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A NOVEL SYNTHESIS OF 4-ALKYL-4-(4-METHOXYPHENYL)CYCLOHEX-2-EN-1-ONES AND THE *SCELETIUM* ALKALOID, O-METHYLJOUBERTIAMINE.

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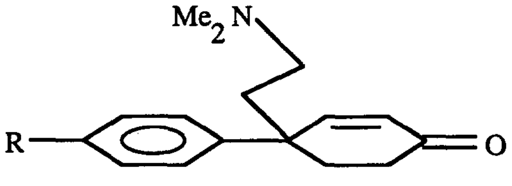
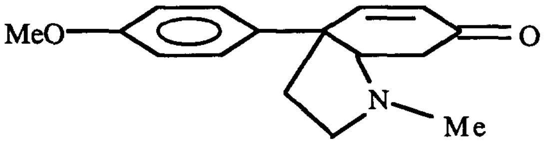
Summary: The dianion formed by reduction of (η^6:η^6-4,4'-dimethoxybiphenyl)-$[Cr(CO)_3]_2$ reacts with electrophiles such as methyl or ethyl triflate or allyl tosylate at -78 °C followed by CF_3CO_2H and I_2 to form 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones.

Many natural products, including the *Sceletium* alkaloids joubertiamine (**1a**), O-methyljoubertiamine (**1b**), mesembrine (**2**) and related derivatives, have the basic skeletal structure of a 4-alkyl-4-arylcyclohex-2-en-1-one.[1] One of the more difficult steps in the synthesis of these molecules is the construction of the quaternary center on the cyclohexenone ring.[2] Several methods for the formation of this quaternary center have been explored including annelations of endocyclic enamines,[3] geminal alkylation at a carbonyl center,[4] Claisen-Eschenmoser rearrangement,[5] Diels-Alder reaction followed by rearrangement,[6] and nucleophilic attack on tricarbonylcyclohexadienyliron complexes.[7,8] We wish to report here a new methodology for synthesis of 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones, and a formal synthesis of O-methyljoubertiamine.



