°C) with evolution of some hydrogen fluoride. The support was then treated with the solution as before and heated to 250–300 °C to obtain 10% tantalum oxyfluoride deposited on the alumina.

Zirconium oxyfluoride (10%) on alumina was prepared as above by treating alumina with zirconium tetrafluoride dissolved in methyl alcohol.

Reagents. Dimethyl ether (99.8%), methyl chloride (99.5%), and ethylene (99.9%) were purchased from Matheson. Dimethyl sulfide (98%) and trimethylamine (99%) were purchased from Aldrich. Dimethylamine was prepared from dimethylamine hydrochloride (Aldrich) with sodium hydroxide. Methylamine (40% in water) was purchased from MCB. $^{13}CH_3OCH_3$ was prepared from $^{13}CH_3I$ (90%, KOR Isotopes) and sodium methoxide by using the Williamson ether synthesis. $CD_3OCH_2CH_3$ was prepared from CD_3I (99%, KOR Isotopes) and sodium ethoxide. $^{13}CH_3OH$ (90%) was purchased from KOR Isotopes.

General Procedure for Heterogeneous Catalytic Conversion of Heterosubstituted Methanes into Ethylene and Lower Olefins. All reactions were carried out at atmospheric pressure in a fixed-bed, continuous-flow, electrically heated 550 × 10 nm Pyrex glass tube reactor, similar to that described in our previous work.[46] Generally 10 g of supported catalyst, previously calcinated, was placed in a stream of dry nitrogen into the reactor, and reactants were introduced in a constant N_2 stream with a gaseous space velocity (volume of gas passed over volume of catalyst per hour) of between 50 and 1000 under conditions shown in Table I. Samples were taken at the outlet of the reactor and analyzed by GC and GC/MS. For isotopic label determination products were passed through a solution of bromine in carbon tetrachloride in order to trap formed olefins as dibromoalkanes and were analyzed as such by GC/MS.

Analyses. GC analyses of the reaction mixtures were conducted on the following instruments: (a) Hewlett Packard 5130 A with a Poropak Q column (12 ft $^1/_8$ in.); (b) Varian 3700 with an OV 101 glass capillary column (50 m). All percentage numbers are corrected for FID response factors and are given in mol %.

MS analyses were carried out on a Hewlett Packard 5985 A GC/MS spectrograph equipped with a Poropak column. For the MS analysis of 1,2-dibromoalkanes an OV 101 column (6 ft $^1/_8$ in.) was used.

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Registry No. CH_3OH, 67-56-1; CH_3OCH_3, 115-10-6; CH_3SCH_3, 75-18-3; CH_3NH_2, 74-89-5; $(CH_3)_2NH$, 124-40-3; $(CH_3)_3N$, 75-50-3; CH_3Cl, 74-87-3; $^{13}CH_3OCH_3$, 88842-43-7; $CD_3OCH_2CH_3$, 16995-14-5; $^{13}CH_3OH$, 14742-26-8; CH_3SH, 74-93-1; WO_3, 1314-35-8; C_2H_4, 74-85-1; CH_4, 74-82-8; propylene, 115-07-1; butylene, 25167-67-3; tantalum oxyfluoride, 20263-47-2; zirconium oxyfluoride, 14984-80-6; pentylene, 25377-72-4.

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The Michael Reaction of Silyl Enol Ethers or Ketene Silyl Acetals with Conjugated Nitro Olefins Activated by the Lewis Acid: New Synthesis of 1,4-Diketones and γ-Keto Esters

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Abstract: New one-pot procedures for the synthesis of 1,4-diketones and γ-keto esters utilizing conjugated nitro olefins are described. Reaction of silyl enol ethers with aliphatic nitro olefins in the presence of a Lewis acid affords 1,4-diketones in good yields, while similar reaction of ketene silyl acetals, derived from various esters, with nitro olefins produces a variety of γ-keto esters, after hydrolytic treatment. Regiospecific addition of carbonyl compounds to nitro olefins was observed in both reactions. 1,4-Diketones obtained could be converted into the corresponding cyclopentenones in high yields.

The Michael addition of carbonyl compounds to conjugated nitro olefins is one of the efficient carbon–carbon bond-forming reactions involving nitro compounds,[1] as well as nitro-free structures.[1c,2] The synthetic potential of nitro olefins also lies in the remarkable versatility of nitro groups in the interconversions of organic functional groups,[1c] among which the transformation of nitro aliphatics into carbonyl compounds, the Nef reaction,[3] is the most important from the synthetic viewpoint. Thus nitro groups are synthetically equivalent to carbonyl groups[4] and they provide *an umpolung of reactivity*[1c] of carbonyl derivatives (Figure 1), hence the Michael addition of this type should promise a new entry to 1,4-dicarbonyl compounds.[5,6]

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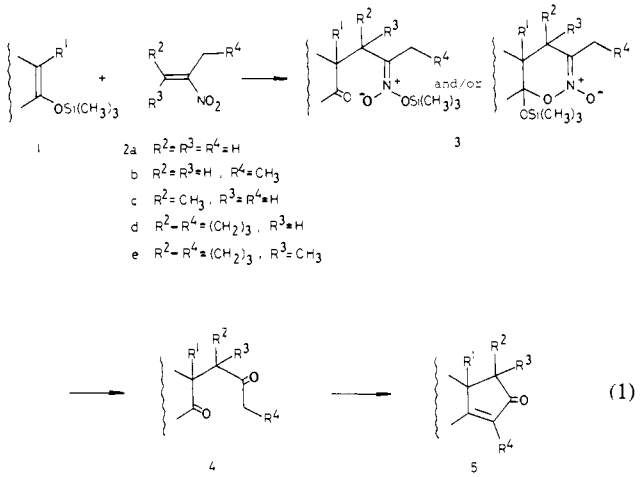
We have intensively investigated the development of nitro olefins as carbonyl synthons with *reactivity umpolung* and their practical utility in bond construction[2b] and recently reported the Lewis acid promoted one-pot synthesis of 1,4-diketones and γ-keto esters from conjugated nitro olefins and trimethylsilyl enol ethers and ketene methyl trimethylsilyl acetals, respectively.[7,8]

In this report, we wish to describe the scope and limitations of this synthetic methodology in detail.

