Synthesis of α,β-Enoyl-CpFe(CO)(PPh₃)

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An Efficient Synthesis of α,β-enoyl-η⁵-(C₅H₅)Fe(CO)(PPh₃) Complexes

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The α,β-enoyl chiral iron complexes, α,β-enoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1) were prepared from α,β-enoyl-(η⁵-C₅H₅)Fe(CO)₂ (2) and triphenylphosphine through a photochemical ligand substitution followed by carbonylation.

Introduction

Organoiron complexes have been playing an important role in the development of useful methodologies in organic synthesis.[1] Among those organoiron complexes, α,β-enoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1) and related complexes have been studied extensively as effective reagents for stereoselective organic transformations.[2,3]

In 1985, Michael type addition of various nucleophiles to α,β-enoyl-(η⁵-C₅H₅)Fe(CO)₂ (2) and α,β-enoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1) were reported, which opened new routes to β-lactams and chiral carboxylic acid derivatives.[2,3] Since the α,β-enoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1) complex is chiral and can act as an effective stereogenic centers for the newly forming chiral carbon in its stereoselective reactions such as Michael-type additions or Diels-Alder reactions, the efficient preparation of these complexes has significant synthetic value.[3] In addition, α,β-enoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1) was used as an intermediate for synthesis of an chiral iron carbene complex that is useful for cyclopropanation.[4] Therefore we decided to develop an efficient way of synthesis of α,β-enoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1).

Results and Discussion

Davies and Liebskind reported synthetic routes to these complexes based on Peterson's method and aldol condensation (Scheme 1), respectively, using (η⁵-C₅H₅)Fe(CO)(PPh₃)(COCH₃) (3) (CHIRAC) as the starting material.[5,6] The CHIRAC (3) can be prepared from [(η⁵-C₅H₅)Fe(CO)₂]₂ in two steps Eq. (1).[5,6] Although the yields of these reactions are reported to be good, the procedures have drawbacks since
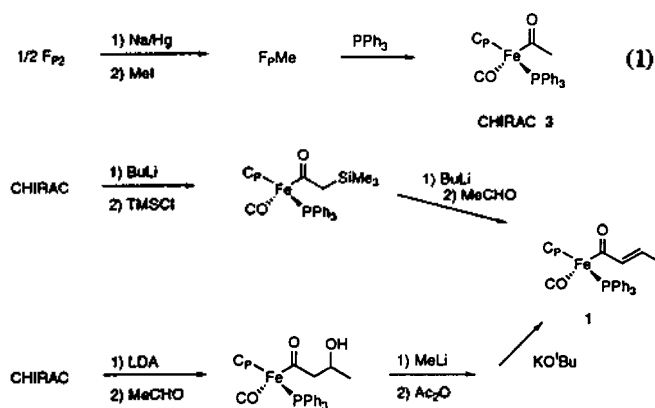
Scheme 1.
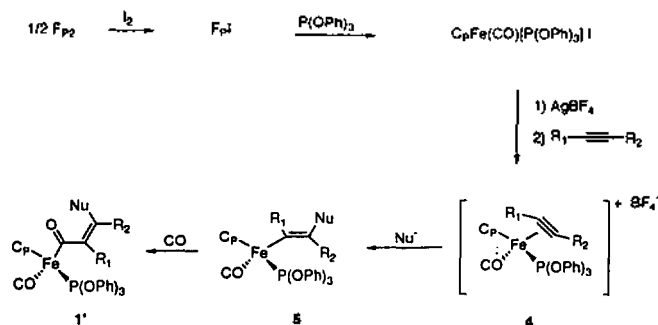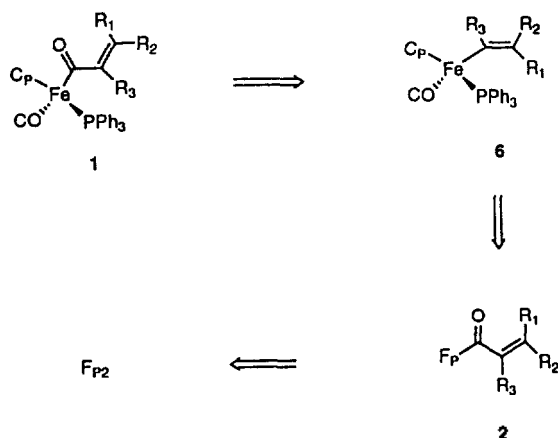
a large amount of an alkyllithium must be used for a practical scale synthesis.

