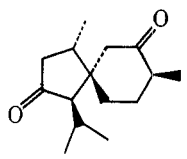
Carbonyl Homologation with α Substitution. A New Approach to Spiroannelation

Summary. A novel approach is described for the geminal alkylation of a ketone carbonyl group to give a quaternary carbon atom bearing substituents suitably functionalized for the *direct* spiroannelation of a cyclohexenone ring.

Sir: Within the past few years, a wide variety of natural products belonging to the several classes of spiro sesquiterpenes have been discovered. Representative examples of these classes include acorone (an acorane) (**1**),[1] β-vetivone (a vetispirane) (**2**),[2] and α-chamigrene (a chamigrane) (**3**).[3] Since



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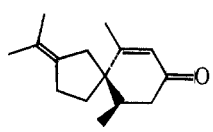

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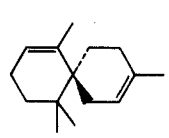

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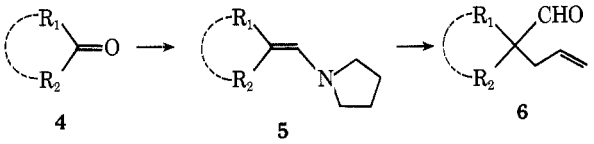
these compounds, along with other members of their respective classes, exhibit a diversity of both skeletal and functional variations, there has been a demand for efficient, general methods for the construction of substituted spirocyclic systems.[4,5] However, many recent approaches toward spiroannelation may be characterized as multistep procedures which are frequently limited in scope because they are designed for the synthesis of specific spiro sesquiterpenes.[1-3,6]

Owing to its synthetic utility, the carbonyl group has evolved as one of the most important and readily accessible functional groups in organic chemistry. Thus, a synthetic procedure for the transformation of a carbonyl group into a quaternary carbon center possessing substituents suitably functionalized for subsequent spiroannelation operations would be especially desirable. We now wish to report an efficient procedure for the direct conversion of ketones into 4,4-disubstituted 2-cyclohexen-1-ones. Application of this approach to cyclic ketones affords a facile method for the construction of spirocyclic ring systems. Furthermore, the newly formed six-membered ring possesses an α,β-unsaturated ketone which may be exploited by subsequent condensation or addition reactions to introduce additional substituents and functional groups.

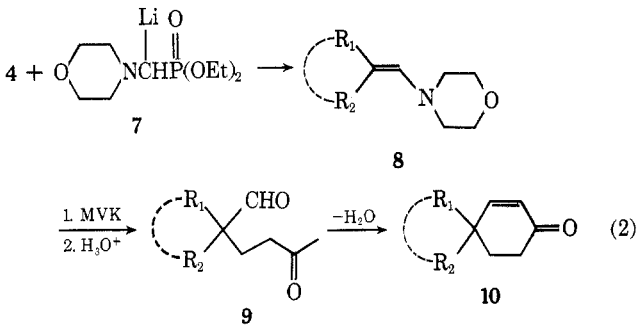
We recently described the utility of diethyl pyrrolidinomethylphosphonate as a reagent for the conversion of ketones **4** into the pyrrolidine enamines of the homologous α-disubstituted aldehydes **5**.[7] Treatment of these enamines with allyl bromide gave α-allyl dialkylaldehydes **6** in good yields (eq 1). Although the newly introduced alkyl appendages of **6**



4 5 6 (1)

can be modified for eventual cyclization to spirocyclic systems, the procedure requires extensive functional group manipulation.[5d] A method for introducing geminal substituents suitably functionalized for direct elaboration to cyclic compounds would have obvious advantages. For example, the introduction of a 3-oxobutyl group would afford a 1,5-dicarbonyl compound which could then be readily converted into a 2-cyclohexen-1-one by aldol-cyclodehydration.[8,9]