When we initiated this research, aliphatic conjugated nitro olefins had very rarely been used in the Michael addition with *monofunctional carbonyl compounds* such as ketones or esters, probably due to the instability of the former compounds under conventional reaction conditions (strong alkaline media), although the addition of active methylene compounds including malonates, acetoacetates, and 1,3-diones to nitro olefins is well-known.[1a]

At the outset of this research, therefore, we envisaged the Lewis acid catalyzed Michael reaction (acidic media) of nitro olefins with *monofunctional carbonyl compounds*,[9] although such a precedent had never been reported. Furthermore, we considered that the use of silyl enol ethers **1** as nucleophiles toward nitro olefins **2** would ideally be suited for the purpose since the feasible Michael adduct, silyl nitronate such as **3**, should readily undergo the Nef reaction to give 1,4-diketones **4** due to the hydrolysis of the Lewis acid *in the same flask*[10] (eq 1).



(1)

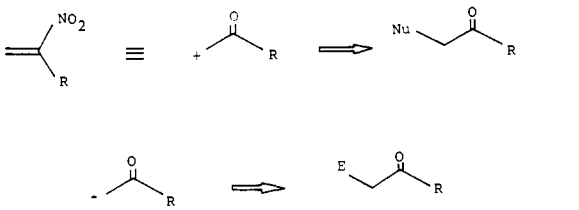
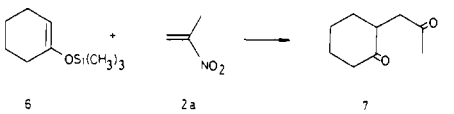


Figure 1. Reactivity umpolung with nitro olefins vs. normal reactivity.

This surmise was proven valid by experiment and a variety of 1,4-diketones, which can serve as potential precursors for the synthesis of naturally occurring cyclopentanoids and furans,[11] were synthesized in a one-pot operation.

We initially focused our attention on the reaction of 1-((trimethylsilyl)oxy)-1-cyclohexene (**6**)[12] with 2-nitropropene (**2a**)[13] as a model reaction and screened a variety of catalysts, solvents, and temperatures for the best conditions conducive to the desired 1,4-diketones.

The Lewis acid titanium tetrachloride ($TiCl_4$) was employed first since Mukaiyama and co-workers have demonstrated in their works that this Lewis acid powerfully activates the reaction of silyl enol ethers and α,β-unsaturated ketones[14] as well as saturated carbonyl compounds.[15] We considered that $TiCl_4$ should also activate nitro olefins for nucleophilic reactions and indeed this Lewis acid was found to effect the Michael reaction of **6** and **2a** in CH_2Cl_2 resulting in formation of 2-(2-oxopropyl)cyclohexanone (**7**)[6i,16] in high yield after hydrolytic treatment (eq 2).[17]



(2)

In order to gain further insight into catalysts, we have studied the reaction of **6** and **2a** in the presence of various other metal salts. Various Lewis acids gave varying yields of **7** in CH_2Cl_2. $TiCl_4$, stannic chloride ($SnCl_4$), and aluminum chloride ($AlCl_3$) gave yields of 83, 85, and 70%, respectively, while no reaction was observed when BF_3 etherate was used. On the other hand, benzyltrimethylammonium fluoride[18] to generate quarternary ammonium enolates from silyl enol ethers and trimethylsilyl trifluoromethanesulfonate[19] and trimethylsilyl iodide[20] which have proven to be efficient catalysts for the cross-aldol reaction of silyl enol ethers with acetals were not efficacious at all in this case.

The solvent effects on this reaction were also studied with use of **6** and **2a**. The best yields were obtained in CH_2Cl_2 while benzene, tetrahydrofuran (THF), and dimethoxyethane (DME) gave yields of 0–23%.

In general, the Nef reaction is pH dependent, i.e., a low pH (0.1–1) favors the Nef reaction, while weak acids pH (3–5) cause the tautomerization of nitronate salts to nitro compounds.[21] Therefore, the pH due to the hydrolysis of the Lewis acid employed

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(9) The Michael reaction of conjugated nitro olefins with carboxylic acid dianions and with ester enolates (basic media) will be published elsewhere.

(10) Three-step synthesis of 1,4-diketones from allylsilane and nitro olefins has recently been reported. See: Ochiai, M.; Arimoto, M.; Fujita, E. *Tetrahedron Lett.* **1981**, *22*, 1115.

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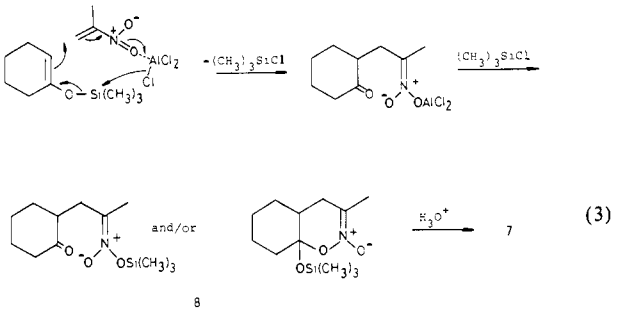
in this reaction may be crucial for the Nef reaction of the silyl nitronate **3**.

The pH due to the hydrolysis of 1 mmol of the Lewis acids $TiCl_4$, $SnCl_4$, and $AlCl_3$, in 1.5 mL of water, was −1, 0.4, and 3.0, respectively. With the first two Lewis acids, the reaction media should be acidic enough for the Nef reaction; however, in the case of $AlCl_3$, it may not be.[22] In fact, the reaction of **6** and **2a** in the presence of $AlCl_3$ followed by hydrolysis with water gave a mixture of **3** ($R^1 = R^2 = R^3 = R^4 = H$) and **7**. It was found, however, that the use of 10% hydrochloric acid (pH 0.3), instead of water, for the Nef reaction resulted in 70% yield of **7** without the isolation of the silyl nitronate **3** ($R^1 = R^2 = R^3 = R^4 = H$).

