correspond. There seems to be no way to bring our remaining low frequency lines into agreement with those observed by Strausz.[4] Our frequencies for the a_1 ring deformation and the b_1 C—H bend are inverted with respect to his in C_2H_2S, and our calculated intensity for the a_1 CH bend in C_2D_2S is much lower. However, in a very recent paper, Krantz and Laureni[10] question the assignment of the observed 657-cm^{-1} band of thiirene which Strausz has assigned to an a_1 ring deformation. Such a band exists, but, because the spectrum is complicated in this region, its rate of appearance, and hence whether or not it is an absorption of thiirene, is difficult to determine. Removing this band, and what might be the corresponding band (in spite of a shift of 24 cm^{-1} to higher frequency) at 681 cm^{-1} in C_2D_2S, would give spectra for both compounds that are now in good agreement, in intensity and frequency, with our calculated results. In both cases the two strongest of the low-frequency absorptions have been observed. Of the remaining bands, that of predicted highest intensity is the a_1 ring deformation, which should lie at lower frequency than the observed bands.

Our best thiirene wave function is still many thousands of reciprocal centimeters too high in energy. Nevertheless, similar wave functions for ethylene and cyclobutadiene have been shown to give useful predictions of vibrational spectra.[8] Individual calculated frequencies may be in error by as much as 400 cm^{-1}, but the overall agreement, in frequency and intensity, between calculated and experimental patterns is strikingly good. While these computed spectra certainly can be helpful, they must not be taken as definitive.

Acknowledgment. We thank Professor J. R. Van Wazer for the use of his group's version of the POLYATOM program. We are grateful to Professors Krantz, Strausz, Bertie, and Torres for helpful discussions of their experimental results. C.S.E. acknowledges support by the Air Force Office of Scientific Research under Grant AFOSR-77-3145.

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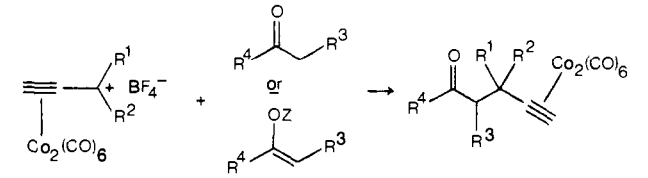
Synthetic Applications of Transition-Metal-Stabilized Carbenium Ions. Selective Alkylation of Ketones and Ketone Derivatives with (Propargyl)dicobalt Hexacarbonyl Cations[1]

Sir:

The selective alkylation of carbonyl compounds has been a long sought goal in organic synthesis. Accordingly, several approaches to this end have been developed, with varying success, to overcome the frequently encountered problems of polyalkylation, competing aldol condensation, and lack of regio- and stereoselectivity.[2] Most of these methods ultimately involve alkylation of the carbonyl-derived *enolate anion*—e.g., use of α-blocking groups and α-activating groups, cleavage of trimethylsilyl enol ethers and enol acetates, and kinetic enolate generation with strong bases. On the other hand, very few useful alkylation procedures are known which combine the ketone directly as its *enol tautomer* or an enol derivative with a suitable alkylating agent. Examples of this latter type include the Mannich reaction,[3] enamine alkylations,[4] and some recently reported additions to silyl enol ethers.[5] The paucity of such reactions probably is due in part to the limited availability of sufficiently electrophilic and flexible alkylating agents.

We have been interested in the alkylating potential of the cobalt-complexed propargyl cations **1**, representatives of a long-recognized but synthetically little-utilized group of highly stable carbenium ions flanked by organotransition metal moieties.[6] Previously, these electrophilic species, conveniently prepared from propargyl alcohols,[7] have been found to C-alkylate aromatics[8] and β-dicarbonyl compounds[1] with great facility and without formation of allenic byproducts. We now report that these same cationic complexes *alkylate ketones regiospecifically as well as trimethylsilyl enol ethers and enol acetates* (**1** → **2**).



