Tetrahedron Letters,Vol.24,No.2,pp 131-134,1983 0040-4039/83/020131-04$03.00/0
Printed in Great Britain

ADDITION OF FUNCTIONALIZED ORGANOLITHIUM REAGENTS TO p-BENZOQUINONES AND CYCLOHEXADIENONES: SYNTHESIS OF FUNCTIONALIZED CYCLOHEXADIENONES, DIENOLS AND DIENEDIOLS

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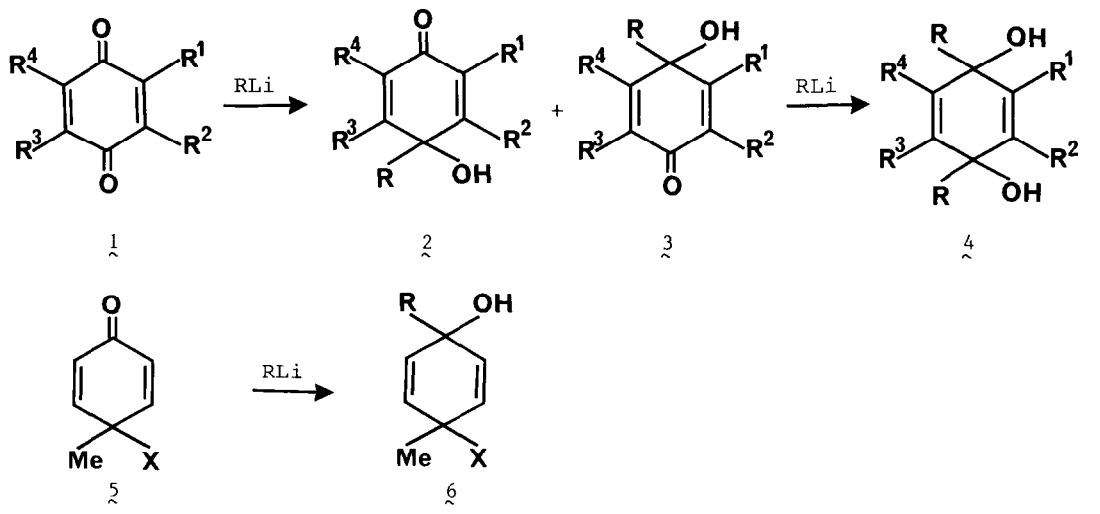
Abstract: Low temperature addition of functionalized alkyllithium reagents to p-benzoquinones produces 4-alkyl-4-hydroxycyclohexa-2,5-dienones, and reaction of excess of the reagents with quinones yields 1,4-dialkylcyclohexa-2,5-diene-1,4-diols. With 4-acetoxy-, 4-hydroxy-, and 4-methoxy-4-methylcyclohexa-2,5-dienones the corresponding dienols are obtained. A one-step synthesis of the antibiotics 4-acetamido- and 4-[(ethoxycarbonyl)methyl]-2,6-dibromo-4-hydroxycyclohexadienones, and the anti-tumour agent jacaranone is described.

In a recent article, Evans et al.[1] pointed out the synthetic utility of cyclohexa-2,5-dienones and their application to the syntheses of naturally occurring aromatic and quinone-derived compounds. For the synthesis of cyclohexadienones from quinones, a method based on the addition of organolithium or organomagnesium reagents to mono-protected quinones has been developed to overcome the unfavourable redox potential in quinone chemistry.[1-7] Other methods[8] of preparing the cyclohexadienones give poor yields of the dienones which are often formed in a mixture with other compounds. Recently, we have shown that at low temperatures simple alkyllithiums add to unprotected quinones to give an excellent yield of cyclohexa-2,5-dienones.[8] Since our original report, Liotta et al. also have reported the 1,2 addition of

Scheme 1:



1 2 3 4

5 6

a $R^1=R^2=R^3=R^4=H$ b $R^1=R^4=Br$; $R^2=R^3=H$ c X=OH(2a) d X=OMe e X=OAc

Table 1: Addition of functionalized organolithiums to quinones and cyclohexadienones.[a]

