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RING ENLARGEMENT REACTION OF 2-(1-ALKENYL)-1-CYCLOBUTYL KETONES. A NEW METHOD FOR THE PREPARATION OF 4-ACYL-1-CYCLOHEXENES

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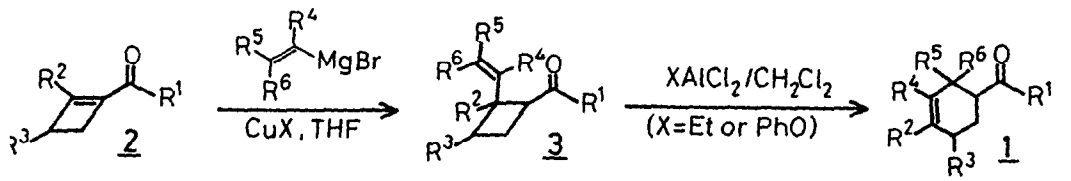
Abstract: Various 1,2-disubstituted 4-acyl-1-cyclohexenes were obtained by the ethylaluminum dichloride promoted ring enlargement reaction of 2-(1-alkenyl)-1-cyclobutyl ketones prepared by the conjugate addition of 1-alkenylmagnesium bromides with 1-cyclobutenyl ketones.

The construction of cyclohexene ring system is one of the most important problems in organic synthesis and numerous methods have been investigated. Among them that have been employed most frequently are the Diels-Alder reaction and related reactions. However, the Diels-Alder reaction between unsymmetrically substituted diene and dienophile suffers the disadvantage that both regioisomers are produced and the proportion of two isomers is inevitably dependent on the structures of diene and dienophile employed.[1] In this communication, we report a convenient method for the selective preparation of 1,2-disubstituted 4-acyl-1-cyclohexenes (1) which correspond to the Diels-Alder adducts of vinyl ketones with unsymmetrically substituted 1,3-butadienes.

The present method consists of the conjugate addition of 1-alkenylmagnesium bromides to 1-cyclobutenyl ketones (2)[2] and the ring enlargement reaction of the resulting adducts (3).



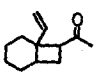
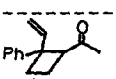
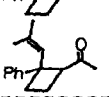
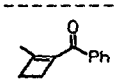
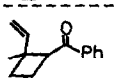
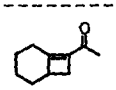
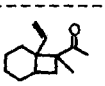
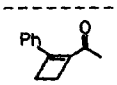
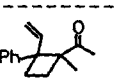
2 3 1

The first step of the preparation of cyclohexene derivatives (1) was ccessfully carried out using diorganocuprates. Cyclobutenyl ketones (2) re treated with slight excess (1.2 equiv.) of the cuprate reagents epared from two moles 1-alkenylmagnesium bromide and one mole copper(I) lt (-40 °C / 40 min or -20 °C / 30 min) in THF to afford the conjugate lition products (3) in good yields. In some cases, addition of TMSCl reased the yields of adducts (3) (runs 2, 5, and 6).[3] The treatment the intermediate enolate with iodomethane also gave 1-methylcyclobutyl ones (3) (runs 8 and 9) (see Table 1).

Next the transformation of the adducts (3) to the cyclohexene deriva-

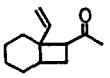
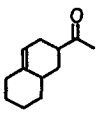
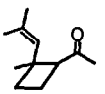
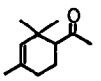
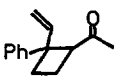
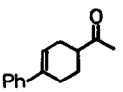
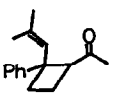
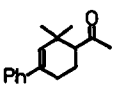
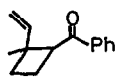
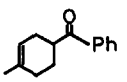
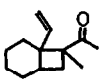
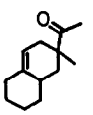
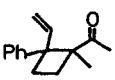
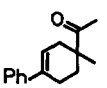
tives (1) was examined using various Lewis acids and $EtAlCl_2$ was found to be an efficient catalyst. The treatment of 3 with double the molar quantity of $EtAlCl_2$ gave 1 as sole ring expanded product without formation of any five-membered ring compound.[4] The reduction of the amount of catalyst, however, caused the serious elongation of reaction time (run 3). Furthermore, it was found that $PhOAlCl_2$ gave better yields when the $EtAlCl_2$ promoted reactions were complicated by unidentified side reactions (runs 11 and 12). The typical experimental procedure for the ring enlargement reaction is as follows: To a hexane solution (1.0 M) of $EtAlCl_2$