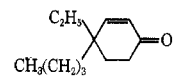
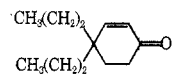
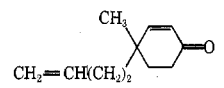
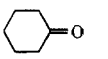
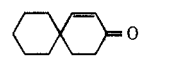
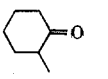
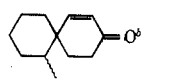
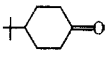
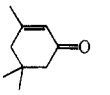
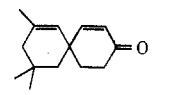
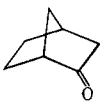
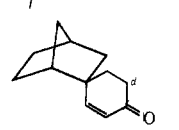
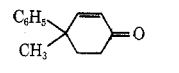
Unfortunately, our initial efforts to react the pyrrolidine enamines **5** with methyl vinyl ketone gave unsatisfactory results. We investigated, therefore, the reaction of ketones **4** with diethyl lithiomorpholinomethylphosphonate[10] (**7**) and obtained the expected morpholine enamines of the homologous aldehydes **8**, which were isolated by flash distillation. Treatment of the crude enamines **8** with methyl vinyl ketone (MVK) followed by acid-catalyzed hydrolysis of the intermediate adduct afforded the δ-keto aldehydes **9** which spontaneously underwent cycloaldolization and dehydration to give the 4,4-disubstituted 2-cyclohexen-1-ones **10** (eq 2).



7 8 9 10 (2)

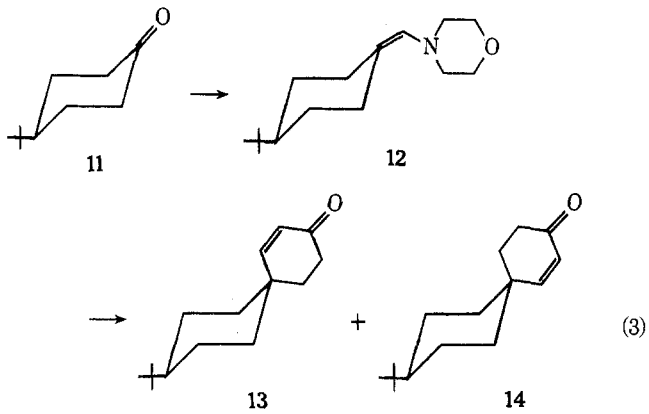
This spiroannelation procedure, which may be executed without the purification of any intermediates, is generally applicable to a wide variety of acyclic, cyclic, aromatic, and α,β-unsaturated ketones, and the product 4,4-disubstituted 2-cyclohexenones may be isolated in fair to moderate *overall* yields (see Table I).[11] Preliminary results have also indicated

Table I. Spiroannelation of Ketones

Ketone 4	Cyclohexenone 10	% yield[a]
$C_2H_5CO(CH_2)_3CH_3$		35
$CH_3(CH_2)_2CO(CH_2)_2CH_3$		36
$CH_3CO(CH_2)_2CH{=}CH_2$		33
		41
		36[b]
		41[c]
		30
		41[d]
$C_6H_5COCH_3$		34

[a] Isolated yield based upon ketone but not optimized. [b] Obtained as an ~9/1 mixture of diastereomers. [c] Obtained as an ~9/1 mixture of diastereomers. [d] As judged by NMR, is >95% one diastereomer.

that this synthetic sequence proceeds with a considerable degree of stereoselectivity. For example, 4-*tert*-butylcyclohexanone (**11**) was smoothly converted to a diastereomeric mixture of the spiro[5.5]undecenones **13** and **14** in a ratio of 9:1 (eq 3).[12] This result is in accord with the expectation that



(3)

the initial reaction of methyl vinyl ketone with the enamine **12** will occur from the less hindered, equatorial face of **12.**

The application of this new spiroannelation procedure to the synthesis of spiro sesquiterpene natural products as well as alkaloid natural products containing spirocyclic rings and quaternary carbon atoms is presently under investigation.

