Novel Cyclopentenone Synthesis by Base-Catalyzed Cyclization of Dienediones

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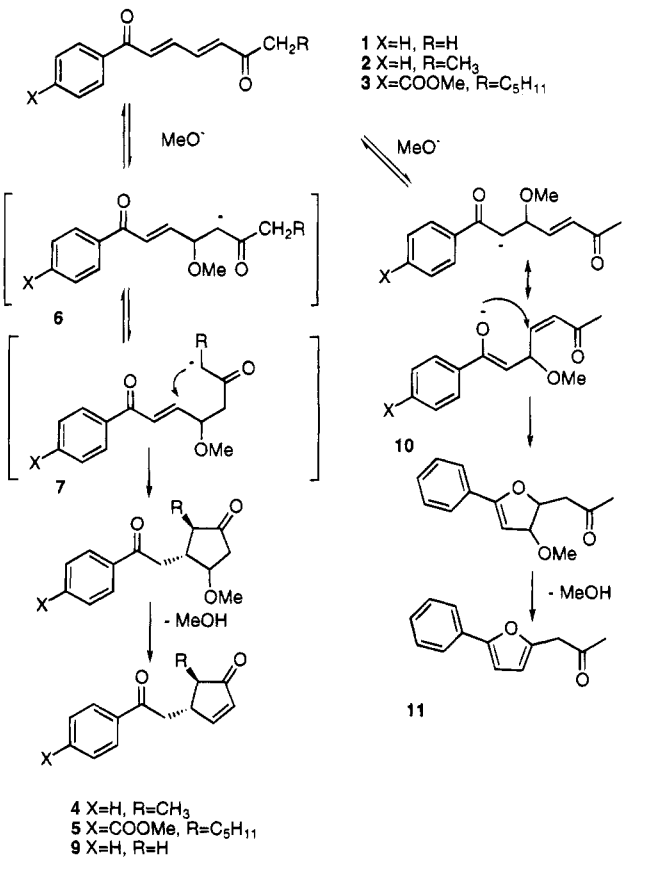
There has been considerable interest in the synthesis and applications of cyclopentenones in natural products synthesis. The methods of cyclopentenone ring formation to this time mainly involve the condensation reaction of 1,4-dicarbonyl functions,[1] Nazarov cyclization of dienones,[2] insertion reaction of an intermediate alkylidenecarbene,[3] Khand-Pauson reactions,[4] 2,5-dihydro-2,5-dimethoxyfuran,[5] and most recently, the tandem Michael addition–carbene insertion reactions of β ketoethynyl(phenyl)iodonium salts.[6] This work describes a novel intramolecular base-catalyzed cyclization of aromatic dienediones to provide disubstituted 4,5-cyclopentenones. The 1,6-dioxo 2,4-diene derivatives can be prepared readily from various published methods.[7–9] The dienediones themselves are of interest because some of them possess anticancer activities.[10]

The aromatic 1,6-dioxo 2,4-dienes **1–3** in this study were prepared by copper sulfate-catalyzed reaction of aromatic diazo ketones with monosubstituted furans.[7] Reaction of **2** and **3** with potassium hydroxide in methanol produces the corresponding 4,5-disubstituted cyclopentenones **4** and **5** in over 60% yield. The formation of the cyclopentenone ring cannot arise by direct proton abstraction followed by addition since the *E,E*-diene possesses a conformation that is stereochemically constrained and disfavors such a mechanism. It is commonly assumed that with an enone a reversible Michael addition of methoxide anion can readily take place.[11] The aromatic 1,6-dioxo 2,4-diene was chosen because of the two internal enone positions present. Attack should favor the more reactive nonaromatic enone to give initially the enolate anion **6**, removing the stereochemical constraint. The anion **6** may cyclize via an intramolecular addition to form a strained methoxycyclopropane ring or the preformed anion can equilibrate to the enolate anion intermediate **7**, which can cyclize to give 3-methoxycyclopentanone. The equilibrium favors the formation of the five-membered ring, which after dehydromethoxylation provides cyclopentenone as shown in Scheme 1.

