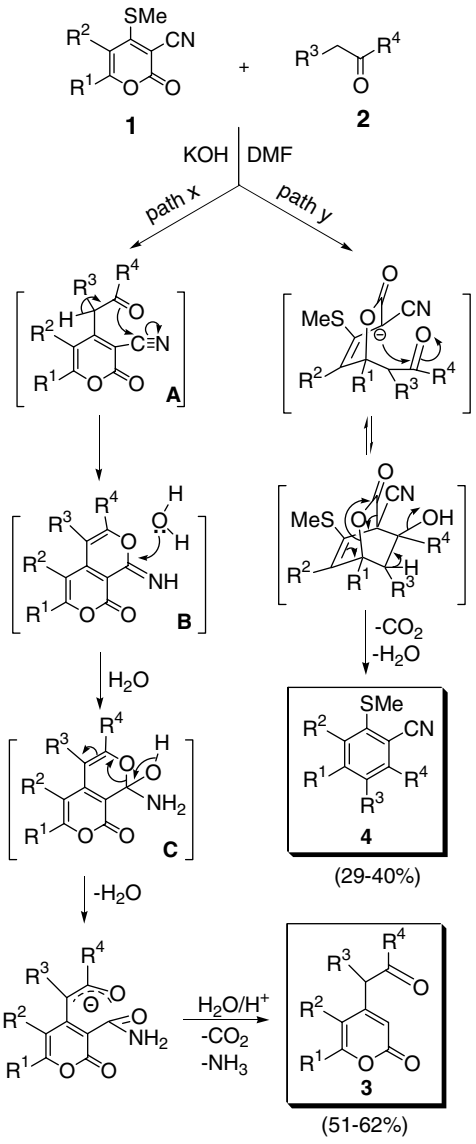
to the synthesis of fused systems such as pyrano[3,4-*c*]-pyran-4,5-diones. Herein, we report an efficient and convenient procedure for the synthesis of 4-(2-oxo-1,2-diarylethyl)-5,6-diaryl-pyran-2-ones and pyrano[3,4-*c*]-pyran-1,8-diones through the reaction of either 3-cyano-5,6-diaryl-2*H*-pyran-2-ones or 3-carbomethoxy-5,6-diaryl-2*H*-pyran-2-ones with functionalized deoxybenzoins or substituted acetophenones, in a single-step, under mild reaction conditions.

During our recent studies[11] on the chemistry of 2*H*-pyran-2-ones, we observed that the reaction of 5,6-diaryl-2*H*-pyran-2-ones with substituted deoxybenzoins to afford 1,2,3,4-tetraarylbenzenes was highly dependent on the reaction conditions and the bases employed. In the presence of KOH in pyridine, the reaction of lactone **1** with **2** furnished exclusively 1,2,3,4-tetraarylbenzenes **4**, but the same reaction in the presence of KOH in dry DMF at room temperature afforded the desired compounds in low yields (29–40%) (Scheme 1).

