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Formation of 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes or multiply substituted *o*-benzoquinones from reactions of 1,4-dilithio-1,3-dienes with dimethyl oxalate

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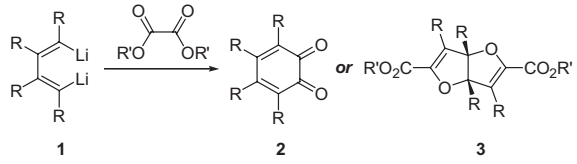
Abstract—Reactions of 1,4-dilithio-1,3-dienes with dimethyl oxalates afforded multiply substituted *o*-benzoquinones or stereodefined 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes in good yields.

Bimetallic reagents 1,4-dilithio-1,3-dienes **1** show unprecedented reaction patterns with organic substrates.[1–6] In addition to novel reaction patterns, experimental results have demonstrated that these dilithio reagents are synthetically useful building blocks.[1–6] As our continuous interest in synthetic applications of these dilithio reagents for organic syntheses, we began to investigate reactions of these dilithio compounds with multi-functional substrates, expecting development of synthetic methods for otherwise unavailable complex structures. In this communication, we would like to report preliminary results obtained from reactions of 1,4-dilithio-1,3-dienes **1** with dimethyl oxalates, which afforded multiply substituted *o*-benzoquinones **2** or stereodefined 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes **3** in good yields (Scheme 1).

o-Benzoquinones are useful building blocks for synthesis of a variety of functionalized compounds.[7–10] Recently, *o*-quinones have been proposed to be active carcinogenic metabolites and have been reported to react with DNA to form both stable and depurinating adducts.[11] Thus, increasing interest has been paid to the synthesis of substituted *o*-benzoquinones.[7–11] On the other hand, dioxabicyclo[3.3.0]-octacycles have also been found in many biologically active compounds, and development of methods for the synthesis of this skeleton has been of interest.[12]



Scheme 1. Reaction of 1,4-dilithio-1,3-dienes **1** with dimethyl oxalates affording multiply substituted *o*-benzoquinones **2** or stereodefined 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes **3**.

The dilithio reagent **1** may react with dimethyl oxalates in 1:1 molar ratio pattern or in 1:2 molar ratio pattern. In case of 1:1 molar ratio reaction pattern, substituted *o*-benzoquinones **2** might be expected (path a, Scheme 2). If the reaction took place in a 1:2 molar ratio pattern, products **4** might be formed (path b, Scheme 2). Addition of dimethyl oxalates to the diethyl ether solution of **1**, generated in situ from their corresponding 1,4-diiodobutadienes and *t*-BuLi,[1–6] did afford the expected substituted 1,2-benzoquinones in good isolated yields (Eq. 1, Table 1).[13] In cases of **1a** and **1b**, besides the substituted *o*-benzoquinones **2**, a different product determined to be 2,6-dioxabicyclo[3.3.0]-octa-3,7-diene **3** was obtained in 14–20% isolated yields. These two

Keywords: Substituted *o*-benzoquinones; Dioxabicyclo [3.3.0]-octacycles; 1,4-Dilithiobutadienes; Dimethyl oxalate.
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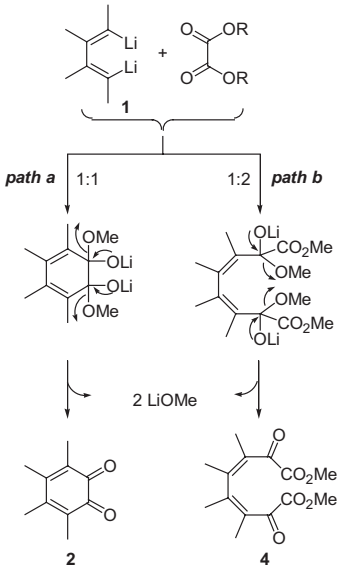
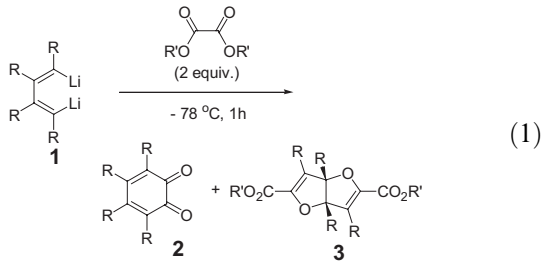
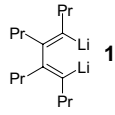
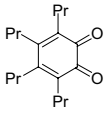
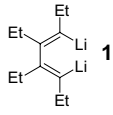
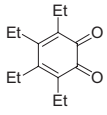
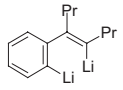
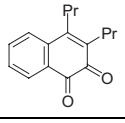


Scheme 2. Expected reaction patterns and products of 1,4-dilithio-1,3-dienes **1** with dimethyl oxalates.

