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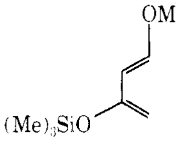
A Diels-Alder Route to Functionalized Cyclohexadienones

Summary: The diene 1-phenylseleno-2-trimethylsilyloxy-4-methoxy-1,3-butadiene provides a direct route to 4-acyl-4-substituted cyclohexadienones.

Sir: Recently our laboratory has been investigating the preparation and use of new dienes for Diels-Alder reactions. The dienes are so arranged as to impart to their cycloadducts ready-made handles for the elaboration of functionality which is otherwise difficultly accessible. Toward this end, we have prepared and demonstrated the utility of enophiles **1**[1-3] and **2**.[4] In the consequence of its overall cycloaddition with olefins, diene **1** is a functional equivalent of $^+$CH=CHC(O)CH$_2^-$. Similarly, diene **2** is a latent version of $^+$C(O)CH$_2$C(O)CH$_2^-$.



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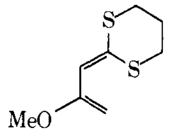
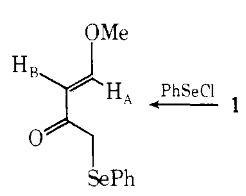


2

Some other very interesting dienes have been reported from a variety of sources.[5]

In the light of the value of α-phenylseleno ketones in the generation of enones, as demonstrated through the elegant research of Reich,[6] and Sharpless,[7] and Grieco,[8] we have studied the possibility of incorporating a phenylseleno grouping into a properly constructed enophile, with the objective of generating the requisite array for the synthesis of 4-acyl-4-substituted cyclohexadienones of the type **5**. Such compounds, which have intriguing possibilities for various synthetic objectives, were virtually unknown.[9] Toward this end, we have prepared 1-phenylseleno-2-trimethylsilyloxy-4-methoxy-1,3-butadiene (**4**) and studied its value in Diels-Alder reactions.

Compound **3**[10a] was obtained in 82% yield by the virtually instantaneous reaction of diene **1** with phenylselenenyl chloride in benzene at room temperature.[11] Resilylation of **3** under the conditions of Kitahara[1] afforded an 80% yield of a diene[12a] [λ_{max}(CHCl$_3$) 3.31, 3.37, 3.45, 3.52, 6.10, 6.31 μm; δ(CDCl$_3$) 0.30 (s, 9), 3.62 (s, 3), 5.52 (d, J = 13 Hz, 1), 5.60 (s, 1), 6.84 (d, J = 13 Hz, 1), 7.2–7.6 (m, 5) ppm]. This compound could not be purified by distillation or chromatography but was used successfully in crude form.



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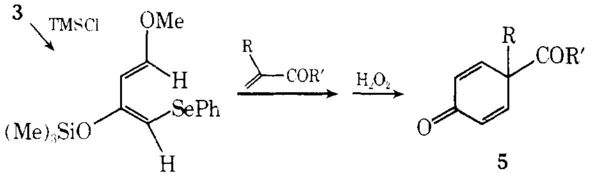
J_{AB} = 13 Hz

Within the limits of NMR analysis, only one geometric isomer could be detected from the silylation reaction.[12b] We believe this to be the trans,cis compound **4**, on the basis of



4

5

analysis of the high-field (250 MHz) NMR spectrum of its maleic anhydride adduct (vide infra).

Compound **4** reacts with methacryloyl chloride in benzene under reflux for 2 h. Treatment of the adduct with methanol–pyridine followed by aqueous hydrogen peroxide afforded, after silica gel chromatography, a 29% yield of 4-methyl-4-carbomethoxycyclohexadienone (**6**).[10a] The less reactive methyl methacrylate in benzene (sealed tube) at 120 °C for 24 h gave an adduct which upon treatment with dilute HCl–THF afforded a 16% overall yield of α'-phenylselenoenone **7**.[10a,13] Treatment of **7** according to Reich[6] gave a 91% yield of dienone **6**.

