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One-pot synthesis of cyclopentadienones through ring contraction of 2*H*-pyran-2-ones☆

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Abstract—A one-pot synthesis of 2,3,5-trisubstituted cyclopentadienones has been delineated through ring contraction of suitably functionalized 2*H*-pyran-2-ones using either cyanoacetamide or methyl cyanoacetate.

Cyclopentadienones are known to display diverse pharmacological activities[1] and are potent synthetic intermediates for the construction of various natural products of therapeutic importance. The biodynamic properties of this class of compounds focused our interest on the synthesis of this important structural motif.[2]

Cyclopentadienones have been synthesized previously by *t*-BuOK catalyzed oxygenation of 4-aryl-2,6-di-*t*-butyl- and 2,4,6-tri-*t*-butyl-phenols in *t*-butanol.[3,4] They are also prepared by coupling propargylic alcohols and their derivatives with cyclopropyl carbene–chromium complexes.[5] Recently, cyclopentadienones have been prepared by a silicon tethered[2 + 2 + 1]cyclo-carbonylation reaction of two alkynes promoted by penta-carbonylation[6] and has the potential to offer a broad range of this class of compounds. Transition metal mediated carbonylative coupling reactions are often used for the insertion of carbonyl groups into organic compounds. Insertion of CO into zirconacyclopentadienes in the presence of a Ni-complex is also an alternative route for cyclopentadienone synthesis.[7] Thus, cobalt carbonyl complex mediated carbonylative alkyne–alkyne coupling reactions have also been used for the construction of cyclopentadienones.[8–11] These compounds are often isolated as η^4-metal complexes because of their unstable nature and tendency to polymerize. Thus there is a need to develop methodology, which is free from the use of metal carbonyls as catalysts and that also has options for varying substitutents in the cyclopentadienone ring, which could in turn provide stability to the molecule.

Herein, we report an innovative one-pot synthesis of 2,3,5-trisubstituted cyclopentadienones through base-induced ring contraction of 6-aryl-4-amino-2*H*-pyran-3-carbonitriles[12] using either cyanoacetamide or methyl cyanoacetate in moderate yields. So far and to our knowledge there have been no reports on the synthesis of cyclopentadienones via ring contraction of suitably functionalized-2*H*-pyran-2-ones. Thus an equimolar mixture of 2*H*-pyran-2-one **1**, cyanoacetamide **2** and powdered KOH in dry DMF was stirred for 24 h at room temperature, poured onto crushed ice and thereafter neutralized with aqueous HCl. The separated precipitate was filtered, dried and purified by silica gel column chromatography to yield a reddish brown solid. Our attempts to isolate any of the potential intermediates so as to establish the course of reaction failed.

A plausible mechanism for this reaction involves nucleophilic attack by the carbanion generated from cyanoacetamide in situ at C6 of the pyran ring with ring opening followed by recyclization involving the carboxyl group and the active methylene group of cyanoacetamide with elimination of water. The cyclic intermediate thus formed undergoes ring contraction with elimination of cyanoacetamide. A similar mechanism is envisaged for methyl cyanoacetate as the nucleophile.

In fact this reaction was carried out to prepare highly functionalized biaryls **4** through ring transformations

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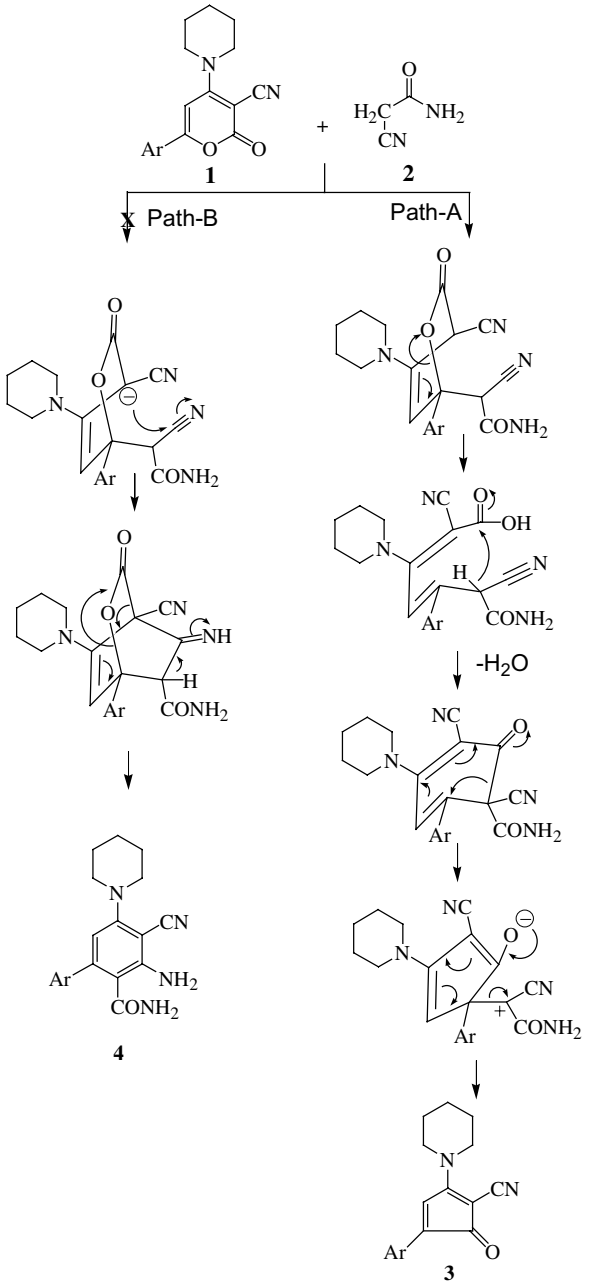
Table 1. Cyclopentadienones derivatives **3a**–**j** produced via Scheme 1