To examine the course of the reaction, we prepared a series of compounds by reacting lactone **1** with substituted methylene carbonyl compounds **2** in the presence of KOH in dry DMF. The precursor 2*H*-pyran-2-ones **1** were prepared by reaction of methyl 2-cyano-3,3-di(methylsulfanyl)acrylate[12] with substituted deoxybenzoins under alkaline conditions in high yields. Various deoxybenzoins were prepared by heating a mixture of functionalized phenyl acetic acid and substituted benzene in polyphosphoric acid as described previously.[13] Thus, a mixture of 3-cyano-5,6-diaryl-2*H*-pyran-2-one **1** and substituted deoxybenzoin was stirred in the presence of KOH in dry DMF at room temperature for 5–8 h (Scheme 1). The reaction was monitored by TLC, which showed two intense blue spots with a large difference in R_f values. A non-polar compound was isolated by neutral alumina column chromatography using 10% chloroform in hexane as eluent and characterized as 1,2,3,4-tetraarylbenzene **4**. The other polar compound **3** was isolated using 1% methanol in chloroform as eluent. The ^{1}H NMR spectrum of **3a** showed two singlets at δ 5.83 and 5.99 ppm for the methine CH and the pyran ring proton, and a multiplet at δ 6.70–7.55 ppm for the twenty aromatic protons. The absence of a signal for SMe at around 1.8–2.5 ppm revealed that the carbanion generated by deoxybenzoin attacked at position 4 of lactone **1**. The absence of an absorbance for CN around 2190–2230 cm^{-1} in the IR spectrum and a molecular ion peak at *m*/*z* 442 was in agreement with the proposed structure of compound **3a** as 4-(2-oxo-1,2-diphenylethyl)-5,6-diphenyl-pyran-2-one. The structure of compound **3e** was unambiguously confirmed by single crystal X-ray analysis[14] as shown in Figure 2. It is interesting to observe removal of the nitrile functionality via imine intermediate **B** followed by in situ hydrolysis. All the compounds synthesized were characterized by spectroscopic analyses.[15]

A plausible mechanism for the formation of 4-(2-oxo-1,2-diarylethyl)-5,6-diaryl-pyran-2-ones **3a**–**f** and 1,2,3,4-tetraarylbenzenes **4a**–**f** is depicted in Scheme 1. The formation of **3a**–**f** may proceed via path x through an attack of the carbanion generated from **2** at position 4 with the elimination of methyl mercaptan followed by intramolecular cyclization involving the carbonyl group and the nitrile functionality of the 2*H*-pyran-2-one **1** to form intermediate **A**. This intermediate on alkaline hydrolysis furnishes 4-(2-oxo-1,2-diarylethyl)-5,6-diaryl-pyran-2-ones **3a**–**f** in 51–62% yields.

Similarly, the transformation of 3-cyano-5,6-diaryl-2*H*-pyran-2-ones **1** into 1,2,3,4-tetraarylbenzenes **4a**–**f** via path y is possibly initiated by the attack of the carbanion generated from deoxybenzoin **2** at C6 of lactone **1**,



	R^1	R^2	R^3	R^4	Yield (%)	
					3	4
a	C_6H_5	C_6H_5	C_6H_5	C_6H_5	56	31
b	C_6H_5	C_6H_5	C_6H_5	4-ClC_6H_4	60	30
c	C_6H_5	C_6H_5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	62	29
d	4-$MeOC_6H_4$	4-$MeOC_6H_4$	C_6H_5	4-ClC_6H_4	57	40
e	4-$MeOC_6H_4$	4-$MeOC_6H_4$	C_6H_5	C_6H_5	51	38
f	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	4-$MeOC_6H_4$	59	32

Scheme 1.

