

A New 4-Substituted-2-Cyclohexenone Synthesis

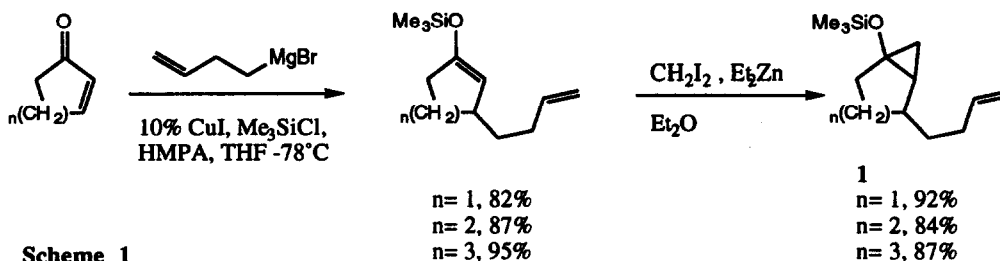
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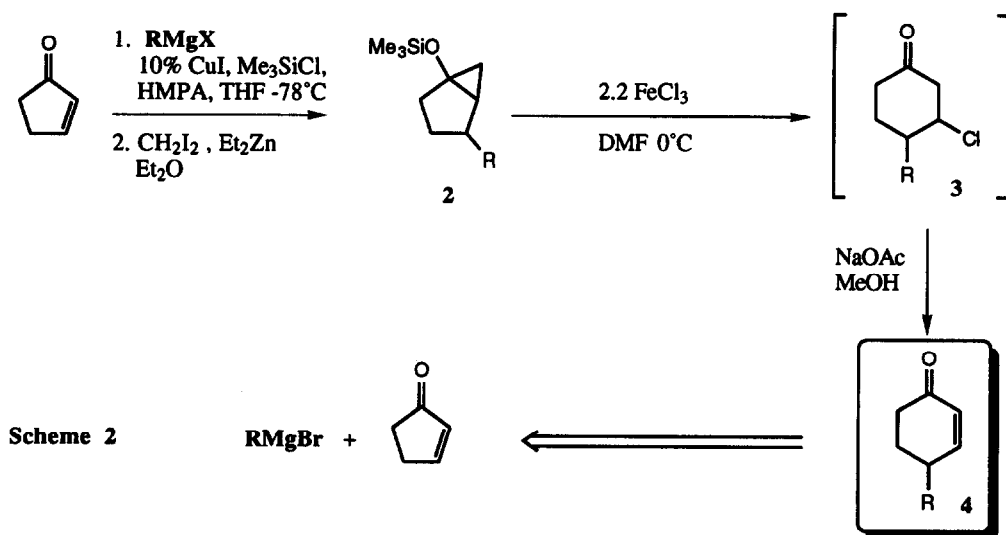
Abstract: Conjugate addition of a variety of Grignard reagents to 2-cyclopentenone followed by cyclopropanation of the resulting enol ethers gave a range of substituted cyclopropyl silyl ethers in good yield. Treatment of these cyclopropyl silyl ethers with ferric chloride in DMF gave the one carbon ring expanded β -chloro ketones which were eliminated to the corresponding 4-substituted-2-cyclohexenones.

4-Substituted-2-cyclohexenones are an important class of starting materials for a variety of synthetic transformations and although there are several general methods for their preparation (e.g. Birch reduction of substituted anisoles¹, nucleophilic substitution of iron tricarbonyl complexes² *etc*) many of these systems containing more complex 4-substituents remain relatively inaccessible. As part of a program investigating the synthesis of various [n.3.0] bicyclic systems we recently developed³ a novel ferric chloride mediated tandem ring expansion-cyclisation sequence using various substituted cyclopropyl silyl ethers. The cyclopropanes were readily available *via* a copper catalysed conjugate addition of Grignard reagents followed by cyclopropanation. For example conjugate addition of butenyl magnesium bromide to a variety of cyclic enones followed by Simmons-Smith cyclopropanation of the resulting silyl enol ethers gave the cyclopropanes **1** in excellent overall yield (Scheme 1).



