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A new synthesis of diferrocenylketones

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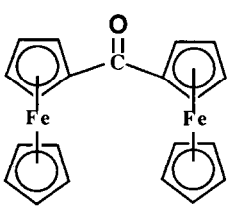
Abstract

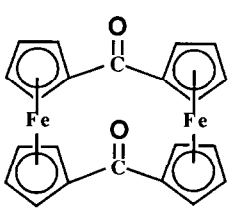
Diferrocenylketone (I) and [1.1]ferrocenophane-1,12-dione (II) have been obtained in 86% and 13% yields, respectively, via a simple route analogous to the Barbier synthesis involving *N,N*-disubstituted carbamylchlorides and the appropriate bromoferrocene derivatives.

Introduction

In our efforts to synthesize new carbonyl bridged biferrocene and ferrocenophane systems, we have developed new, simple syntheses of both diferrocenylketone and [1.1]-ferrocenophane-1,12-dione. This synthetic route is unique in that it not only provides a convenient preparation of these compounds but it also illustrates the use of butyllithium in place of lithium metal in Barbier-like reactions. The Barbier synthesis consists of the formation of a organolithium or Grignard reagent in the presence of a carbonyl compound to produce a ketone. The organolithium or Grignard species, usually generated by employing lithium metal or magnesium metal, subsequently reacts by way of a radical mechanism with the carbonyl compound to form the ketone. Our results illustrate that this type of reaction mechanism can take plaze by utilizing butyllithium.



I



II

Diferrocenylketone (I) has previously been prepared via Friedel–Crafts acylations [1–4] and via oxidations of diferrocenylcarbinol [5,6]; however, reported here is a one-step synthesis utilizing a radical species formed in the metal–halogen exchange reaction and a disubstituted carbamylchloride.

One of the first preparations of diferrocenylketone was via a Friedel–Crafts reaction. Ferrocene was treated with aluminum trichloride, and oxalyl chloride [4]

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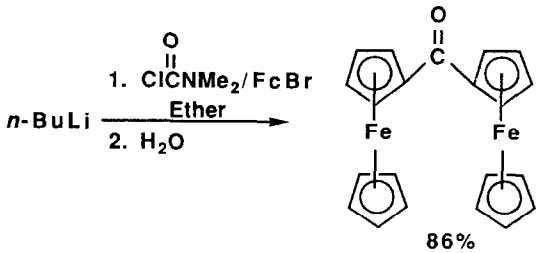
or phosgene [1] which resulted in low yields of the ketone. This reaction also has the disadvantage of working with highly toxic and dangerous reagents. A more commonly used acylation is the reaction between ferrocenecarboxaldehyde [5,7–15] and ferrocene in the presence of $AlCl_3$ to yield diferrocenylcarbinol [5,6]. Reported diferrocenylcarbinol yields are comparable to our results; however, the overall conversion to the alcohol is lower and the alcohol must still undergo an oxidation step to the ketone. An analogous procedure reacts ferrocenylcarboxylic acid [2,16] with phosphorus pentachloride and ferrocene in the presence of $AlCl_3$ to obtain diferrocenylketone in a considerably lower yield.

The method presented, utilizing bromoferrocene, butyllithium, and a carbamyl chloride, resembles the Barbier synthesis by the formation of a radical species in the presence of *N*,*N*-dimethyl carbamylchloride and their subsequent reaction to give diferrocenylketone (I).



This route was then employed to obtain the highly desirable [1.1]ferrocenophane-1,12-dione (II). Previous preparations of the diketone involve more expensive and difficult to prepare precursors [19–21]. One of the first preparations of [1.1]ferrocenophane-1,12-dione involves the Friedel–Crafts reaction between ferrocene and 1,1′-bis(chlorocarbonyl)ferrocene in the presence of $AlCl_3$ to yield between 3 and 7% of the desired diketone [19,20]. Another procedure involves the oxidation of [1.1]ferrocenophane with MnO_2 to yield an impressive 89% of the diketone [20]; however, the starting ferrocenophane system is not trivial to prepare [22].