Of interest is the observation that reaction of **6** and **2a** in the presence of $AlCl_3$ afforded the intermediate silyl nitronate free from the 1,4-diketone **7** after workup with an aqueous potassium carbonate solution. Although the structure of the intermediate could not be fully characterized owing to its hydrolytic instability,[23] its IR spectrum (strong bands at 1628, 1255, 1164, 1148, and 848 cm^{-1}) and ^1H NMR spectrum (0.13 and 0.15 ppm due to $(CH_3)_3Si$– and 1.87–1.92 ppm due to olefinic methyls) implied unambigously the intermediacy of silyl nitronates such as **8**, hence the reaction presumably proceeds via the pathway in eq 3.



(3)

To illustrate the potential of our 1,4-diketone synthesis, a number of reactions of various silyl enol ethers with a variety of nitro olefins, 2-nitropropene (**2a**), 2-nitro-1-butene (**2b**),[7] and 2-nitro-2-butene (**2c**),[7] were examined, and the corresponding 1,4-diketones were obtained in good yields (Table I).

As seen from Table I, the reaction of silyl enol ethers derived from cyclopentanones gave rise to lower yields of diketones in comparison with cyclohexanone homologues. For example, the reaction of 2-methyl-1-((trimethylsilyl)oxy)-1-cyclopentene (**10**) and **2a** afforded the diketone **16** along with the corresponding nitro ketone **17**, which was easily converted into **16** in a high yield under the standard Nef reaction conditions (Experimental Section).

An important feature of the present method is facile and regiospecific introduction of substituted 2-oxoalkyl substituents α to a ketone functionality. In all cases, the addition of silyl enol ethers of unsymmetrical ketones takes place regiospecifically at the olefinic position derived from the silyl enol ether.

A number of effective methods of adding an acetonyl side chain to the α carbon of ketones or their equivalents have recently been reported[6] by the stimulation from the synthesis of natural cyclopentanoids. Each has, however, an essential limitation in its extension to other 2-oxoalkyl substituents except the acetonyl group because such reagents have thus far not been readily accessible.

Another advantage of the new method is that a wide variety of α-, β-, and α,β-substituted nitroethylenes **2** are readily available from nitro alkanes via an aldol-type addition with carbonyl compounds (Henry reaction) followed by dehydration[24] or by other procedures recently reported.[25] With these nitroethylenes various substituted cyclopentenones may be derivable from an annulation reaction (eq 1).

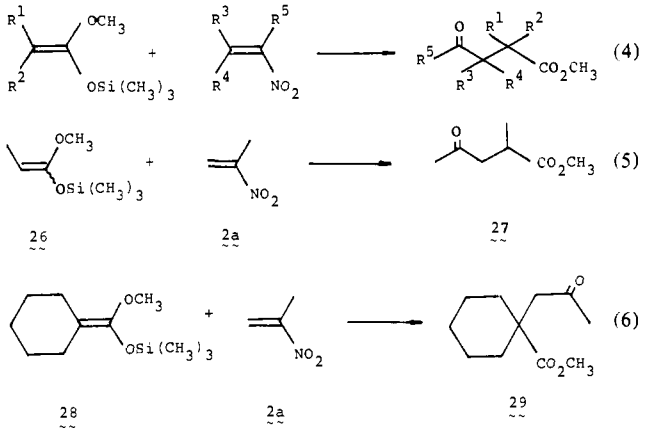
Thus when 1,4-diketones obtained were submitted to the cyclization conditions (alcoholic potassium hydroxide), the corresponding cyclopentenones were produced in high yields except for 2-(2-oxopropyl)cyclopentanone (**15**), which resulted in a complex mixture even under the controlled reaction conditions (Table I).

These cyclopentenones should be potential precursors for the synthesis of natural cyclopentanoids. In fact, dihydrojasmone (**25**), a constituent of bergamot oil, was synthesized in two steps[6i,11b] from **2a** and 2-((trimethylsilyl)oxy)-1-octene (**11**).

Other successful applications are the recent total syntheses of (±)-gymnomitrol by Welch et al.[11c] and (±)-isocomene by Paquette et al.[11d] starting from bicyclic enone **23** and **24**, respectively.

The silyl enol ethers used in the reaction described so far were those derived from only ketones. Consequently, to furnish the added versatility of the new method, it remained to examine synthetic behavior of silyl enol ethers derived from esters viz. ketene silyl acetals.[26]

As the accompanying equation illustrates, it would be expected to provide a new method for the synthesis of γ-keto esters,[8,27] which are highly useful intermediates in organic synthesis, provided the Lewis acid promoted reaction of nitro olefins with ketene silyl acetals takes place in a similar fashion as with the silyl enol ethers derived from ketones (eq 4).



At first, the reaction of methyl ketene methyl trimethylsilyl acetal (**26**)[26] and 2-nitropropene (**2a**) was attempted.

Following essentially the same procedure, when the ketene silyl acetal **26** was allowed to react with **2a** at −78 °C in the presence of $TiCl_4$, the desired γ-keto ester **27**[28] was obtained in 58% yield after the esterification of free acid, produced by the hydrolysis

(22) Nitronic acids have been isololated in the reaction of allylsilane with nitro olefins in the presence of aluminum chloride. See ref 10.

(23) Trimethylsilyl nitronates of secondary nitro alkanes are known to be less stable than those derived from primary nitro alkanes. Colvin, E. W.; Seebach, D. *J. Chem. Soc., Chem. Commun.* **1978**, 689.

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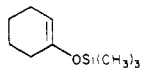
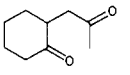
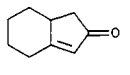
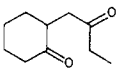
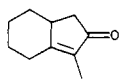
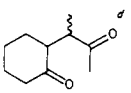
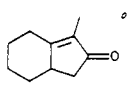
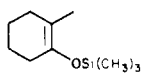
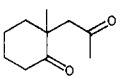
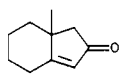
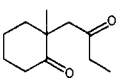
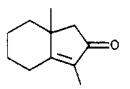
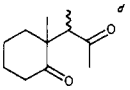
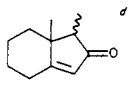
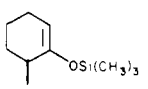
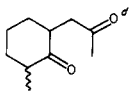
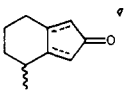
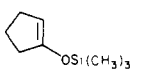
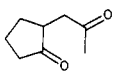
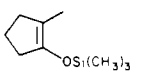
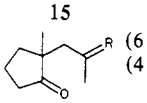
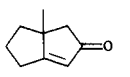
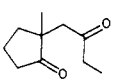
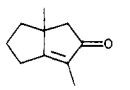
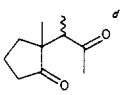
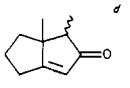
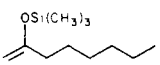
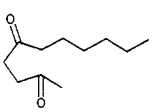
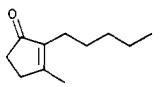
Table I. Synthesis of 1,4-Diketones and Cyclopentenones

