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An efficient synthesis of 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones from a suitably functionalized 2*H*-pyran-2-one☆

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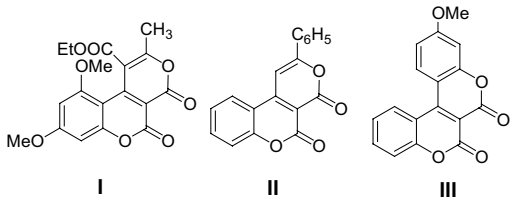
Abstract—An efficient synthesis of ethyl 7-aryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-dione-1-carboxylate **5**, and ethyl 6-aryl-3-cyano-2*H*-pyran-2-one-4-acetate **6** has been delineated by reaction of suitably functionalized 2*H*-pyran-2-ones **1** with ethyl acetoacetate **2**.

An extensive computerized literature survey on the chemistry of pyrano[3,4-*c*]-4,5-diones revealed that this type of compound had not been reported earlier, except for one paper describing MO calculations, correlation of delocalization energy, π-bond order, and π-charge density of theoretical pyranopyrandiones.[1] Several compounds of the type **I**–**III**, are known in the literature in which the pyrano[3,4-*c*]pyran-4,5-dione ring system is a part of their molecular structure.[2–4] These compounds display antibacterial and antifungal activities.[2]



I **II** **III**

Ethyl 7,10-dimethoxy-2-methyl-4*H*,5*H*-benzopyrano[3,4-*c*]pyran-4,5-dione-1-carboxylate **I** has been prepared[2] by Michael addition–cyclization of a suitably functionalized coumarin while 2-phenyl 4*H*,5*H*-pyrano[3,4-*c*]benzpyran-4,5-dione **II** was synthesized[3] from the reaction of 4-(2,2-dimethyl)-4,6-dioxo-1,3-dioxan-5-ylidene-2,6-diphenyl-4*H*-pyran with a secondary amine. The 3-methoxy-benzpyrano[3,4-*c*]benzpyran-6,7-dione **III** has been obtained from the reaction of 3-methoxyphenol and diethyl ethoxymethylenemalonate. The unexplored chemistry of the 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-dione ring system, inspired us to develop a synthesis of this class of compounds to assess their therapeutic potential.

We report here an efficient one-pot synthesis of 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones from the reaction of suitably functionalized *2H*-pyran-2-ones **1** with ethyl acetoacetate **2**. The precursors, 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles **1**, used for the synthesis of pyrano[3,4-*c*]pyran-4,5-diones were prepared[5] by the reaction of aryl methyl ketones with methyl 3,3-dimethylthio-2-cyanoacrylate. The molecular make-up of the 2*H*-pyran-2-one is such that it may be considered as a cyclic ketene hemithioacetal of which positions 4 and 6 are prone to nucleophilic attack due to extended conjugation and the presence of an electron withdrawing substituent at position 3 of the pyran ring. The high electrophilicity at position 6 compared to position 4 in 2*H*-pyran-2-one **1**, led to the expectation that attack of the carbanion, generated from ethyl acetoacetate would occur at position 6 of the pyran ring with ring opening followed by cyclization involving either $COCH_3$ or $COOC_2H_5$ and C-3 of the pyran ring to yield either **7** or **8**, or both. However, neither **7** or **8** were isolated from the reaction mixture. Position 4 of the pyran ring being a soft electrophilic center easily underwent nucleophilic substitution with the carbanion, generated from ethyl acetoacetate to form the probable intermediate **3**, which cyclized in situ to give 4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-diones **5**, or alternatively was hydrolyzed to **6** under alkaline condition. Thus, an equimolar mixture of

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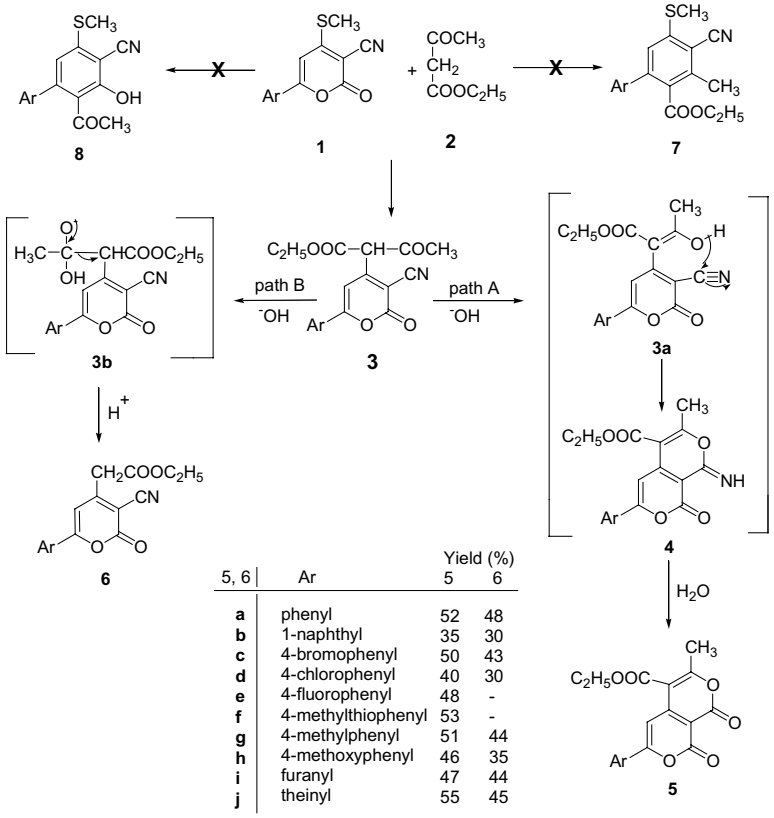

