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Novel access to cyclohexane-1,4-diones and 1,4-hydroquinones via radical 1,2-acyl rearrangement on 2-(halomethyl)cyclopentane-1,3-diones using cobaloxime-mediated electroreduction or tributyltin hydride

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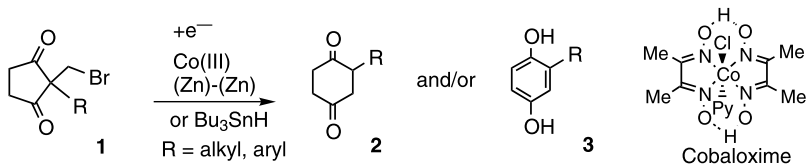
Abstract—A new preparative access to synthetically useful cyclohexane-1,4-diones **2** and their oxidized analogues, hydroquinones **3**, with the option of introducing alkyl and aryl substituents, was developed by radical 1,2-acyl rearrangement on 2-(halomethyl)cyclopentane-1,3-diones **1**, accessible from 1,2-bis(trimethylsiloxy)cyclobutene and α-bromo ketone dimethyl acetals. The electroreduction of monoacetals of **1** in the presence of cobaloxime as a catalyst afforded the cyclohexane-1,4-dione monoacetals in good yields. The Bu_3SnH-reduction of 2-aryl **1** under refluxing in benzene effected the rearrangement, affording **2**, and when the reaction was prolonged, aromatization to **3** proceeded in moderate yields.

Cyclohexane-1,4-diones **2** are fundamental compounds in organic synthesis especially as intermediates for bioactive compounds[1] as well as speciality chemicals such as TCNQ.[2] In contrast to the easy availability of their congeners, cyclohexane-1,2-diones and 1,3-diones, by the intermolecular and intramolecular Claisen condensations, cyclohexane-1,4-diones are not obtained by this condensation.[3] On the other hand, catalytic hydrogenation or dissolving metal reduction of catechols, resorcinols, and hydroquinones can promise a large-scale preparation of the corresponding cyclohexanediones, which is, however, less selective due to overreduction.[4] Furthermore, hydroquinone synthesis is also currently an important issue because of its significant role in bioactive compounds.[5] Here we report a novel synthetic access to cyclohexane-1,4-diones **2** as well as their oxidized analogues, 1,4-hydroquinones **3**, from 2-(bromomethyl)cyclopentane-1,3-diones **1** by a radical 1,2-acyl rearrangement tactics which has recently attracted intensive interest from the synthetic[6,7] and biological[8] points of view (Scheme 1).

As shown in the general strategy in Scheme 2, the starting 2-alkyl- or 2-aryl **1** for the radical rearrangements were easily prepared by employing Nakamura's protocol[9] for cyclopentane-1,3-dione synthesis, slightly modified by using a lanthanide catalyst such as $Yb(OTf)_3$.[10] Thus, the aldol reaction of 1,2-



Scheme 1.

Keywords: biaryls; catalysts; cobalt and compounds; cyclohexanones; electrochemical reactions; phenols; radicals and radical reactions; rearrangement.

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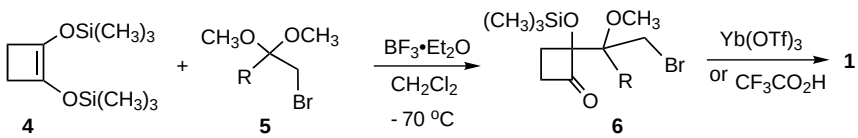
bis(trimethylsiloxy)cyclobutene (**4**) and α-bromoketone dimethyl acetal **5** by use of $BF_3{\cdot}Et_2O$, giving the adducts **6**, was followed by treatment with $Yb(OTf)_3$ at room temperature to afford **1** as a result of the pinacol-type rearrangement of **6**. Typically, the compound **1c** ($R = C_6H_4OMe$-4) was obtained in 71% overall yield from **5c** (Scheme 2).