Reger reported an effective route to **1** starting from cationic chiral iron-η²-alkyne complexes, {(η⁵-C₅H₅)Fe(CO)[P(OPh)₃](R₁C≡CR₂)}⁺BF₄⁻ (4), through the nucleophilic addition to **4** and the following oxidative carbonylation of η¹-alkenyl-(η⁵-C₅H₅)Fe(CO)[P(OPh)₃] (5) (Scheme 2).[7] Reger's method is general to a variety of {(η⁵-C₅H₅)Fe(CO)[P(OPh)₃](η²-R₁C≡CR₂)}⁺BF₄⁻ complexes (4). However, this method has limitations, *viz.*, triphenyl phosphite should be used, and the availability of alkynes is not necessarily large. In addition, synthesis of complex **4** requires three steps from [(η⁵-C₅H₅)Fe(CO)₂]₂.

Scheme 2.

Scheme 3.

Table 1. Synthesis of α,β-Enoyl-[η⁵-C₅H₅)Fe(CO)(PPh₃)]

Entry	R^1	R^2	R^3	Conditions[a]		Catalyst/mol%		Isolated
				Temp/°C	Time/h	Ce(IV)	AgBF₄	Yield (%)
1-a	H	Ph	H	25	15	10		50
"				25	15		10	10
1-b	Me	H	H					
1-c	H	Me	H					
1-b&c				25	15	15		68
"				25	15		20	28
1-d	Me	Me	H	−78	15	15		79
"				−78	15		15	68

[a] Typical reactions were run with 1.0 mmol of α,β-enoyl-(η⁵-C₅H₅)Fe(CO)₂ and 1.15 mmol of triphenylphosphine without isolation of η¹-alkenyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) after the photolysis.

Scheme 4.

As we found that α,β-enoyl-(η⁵-C₅H₅)Fe(CO)₂ complexes (**2**) were readily prepared by the reaction of α,β-enoyl chlorides with Na[(η⁵-C₅H₅)Fe(CO)₂] followed by a flash chromatography on silica gel in good yields,[2] we examined a short-cut route to chiral α,β-enoyliron complexes (**1**) from **2**. Our synthetic route includes the photochemical ligand substitution of α,β-enoyl-(η⁵-C₅H₅)Fe(CO)₂ (**2**) and the oxidative carbonylation of η¹-alkenyl-[(η⁵-C₅H₅)Fe(CO)(PPh₃)] (**6**), as shown in Scheme 3.
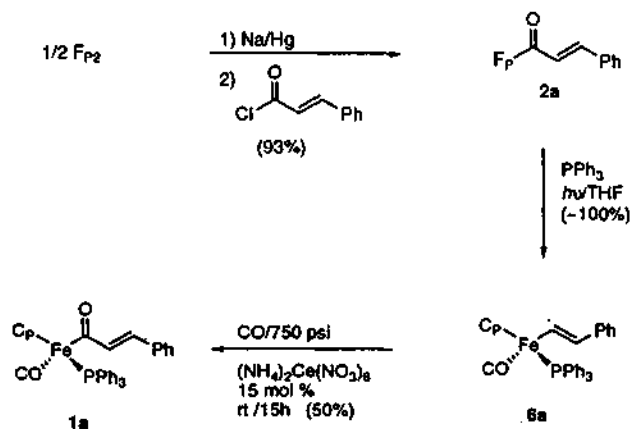
Through the proposed synthetic pathway, desired chiral α,β-enoyliron complexes (**1**) were obtained in two steps from the readily available α,β-enoyl-(η⁵-C₅H₅)Fe(CO)₂ (**2**). The intermediate chiral η¹-alkenyliron complexes (**6**) can be isolated. However, the isolation of **6** is not always necessary for the synthesis of **1**. Thus usually an oxidant was added to the reaction mixture of photolysis and the mixture was stirred under carbon monoxide in an autoclave.