Scheme 1



Evidence for this mechanism lies with the fact that the use of non nucleophilic bases such as sodium hydride or butyllithium did not lead to the formation of cyclopentenone. Furthermore, the alkyl substituents on the carbonyl function were found to influence the ease of equilibration between the initially formed secondary enolate anion **6** with **7**. With the ethyl and hexyl substituents in **2** and **3**, the preformed enolates equilibrate smoothly to the enolate **7**, which cyclizes exclusively to cyclopentenone of the more stable trans stereochemistry. In the ^{1}H NMR spectrum of **4**, the secondary methyl shows as a clear doublet at δ 1.27 (J = 7.4 Hz); and by double irradiation at δ 1.27 the doublet of quartet at δ 2.05 turns into a doublet (J = 1.9 Hz), which is in agreement with a trans disposition of the two protons at the substituted cyclopentenone ring junctions. In the coupling of C-4 and C-5 protons of cyclopentenone derivatives, it is well known that $J_{cis} > J_{trans}$ (J_{cis} = 6–8 Hz ; J_{trans} = 2–3 Hz). The methyl-substituted compound **1**, on the other hand, showed no tendency of the preformed enolate anion **6**, to equilibrate from a secondary enolate to a less stable primary enolate, thus preventing the formation of cyclopentenone **9**. This did not, however, force the formation of the strained cyclopropane ring, the formation of which is reversible. Instead, the product results from attack of the methoxide anion on the more stable internal aromatic enone to give intermediate **10**, followed by an internal Michael addition of the resulting oxygen anion of the enolate, furnishing the furan derivative **11** in low yield after dehydromethoxylation. There are no regioselectivity problems for cyclopentenone synthesis using aromatic 1,6-dioxo 2,4-diene where only one position is enolizable. This should not impose any limitations on the synthetic application of this method,

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as the aromatic ketone may be transformed into an ester via Baeyer–Villiger oxidation[12] at a latter synthetic sequence.

In summary, conversion of readily accessible aromatic 1,6-dioxo 2,4-diene in a one-pot reaction by tandem Michael reactions with the intermolecular addition of methoxide anion, followed by equilibration of the enolate and an intramolecular Michael cyclization sequence thus constitutes a new synthetic method for 4,5-disubstituted cyclopentenones. The overall reaction sequence can be used to prepare a diverse array of cyclopentenones for natural products synthesis since numerous aromatic substituted 1,6-dioxo 2,4-diene can be prepared from readily available 2-substituted furans and aromatic diazo ketones. The 4,5-disubstituted cyclopentenones provided by our method can be further funtionalized to give 2,3,4,5-tetrasubstituted cyclopentanones by further Michael addition.

Experimental Section

Preparation of Dienediones. A solution of the diazo ketone[13] in dichloromethane was added dropwise to a solution of substituted furan[14] and catalytic amount of anhydrous copper sulfate in dichloromethane and stirred at room temperature of 6 h. After the usual workup and chromatography on silica gel column, the *E,E*-isomers were obtained as the major product in each case.

1-Phenyl-1,6-dioxo-hepta-2,4-(*E,E*)-diene (1): yield of 65% as yellow solid; mp 72–73 °C; IR ($CHCl_3$) 1695, 1663, 1600, 1569 cm^{-1}; ^1H NMR ($CDCl_3$) 8.32 (1H, dd, J = 15, 12 Hz), 7.94–7.91 (2H, m), 7.60–7.47 (3H, m), 7.09 (1H, d, J = 15 Hz), 6.60 (1H, dd, J = 12, 11 Hz), 6.36 (1H, d, J = 11 Hz), 2.89 (3H, s); mass (m/z) 200. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.64; H, 6.01.

