Tetrahedron Letters Vol. 21, pp 2337 - 2340
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0040-4039/80/0608-2337$02.00/0

C-ACYLATION OF ENOLATES FROM LITHIUM DIMETHYLCUPRATE ADDITION TO α,β-UNSATURATED KETONES

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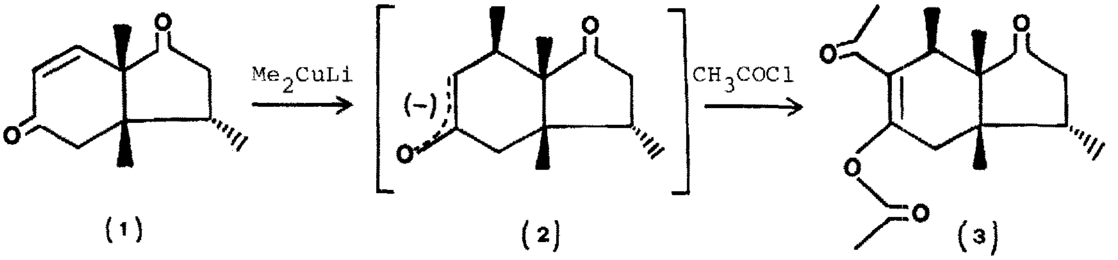
The enolates from 1,4 addition of lithium dimethylcuprate to 2-cyclohexenone, 2-cyclopentenone and methyl vinyl ketone, with acetyl chloride, give only C-acylated products and not O-acylated products as previously reported in literature.

During our work on the total synthesis of Pinguisone[1], a compound isolated from the liverwort Aneura Pinguis L[2], we found that the reaction of the α,β-unsaturated ketone (1) with Me_2CuLi[3] in ether solution at -25°C followed by quenching of the intermediate enolate (2) *with an excess of* acetyl chloride at 0°C leads exclusively to the acylated β-diketone (3); the structure of (3) as well as its absolute stereochemistry have been confirmed by X-ray analysis[4].

Scheme 1

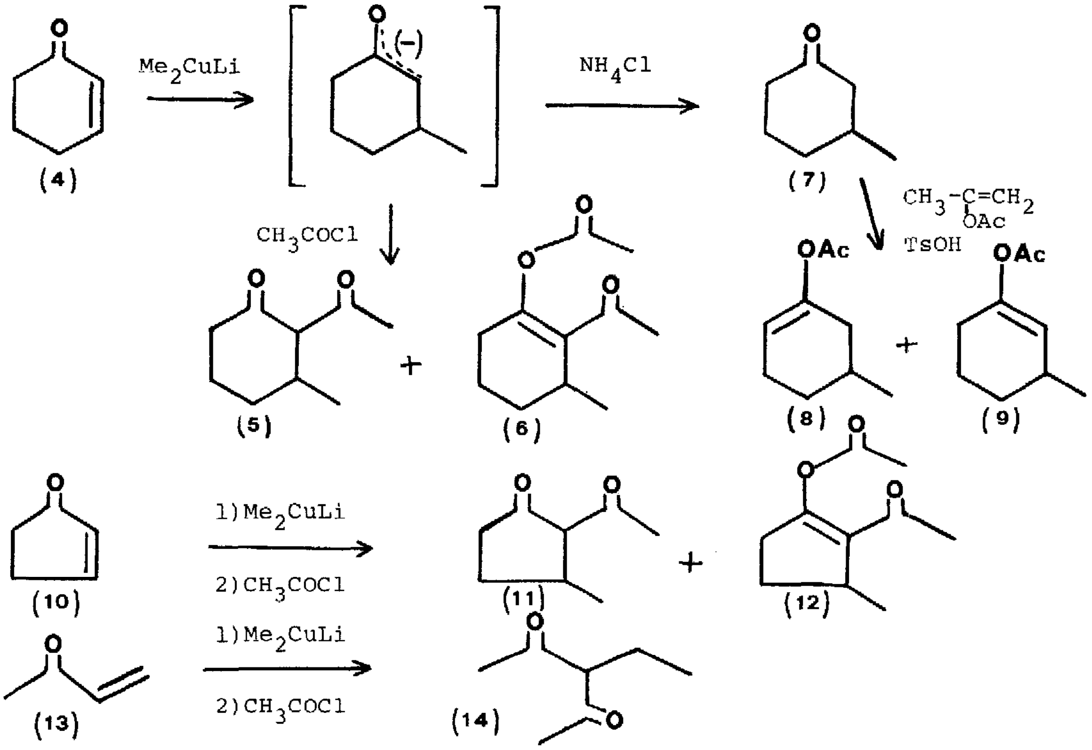


These results suggested that the enolate (2) gives C-acylation rather than O-acylation, the compound (3) being likely the product of a further acylation of a β-diketone system formed in the first step of the reaction.

As far as we know, this is the first example of a C-acylation of an enolate derived from the conjugated addition of Me_2CuLi to α,β-unsaturated ketones. In fact, Kurozumi et al. reported[5] that these enolates, in contrast to those obtained with other organocuprates, give, with acetyl chloride, O-acylated products only.

