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The preparation of (5-aryl-3-isoxazolyl)-ferrocenes from dilithiated acetylferrocene oxime and aromatic esters

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Abstract

Acetylferrocene oxime was dilithiated with excess lithium diisopropylamide and the resulting C(α),O-dilithiated oxime was condensed at the carbanion-type center with aromatic esters to yield C-acylated intermediates that were quenched and acid-cyclized to the (5-aryl-3-isoxazolyl)-ferrocenes (isoxazolyl-ferrocenes). The resulting products were isolated in yields ranging from 20–76% and purified by recrystallization from ethanol.

Keywords: Iron; Lithium; Metallocenes; (5-Aryl-3-isoxazolyl)-ferrocenes; C(α),O-dilithiated oxime of acetylferrocene; C-Acylation/cyclodehydration

1. Introduction

Recently, two methods have been reported for the preparation of (5-aryl-3-isoxazolyl)-ferrocenes [1] and/or (3-aryl-5-isoxazolyl)-ferrocenes [2], referred to as isoxazolyl-ferrocenes. In the first method, (1-oxo-3-aryl-2-propenyl)-ferrocenes (cinnamoyl ferrocenes) were condensed with hydroxylamine to give 1,2- and 1,4-addition products that were then cyclized to the isomeric dihydroisoxazolyl-ferrocenes. The dihydroisoxazolyl-ferrocenes were oxidized to isoxazolyl-ferrocenes, which were separated by preparative TLC (eluting with benzene) (Eq. (1), Method 1). Due to the similar physical properties of the isoxazolyl-ferrocenes and the possibility of numerous side reactions, low yields were obtained by this procedure. This overall method of 1,2- and 1,4-conjugate addition of hydroxylamine has a history of being conducive for the preparation of dihydroisoxazoles (isoxazolines) instead of isoxazoles [3]. The second method involves ethynyl-ferrocene that underwent 1,3-dipolar cycloadditions with benzonitrile N-oxides for the preparation of (3-aryl-5-isoxazolyl)-ferrocenes, which were free from isomeric (5-aryl-3-isoxazolyl)-ferrocenes (Eq. (1), Method 2). While this is one of the syntheses available for the preparation of primarily unsymmetrical isoxazoles [4], its use for the preparation of isoxazolyl-ferrocenes depends on the availability of starting materials and making cyano N-oxides [2,5].

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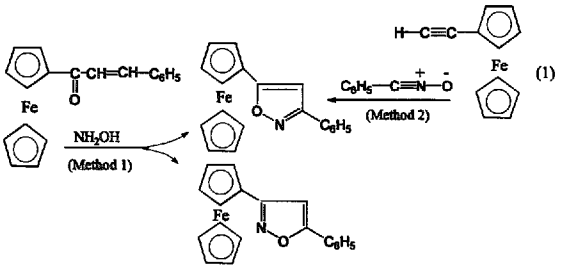


One of the favored traditional preparations of unsymmetrical isoxazoles involves the condensation/cyclization of unsymmetrical 1,3-diketones with hydroxylamine [6]. Even with this straightforward condensation procedure, the problem of separating similar isomeric isoxazole products adds an additional task. Also, this preparative method has only been used for making isoxazolyl-ferrocenes, which have resulted from the condensation of (1,3-dioxobutyl)-ferrocene (acetoacetyl-ferrocene) with hydroxylamine and two products resulted [7]. Other preparations of (1,3-dioxo-3-arylpropyl)-ferrocenes (aroylacetyl-ferrocenes) are known, such as the strong base condensation of acetylferrocene with benzoate esters [8], but their subsequent reaction with hydroxylamine has not been reported.

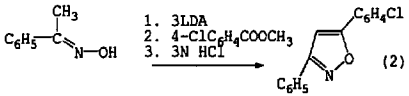
An unequivocal strong-base method for the preparation of unsymmetrical 3,5-disubstituted isoxazoles has been developed where C(α),O-oximes of ketones, such as acetophenone, were dilithiated with excess lithium diisopropylamide (LDA) (oxime:LDA = 1:3) or an equivalent amount of *n*-butyllithium (oxime:^{n}BuLi = 1:2). This was followed by condensation with esters, such as methyl 4-chlorobenzoate, to give C-acylated intermediates that were cyclodehydrated with dilute acid

Table 1
(5-Aryl-3-isoxazolyl)-ferrocenes from dilithiated acetylferrocene oxime illustrated in Eq. (3)