The electrochemical reactions were carried out in the same manner as reported without adding 40% NaOH and the electricities were passed until most of the substrates were consumed.[11] As shown in Table 1, the electrolysis of the 2-methylcyclopentane-1,3-dione **1a** produced the desired cyclohexane-1,4-dione **2a** in 61% yield. However, in this case, formation of a small amount of methyl 4-oxo-5-methyl-5-hexenoate (3%) was found as a result of retro-Claisen condensation and elimination of the bromide ion presumably due to an electrogenerated base such as $Zn(OMe)_2$. To our disappointment, the 2-aryl derivative **2c** was more susceptible to ring cleavage with electrogenerated bases, forming not the desired 1,4-cyclohexanedione but the ring-opened 4-oxo-5-hexenoate. Subsequently, in order to avoid the retro-Claisen condensation, the cyclopentane-1,3-diones **1** with alkyl and aryl substituents were protected as monoacetals **7** and then submitted to the electrolysis. In the event, the desired cyclohexane-1,4-dione monoacetals **8** were obtained cleanly in 69–74% yields by the electroreduction of **7** with cobaloxime.[12] However, in these cases, the desired 2-cyclohexenones were not found.[6c,d]

In a previous paper, we reported the cobalt-mediated electroreduction of 2-alkyl-2-bromomethylcycloalkanones, giving the corresponding one carbon-enlarged 2-cycloalkenenones. This can be best explained by the 1,2-acyl rearrangement of the 3-oxomethyl radical, which is followed by the concomitant recombination of the homologated cycloalkyl radical with the cobalt(II) species and the subsequent β-elimination of the thus-formed alkyl-cobalt complex.[6d] However, this enone synthesis was not viable with the substrates examined in this study. Since the amount of 2-methylcyclopentane-1,3-diones **11**, possibly produced from either the radical **i** or the anionic species **v**, was very small, the radical process was considered to be dominant for the present 1,2-acyl rearrangement reaction (Scheme 3).[13] We anticipated that the 2-oxoalkyl radical intermediate **iii** formed by the 1,2-acyl rearrangement of **1** via **i** and **ii** was less reactive towards the cobalt(II) reagent to form the alkyl-cobalt complex because this species was stabilized by delocalization with the adjacent carbonyl group,[14] and then converted to the anionic species **iv** by electrochemical one-electron reduction, producing the saturated **2** after protonation. Similarly, the formation of **10** from the β-keto ester derivative **9** was also explained along this line (Table 1, entry 5). In the case of the acetal **7** (entries 3 and 4), on the other hand, the radical intermediate after the rearrangement is likely to be hindered by the neighboring acetal group to form the alkyl-cobalt intermediate, and then converted to the saturated **8** by the subsequent one-electron reduction and protonation.

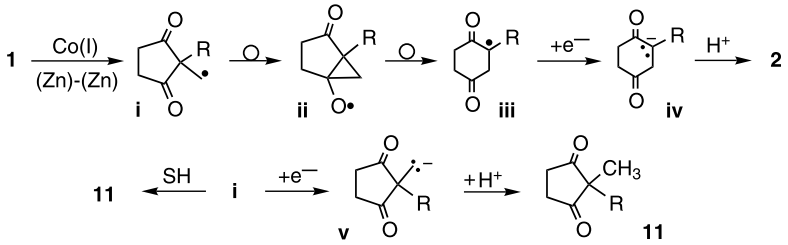


Scheme 2.

Table 1. Electrochemical cobaloxime-mediated radical 1,2-acyl rearrangements[a]

Entry	Substrates R	F/mol (Co(III), mol%)	Products, Yield/%[b] Rearranged		Others[c]
1	**a**: CH_3	7.0 (18)	**2**	61	3
2	**c**: $C_6H_4OCH_3$-4	20 (20)	**2**	--	59
3	**a**: CH_3	15.4 (21)	**8**	74	--
4	**b**: C_6H_5	15.1 (20)	**8**	69	--
5[d]			**10**	56	

[a]Unless otherwise noted, electrochemical reactions were carried out by using the substratres (0.11-1.41 mmol), cobaloxime (18-21 mol%) in an MeOH (7 mL)-Et_4NOTs (300 mg)-(Zn)-(Zn) system under an applied voltage of 3 V at room temperature for passage of 7.0-19.9 F/mol of electricity. [b]Isolated yields by column chromatography (SiO_2). [c]Others are ring-opened 4-oxohexenoates. [d]Carried out in DMF with [Co(III)(DO)(DOH)pn]$C1_2$.



Scheme 3.

Table 2. Reductions of 2-aryl **1** with Bu_3SnH in benzene[a]

Entry	Substrates **1** R		Reflux h	Products, Yield, %[b] Cyclohexane-1,4-diones **2**	Hydroquinones **3**
1	—Ph	**b**	12	75	--
2			44	--	46
3	—C6H4—OMe	**c**	18	70	--
4			40	--	42
5	—C6H4—Me	**d**	4	75	--
6			42	--	43
7		**e**	29	--	48

[a]Carried out by using **1** (0.13~0.19 mmol), *n*-Bu_3SnH (1.2 eq.) and AIBN (0.1 eq.) in benzene (3 mL) at reflux. [b]Isolated yields by column chromatography (SiO_2).