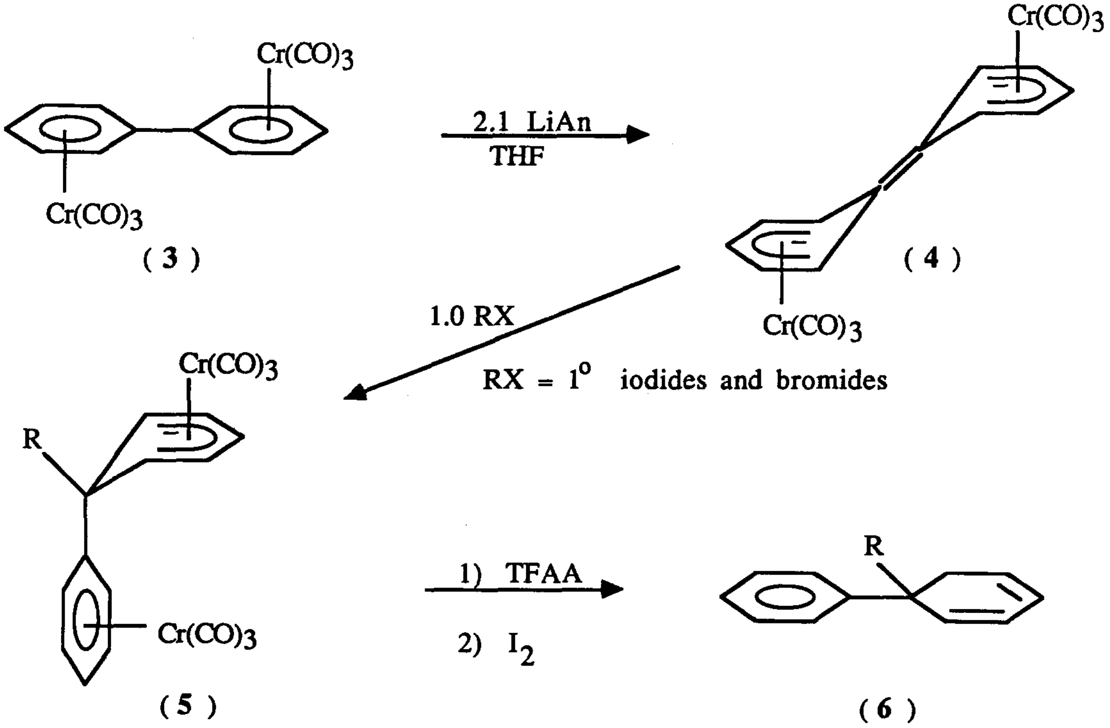
(**1a**) R = H

(**1b**) R = OMe



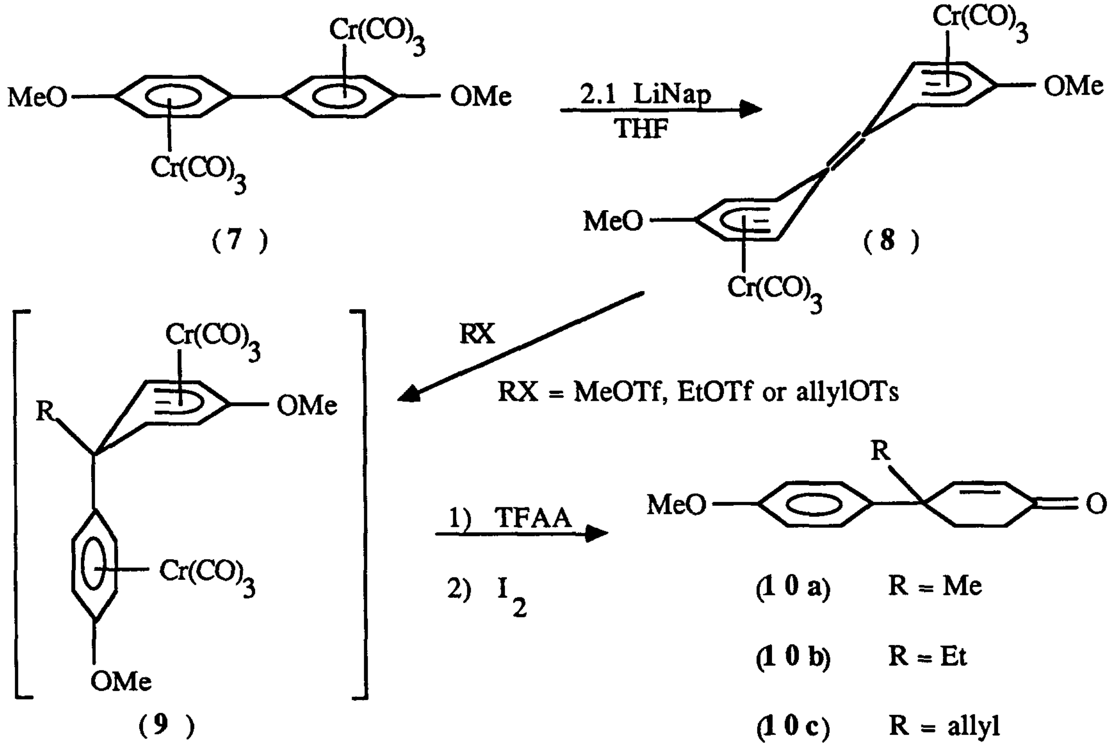
(**2**)

Recent work[9] has demonstrated a new methodology in the synthesis of 5-alkyl-5-phenyl-1,3-cyclohexadienes. As shown in Scheme 1, (η^6:η^6-biphenyl)bis(tricarbonylchromium) (**3**) was reduced with 2.1 eq. lithium anthracenide (LiAn) to a stable dianion (**4**) which was reacted with methyl or primary alkyl halides to form the substituted (η^5-cyclohexadienyl)tricarbonylchromium anion (**5**), in a highly regio- and stereoselective reaction.[10] This anion was protonated *in situ* with CF_3CO_2H and oxidized with I_2 or air promoting loss of the remaining $Cr(CO)_3$ group, to generate the 5-alkyl-5-phenyl-1,3-cyclohexadiene (**6**) in excellent yields.[11]



SCHEME 1

We considered that the 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one system of O-methyljoubertiamine might be attained using a methodology similar to that explored for the (η^6:η^6-biphenyl)bis(tricarbonylchromium) model system. The route selected involved alkylation of the dianion generated from the symmetrically disubstituted biphenyl system, (η^6:η^6-4,4'-dimethoxybiphenyl)bis(tricarbonylchromium) (**7**), the chemistry of which has not been previously explored. (η^6:η^6-4,4'-Dimethoxybiphenyl)bis(tricarbonylchromium) was synthesized from 4,4'-dimethoxybiphenyl and $Cr(CO)_6$ using standard methods.[12] Initial attempts at reduction of this complex to its dianion (**8**) at room temperature with lithium naphthalide (LiNap) or sodium amalgam resulted in the formation of large amounts of 4-methoxybiphenyl. Electrochemical results indicate that the dianion (**8**) is unstable at room temperature, but becomes much more stable at lower temperatures.[13] Subsequent reductions with lithium naphthalide were performed at -78 °C. Attempted reactions of primary alkyl iodides and bromides using several variations of these conditions did not result in the desired alkylations. Reactions with methyl or ethyl triflate and allyl tosylate, however, followed by workup with trifluoroacetic acid and iodine did result in the formation of the desired 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one products (**10a** - **10c**) in fair yields.[14] We postulate that the initial alkylation occurs at the phenyl-substituted ring position to generate the anion (**9**), a species very similar to the anion (**5**) which has been characterized by ^1H and ^{13}C NMR. Protonation with excess trifluoroacetic acid generates a dienol ether, which rearranges under the acidic conditions to the 4-alkyl-4-(η^6-4-methoxyphenyltricarbonylchromium)cyclohex-2-en-1-one.[15] Cleavage of the remaining $Cr(CO)_3$ group with iodine generates the free 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one product.