Taking into account the usefulness of regiospecific C-acylation of metal enolates in organic synthesis, we reinvestigated the work of the Japanese group using the same simple substrates viz. 2-cyclohexenone, 2-cyclopentenone and methyl vinyl ketone. In a typical procedure, 2-cyclohexenone (1 mmole) was treated with Me_2CuLi (1.5 mmoles) at -25 °C for 1h and the resulting anion quenched with acetyl chloride (10 mmoles) at -25 °C for 1h and then at 0 °C for 2h; the gas-chromatographic analysis[6] of the reaction mixture, after the usual work up with concentrated ammonium hydroxide-crushed ice in a ratio of approximately 1:2 and extraction with ether, showed two peaks corresponding to (5) and (6) (a GC-MS analysis gave for (5) $M^{+\cdot}$ 154 and for (6) $M^{+\cdot}$ 196) in a ratio 1:1.

Scheme 2



Hydrolysis of the reaction mixture with KOH in MeOH afforded only one product showing the same retention time of (5) in GLC which was purified by distillation: b.p. 108-110°C (18 mmHg); ν_{max} (liquid film) 1720, 1605 cm^{-1} ; λ_{max} (EtOH) 292 (ε = 5440); δ(CDCl$_3$) 16.2 (s, 1H), 2.2 (s, 3H), 1.1 (d, J=7Hz, 3H); m/e 154 (M$^{+\cdot}$, 13%), 139 (23%), 112 (40%), 97 (100%).

In order to verify the absence of O-acylated products, we prepared the compounds (8) and (9) from 3-methylcyclohexanone and isopropenylacetate in the presence of TsOH. A comparative GLC analysis of the reaction mixture and of the compounds (8) and (9) showed a remarkable difference in their retention times. We then extended our study to improve the yields of the reaction and to test the other simple substrates.

Table 1

Entry	Substrate	Reaction conditions[a]	Yields[b]	Yields in β-diketone[c]
1	(4)	Me$_2$CuLi, Et$_2$O CH$_3$COCl, 0°C, 2h	(5), 14.1% (6), 13.5%	(5), 27.6%
2	(4)	Me$_2$CuLi, Et$_2$O CH$_3$COCl, r.t. 1h	(5), 54.5% (6), 18.0%	(5), 72.5%
3	(4)	Me$_2$CuLi, Et$_2$O CH$_3$COBr, r.t. 1h	(5), 35.0% (6), 15.0%	(5), 50.0%
4	(4)	Me$_2$CuLi,(i-Pr)$_2$O CH$_3$COCl, r.t. 1h	(5), 53.6% (6), 33.4%	(5), 87.0%
5	(10)	Me$_2$CuLi,(i-Pr)$_2$O CH$_3$COCl, r.t. 2h	(11), 1.4% (12), 28.5%	(11)[d], 29.9%
6	(10)	Me$_2$CuLi,(i-Pr)$_2$O CH$_3$COCl, r.t. 17h	(11), 2.4% (12), 44.7%	(11)[d], 47.1%
7	(13)	Me$_2$CuLi,(i-Pr)$_2$O CH$_3$COCl, r.t. 1h	(14), 30.0%	(14)[d], 30.0%

a) Reagents, solvents, temperature and reaction time for C-acylation step.
b) Yields were calculated with GLC method using naphthalene as internal standard.
c) After hydrolysis of the reaction mixture with KOH in MeOH at r.t. for 1h.
d) Pure analytical samples gave spectral data in agreement with the reported structures.

As the data reported in the Table 1 show, an increase of the temperature during the C-acylation step improves the yields of (5) + (6), whereas the use of more reactive acyl halides doesn't. The choice of the solvent is another important factor effecting the yields; the best results were obtained with a low ionizing solvent as di-iso-propylether. This finding agrees with that reported by Näf and Decorzant[7] for the C-acylation of the enolates derived from 1,4 addition to α,β-unsaturated ketones of Grignard reagents in the presence of CuI. Moreover our results prove that the conclusions of the Japanese workers on the use of polar solvents in such a kind of acylation must be reconsidered.

We applied the same methods to 2-cyclopentenone and methyl vinyl ketone. In order to obtain the compounds (11) + (12) in appreciable yields longer reaction times were required; furthermore the difference in pKa between 2-acetylcyclopentanone (pKa=7.41) and 2-acetylcyclohexanone (pKa=9.65) led us to the use of a $NaHCO_3$-NH_4Cl mixture instead of ammonium hydroxide-crushed ice to avoid loss of the product. By a similar reaction pathway, the compound (14) was obtained from methyl vinyl ketone.

The application of this method has been extended to other acylating agents and it will be the subject of a further publication.

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3) In all cases, Me_2CuLi was prepared at -25°C under argon atmosphere by adding 1.5 mmoles of a 2M ethereal solution of MeLi to a stirred suspension of CuI in anhydrous di-ethylether (or di-iso-propylether).
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6) All gas-chromatographic analyses were run on Dani 3600 gas-chromatograph equipped with a glass column (CW 20M 3% on Chromosorb); programmed temperature 100°C (4 min)-180°C (15 min), 10°C/min.
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(Received in UK 14 April 1980)