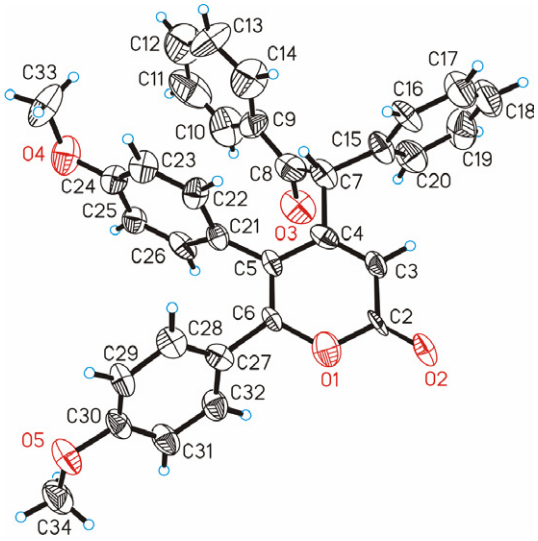


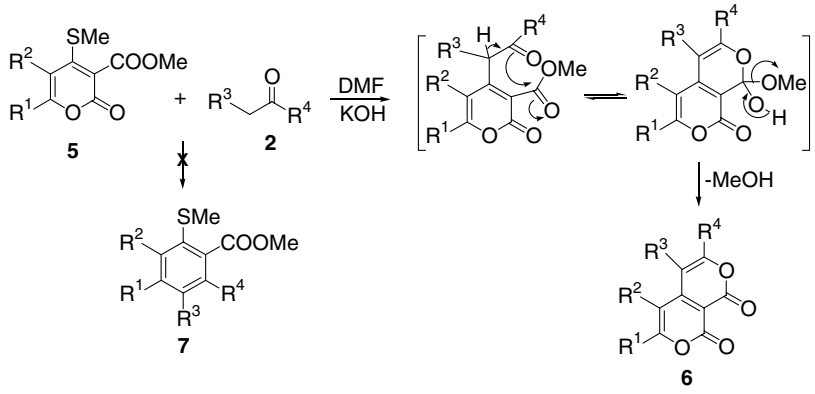
Figure 2. ORTEP diagram of 5,6-bis-(4-methoxyphenyl)-4-(2-oxo-1,2-diphenylethyl)pyran-2-one **3e** with arbitrary numbering.

followed by intramolecular cyclization involving the carbonyl functionality of **2** and C3 of the pyranone ring and elimination of carbon dioxide and water to yield **4a**–**f**.

To check the reaction course with other electron withdrawing substituents, we investigated the reaction of 3-carbomethoxy-5,6-diaryl-2*H*-pyran-2-ones[11a] **5** with ketones **2** in the presence of KOH in dry DMF at room temperature. 2*H*-Pyran-2-ones[11b] **5** were prepared by reaction of methyl 2-carbomethoxy-3,3-di(methylsulfanyl)acrylate[12] with substituted acetophenones, propiophenones or deoxybenzoins under alkaline conditions in high yields. Thus, a mixture of 2*H*-pyran-2-one **5** and ketone **2** in the presence of powdered KOH in DMF was stirred at room temperature for 8–11 h (Scheme 2). The reaction was monitored by TLC and on completion was poured into ice water and neutralized with dilute HCl. The crude product thus obtained was purified on a neutral alumina column using 1% methanol in chloroform as eluent. In the ^{1}H NMR spectrum of **6a**, two singlets at δ 3.68 and 3.73 ppm were attributed to two methoxy group protons. Two doublets at δ 6.33 and 6.53 ppm and three multiplets at δ 6.57–6.66, 6.80–6.94 and 6.97–7.22 ppm were due to the aromatic protons. The absence of resonances for SCH_3 and $COOCH_3$ protons and the presence of two lactone-carbonyl peaks at 1710 and 1782 cm^{-1} in the IR spectrum confirmed the structure of **6a** as 3,4-bis-(4-methoxyphenyl)-5,6-diphenyl-pyrano[3,4-*c*]pyran-1,8-dione. We isolated exclusively a single product, 3,4-bis-(4-methoxyphenyl)-5,6-diphenyl-pyrano[3,4-*c*]pyran-1,8-dione **6a**, from the reaction mixture and no formation of 1,2,3,4-tetraaryl benzene **7** was observed. The structure of one of the compounds, **6b** was unambiguously confirmed by single crystal X-ray analysis[16] as shown in Figure 3. All the compounds synthesized were characterized by spectroscopic analyses.[17]

The transformation of substituted 3-carbomethoxy-5,6-diaryl-2*H*-pyran-2-ones **5** into pyrano[3,4-*c*]pyran-1,8-dione derivatives **6a**–**f** is possibly initiated by the attack of the carbanion of **2** at C-4 of lactone **5**, followed by intramolecular cyclization involving the carbonyl functionality of the ketone and COOMe of the pyran-2-one and elimination of MeOH to furnish **6a**–**f** in 64–84% yields.