1-Phenyl-1,6-dioxoocta-2,4-(*E,E*)-diene (2): yield of 70% as bright yellow solid; mp 109–110 °C; IR ($CHCl_3$) 1694, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) 8.34 (1H, dd, J = 15, 12 Hz), 7.93 (2H, d), 7.57–7.71(3H, m), 7.06 (1H, d, J = 15 Hz), 6.60 (1H, dd, J = 12, 11 Hz), 6.36 (1H, d, J = 11 Hz), 2.57 (2H, q), 1.11 (3H, t); mass (m/z) 214. Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.39; H, 6.52.

1-[(4-Methoxycarbonyl)phenyl]-1,6-dioxo-dodeca-2,4-(E,E)-diene (3): yield of 60% as pale yellowish solid; mp 137–138 °C; IR ($CHCl_3$) 1724, 1690, 1665, 1603, 1572 cm^{-1}; ^1H NMR ($CDCl_3$) 8.34 (1H, dd, J = 15, 11 Hz), 8.15 (2H, d), 7.96 (2H, d), 7.02 (1H, d, J = 15 Hz), 6.59 (1H, dd, J = 12, 11 Hz), 6.38 (1H, d, J = 11 Hz), 3.96 (3H, s), 2.54 (2H, t), 1.20–1.60 (8H, m), 0.88 (3H, t); mass (m/z) 328. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.36. Found: C, 72.92; H, 7.40.

General Procedure. MeOH–KOH Cyclization. A methanolic KOH solution (0.1 molar ratio) was added to a solution of 1,6-dioxo-2,4-diene (1 mmol) in 10 mL of methanol at room temperature and stirred for 6 h. The methanol was first removed under vacuum, and cold water was added. The aqueous solution was neutralized with dilute 10% HCl and extracted with dichloromethane, dried (Na_2SO_4), and evaporated to give the crude product (brownish gum, 90%) which can be purified by preparative TLC (silica gel, EtOAc/hexanes; 1:3), yielding yellowish crystals (60–70% yield).

4-Phenacyl-5-methyl-1-oxocyclopent-2-ene (4): yield of 65% as pale yellowish solid; mp 60–61 °C; IR ($CHCl_3$) 1703, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) 7.96 (2H, d, ArH), 7.68 (1H, dd, J = 2.5 and 6.5 Hz, enone-H), 7.60–7.45 (3H, m, ArH), 6.19 (1H, dd, J = 1.2 and 6.5 Hz, enone-H), 3.20 (3H, m, CH_2, CH), 2.05 (1H, d of q, J = 1.9 and 7.4 Hz, CH), 1.27 (3H, d, J = 7.4 Hz, Me); exact mass 214.2623 (calcd for $C_{14}H_{14}O_2$ 214.2426). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: 78.15; H, 6.71%.

4-(4′-Carbomethoxyphenacyl)-5-pentyl-1-oxocyclopent-2-ene (5): yield of 63% as yellow solid; mp 70–71 °C; IR ($CHCl_3$) 1718, 1695, 1684, 1583 cm^{-1}; ^{1} H NMR ($CDCl_3$) 8.14 (1H, d), 8.03 (2H, d), 7.71 (1H, dd, J = 2.5, 5.7 Hz), 6.18 (1H, dd, J = 1.5, 5.7 Hz), 3.69 (3H, s), 3.24 (3H, m), 2.05 (1H, d of t, J = 1.8, 5.5 Hz), 1.90 and 1.20 (8H, m), 0.88 (3H, t); mass (m/z) 328. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.14, H, 7.36. Found: C, 73.06; H, 7.39.

2-Phenyl-5-acetonylfuran (11): yield of 10% as a brownish oil; IR ($CHCl_3$) 1687, 1598 cm^{-1}; ^{1} H NMR ($CDCl_3$) 8.00 (2H, d), 7.54 (3H, m), 6.98 (1H, J = 1.8 Hz), 5.91 (1H, J = 1.8 Hz), 4.25 (2H, s), 2.26 (3H, s); exact mass 200.0847 (calcd for $C_{13}H_{12}O_2$ 200.0842).

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