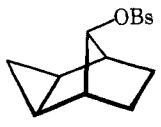
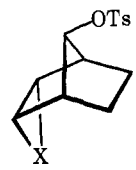
comparable conditions was >90 min. At 160°, **8** is essentially quantitatively transformed into dihydroindene **12** at a convenient rate.

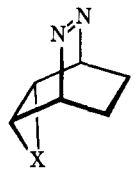
As regards neighboring group reactivity of edge-fused three- and four-membered carbocyclic rings proximately disposed to developing cationic centers, recent investigations have established not only the necessity of proper stereochemical orientation but also a marked dependence on ring size. For example, whereas the solvolytic rate constant for **17** is merely comparable to that of the 7-norbornyl derivative, tosylate **18a** exhibits a rate acceleration of 10^{14}.[13] Anchimeric assistance by cyclobutene (**18b**, k_{rel} = $10^{5.8}$) and cyclobutane rings (**18c**, $k_{rel} = 10^{4.3}$) positioned endo on the norbornyl framework is seen to be only a small fraction of that provided by the cyclopropyl group.[14] In related azo systems, **19a** suffers loss of nitrogen 10^{17} times faster than 2,3-diazabicyclo[2.2.2]-oct-2-ene while **19b** is only 10^4 times more reactive.[15] These effects appear not to arise from factors associated with strain release. This conclusion is supported by the behavior of **20** whose large solvolytic rate (k_{rel} = 10^{12}) cannot be attributed to overall relief of strain since the major solvolysis product is structurally identical by virtue of a triply degenerate rearrangement.[16]



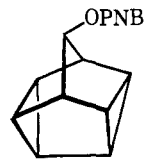
17



18a, X = CH_2
b, X = CH=CH
c, X = CH_2CH_2



19a, X = CH_2
b, X = CH_2CH_2



20

In the case of **8** and **15**, the small rings are exo fused. As a result, the bent bonds are not favorably oriented for overlap as C–N cleavage begins. Accordingly, concerted loss of nitrogen is not possible. Nevertheless, the data require that production of the transient 1,4 diradicals from **8** and **15** be followed by cleavage of that adjacent C–C linkage endowed with the greatest "bent-bond" character.[17] In other words, despite geometrically enforced inoperability of synchronous reactions in exo-fused systems, the relative efficiencies of strained bond cleavage reactions are also dictated chiefly by bond hybridization factors.

Irrespective of the stereochemistry of **12**, it must be appreciated that the degree of substitution on **10** does not permit the present work to contribute substantially toward the mechanistic solution of the bicyclo[6.1.0]-nonatriene to 8,9-dihydroindene rearrangement. The presence of the two phenyl groups is perhaps too great a complication of the molecule for the results to be directly applicable to ultimate clarification of that particular problem.

Acknowledgment. We express appreciation to the donors of the Petroleum Research Fund for their financial support, to Dr. Paul Demarco for assistance with the NOE and LIS studies, to Mr. Louis Leichter for help with the variable temperature nmr experiments, and to Dr. Stanley Wilson for his part in the kinetic determinations.

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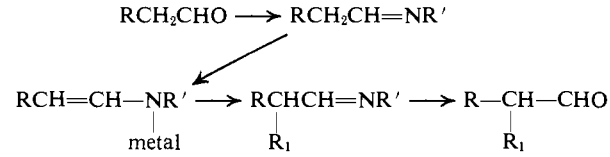
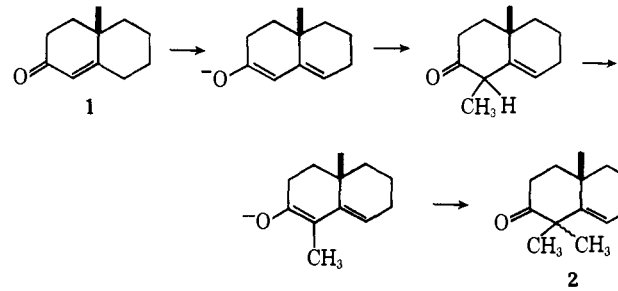
Monoalkylation of α,β-Unsaturated Ketones *via* Metalloenamines

Sir:

We demonstrated a few years ago[1] that aldehydes and ketones can be monoalkylated by making use of the metalloenamines derived by the treatment of the corresponding *N*-alkylimines with strong bases, such as Grignard reagents.