trimethylsilyl enol ether	nitro olefin	Lewis acid	1,4-diketone	isolated yield, %	cyclopentenone	isolated yield, %
 6	 2a	$SnCl_4$ $TiCl_4$ $AlCl_3$	 7	85[a] 83 70[b]		83[m]
	 2b	$TiCl_4$ $SnCl_4$		76[c] 62		89[n]
	 2c	$AlCl_3$ $SnCl_4$ $TiCl_4$		63[b,e] 50 41		80[n]
 9	2a	$TiCl_4$ $SnCl_4$		70[f] 60		93[p]
	2b	$SnCl_4$ $TiCl_4$	 12	82[g] 62	 20	87
	2c	$TiCl_4$ $SnCl_4$	 13	71 63	 21	85
	2a	$SnCl_4$ $TiCl_4$	 14	63[h] 60	 22	81
	2a	$SnCl_4$ $SnCl_4$ $TiCl_4$	 15	70[i,j] 63 61		
 10	2a	$SnCl_4$ $TiCl_4$	 (68:32) (47:53) 16, R = O;[k] 17, R = H, NO_2[d]	60 53	 23	79[r]
	2b	$SnCl_4$	 18	41	 24	88
	2c	$SnCl_4$	 19	36		64[s]
 11	2a	$SnCl_4$ $TiCl_4$		65[l] 63	 25	80[t]

[a] References 6 and 7b. [b] 10% hydrochloric acid was used for hydrolytic treatment. [c] References 6h, 39, and 40. [d] Diastereomeric mixture. [e] References 39 and 40. [f] References 6i, 39, and 41. [g] Reference 39. [h] References 6i and 41. [i] Benzene was used as solvent. [j] References 6h and 42. [k] References 11c and 43. [l] References 11a and 11b. [m] References 6i, 25a, and 44. [n] References 32, 40, 44d,e,g, and 45. [o] Double bond isomerization product. [p] References 6i, 44c,g, and 46. [q] Mixture of double bond isomers and diastereomers. [r] References 11c and 47. [s] References 47. [t] Reference 11b.

of the product, with diazomethane. It was noteworthy, to our surprise, that the employment of $SnCl_4$ gave none of the product, in sharp contrast to the reaction of silyl enol ethers with nitro olefins (vide ante).

In turn, we focused our attention on the reaction of ketene silyl acetal **28**[26] and **2a** from the synthetic viewpoint; however, the desired product **29** was not obtained at all under the same reaction conditions described above. Hence, we investigated this reaction in more detail.

From the results shown in Table II, the notable observation was the remarkable solvent effects on the Nef reaction, i.e., the replacement of the solvent from CH_2Cl_2 to DME *at the stage of hydrolysis* resulted in a great enhancement of the yield. In addition, the additive of titanium tetraisopropoxide [$Ti(O\text{-}i\text{-}Pr)_4$]

Table II. Reaction of the Ketene Silyl Acetal 28 with 2-Nitropropene 2a[a]

Lewis acid	Nef reaction conditions: solvent	temp, °C	isolated yield of 29, %
$TiCl_4$	H_2O–CH_2Cl_2	60	
$TiCl_4$-Ti(O-*i*-Pr)$_4$	H_2O–CH_2Cl_2	60	35
$TiCl_4$	H_2O–DME	90	68
$TiCl_4$-Ti(O-*i*-Pr)$_4$	H_2O–DME	90	79

[a] CH_2Cl_2 was used as solvent.

to suppress the hydrolysis of ketene silyl acetals,[29] which are generally highly susceptible to acids, was found to contribute effectively to the improvement of the yield. Also the temperature of hydrolysis may affect this result to some extent.

Thus the improved procedure finally afforded the desired product, methyl 1-(2-oxopropyl)cyclohexanecarboxylate (**29**), in 79% yield (Experimental Section).

With the optimum reaction conditions in hand, we subsequently examined the reaction of various ketene silyl acetals with a variety of nitro olefins. Ketene silyl acetals used herein were readily available from the corresponding esters according to the known procedure.[26] The results are summarized in Table III.

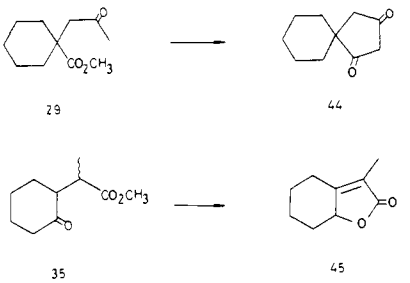
A number of general trends are evident from the data in Table III. As seen, yields of γ-keto esters largely depend on the degree of substitution at the reaction sites of both reactants, particularly on that of the nitro olefins. 2-Nitropropene (**2a**) and 2-nitro-1-butene (**2b**), possessing no substituents at the β carbon, smoothly reacted with all types of ketene silyl acetals to afford γ-keto esters in good yields. On the other hand, the reactivity of cyclic nitro olefins **2d** and **2e**[25] decreased. presumably due to steric hindrance, and an excess of ketene silyl acetal was required to optimize the yield. Particularly, the reaction of 2-methyl-1-nitro-1-cyclohexene (**2e**), a fully substituted nitro olefin, with dimethyl ketene silyl acetal **30** was extremely sluggish and the α,α,β,β-tetrasubstituted γ-keto ester was not detected even when a large excess of the acetal **30** was used.

In the reaction of 2-methyl-1-nitro-1-cyclohexene (**2e**) with the ketene silyl acetal **26**, lactone **37** was obtained as a mixture of diastereomers along with the expected γ-keto ester **36** in 73% combined yield. Apparently, the former compound **37** was produced from the corresponding keto acid resulting from hydrolysis of the keto ester **36** in the reaction media.

