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Preparation and Reactivity of Lithium 1,4-Dioxenyl Cuprates

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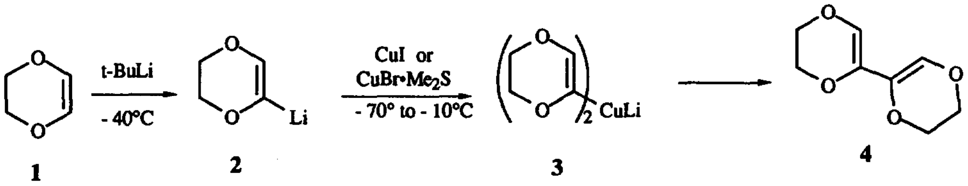
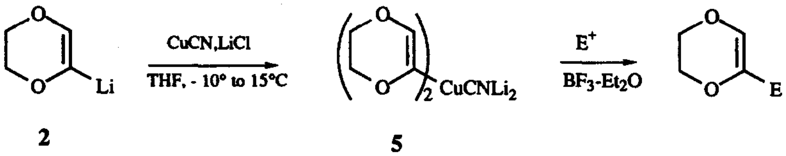
***Abstract:** Reactions of lower and higher order cuprates generated from lithiated 1,4-dioxene and copper (I) species, with epoxides and α,β-unsaturated ketones are described.*

1,4-dioxene **1** has found to be a valuable reagent for C-C bond formation with simultaneous introduction of oxygenated functionalities.[1] In particular, addition of dioxenyllithium **2** to ketones and aldehydes leads to allylic alcohols, which may be transformed into a variety of functionalized compounds via e.g. dehydration, oxidation or hydrolysis.[2] In order to extend the synthetic utility of the dioxenyl moiety, we now report the development of new 1,4-dioxenyl cuprates and their reactivity toward some conjugated enones and epoxides.

Initial attempts to deliver the dioxenyl ligand to cyclohexenone by using the lower order cuprate **3** were unsuccessful. Thus treatment of dioxenyllithium **2** (2 equiv) with CuI or $CuBr{\bullet}Me_2S$ complex (1 equiv) in THF at -70°C followed by addition of 2-cyclohexen-1-one led only to dimer **4**[3] along with the recovered unchanged ketone. The formation of Wurtz-like coupling material **4**, which has been observed particularly with 5-methoxy-3,4-dihydro-2H-pyran,[4] is presumably the result of lack of reactivity and thermal instability associated with Gilman reagents (R_2CuLi).[5] However, when boron trifluoride etherate (1 equiv) was added, the reactivity of the cuprate reagent was dramatically increased : the expected 1,4-addition product **6** from cyclohexenone and **3** was isolated in 75% yield. This effect was also observed with epoxides albeit to a lesser extent. Thus, epoxystyrene **7** was regioselectively opened, affording primary homoallylic alcohol **8** in moderate yield (41%), cyclohexene oxide **9** gave **10** only in 13% yield, and benzyl glycidol **11** was completely unreactive under the same conditions (see Table).



In an effort to improve the efficiency of these reactions we next examined the higher order cyanocuprate 5.[5,6] Optimal conditions for the generation of lithium di(1,4-dioxenyl)cyano cuprate **5** was found by addition of one equivalent of dioxenyllithium to 0.5 equivalent of cuprous cyanide solubilized as its lithium chloride (0.5 equiv) complex[7] at -15°C. The reactivity of this cuprate was assessed by its conjugate addition to cyclic enones and by nucleophilic epoxide opening. As for lower order cuprates, the presence of $BF_3{\bullet}Et_2O$ led to enhancement in product yields relative to those observed in the absence of this Lewis acid. The results are summarized in the Table.



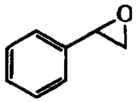
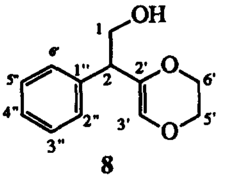
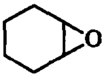
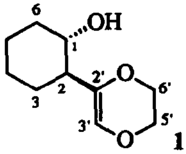
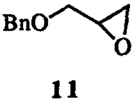
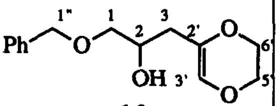
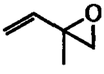
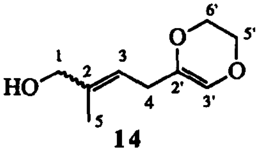
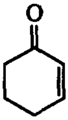
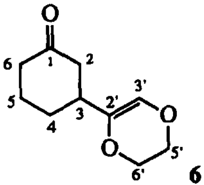
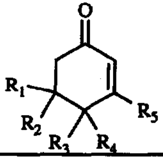
A typical experimental procedure is as follows: t-BuLi 1.7M (9 mL, 15.3 mmol) was added dropwise to 1,4-dioxene (1.5 g, 17.4 mmol) cooled to -30°C and the resulting white precipitate was stirred at -10°C for 30 min. Freshly distilled THF (20 mL) was then added and the resulting solution was transfered via cannula to a solution of cuprous cyanide (685 mg, 7.65 mmol) and lithium chloride (324 mg, 7.65 mmol) in 10 mL of dry THF at -15°C. The reaction mixture which gradually turned yellow then red was vigorously stirred until homogenization which generally occured between -10°C and +15°C. The resulting mixture was cooled to -70°C and the electrophile (3.82 mmol) and $BF_3{\bullet}Et_2O$ (7.65 mmol) were successively added. The reaction was monitored by TLC until complete conversion. The reaction mixture was then poured into a rapidly stirring solution of 10% aqueous ammonium hydroxide and ammonium chloride. After stirring for 30 min, the aqueous layer was extracted with ether. Further work-up and purification by flash chromatography on silica gel gave the desired addition product.

