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Concise synthesis of multiply substituted stereodefined *cis*,*cis*-2,4-diene-1,6-dials, *cis*,*cis*-2,4-diene-1,6-diols and further applications

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Abstract—Reactions of 1,4-dilithio-1,3-dienes with DMF afforded multiply substituted stereodefined *cis*,*cis*-2,4-diene-1,6-dials in high yields. Treatment of these 1,6-dials with $LiAlH_4$ or RLi resulted in the formation of their corresponding 1,6-diols. These bifunctional compounds, *cis*,*cis*-2,4-diene-1,6-dials and -1,6-diols are otherwise not readily available. Further reaction of these 1,6-diols with an aldehyde catalyzed by strong acids led to the formation of oxacycles of novel structures.

Conjugated organic systems have attracted much attention since new materials and functional structures can be expected. 2,4-Diene-1,6-bis-electrophile (Fig. 1), which contains a butadienyl conjugated skeleton and two terminal functional groups to be manipulated, represents one of the useful building units for preparation of both cyclic and linear conjugated compounds.[1–7] As part of our continuing interest in synthetic applications of 1,3-butadienyl 1,4-dilithio reagents,[8–16] we began to investigate reactions of these dilithio compounds with easily available organic substrates, expecting development of synthetic methods for 2,4-diene-1,6-bis-electrophiles, which are very useful but otherwise not readily available. In this communication, we would like to report preliminary results obtained from reactions of 1,4-dilithio-1,3-dienes with DMF, which afforded multiply substituted stereodefined *cis*,*cis*-2,4-diene-1,6-dials (**1**, Fig. 1) in high yields. Further transformation of these 1,6-dials afforded multiply substituted stereodefined *cis*,*cis*-2,4-diene-1,6-diols (**2**, Fig. 1), and furan derivatives of novel structure.

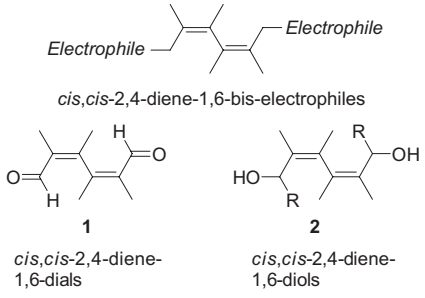

Figure 1.

Reaction of *N*,*N*-disubstituted amides, such as *N*,*N*-dimethylformamide (DMF), with organolithium reagents has been of significant interest since it provides an alternative method for preparation of carbonyl compounds.[17] However, this reaction is somewhat unpredictable.[17] Deniau and Enders reported that reaction of a dilithium reagent with DMF afforded, instead of linear carbonyl compounds, a cyclic product.[18] When 1,4-dilithio-1,3-dienes **3a**–**e** were treated with DMF,[19]

Keywords: Multi-substituted *cis*,*cis*-2,4-diene-1,6-dials; Multi-substituted *cis*,*cis*-2,4-diene-1,6-diols; 1,4-Dilithiobutadienes.
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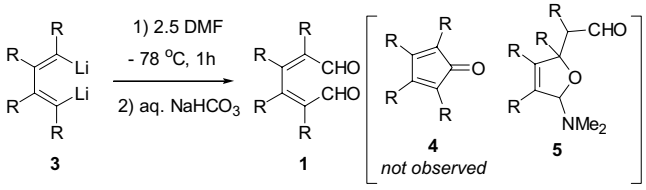
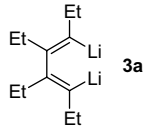
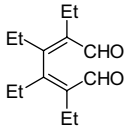
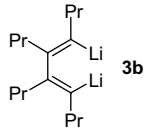
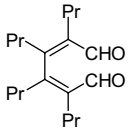
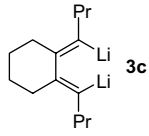
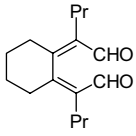
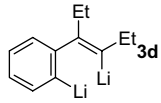
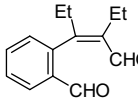
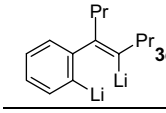
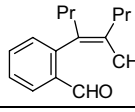


Scheme 1.

