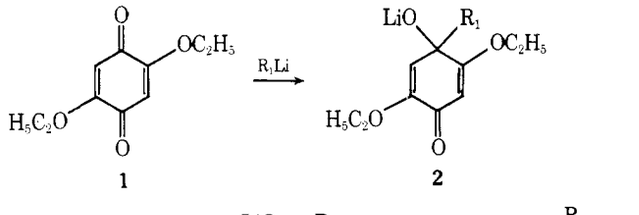
A Simple Synthetic Route to 2,5-Disubstituted 1,4-Benzoquinones

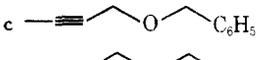
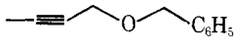
Summary: For the first time synthetic methodology is presented which allows the facile construction of 1,4-benzoquinones which are alkylated, alkynylated, or arylated at the 2,5 positions. Specifically, 2,5-diethoxy- and 2,5-dichloro-3,6-dimethoxy-1,4-benzoquinone react with organolithium reagents via 1,2 addition to the carbonyl groups. The enol ether linkages in the resulting adducts undergo acid hydrolysis to give the 2,5-disubstituted 1,4-benzoquinones.

Sir: A wide variety of naturally occurring quinones exist in which the nucleus is functionalized at the 2 and 5 positions.[1] However, no synthetic methodology currently exists which allows the facile construction of such structural features. Described here is a method which provides a simple, "one pot" solution to this problem. Specifically, we have observed that organolithium reagents undergo 1,2 addition to the carbonyl groups of 2,5-diethoxy-1,4-benzoquinone[2] (1). Acid hydrolysis of the resulting adducts, **3a–d,** gives the corresponding 2,5-disubstituted 1,4-benzoquinones (**4a–d**) in respectible yields. This total transformation can be accomplished without isolation of the intermediate products. It is also noteworthy that this technique can be employed to make unsymmetrically substituted quinones by utilizing two different organolithium reagents. This methodology for the synthesis of unsymmetrical quinones is particularly good when lithium alkynylide is employed as the first reagent. Attempts to make unsymmetrical alkyl, aryl, or alkylaryl 1,4-benzoquinones generally gave an appreciable amount of the symmetrical quinone. However, since the alkynyl group possesses significant synthetic versatility, one can envisage its utility for the construction of a large variety of unsymmetrically substituted quinones.

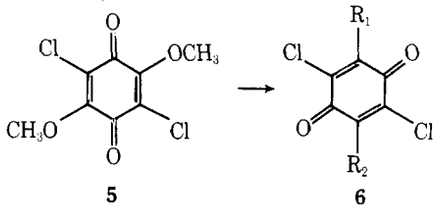
The general procedure involves treatment of a diethyl ether/THF (1:1) solution of the quinone with the organolithium reagents (Scheme I). The reaction is accomplished at −22 to 0 °C depending upon the specific example. After approximately 8 h the reaction mixture is quenched with ammonium chloride and a few drops of 2 N H_2SO_4 are added, which accomplishes the hydrolysis of one of the enol ether linkages. The solvent is then removed in vacuo and the residue dissolved in a mixture of glyme and concentrated H_2SO_4, which accomplishes the final hydrolysis. The quinone products were then isolated by column chromatography on silica gel. The structures of the new products were assigned on the basis of the following data. 2,5-Di(3-benzyloxy-1-propynyl)-1,4-benzoquinone (**4c**); mp 70–72 °C; ^1H NMR ($CDCl_3$, δ) 4.33 (s, 2 H), 4.53 (s, 2 H), 6.97 (s, 1 H), 7.40 (s, 5 H); IR (Nujol, cm^{-1}) 2215, 1650, 1570. Anal. C, 78.82; H, 5.20. 2-(3-Benzyloxy-1-propynyl)-5-phenyl-1,4-benzoquinone (**4d**); mp 96–97 °C; ^1H NMR ($CDCl_3$, δ) 4.37 (s, 2 H), 4.70 (s, 2 H), 6.97 (s, 1 H), 7.03 (s, 1 H), 7.43 (s, 5 H), 7.50 (s, 5 H); IR (Nujol, cm^{-1}) 2210, 1657, 1645, 1597, 1585. Anal. C, 80.73; H, 4.95.