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Supplementary Material Available. Characterization of all new compounds, together with representative experimental details (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For a recent synthesis of acorone and related sesquiterpenes, see J. N. Marx and L. R. Norman, *J. Org. Chem.*, **40**, 1602 (1975), and references therein.
(2) For a recent synthesis of β-vetivone and related vetispiranes, see W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc.*, **97**, 1622 (1975), and references therein.
(3) For a synthesis of α-chamigrene, see J. D. White, S. Torii, and J. Nogami, *Tetrahedron Lett.*, 2879 (1974).
(4) (a) For a recent review of procedures for spiroannelation, see A. P. Krapcho, *Synthesis*, 383 (1974); (b) for a review of the application of sulfonium cyclopropylides to the construction of spirocyclic rings, see B. M. Trost, *Acc. Chem. Res.*, **7**, 85 (1974).
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(8) G. Stork, A. Brizzolora, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(9) H. Christol, F. Plénat, and J. Saloncon, *Bull. Soc. Chim. Fr.*, 4468 (1970).
(10) E. K. Fields, *J. Am. Chem. Soc.*, **74**, 1528 (1952).
(11) All compounds were adequately characterized by spectral methods (ir, NMR, MS), and all new compounds gave satisfactory high resolution mass spectral and/or combustion analytical data.
(12) Although the two isomers **13** (major) and **14** (minor) were inseparable by preparative chromatographic techniques, their presence is easily detected by analytical GLC and ^{1}H and ^{13}C NMR spectra: **13**, ^{1}H NMR ($CDCl_3$, TMS) δ 7.17 (d, J = 10 Hz, -CH=CHCO-) and ^{13}C NMR ($CDCl_3$, TMS) δ 155.4 (-CH=CHCO-); **14**, ^{1}H NMR ($CDCl_3$, TMS) δ 6.52 (d, J = 10 Hz, -CH=CHCO-) and ^{13}C NMR ($CDCl_3$, TMS) δ 160.7 (-CH=CHCO-). The stereochemical assignment with respect to the newly created chiral center may be made on the basis of the ^{1}H and ^{13}C NMR spectra. The β-vinyl proton of the major isomer **13** is *deshielded* relative to the β-vinyl proton of **14**, owing to steric crowding. As expected the β-vinyl carbon of **13** is *shielded* relative to the β-vinyl carbon of **14** owing to steric compression.

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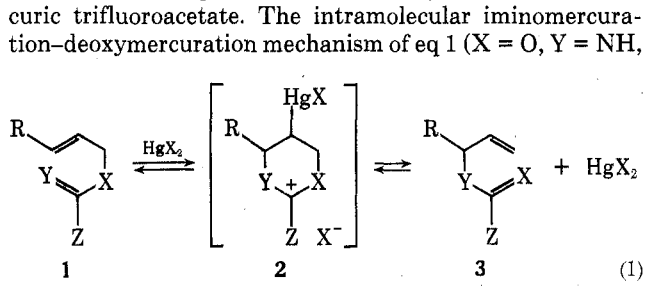
Mercury(II)-Catalyzed 3,3-Sigmatropic Rearrangements of Allylic *N,N*-Dimethylcarbamates. A Mild Method for Allylic Equilibrations and Contrathermodynamic Allylic Isomer Enrichments

Summary: Allylic *N,N*-dimethylcarbamates undergo allylic equilibration in high yield when treated at 25 °C in THF with catalytic amounts of mercuric trifluoroacetate. In certain cases the use of excess mercuric trifluoroacetate allows the less stable allylic isomer to be trapped.

Sir: The 1,3-isomerization of allylic alcohols and allylic alcohol derivatives has been investigated mechanistically for years,[1-3] and plays a key role in several synthetic[4] and commercial processes.[5] Popular methods for affecting this transformation include Lewis acid, protic acid, and transition metal catalyzed isomerization of allylic alcohols, or the corresponding acetates. Overall yields vary from 25 to 85%, and isomer conversions often only approach the equilibrium values.[1-5] Although methodology is well established[6] for the contrathermodynamic isomerization of alkenes, to our knowledge, no method exists for achieving contrathermodynamic *allylic* isomerizations.

The first examples of mercuric ion catalyzed [3,3]-sigmatropic rearrangements were recently reported from our laboratory.[7] This study revealed that trichloroacetimidic esters of 2-alken-1-ols **1** (X = O, Y = NH, Z = CCl_3) underwent rapid isomerization to the corresponding allylic trichloroacetamides **3** (X = O, Y = NH, Z = CCl_3) when treated in an aprotic solvent, at room temperature, with a catalytic amount of mercuric trifluoroacetate. The intramolecular iminomercuration–deoxymercuration mechanism of eq 1 (X = O, Y = NH, Z = CCl_3) was suggested for this catalyzed transformation.[7-9]



(1)

We anticipated that mercury(II) salts would catalyze the allylic isomerization (**1** → **3**) of other functional groups, and subsequent work in this laboratory has confirmed this expectation. In this communication we wish to report that mercuric trifluoroacetate is an effective catalyst at room temperature for the allylic equilibrium of *N,N*-dimethylcarbamic esters of allylic alcohols. Moreover, we wish to report that in certain cases a modification of this process results in the first approach to achieving contrathermodynamic allylic isomerizations.

Treatment of the allylic carbamate isomers **4a** and **5a** at room temperature for 4–11 h with 0.4 equiv of *anhydrous* mercuric trifluoroacetate in dry tetrahydorfuran (THF) re-