It is noteworthy that vinyl ketene silyl acetal **33** prepared from methyl tiglate gave the α-acetonylated product **43** selectively. We consider that the highly selective α substitution of **33** can be better rationalized by assuming that the ten-membered transition state involving the Lewis acid will be favored over the twelve-membered transition state as that in the reaction of silyl enol ethers with nitro olefins (see eq 3) or with α,β-unsaturated carbonyl compounds.[13]

Although numerous synthetic methods of γ-keto esters have been reported,[27] they have methodological limitations in the synthesis of α- and/or β-alkylated γ-keto esters especially in the synthesis of α,α-disubstituted ones. The new method described herein proved to be highly efficient for the synthesis of α- and/or β-substituted γ-keto esters involving α,α-disubstituted derivatives.

With a variety of γ-keto esters in hand, a few synthetically useful transformations were examined. Methyl 1-(2-oxopropyl)cyclohexanecarboxylate (**29**) was treated with potassium triphenylmethoxide[30] to give a spiro β-diketone **44**[31] in 52% yield, while methyl 2-(2-oxocyclohexyl)propionate (**35**)[32] was converted into butenolide **45**[33] in 74% yield on treatment with active alumina in refluxing benzene. On the other hand, we have succeeded in the first total synthesis of curzerenone and epicurzerenone,[34] representative furanoelemanoids isolated from the rhizomes of *Curcuma zedoaria* Roscoe,[35] using **43** as starting material.



(7)

In conclusion, it is noted that conjugated nitro olefins are strongly activated by Lewis acids, and a wide variety of 1,4-diketones and γ-keto esters are obtained in good yields by the reaction with various silyl enol ethers and ketene silyl acetals, respectively. Further, in view of ready accessibility of starting materials, high regiospecificity, and simple manipulation, the present methods provide a new tool in organic synthesis.

Experimental Section

Melting points are uncorrected and boiling points indicate bath temperatures on evaporative distillation of liquid products. IR spectra were recorded on a Hitachi EPI-S2 spectrophotometer. ^1H NMR spectra were measured on a Jeol C-60HL spectrometer (60 MHz). *J* indicates coupling constants in hertz.

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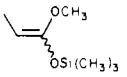
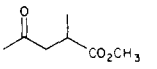
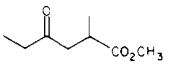
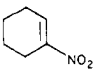
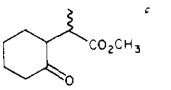
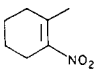
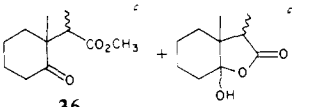
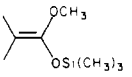
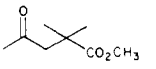
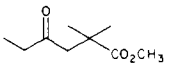
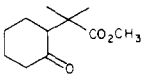
Table III. Synthesis of γ-Keto Esters

ketene silyl acetal	nitro olefin	molar ratio[h]	product	isolated yield,[a] %
 26	 2a	1:1.5	 27	64[b]
	 2b	1:1.5	 34	63
	 2d	1.5:1	 35	70[d]
	 2e	3:1	 36 (44:56) 37	73
 30	2a	1:1.5		66[e]
	2b	1:1.5		68[f]
	2d	1.5:1	 38	25
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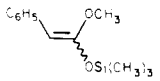
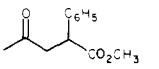
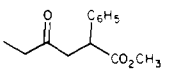
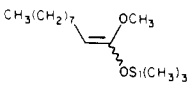
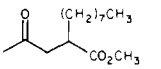
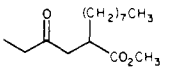
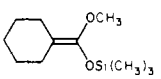
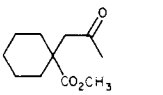
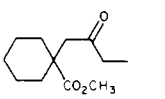
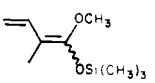
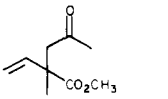
 31	2a	1:1.5		82[g]
	2b	1:1.5	 39	79
 32	2a	1:1.5	 40	84
	2b	1:1.5	 41	81
 28	2a	1:1.5	 29	79
	2b	1:1.5	 42	78
 33	2a	1:1.5	 43	46

[a] The yield refers to the minor reactant (1 mmol). [b] References 28 and 48. [c] Diastereomeric mixture. [d] Reference 32. [e] Reference 49. [f] Reference 50. [g] Reference 51. [h] Molar ratio of ketene silyl acetal and nitro olefin.

General Procedure for the Synthesis of 1,4-Diketones from Silyl Enol Ethers and Conjugated Nitro Olefins.[7b] A nitro olefin (1.5 mmol) was added rapidly to a dry CH_2Cl_2 solution (4 mL) of the Lewis acid (1 mmol) under an argon (or nitrogen) atmosphere at −78 °C and the mixture was stirred at the same temperature for 10 min. Then a silyl enol ether (1 mmol) was added dropwise over 5 min, and the resulting mixture was stirred at −78 °C for an additional h and then gradually warmed to 0 °C over 2–2.5 h. Water (1.5 mL) (10% hydrochloric acid

(1.5 mL) in the case of $AlCl_3$) was added and the resultant heterogeneous mixture was stirred at reflux for 2 h. The mixture was cooled to room temperature and extracted with ethyl acetate. The extract was washed with water and saturated brine and evaporated. The residue was passed through a short alumina column (Woelm activity III) with the aid of ether. Distillation of the eluate gave pure product(s).

2-Methyl-2-(1-methyl-2-oxopropyl)cyclohexanone (13): bp 88–89 °C (0.2 mmHg); IR (neat) 1701 cm^{-1}; ^1H NMR (CCl_4) δ 1.03 (s, 3 H), 1.01 and 1.15 (d, each, 3 H in total, J = 7.5), 2.07 and 2.10 (s, each, 3 H in total), 1.3–2.5 (m, 8 H), 2.80 and 2.93 (q, each, 1 H in total, J = 7.5). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.49; H, 10.30.

