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SYNTHESIS OF 6-ALKYL-6-METHOXYCARBONYL-2,4-CYCLOHEXADIEN-1-ONES AND CYCLOHEXADIENONE KETALS

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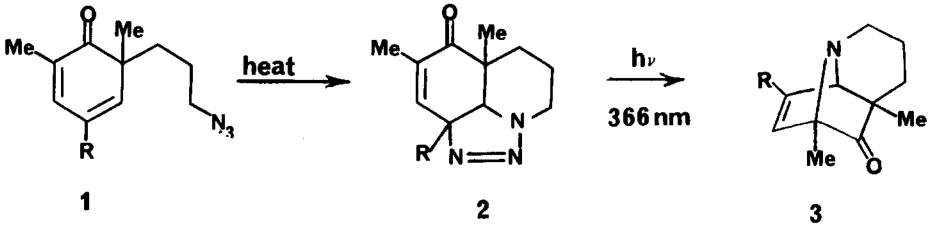
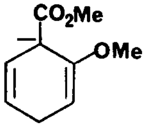
The title compounds are readily available by reductive-alkylation of o-methoxybenzoic acid esters followed by a bromination-dehydrobromination sequence.

2,4-Cyclohexadienones undergo mechanistically interesting and synthetically useful photorearrangements.[1] The Diels-Alder reactivity of these linearly conjugated dienes has been studied and there have been applications of this reaction to the synthesis of natural products.[2] Despite the potential for their use in chemical studies, there has been relatively little effort expended in the development of efficient, general methods for 2,4-cyclohexadienone preparation. Phenolic carbon alkylation[3] is the most expeditious route to 2,4-cyclohexadienones; however, this method is obviously limited to the use of symmetrically substituted phenols and reactive alkylation reagents. Other less general methods involve phenol[4] and substituted benzene ring[5] oxidation, as well as alkylation-oxidation of 2-cyclohexenone derivatives.[6]

We recently have developed methods for accomplishing the synthetic equivalence of an intramolecular cycloaddition between a diene and a nitrene; e.g., 1 → 2 → 3.[7] The corresponding diene-carbene equivalence also is under investigation.[8] In this preliminary work, the phenolic C-alkylation route has provided substrates of type 1. To apply this chemistry to the synthesis of natural products requires development of general methods for preparation of 6,6-disubstituted-2,4-cyclohexadienones. In this note, we describe a simple, potentially general 2,4-cyclohexadienone synthesis.



The Birch reductive alkylation of benzoic acid derivatives is now a well established method for preparation of 1,4-cyclohexadienes.[9] Cyclohexadienes 5a-c are prepared by the procedure developed by Mander and coworkers.[9c] Reactions of 5a-c with N-bromoacetamide in methanol[10] give bromo ketals 7a-c in quantitative yield. Dehydrobromination of 7a and 7b to diene ketals 8a and 8b, respectively, is cleanly effected by t-BuOK (2.2 equiv) in refluxing t-BuOH. Initial attempts at base-induced elimination in 7c resulted in an uncharacterized mixture of products. Diene ketals 8a and 8b undergo rapid hydrolysis to 2,4-cyclohexadienones 9a and 9b, even in $CDCl_3$ if no attempt is made to remove acidic contaminants. NMR spectra of 8 can be recorded in C_6D_6 without special precautions.



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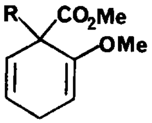
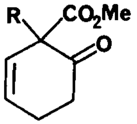


5a, R = Me
b, R = Et
c, R = $CH_2CH_2CH_2Cl$



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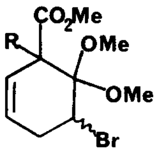

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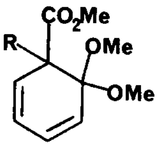

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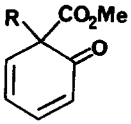

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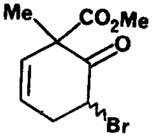
Hydrolysis of enol esters 5a-c (10% HCl, MeOH, 25°C) provides β,γ-enones 6a-c. Reaction of 6a-c with N-bromosuccinimide in refluxing benzene solution (2h, continuous sun lamp irradiation) results in formation of 2,4-cyclohexadienones 9a-c. Presumably, allylic bromination of 6 occurs to give a β-bromo ketone, from which rapid dehydrobromination occurs under these reaction conditions to give 9. We do not believe that α-bromo ketone 10 is an intermediate in the formation of 9a; 7a may be cleanly converted to 10 and 10 is stable in refluxing benzene solution in the presence of p-toluenesulfonic acid (2h).



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Product yields and physical data for compounds prepared in this study are recorded in the table.[11] It should be noted that product yields for 8a, 8b, 9a-c have not been optimized. The 6-alkyl-6-methoxycarbonyl-2,4-cyclohexadienones 9 are stable to silica gel chromatography and distillation by at least the Kugelrohr technique. They may be stored in a refrigerator for extended periods (at least several weeks) without significant decomposition. They do not appear to be as susceptible to dimerization as are the 6,6-dialkyl analogs.[12]

Table

Compound	Yield	m.p. or b.p. (Kugelrohr)
5c	67%	38-39°C
6a	87%	85°C (2.4mm)
6b	96%	75°C (1.5mm)
6c	98%	*
7a	quantitative	69-71°C
7b	quantitative	103-104°C
7c	quantitative	*
8a	52%	-
8b	43%	-
9a	68%	105°C (1.6mm)
9b	85%	95°C (1.7mm)
9c	52%	*

* Isolated by silica gel chromatography (HPLC)

The chemistry reported herein provides 1) the first potentially general method for preparation of 2,4-cyclohexadienones; 2) the first reported synthesis of ketals of 2,4-cyclohexadienones (e.g., 8); and 3) the first reported synthesis of 6-alkyl-6-alkoxycarbonyl-2,4-cyclohexadienones 9. These results greatly extend the flexibility of the diene-nitrene and diene-carbene synthetic equivalencies represented by the conversion 1 → 2 → 3. Furthermore, we are particularly interested in the photochemistry of systems of type 8 and 9. Applications of 2,4-cyclohexadienone chemistry will be reported in the near future.

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11. Compounds 5c, 6a-c, 7a-c, and 9a-c gave satisfactory elemental analysis; analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan. Cyclohexadiene 5a and 5b are reported in reference 9c. All compounds reported gave ^{1}H NMR, IR, MS and UV spectra completely in accord with the assigned structures.

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