a; $R^1 = R^2 = H$
b; $R^1 = H, R^2 = Ph$
c; $R^1 = R^2 = CH_3$

Simple dissolution of the complexes **1** in an excess of the dry ketone at 0 °C results in a rapid reaction (30–90 min) from which the α-alkylated products, dark red oils or low melting solids, are easily isolated upon addition of solid $NaHCO_3$ and $MgSO_4$, filtration, evaporation of excess substrate, and chromatography over silica gel.[9] Results with some representative ketones are presented in Table I. The key features to be noted are (1) the generally good yields of exclusively *mono*alkylated products which are obtained and (2) the remarkable regioselectivity found in reactions with unsymmetrical ketones. The only other organometallic products isolated were the alcohols $(R^1C{\equiv}CCR^2R^3OH)Co_2(CO)_6$ and ethers, $[Co_2(CO)_6(R^1C{\equiv}CCR^2R^3)]_2O$, resulting from competing reaction with residual water in the ketones. The specificity towards monoalkylation, while not unexpected considering the high ketone/complex ratio (~100:1) employed, is still nonetheless significant in view of the substantial amounts of polyalkylation obtained in many enolate alkylations, despite controlled addition of alkyl halide to preformed enolate.[10]

The regioselectivity observed is qualitatively as expected for attack of the electrophilic complex on the thermodynamically favored, more highly substituted enol. The degree of selectivity (≥95%)[11] is exceptional, however, when compared with that of most other acid-catalyzed α-substitution reactions of ketones such as deuteration,[12] halogenation,[12-14] and the Mannich reaction.[15] Further experiments are planned which will test the limits of this regiospecificity and attempt to establish its origin.

The use of the ketone as solvent is an obvious limitation of this alkylation procedure, making impractical its application to solid or precious substrates. Thus far our initial efforts to carry out these reactions stoichiometrically in a solvent have

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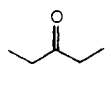
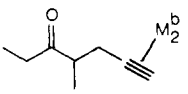
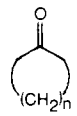
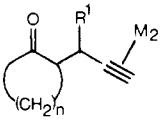
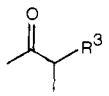
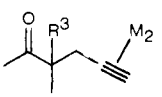
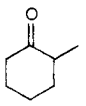
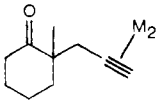
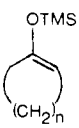
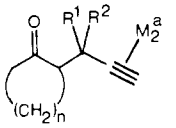
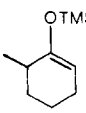
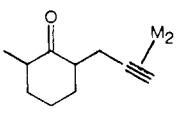
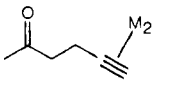
Table I. Alkylation of Ketones with $[(HC{\equiv}CCHR^1)Co_2(CO)_6]^+BF_4^-$

Substrate	Product	Yield, %[a]
		84
		
n = 2	R^1 = H	83
n = 2	R^1 = Ph	62
n = 3	R^1 = H	81
		
R^3 = H		77
R^3 = CH_3		70
		80

[a] Pure product, after chromatography. [b] $M_2 = Co_2(CO)_6$.

Table II. Alkylation of Enol Derivatives with $[(HC{\equiv}CCR^1R^2)Co_2(CO)_6]^+BF_4^-$

Substrate	Product	Yield, %		
		2a	**2b**	**2c**
				
n = 2		76	100[b]	60[c]
n = 3		75	97[b,d]	58[e]
		51[g]		
		96[h]		

[a] $M_2 = Co_2(CO)_6$. [b] Yield before chromatography; one product by TLC. [c] 22% elimination product, $(HC{\equiv}CCMe{=}CH_2)(Co_2(CO)_6$, obtained. [d] Approximate 1:1 mixture of diastereomers, separable by chromatography. [e] 17% $(HC{\equiv}CCMe{=}CH_2)Co_2(CO)_6$ obtained. [f] About 5–10% 2-methyl isomer present. [g] 7% 2,2-substituted isomer produced; 2,6-product obtained as a 3:1 chromatographically separable mixture of geometrical isomers. [h] Benzene added to reaction mixture to trap CH_3CO^+.

resulted in substantially reduced yields.[16]