As a typical example, using a pyrex reaction vessel with Hg-arc lamp, photolysis (>280 nm) of the yellow solution of cinnamoyl-η⁵-(C₅H₅)Fe(CO)₂ (**2a**) and triphenylphosphine in tetrahydrofuran gave a chiral styryliron complex, η¹-β-styryl-(η⁵-C₅H₅)Fe(CO)(PPh₃): (**6a**), as orange powder in quantitative yield. The carbonylation of 6a in the presence of ammonium cerium(IV) nitrate, (NH₄)₂Ce(NO₃)₆, (15 mol%) in tetrahydrofuran or acetonitrile at room temperature under carbon monoxide (51 atm, 750 psi) for 15 h gave a chiral cinnamoyliron complex, *E*-cinnamoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (**1a**), in 50% yield. In a similar manner, crotonyl and 3-methylcrotonoyliron complexes (**1b-d**) were synthesized in 68 and 79%

yields, respectively.

Although the oxidative carbonylations were carried out at room temperature for the syntheses of cinnamoyl and crotonyliron complexes (**1a-c**), the reaction of 3-methylcrotonoyliron complex (**1d**) proceeded smoothly at −78°C. Typical results are summarized in Table 1.

As catalysts for the oxidative carbonylation process, ammonium cerium(IV) nitrate, silver tetrafluoroborate and boron trifluoride etherate were examined. The ammonium cerium(IV) nitrate and silver tetrafluoroborate were active while boron trifluoride etherate was inactive. As shown in Table 1, the ammonium cerium(IV) nitrate gave better yields than silver tetrafluoroborate. The yields are dependent on the amount of catalyst, but the use of more than 15 mol% of catalyst does not give any better results.

Experimental

Tetrahydrofuran was freshly distilled from sodium/benzophenone under nitrogen. The following chemicals were purchased from Aldrich and used as received: boron trifluoride etherate, triphenylphosphine, Fp dimer, ammonium cerium (IV) nitrate, silver tetrafluoroborate and acid chlorides except cinnamoyl chloride which was prepared from cinnamic acid by a standard procedure.[8] Activated neutral alumina and ba-

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sic alumina, 80-200 mesh, were purchased from Fisher Scientific Co. Silica gel 60, 230-400 mesh, was purchased from Brinkmann Instruments Inc. Infrared spectra were recorded on a Perkin-Elmer 1310 infrared spectrophotometer or a BIO-RAD FTS 7PC. NMR spectra were measured at 80 MHz on a Bruker WP 80 CW or a Varian CFT-80 spectrometer, at 300 MHz on a Nicolet NT 300 spectrometer or a General Electric QE 300 spectrometer. All ¹H NMR absorptions were expressed in parts per million (δ) relative to tetramethylsilane (Me₄Si) as an internal standard. All ³¹P NMR absorptions were expressed in parts per million (δ) relative to 85% phosphoric acid (H₃PO₄) as an external standard. Melting points were determined on a Thomas Hoover capillary melting point apparatus and reported uncorrected. Analytical TLC was conducted on precoated aluminum plates available from E. M. Chemicals (silica gel 60 F254 or neutral aluminiumoxide 60 F245). Combustion analyses were performed by M-H-W Laboratories in Phoenix, AZ. All reactions were run under a nitrogen atmosphere with a mineral oil bubbler so the system was maintained under a positive nitrogen pressure unless otherwise stated.

