

Conjugate Additions of Carbon Nucleophiles to Cyclopentadienones

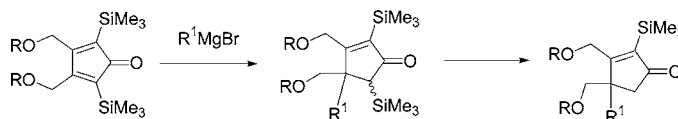
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ABSTRACT



Reactions of cyclopentadienones **1** with alkylmagnesium bromides were investigated and gave 1,4 adduct and/or 1,2 adduct.

Cyclopentadienones have attracted chemists' attention due to their high degree of synthetic potential.¹ However, there are not many cyclopentadienones available as monomers because they are prone to dimerize via Diels–Alder reaction.^{1,2} Their limited accessibility has prevented the systematic study of their reactivity toward various nucleophiles, especially carbon nucleophiles. The only cyclopentadienone that has received significant attention in this regard is the tetraphenyl derivative.³ 2,5-Bis(trimethylsilyl)-3,4-bis(hydroxymethyl)cyclopentadienone (**1a**), which was obtained through silicon-tethered Fe(CO)₅-promoted cyclocarbonyla-

tion,⁴ affords an opportunity to investigate its reactivity toward carbon nucleophiles.

Reaction of **1a** with methylmagnesium bromide or vinylmagnesium bromide gave 1,4 adducts, **2a** and **2b**, respectively, in good yields. In contrast, allylmagnesium bromide gave the 1,2 adduct **3c** (Table 1). The dependence of regioselectivity on the nucleophile can be partially rationalized by the electronic effect of the α -trimethylsilyl group, which is known to promote 1,4 addition to α,β -unsaturated ketones⁵ and the directing effect of two neighboring hydroxy groups,⁶ which will initially form the alkylmagnesium

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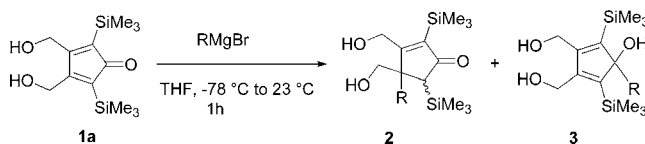
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(3) For heteroatom nucleophiles, see: Muckensturm, B. *Tetrahedron* **1975**, *31*, 1933. Arackal, T. J.; Eistert, B. *Chem. Ber.* **1973**, *106*, 3788. Eistert, B.; Arackal, T. *J. Chem. Ber.* **1971**, *104*, 3048. Gallagher, M. J.; Jenkins, I. D. *J. Chem. Soc. C* **1971**, 210. Miller, J. A. *Tetrahedron Lett.* **1969**, 4335. Miller, J. A.; Stevenson, G. M.; Williams, B. C. *J. Chem. Soc. C* **1971**, 2714. For carbon nucleophiles, see: Eagan, R. L.; Ogliaruso, M. A.; Arison, B. H.; Springer, J. P. *J. Org. Chem.* **1984**, *49*, 4248. Bergman, E. D.; Bertier, G.; Ginsburg, D.; Hirshberg, Y.; Lavie, D. Pinchas, S.; Pullman, B.; Pullman, A. *Bull. Soc. Chim. Fr.* **1951**, *18*, 661.

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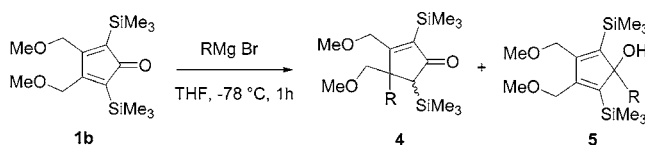
(6) For an example in which a hydroxy group controls the regio- and stereoselectivity of nucleophilic additions to γ -hydroxyenones, see: Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127. For more examples of the neighboring group effect in addition of Grignard reagents, see: Richey, H. G., Jr.; Willinks, C. W., Jr. *J. Org. Chem.* **1980**, *45*, 5027. Richey, H. G., Jr.; Bension, R. M. *J. Org. Chem.* **1980**, *45*, 5036. Richey, H. G., Jr.; Moses, L. M.; Domalski, M. S.; Erickson, W. F.; Heyn, A. S. *J. Org. Chem.* **1981**, *46*, 3773. Richey, H. G., Jr.; Domalski, M. S. *J. Org. Chem.* **1981**, *46*, 3780. Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587. Eisch, J. J.; Merkley, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1148. Chérest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swieczewski, G. *Tetrahedron Lett.* **1966**, 875.

Table 1. Addition of Grignard Reagents to Cyclopentadienone **1a**

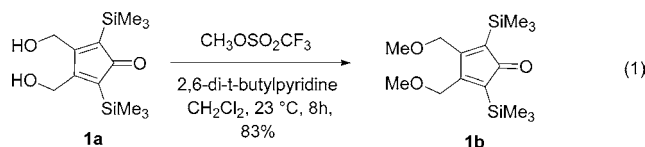
entry	R	product	yield (%)
1	methyl	2a	95
2	vinyl	2b	82
3	allyl	3c	86

alkoxide with the Grignard reagent before the addition occurs. In the case of allylmagnesium bromide, which is known to have a different mechanism in addition reactions,⁷ 1,2 addition occurred. We speculate that, in the case of methyl and vinyl derivatives, intramolecular delivery of the bound nucleophile, the alkyl group on the alkylmagnesium alkoxide, to a proximate electrophilic center favors 1,4 addition. For the allyl system, reaction at the distal carbon would require a seven-membered ring transition state and so intermolecular delivery in a 1,2 fashion is favored.