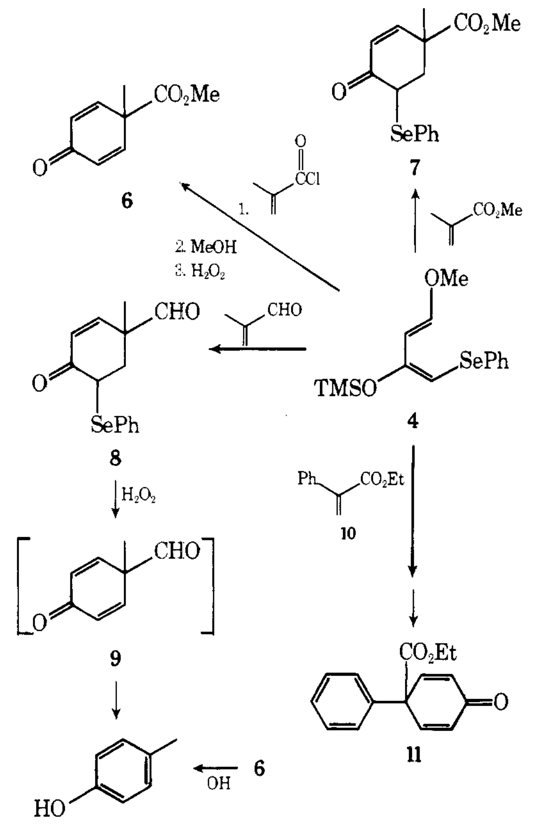
Reaction of **4** with methacrolein (C$_6$H$_6$, reflux; 40 h) followed by workup as above afforded enone **8**[10a,13] in 38% yield (from **3**). Several attempts at oxidative deselenation using aqueous hydrogen peroxide afforded a virtually quantitative yield of *p*-cresol, presumably via the labile 4-methyl-4-formylcyclohexadienone (**9**). Similarly, treatment of dienone **6** with methanolic KOH gave *p*-cresol virtually instantaneously. The chemistry of the 4-acylated 4-substituted cyclohexadienones will be more fully described in a future publication.

Thus, while the cycloaddition reactions of **4** with easily polymerizable methacrylyl dienophiles lead to interesting new systems, the yields thus far are disappointing. The enophilic efficacy of **4** is far less than that of **1**. However, the power of the method is foreshadowed in its use with the less fragile dienophile, ethyl 2-phenylacrylate (**10**). The reaction of **4** with **10** was conducted in benzene (sealed tube) at 115 °C for 24 h. Workup with dilute acid followed by oxidative deselenation afforded a 50% overall yield of 4-phenyl-4-carbethoxycyclohexadienone (**11**).[10a,b]

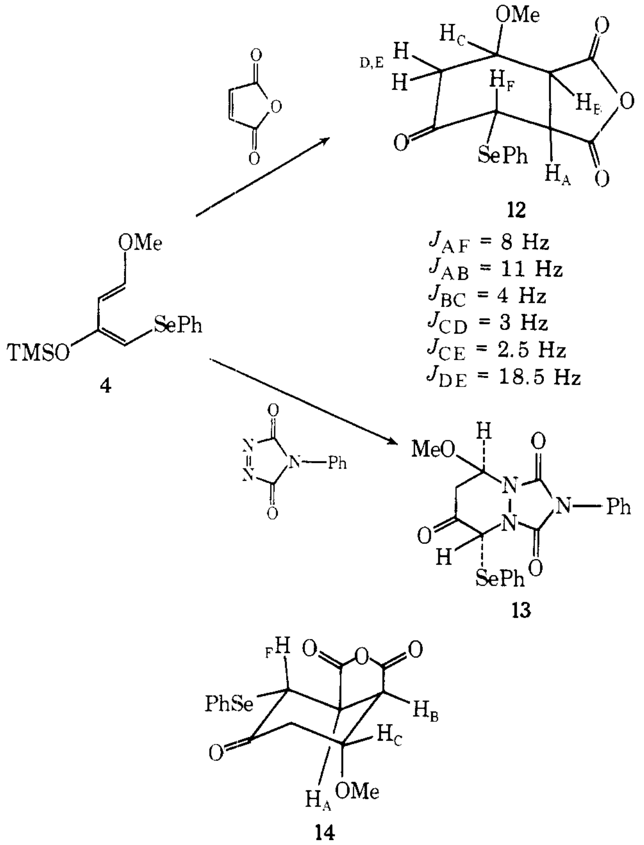
Compound **4** reacts with maleic anhydride and with 4-phenyltriazoline-3,5-dione at room temperature. After workup with dilute acid, methoxy ketones **12**[10] (mp 136–137 °C) and **13**[10a] (mp 213–214 °C) were obtained in 67 and 77% yields, respectively.

Hydrolysis of the maleic anhydride adduct with DCl–MeCO$_2$D–D$_2$O led to the introduction of one deuterium atom at the methylene center adjacent to the ketone of **12**. Therefore, it may safely be assumed that under the conditions of the experiment there is no epimerization of the methine center bearing the phenylseleno function. Accordingly, the relative configurations of the adduct itself may be derivable from the ketone. The pertinent coupling constants of the ketone are shown with the structure.