Scheme I

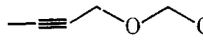


	R_1	R_2	Yield, %
a	C_6H_5	C_6H_5	62[3a]
b	CH_3	CH_3	52[3b]
c			56
d		C_6H_5	60

It was of interest to extend the scope of this reaction to include more highly substituted quinones, particularly those having halogens at the 3 and 6 positions. In certain situations quinones such as these provide a synthetic advantage, since the halogen substituents are easily replaced by a variety of nucleophiles. For example, hydroxyquinones can be obtained from the corresponding chloroquinones under hydrolytic conditions, and a number of natural products contain the 2,5-dialkyl- (or aryl-) 3,6-dihydroxy-1,4-benzoquinone moiety.[1] A specific example is polyporic acid, 2,5-dihydroxy-3,6-diphenyl-1,4-benzoquinone, which has been obtained by hydrolysis of the corresponding 2,5-dichloroquinone **6a**.[4] It was, in fact, found that when 2,5-dichloro-3,6-dimethoxy-1,4-benzoquinone (**5**)[5] was subjected to the methodology outlined here, the corresponding 2,5-disubstituted-3,6-dichloro-1,4-benzoquinones **6a–d** were realized.



5 **6**

	R_1	R_2	Yield, %
a	C_6H_5	C_6H_5	50
b	C_6H_4-*p*-OCH_3	C_6H_4-*p*-OCH_3	50[6b]
c	CH_3	CH_3	64[7]
d		CH_3	55

Structural data for the previously unknown 2-(3-benzyloxy-1-propynyl)-3,6-dichloro-5-methyl-1,4-benzoquinone (**6d**) follows: mp 99–100 °C; ^1H NMR ($CDCl_3$, δ) 2.18 (s, 3 H), 4.40 (s, 2 H), 4.60 (s, 2 H), 7.45 (s, 3 H); IR (Nujol, cm^{-1}) 2270, 1680, 1670, 1570. Anal. C, 60.95; H, 3.74; Cl, 21.10.

Although a systematic study of the reactions of quinones with organometallic reagents has never appeared, one thinks of such reactions as being fraught with difficulties due to electron-transfer processes. Indeed it has been observed that Grignard reagents react with simple quinones to give very complex reaction mixtures.[8] In the work described here, one is presumably circumventing such complex reaction pathways by utilizing the alkoxy-substituted quinones. The reduction

potential of such quinones would be lowered and electron transfer reduced.[9]

The synthetic methodology outlined in this manuscript provides potentially the simplest route to 2,5-disubstituted 1,4-benzoquinones and complements recent advances directed toward the monoalkylation or arylation of the quinone nucleus. Particularly noteworthy in this regard are the utilization of trimethylsilyl cyanide (TMSCN) protected quinones,[10] the use of lithium salts of 1-bromo-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (a latent quinone carbanion),[11] the reactions of quinones or protected bromoquinols with π-allyl–nickel complexes,[12] the utilization of monoketals of quinones,[13] and the use of 1,4-dimethoxynaphthyllithium.[14]

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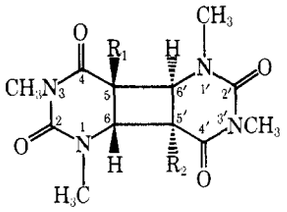
C-Alkylation and Deuterium Exchange of Cyclobutane–Dipyrimidines

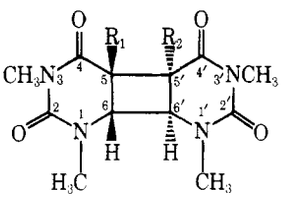
Summary: A novel method for C-alkylation and deuteration of pyrimidine dimers with retention of configuration is described.