Results and discussion

Ferrocenyllithium, obtained from bromoferrocene [17] and butyllithium, was treated with a series of carbonyl reagents in order to obtain the diferrocenylketone. *N*,*N*-Diethylcarbamyl chloride, *N*,*N*-dimethylcarbamyl chloride, diethyl carbonate, and carbon dioxide gas have all been used in attempts to the synthesize the ketone. The carbamylchloride reagents did produce diferrocenylketone in low yield along with equivalent amounts of ferrocenemonocarboxylic acid. Trace amounts of triferrocenylmethanol, n-butylferrocenylketone, and *N*,*N*-dimethyl (or diethyl) ferrocenyl amide were all identified by ^1H NMR and mass spectra. The carbonate and $CO_{2(g)}$ reagents produced ferrocenemonocarboxylic acid as the major product.

The results of these experiments prompted us to change our sequence of addition in the reaction. Bromoferrocene and *N*,*N*-dimethylcarbamylchloride (or *N*,*N*-diethylcarbamylchloride) in dry THF was added dropwise to a cooled solution of n-butyllithium in hexanes to give the desired diferrocenylketone as well as two other products. The reaction mixture was separated by flash chromatography [18] to yield the starting material, bromoferrocene, a small amount of the mixed n-butylfer-

rocenylketone, and diferrocenylketone in 86% recovered yield. An attempt to obtain quantitative yield by increasing the amount of n-butyllithium failed to produce more of the ketone and prevented the recovery of any starting material.

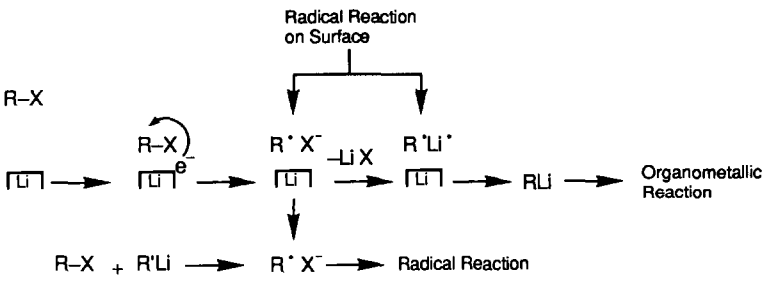
This procedure was then employed to obtain [1.1]ferrocenophane-1,12-dione by replacing the bromoferrocene with 1,1′-dibromoferrocene. The diketone was obtained in 9–10% yield, (13.3% yield based on recovered 1,1′-dibromoferrocene) along with a series of substituted biferrocene derivatives and recovery of 30–40% 1,1′-dibromoferrocene. Extensive studies utilizing 1,1′-diiodoferrocene failed to produce any of the desired diketone, however they did produce several mono- and disubstituted biferrocenylketones.

The preparation of diferrocenylketone via a carbamylchloride from the described reaction not only provides a new, improved, one-step synthesis of diferrocenylketone but also indicates that *N*,*N*-disubstituted carbamylchlorides are useful reagents in ketone synthesis. More importantly, to the best of our knowledge, this is the first time a Barbier-like reaction has been achieved by utilizing n-butylithium as a substitute for lithium metal.

Molle and Bauer have demonstrated that the Barbier synthesis may not actually contain a typical form of the organometallic compound [23]. They have demonstrated that a radical pathway can exist involving a radical anion ($R^{\cdot}X^{-}$) which is subsequently trapped by a carbonyl compound or radical ketyl species to produce the new carbonyl compound.

General theories on the mechanism of the Barbier synthesis include an *in situ* generation of an organometallic compound, although this has never been explicitly shown [24–26]. Scheme 1 illustrates a series of steps where an anion radical ($R^{\cdot}X^{-}$) forms on the metal surface as a result of a single electron transfer between the metal and the halide. This anion radical can react with the carbonyl compound, ketyl-like radical or evolve into an intimate pair of radicals ($R^{\cdot}Li^{\cdot}$) to produce the organometallic compound that then reacts with the carbonyl compound.

Utilizing an adamantane system and varying the sequence of addition of the lithium metal and the ketone reagent, Molle and Bauer concluded that no organometallic compound formation was observed for the Barbier reaction. The products obtained were representative of a radical pathway that impedes the formation of the organolithium compound. Looking for an alternative radical route, they then investigated the formation of a radical ketyl from the ketone reagents and subsequent reaction with an alkyl halide. They obtained products that typified the presence of ketyl radicals. Early hypotheses on the Barbier mechanism proposed the



Scheme 1

formation of ketyl radicals and subsequent reaction with an alkyl halide to produce the corresponding alcohol [27]. Experiments by Molle and Bauer [23] indicated that although ketyl radicals did exist, they did not react with aryl or alkyl halides, and that only pinacol products formed.

