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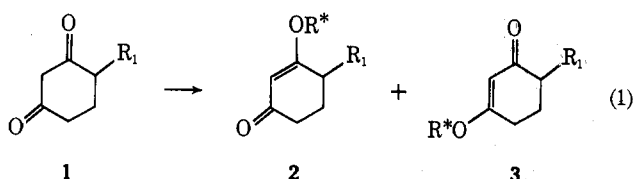
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The Regiospecific Alkylation of Cyclic β Diketone Enol Ethers. A General Synthesis of 4-Alkylcyclohexenones

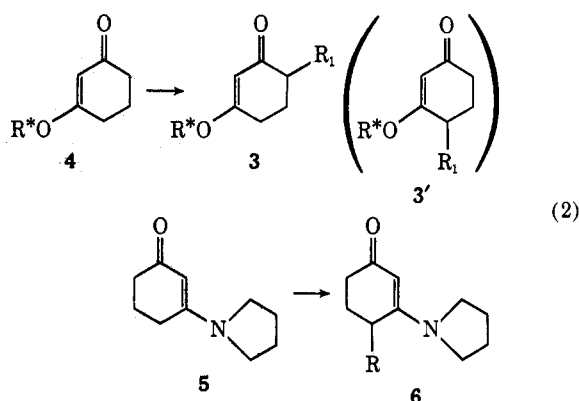
Summary: The alkylation of the kinetic enolate derived from 3-alkoxycyclohexenones is shown to take place in high yield at C₄, thus leading to a general synthesis of 4-alkyl-2-cyclohexenones free of double-bond isomers.

Sir: Enol ethers of cyclic β diketones are very valuable synthetic intermediates, *e.g.*, in the construction of cyclohexenones.¹ Unfortunately, there is no general method for the regiospecific formation of a given enol ether when the starting diketone is unsymmetrical. In such a situation, enol ether formation leads to mixtures of the two possible products (*cf.* 1 \rightarrow 2 and 3, eq 1).



We now wish to present a solution to this problem which should greatly extend the utility of cyclic β diketones as synthetic intermediates: We have found that monoalkylation of the enol ether of symmetrical cyclic β diketones, *e.g.*, 4, can be effected regiospecifically to give 3, a result especially noteworthy as the alkylation of the related enamine has recently been reported to follow a different course (*e.g.*, 5 \rightarrow 6,² eq 2).

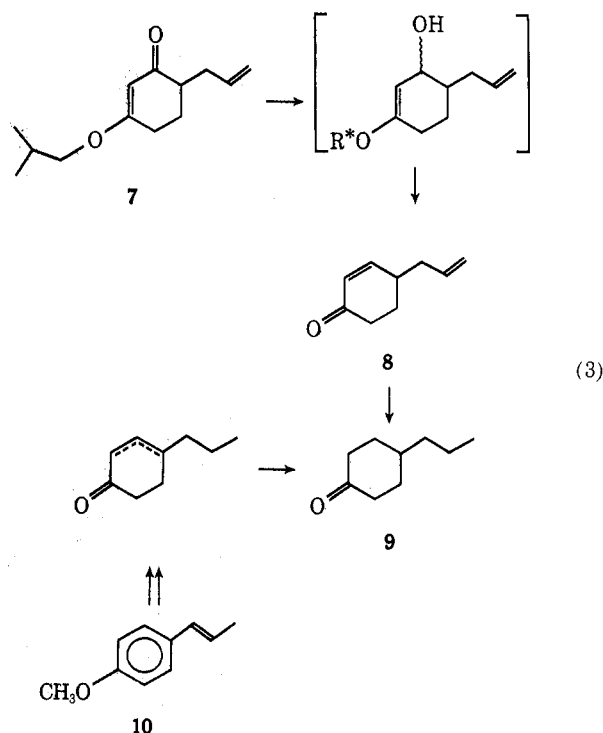
The alkylations are especially clean with reactive (allylic) halides. For instance, the lithium enolate (made at -78° in tetrahydrofuran with lithium diisopropylamide) of 4 ($R^* = \text{isobutyl}$)³ was treated with 1.1 equiv of allyl bromide, finally at room temperature, to yield, in almost quantitative yield, the monoalkylated product (7) of 3 ($R^* = \text{isobutyl}$; $R_1 = \text{allyl}$), needles of mp $37-38^\circ$. The gross structure was only compatible with either 3 or 3' because of the mass spectrum (*m/e* 208) and the obvious presence of one allyl residue in the



nmr, which retained the vinyl hydrogen of the enone system as a singlet at δ 5.3.

The correctness of structure 3 was demonstrated by a sequence which also serves to illustrate one of the important uses of substances of this type, the *synthesis of pure 4-alkyl- Δ^2 -cyclohexenones*, essentially free from the (usually) more stable Δ^3 isomer. Lithium aluminum hydride reduction (refluxing ether) and hydrolysis (2 *N* hydrochloric acid, 30-min stirring, room temperature), gave, in $\sim 80\%$ overall yield from 4, 4-allyl-2-cyclohexenone (8, eq 3), bp $87-88^\circ$ (7 mm), *m/e* 136.0863, free of β,γ isomer as shown by the nmr (1 H split doublet at δ 7.0 due to the β hydrogen of the α,β system) and the ir absorption at 5.93μ .

