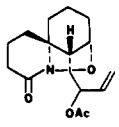
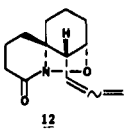
tion, whereas axial incorporation was, in fact, desired for the preparation of **2**. This assignment was further corroborated by subsequent transformations as detailed below.

Oxidative cleavage of the unsaturation in **9** (OsO_4, $NaIO_4$, aqueous THF, 0 °C) gave aldehyde **10** in 89% yield. Attempted incorporation of a two-carbon fragment by Wittig reaction with ethylidenetriphenylphosphorane proved unexpectedly difficult and isolated yields of the desired product in excess of ca. 40% could not be realized despite extensive experimentation. Isolation of product was also complicated by its low solubility in most organic solvents and the unusually high polarity found to be characteristic of this ring system. However, aldehyde **10** could be easily converted to the desired butyl compound (**13**) in 71% overall yield by the following series of reactions, which were conveniently conducted without purification of intermediates: (1) reaction with 1.1 equiv of vinylmagnesium bromide in THF at −78 °C for 15 min, followed by addition of excess (3 equiv) acetic anhydride and warming to room temperature, to afford **11**; (2) palladium-catalyzed elimination of acetic acid[14] (0.01 equiv of $Pd(OAc)_2$, 0.10 equiv $P(Ph)_3$, dioxane reflux) to yield diene **12**; and (3) hydrogenation over Adams catalyst in ethyl acetate.



11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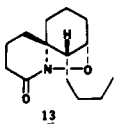
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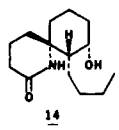

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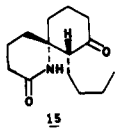

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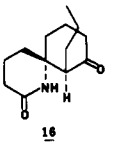

16

Reduction[15] of **13** with 6% sodium amalgam in isopropyl alcohol at room temperature cleanly afforded the hydroxy lactam **14** in 94% isolated yield. Comparison with authentic **2** clearly revealed that **14** was in fact epimeric with **2** [silica gel, TLC R_f values of 0.29 and 0.35 for **2** and **14**, respectively, in MeOH–$CHCl_3$ (8:92)] and necessitated an adjustment of stereochemistry at C_7 along previously reported lines. Oxidation of **14** with Me_2SO–oxalyl chloride according to the procedure of Swern[16] afforded ketone **15** essentially quantitatively, which was epimerized to a 1:4 mixture of **15** and **16** according to the published procedure.[2b] Reduction as described by Kishi and co-workers[2b] then yielded **2**, which was identical with an authentic sample by the usual criteria (^1H NMR, IR, ^{13}C NMR, MS, TLC, HPLC).[17]

Although the approach delineated above suffers from a loss of stereocontrol in the incorporation of the allyl unit, it is nonetheless intriguing that incorporation of the allyl unit is, in fact, stereoselective. Further investigations and applications of the ene and organotin methodologies outlined herein are being pursued.[18]

Registry No. 1c, 55254-30-3; **2**, 55228-76-7; **3**, 51029-28-8; **4**, 82537-60-8; **5**, 82570-97-6; **6**, 82537-61-9; **9**, 82537-62-0; **10**, 82537-63-1; **11**, 82537-64-2; **12**, 82537-65-3; **13**, 82537-66-4; **14**, 82570-98-7; **15**, 56459-12-2; **16**, 56459-13-3; (2-iodoethyl)-1-cyclohexene, 82201-80-7; allyltri-*n*-butyltin, 24850-33-7.

Supplementary Material Available: Full experimental details including spectra and analytical data (10 pages). Ordering information is given on any current masthead page.

(18) Support of this research by the National Science Foundation and Eli Lilly Co. is gratefully acknowledged.

† Fellow of the Alfred P. Sloan Foundation, 1981–1983.

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Alkynylquinones. Synthesis of 2-Alkynyl-5-methoxy-1,4-benzoquinones

Summary: An experimentally simple and efficient synthesis of 2-alkynyl-5-methoxy-1,4-benzoquinones is described. This involves the 1,2-addition of lithium acetylides to 4,5-dimethoxy-1,2-benzoquinone to give the quinols **2a–i**. Hydrolysis of these adducts with dilute acids gives the quinones in overall yields ranging from 61% to 92%.