Preparation of (η⁵-C₅H₅)Fe(CO)(PPh₃)(COCH : CHPh) (1a).³ᵉ,³ᶠ A pyrex photoreaction vessel containing a yellow solution of triphenylphosphine (301.6 mg, 1.15 mmol) and cinnamoyl-(η⁵-C₅H₅)Fe(CO)₂ (308 mg, 1.0 mmol) in degassed THF (35 m*l*), which was equipped with tap-water cooling jacket and a magnetic stirrer, was irradiated with 550 W Hg-arc lamp for two hours. The resulting red solution was transferred to a pyrex reaction vessel in a stainless steel autoclave and ammonium cerium(IV) nitrate (82 mg, 15 mol%) was added to it. After the air was substituted by carbon monoxide, the autoclave was pressurized with carbon monoxide (750 psi; 51 bar) and the reaction mixture was stirred for 20 h at room temperature. Then, carbon monoxide was discharged and water (15 m*l*) was added to the reaction mixture. The mixure was extracted with dichloromethane (25 m*l*×3), dried over anhydrous sodium sulfate, and solvent was removed to give a crude product (1a) as brown oil, which was purified on neutral alumina column with hexane-ethyl acetate as eluent (hexane/EtOAc=5) to yield pure (*E*)-cinnamoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1a) (272 mg, 50%) as orange soild: mp. (dec.) 122-125 ℃ ; IR (KBr plate, v_{CO}, cm⁻¹) 1920, 1610; ¹H NMR (CDCl₃, TMS, δ) 4.48 (d, J=1.2 Hz, 5H, Cp), 6.05 (d, J=16 Hz, 1H, -CH=), 7.0 (d, J=16 Hz, 1H, -CH=), 7.2-7.6 (m, 20H, Ph); ³¹P NMR (acetone-d_6, H₃PO₄ (external, 85%), δ) 80.6 (s).

Preparation of (η⁵-C₅H₅)Fe(CO)(PPh₃)(CH : CHPh)(6 a). Although the procedure described above does not require the isolation of stylyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (6a), this complex was isolated from the reaction mixture of photolysis as stable orange solid (510 mg, 98%) through a chromatographic separation on a neutral alumina column: mp. 152-155 ℃ (dec.); IR (KBr plate, v_{CO}, cm⁻¹) 1930; ¹H NMR (CDCl₃, TMS, δ) 4.41 (d, J=1.2 Hz, 5H, Cp), 6.36 (dd, J=17, 3 Hz, 1H, -CH=), 7.2-7.7 (m, 20H, Ph), 7.96 (dd, J=17, 6 Hz, 1H, -CH=).

Preparation of (η⁵-C₅H₅)Fe(CO)(PPh₃)(COCH : CHMe) (1b, 1c).³ᵇ,³ᵉ In the same method to that for the preparation of cinnamoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1a), the solution of triphenylphosphine (302 mg, 1.15 mmole) and (η⁵-C₅H₅)Fe(CO)₂(COCH : CHMe) (260 mg, 1 mmole) in THF (35

m*l*) was irradiated, and then the resulting red solution was carbonylated. The workup and column chromatography on neutral alumina, which are the same as above, gave (*E*)-and (Z)-crotonyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1b, 1c) (Z/E=5/2) (327 mg, 68%). Z isomer (1b): mp. (dec.) 149-151 ℃ ; IR (KBr plate, v_{CO}, cm⁻¹) 1915, 1620; ¹H NMR (CDCl₃, TMS, δ) 1.31 (dd, J=7.0, 1.3 Hz, 3H, Me), 4.41 (d, J=1.1 Hz, 5H, Cp), 4.72 (dq, J=12.0, 7.0 Hz, 1H, =CH-), 6.54 (dq, J=12.0, 1.3 Hz, 1H, =CH-), 7.3-7.6 (m, 15H, Ph). *E* isomer (1c): mp. 137-139℃ ; IR (KBr plate, v_{CO}, cm⁻¹) 1913, 1623; ¹H NMR (CDCl₃, TMS, δ) 1.56 (dd, J=6.8, 1.5 Hz, 3H, Me), 4.42 (d, J=1.2 Hz, 5H, Cp), 5.47 (dq, J=15.0, 6.8 Hz, 1H, =CH-), 6.47 (dq, J=15.0, 1.5 Hz, 1H, =CH-), 7.3-7.5 (m, 15H, Ph).