In the hope of securing more details about the effects of the hydroxyl groups, 2,5-bis(trimethylsilyl)-3,4-bis(methoxymethyl)cyclopentadienone (**1b**), prepared by methylation on both hydroxy groups of **1a** (eq 1),⁸ was also subjected to reaction with Grignard reagents (Table 2).

Table 2. Addition of Grignard Reagents to Cyclopentadienone **1b**

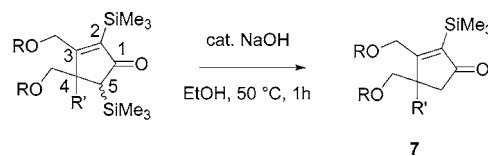
entry	R	1,4 adduct (yield)	1,2 adduct (yield)	total yield (%)
1	methyl		5a (95)	95
2	ethyl	4b (31)	5b (43)	74
3	isopropyl	4c (41)	5c (50)	91
4	vinyl	4d (87)		87
5	allyl	4e (83)		83



Since a Grignard reagent can be added to the “enone” either in 1,2 fashion or in 1,4 fashion,⁹ the results shown in Table 2 are not surprising. However, the marked dependence of regioselectivity on the nature of R and the contrast in behavior of complexes **1a** and **1b** are very interesting.

Methylmagnesium bromide gave exclusively the 1,2 adduct **5a**, while ethyl and isopropylmagnesium bromide gave not only 1,2 adduct (**5b** and **5c**, respectively) but also 1,4 adduct (**4b** and **4c**, respectively) in ca. 1:1 ratios. Vinyl- and allylmagnesium bromide gave exclusively 1,4 adducts (**4d** and **4e**, respectively). It appears that hydroxyl groups in **1a** play an important role in the case of methyl and allylmagnesium bromide, as the change to methyl ethers in **1b** leads to dramatic changes in regioselectivity.

The 1,4 adducts were obtained as a mixture of C(5)-diastereomers in various ratios (Table 3). ¹H NMR analysis

Table 3. Diastereomeric Ratios of 1,4 Adducts (**2** and **4**) and Desilylation Yields

entry	R	R'	diastereomeric ratio of adduct	product	yield (%)
1	H	methyl	2a (1:-- ^a) ^b	7a	94
2	H	vinyl	2b (1:-- ^a) ^b	7b	87
3	Me	ethyl	4b (1:1.1) ^b	7c	93
4	Me	isopropyl	4c (1:1.2) ^b	7d	94
5	Me	vinyl	4d (1:-- ^a) ^b	7e	91
6	Me	allyl	4e (1:1.5) ^c	7f	95

^a Only one diastereomer was detected by NMR. ^b Product was isolated as a mixture of diastereomers, and the ratio was determined by NMR. ^c Two diastereomers were separated, and their ratio is based on the isolated yields.

of the mixture of C(5)-diastereomers **2a** and **2b** show high ratios of the one diastereomer to the other. However, it was observed that those diastereomeric mixtures (**2a** and **2b**) readily undergo both epimerization¹⁰ and desilylation. On the other hand, C(5)-diastereomeric mixtures **4b–e** are sufficiently stable to be isolated and fully characterized. For an example, the two C(5)-diastereomers in mixture **4e** were separated by silica gel chromatography and their stereochemistries were determined by NOESY data indicating that the anti adduct, where R = allyl and H on C(5) have anti relationship, is the major product. Also, it is noteworthy that the ¹H NMR spectra of 1,4 adducts show two distinct AB quartets owing to two sets of diastereotopic methylene protons,¹¹ whereas the 1,2 adducts show one AB quartet owing to two equivalent sets of diastereotopic methylene protons.

(7) For a review of allylic organometallic compounds, see: Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1. For examples that involve γ -addition of allylmagnesium halides, see: Hussain, I.; Komasa, T.; Ohga, M.; Nokami, J. *Synlett* **2002**, 640. Miginiac, L.; Miginiac, P.; Provost, C. *Bull. Soc. Chim. Fr.* **1965**, 3560. Benkeser, R. A. *Synthesis* **1971**, 7, 347.

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(10) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77.

The 1,4 adducts were transformed into **7** by treatment with a catalytic amount of NaOH in ethanol, which is known not to affect vinylsilanes (Table 3).¹²

The cyclopentenones **7** can be versatile intermediates for the synthesis of natural products.¹³ While it is possible to partly rationalize the regiochemistry during additions to **1a**,

(11) For *anti-4e* (1,4-anti adduct), the two AB quartets are at δ 4.26 and 4.16 ppm (ABq, $J = 12.4$ Hz, 2H) and δ 3.50 and 3.43 ppm (ABq, $J = 9.3$ Hz, 2H). For the other 1,4 adducts, refer to Supporting Information.

(12) For a review of cleavage reactions of the C–Si bond, see: Chvalovsky, V. *Org. React.* **1972**, *3*, 191.

(13) For examples of a related structure that has been used as an intermediate in the synthesis of natural products, see: Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080. Geng, F.; Liu, J.; Paquette, L. A. *Org. Lett.* **2002**, *4*, 71.

we do not yet have a good understanding of the factors that control the behavior of **1b** toward alkylmagnesium halides. Further investigations of these reactions are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ¹H NMR and ¹³C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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