Table 1. Conjugate addition of Grignard reagents to 1-cyclobutenyl ketones (2)

run	Cyclobutenyl ketone (2)	RMgX	Temp °C	Time min	CuX	Product(3)[a]	Yield %
1			-40	280	$CuBr \cdot SMe_2$		69
2			-40	120	CuI		72[b]
3			-20	30	CuI		80
4			-20	120	$CuBr \cdot SMe_2$		88
5			-20	120	CuI		74[b]
6			-20	120	CuI		80[b]
7			-20	50	CuI		58
8			-20	120	$CuBr \cdot SMe_2$		73[c]
9			-20	50	$CuBr \cdot SMe_2$		63[c]

a) All compounds were identified by IR and NMR spectra. b) The reaction was carried out in the presence of TMSCl. c) The product was obtained by the treatment of the intermediate enolate with MeI (10 equiv.) and HMPA (1 ml/1 mmol of 2) at r.t. overnight.

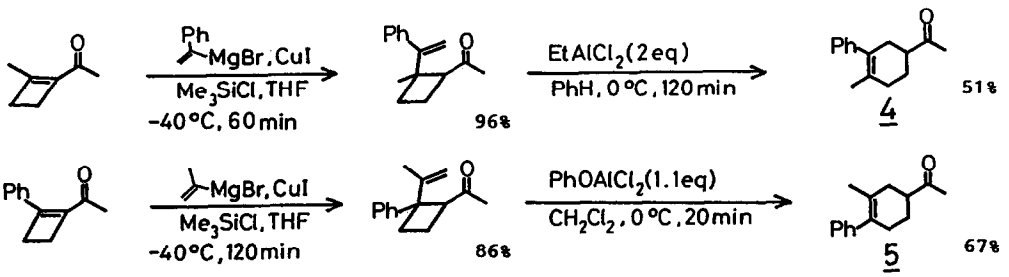
Table 2. The Ring enlargement Reaction of 2-(1-alkenyl)-1-cyclobutyl ketones (3)[a)]

run	Cyclobutyl ketone (3)	$XAlCl_2$ (eq)	Solvent	Time min	Product(1)[b)]	Yield %
1		$EtAlCl_2$ (2)	PhH	50		70
2		$EtAlCl_2$ (2)	CH_2Cl_2	15		61
3		$EtAlCl_2$ (0.5)	CH_2Cl_2	1500		69
4		$PhOAlCl_2$ (2)	CH_2Cl_2	60		75
5		$EtAlCl_2$ (2)	CH_2Cl_2	30		51
6		$EtAlCl_2$ (2)	CH_2Cl_2	35		69
7		$EtAlCl_2$ (2)	PhH	25		67
8		$EtAlCl_2$ (2)	CH_2Cl_2	5		89
9		$EtAlCl_2$ (2)	PhH	5		83
10		$EtAlCl_2$ (1.2)	CH_2Cl_2	35		66
11		$PhOAlCl_2$ (2)	CH_2Cl_2	60		53
12		$PhOAlCl_2$ (2)	CH_2Cl_2	15		67

a) All reaction were performed with a same procedure as described in the text, unless otherwise noted. b) The structures of these compounds were supported by IR and NMR spectra.

(2.4 mmol) diluted with an equal volume of CH_2Cl_2 was added a CH_2Cl_2 (4.8 ml) solution of 1-acetyl-2-isopropenyl-2-methylcyclobutane (182 mg, 1.2 mmol) at 0 °C. After being stirred for 35 min, the reaction was quenched by addition of 1M HCl. The organic material was extracted with CH_2Cl_2 and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane : AcOEt = 95 : 5) and then 4-acetyl-1,2-dimethyl-1-cyclohexene (125 mg, 69%) was obtained. In a similar manner, various cyclohexenyl ketones (1) were synthesized in good yields and the results are summarized in the Table 2.

The synthetic utility of the present method was demonstrated by the following scheme. The two position isomers (4 and 5) can be synthesized selectively utilizing different cyclobutenyl ketones and Grignard reagents.



Further, it is well known that the Diels-Alder reaction is sensitive to sterical hindrance; tri and tetrasubstituted olefins or dienes with substituents at the terminal carbons react only very slow.[1] On the other hand, the cyclohexenes which correspond to the adducts of 1,1-disubstituted 1,3-butadiene with methyl vinyl ketone could be obtained as noted above (runs 7 and 9, Table 2). Therefore, the present method provides an alternative route to such cyclohexene derivatives.

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3) E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, Tetrahedron Lett., 27, 4029 (1986).
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