It was tempting to see if the very troublesome problem of the monoalkylation of α,β-unsaturated ketones[2] might be resolvable in the same manner. This was particularly interesting as all attempts to stop dialkylation, at least with small molecules like methyl iodide, have uniformly led to variable amounts of dialkylated material, presumably because of very rapid proton transfer in the intermediate β,γ-unsaturated ketone (*cf.* **1** → **2**).



1 **2**

(1) G. Stork and S. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(2) Such a monoalkylation can sometimes be effected with the corresponding enamines (*cf.* G. Stork and G. Birnbaum, *Tetrahedron Lett.*, 313 (1961)) but the method is generally not applicable when C-alkylation is attempted with systems having an axial substituent in a 1,3 relationship, as in the cases illustrated here.

(13) (a) H. Tanida, T. Tsuji, and T. Irie, *J. Amer. Chem. Soc.*, **89**, 1953 (1967); (b) M. A. Battiste, C. L. Deyrup, R. E. Pincock, and J. Haywood-Farmer, *ibid.*, **89**, 1954 (1967); (c) J. Haywood-Farmer and R. E. Pincock, *ibid.*, **91**, 3020 (1969).

(14) (a) M. Sakai, A. Diaz, and S. Winstein, *ibid.*, **92**, 4452 (1970); (b) M. A. Battiste and J. W. Nebzydoski, *ibid.*, **92**, 4450 (1970).

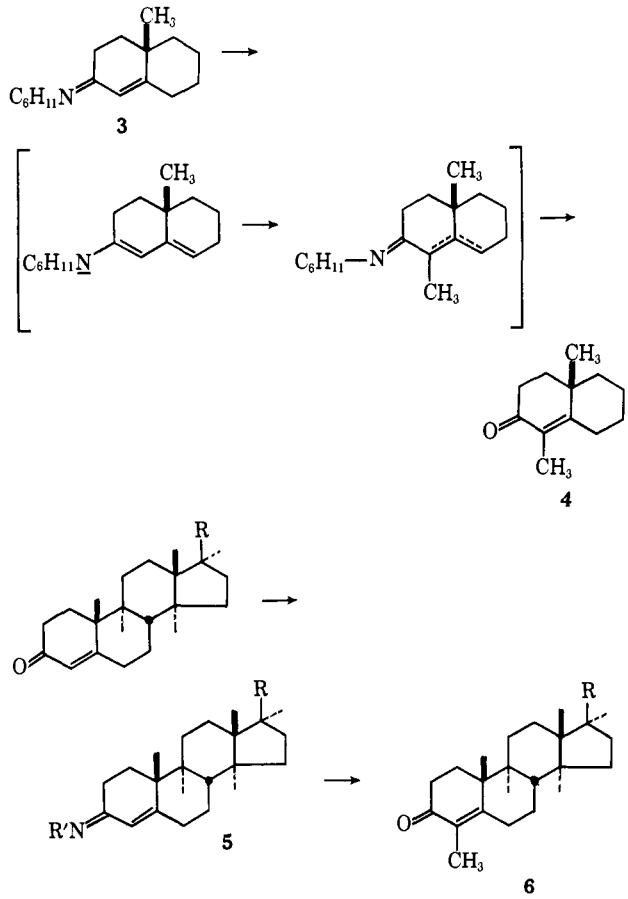
(15) E. L. Allred and J. C. Hinshaw, *Chem. Commun.*, 1021 (1969).

(16) R. M. Coates and J. L. Kirkpatrick, *J. Amer. Chem. Soc.*, **90**, 4162 (1968); **92**, 4883 (1970).

(17) The calculated degree of "bent bonding" for cyclobutane is about one-third that calculated for cyclopropane: C. A. Coulson and T. H. Goodwin, *J. Chem. Soc.*, 2851 (1962); 3161 (1963). On the other hand, strain estimates[4] show cyclobutene to be 2.5 kcal/mol more strained than cyclopropane.

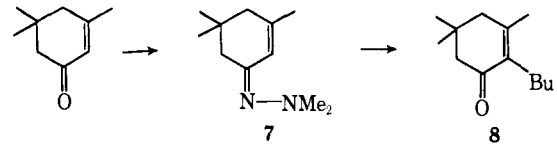
We now report that monoalkylations of α,β-unsaturated ketones can indeed be carried out in good to excellent yields by the metalloenamine route.[3] A variety of conditions have been used with 10-methyl-$\Delta^{1,9}$-2-octalone (**1**), cholestenone, and testosterone benzoate, as their *N*-cyclohexylimines or *N,N*-dimethylhydrazones (obtained in almost quantitative yields by azeotropic distillation with toluene for the former and benzene for the latter, using *p*-toluenesulfonic acid as catalyst), while the bases used were butyllithium, lithium diisopropylamide, sodium hydride, and the lithium salt of hexamethyldisilazane. In general, the best results have been obtained with lithium diisopropylamide.