Table 1. Reaction of dillithiobutadienes **3** with DMF affording multi-substituted *cis*,*cis*-2,4-diene-1,6-dials **1**[a]

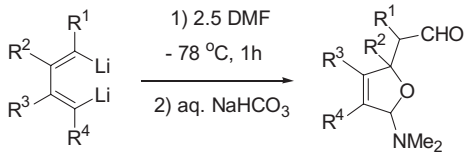
Dilithio reagent **3**	Product **1**	Yield/%[b]
 **3a**	 **1a**	61
 **3b**	 **1b**	51
 **3c**	 **1c**	44
 **3d**	 **1d**	83
 **3e**	 **1e**	77

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

the reaction proceeded smoothly, affording their corresponding 1,6-dials **1** (Scheme 1). Results are given in Table 1.

Unlike reactions between **3** and other substrates,[8–16] no cooperative action of the two alkenyllithio moieties towards one molecule of DMF was observed in these reactions, thus no formation of **4** was observed.[20] Instead, a small amount of compounds **5**, which were obviously formed from one molecule of **3** and two molecules of DMF, was obtained in a few cases when **3a**–**e** was used. Interestingly, although the reason is not clear yet, dilithio reagents **3f** and **3g** reacted with DMF to give **5a** and **5b** as the sole products, respectively (Eq. 1). No formation of their corresponding 1,6-dials was observed. Product **5a** was obtained as a mixture of more than five isomers with two major ones. The stereochemistry of both **5a** and **5b** has not been determined.

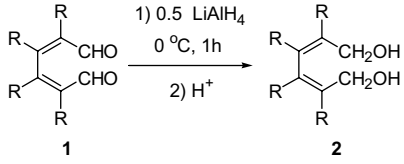
Reduction of thus formed 1,6-dials **1** with $LiAlH_4$ afforded their corresponding 1,6-diols **2** cleanly in excellent isolated yields (Table 2).[21] These types of 1,6-diols **2**



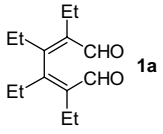
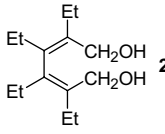
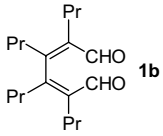
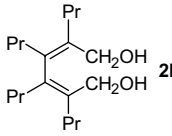
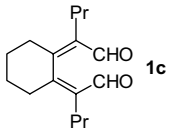
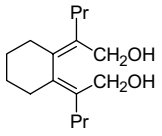
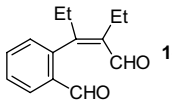
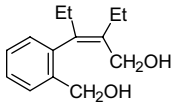
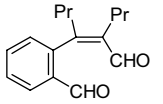
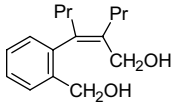
(1)

3f: $R^1 = R^2 = Me$, $R^3 = R^4 = Ph$
3g: $R^1 = R^4 = SiMe_3$, $R^2 = R^3 = Me$
5a: $R^1 = R^2 = Me$, $R^3 = R^4 = Ph$, combined isolated yield 55%
5b: $R^1 = R^4 = SiMe_3$, $R^2 = R^3 = Me$, 39% isolated yield

Table 2. Preparation of multi-substituted *cis*,*cis*-2,4-diene-1,6-diols **2** from 1,6-dials **1** and $LiAlH_4$[a]



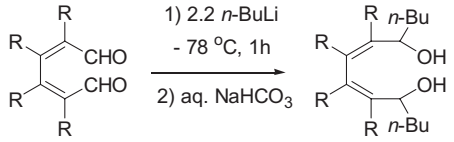
(2)