2-Methyl-2-(2-oxopropyl)cyclopentanone (16)[11c,43] and 2-Methyl-2-(2-nitropropyl)cyclopentanone (17). These products were separated by preparative silica gel TLC (CH_2Cl_2 as solvent). **16**: bp 60 °C (0.2 mmHg); IR (neat) 1732, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 2.05 (s, 3 H), 2.73 (br s, 2 H), 1.5–2.5 (m, 6 H). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.30; H, 9.42. **17**: bp 100 °C (0.3 mmHg); IR (neat) 1735, 1550, 1358 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 and 1.00 (s, each, 3 H in total), 1.50 (d, 3 H, J = 6.5), 1.5–2.5 (m, 8 H), 4.2–5.0 (m, 1 H). Anal. Calcd for $C_9H_{15}O_3N$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.51; H, 8.24; N, 7.38.

Conversion of 17 into 16. A solution of **17** (125 mg, 0.67 mmol) in absolute ethanol (1.2 mL) was added dropwise to a solution of NaOH (30 mg, 0.74 mmol) in ethanol (0.8 mL) under nitrogen at room temperature. The mixture was stirred for 5 min and the solvent evaporated in vacuo at room temperature. Dry ether (4 mL) was added to the residue and white solids were collected by filtration to give 126 mg (91%) of the sodium nitronate, mp 208–209 °C dec.

To a solution of the above salt (103 mg, 0.5 mmol) in water (3 mL) was added 10% hydrochloric acid (0.6 mL) at room temperature, and the resulting solution was allowed to stand overnight at room temperature. The mixture was extracted with ether, and the extract was washed with water and saturated brine. Removal of the solvent gave 58 mg (76%) of the diketone **16**.

2-Methyl-2-(2-oxobutyl)cyclopentanone (18): bp 85 °C (0.2 mmHg); IR (neat) 1734, 1710 cm^{-1}; ^1H NMR (CCl_4) δ 0.92 (s, 3 H), 0.98 (t, 3 H, J = 7), 2.28 (q, 2 H, J = 7), 2.57 (ABq, 2 H, J = 17), 1.5–2.3 (m, 6 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.59.

2-Methyl-2-(1-methyl-2-oxopropyl)cyclopentanone (19): bp 80 °C (0.2 mmHg); IR (neat) 1738, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 and 1.01 (s, each, 3 H in total), 1.07 and 1.20 (d, each, 3 H in total, J = 7), 2.05 and 2.12 (s, each, 3 H in total), 1.3–2.5 (m, 6 H), 2.5–3.1 (m, 1 H). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.09; H, 9.74.

General Procedure for the Synthesis of Cyclopentenones from 1,4-Diketones. A mixture of a diketone (1 mmol) and potassium hydroxide (5 mmol) in 90% ethanol (11 mL) was stirred at reflux for 1.5–5 h under nitrogen. The cooled reaction mixture was poured into water and neutralized with 7% hydrochloric acid and extracted with ether. The ether extract was washed with saturated brine. Evaporation of the solvent left an oil, which was purified by distillation or silica gel TLC (CH_2Cl_2–ether (5:1) as solvent).

3,7a-Dimethyl-1,4,5,6,7,7a-hexahydroinden-2(2*H*)-one (20): bp 88–89 °C (0.2 mmHg); IR (CCl_4) 1700, 1650 cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (s, 3 H), 1.60 (s, 3 H), 2.07 (s, 2 H), 1.0–2.9 (m, 8 H). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.41; H, 9.94.

1,7a-Dimethyl-1,4,5,6,7,7a-hexahydroinden-2(2*H*)-one (21): bp 86–87 °C (0.2 mmHg); IR (neat) 1700, 1622 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (d, 3 H, J = 7), 1.04 and 1.24 (s, each, 3 H in total), 1.3–2.8 (m, 9 H), 5.60 (br s, 1 H). Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.16; H, 9.61.

4-Methyl-1,4,5,6,7,7a-hexahydroinden-2(2*H*)-one (22): bp 76–78 °C (0.2 mmHg); IR (CCl_4) 1710, 1625 cm^{-1}; ^1H NMR (CCl_4) δ 0.8–1.2 (m, 3 H), 1.0–3.0 (m, 10 H), 5.60 (br s, 1 H). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.79; H, 9.08.

3,6a-Dimethyl-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (24): bp 66 °C (0.2 mmHg); IR (neat) 1704, 1665 cm^{-1}; ^1H NMR (CCl_4) δ 1.10 (s, 3 H), 1.60 (s, 3 H), 2.17 (br s, 2 H), 1.2–2.7 (m, 6 H). Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.72; H, 9.52.

General Procedure for the Synthesis of γ-Keto Esters from Ketene Silyl Acetals and Conjugated Nitro Olefins. A nitro olefin (1.5 mmol) was added to a solution of $TiCl_4$ (190 mg, 1 mmol) and Ti(*i*-PrO)$_4$ (284 mg, 1 mmol) in dry CH_2Cl_2 (4 mL) under argon at −78 °C. After 10 min of stirring, a ketene silyl acetal (1 mmol) was added dropwise over a 5-min period and the resulting mixture was stirred for an additional hour at −78 °C and then allowed to warm to 0 °C over 2 h. Water (1.5 mL) and DME (4 mL) were added and CH_2Cl_2 was distilled off. The resulting mixture was stirred at reflux for 3 h. The cooled mixture was extracted with ethyl acetate, and the extract was washed with water and saturated brine. Evaporation of the solvent left an oil, which was dissolved in ether (4 mL) and treated with ethereal diazomethane at 0 °C. Removal of the solvent gave an oil which was purified by silica gel TLC (petroleum ether–ether (7:3) as solvent) to afford a γ-keto ester.

The above procedure was also followed in cases where nitro olefins were minor reactants.

Methyl 1-(2-oxopropyl)cyclohexanecarboxylate (29): bp 135 °C (20 mmHg); IR (CCl_4) 1740, 1722 cm^{-1}; ^1H NMR (CCl_4) δ 1.1–2.0 (m, 10 H), 2.00 (s, 3 H), 2.63 (s, 2 H), 3.59 (s, 3 H). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.93; H, 9.28.

Methyl 2-methyl-4-oxohexanoate (34): bp 115 °C (40 mmHg); IR (CCl_4) 1736, 1720 cm^{-1}; ^1H NMR (CCl_4) δ 1.05 (t, 3 H, J = 7), 1.16 (d, 3 H, J = 7), 2.08–3.00 (m, 5 H), 3.61 (s, 3 H). Anal. Calcd for $C_8H_{14}O_3$; C, 60.74; H, 8.92. Found: C, 60.83; H, 8.93.