SCHEME 2

Isolation of 4-allyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**10c**) completes a formal synthesis of O-methyljoubertiamine (**1a**). Martin and coworkers[4a] have converted (**10c**) to O-methyljoubertiamine in one pot in 75 % yield by an ozonolysis, followed by a reductive amination using $NaBH_3CN$ in the presence of Me_2NH_2Cl.

In summary, the dianion formed by reduction of (η^6:η^6-4,4'-dimethoxybiphenyl)$[Cr(CO)_3]_2$ can be reacted under the described conditions with electrophiles such as methyl or ethyl triflate or allyl tosylate. Alkylation occurs at the phenyl-substituted ring carbon, just as in the case of (η^6:η^6-biphenyl)bis-(tricarbonylchromium). Appropriate workup using CF_3CO_2H and I_2 completes a short and direct route to the synthetically important 4-alkyl-4-(4-methoxyphenyl)cyclohex-2-en-1-ones in fair yields from an inexpensive, symmetrical starting material. Work on these and related metal complexes continues in our laboratories to further explore the generality and utility of this chemistry toward the synthesis of other interesting products.

Acknowledgements. We gratefully ackowledge support of this work by the National Science Foundation (Grant CHE-8719728). We would also like to thank S. M. Pankas for assistance in preparing the (η^6:η^6-4,4'-dimethoxybiphenyl)$[Cr(CO)_3]_2$ and Dr. T. -C. Wu for providing the allyl tosylate.

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10. The stereochemistry of the alkyl group in the anionic intermediate has not yet been proven exo or endo relative to the attached $Cr(CO)_3$ group, but the reaction is stereospecific. Spectroscopic evidence indicates that protonation of the $(\eta^5:\eta^5$-biphenyl)bis(tricarbonylchromium) dianion occurs endo.[9b]
11. See reference 9 for characterization of the $(\eta^5:\eta^5$-biphenyl)bis-(tricarbonylchromium) dianion and other intermediates along this reaction pathway.
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13. Cyclic voltammetry of $(\eta^6:\eta^6$-4,4'-dimethoxybiphenyl)bis(tricarbonylchromium) in THF (0.2 M TBAP, 22 °C, HMDE) generates a chemically irreversible wave at -1.95 V (vs. the Ag/AgCl, saturated NaCl(aq) reference electrode) indicating an unstable dianion is formed. This situation is very different from that observed for other (conjugated arene)bis(tricarbonylchromium) complexes, which have been observed to form stable dianions.[9] Presumably, reduction of the $(\eta^6:\eta^6$-4,4'-dimethoxybiphenyl)bis(tricarbonylchromium) to its dianion at room temperature results in facile loss of a methoxy group. Lowering the temperature in the electrochemical cell to -40 °C results in a much more chemically reversible wave in the cyclic voltammagram.
14. Isolated yields for 4-methyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**10a**), 4-ethyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**10b**) and 4-allyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**10c**) are 30%, 23% and 17%, respectively, from $(\eta^6:\eta^6$-4,4'-dimethoxybiphenyl)bis(tricarbonylchromium). All compounds discussed have been fully characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectral analysis. IR and NMR data for 4-allyl-4-(4-methoxyphenyl)cyclohex-2-en-1-one (**10c**) are in agreement with that reported in the literature.[4a]
15. $(\eta^6$-Anisole)tricarbonylchromium has been reacted with nucleophiles to generate anionic intermediates similar to (**9**). Protonation of these species with excess trifluoroacetic acid also resulted in the production of conjugated cyclohexenones. Semmelhack, M. F.; Harrison, J. J.; Thebtaranonth, Y. *J. Org. Chem.* **1979**, 44, 3275-3277.

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