Scheme 1

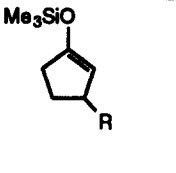
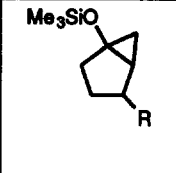
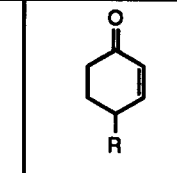


It occurred to us that application of this conjugate addition/cyclopropanation methodology to 2-cyclopentenone with a variety of Grignard reagents would give the corresponding substituted cyclopropyl ethers **2**. Ring expansion with ferric chloride would yield the β -chloro ketones **3** which after elimination with base would yield the 4-substituted-2-cyclohexenones **4**. The overall process would provide convenient access to these useful substituted cyclohexenones where the only limiting factor would be the availability of the starting Grignard reagent (Scheme 2).



In general the copper catalysed addition³ of the Grignard reagents to 2-cyclopentenone proceeded smoothly to give excellent yields of the silyl enol ethers. The only two exceptions were entries 2 and 3; the *t*-butyl and allyl examples respectively. In the case of *t*-butyl magnesium bromide 1,4- addition appeared to be very slow and *t*-butyltrimethylsilane was a major product resulting from the reaction of the Grignard reagent with the *in situ* chlorotrimethylsilane. This problem was overcome by utilising the higher order cyanocuprate as discussed by Corey⁴. Copper catalysed addition of allyl magnesium bromide to 2-cyclopentenone using our previously adopted method³ gave only the silyl ether of the 1,2-addition product. This was not totally unexpected given that allyl cuprates are notoriously difficult to work with⁵. A neat solution to this problem was provided by using the method developed by Lipshutz⁶. Cyclopropanation of the enol ethers with diethyl zinc and diiodomethane⁷ proceeded well in all cases to give excellent yields of the corresponding cyclopropyl ethers. It is interesting to note that in the examples where there are two alkene moieties (entries 3 and 4) cyclopropanation is exclusive for the enol ether, and even when a two fold excess of the reagents were used none of the dicyclopropane was ever detected. Ring expansion⁷ with ferric chloride in DMF followed by base treatment of the resulting crude β -chloro ketones⁹ (MeOH/NaOAc) gave the requisite 4-substituted-2-cyclohexenones **4** in moderate to good yield.

The following table summarises our results:

Table: The synthesis of 4-substituted-2-cyclohexenones¹⁰

Entry	RMgX			
1	<i>n</i> -BuMgBr ^a	99% ^b	93%	54%
2	<i>t</i> -BuMgBr ^a (<i>t</i> -Bu) ₂ CuCNLi ₂ ^c	22% ^b 55%	74%	48%
3	 MgBr	74% ^d	78%	45%
4	 ^a MgBr	82% ^b	92%	45%
5	PhMgBr ^a	94% ^b	80%	53%
6	PhCH ₂ MgCl ^e	89% ^b	87%	71%

^a Prepared from the corresponding bromide and magnesium *via* conventional methods in tetrahydrofuran.

^b Prepared by conjugate addition of corresponding Grignard reagent according to the method in Ref. 3.

^c Prepared from *t*BuLi and CuCN according to the procedure of Corey⁴.

^d Prepared by conjugate addition of allyl magnesium bromide (Aldrich) according to the procedure developed by Lipshutz⁶.

^e Benzyl magnesium chloride prepared according to the procedure developed by Brown⁸.

In summary we have demonstrated a novel and effective method for the synthesis of 4-substituted-2-cyclohexenones from cyclopropyl silyl ethers, which in turn are readily available from 2-cyclopentenone via an efficient conjugate addition-cyclopropanation sequence. Present studies are concerned with the possibility of utilising this methodology for the synthesis of 4,4-disubstituted cyclohexenones from the corresponding 3-substituted cyclopentenones.

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9. In most cases TLC analysis of the crude reaction mixture at this stage showed it to comprise of a mixture of the β -chloro ketone and the eliminated cyclohexenone.
10. All new compounds fully characterised by IR, ^1H and ^{13}C NMR and HRMS.

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