Sir: Recently we described an efficient method for the synthesis of 2,5-dialkylated 1,4-benzoquinones involving the 1,2-addition of organolithium reagents to 2,5-dialkoxy-1,4-benzoquinones followed by acid hydrolysis of the resulting adducts.[1] Here we report an extension of this methodology that provides an experimentally simple and high-yield procedure for the construction of 2-alkynyl-5-methoxy-1,4-benzoquinones. Such compounds are of potential interest since alkynylquinones have received very little attention.[2] In addition, the fact that alkynyl groups can be converted to a large variety of other functionalities,[3] along with the observation that many natural quinones possess the 2-alkylated 5-oxygenated 1,4-benzoquinone framework,[4] provided a further stimulus for this study. Of particular interest will be the utilization of alkynylcyclohexadienones, **2**, and alkynylquinones, **3**, for the synthesis of prodrugs. Indeed, 2-alkynyl-5-methoxy-1,4-benzoquinones are ideally suited to function as precursors to bioreductive alkylating agents.[5]

Specifically, 4,5-dimethoxy-1,2-benzoquinone (**1**)[6] was treated with a variety of lithium acetylides to give excellent yields (70–95%) of the corresponding 6-alkynyl-6-hydroxy-3,4-dimethoxy-2,4-cyclohexadienones **2a–i**. Treatment of adducts **2a–g** with dilute sulfuric acid resulted in hydrolysis of the acid-sensitive β-hydroxy enol