Quinone or dienone	Solvent (mL)	RLi RH	RLi mmol	Hydroquinone	Dienone 2	Dienone 3	Dienol or dienediol (cis:trans)
1a	ether (28)	$MeCO_2Me$	1.2	10	86	-	4
1a	THF (18)	$MeCO_2Me$	4	1	-	-	99(75:25)
1a[b]	THF (600)	$MeCO_2Me$	400	3	-	-	97(74:26)
1a	ether (24)	$MeCO_2Bu^t$	1	6	91	-	3
1a	ether (24)	MeCN	1	43	54	-	3
1a	THF (18)	MeCN	4	25	-	-	75(55:45)
1a	THF (12)	BSA[c]	1	23	70	-	7
1a[d]	THF (12)	BSA	1	40	60	-	-
1a	THF (12)	BSA	2.8	7	-	-	93(75:25)
1a	THF (20)	$MeSO_2Me$[e]	3	41	58	-	1
1b	THF (12)	$MeCO_2Me$	1	16	59	9	15
1b	THF (12)	$MeCO_2Me$	3	3	-	-	97(75:25)
1b	THF (24)	$MeCO_2Et$	1	22	59	6	12
1b	ether (24)	MeCN	1	20	63	7	10
1b	THF (12)	BSA	1	37	60	1	2
1b	THF (12)	BSA	3	22	-	-	78
5c	THF (12)	$MeCO_2Me$	2.2	-	60	-	40(88:12)
5c	THF (6)	$MeCO_2Me$	1.1	-	-	-	100(65:35)
5c	THF (8)	$MeCOO^-$[f]	1.5	-	-	-	-[g]

[a]Unless otherwise stated 1 mmol of quinone or dienone was reacted for 60 min at -78°C. [b]Added 100 mmol of quinone in 200 ml THF over 1 hr. [c]O,N-bis(trimethylsilyl)acetamide(BSA). [d]LiBSA in THF at -78°C added to quinone in THF at -78°C. [e]Used as dianion. [f]LDA used alone to generate the anion of the acetate. [g]Complex mixture of 1,2 and 1,4 addition products.

simple carbanions to quinones[9] and we have also noted the 1,2 addition of Grignard reagents to quinones.[10] In this communication we report that functionalized alkyllithium reagents also add with ease to unprotected quinones to give good yields of functionalized cyclohexadienones.

We have investigated the low temperature addition of various functionalized organolithium reagents using p-benzoquinone and 2,6-dibromo-p-benzoquinone as model compounds, the former chosen because it is the simplest quinone available and the latter because of the sensitive bromine substitutents. They were also selected because by the addition of the appropriate anion they could directly yield the natural products jacaranone, and 4-acetamido- and 4-[(ethoxycarbonyl)methyl]-2,6-dibromo-4-hydroxycyclohexadienones. The results are presented in Table 1 and Scheme 1 and they show that at low temperature benzoquinones readily react with functionalized alkyllithium reagents to give functionalized hydroxycyclohexadienones. With an excess of the reagent, functionalized cyclohexadienediols were formed. The addition of

functionalized alkyllithium reagents to various cyclohexadienones was also investigated. Excellent yields of the corresponding cyclohexadienols were obtained.

In general, the small scale experiments were carried out under an argon atmosphere by the rapid addition of quinone or cyclohexadienone in the appropriate solvent to a cold solution of the functionalized lithium reagent in the desired solvent at low temperature. Either lithium diisopropylamide (LDA) or n-butyllithium was used to generate the lithium reagents. The large scale reactions for the preparation of functionalized cyclohexadienones were carried out by the dropwise addition of the lithium reagent at -78°C to the quinone solution at -78°C. This reverse addition substantially reduced the amount of the dienediol formed and also reduced to some extent the amount of hydroquinone. For the synthesis of dienediols, the solution of the quinone was added dropwise to the lithium reagent at low temperature. Excess aqueous ammonium chloride was employed for neutralization in the work up of the reaction products.

