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REGIOSPECIFIC ACYLATION OF ORGANOCOPPER ENOLATES: A NEW SYNTHESIS OF 7-OXOPROSTAGLANDINS

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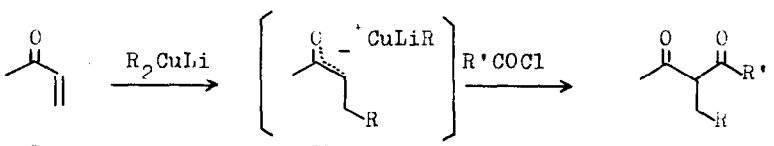
The in situ use of enolates is an important procedure in organic synthesis to make a new carbon-carbon bond at the α-position of a carbonyl function.[1-5] While considerable studies[6-8] have been made dealing with problems to control C- or O-acylation of metal enolates, it is often difficult to achieve regiospecific C-acylation of metal enolates.

In this paper we wish to report the regiospecific acylation of organocopper enolates with acyl chloride which is depicted generally in Scheme 1. The enolates II generated by conjugate addition of organocopper lithium reagents to the α,β-unsaturated ketones I were allowed to react with acyl chloride to afford the α-acylated-β-alkylated ketones III. This result provides a simple method to synthesize β-diketone systems[9] such as III.

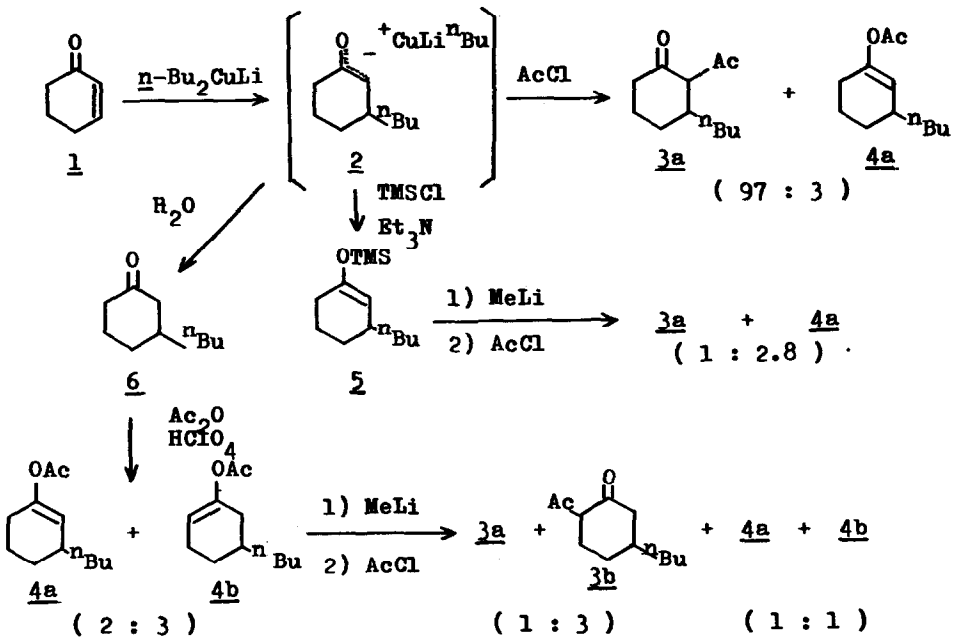
Scheme 1



I II III

When 2-cyclohexenone (1) was treated with lithium di-n-butylcuprate, and then with acetyl chloride gave 2-acetyl-3-n-butylcyclohexanone (3a) (97%) accompanied by a small amount of 1-acetoxy-3-n-butylcyclohexene (4a) (3%). To confirm the regiospecificity of this reaction, following experiments were carried out. When the formed copper enolate 2 was trapped with trimethylsilyl chloride[5,10] to afford silyl ether 5 which was treated with methyl lithium, and then with acetyl chloride,[8] a mixture of 3a and 4a was given in a ratio of 1:2.8. Furthermore, when the enol acetates (4a and 4b in a ratio of 2:3) prepared from 3-n-butylcyclohexanone (6) were treated with methyl lithium, then acetyl chloride, the isomeric mixture of the C-acylated products (3a and 3b in a ratio of 1:3) and the O-acylated products (4a and 4b in a ratio of 1:1) were obtained in a ratio of 5:1, respectively (Scheme 2).

Scheme 2



The experimental results of the acylation of organocopper enolates are summarized in Table 1. As shown in the entry 3 of Table 1, when acetic anhydride was used as an acylating agent without tri-n-butylphosphine as a ligand, reaction products consisted of the β-diketone 3a (9%), and the O-acylated products (30%) of 3a. In these experiments, hexamethylphosphoric triamide(HMPA) was found to be effective for the C-acylation.

It has been observed that enolates generated by the conjugate addition of lithium dimethylcuprate or of Grignard reagents in the presence of copper salt with acid halides or acetic anhydride gives mainly their enol acetates, i.e. O-acylated products.[11-14] In our case, however, reaction of the copper lithium enolates with acetyl chloride led predominantly to C-acylation.[15] We are interested in the regiospecificity of this reaction in connection with the recently reported regiospecific alkylation[1-5] of organocopper enolates.

