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A NEW METHOD FOR PROTECTION OF CARBONYL COMPOUNDS AS 5-METHYLENE-1,3-DIOXANES

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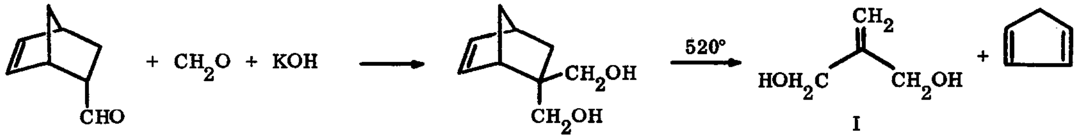
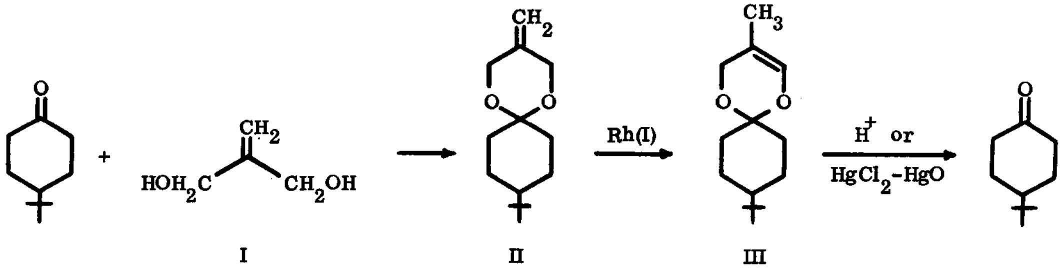
In the course of synthetic studies under way in these Laboratories, the need arose for a carbonyl protecting group which could be selectively removed under mild conditions and which itself introduced no new asymmetric centers. Our previous experience with protecting groups cleavable by transition metal reagents[1] suggested that carbonyl groups when protected as 5-methylene-1,3-dioxanes would be stable to most reagents which attack carbonyl groups (e.g., AlH_4^-, BH_4^-, RLi) and that deprotection could be effected by Rh(I) catalyzed isomerization to an enol ether followed by hydrolysis.

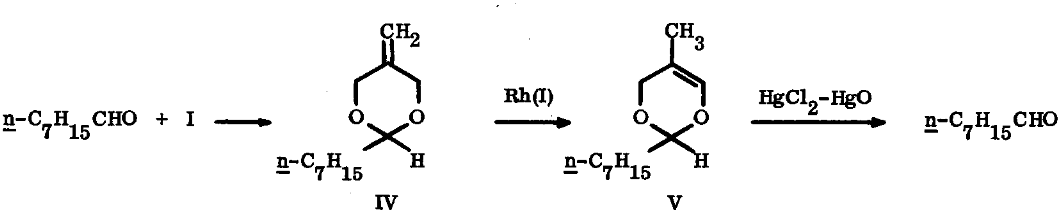
The requisite diol, 2-methylene-1,3-propanediol (I), could be prepared conveniently from the commercially available 5-norbornene-2-carboxaldehyde by a modification of an earlier procedure[2] using a Cannizzaro reaction with formaldehyde followed by a retro Diels-Alder reaction at 520°.



I

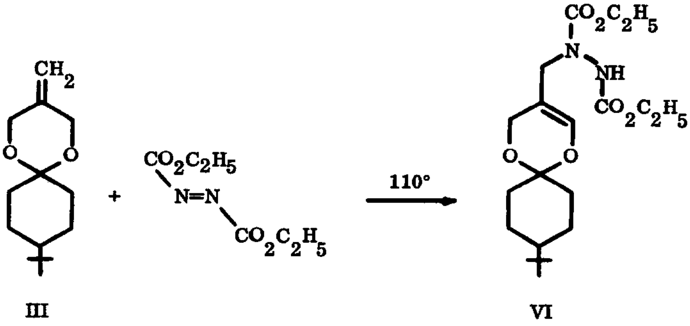
Ketalization of 4-t-butylcyclohexanone with 1.5 equiv of I catalyzed by p-toluenesulfonic acid in benzene at reflux with azeotropic removal of water gave II in 89% yield. Similarly, the acetal of n-octanal (IV) could be isolated in 92% yield.





When treated with a catalytic amount of $RhCl(PPh_3)_3$ at reflux (as previously described[1]), II and IV were isomerized to the enol ethers III and V (96 and 97% yield,[3] respectively), the equilibrium mixture consisting entirely of the endocyclic, trisubstituted enol ether. Hydrolysis of III with 10 : 1 (by volume) THF--1 N HCl at room temperature for 1.5 hr gave 4-t-butylcyclohexanone in 98% yield.[4] Alternatively, III and V could be hydrolyzed under essentially neutral conditions by stirring with 1 equiv each of $HgCl_2$ and yellow HgO in 10% aqueous acetone for 2 hr,[5] giving 4-t-butylcyclohexanone and n-octanal in 96 and 85% yields,[4] respectively.