1,6-Dials **1**	Product **2**	Yield/%[b]
 **1a**	 **2a**	82
 **1b**	 **2b**	81
 **1c**	 **2c**	77
 **1d**	 **2d**	86
 **1e**	 **2e**	93

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

have been reported to prepare a variety of complex structures.[5–7] Treatment of 1,6-dials **1** with *n*-BuLi also result in formation of different types of 1,6-diols in good isolated yields (Eq. 3).[5–7,13,15]

A novel application of 1,6-diols was developed. Thus reaction of 1,6-diol **2h** with 4-fluorobenzaldehyde in the presence of high concentrated H_2SO_4 afforded the fused ring oxacycle **6** in 68% isolated yield (Eq. 4). The structures of the starting 1,6-diol **2h**[13] (Fig. 2) and



(3)

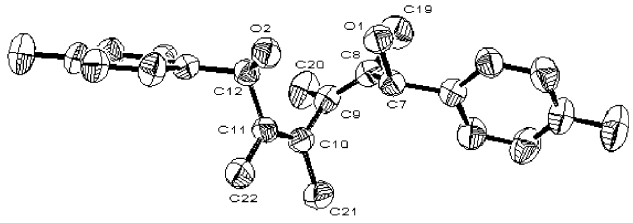


Figure 2. X-ray structure of **2h**.

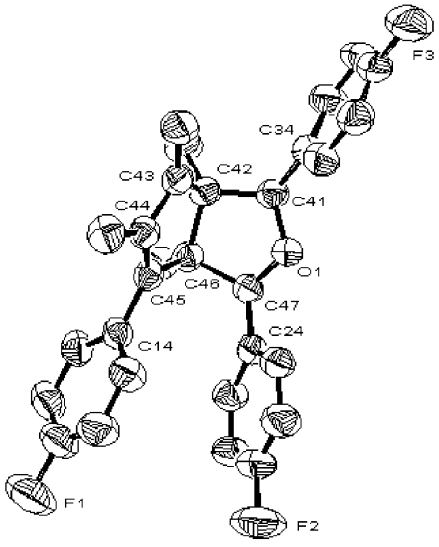
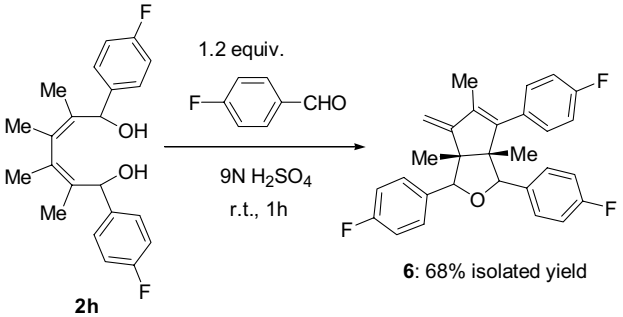
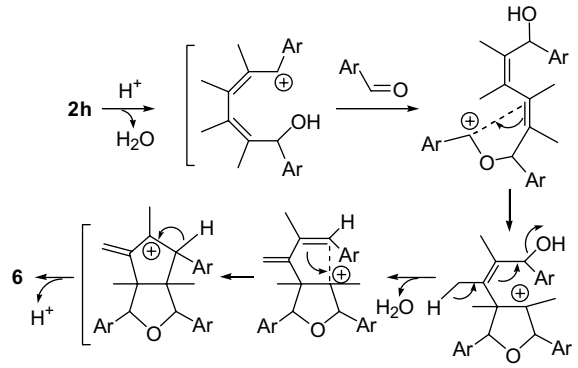


Figure 3. X-ray structure of **6**.

the product **6** (Fig. 3) have been determined by single crystal X-ray structural analysis.[22,23]



(4)



Scheme 2.