3	Ar	Yield % (3)
a	Phenyl	48
b	1-Naphthyl	47
c	4-Fluorophenyl	49
d	4-Chlorophenyl	50
e	4-Bromophenyl	52
f	4-Methylphenyl	48
g	4-Methoxyphenyl	51
h	3,4-Dichlorophenyl	49
i	3-Chloro-4-methylthiophenyl	42



Scheme 1. Preparation of cyclopentadienones.

of 2*H*-pyran-2-ones by cyanoacetamide under basic conditions. However, the usual work-up and purification of

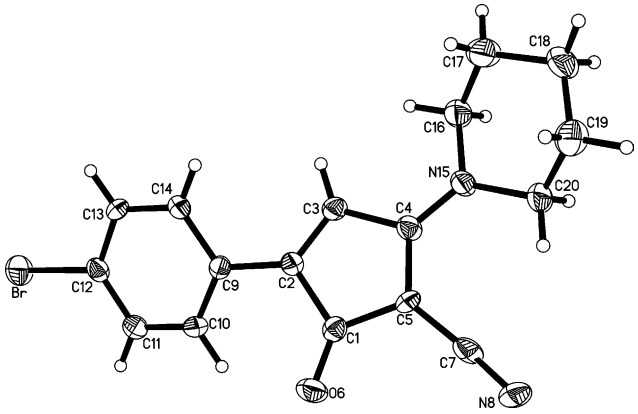


Figure 1. Displacement ellipsoid plot (30% probability) of the X-ray crystal structure of **3e**.

the crude product by column chromatography led to functionalized cyclopentadienones **3** (Table 1) in lieu of biaryls **4** by following pathway-A as depicted in Scheme 1.

The isolated products were characterized[13] by NMR and mass spectrometry and also through single crystal X-ray diffraction analysis in the case of **3e**.[14] The X-ray crystal structure of **3e** is shown in Figure 1 along with the atomic numbering scheme, and unambiguously confirmed the structure of **3e** as 4-(4-bromophenyl)-5-oxo-2-piperidin-1-yl-cyclopenta-1,3-dienecarbonitrile.

Under similar conditions, the reaction of 2*H*-pyran-2-one **1** with methyl cyanoacetate in lieu of cyanoacetamide gave the same products. The ^{1}H NMR spectrum of **3d** showed two broad singlets at 1.85 (6H of piperidine). The multiplets at δ 3.76–3.80 and δ 4.09–4.13 were attributed to the two NCH_2 protons. Two doublets at δ 7.37 and 7.79 were assigned to the *ortho* coupled aromatic protons.

In conclusion, our methodology for the construction of cyclopentadienones is superior to known literature procedures in respect of the easy work-up, mild reaction conditions, use of economical reactants and absence of catalyst. It also provides an option for varying the substituents on the cyclopentadienone ring.

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13. Typical procedure for **3**: A mixture of 2*H*-pyran-2-one **1** (1 mmol), cyanoacetamide (1 mmol) and powdered KOH (1.5 mmol) in dry DMF was stirred for 24 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 a reddish brown solid. Compound **3d**: mp 198–200 °C, IR (KBr) $\nu = 2190\,cm^{-1}$ (CN), $1620\,cm^{-1}$ (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.85 (br s, 6H, $3CH_2$), 3.76–3.80 (m, 2H, NCH_2), 4.09–4.13 (m, 2H, NCH_2), 7.04 (s, 1H, CH), 7.37 (d, $J = 8.5$ Hz, 2H, ArH), 7.79 (d, $J = 8.5$ Hz, 2H, ArH); MS (FAB) 299 (M^++1). Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.16; H, 5.12; N, 9.42.
14. X-ray crystal data of **3e**: $C_{17}H_{15}BrN_2O$, $M = 343.22$, orthorhombic, Pbca, $a = 15.247(2)$ Å, $b = 7.585(1)$ Å, $c = 25.697(4)$ Å, $V = 2971.8(7)$ Å^3, $Z = 8$, $D_c = 1.534\,g\,cm^{-1}$, μ (Mo-Kα) $= 2.77\,mm^{-1}$, $F(000) = 1392$, brown rectangular crystal, size $0.42 \times 0.22 \times 0.20$ mm, 3415 reflections measured, 2614 unique, $R_w = 0.14$ for all data, conventional $R = 0.069$ for 1087 $Fo > 4sig(Fo)$, $S = 0.997$ for all data and 190 parameters. Unit cell determination and intensity data collection ($2\theta = 50°$) was 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 Instruments Inc.: Madison, Wisconsin, USA 1996) used for data collection and data processing], SHELXTL-NT [(Bruker AXS Inc.: Madison, Wisconsin, USA 1997) used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposit No: 243029).