If it is assumed that cycloaddition has occurred in the usual suprafacial, endo sense, these coupling patterns of the maleic



anhydride adduct define its stereochemistry to be that shown in structure **12**, wherein the methoxyl group is quasi-axial and the phenylseleno group is quasi-equatorial to the extended boat system. No other configurational isomer fulfilling the condition that the methoxyl be trans to H_B can be readily accommodated by the data. Given the E stereochemistry of the methoxyl group in **3** and **4**, the phenylseleno group in **4** is provisionally formulated as E (i.e., cis to the 2,3 single bond).[14]



J_{AF} = 8 Hz
J_{AB} = 11 Hz
J_{BC} = 4 Hz
J_{CD} = 3 Hz
J_{CE} = 2.5 Hz
J_{DE} = 18.5 Hz

Given the truism of cis addition in the dienic component of the Diels–Alder reaction, and given the E stereochemistry of the methoxy group in precursor **3** (J_{AB} = 13 Hz) and, therefore, in **4**, the stereochemistry of the phenylseleno group in **4** is formulated as E (i.e., cis to the 2,3 single bond).

While the facility of the Diels–Alder reaction of **4** may seem incompatible with formulation of a cis 1-substituted butadiene configuration, the synergistic activity influences of the methoxy and the OTMS groups would be expected to be very powerful. Furthermore, it may well be that the deactivation of a cis substituent at the 1 position of a butadiene is less pronounced in the presence of a bulky substituent at the 2 position. Such a substituent would tend to disfavor the nonreactive s-trans conformer.

The chemistry of the systems made available by the highly functionalized diene **4** is being studied. These results as well as further studies of new functionalized systems, which enhance the power of the Diels–Alder logic in organic synthesis, will be described in due course.

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(10) The structure of this compound is in accord with (a) its infrared, NMR, and mass spectra and (b) its combustion analysis within 0.3% of theory.
(11) The related sulfenylation of silyl enol ethers was first described by S. Mura, J. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972), and more recently rediscovered by D. Seebach and M. Teschner, *Chem. Ber.*, **109**, 1601 (1976).
(12) (a) Compound **4** is contaminated with varying but small amounts of its precursor, **3**. The NMR spectral data reported for **4** involve subtraction of the resonances clearly ascribable to **3**. No other contaminants are apparent from the NMR spectrum. (b) For another example of apparent formation of a single silyl enol ether from a similar substrate, see ref 5e.
(13) The α'-phenylselenoenones from the reactions of **4** with methacrolein, and with methyl methacrylate are obtained as a 1:1 mixture of epimers. Apparently these Diels–Alder reactions lack significant endo selectivity.
(14) Of course, we cannot rule out the formal possibility of structure **14** for the adduct. This structure embraces the observed coupling constants, and by the principle of suprafacial addition, defines a Z configuration (i.e. cis to the OTMS group) in the diene. However, **14** would be the result of an unprecedented stereospecific exo cycloaddition of maleic anhydride to an

acyclic diene and must be regarded as unlikely. Studies which would allow for an unambiguous stereochemical assignment are currently in progress and will be described in the full paper on this subject.

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Selective Carbon–Carbon Bond Formation via Transition Metal Catalysis. 3.[1] A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by the Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides

Summary: The reaction of aryl- and benzylzinc derivatives with aryl bromides or iodides in the presence of a catalytic amount of a Ni or Pd catalyst provides a general and highly chemo- and regioselective route to unsymmetrical biaryls and diarylmethanes, the amounts of homocoupled biaryls being < 5%.

Sir: Recently, the Ni- or Pd-catalyzed reactions of organometallics containing highly electropositive main group metals, such as Li and Mg, with organic halides have provided a new approach to selective cross-coupling.[2,3] In particular, the ability of organoaluminum compounds,[1] which are generally much less reactive toward electrophiles than the corresponding Li and Mg derivatives, to readily undergo similar catalytic reactions, has been exploited in developing new cross-coupling reactions which are chemo-, regio- and stereoselective. Some of these reactions have provided synthetic procedures that are more satisfactory than those involving other organometallics, including organocuprates.[4]

We now report that organozinc compounds readily participate in the Ni- or Pd-catalyzed cross-coupling reaction, thereby providing a general and mild procedure for the preparation of unsymmetrical biaryls and diarylmethanes which features high chemo- and regioselectivity as well as high cross-/homo-coupling ratios[5,6] (eq 1).

$$\mathrm{RZnX} + \mathrm{ArX'} \xrightarrow[\text{cat. } \mathrm{Cl_2Pd(PPh_3)_2} + (i\text{-}\mathrm{Bu})_2\mathrm{AlH}]{\text{cat. } \mathrm{Ni(PPh_3)_4} \text{ or}} \mathrm{R{-}Ar} \qquad (1)$$

$$\mathrm{R} = \mathrm{Ar} \text{ or } \mathrm{ArCH_2};\ \mathrm{X} = \mathrm{Br, Cl, or\ Ar};\ \mathrm{X'} = \mathrm{Br \text{ or } I}$$

