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A NEW PROCEDURE FOR ALKYLATION OF ISOPHORONE AT THE 4-POSITION

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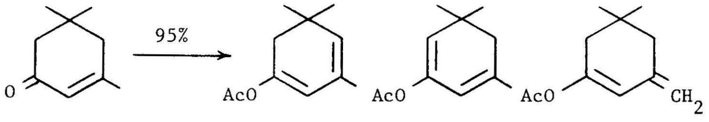
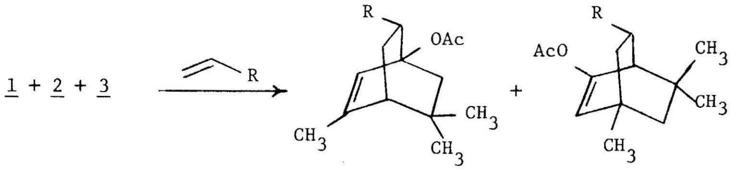
During the course of work directed at developing new processes for building the basic ionone skeleton, we have found a simple and general procedure for alkylating isophorone at the 4-position[1] via a Diels-Alder/retroaldol sequence.

Isophorone was easily converted in high yield (95%) to a mixture of the three possible enol acetates (1 : 2 : 3) ratio of 34 : 22 : 43 by acid catalyzed (p-toluenesulfonic acid) exchange with isopropenyl acetate. When this equilibrium enol acetate mixture was heated with unsymmetric dienophiles, such as methyl vinyl ketone (or acrylonitrile, etc.), Diels-Alder adducts of 1 and 2 were produced (but not in the original ratio of 1 : 2*)[2]. Although several isomers were possible from each of the enol acetates 1 and 2, only two isomers were detected, one (4) resulting from 1 and one (5) from 2*.



Isophorone 1 2 3



4 5

a) R = $-COCH_3$
b) R = $-CN$

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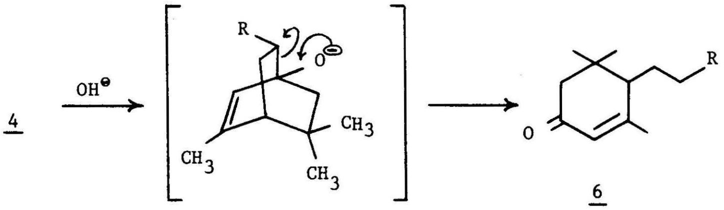
* In the cases studied a ratio of 4 > 5 was always observed.

We have now found that base retroaldolization of compounds of the general structure 4, where R is an electronegative, group (i.e., R = $-COCH_3$, -CN, etc.), leads to formation of 4-substituted isophorone derivatives[3], 6 , in high yield.



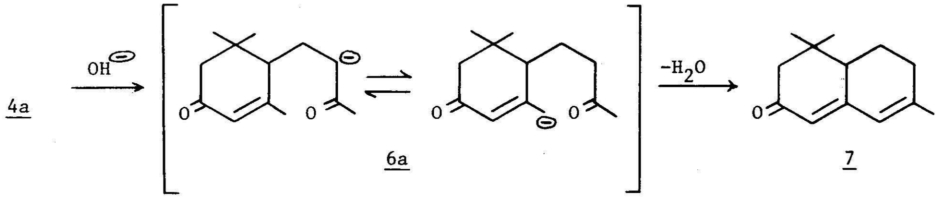
When the isophorone enol acetates were heated with methyl vinyl ketone (90→135°, 24 hrs.), a mixture of 4a and 5a (R = $-COCH_3$) was produced in a ratio of 3 : 1, respectively (ca. 85% yield).

Identification of 4a as 1-acetoxy-3,3,5-trimethyl-7-acetyl-bicyclo-[2.2.2]-oct-5-ene, b.p. 132°/4 mm., was based on the following: Infrared spectrum: λmax (film) 5.75, 5.84, 7.32, 8.80μ ; nmr $(CDCl_3)$: Singlet methyls at 9.13τ (3H) and 8.93τ (3H) corresponding to the methyls on the C-3 carbon, an allylic methyl as a doublet at 8.15τ (3H, J≃1.7 cps), acetyl and acetoxy methyls as singlets at 8.01τ (3H) and 7.92τ (3H), the C-7 proton appeared as a pair of doublets centered at 6.66τ (1H) and the C-6 proton appeared at 4.18τ (1H); mass spectrum: molecular ion at m/e 250.