An alternative means of isomerization of the 5-methylene-1,3-dioxane to an enol ether is provided by the ene reaction with diethylazodicarboxylate.[6]

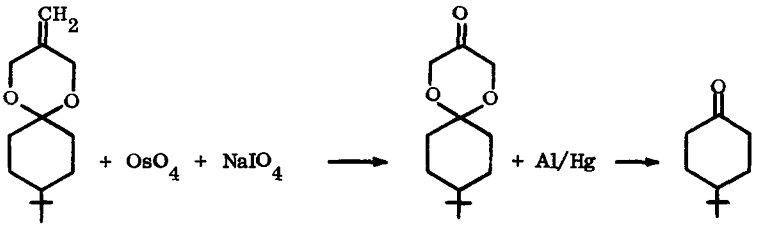


Heating of III at reflux in toluene with 1.2 equiv of diethylazodicarboxylate for 14 hr gave VI (81%

yield), which upon hydrolysis with $HgCl_2$-HgO gave 4-t-butylcyclohexanone in 93% yield.[3] This procedure allows regeneration of the carbonyl compound under strictly neutral conditions.

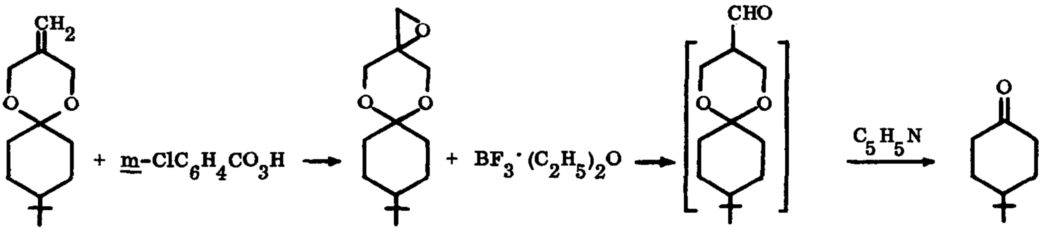
The properties of the methylene group in III suggested several additional methods of deprotection. Ethylene ketals have been removed by reaction with the hydride transfer reagent trityl tetrafluoroborate for up to 3 hr at room temperature followed by hydrolysis of the resulting oxonium salt.[7] With the additional stabilization provided by the double bond in III, treatment with 1.1 equiv of trityl tetrafluoroborate for only 2 min at 0° in methylene chloride followed by addition of water gave the ketone in 86% yield.[3]

The methylene group in III could be oxidatively cleaved to the ketone VII with $NaIO_4$-OsO_4.[8] Reaction of VII with 4 equiv of Al/Hg in 2% aqueous THF at room temperature for 4 hr regenerated 4-t-butylcyclohexanone in 80% yield[3] from III.



III VII

Finally, the methylene group in III could be epoxidized quantitatively using 2 equiv of m-chloroperbenzoic acid in methylene chloride at 25° for 14 hr. Rearrangement of this epoxide, VIII, with 0.3 equiv of $BF_3 \cdot (C_2H_5)_2O$ in ether at 0° for 5 min gave the sensitive β-alkoxy aldehyde IX which was cleaved *in situ* by treatment with excess pyridine for 15 min followed by aqueous workup to give the parent ketone in 80% yield[3] from III.



III VIII IX

Preparation of 2-methylene-1, 3-propanediol. 5-Norbornene-2-carboxaldehyde (10 g, 80 mmol), excess 37% formalin solution (20 ml), and potassium hydroxide (4.5 g, 80 mmol) were dissolved in 70 ml of ethanol and stirred overnight. The solution was neutralized with carbon dioxide and concentrated. The resulting syrup was taken up in 45 ml of benzene and after filtration the benzene solution was added dropwise over 45 min to the top of a 22-cm Vycor column packed with quartz chips heated to 520°. Argon was swept through the column so that the contact time was 10 sec. The product was collected in a trap cooled to -78°. Water was added and the water layer was washed once with pentane. Concentration of the water extracts and distillation gave 4.59 g (63%) of I, bp 127-129° (32 mm).

The ease of introduction and range of selective methods available for deprotection recommend the 5-methylene-1, 3-dioxane group as a worthwhile candidate for carbonyl protection.[9]

References

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3. Yields are based on isolated products, where necessary purified by thin layer chromatography on silica gel plates.
4. Yield determined by vapor phase chromatography using the internal standard method.
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6. T.-L. Ho and C. M. Wong, Syn. Comm., **4**, 109 (1974).
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