We next examined the Bu_3SnH-induced radical rearrangement of aryl-substituted **1**. When carried out in benzene for about 12–18 h, 2-arylcyclohexane-1,4-diones **2** were, as expected, produced as a result of the usual radical 1,2-acyl rearrangement. However, when the reactions were prolonged for about 40 h, hydroquinones **3** were obtained as a major product. This aromatization of **2** to **3** was only found with the aryl derivatives; no aromatization was detected with alkyl derivative **2a** (R = Me). As shown in Table 2, biaryls substituted with a hydroquinone ring are generally formed, though in moderate yields (42–48%).[12] At present, we are unable to explain the aromatization of the aryl substituted cyclohexane-1,4-diones under the conditions using a reducing reagent. However, we have found that this kind of aromatization occurred by heating **2** with tributylditin ($(Bu_3Sn)_2$) which was produced in the radical rearrangement of **1** with Bu_3SnH. For example, treatment of **2b** with 1.2 equiv. of $(Bu_3Sn)_2$ in refluxing benzene for 43 h produced **3b** (36% yield) and the recovery of **2b** (12%).[15] Further experiments to gain mechanistic insight into this phenomenon are under investigation.

In summary, we have developed new synthetic procedures for cyclohexane-1,4-diones and 1,4-hydroquinones with alkyl and aryl substituents using 1,2-acyl rearrangement tactics. Especially, the present method allows introduction of an aryl group at the position α to the carbonyl function with wide diversity.[16]

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12. Spectral data of representative compounds listed in Tables 1 and 2 are as follows. **8b**: IR (film) 2961, 2892, 1717, 1497, 1453, 1418, 1304, 1265, 1227, 1156, 1084, 1047, 1015, 984, 951, 914, 799, 760 cm^{-1}; ^1H NMR (400 MHz) δ 1.98–2.03 (m, 2H), 2.40–2.53 (m, 2H), 2.68–2.76 (m, 1H), 2.99–3.13 (m, 2H), 3.24–3.29 (m, 1H), 3.55–3.61 (m, 1H), 3.70–3.81 (m, 2H), 7.26 (m, 5H); ^{13}C NMR (100 MHz) δ 34.7, 38.7, 44.3, 50.0, 65.2, 65.3, 108.4, 127.0, 127.8, 129.1, 138.3, 209.7. **3c**: IR (KBr) 3418, 2921, 2841, 1626, 1609, 1499, 1453, 1331, 1240, 1107, 1024, 828, 777 cm^{-1}; ^1H NMR (400 MHz) δ 3.84 (s, 3H), 4.65 (s, 1H), 4.85 (s, 1H), 6.67–6.73 (m, 2H), 6.80–6.85 (m, 1H), 6.96–7.03 (m, 2H), 7.34–7.40 (m, 2H); ^{13}C NMR (100 MHz) δ 55.4, 114.6, 115.3, 116.4, 116.5, 128.4, 128.9, 130.0, 146.3, 149.1, 159.1.
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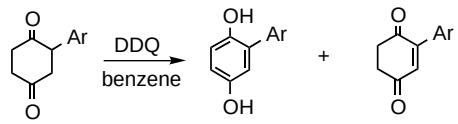
15. In addition, the compound **2c** can easily be oxidized to the hydroquinone **3c** (53%) and the cyclohex-2-ene-1,4-dione **12** (20%) by treatment with DDQ (1.2 equiv.) (80°C for 30 h). **12**: IR (KBr) 1695, 1666, 1602, 1567, 1513, 1267, 1189, 1031, 838 cm^{-1}; ^1H NMR (400 MHz) δ 2.95 (m, 2H), 3.05 (m, 2H), 3.83 (s, 3H), 6.80 (s, 1H), 6.93 (d, $J=8.8$ Hz, 2H), 7.44 (d, $J=8.8$ Hz, 2H); ^{13}C NMR (75.5 MHz) δ 37.0, 38.7, 55.4, 114.1, 125.0, 130.7, 135.2, 150.1, 161.5, 197.5, 198.0.



2c **3c** **12** (Ar = C_6H_4OMe-4)

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