Methyl 2-(1-methyl-2-oxocyclohexyl)propionate (36) and 7aβ-Hydroxy-3,3aβ-dimethylhexahydrobenzofuran-2(3*H*)-one (37). **36**: bp 140 °C (20 mmHg); IR (CCl_4) 1740, 1716 cm^{-1}; ^1H NMR (CCl_4) δ 0.97–1.20 (m, 6 H), 1.3–2.6 (m, 8 H), 2.95 (q, 1 H, J = 7), 3.55 and 3.59 (s, each, 3 H in total). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.28; H, 8.82. **37**: mp 110–116 °C (recrystallized once from petroleum ether); IR (CCl_4) 3360, 1754 cm^{-1}; ^1H NMR (CCl_4) δ 0.7–2.5 (m, 14 H), 2.7–3.2 (m, 1 H), 3.83 (br s, 1 H, OH). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.07; H, 8.89.

Methyl 2-methyl-2-(2-oxocyclohexyl)propionate (38): bp 120 °C (15 mmHg); IR (CCl_4) 1738, 1724, 1710 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (s, 3 H), 1.18 (s, 3 H), 1.2–3.0 (m, 9 H), 3.62 (s, 3 H). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.89; H, 9.22.

Methyl 4-oxo-2-phenylhexanoate (39): bp 110 °C (0.9 mmHg); IR (CCl_4) 1738, 1722 cm^{-1}; ^1H NMR (CCl_4) δ 1.01 (t, 3 H, J = 7.5), 2.33 (q, 2 H, J = 7.5), 2.48 (dd, 1 H, J = 18 and 4), 3.22 (dd, 1 H, J = 18 and 10), 3.56 (s, 3 H), 4.00 (dd, 1 H, J = 10 and 4), 7.16 (s, 5 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.75; H, 6.99.

Methyl 2-(2-oxopropyl)decanoate (40): bp 100 °C (3 mmHg); IR (CCl_4) 1736, 1724 cm^{-1}; ^1H NMR δ 0.88 (t, 3 H, J = 7), 1.27 (br s, 14 H), 2.05 (s, 3 H), 2.1–3.0 (m, 3 H), 3.67 (s, 3 H). Anal. Calcd for $C_{14}H_{20}O_3$: C, 69.38; H, 10.81. Found: C, 69.26; H, 11.13.

Methyl 2-(2-oxobutyl)decanoate (41): bp 135 °C (2 mmHg); IR (CCl_4) 1736, 1721 cm^{-1}; ^1H NMR (CCl_4) δ 1.01 (t, 3 H, J = 7), 0.7–1.6 (m, 17 H), 2.33 (q, 2 H, J = 7), 2.35–2.9 (m, 3 H), 3.53 (s, 3 H). Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.65; H, 11.21.

Methyl 1-(2-oxobutyl)cyclohexanecarboxylate (42): bp 135 °C (10 mmHg); IR (CCl_4) 1742, 1722 cm^{-1}; ^1H NMR (CCl_4) δ 1.01 (t, 3 H, J = 7), 1.1–2.1 (m, 10 H), 2.30 (q, 2 H, J = 7), 2.60 (s, 2 H), 3.61 (s, 3 H). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.75; H, 9.35.

Methyl 2-vinyl-2-methyl-4-oxopentanoate (43): bp 70 °C (2 mmHg); IR (neat) 1735, 1720 cm^{-1}; ^1H NMR (CCl_4) δ 1.30 (s, 3 H), 2.03 (s, 3 H), 2.62 (d, AB type, 1 H, J = 18), 2.88 (d, AB type, 1 H, J = 18), 3.61 (s, 3 H), 4.99 (d, 1 H, J = 18), 5.00 (d, 1 H, J = 10), 5.96 (dd, 1 H, J = 18 and 10). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.45; H, 8.46.

Spiro[4.5]decane-1,3-dione (44).[31] A mixture of triphenylmethanol (780 mg, 3 mmol) and potassium (100 mg, 2.5 mmol) in dry xylene (8.5 mL) was stirred under argon at reflux for 1 h. A solution of **29** (198 mg, 1 mmol) in dry xylene (2 mL) was added dropwise at reflux over a 50-min period, and the mixture was stirred at reflux for an additional hour. The cooled mixture was extracted with three portions of water (3 mL). The combined aqueous layer was acidified with 20% hydrochloric acid at 0 °C, and the water was evaporated in vacuo to give solids which were purified by silica gel TLC (CH_2Cl_2–ether (2:1) as solvent) yielding 86 mg (52%) of **44**, mp 180.5–181 °C (recrystallized from ethyl acetate–methanol) (lit.[31] mp 180 °C).

3-Methyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one (45).[33,52] A mixture of **35** (92 mg, 0.5 mmol) and active alumina (2 g) in dry benzene (3 mL) was stirred under nitrogen at reflux for 1.5 h. The cooled mixture was filtered, and the solvent was evaporated to give 56 mg (74%) of pure **45**.

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Registry No. 2a, 4749-28-4; **2b**, 2783-12-2; **2c**, 4812-23-1; **2d**, 2562-37-0; **2e**, 36601-70-4; **6**, 6651-36-1; **7**, 6126-53-0; **9**, 19980-35-9; **10**, 19980-34-8; **11**, 55314-45-9; **12**, 60415-92-1; **13** (isomer 1), 60415-93-2; **13** (isomer 2), 60416-03-7; **14** (isomer 1), 60450-46-6; **14** (isomer 2), 60416-04-8; **15**, 60415-94-3; **16**, 60415-95-4; **17**, 88868-96-6; **17** (isomer 2), 88868-97-7; **17** sodium nitronate salt, 88869-11-8; **18**, 60415-96-5; **19** (isomer 1), 88868-98-8; **19** (isomer 2), 88868-99-9; **20**, 60415-97-6; **21** (isomer 1), 60415-98-7; **21** (isomer 2), 60416-05-9; **21**, 88869-00-5; **23**, 60416-00-4; **24**, 60416-01-5; **25**, 1128-08-1; **26**, 34880-70-1; **27**,