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Table I. Spectral Data

compd	mp, °C	NMR ($CDCl_3$) δ	IR (KBr), cm^{-1}	MS
2a	125-126	3.84 (s) 3 H, 3.90 (s) 3 H, 3.95 (br s) 1 H, 5.52 (s) 2 H, 7.35 (m) 5 H	3460 (m), 3307 (br), 2205 (w), 1661 (s), 1651 (s), 1583 (s), 751 (s), 683 (m)	271.0 (CI)
2b	125.5-126.5	3.70 (s) 3 H, 3.83 (s) 3 H, 4.10 (s) 1 H, 4.14 (s) 2 H, 4.53 (s) 2 H, 5.45 (s) 1 H, 5.50 (s) 1 H, 7.30 (s) 5 H	3375 (br), 1640 (s), 1580 (s), 730 (s), 688 (s)	314.1 (EI)
2c	83-84	0.86 (m) 2 H, 141 (m) 6 H, 2.15 (m) 2 H, 3.73 (s) 4 H, 3.87 (s) 3 H, 5.44 (s) 1 H, 5.48 (s) 1 H	3435 (br), 2205 (s), 1650 (s), 1582 (s)	241.2 (CI)
2d	123.5-124	1.67 (t, J = 1 Hz) 3 H, 3.57 (s) 3 H, 3.67 (s) 1 H, 3.71 (s) 3 H, 5.13 (m) 2 H, 5.29 (s) 1 H, 5.33 (s) 1 H	3202 br, 2208 (w), 1650 (s), 1580 (s)	235.1 (CI)
2e	114.8-115.2	1.66 (m) 4 H, 2.01 (t, J = 4 Hz) 1 H, 2.27 (m) 4 H, 3.81 (s) 4 H, 3.95 (s) 3 H, 5.53 (s) 1 H, 5.56 (s) 1 H	3330 (br), 3270 (s), 2210 (m), 1642 (s), 1582 (s)	275.1 (CI)
2f	102-103	1.30 (t, J = 7 Hz) 3 H, 3.76 (s) 3 H, 3.97 (s) 1 H, 4.23 (q, J = 7 Hz) 2 H, 5.43 (s) 1 H, 5.55 (s) 1 H	3450 (s), 2215 (s), 1720 (s), 1659 (s), 1580 (s)	267.1 (CI)
2g	133-134	2.54 (s) 1 H, 3.74 (s) 3 H, 3.88 (s) 3 H, 4.08 (br s) 1 H, 5.46 (s) 1 H, 5.53 (s) 1 H	3450 (s), 3271 (s), 1642 (s), 1582 (s)	195.1 (CI)
2h	71-80	1.33 (t, J = 7 Hz) 3 H, 3.63 (s) 1 H, 3.72 (s) 3 H, 3.86 (s) 3 H, 4.10 (q, J = 7 Hz) 2 H, 5.45 (s) 1 H, 5.47 (s) 1 H	3500 (br), 2225 (s), 1740 (m), 1654 (m), 1587 (s)	238.0 (EI)
2i	65-73	1.03 (t, J = 7 Hz) 6 H, 2.50 (q, J = 7 Hz) 4 H, 3.43 (s) 2 H, 3.72 (s) 3 H, 3.82 (s) 3 H, 4.94 (br) 1 H, 5.44 (s) 1 H, 5.48 (s) 1 H	2950 (br), 1680 (s), 1653 (s), 1584 (s)	279 (EI)
3a	171-171.8	3.85 (s) 3 H, 5.98 (s) 1 H, 6.90 (s) 1 H, 7.45 (m) 5 H	2205 (m), 1668 (s), 1650 (s), 1620 (m), 1582 (s), 764 (s), 685 (s)	238.1 (EI)
3b	90-91.4	3.83 (s) 3 H, 4.42 (d, J = 0.6 Hz) 2 H, 4.66 (s) 2 H, 6.82 (t, J = 0.6 Hz) 1 H, 7.35 (m) 5 H	2213 (m), 1670 (s), 1645 (s), 1622 (s), 1597 (s), 750 (s), 690 (s)	177 (CI) 176 (EI) (MW-PhCHO)
3c	90-91.5	0.94 (m) 3 H, 1.50 (m) 4 H, 2.50 (t) 2 H, 3.82 (s) 3 H, 5.93 (s) 1 H, 6.76 (s) 1 H	2211 (m), 1663 (s), 1645 (s), 1623 (s), 1588 (s)	219.1 (CI)
3d		1.98 (m) 3 H, 3.83 (s) 3 H, 5.46 (m) 1 H, 5.54 (m) 1 H, 5.94 (s) 1 H, 6.80 (s) 1 H	2198 (m), 1667 (s), 1623 (s), 1610 (s), 1575 (s)	202.2 (EI)
3e	105-106	1.80 (m) 4 H, 2.03 (t) 1 H, 2.31 (m) 2 H, 2.61 (m) 2 H, 3.88 (s) 3 H, 5.98 (s) 1 H, 6.82 (s) 1 H	3250 (s), 2221 (m), 1663 (s), 1645 (s), 1624 (s), 1589 (s)	243.1 (CI)
3f		1.35 (t, J = 7 Hz) 3 H, 3.87 (s) 3 H, 4.30 (q, J = 7 Hz) 2 H, 6.02 (s) 1 H, 7.01 (s) 1 H	2220 (m), 2100 (m), 1715 (s), 1682 (s), 1660 (s), 1624 (s), 1590 (s)	236 (EI) 237 (CI) hydroquinone
3g	darkens ≈130	3.82 (d, J = 0.6 Hz) 1 H, 3.93 (s) 3 H, 6.07 (s) 1 H, 7.00 (d, J = 0.6 Hz) 1 H	3240 (s), 2100 (m), 1670 (s), 1643 (s), 1622 (s), 1584 (s)	162.1 (EI)

ether moiety to give the corresponding 2-alkynyl-5-methoxy-1,4-benzoquinones **3a–g** in isolated yields of 85–97% (Scheme I). Attempts to hydrolyze adducts **2h–i** to the corresponding quinones resulted in complex mixtures.

The general procedure for accomplishing these transformations is outlined below. A solution of 1.1 equiv of the alkyne in 75 mL of dry THF under an argon atmosphere was stirred at −78 °C while 1.05 equiv of *n*-BuLi (1.5 M in hexane) was added dropwise. The solution was stirred for 30 min and then transferred dropwise, via cannula, to a suspension of 1.00 g (1 equiv) of quinone **1** in 400 mL of dry THF at −78 °C. After 1 h the reaction solution was quenched with aqueous NH_4Cl. The organic layer was collected and the aqueous layer was washed twice with 50 mL of CH_2Cl_2. The combined organic layer was dried and concentrated, and the residue was absorbed on silica gel. This was subjected to flash chromatography (hexane/ethyl acetate, 1:1) to give the purified products **2a–i**.