The experimental results are summarized in Table I. The development of the procedure for the preparation of biaryls is based on the following findings. First, in order to find a class of aryl metals that are highly suited for the desired aryl–aryl cross-coupling, phenyllithium, phenylmagnesium bromide, phenylzinc chloride,[7] and phenyldiisobutylalalane[8] (50 mol % excess)[9] were treated with *p*-iodoanisole in the presence of 5 mol % of a catalyst prepared by the reaction of $\mathrm{Cl_2Pd(PPh_3)_2}$ with 2 equiv of diisobutylaluminum hydride (DIBAH). The results have indicated that phenyllithium is unsatisfactory, since it undergoes an extensive halogen–metal exchange reaction leading to the formation of all three expected biaryls in comparable yields. Although all the other phenylmetals gave high yields of 4-methoxybiphenyl [71% (Mg), 72% (Al), and 87% (Zn)], the amount of biphenyl formed as a by-product was considerably less with the Zn reagent (3%) than with the Mg and Al reagents (16–25%)[9] (entries 2–4), As GLC examination, after hydrolysis, of the starting arylmetals indicated the essential absence (<2%) of biphenyl, most of the biphenyl in the Mg and Al cases must have been formed in competition with the desired cross-coupling reaction.[10] These results, together with the ability of arylzinc derivatives to tolerate various electrophilic functional groups, such as nitrile and ester, make the arylzinc derivatives the reagents of choice (entries 5–8). Both arylzinc chloride and diarylzinc, which are readily

Table I. Preparation of Biaryls and Diarylmethanes by the Ni- or Pd-Catalyzed Reaction of Organometallic Reagents with Aryl Halides[a]

Entry	Organometallic reagent	ArX	Catalyst[b]	Yield[c] of Ar–Ar′ or $\mathrm{PhCH_2Ar}$, %
1	PhZnCl	*p*-Iodoanisole	A	85
2	PhZnCl	*p*-Iodoanisole	B	87
3	PhMgBr	*p*-Iodoanisole	B	71[d]
4	$\mathrm{PhAl(Bu\text{-}}i)_2$	*p*-Iodoanisole	B	72[e]
5	PhZnCl	*p*-Bromobenzonitrile	A	90
6	$\mathrm{Ph_2Zn}$	*p*-Bromobenzonitrile	A	85
7	PhZnCl	Methyl *p*-bromobenzoate	A	70
8	PhZnCl	*p*-Iodonitrobenzene	B	90(74[f])
9	*m*-TolZnCl	*m*-Iodotoluene	A	95
10	$\mathrm{PhCH_2MgCl}$	Bromobenzene	A	80
11	$\mathrm{PhCH_2MgCl}$	Bromobenzene	B	86[g]
12	$\mathrm{PhCH_2ZnBr}$	Methyl *p*-bromobenzoate	A	85[h]
13	$\mathrm{PhCH_2MgCl}$	Methyl *p*-bromobenzoate	A	12[i]
14	$\mathrm{PhCH_2ZnBr}$	*p*-Bromobenzonitrile	A	92
15	$\mathrm{PhCH_2MgCl}$	*p*-Bromobenzonitrile	A	50[j]
16	$\mathrm{PhCH_2MgCl}$	*p*-Bromoanisole	A	75[k]
17	$\mathrm{PhCH_2ZnBr}$	*p*-Iodonitrobenzene	B	88(74[f])

[a] Unless otherwise mentioned, the temperature and time of reaction were ca. 25 °C and 1–2 h, respectively. The amount of the catalyst in each case was 5 mol %. [b] A = $\mathrm{Ni(PPh_3)_4}$ prepared in situ by the reaction of $\mathrm{Ni(acac)_2}$, $\mathrm{PPh_3}$ and $(i\text{-}\mathrm{Bu})_2\mathrm{AlH}$ (1:4:1). B = $\mathrm{Cl_2Pd(PPH_3)_2}$ + $(i\text{-}\mathrm{Bn})_2\mathrm{AlH}$ (1:2). [c] By GLC. Based on aryl halides introduced. The amount of biaryl in each case was <5%, and that of bibenzyl in the diarylmethane synthesis was <2%, unless otherwise mentioned. [d] The yield of biphenyl was 16%. [e] The yield of biphenyl was 25%, and the reaction was carried out at 50 °C. [f] Yield by isolation. [g] 3 h at 50 °C. [h] 6 h. [i] Although 38% of methyl *p*-bromobenzoate remained unreacted, benzylmagnesium chloride was consumed completely. [j] All *p*-bromobenzonitrile was consumed. [k] 6 h. *p*-Bromoanisole remained unreacted (12–13%).