5, 6	Ar	Yield (%) 5	6
a	phenyl	52	48
b	1-naphthyl	35	30
c	4-bromophenyl	50	43
d	4-chlorophenyl	40	30
e	4-fluorophenyl	48	-
f	4-methylthiophenyl	53	-
g	4-methylphenyl	51	44
h	4-methoxyphenyl	46	35
i	furanyl	47	44
j	theinyl	55	45

Scheme 1.

2*H*-pyran-2-one **1**, ethyl acetoacetate **2**, under alkaline conditions was stirred for 30 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. The crude product was purified by Si-gel column chromatography. Two compounds were isolated from this reaction and were identified as ethyl 6-aryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-dione-1-carboxylate **5**, and ethyl 6-aryl-3-cyano-2*H*-pyran-2-one-4-acetate **6** in an almost equal ratio. All the compounds synthesized were characterized by elemental and spectroscopic analyses.[6]

A plausible mechanism for the formation of products **5** and **6** is depicted in the Scheme 1. The first step in this reaction is the attack of the carbanion generated in situ from ethyl acetoacetate **2** at position 4 of the pyran ring of **1** to form substitution product **3**, which via path A or B forms products **5** and **6**. In the presence of alkali, the intermediate **3** is hydrolyzed to product **6** in situ by following path B, while the tautomerized intermediate **3a** cyclizes to form **4**, following path A, which is then hydrolyzed to ethyl 7-aryl-2-methyl-4*H*,5*H*-pyrano[3,4-*c*]pyran-4,5-dione-1-carboxylate **5**. The possibility of the isolated product being **4** was ruled out on the basis of nitrogen and spectroscopic analyses. The elemental analysis and resemblance of molecular ion peak with the structure **5** ruled out the possibility of product **4**.

Our methodology provides an easy access to the synthesis of the 4*H*,5*H*-pyrano[3,4-*c*]-4,5-dione ring system **5**, and ethyl 6-aryl-3-cyano-2*H*-pyran-2-one-4-acetate **6** in moderate yield and in one step. The work-up for this reaction is very simple and the synthesis is very economical.

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6. Typical procedure for **5** and **6**: A mixture of 2*H*-pyran-2-one **1** (1 mmol), ethyl acetoacetate (1 mmol), and powdered KOH (1.5 mmol) in dry DMF was stirred for 30 h at room temperature. The reaction mixture was poured onto 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 to afford **5** and **6** in an almost equal ratio. **5a**: Yield 52%; mp 190–194 °C; IR (KBr) ν 1711 cm^{-1} (CO) 1785 cm^{-1} (CO); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, J = 7.2 Hz, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.49 (q, J = 7.2 Hz, 2H, OCH_2), 7.29 (s, 1H, CH), 7.49–7.60 (m, 3H, ArH), 7.91–7.94 (m, 2H, ArH); MS (FAB) 327 (M^++1). Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.07; H, 4.37. **6a**: Yield 48%; mp 152–154 °C; IR (KBr) ν 1720 cm^{-1} (CO) 2224 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, 3H, J = 7.1 Hz, CH_3), 3.82 (s, 2H, CH_2), 4.26 (q, 2H, J = 7.1 Hz, OCH_2), 6.88 (s, 1H, CH), 7.40–7.60 (m, 3H, ArH), 7.85–7.90 (m, 2H, ArH); MS (FAB) 284 (M^++1). **5c**: Yield 50%; mp 194–196 °C; IR (KBr) ν 1720 cm^{-1} (CO) 1791 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) 1.45 (t, J = 7.1 Hz, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.47 (q, J = 7.2 Hz, 2H, OCH_2), 7.29 (s, 1H, CH), 7.64 (d, J = 8.8 Hz, 2H, ArH), 7.78 (d, J = 8.8 Hz, 2H, ArH); MS (FAB) 405 (M^++1). Anal. Calcd for $C_{18}H_{13}O_6Br$: C, 53.36; H, 3.23. Found: C, 53.04; H, 3.26. **6c**: Yield 43%; mp 166–168 °C; IR (KBr) ν 1720 cm^{-1} (CO) 2214 cm^{-1} (CN); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 3H, CH_3), 3.82 (s, 2H, CH_2), 4.26 (q, J = 7.0 Hz, 2H, OCH_2), 6.87 (s, 1H, CH), 7.66 (d, J = 9.0 Hz, 2H, ArH), 7.74 (d, J = 9.0 Hz, 2H, ArH); MS (FAB) 362 (M^++1). Anal. Calcd for $C_{16}H_{12}BrNO_4$: C, 53.06; H, 3.34; N, 3.87. Found: C, 53.29; H, 3.42; N, 3.75.