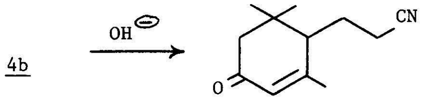
The bicyclic keto-acetate, 5a, b.p. 130°/2.5 mm., was identified as 1,3,3-trimethyl-5-acetoxy-8-acetyl-bicyclo-[2.2.2]-oct-5-ene from the following data: Infrared spectrum: λmax (film) 5.75, 5.84, 6.03, 8.09, 8.58, 8.73μ ; nmr $(CDCl_3)$: singlet methyls on the C-3 carbon at 9.09τ (3H) and 8.94τ (3H), the methyl on the C-1 carbon appeared as a singlet at 8.89τ (3H), the acetyl and acetoxy methyls appeared as singlets at 7.95τ (3H) and 7.86τ (3H) while the C-6 olefinic proton appeared at 4.54τ (1H); mass spectrum: molecular ion at m/e 250.

When the adduct 4a (5 g.) was agitated for 4 hours with sodium hydroxide (3 g.) in methanol (50 cc.) at room temperature, 4,4α,5,6-tetrahydro-4,4,7-trimethyl-2(3H)-napthalenone (7, 3.65 g, 96%) was produced which exhibited the following characteristics: m.p. 93-95° (from hexane); ultraviolet spectrum λ_{max}^{Etoh} 292 mμ ; Infrared spectrum: 6.05, 6.12 and 6.27μ indicative of an α,β,γ,δ -unsaturated ketone; nmr spectrum: two olefinic protons at 3.90τ and 4.22τ , a methylene adjacent to a carbonyl at 7.68τ (2H), an allylic methylene at 7.82τ (2H), a vinyl methyl at 8.07τ (3H) and two tertiary methyls at 8.87τ (3H) and 9.10τ (3H); mass spectrum:

molecular ion at m/e 190. This sample was identical in all respects with an authentic sample prepared from 4-ketodihydroionone[4]. This transformation undoubtedly occurs by saponification of the tertiary acetate of 4a followed by a retroaldolization to the intermediate anion 6a which on realdolization produces 7.



In the special case above, 7 was produced by realdolization of the intermediate 6a but, ordinarily, when 4 possesses an R group without a properly disposed active methyl or methylene, the reaction stops after retroaldolization. For example, 4b (R = -CN) when treated as above opens to give 6b in *ca*. 90% yield. The structure of 6b was readily confirmed by its characteristic spectra: Infrared spectrum: λmax (film) 4.45, 6.0μ ; nmr ($CDCl_3$): gem dimethyl at



8.91τ (6H), allylic methyl at 7.96τ (3H, doublet J≃1.3 Hz), vinylic proton at 4.12τ (1H, quartet); mass spectrum: molecular ion at m/e 191.

The general procedure described herein for producing 4-substituted isophorones and ionone derivatives should find wide applicability in the synthesis of natural products derived from carotene degradation.

Acknowledgements:

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REFERENCES

1. Other approaches at alkylating isophorone at the 4-position generally proceed via a 4-ketoisophorone or epoxy derivatives from β-phorone. For example, see J. Meinwald and L. Hendry, Tetrahedron Letters, 1969, 1657.

2. C. M. Cimarusti and J. Wolinski, J. Am. Chem. Soc., 90, 113 (1968); see also H. Nozaki, T. Yamaguti, S. Ueda and K. Kondo, Tetrahedron, 24, 1445 (1968) for analogous type reactions with isophorone dienamines.

3. The work reported in this communication may be considered as a convenient (but, related) alternative to the elegant procedures of Birch for producing 4-substituted cyclohexenones; see A. J. Birch and J. F. Hill, J. Chem. Soc. (C), 1966, 2324; 1967, 125; A. J. Birch, P. L. Macdonald and V. H. Powell, Tetrahedron Letters, 1969, 351.

4. D. L. Roberts, U. S. Patent 3,217,717 (November 16, 1965).