The above limitation can be circumvented conveniently by combining the cobalt complexes with the corresponding trimethylsilyl enol ethers and enol acetates. Thus addition of the cation salts **1a–c** to equimolar CH_2Cl_2 solutions of these enol derivatives at 0 °C produced after 30–60 min moderate to excellent yields of monoalkylated products following the workup described previously (Table II). Particularly noteworthy is the fairly efficient generation of quaternary centers combining the dimethyl-substituted cation **1c** with Me_3Si ethers. This is in contrast to reactions of the corresponding propargyl halides with enolates and enamines which yield mainly elimination and allenic byproducts.[17] The accessibility of the less-substituted Me_3Si ethers[18] makes it possible by this method to introduce the propargyl unit regioselectively at the less substituted α carbon of an unsymmetrical ketone, as illustrated by alkylation of the kinetically preferred Me_3Si ether from 2-methylcyclohexanone. Furthermore, with the ready availability of the more highly substituted enol acetate regiosomers,[18] regiospecific production of 2,2-disubstituted ketones could be accomplished in a stoichiometric fashion.

Finally we note that the $-Co_2(CO_6)$ unit is efficiently removed by the procedure that we described earlier,[19] liberating the metal-free alkylated ketones. For example, treatment of the complex from **1a** and cyclohexanone with an excess of $Fe(NO_3)_3{\cdot}9H_2O$ (EtOH, 20 °C, 1 h) afforded 2-propargylcyclohexanone[20] in 98% yield after standard aqueous workup.

Considering the synthetic versatility of the carbon–carbon triple bond, this method constitutes an attractive and potentially flexible alkylation procedure.[21] Utilization of these reactions in natural product synthesis is under investigation.

Acknowledgments. We are grateful for support provided by the National Institutes of Health (GM 26760-01) and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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(16) Reaction rates in CH_2Cl_2 or ether, which do not dissolve the salts, are very slow resulting in formation of substantial amounts of the coupling products $(HC{\equiv}CCR^1R^2)_2[Co_2(CO)_6]_2$. The dipolar aprotic solvents DMF and acetonitrile appear to react with the cationic complexes.
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(21) We have also prepared cationic complexes derived from internal alkynes, e.g., $(CH_3C{\equiv}CCHPh)Co_2(CO)_6^+$ and $(C_5H_{11}C{\equiv}CCH_2)Co_2(CO)_6^+$. The latter

complex has been utilized in a highly efficient dihydrojasmone synthesis.[22]

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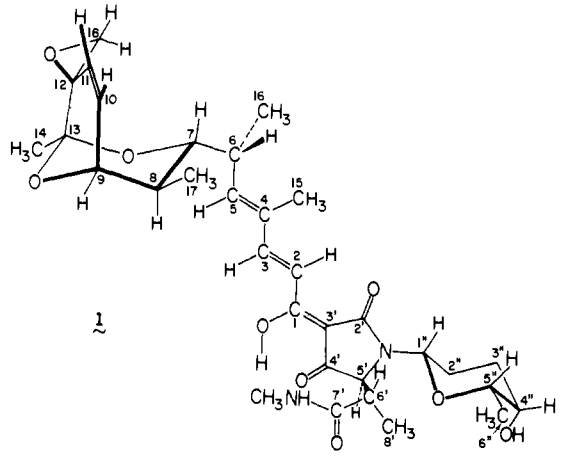
Biosynthetic Incorporation of Propionate and Methionine into Streptolydigin[1]

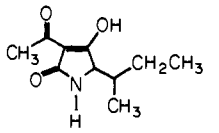
Sir:

The antibiotic streptolydigin, to which structure **1** was assigned here some years ago,[2,3] continues to be of biological interest for its potent inhibition of Gram-positive bacteria[4] and *E. coli* DNA-directed RNA polymerase[5] and its selective inhibition of terminal deoxyribonucleotidyl transferase from leukemic cells[6] and of replication of Col E1 plasmid DNA in *E. coli*.[7] Streptolydigin and the closely related tirandamycin[3,8] have also been the subjects of recent intensive studies directed toward partial[9,10] and total[11] syntheses, and closely related antibiotics continue to be discovered.[12]

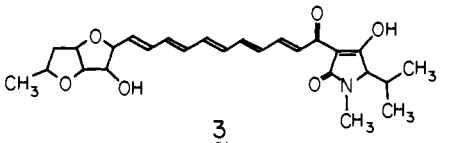


1

Streptolydigin is an example of an acyltetramic acid, a class of compounds which includes the antitumor agent tenuazonic acid (**2**),[13] the toxin erythroskyrine (**3**),[14] the antitrypanosomal

