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LITHIATION OF 2,6,6-1-[2-(1,4-DIOXENYL)]-1-CYCLOHEXENE: AN UNEXPECTED DIOXENE RING-CLEAVAGE

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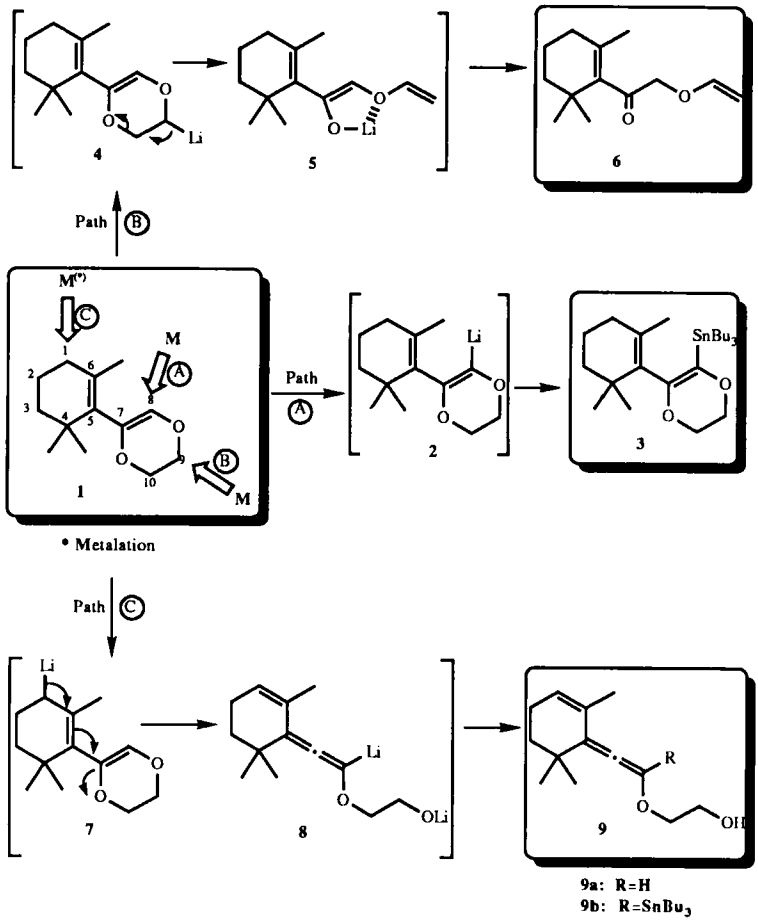
***Summary** : Metalation of the title compound **1** with strong lithiating agents leads to ring-opened products. Conditions for regioselective deprotonation affording either α,β-unsaturated ketone **6** or allenic product **9** are described.*

In the course of our ongoing studies on the use of 1,4-dioxene in organic synthesis[1], we have recently described the preparation of substituted 2-vinyl-dioxenes[2]. In particular, 2,6,6-1[2-(1,4-dioxenyl)]-1-cyclohexene **1**, readily obtained from 2,2,6-trimethylcyclohexanone, appeared to be a useful intermediate in the synthesis of natural products. To this end, we argued that **1** would undergo regioselective metalation affording vinyllithium derivative **2** which could react with various electrophiles. Instead, treatment of **1** with lithiating reagents gave ring opened compounds **6** and **9** as major products. We present here these unexpected results.

According to early reports of Baldwin, Boeckman and others[3] related to metalation of cyclic and acyclic vinyl ethers, and to our experience on lithiation of unsubstituted 1,4-dioxene[1], we assumed that lithiation of **1** with t-BuLi should preferably occur at the position adjacent to the oxygen atom leading to vinyllithium derivative **2** (scheme, path A). Unexpectedly, treatment of **1** with t-BuLi in THF at - 70°C, followed by quenching of the reaction mixture with $ClSnBu_3$ gave compound **6** as the major product.



Scheme

The formation of **6** probably proceed through deprotonation α to heteroatom (at C-9 position), followed by eliminative cleavage of the dioxene ring as indicated in the scheme (path B). This oriented metalation can be understood in terms of steric hindrance around the more acidic vinyl hydrogen which might render the approach of a bulky base such as t-BuLi difficult. Moreover, it is not unreasonable to assume that the formation of intermediate **5** is the result of a more favorable lithium ion association with the oxygen atoms[4].