Addition of methyl lithioacetate to p-benzoquinone gave in excellent yield the natural product jacaranone (2*a*, R = CH_2COOMe), which has been isolated from the extract of *Jacavanada caucana* Pittier and which has been shown to have significant anti-tumour activity.[6,11] Jacaranone has been synthesized previously[6] by using protected p-benzoquinone, which involves blocking one of the carbonyl groups with trimethylsilyl cyanide and reaction of the sensitive trimethylsilylcyanohydrin thus obtained with methyl lithioacetate, followed by deprotection with silver fluoride. Addition of ethyl lithioacetate to dibromobenzoquinone (1*b*) furnished the antibiotic 2*b* (R = CH_2COOEt), which has been isolated from the mollusk *Tylodine fungina*.[3,12] Similarly the reaction of 1*b* with the anion generated by the action of n-BuLi on N,O-bis(trimethylsilyl)acetamide (BSA), yielded the broad spectrum antibiotic 2*b* (R = CH_2CONH_2), isolated from marine sponges of the genus *Verongia*.[3,13] Both of these antibiotics were synthesized[3] using the trimethylsilylcyanohydrin derivative of 1*b*. The yields of the antibiotics compare favourably with those obtained from the protected quinones by Evans et al.[3] (yield of 2*b* from trimethylsilylcyanohydrin of quinone: R = CH_2COOEt 77%; R = CH_2CONH_2 37%).

Addition of an excess of the functionalized organolithium reagent to quinones produced an excellent yield of the functionalized cyclohexadienediols 4. One of the two possible diastereoisomeric diols predominated in the product mixture. By analogy with the known preferential formation of the *cis*-diols by the *trans*-addition of alkyllithiums to hydroxydienones[8] the predominant diol is most likely the *cis*. It appears that because of electrical repulsion, the second molecule of alkyllithium preferentially adds *trans* to the OLi group of the hydroxydienone formed by the addition of the first molecule of alkyllithium to quinone. Reaction of the hydroxydienone with a different alkyllithium produces a mixed dienediol. Arene oxides are obtained in the biological oxidation of arenes and are implicated in the carcinogenisis exhibited by arenes. Bruice et al.[14] have identified cyclohexadienediols as intermediates in the biological breakdown of arene oxides. The direct synthesis of cyclohexadienediols described here will facilitate the investigation of the role these compounds play in the carcinogenicity of arene oxides.

Methyl lithioacetate readily added to methoxydienone 5*d* to give in quantitative yield the methoxydienol 6*d* (R = CH_2COOMe). Although not investigated thus far, other alkyllithium

reagents are expected to behave similarly. Treatment of the acetoxydienone 5e with LDA appeared to give both 1,2 and 1,4 internal addition products.

The ready low temperature addition of functionalized organolithium reagents to unprotected quinones to yield hydroxydienones eliminates, at least in the systems investigated thus far, the need for the use of the expensive and cumbersome reversible protection of quinones. The availability of a large number of quinones with varying degree of substitution and functionalization coupled with the fact that the practicing organic chemist has access to a vast number of functionalized carbanions and reverse polarity equivalents will make this method of synthesis of the dienones attractive. The hydroxydienones can be aromatized to yield suitably substitued arenes.[1] They can also be acylated, alkylated or converted to halodienones which can undergo substitution with nucleophiles. Aromatizations of the dienones are particularly important in connection with the syntheses of aromatic natural products in which the aromatics act as positive synthons and the substituents as negative synthons.[1] Much of the addition chemistry of quinones to date has been Michael-type addition of nucleophiles to the α-enone moiety present in the quinone.[15] It is hoped that the 1,2 addition of organometal reagents reported by us will aid in the full exploitation of the synthetic potential of the high degree of functionalization built in the quinone molecule. The full scope of this addition reaction is under investigation.

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(Received in USA 28 May 1982)