Combining this information of the lack of formation of an organolithium compound, presence of ketyl radicals, and that the ketyl radical does not react with an aryl or alkyl halide, Molle and Bauer proposed a mechanism whereby a reaction between the ketyl radicals and the transitory species ($R^{\cdot}X^{-}$ or $R^{\cdot}Li^{+}/Li$) of the organometallic compound occurs to produce the final product. Further work by Molle and Bauer demonstrated that this radical pathway can often be in competition with an organometallic pathway and that with different compounds and conditions the formation of the organometallic species prevails. It is the stability of the radical anion or transitory radical species that can determine the pathway as radical or organometallic. When the radical species stability increases, the radical pathway is favored over the organometallic pathway and *vice versa*.

Comparing this information to the ferrocenyl systems there are two important points to note. To the best of our knowledge, this is the first time that a Barbier-type synthesis has been achieved with an alkyllithium reagent versus lithium metal. This may not be unexpected as it is well established [28–32] that free radicals are formed during metal–halogen exchange reactions involving alkyllithium compounds with alkyl halides. Generally their formation has been associated with Wurtz-type coupling reactions. However studies involving observation of nuclear polarization in NMR spectra [28,31] (CIDNP; Chemically Induced Dynamic Nuclear Polarization) and ESR spectroscopy [30] verify the detection of radical intermediates. Therefore, a route involving alkyllithium reagents can involve unpaired electron species and a radical pathway must be included in discussions of mechanisms of such reactions. It would be interesting to investigate the reaction of the adamantane system in the presence of an alkyllithium species and compare the results to Molle and Bauer's work.

Secondly, it is feasible that the formation of diferrocenyl ketone occurs via an analogous mechanism to the one proposed by Garst and modified by Molle and Bauer. In our initial work on the ferrocenylketone systems, attempts were made to first prepare the ferrocenyllithium species and follow its preparation with the addition of the carbonyl compound to form the ketone. Little or no formation of the desired ketone occurred in this case. However, when Barbier-like conditions were employed with the ferrocenyl systems, good yields of the desired ketones were produced. This work leads us to propose for the diferrocenylketone system that the radical pathway is favored over the organometallic pathway and the mechanism is similar to the one suggested by Garst, and Molle and Bauer. It is probably the transitory [$Fc^{\cdot}Br^{-}$] species that reacts directly with the carbonyl compound or the ketyl-like radical formed from the carbonyl compound to yield the desired diferrocenylketone.

This study has provided a new one-step high yielding synthesis of diferrocenylketone. It has also illustrated that a Barbier type of synthesis is a valuble method of preparing ketones and that carbamylchlorides are useful reagents in such reactions. The results demonstrate that alkyllithium compounds can be substituted in some cases for lithium metal and that the mechanism involved favors a radical pathway over an organometallic pathway.

Experimental

All reactions were carried out under prepurified argon. Solvents were dried and purifed by distillation from sodium. Infrared spectra were recorded on a Mattson Instruments Polaris Nu-10000 FT-IR spectrometer with an IR-12050 detector or a Perkin-Elmer 339B spectrophotometer; ^{1}H NMR spectra were obtained on a Varian XL-400 (400 MHz) spectrometer with tetramethylsilane as an internal standard. Low-resolution mass spectra were obtained on a VG Instruments 70-S gas chromatograph/mass spectrometer at the Johns Hopkins University.