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TABLE - Metalation of 1

Entry	Lithiating Base	Conditions	Products [Yields* (%)]			
			3	**6**	**9**	**1**
1	t-BuLi (1.1 eq.)	a) THF, -70°C b) Bu_3SnCl	15	32	—	25
2	n-BuLi/ t-BuOK	THF, -70°C	—	75	—	—
3	t-BuLi (3 eq.)	THF-HMPA**	—	38	20	—
4	sec-BuLi (1.1 eq)	a) THF-TMEDA*** -70°C b) Bu_3SnCl	—	47	—	11
5	PhLi (3 eq)	THF-HMPA (4 : 1)	—	—	53	—

*Yields are unoptimized and refer to isolated material, purified by flash chromatography

**Hexamethylphosphoramide ***N,N,N',N'-tetramethylenediamine.

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In presence of hexamethylphosphoramide (HMPA) as cosolvant, metalation of **1** with t-BuLi led to **6** along with the alkoxyallenic product **9a**. The unexpected formation of this compound is probably initiated by allylic deprotonation (C-1 position). In this reaction, the driving force is also likely to be provided by the eliminative dioxene ring-opening (scheme, path C).When the reaction mixture was quenched with Bu_3SnCl, allenic stannane **9b** was formed in agreement with a lithiated intermediate of structure **8**.

In order to determine the optimal conditions for regioselective metalation of **1**, other lithiating reagents (n-BuLi, n-BuLi/t-BuOK, sec-BuLi, PhLi, LDA) with or without chelating agents (HMPA, TMEDA) were investigated. The most signifiant results are summarized in the Table.

As can be seen in the Table, the best conditions found for regioselective metalation at C-9 position affording exclusively α,β-unsaturated ketone **6** was n-BuLi/t-BuOK (Schlosser's base)[5] in THF at - 70°C. In contrast metalation at the allylic position (C-1) was performed by mean of an excess PhLi in the presence of

HMPA[6]. This reaction lead exclusively to the allenic product **9a** (entry 5). Unfortunately, we were unable to find conditions to cleanly convert **1** into the desired **3** .

As expected, n-BuLi and LDA have been found ineffective. The starting diene **1** was recovered completely unchanged after treatment with LDA, LDA-HMPA or n-BuLi ; it was moreover the major component along with small amounts of **6** and **9a** when n-BuLi/HMPA was used as metalating reagent.

Although unexpected, the dioxene ring-cleavage of **1** afforded compounds **6** and **9** which may be useful intermediates for the synthesis of natural products.

EXPERIMENTAL

All reactions were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. N,N,N',N'-tetramethylene-diamine (TMEDA) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride and stored over molecular sieves. IR spectra were recorded on a Perkin-Elmer spectrometer 399 as solutions in CCl_4. ^1H and ^{13}C NMR were recorded on a Bruker W.P.200 instrument as solutions in $CDCl_3$. All reactions were monitored by TLC carried out on 0.2 mm E. Merck silica gel plates ($60F_{254}$) using U.V. light and 5 % ethanolic-phosphomolybdic acid and heat as developing agent. Flash chromatography was performed on 50-63 mm, (400-230 mesh) silica gel 60.

Reaction of **1** with t-BuLi (entry 1)

To a stirred solution of **1** (208 mg, 1 mmol) in THF (1.5 ml) cooled at - 78°C was added t-BuLi (1.7 M/pentane, 0.65 ml, 1.1 mmol). After 2 h, neat tributyltin chloride (0.55 ml, 2 eq.) was rapidely added at - 78°C and the mixture was allowed to warm to 0°C. Stirring at 0°C was continued for 2.5 h before addition of aqueous ammonium chloride. The mixture was extracted with ether and the organic extracts were washed with 10 % KF solution, water, brine and dried (K_2CO_3). The crude product was separated by flash chromatrography with ether-petroleum ether (5 : 95) as eluant affording :

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a) 75 mg (15 %) of **3** as light yellow oil : IR 3620, 1945, 1410, 1070 cm^{-1} ^1H NMR δ 1.09 (s, 3H) ; 1.10 (s, 3H) ; 1.75 (s, 3H) ; 2.00 (t, J = 6.4 Hz, 2H) ; 3.94 - 3.96 (m, 2H) ; 4.09 - 4.11 (m, 2H) ; ^{13}C NMR δ 10.3 (t), 13.8 (q), 19.1 (t), 22.1 (q), 27.4 (t), 29.0 (q) , 29.1 (t), 30.0 (q), 32.0 (t), 32.0 (t), 34,0(s), 39.1 (t), 64.2 (t), 64.7 (t), 134.7 (s), 135.8 (s), 139.8 (s), 140.6 (s).

b) 52 mg (25 %) of starting diene **1**[2] .

c) 68 mg (32 %) of **6** as colorless liquid : IR 1715, 1700, 1640, 1615, 1200, 900 cm^{-1} ; ^1H NMR δ 1.03 (s, 6H) ; 1.46 (m, 2H); 1.56 (s, 3H) ; 1,66(m,2H) ; 1.94 (t, J = 6.4 Hz, 2H) ; 4.06 (dd, J = 6.4 and 2.4 Hz, 1H) ; 4.19 (dd, J = 14.2 and 2.4 Hz, 1H) ; 4.35 (s, 2H) ; 6.45 (dd, J = 14.2 and 6.4 Hz, 1H) ; ^{13}C NMR δ 18.8 (t), 21.1 (q), 28.6 (q, 2C), 31.2 (t), 33.3 (s), 38.6 (t), 74.0 (t), 87.9 (t), 132.4 (s), 139.7 (s), 151.0 (d), 205.4 (s).