As shown in the Table, reaction of **5** with acyclic epoxides gave expected products in good yield. However, with poorly reactive cyclohexene oxide **9**, the dioxenyl adduct **10** was isolated in only 16% yield[8] as the trans isomer.[9] As expected, reaction of **5** with isoprene oxide **13** resulted in a regiospecific S_N2' opening[10] in high yield. With styrene oxide, the reaction was found to proceed with complete regioselectivity with nucleophilic attack at the more hindered benzylic position.[11]

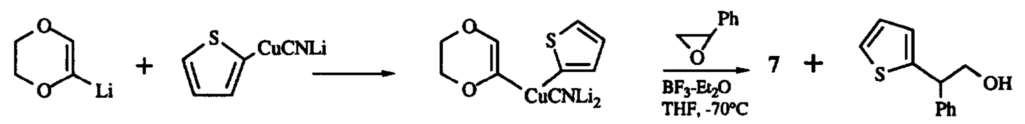
Reaction of cyanocuprate **5** with cyclohexenone gave the highest yield of adduct **6** (94%). At the same time, no coupling material **4** was detected. However, the efficacy of this cuprate sharply dropped with substituted cyclohexenones. Thus, 3-methylcyclohexenone **15**, isophorone **16** and 4,4-dimethylcyclohexenone **17** failed to yield any adduct. *It is worthy of note that addition of trimethylsilyl chloride instead of* $BF_3{\bullet}Et_2O$ *to the reaction of* **5** with cyclohexenone has no effect, the starting enone being recovered unchanged.

Incorporation of a dummy ligand was also examined. Thus, when mixed cyanocuprate **18** formed *in situ* from commercially available lithium 2-thienylcyanocuprate (1 equiv) and dioxenyllithium (1 equiv) in THF at -70°C was allowed to react with epoxystyrene in the presence of $BF_3{\bullet}Et_3O$, the expected dioxenyl derivative **8** was isolated along with **19**[3] which was produced by the delivery of the thienyl ligand as nucleophile.

Table

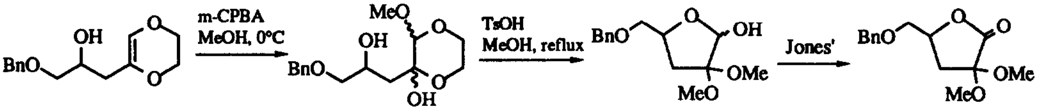
Electrophiles	Products	Yields[a] Physical State	Spectroscopic Data
 **7**	 **8**	3[b] : 67 % 5[c] : 41 % crystal mp = 66-67°C (Petroleum Ether)	^{1}H NMR : 7.20-7.13 (m, 5H, Ph); 5.85 (s, 1H, 3'); 3.90-3.77 (m, 5H, 5', 6' & 1); 3.60 (dd, 1H, 1, J = 6.1 & 10.8); 3.24 (dd, 1H, 2, J = 6.1 & 8.0); 2.35 (s broad, 1H, OH) ppm. ^{13}C NMR: 139.5 (s, 2'); 136.6 (s, 1"); 128.3 (d, 2" & 6" or 3" & 5"); 128.0 (d, 2"&6" or 3"&5"); 126.8 (d); 124.1 (d); 64.5 (t, 6' or 5'); 63.8 (t, 5' or 6'); 63.5 (t, 1); 49.4 (d, 2) ppm.
 **9**	 **10**	3 : 13 % 5 : 16 % crystal mp = 75-76°C (Petroleum Ether)	^{1}H RMN : 5.88 (s, 1H, 3'); 4.05-3.93 (m, 4H, 5' & 6'); 3.42 (dt, 1H, 1, J = 4.4 et 9.5); 2.27 (s broad, 1H, OH); 1.98 (m, 1H, 2); 1.70-1.00 (m, 8H, 3, 4, 5 & 6) ppm. ^{13}C RMN : 137.6 (s, 2'); 123.3 (d, 3'); 70.6 (d, 1); 64.7 (t, 5' or 6'); 64.1 (t, 6' ou 5'); 47.8 (d, 2); 34.1 (t); 28.8 (t); 25.5 (t); 24.6 (t) ppm.
 **11**	 **12**	3 : 0 % 5 : 66 % oil	^{1}H NMR : 7.37-7.28 (m, 5H, Ph); 5.89 (s, 1H, 3'); 4.56 (s, 2H, 1"); 4.07-3.92 (m, 5H, 2, 5' & 6'); 3.54 (dd, 1H, 1, J = 4.0 & 9.6); 3.43 (dd, 1H, 1, J = 6.5 & 9.6); 2.97 (s broad, 1H, OH); 2.17 (d, 2H, 3, J = 6) ppm. ^{13}C RMN : 137.9 (s, Ph); 135.9 (s, 2'); 128.1 (d); 127.5 (d); 123.3 (d, 3'); 73.4 (t, 1"); 73.0 (t, 1); 68.0 (d, 2); 64.3 (t, 5' or 6'); 63.5 (t, 6' or 5'); 34.5 (t, 3) ppm.
 **13**	 **14**	5 : 88 % oil	^{1}H NMR : 5.68 (s, 1H, 3'); 5.29 (td, 1H, 3, J = 7 & 1.3); 3.94-3.80 (m, 6H, 1, 5' et 6'); 3.17 (s, 1H, OH); 2,58 (d, 2H, 4, J = 7); 1.53 (s, 3H, Me 5) ppm. ^{13}C RMN : 136.7 (s); 136.1 (s); 121.7 (d); 120.5 (d); 67.8 (t, 1); 64.4 (t, 5' or 6'); 63.5 (t, 5' or 6'); 28.6 (t, 4); 13.2 (q, Me 5) ppm.
	 **6**	3 : 75 % 5 : 94 % oil	^{1}H NMR : 5.60 (s, 1H, 3'); 3.81-3.67 (m, 4H, 5' & 6'); 2.11-1.30 (m, 9H) ppm. ^{13}C NMR : 209.8 (s, 1); 138.6 (s, 2'); 121.4 (d, 3'); 64.1 (t, 5' or 6'); 63.4 (t, 6' or 5'); 44.5 (t); 40.5 (t); 39.4 (d, 3); 28.5 (t); 24.1 (t) ppm.
	**15** : $R_1 = R_2 = R_3 = R_4 = H, R_5 = Me$ **16** : $R_1 = R_2 = R_5 = Me, R_3 = R_4 = H$ **17** : $R_1 = R_2 = R_5 = H, R_3 = R_4 = Me$ no reaction		