For instance, the distilled imine, **3**, bp 125° (0.1 mm), from **1** and cyclohexylamine, was added under nitrogen to a tetrahydrofuran solution containing a slight deficiency (to allow equilibration of kinetically formed enamide ion) of lithium diisopropylamide (made from butyllithium and diisopropylamine *in situ*). After refluxing for 8 hr, an excess of methyl iodide in tetrahydrofuran was added and, after refluxing overnight, the alkylated imine was hydrolyzed by heating with aqueous sodium acetate–acetic acid–water (1:2:2) for 4 hr. Isolation then gave, with about 95% recovery, a mixture consisting of ~90% of 1,10-dimethyl-$\Delta^{1,9}$-2-octalone[4] (**4**) and 10% of the starting unalkylated enone.



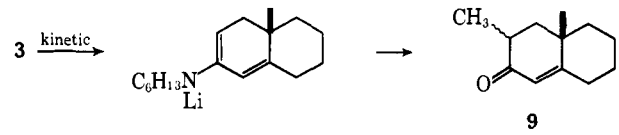
Similarly, the crude *N,N*-dimethylhydrazone of Δ^4-cholestenone[5] (**5**, R = C_8H_{17}, R′ = $(CH_3)_2N$–, excess hydrazine removed by heating under vacuum) was treated in benzene at 5° with about 1 equiv of lithium butyl solution. After standing at room temperature for 0.5 hr, a 20% excess of methyl iodide in benzene was added, followed by stirring for 1.5 hr at room temperature. Hydrolysis as before and chromatography of the product on silica gel gave 53% of pure 4-methyl-Δ^4-cholestenone[6] (**6**, R = C_8H_{17}) and 25% of recovered cholestenone.

The crude cyclohexylimine of testosterone benzoate (**5**, R = $C_6H_5C(=O)O$–, R′ = C_6H_{13}–, amorphous solid) and 3 equiv of lithium diisopropylamide in dry tetrahydrofuran at −50°, followed by an excess of methyl iodide and refluxing overnight, gave, after hydrolysis and rebenzoylation (benzoyl chloride–pyridine), 4-methyltestosterone benzoate[6] (**6**, R = $C_6H_5C(=O)O$–), isolated in 56% yield by chromatography on silica gel. Simpler α,β-unsaturated ketones can, of course, also be monoalkylated by this method. For instance, overnight refluxing of a mixture of isophorone *N,N*-dimethylhydrazone (**7**) with 1 equiv of sodium hydride in tetrahydrofuran containing 10% hexamethylphosphoramide, followed by reaction with butyl iodide (3 hr, room temperature) and hydrolysis with hot 6 *N* hydrochloric acid (1 hr), gave butylisophorone (**8**) in 70% yield.[7]



The success of these monoalkylations illustrates again[1] the relatively slow proton transfer with imines coupled with the reluctance of enamines (and of metalloenamines) toward dialkylation.

The slow proton transfer is impressively demonstrated by the formation of a mixture containing about 60% of 3,10-dimethyl-$\Delta^{1,9}$-2-octalone (**9**)[8] by methylation of the (largely kinetic) anion formed using 100% excess of lithium butyl from the cyclohexylimine of 10-methyl-$\Delta^{1,9}$-2-octalone (**3**).



Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for support of this work.

(3) Some preliminary experiments on this method were carried out a number of years ago by Dr. E. J. Warawa and by Susan Dowd in this laboratory.

(4) P. J. Kropp, *J. Org. Chem.*, **29**, 3110 (1964). This and other known substances (**6**, R = C_8H_{17}; **6**, R = $C_6H_5C(=O)O$–; and **9**) were identified by comparison with authentic samples (tlc behavior, ir and nmr spectra, melting point, or vpc (when applicable)).

(5) M. Avaro, J. Levisalles, and H. Rudler, *Chem. Commun.*, 445 (1969).

(6) N. W. Atwater, *J. Amer. Chem. Soc.*, **82**, 2847 (1960).

(7) This experiment was performed by Mr. Richard Gross. The structure was established by spectral properties (ir, nmr), mass spectrum, and comparison with unambiguously synthesized material.

(8) J. Colonge, J. Dreux, and J. P. Kehlstadt, *Bull. Soc. Chim. Fr.*, 1404 (1954). There was also formed *ca.* 23% of **4**.

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