Table 1. Reaction of dilithiobutadienes **1** with carboxylates in 1:1 molar ratio pattern to afford 1,2-benzoquinones **2**[a]



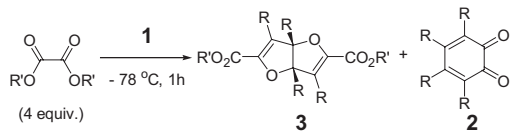
(1)

Dilithio reagent **1**	OR′	Product **2**	Yield (%)[b]
 **1a**	OMe	 **2a**	46
1a	OEt	**2a**	41
 **1b**	OMe	 **2b**	49
1b	OEt	**2b**	45
 **1c**	OMe	 **2c**	52

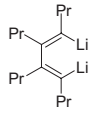
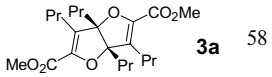
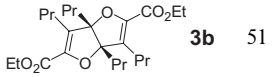
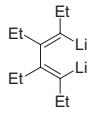
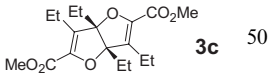
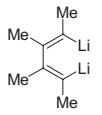
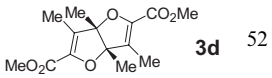
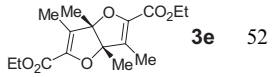
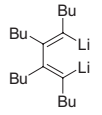
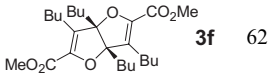
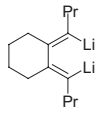
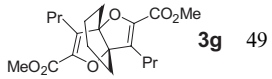
[a] Reaction conditions are given in Eq. 1.
[b] Isolated yields.

products **2** and **3** could be easily separated using column chromatography. For reaction of **1c**, quinone **2c** was obtained as the only product in 52% isolated yield. When one equivalent of dimethyl oxalates was used, the reactions gave the same products, but in lower yields with about 30% of **1** unreacted.

Table 2. Reaction of dilithiobutadienes **1** with carboxylates in 1:2 molar ratio pattern to afford stereodefined 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes **3**[a]



(2)

Dilithio reagent **1**	OR′	Product **3**	Yield (%)[b]
 **1a**	OMe	 **3a**	58
1a	OEt	 **3b**	51
 **1b**	OMe	 **3c**	50
 **1d**	OMe	 **3d**	52
1d	OEt	 **3e**	52
 **1e**	OMe	 **3f**	62
 **1f**	OMe	 **3g**	49

[a] Reaction conditions are given in Eq. 2.
[b] Isolated yields.

As shown in Scheme 2, products **4** might be formed if the reaction of **1** with dimethyl oxalates proceeded in 1:2 molar ratio reaction pattern. However, even with 4 equiv of dimethyl oxalates, no formation of products **4** was observed. Instead, interestingly, stereodefined 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes **3** were obtained, though in low yields. Since this type of compounds is important and can not be readily prepared by other methods, we tried to improve yields of products.

It is obvious that products **3** are formed from the reaction pattern of 1:2 molar ratio, thus concentration of dimethyl oxalates might be very important. Higher concentration of dimethyl oxalates should be better for the formation of **3**. Therefore, we changed the addition order of reagents. The diethyl ether solution of **1** was added to dimethyl oxalates in diethyl ether solution. Indeed, this was the right order to mix these reagents and the reaction gave stereodefined 2,6-dioxabi-

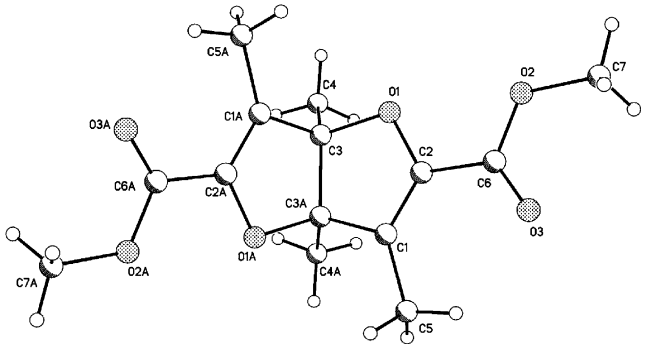
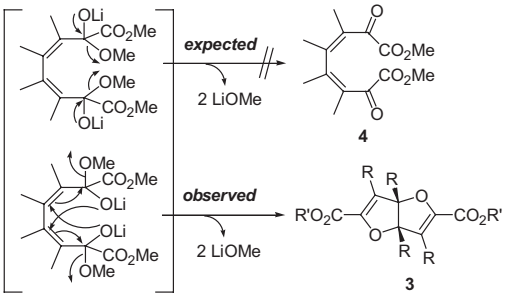


Figure 1. X-ray structure of **3d**. Selected bond lengths [Å]: C1–C2 1.330 (2), C1–C3A 1.502 (2), C3A–C3 1.557 (3), C3–O1 1.4692 (18), O1–C2 1.377 (2).