The quinones **3a–g** were obtained as follows. To a stirred ethyl acetate (50 mL) solution of **2** (1 g) was added 6 drops of 50% aqueous H_2SO_4. After 1 h the solution was washed twice with 50 mL of 2% aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was washed with 50 mL of CH_2Cl_2. The organic layers were combined and dried, and the solvent was removed in vacuo. Flash chromatography of the resulting residue (silica gel; hexane/ethyl acetate, 1:1) gave the purified quinones.

The structural assignments of **2a–i** and **3a–g** are based upon the spectral data provided in Table I.[7]

In summary, the synthetic methodology outlined in this paper provides possibly the simplest known route to 2-alkylated 5-methoxy-1,4-benzoquinones and compliments recent advances directed toward the mono- and dialkylation and arylation of the quinone nucleus. Particularly noteworthy in this regard are the utilization of 2,5-diethoxy-1,4-benzoquinone as a reagent for the synthesis of 2,5-dialkylated 1,4-quinones,[1] the employment of trimethylsilyl cyanide protected quinones,[8] the use of lithium salts of 1-bromo-3,3,6,6-tetramethoxy-1,4-cyclohexadienes[9]

(7) Satisfactory analytical data was obtained for all new compounds except **2h**, **2i**, **3d**, and **3f**, which were all relatively unstable and slowly decomposed. However, all spectral data are in strict accord with their proposed structures.

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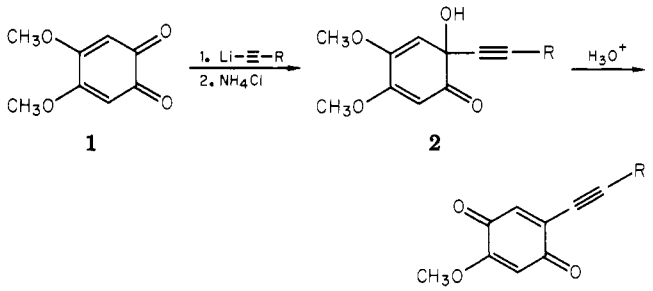
Scheme I



	R	% yield of 2	% yield of 3
a	C_6H_5	95	97
b	$CH_2OCH_2C_6H_5$	95	92
c	$(CH_2)_3CH_3$	94	94
d	$C(CH_3)=CH_2$	90	94[a]
e	$(CH_2)_4C\equiv CH$	71[b]	85
f	$CO_2C_2H_5$	92	94[c]
g	H	70	94
h	OC_2H_5	80	
i	$CH_2N(C_2H_5)_2$	90	

[a] Product slowly decomposes upon removal of solvent. [b] Five equivalents of the octadiyne was used to maximize the yield. [c] Crude yield.

(a latent quinone carbanion), the reactions of quinones or protected bromoquinols with π-allylnickel complexes,[10] the utilization of monoketals of quinones,[11] the use of (1,4-dimethoxynaphthyl)lithium reagents,[12] and the reactions of quinones with alkylboranes.[13]

Finally, it should be noted that the quinols, **2a–i**, possess multifunctionality that is amenable to both nucleophilic and electrophilic reagents as well as cycloaddition reactions.[14] In addition, alkynylquinones have not been reported prior to this work and our previous report on the synthesis of 2,5-dialkylated 1,4-quinones. As a result, their chemistry is nearly unexplored and thus warrants study.

Acknowledgment. We express our appreciation to the National Cancer Institute (CA-11890) for financial support of this work.