Preparation of (η⁵-C₅H₅)Fe(CO)(PPh₃)(COCH : CMe₂) (1d). In a manner similar to that for the preparation of cinnamoyl-(η⁵-C₅H₅)Fe(CO)(PPh₃) (1a), the solution of triphenylphosphine (302 mg, 1.15 mmole) and 3-methylcrotonoyl-Fp (260 mg, 1.0 mmole) was irradiated and the resulting red solution was carbonylated at −78 ℃. The workup and column chromatography on neutral alumina, which are same as above, gave 3-methylcrotonoyl-(η⁵-C₅H₅)-Fe(CO)(PPh₃) (1d) (392 mg, 79.3%) as an orange powder: mp. (dec.) 126-127 ℃ ; IR (KBr plate, v_{CO}, cm⁻¹) 1913, 1623; ¹H NMR (CDCl₃, TMS, δ) 7.5-7.2 (m, 15H, Ph), 6.57 (m, 1H, -COCH=), 4.41 (d, J_{PH}= 1.2 Hz, 5H, Cp), 1.55 (d, J=1.0 Hz, 3H, Me), 1.26 (d, J=1.0 Hz, 3H, Me); ³¹P {¹H} NMR (Acetone-d_6, H₃PO₄ (85%, external), δ) 80.5 (s). Anal. Calcd. for C₂₉H₂₇FeO₂P: C, 70.46; H, 5.51; P, 6.27. Found: C, 70.28; H, 5.66; P, 6.50.

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Molecular Dynamics Simulation on thermodynamic and Structural Properties of Liquid Hydrocarbons : Normal Alkanes

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A series of aliphatic hydrocarbons, methane to hexane in the liquid state, are modeled with the molecular mechanical potential parameters treating all hydrogen degrees of freedom explicitly. Thermodynamic properties (heat capacities and heats of vaporization) are calculated from relatively short (20ps) molecular dynamics trajectories. The liquid state structures are also examined through various radial distribution functions. Molecular dynamics simulations reproduce experimentally measured properties within a few percent errors, thus indicate that the present set of all-hydrogen parameters is suitable for simulating macromolecular systems in bulk.

Introduction

A detailed model for complex organic and biochemical systems includes not only reactants but also surrounding molecules acting as solvent. A complete description of such a system as bulk matter would contain sub-Avogadro's number of atoms, $\sim 10.^{22}$ For each atom, we have to deal with 6 phase space coordinates (position and velocity) while carrying out molecular dynamics simulations.

One way to approach to the problem of 10^{22} degrees of freedom is to utilize the model system with a stochastic boundary. Only a part of the universe within the boundary is simulated with the normal molecular dynamics and the rest is regarded as the stochastic thermal bath to the system.[1] Another way is to set up a periodic boundary surrounding the system of interests.[2] We need to include 1,000 to 10,000 atoms within the boundary depending on the problem at hand. The problem of a bulk system can be safely reduced to 10^4 degrees of freedom in size.

Commonly used theoretical methodologies in molecular simulations are Monte Carlo (MC) and molecular dynamics (MD). Both methods are based on a molecular mechanical energy function designed to handle thousands of degrees of freedom efficiently. The Born-Oppenheimer potential surface is parameterized with a standard form of empirical potential function. Through molecular simulations, we generate or sample phase space trajectories over the potential energy surface.

With limited computing resources, we have been using the united atom representation of molecules with polar hydrogen parameters. In the polar hydrogen model, nonpolar hydrogen is merged into the heavy atom that binds the hydrogen. For example, the methyl group is replaced with one atom that represents the force field of CH_3 moiety. The united atom representation has certain advantages in reducing

computational demands with sacrificing less important degrees of freedom such as CH stretching or HCH bending motions. The previous MC simulation showed that a variety of thermodynamic and conformational properties of molecular systems could be calculated with a few percent errors using the united atom model.[3]

With much increased computing resources enough to fulfill the needs of extended molecular simulations, it is desired to include all degrees of freedom explicitly. All-hydrogen parameters are under development. Harvard group have made a preliminary release of all-hydrogen parameter sets for protein, nucleic acid and lipid simulations and is about to complete such the task.[4]

As a part of all-hydrogen parameter development efforts, it is appropriate and necessary to perform molecular simulations with the subset of parameters for model compounds. In this work, we have carried out molecular dynamics simulations on a series of saturated hydrocarbons. Thermodynamic and structural properties of the liquid state of methane to hexane series are evaluated from the dynamics trajectories. Comparison to known experimental results provides an indicator for goodness of the all-hydrogen parameter set.

Hydrocarbon is the backbone in most organic molecular structure and therefore the present work is considered to be the first step forward to developing molecular models for organic solvents.

Theory and Computational Methods

Molecular Model. The standard all-hydrogen potential function of CHARMM (Chemistry at HARvard Macromolecular Mechanics)[5] is employed to build molecular models for the series of hydrocarbons. The empirical energy function is partitioned as