The following representative experimental procedure was employed; To lithium di-n-butylcuprate complex, prepared from 3.90 g (10 mmol) of tri-n-butylphosphine-copper(I) iodide complex[16] and 15.3 ml (20 mmol) of 1.31 M n-butyllithium hexane solution in 30 ml of ether at -78° for 30 min, was added 960 mg (10 mmol) of 2-cyclohexenone (1) dissolved in 5 ml of ether. After stirring for 30 min at -78°, a solution of 4 ml (56 mmol) of acetyl chloride in 10 ml of ether and 5 ml of HMPA was rapidly added at 0°. After stirring at room

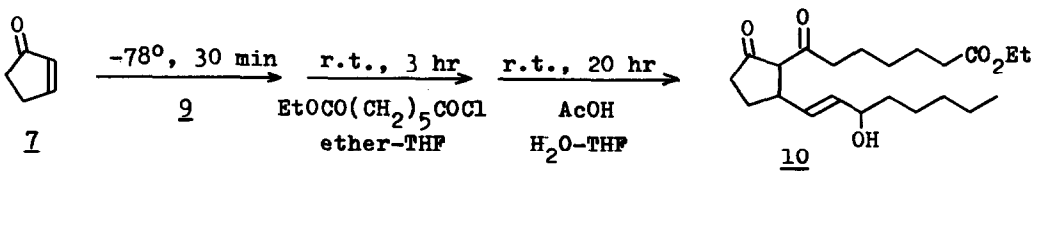
Table 1

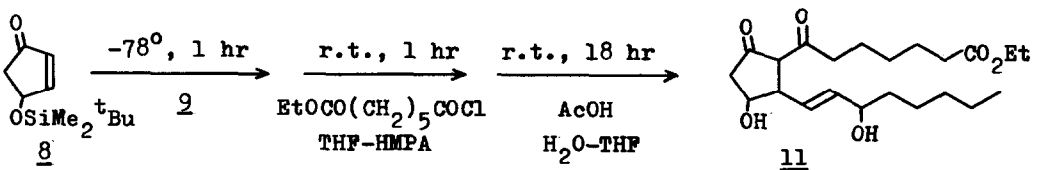
Entry	Organocopper Reagent	α,β-Unsaturated Ketone	Acylating Agent	Solvent System	Isolated Yield(%)[a,b] of β-Diketone
1	$n\text{-Bu}_2\text{CuLi}$	2-cyclohexenone	CH_3COCl	ether-HMPA	92
2	$n\text{-Bu}_2\text{CuLi}$	2-cyclohexenone	CH_3COCl	ether	56[e]
3	$n\text{-Bu}_2\text{CuLi}$[c]	2-cyclohexenone	$(CH_3CO)_2O$	ether-HMPA	9(39[d])[e]
4	$n\text{-Bu}_2\text{CuLi}$	2-cyclopentenone	CH_3COCl	ether-HMPA	38(59[d])[e]
5	$n\text{-Bu}_2\text{CuLi}$	methyl vinyl ketone	PhCOCl	ether-HMPA	52[e]

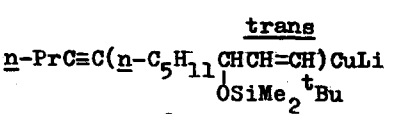
a) Isolation yields were not optimized.
b) Each product gave satisfactory spectral data.
c) Without tri-n-butylphosphine as ligand.
d) Including further O-acylated products of the β-diketone.
e) The rest of the products was the β-alkylated product of the enone.

temperature for 4 hr, the mixture was treated with aqueous sodium bicarbonate, then aqueous ammoniacal ammonium chloride to give 1.81 g (b.p. 64-66°/0.06 mmHg, 92%) of 2-acetyl-3-n-butylcyclohexanone 3a: [ir, 3350, 1710, 1690, 1600, 980, and 745 cm^{-1}; nmr (CCl_4), δ 0.90 (3H), 1.3, 1.67, 2.27 (13H), 2.10 (3H), 16.13 (1H), mass (70eV, m/e), 196 (M^+)]. This product exhibited a positive ferric chloride test showing β-dicarbonyl function.

To demonstrate the applicability of this acylation reaction, we synthesized two new prostaglandin analogs 10 and 11 from 2-cyclopentenone (7) and 2-cyclopentenone derivative (8)[17], respectively. The spectral data of these two







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compounds were as follows; dl-7-oxo-11-deoxyprostaglandin E_1 ethyl ester 10, [ir, 3450, 1730, 1710, 1635, 1170, 1030, and 970 cm^{-1}; mass (11eV), m/e 380 (M^+), 362 ($M-H_2O$), base peak); tlc (ether), R_f 0.38], dl-7-oxoprostaglandin E_1 ethyl ester 11, [ir, 3400, 1730, 1715, 1635, 1180, 1030, and 975 cm^{-1}; mass (11eV), m/e 378 ($M-H_2O$), 360 ($M-2\times H_2O$); tlc (ether), R_f 0.08]. The nmr spectra of 10 and 11 also supported their structures. Investigation on the derivation of these oxo-prostaglandins 10 and 11, and their biological activities are currently in progress.

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