Registry No. 1, 21086-65-7; **2a**, 82511-09-9; **2b**, 82511-10-2; **2c**, 82521-45-7; **2d**, 82511-11-3; **2e**, 82511-12-4; **2f**, 82511-13-5; **2g**, 82511-14-6; **2h**, 82511-15-7; **2i**, 82511-16-8; **3a**, 82511-17-9; **3b**, 82511-18-0; **3c**, 82511-19-1; **3d**, 82511-20-4; **3e**, 82511-21-5; **3f**, 82511-22-6; **3g**, 82511-23-7; $LiC\equiv CC_6H_5$, 4440-01-1; $LiC\equiv CCH_2OCH_2C_6H_5$, 64080-63-3; $LiC\equiv C(CH_2)_3CH_3$, 17689-03-1; $LiC\equiv CC(CH_3)=CH_2$, 38341-85-4; $LiC\equiv C(CH_2)_4C\equiv CH$, 82511-24-8; $LiC\equiv CCO_2C_2H_5$, 72036-30-7; $LiC\equiv CH$, 1111-64-4; $LiC\equiv COC_2H_5$, 31612-88-1; $LiC\equiv CCH_2N(C_2H_5)_2$, 82511-25-9.

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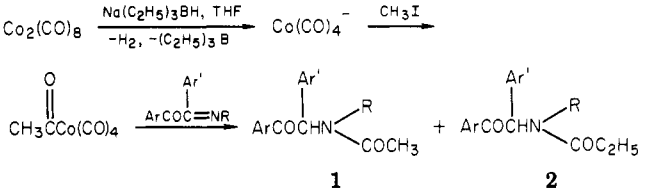
Metal Carbonyl Catalysis of Organoborane Reactions. Cobalt Carbonyl Catalyzed Reductive Carbonylation of Schiff Bases

Summary: Schiff bases react with trialkyl or triarylboranes and carbon monoxide, in the presence of catalytic amounts of cobalt carbonyl, to give amides.

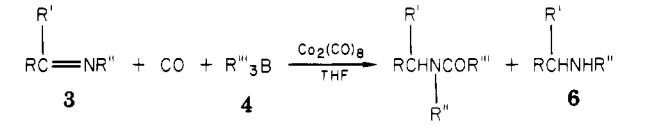
Sir: We recently reported that the stoichiometric reaction of α-keto imines with acetylcobalt tetracarbonyl affords the acetamide **1** as the principal product with the unexpected propionamide **2** being obtained as a byproduct in several cases.[1] The acetylcobalt carbonyl was generated in situ by first reacting dicobalt octacarbonyl with triethylborohydride to give the mononuclear anion[2] and then treating the latter with methyl iodide under a carbon monoxide atmosphere.



As previously noted, methyl iodide is not required for the formation of **2**. Furthermore, while the reductive acylation reaction (giving **1**) is sensitive to steric effects, we have subsequently found that this factor is of less significance for the preparation of **2**. Specifically, **2** (Ar = Ar′ = Ph, R = 2,6-$(CH_3)_2C_6H_3$) was obtained in 61% yield by reaction of the appropriate α-keto imine, for 24 h, with the solution resulting from $Co_2(CO)_8$ and triethylborohydride. The same reaction, with added methyl iodide, effected over a 120-h reaction period (essentially no reaction occurred after 24 h), afforded **1** (Ar = Ar′ = Ph, R = 2,6-$(CH_3)_2C_6H_3$) in only 6% yield.[1]

It seemed conceivable that triethylborane, formed during the generation of the cobalt tetracarbonyl anion, participates in the reaction that gives **2**. It this reasoning is correct, then the reaction of α-keto imines (or other Schiff bases) with organoboranes and carbon monoxide should afford a variety of β-keto amides. *No* reaction occurs under these conditions. However, it was gratifying to learn that the presence of catalytic amounts of cobalt carbonyl does indeed result in the reductive carbonylation and alkylation of Schiff bases by organoboranes and carbon monoxide. We now report on this new catalytic process.

Carbonylation of a Schiff base (**3**) with an equimolar amount of an organoborane (**4**) and a catalytic quantity of dicobalt octacarbonyl affords the amides **5** in good yields (Table I). This reaction can be effected, in tetrahydrofuran (THF) or hexane, under mild conditions [60 °C (1 atm of pressure)]. The reaction is faster in THF than in hexane, and the product yields are higher in THF. The saturated amine (**6**) was also formed in some instances.



As the results in Table I indicate, the metal carbonyl catalyzed reaction is a versatile one since variations can be made on the nature of both the organoborane and the

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