The carbomethoxy group at position 3 of 2*H*-pyran-2-one **5** dictated the reaction course towards the formation of pyrano[3,4-*c*]pyran-1,8-diones. In contrast, the cyano group at position 3 of 2*H*-pyran-2-one **1** favoured the



Entry	R^1	R^2	R^3	R^4	Reaction time (h)	Yield* (%)
6a	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	C$_6$H$_5$	C$_6$H$_5$	10	66
6b	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	9	64
6c	C$_6$H$_5$	Me	C$_6$H$_5$	*i*-propyl	8	84
6d	4-MeC$_6$H$_4$	H	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	8	74
6e	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	H	3,4-CH$_2$O$_2$C$_6$H$_3$	9	65
6f	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	H	4-MeOC$_6$H$_4$	11	68

* Yields are calculated with respect to consumption of 2*H*-pyran-2-one.

Scheme 2.

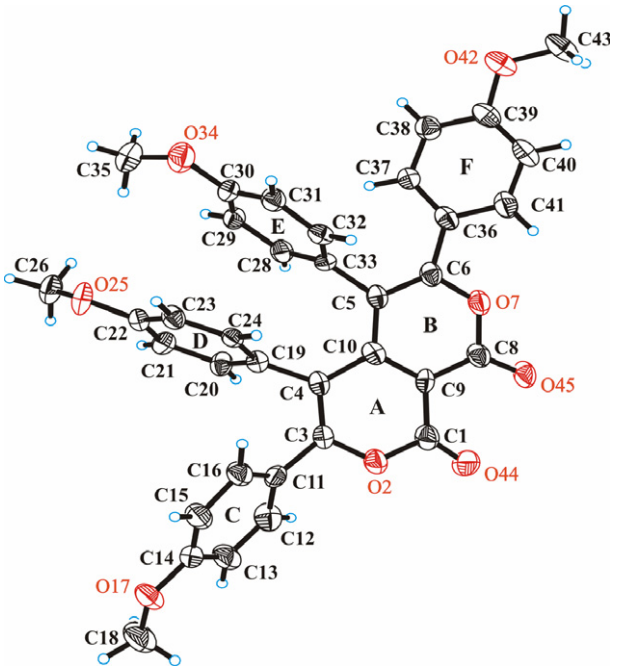


Figure 3. ORTEP diagram of 3,4,5,6-tetrakis-(4-methoxyphenyl)-pyrano[3,4-*c*]pyran-1,8-dione **6b** with arbitrary numbering.

synthesis of 4-(2-oxo-1,2-diarylethyl-5,6-diaryl-pyran-2-ones **3** as the major products.

In summary, we have developed a new method for the synthesis of highly functionalized 4-(2-oxo-1,2-diarylethyl)-5,6-diaryl-pyran-2-ones, pyrano[3,4-*c*]pyran-1,8-diones and 1,2,3,4-tetraarylbenzenes through carbanion-induced ring transformation of functionalized 2*H*-pyran-2-ones in moderate to good yields. We observed that the formation of arylated 2*H*-pyran-2-one and pyrano[3,4-*c*]pyran-1,8-dione could be controlled by changing the nature of the electron withdrawing groups at position 3 of the starting 2*H*-pyran-2-ones. This protocol offers the flexibility of substituent variation in the molecular architecture of the pyran-2-one scaffolds. In addition, the decyanation step during the formation of compound **3** via an imine intermediate is unusual and has not been reported prior to this study.