Given in Scheme 2 is a proposed reaction mechanism for the formation of **6** from **2h** and 4-fluorobenzaldehyde in the presence of high concentrated H_2SO_4. Further application of these otherwise unavailable stereodefined 2,4-diene-1,6-bis-electrophiles is in progress.

Acknowledgments

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19. Typical procedure for the preparation of 1,6-dial **1a**. To a 50 mL Schlenk tube containing 2.0 mmol of 1,2,3,4-tetraethyl-1,4-dilitho-1,3-diene **3a** in 20 mL diethyl ether at −78 °C was added 5.0 mmol of DMF. After the reaction mixture was stirred at −78 °C for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The extract was washed with water and brine and dried over $MgSO_4$. The solvent was then evaporated in vacuo and the residue was purified by column chromatograph (silica gel, diethyl ether/petroleum ether in 1:30) to afford the product **1a**. Colourless liquid. Isolated yield 61% (271 mg). IR (neat) 1673 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS): δ 1.01–1.09 (m, 12H), 2.26–2.49 (m, 6H), 2.66–2.79 (m, 2H), 9.59 (s, 2H); ^{13}C NMR ($CDCl_3$, TMS): δ 11.8, 13.7, 18.5, 25.7, 143.5, 157.4, 192.3; HRMS calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1611.
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21. Typical procedure for the preparation of 1,6-diol **2a**. To a 50 mL Schlenk tube containing 2.0 mmol of **1a** in 20 mL of ethyl ether, 1.0 mmol of $LiAlH_4$ was added at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, the reaction was quenched with 6 N H_2SO_4 and extracted with ether. The extract was washed with $NaHCO_3$, water and brine and dried over Na_2SO_4. The solvent was then evaporated in vacuo and the residue was purified by column chromatograph (silica gel, diethyl ether/petroleum ether in 1:3) to afford the product **2a**. White solid. Isolated yield 82% (371 mg). Mp 70–71 °C; ^1H NMR ($CDCl_3$, TMS): δ 0.84 (t, J = 7.5 Hz, 6H), 1.04 (t, J = 7.5 Hz, 6H), 1.74–1.97 (m, 2H), 2.08–2.48 (m, 6H), 3.61–3.83 (m, 2H), 3.91–4.20 (m, 4H); ^{13}C NMR ($CDCl_3$, TMS): δ 12.2, 13.5, 22.4, 23.2, 61.9, 136.1, 138.6; HRMS calcd for $[C_{14}H_{26}O_2Na]^+$ 249.1825, found 249.1821.
22. X-ray crystallographic data for **2h**: A colourless crystal having approximate dimensions of 0.40 × 0.35 × 0.08 mm was mounted on a glass fibre. X-ray data were collected on a Rigaku RAXIS RAPID IP diffractometer with graphite-monochromated Mo/Kα radiation (λ = 0.71073 Å). $C_{22}H_{24}F_2O_2$, fw = 358.41, triclinic, space group P-1, a = 12.061(1) Å, b = 13.239(2) Å, c = 6.963(1) Å, V = 965.6(2) $Å^3$; Z = 2; D_{calcd} = 1.233 g cm^{-3}; R_1 = 0.0595, wR_2 = 0.1389. CCDC 268480.
23. X-ray crystallographic data for **6**: A colourless crystal having approximate dimensions of 0.40 × 0.30 × 0.15 mm was mounted on a glass fibre. X-ray data were collected on a Rigaku RAXIS RAPID IP diffractometer with graphite-monochromated Mo/Kα radiation (λ = 0.71073 Å). $C_{29}H_{25}F_3O$, fw = 446.49, triclinic, space group P-1, a = 10.728(1) Å, b = 12.137(2) Å, c = 9.271(1) Å, V = 1140.2(3) $Å^3$; Z = 2; D_{calcd} = 1.301 g cm^{-3}; R_1 = 0.0486, wR_2 = 0.1133. CCDC 268382.