Catalytic hydrogenation of 8 (10% Pd/C in ethanol) gave 4-propylcyclohexanone 9, identical (by glc on 5% SE-30, 100° , and ir) with an authentic sample made from anethole (10) by the sequence Birch reduction (lithium-ammonia-methanol), hydrolysis (3 *N* hydrochloric acid-aqueous methanol), and hydrogenation of the α,β - β,γ mixture of 4-propylcyclohexenones (eq 3).



(1) G. F. Woods, P. H. Griswold, Jr., B. H. Armbrecht, D. I. Blumenthal, and P. Planinger, *J. Amer. Chem. Soc.*, **71**, 2028 (1949); R. L. Frank and H. K. Hall, Jr., *ibid.*, **72**, 1645 (1950).

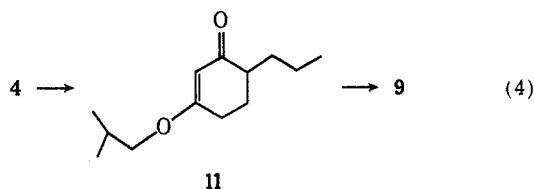
(2) M. Yoshimoto, N. Ishida, and T. Hiraoka, *Tetrahedron Lett.*, 39 (1973).

(3) J. Panouse and C. Sanié, *Bull. Soc. Chim. Fr.*, 1272 (1956).

It is especially remarkable and synthetically useful that proton transfer reactions between the initial lithium enolates of 1,3 diketone enol ethers (*e.g.*, of 4) and the monoalkylated product (*e.g.*, 3) are extremely

slow, thus leading to excellent yields of monoalkylated products, in spite of the rather slow alkylation of these lithium enolates in tetrahydrofuran.

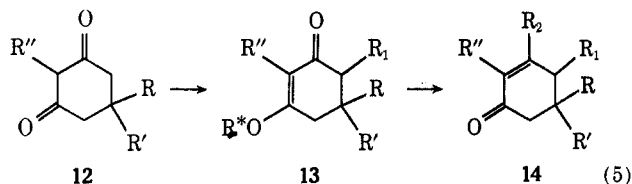
The low reactivity of the lithium enolate of **4** ($R^* =$ isobutyl) in tetrahydrofuran, presumably due to aggregation, is illustrated by the fact that, using propyl bromide under the same conditions which lead to almost quantitative alkylation with allyl bromide, only starting enol ether is recovered. It is, however, possible to achieve alkylation by the use of alkyl iodides in the presence of some hexamethylphosphoramide. Thus, under the same condition as with allyl bromide, but in the presence of 1.1 equiv of hexamethylphosphoramide, **4** ($R^* =$ isobutyl) gave with 1 equiv of propyl iodide, in 24 hr at room temperature, a mixture consisting of 65% **11**, (eq 4), in addition to 29% starting enol ether and ~6% dialkylated material.⁴



The alkylation of enol ethers derived from symmetrical cyclohexane-1,3-diones can lead to a great variety of cyclohexenone derivatives. Starting with readily available cyclohexane 1,3-diones such as **12** in which R , R' , and R'' are either H or alkyl (aryl), the

(4) These products could be separated by silica gel chromatography which gave (benzene, then benzene-ethyl acetate) starting material, followed by the dialkylated product, and finally the monoalkylated product **11**. Retention times, on a 10-ft. 2% Carbowax column at 148°, were ~3, 7, and 5 min, respectively. Structures followed from direct comparison and mass, nmr, and ir spectra. The monoalkylated compound **11** was also converted (cf. **7** → **9**) to 4-propylcyclohexanone (**9**).

sequence involving alkylation of the corresponding enol ether with R_1X leads first to **13** and then, *via* either lithium aluminum hydride reduction or Grignard addition followed by hydrolysis, to cyclohexenones **14** in which $R_1 =$ alkyl and R , R' , R'' , and R_2 are either alkyl, aryl, or hydrogen (eq 5).



The procedure for the large scale synthesis of **7** is given in detail. **4** ($R^* =$ isobutyl) (84.1 g) in 125 ml of dry tetrahydrofuran was added over 1.5 hr at -78° under nitrogen to a solution containing ~1 equiv of lithium diisopropylamide (made *in situ* at -20° from 229 ml of 2.29 *M* *n*-butyllithium and 55.8 g of diisopropylamine). After 45 min, a solution of 66.5 g of allyl bromide in 100 ml of tetrahydrofuran was added over 20 min. The solution was allowed to warm to room temperature in ~4 hr, 5 ml of water was added, and the solvent was evaporated. Extraction and work-up as usual gave 103.5 g (~98%) of **7**, pure by tlc (15% ethyl acetate-benzene on silica gel), which crystallized on standing in long colorless needles, mp $37-38^\circ$ after crystallization from ether-acetone at Dry Ice temperature.

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