Sir: Generally, it is agreed[1-5] that the most significant breakthrough in nucleic acid photochemistry was the isolation and identification of the thymine dimer (Thy<>Thy)[6] by Beukers and Berends[7] and by Wang.[8] As pyrimidine (Pyr) photodimerization has gained significance in biological systems,[9,10] it has become one of the most intensively studied topics.[11] However, reports concerning studies of the chemistry of Pyr dimers are infrequent.[2,12]

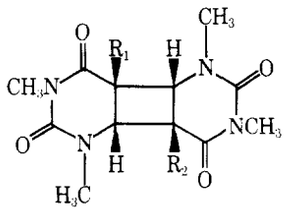
N-Methylation of uracil dimer (Ura<>Ura) was first found[13] to give primarily Me^3Ura<>Me^3Ura. With dimethyl sulfate and diazomethane, Ura<>Ura yielded a mixture of di- and trimethyl derivatives.[2] However, complete methylation was obtained when *cis,syn-* and *cis,anti-*Ura<>Ura were treated with methyl iodide and silver oxide in dimethylformamide.[14] Finally, the complete methylation of



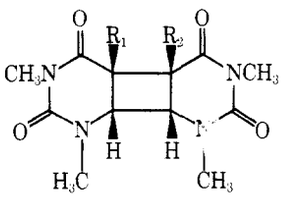
I(trans,anti)



II(trans,syn)



III(cis,anti)



IV(cis,syn)

a, $R_1 = R_2 = H$	Me_2Ura<>Me_2Ura
b, $R_1 = CH_3$; $R_2 = H$	Me_2Thy<>Me_2Ura
c, $R_1 = CH_3$; $R_2 = CH_3$	Me_2Thy<>Me_2Thy
d, $R_1 = CH_2CH_3$; $R_2 = H$	Me_2EtUra<>Me_2Ura
e, $R_1 = R_2 = CH_2CH_3$	Me_2EtUra<>Me_2EtUra
f, $R_1 = R_2 = C_6H_5CH_2$	Me_2BzUra<>Me_2BzUra
g, $R_1 = R_2 = D$	Me_2d_1Ura<>Me_2d_1Ura

the four isomeric Ura<>Ura to their corresponding Me_2Ura<>Me_2Ura was found to be feasible in dimethyl sulfoxide.[15]

Unexpectedly, we discovered that subsequent to complete N-methylation, C-methylation occurred when *trans,syn-* and *trans,anti-*Ura<>Ura were treated under similar conditions. This finding prompted us to investigate further the C-alkylation of cyclobutane derivatives.

The general procedure for C-alkylation was as follows. First, silver oxide (2 mmol, 460 mg) was added to a solution of Me_2Ura<>Me_2Ura (0.2 mmol, 56 mg) in $HCON(CH_3)_2$ (2 mL). To this mixture, 12 mmol of an alkyl halide was added; this was stirred for an appropriate period at ambient temperature. This reaction mixture was then poured into 200 mL of 5% NaCN solution to decompose the "silver complex".[16] The product was extracted three times with 200 mL of chloroform. Chloroform was evaporated from the combined extracts, and the residue was applied on silica gel thin-layer plates for chromatography with an eluent of chloroform/acetone (2:1). We found that the R_f values for dialkylated compounds are greater than the value of the monoalkylated products which, in turn, are greater than those of the starting materials. For this reason, these product mixtures were easily separated. The product was then eluted with methanol and recrystallized. The reaction conditions and the properties of the alkylation products are summarized in Table I.

We found that C-methylation of cis isomers is slower than for trans isomers (see Table I). This appears to correlate with our observation in deuterium exchange of the dimers. In this process, a solution of a dimer in D_2O was treated with 2 molar equiv. of silver oxide at ambient temperature with stirring for 24 h, and the insoluble material was removed by filtration. The deuterated product was then extracted from the filtrate with chloroform. After being dried over anhydrous Na_2SO_4, chloroform was evaporated. The residue was dissolved in $CDCl_3$ for the NMR analysis of the extents of deuteration. As can be seen from Table II, deuterated Ia and IIa both showed only three singlets, with the disappearance of the signal corresponding to C(5)H. This clearly indicates that "complete"deuteration at C(5) to C(5)D occurred. However, after similar deuterium exchange, IIIa and IVa gave quite complex spectra showing a pair of "pseudo" triplets for C(5)H and C(6)H. This evidence suggests that cis dimers were only par-