Acknowledgements

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14. *Crystal data of compound* **3e**: CCDC No. 661420 contains the supplementary crystallographic data; $C_{33}H_{26}O_5$, $M = 502.54$, triclinic, space group $P(-1)$, $a = 9.064(2)$ $b = 12.029(2)$, $c = 12.791(2)$ Å, $\alpha = 83.260(10)$, $\beta = 88.420(10)$, $\gamma = 69.850(10)°$, $V = 1300.1(4)$ Å^3, $T = 293$ K, $Z = 2$, $\mu(\text{MoK}\alpha) = 0.086$ mm^{-1}, $F(000) = 528$, rectangular plate, colourless, $0.25 \times 0.225 \times 0.15$ mm, 5527 reflections measured ($R_{\text{int}} = 0.0539$), 4578 unique, $wR_2 = 0.4652$ for all data, conventional $R = 0.1290$ [$(\Delta/\sigma)_{\max} = 000$)] on F-values of 1078 reflections with $I > 2\sigma(I)$, $S = 1.018$ for all data and 345 parameters. Unit cell determination and intensity data collection ($2\theta = 50°$) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA; 1996], SHELXTL-NT [Bruker AXS: Madison, Wisconsin, USA 1997].
15. *General procedure for the synthesis of compounds* **3a–f** and **4a–f**: A mixture of 4-methylsulfanyl-2-oxo-5,6-diaryl-2*H*-

pyran-3-carbonitrile **1** (1 mmol), deoxybenzoin **2** (1.2 mmol) and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 5–8 h. On completion, the reaction mixture was poured into ice water with vigorous stirring and finally neutralized with dilute HCl. The solid thus obtained was filtered and purified on a neutral alumina column using 10% chloroform in hexane as eluent; *Compound* **3a**: white solid; mp >250 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.83 (s, 1H, CH), 5.99 (s, 1H, CH), 6.70–7.55 (m, 20H, ArH); ^{13}CNMR (50.0 MHz, $CDCl_3$) 56.66, 109.49, 118.45, 119.91, 126.61, 127.31, 128.01, 128.34, 128.77, 129.40, 129.82, 131.74, 132.10, 132.49, 133.51, 134.92, 135.89, 136.33, 146.20, 153.47, 162.36, 197.07; IR (KBr) 1635 cm^{-1} (CO); MS (FAB) 442 (M^+); *Compound* **4a**: mp: 216–218 °C.[11a]

16. *The crystal data of compound* **6b**: CCDC No. 661421 contains the supplementary crystallographic data; $C_{36}H_{28}O_8$, $M = 588.58$, triclinic, $P\bar{1}$, $a = 13.355(1)$ Å, $b = 14.968(2)$ Å, $c = 16.467(2)$ Å, $\alpha = 100.45(1)$, $\beta = 91.600(1)$, $\gamma = 115.15(1)°$, $V = 2892.9(6)$ Å^3, $Z = 4$, $D_c = 1.351$ g cm^{-3}, μ (MoKα) = 0.096 mm^{-1}, $F(000) = 1232$, rectangular block, colourless, size = 0.25 × 0.3 × 0.125 mm, 11509 reflections measured ($R_{int} = 0.0413$), 10082 unique, $wR_2 = 0.41$ for all data, conventional $R = 0.041$ [$(\Delta/\sigma)_{max} = 000$)] on F-values of 4330 reflections with $I > 2\sigma(I)$, $S = 1.228$ for all data and 802 parameters. Unit cell determination and intensity data collection ($2\theta = 50°$) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA; 1996], SHELXTL-NT [Bruker AXS: Madison, Wisconsin, USA; 1997].
17. *General procedure for the synthesis of* **6**: A mixture of 2*H*-pyran-2-one **5** (1 mmol) and substituted ketone **2** (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 8–11 h. On completion, the reaction mixture was poured into ice water with vigorous stirring and finally neutralized with dilute HCl. The solid thus obtained was filtered and purified on a neutral alumina column using 1% methanol in chloroform as eluent; *Compound* **6a**: yellow solid; mp 178–180 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 6.33 (d, $J = 8.6$ Hz, 2H, ArH), 6.53 (d, $J = 8.6$ Hz, 2H, ArH), 6.57–6.66 (m, 4H, ArH), 6.80–6.94 (m, 3H, ArH), 6.97–7.22 (m, 7H, ArH); IR (KBr) 1710 (CO), 1782 cm^{-1} (CO); MS (FAB) 529 (M^++1); HRMS calcd for $C_{34}H_{24}O_6$: 528.1573. Found: 528.1573.