Scheme 3. A proposed mechanism for the formation of 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes **3**.

cyclo[3.3.0]-octa-3,7-dienes **3** in good isolated yields (Eq. 2, Table 2).[14] In cases of **1a**,**b**, and **1e**, in addition to **3**, *o*-benzoquinones **2** were obtained in less than 20% yields. These two products **2** and **3** could be easily separated using column chromatography. For reactions of **1d** and **1f**, 2,6-dioxabicyclo[3.3.0]-octa-3,7-dienes **3d**,**e**, and **3g** were obtained as the only products, respectively, in 52%, 52%, and 49% isolated yield. The structure of **3d** has been determined by single-crystal X-ray structural analysis (Fig. 1).[15]

A proposed mechanism is shown in Scheme 3. Further application of this synthetically useful method involving other multi-functionalized substrates is in progress.

Acknowledgements

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12. Nguyen, V.-H.; Nishino, H. *Tetrahedron Lett.* **2004**, *45*, 3373–3377, and references cited therein.
13. Typical procedure for the preparation of 1,2-benzoquinone **2a**. To a 50 mL Schlenk tube containing 2.0 mmol of 1,2,3,4-tetrapropyl-1,4-dilitho-1,3-diene **1a** in 20 mL diethyl ether at −78 °C was added 4.0 mmol of dimethyl oxalate. After the reaction mixture was stirred at −78 °C for 1 h, the reaction was quenched by pouring the mixture into saturated aqueous NH_4Cl solution and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. The solvent was then evaporated in vacuo to give a red oil, which was purified by column chromatograph (silica gel, diethyl ether/petroleum ether in 1: 30) to afford the product **2a**. Deep red liquid. Isolated yield 46% (254 mg). IR (neat) 1652 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS): δ 0.95 (t, $J = 7.3$ Hz, 6H), 1.06 (t, $J = 7.3$ Hz, 6H), 1.28–1.64 (m, 4H), 2.16–2.43 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS): δ 14.4, 14.6, 22.9, 23.4, 28.3, 32.4, 137.6, 151.7, 180.9.
14. Typical procedure for the preparation of 2,6-dioxabicyclo[3.3.0]-octa-3,7-diene **3a**. To a 50 mL Schlenk tube containing the solution of 8.0 mmol of dimethyl oxalates in 10 mL of ethyl ether at −78 °C, was added dropwise the solution of 2.0 mmol 1,2,3,4-tetrapropyl-1,4-dilitho-1,3-diene **1a** in 20 mL ethyl ether via a syringe. After the reaction mixture was stirred at −78 °C for 1 h, the reaction was quenched by pouring the mixture into aqueous 3 N HCl solution and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. The solvent was then evaporated in vacuo to give yellow residue, which was purified by column chromatograph (silica gel, diethyl ether/petroleum ether in 1:30) to afford the product **3a**. White solid, isolated yield 58% yield (456 mg), mp 86–87 °C. IR (KBr) 1726 cm^{-1} (C=O);

^{1}H NMR ($CDCl_3$, TMS): δ 0.69–1.03 (m, 12H), 1.07–1.64 (m, 8H), 1.75–2.22 (m, 6H), 2.45–2.77 (m, 2H), 3.81 (s, 6H); ^{13}C NMR ($CDCl_3$, TMS): δ 14.3, 14.6, 17.3, 22.9, 26.2, 33.4, 51.9, 98.8, 129.3, 141.4, 161.3; HRMS calcd for $C_{22}H_{34}O_6$ 394.2355, found 394.2357.

15. X-ray crystallographic data for **3d**: A colorless block crystal having approximate dimensions of $0.5 \times 0.35 \times 0.30$ mm was mounted on a glass fiber. X-ray data were collected on a Rigaku RAXIS RAPID IP diffractometer with graphite-monochromated Mo/Kα radiation ($\delta = 0.71073$ Å). $C_{14}H_{18}O_6$, $f_w = 282.28$, monoclinic, space group $C2/c$, $a = 19.329(4)$ Å, $b = 5.9661(12)$ Å, $c = 13.218(3)$ Å, $V = 1465.5(5)$ Å^3; $Z = 4$; $D_{calc} = 1.279$ g cm^{-3}; $R_1 = 0.0422$, $wR_2 = 0.0922$. CCDC 240171.