32811-25-9; **28**, 40195-26-4; **29**, 75436-61-2; **30**, 31469-15-5; **31**, 40195-27-5; **32**, 88869-01-6; **33**, 75436-68-9; **34**, 75436-59-8; **35** (isomer 1), 88869-02-7; **35** (isomer 2), 88869-03-8; **36** (isomer 1), 88869-04-9; **36** (isomer 2), 88869-05-0; **37** (isomer 1), 88869-06-1; **37** (isomer 2), 88869-07-2; **38**, 75436-65-6; **39**, 84796-94-1; **40**, 75436-60-1; **41**, 88869-08-3; **42**, 88869-09-4; **43**, 75436-67-8; **44**, 88869-10-7; **45**, 15174-78-4; $SnCl_4$, 7646-78-8; $TiCl_4$, 7550-45-0; $AlCl_3$, 7446-70-0; Ti(OPr-*i*)$_4$, 546-68-9; 2-(2-oxobutyl)cyclohexanone, 29943-11-1; 2-(1-methyl-2-oxopropyl)cyclohexanone (isomer 1), 60415-91-0; 2-(1-methyl-2-oxopropyl)cyclohexanone (isomer 2), 60416-02-6; 2-methyl-2-(2-oxopropyl)cyclohexanone, 27943-50-6; 1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one, 39163-29-6; 3-methyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one, 24730-98-1; 7a-methyl-1,4,5,6,7,7a-hexahydro-2*H*-inden-2-one, 16508-51-3; [(6-methyl-1-cyclohexen-1-yl)oxy]trimethylsilane, 19980-33-7; (1-cyclopenten-1-yloxy)trimethylsilane, 19980-43-9; 2,5-undecanedione, 7018-92-0; *cis*-1,6a-dimethyl-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone, 74320-65-3; *trans*-1,6a-dimethyl-4,5,6,6a-tetrahydro-2(1*H*)-pentalenone, 74320-92-6; methyl 2,2-dimethyl-4-oxopentanoate, 66372-99-4; methyl 2,2-dimethyl-4-oxohexanoate, 15118-75-9; methyl 2-phenyl-4-oxopentanoate, 74457-44-6.

Crystal Field of Atypical Low-Spin Ferriheme Complexes†

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Abstract: Recently reported heme model complexes including bis(piperidine) and bis(2-methylimidazole) complexes of (tetraphenylporphyrin)iron(III) and (protoporphyrin IX)iron(III) exhibit electron paramagnetic resonance spectra with unusually large values of g. Previous assignments of the other q values were incorrect, however; these led to the creation of a separate category of HALS (highly anisotropic low spin) complexes. Correct assignment of the g values leads to a crystal field model in which the low-spin complexes all fall into a single continuous category. The values of V/Δ are merely smaller for the so-called HALS species, due primarily to a decrease in V. The more axial nature of the bis(2-methylimidazole) complexes may be due to a difference in the orientation of the planar axial ligands between the bis(imidazole) and bis(2-methylimidazole) complexes.

Introduction

Ferric heme complexes with strong field axial ligands are low spin by EPR and magnetic susceptibility criteria. Griffiths[1] described these complexes by using a hole formulation that considered the low-lying t_{2g} set of d orbitals. Blumberg, Peisach, and co-workers[2,3] have classified low-spin heme complexes by using the tetragonal and rhombic splittings within the t_{2g} set.

Heme proteins such as cytochrome b_5 and cytochrome c are low spin in the native state at neutral pH.[4,5] Other heme proteins such as hemoglobin and myoglobin are low spin in the presence of exogenous ligands such as cyanide or azide.[6,7] The EPR spectra of these proteins is primarily determined by the nature of the axial ligands.[2,3] For example, the EPR spectrum of cytochrome b_5, in which both axial ligands are histidine residues, closely resembles that of (protoporphyrin IX) bis(imidazole)iron(III). Other heme proteins, such as the b cytochromes of the inner mitochondrial membrane, exhibit much greater apparent g tensor anisotropy.[8] Ligand identification in these proteins is uncertain.

Recently, Migata and Iwaizumi[9] reported the EPR parameters of a series of low-spin ferrihemes which they termed "HALS" (highly anisotropic low spin) complexes. These were distinguished from conventional low-spin complexes primarily by the large numerical value of g_z. Crystal field analysis indicated that the tetragonal and rhombic crystal field terms (Δ and V) were both smaller in HALS complexes than conventional low-spin complexes, while the ratio of V to Δ remained relatively constant. The sum of the squares of the coefficients of the basis set of t_{2g} orbitals in the ground-state doublet deviated significantly from unity, an anomaly which the authors attributed to configuration interaction.

In this paper we will show that the crystal field analysis in at least some (and presumably all) of the interesting HALS complexes described by Migata and Iwaizumi is based on an incorrect assignment of g values. The so-called LS and HALS groups are in fact part of a continuous distribution of low-spin complexes all of which are probably well approximated by the t_{2g} hole model.[1,10] The substituted imidazole complexes are of particular interest as models for the b cytochromes of mitochondria, although the analogies between steric hindrance in these complexes and possible restrictions on ligand rotation by a protein are far from perfect.

Experimental Section

(Protoporphyrin IX)iron(III) chloride and nitrogenous bases[11] were obtained from Sigma. (PPIX)$Fe^{III}Cl$ and (tetraphenylporphyrin)iron(III) chloride were the gift of Alan Adler. Dichloroethane, *N*,*N*-dimethylformamide, and dimethyl sulfoxide were used as solvents. Solutions of the complexes were prepared by dissolving the iron porphyrins in dichloroethane solutions of the bases. EPR spectra were recorded by using a Varian E-109 spectrometer. Low temperatures were obtained with an Air Products flowing helium cryostat.

Results

Addition of (PPIX) $Fe^{III}Cl$ and (TPP) $Fe^{III}Cl$ to dichloroethane solutions of imidazole produced red (PPIX) and green (TPP)

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(11) Abbreviations used in this communication are as follows: PPIX, protoporphyrin IX; PPIXDME, protoporphyrin IX dimethyl ester; TPP, tetraphenylporphyrin; ImH, imidazole; 4-Me-ImH, 4-methylimidazole; 4-Ph-ImH, 4-phenylimidazole; N-MeIm, *N*-methylimidazole; 2-Me-ImH, 2-methylimidazole; EPR, electron paramagnetic resonance.

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