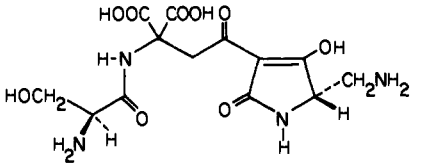


2



3

compound malonomicin (**4**),[15] and numerous other representatives. Biosynthesis of acyltetramic acids has been shown to involve condensation of an amino acid and a polyketide. Thus,



4

2 is derived from 1 mol of isoleucine and 2 mol of acetate,[16] **3** from valine, 1 mol of acetate, and 9 mol of malonate,[17] and **4** from 2,3-diaminopropanoic acid, acetate, a C_4 dicarboxylic acid, CO_2, and serine.[18] In principle, **1** should then be derived from β-methylaspartic acid (carbons 4′-8′), a hexose (carbons 1″-6″), and a polyketide derived *either* from acetate (carbons

Table I. Incorporation of Labeled Precursors into Streptolydigin[a]

precursor				streptolydigin			
compd	sp act., μCi/mmol	amount, μCi	total vol., mL	sp act., μCi/mmol	amount, mg	incorpn, %	% of label in streptolic acid[b]
sodium [*methyl*-^{14}C]propionate	4.8	0.16	50	0.50	3.1	1.6	100
	0.003	1.87	500	0.18	18.6	0.3	ND[c]
L-[*methyl*-^{14}C]methionine	14.9	7.08	50	11.06	1.0	0.25	2
	0.012	1.61	2000	0.20	59.0	1.25	ND
sodium [*carboxy*-^{14}C]acetate	2.2	5.84	50	0.69	1.0	0.02	ND
[*carboxy*-^{14}C]malonic acid	40	1.97	50	0.70	0.6	0.04	ND
D-[U-^{14}C]glucose	198	2.47	50	0.82	5.6	0.3	ND
DL-[1-^{14}C]glutamic acid	15.2	2.36	50	0.06	2.5	0.01	ND
DL-[4-^{14}C]aspartic acid	0.76	2.34	50	0.07	1.4	0.007	ND

precursor				streptolydigin			
compd	enrichment, % ^{13}C	amount, mg	total vol., L	enrichment, av %[d]	amount, mg	incorpn, %[e]	dilution[f]
sodium [*carboxy*-^{13}C]propionate	90	500	2.0	0.61	140	0.97	4.6
L-[*methyl*-^{13}C]methionine	60	500	2.0	0.36	164	1.56	5.2

[a] The labeled compounds were added to 50-mL aliquots of *S. lydicus* cultures in 500-mL Erlenmeyer flasks. The growth medium contained brewers yeast, 0.25%; $CaCO_3$, 0.6%; sucrose, 3%; $(NH_4)_2SO_4$, 0.2%; soybean meal, 2%; and distilled water. This was inoculated with 2.5 mL of a 72-h culture of *S. lydicus* (grown in Bacto-peptone, 0.75%; yeast extract, 0.25%; glucose, 0.5%; and distilled water) and incubated on a rotary shaker at 30 °C for 96 h. Streptolydigin was harvested by a modification of a previously reported method.[21] The culture broth was adjusted to pH 8.0 using 2 N NaOH, heated at 60 °C for 10 min and centrifuged. The supernatant was extracted using methylene chloride. The organic fraction was washed with citrate buffer and the volume reduced. Streptolydigin was precipitated by the addition of *n*-hexane, and was further purified over silica gel or using LC. [^{13}C]Streptolydigin was used directly following hexane treatment. [b] Streptolic acid was prepared from streptolydigin by periodate oxidation using the method described previously.[22] The product was purified by LC using the solvent MeOH–H_2O–AcOH (60:40:1) on a C_{18} μ-Bondapak reversed-phase column. [c] ND = not determined. [d] Calculated by summing the values in Table II and dividing by the total number of carbons to give the average ^{13}C per carbon and then subtracting natural abundance ^{13}C (taken as 1.11). [e] Calculated from ^{13}C data using enrichment values. [f] Enrichment of precursor divided by the enrichment (total) of the product.

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