[a] Isolated yields of analytically pure compounds ; [b] Using lower order cuprate 3 ; [c] Using higher order cuprate 5.



2 18 19

Although dioxenyl cuprates are less reactive than their divinyl or di(α-alkoxyvinyl)[5] analogs, they are useful reagents for the introduction of the dioxenyl moiety into conjugated enones and epoxides. An application of this new reagent to the synthesis of butanolide **22** starting from benzyl glycidol **11** is illustrated in the following scheme.



12 20 21 22

Conversion of the homoallylic alcohol **12** to the deoxyribose derivative **21** has been achieved by oxidation with m-CPBA in methanol at 0°C followed by treatment of the crude mixture **20** with TsOH in refluxing methanol. Oxidation of the resulting anomeric mixture **21** with Ag_2CO_3 on Celite or with Jones reagent afforded **22** in nearly quantitative yield.

References and Notes

1. For a recent application of 1,4-dioxene to the synthesis of the AB ring system of forskolin see: Blanchot-Courtois, V.; Fétizon, M.; Hanna, I. *Tetrahedron Lett.* **1992**, *33*, 5061-5064.
2. For a review on the chemistry of 1,4-dioxene see: Fétizon, M.; Goulaouic, P.; Hanna, I. *Heterocycles* **1989**, *28*, 521.
3. All new compouds have been fully characterized by IR, 200-MHz ^1H NMR and ^{13}C NMR spectroscopy and possess satisfactory C,H analyses or exact mass.
4. Cox,T. P.; Lister, S. Gallagher, T. *J. Chem. Soc. Perkin Trans. I* **1990**, 3151.
5 For a recent review on organocopper reagents see: Lipshutz, B.H.; Sengupta,S. in *Org. React.* **1991**, *41*, pp.135-632.
6. For a review on higher order cyanocuprates see: Lipshutz, B. H. *Synlett* **1990**, 119.
7. Knochel,P.; Yeh, M.C.P.; Berk, S. C.;Talbent, J. *J. Org. Chem.* **1988**, *53*, 2390.
8. The reduced reactivity of cyclohexene oxide toward lithium dihydropyranyl cuprate has recently been reported : Alexakis, A.; Hanaizi, J.; Jachiet, D.; Normant, J.F. *Tetrahedron Lett.* **1990**, *31*, 1271.
9. The opening of such epoxides by a purely anti process with organocopper reagents has been reported . Alexakis, A;; Jachiet, D.; Normant, J.F. *Tetrahedron* **1986**, *42*, 5607.
10. For a review on S_N2'addition of organocopper reagents to vinyloxiranes, see : Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503.
11. In the presence of a Lewis acid, the preferred site of attack is the position which can best accomodate a positive charge. For example see: Moberg, C.; Rakos, L.; Tottie, L. *Tetrahedron Lett.* **1992**, *33*, 1291 and references cited therein.

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