Reaction of **1** with t-BuLi-HMPA (entry 3)

To a stirred solution of **1** (208 mg, 1 mmol) in THF (1.5 ml) and HMPA (0.5 ml) cooled at - 70°C was added t-BuLi (1.7 M/pentane, 1.7 ml, 3 mmol) and stirring was continued for 1 h at - 70°C. After hydrolysis with aqueous ammonium chloride and extraction with ether, the crude product was flash chromatographed with ether-petroleum ether (1 : 9 then 1 : 4) as eluant affording **6** (80 mg, 38 %) and **9a** (40 mg, 20 %) as colorless liquid :

IR 3620, 1945, 1410, 1070 cm^{-1} ; ^1H NMR δ 0.97 (s, 3H) ; 1.00 (s, 3H) ; 1.46 (t, J = 6.2 Hz, 2H) ; 1.66 (br. s, 3H) ; 2.08 - 2.10 (m, 3H) ; 3.55 (t, J = 4.1 Hz, 2H) ; 3.75 (t, J = 4.1 Hz, 2H) ; 5.65 (m, 1H) ; 6.64 (s, 1H) ; ^{13}C NMR δ 21.6 (q), 23.1 (t), 28.2 (q), 28.4 (q), 33.8 (s), 36.1 (t), 61.6 (t), 69.2 (t), 123.4 (d), 127.0 (d), 128.1 (s), 129.4 (s), 189.0 (s).

When the reaction mixture was quenched with Bu_3SnCl, allenic stannane 9b was obtained as light yellow oil:

IR 3590, 1890, 1630, 1450, 1070, 1045 cm^{-1} ; ^1H NMR δ 0.77-1.50 (m, 37H), 1.65 (d, J=1,3 Hz, 3H), 1.80-1.90(m, 1H), 2.00-2.14(m, 2H), 3.57-3.71(m, 4H), 5.50-5.60(m, 1H); ^{13}C NMR δ 10.5(t, 3C), 13.8(q,3C), 21.9(q), 23.2(t), 27.3(t, 3C), 28.2(q), 28.7(q), 29.3(t, 3C), 33.3(s), 36.5(t), 61.9(t), 70.5(t), 120.7(s), 124.7(d), 130.4(s), 132,4(s), 190.3(s).

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Reaction of **1** with n-BuLi/t-BuOK (Schlosser's base) (entry 2)

To a stirred suspension of t-BuOK (260 mg, 1.78 mmol) in THF (2 ml) cooled at -70°C was added n-BuLi (1.6 M/hexane, 1.4 ml, 2.24 mmol). After stirring for 15 min, a solution of diene **1** (180 mg, 0.86 mmol) in THF (1 ml) was added dropwise at - 70°C and stirring was continued until the disappearance of starting material (4 h). Hydrolysis with aqueous NH_4Cl and extraction with ether gave the crude product which was purified by flash chromatography affording 140 mg of **6** (75 %).

Reaction of **1** with PhLi-HMPA (4 : 1) (entry 5)

To a stirred solution of **1** (150 mg, 0.72 mmol) in THF (2 ml) and HMPA (0.6 ml) cooled at - 70°C, was added PhLi (2.0 M in cyclohexane/ether, 1.1 ml, 2.2 mmol). Stirring was continued at the same temperature until the disappearance of the starting material. After hydrolysis with aqueous NH_4Cl and extraction with ether, the crude product was purified by flash chromatography with ether-petroleum ether (1 : 3) as eluant affording 80 mg (53 %) of pure **9a** .

REFERENCES AND NOTES

1 . For the review on 1,4-dioxene in organic synthesis, see : Fétizon, M., Goulaouic, P., Hanna, I. ; Heterocycles, 1989,**28,** 521.

2 . Fétizon, M., Goulaouic, P., Hanna, I., Prangé, T. ; J. Org. Chem., 1988, **53,** 5672 .

3 . Boeckman, R.K., Bruza, K.J. ; Tetrahedron, 1981, **37,** 3997 and references cited therein.

4 . For a review on stereo- and regiocontrol by complex induced proximity effects, see : Beak, P., Meyers, A.I. ; Acc. Chem. Res., 1986, **19,** 356.

5 . For a review on this superbase, see : Schlosser, M. ; Pure Appl. Chem., 1988, **60,** 1627.

6 . For the reactivity of lithium reagent-HMPA complexes, see : Reich, H.J., Greew, D.P. ; J. Am. Chem. Soc., 1989, **111,** 8729 and references cited therein.

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