Preparation of diferrocenylketone

Butyllithium (4 ml, 2.5 *M*, 10 mmol) was cooled to −10 °C in a 100 ml, three-neck, round-bottom flask equipped with stir bar, gas adapter, and septum. A solution of bromoferrocene (2.65 g, 10 mmol) and freshly distilled *N*,*N*-dimethylcarbamyl chloride (0.46 ml, 5 mmol) in 15 ml of dry THF was added dropwise via syringe over 30 min. The reaction was stirred at −10 °C under argon for 90 min then was slowly warmed to room temperature. The reaction mixture was treated with H_2O (4 ml) followed by 3.5 *M* HCL (4 ml) and this procedure was repeated twice. An additional 70 ml of H_2O was added. The reaction mixture was extracted with ether (3x, 50 ml). The combined ether layers were dried over $CaCl_2$ and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on silica. Elution began with 98% hexanes/2% ethyl acetate and the polarity was slowly increased with ethyl acetate. The first band was bromoferrocene (1.05 g, 39%). The second band was an oil, n-butylferrocenylketone (0.150 g, 5.5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (2H, t), 4.49 (2H, t), 4.20 (5H, s), 2.70 (2H, t), 1.70 (2H, m), 1.42 (2H, m), 0.97 (3H,t); MS *m/z* (relative intensity) 270(100), 213(20), 185(29). The third band was diferrocenylketone (0.86 g, 43%/86% based on recovered starting material); m.p. 209–210 °C (lit [1] m.p. 210–211 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (4H, t), 4.56 (4H, t), 4.233 (10H, s); IR (solid sample, cm^{-1}) 3208, 3125, 1610, 1467, 1295, 1203, 1056, 808, 580, 481; mass spectrum, *m/z* (relative intensity) 398 (100), 305 (15), 186 (9).

Preparation of [1.1]ferrocenophane-1,12-dione

Butyl lithium (2 ml, 2.5 *M*, 5 mmol) was cooled to −10 to −15 °C in a 100 ml, three-neck, round-bottom flask, equipped with a stir bar, gas adapter, and septum. A solution of freshly sublimed 1,1′-dibromoferrocene (0.8 g, 2.3 mmol) and freshly distilled dimethylcarbamyl chloride (0.21 ml, 2.3 mmol) was dissolved into 5 ml of dry THF and added dropwise via a syringe over a period of five min. The reaction was maintained at −10 °C for 1 h and then slowly warmed to 0 °C. Five milliliters of H_2O were added in 1 ml portions and the solution stirred for 15 min. A precipitate formed and was filtered, repeatedly washed with ether, and determined to be [1.1]-ferrocenophane-1,12-dione (46 mg, 9.3%, 13.3% based on recovered starting material); ^{1}H NMR (400 MHz, C_6D_6) δ 4.51 (8H, t), 4.92 (8H, t); MS *m/z* (relative intensity) 425 (29), 424 (100), 422 (13), 330 (11). IR (KBr, cm^{-1}) 3140, 1610, 1600, 1475, 1470, 1300, 1070, 815, 508, 480. The organic solution was extracted with H_2O (3x, 30 ml). The combined H_2O layers were then back extracted with ether (50 ml). The combined organic layers were dried over sodium sulfite, filtered, and solvent removed *in vacuo* to yield a red oily residue. This material was

subjected to flash chromatography to yield recovered 1,1′-dibromoferrocene and a series of six substituted ferrocenes and biferrocenes. The first band was determined to be recovered 1,1′-dibromoferrocene (0.24 g, 30%). The subsequent bands are as follows: ferrocenylbutylketone (50 mg, 8%), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (2H,t), 4.42 (2H,t), 4.13 (5H,s), 2.64 (2H,t), 1.63 (2H,quintet), 1.36–1.34, overlapping multiplets, (2H,m), 0.90 (3H,t); MS *m/z* (relative intensity) 271(19), 270(100), 228(19), 185(28), 121(26), 56(21); bis-1,1′-(1-oxopentyl)ferrocene (65 mg, 8%), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (4H,t), 4.41 (4H,t), 2.59 (4H,t), 1.61 (4H,m), 1.36–1.34 (4H,m), 0.90 (6H,t); MS *m/z* (relative intensity) 355(24), 354(100), 121(21), 56(10); 1′,6′-bis-(1-oxopentyl)diferrocenylketone (160 mg, 25%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (4H,t), 4.75 (4H,t), 4.54 (4H,t), 4.46 (4H,t), 2.60 (4H,t), 1.63 (4H,m), 1.37 (4H,m), 0.94 (6H,t); MS *m/z* (relative intensity) 567(21), 566(57), 417(28), 325(15), 241(10), 86(42), 84(65), 51(33), 49(100); 1′,6′-bis(dimethylamide)diferrocenylketone (50 mg, 8%), ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (4H,t), 4.62 (4H,t), 4.61 (4H,t), 4.30 (4H,t), 3.02 (24H,m); MS *m/z* (relative intensity) 541(36), 540(100), 404(43), 312(27). Trace amounts of trisubstituted ferrocenes and biferrocenes were also determined by mass spectrum and ^{1}H NMR.

Acknowledgement

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