Prod. no.	Ar	Molecular formula	Yield (%)	M.p. (°C)	Combust. Anal. Found/(calc.)		
					C	H	N
1	C_6H_5	$C_{19}H_{15}FeNO$	53	179–181 [a,b]	—	—	—
2	4-$CH_3C_6H_4$	$C_{20}H_{18}FeNO$	76	184–185	69.41 (69.79)	5.16 (5.27)	4.00 (4.07)
3	3-$CH_3C_6H_4$	$C_{20}H_{18}FeNO$	36	152–155	69.65 (69.79)	5.51 (5.27)	4.01 (4.07)
4	3,5-$(CH_3)_2C_6H_3$	$C_{21}H_{19}FeNO$	29	132–134	70.24 (70.61)	5.60 (5.36)	3.82 (3.92)
5	4-$(CH_3)_3CC_6H_4$	$C_{21}H_{23}FeNO$	72	178–181	71.55 (71.70)	6.22 (6.02)	3.51 (3.64)
6	4-$CH_3OC_6H_4$	$C_{20}H_{17}FeNO_2$	46	163–165	66.74 (66.88)	5.16 (4.77)	3.79 (3.90)
7	3,4-$(CH_30)_2C_6H_3$	$C_{21}H_{19}FeNO_3$	46	171–173	64.57 (64.80)	5.09 (4.92)	3.34 (3.60)
8	3,4,5-$(CH_3O)_3C_6H_2$	$C_{22}H_{21}FeNO_4$ [c]	20	145–148	62.85 (63.03)	4.95 (5.05)	3.28 (3.34)
9	3-ClC_6H_4	$C_{19}H_{14}ClFeNO$	25	123–126	62.70 (62.76)	3.96 (3.88)	3.78 (3.85)
10	3-BrC_6H_4	$C_{19}H_{14}BrFeNO$	46	125–127	56.16 (55.92)	3.61 (3.46)	3.31 (3.43)
11	C_5H_4N [d]	$C_{18}H_{14}FeN_2O$	62	183–185	65.50 (65.48)	4.34 (4.27)	8.33 (8.48)

[a] M.p. 178°C [1,2].
[b] FAB: $(M+H)^+$, 329.
[c] C-acylated oxime **12**, 52% (M.p.) 172–174°C (ethanol). Combust. anal. for $C_{22}H_{23}FeNO_5$. Found (calc.): C, 60.33 (60.43); H, 5.32 (5.30); N, 3.13 (3.20).
[d] Ester used: methyl nicotinate.

to unsymmetrical isoxazoles [9] (Eq. (2)). Since the regioselective condensation of the carbanion-type center with the ester formed the C-acylated intermediate, only a single bond was formed during the cyclodehydration step resulting in one isoxazole. All of the isoxazoles synthesized were readily recrystallized from routine solvents. Another oxime strong-base preparation of unsymmetrical isoxazoles involved dilithiation of C(α),O-oximes with *n*-butyllithium, followed by condensation/cyclization using *N*,*N*-dimethylbenzamides or *N*,*N*-dimethylformamide [10]. When substituted *N*,*N*-dimethylbenzamides are used, chromatographic purification of products may be necessary, and these electrophilic reagents are not as readily available as carboxylic acid esters.

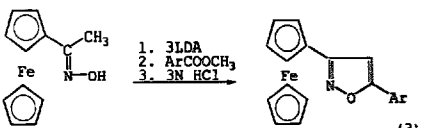


(2)

There are a limited number of reports dealing with the preparation of isoxazolyl-ferrocenes or related materials in addition to those already cited [11], and there are approximately 30 studies dealing with the preparation and use of acetylferrocene oxime. Acetylferrocene oxime metalation with strong bases, such as LDA, followed by condensation with electrophilic reagents, has not been reported.

2. Results

The current investigation focused on the dilithiation/condensation/cyclization of acetylferrocene oxime with select esters to afford the desired isoxazolyl-ferrocenes **1–11** (Eq. (3)). An excess of LDA (oxime:base:ester = 1:3:1) was used instead of *n*-butyllithium (oxime:base:ester = 1:2:0.5) for the dilithiation of acetylferrocene oxime. The overall experimental conditions were similar to those used with C(α),O-oximes of ketones [9]. Both the dilithiation and the subsequent condensation with an ester were performed in tetrahydrofuran (THF) at 0 °C. The cyclization was readily effected with 3 N hydrochloric acid. After workup, a single product resulted, which was recrystallized from ethanol. There were several subtle differences between this preparation and former preparations with dilithiated oximes used for the preparation of other isoxazoles [9]. The time of acid cyclization under reflux was 1–2 min instead of 45–60 min. Apparently, the heated and stirred two-phase system containing 3 N HCl/THF attacked the ferrocenyl moiety and markedly reduced the yield, or destroyed the molecule entirely. Also, during workup, a solution of the product, which had been dissolved in ether and organic solvents after extraction, was filtered several times to remove insoluble material. When the solid containing mostly isoxazolyl-ferrocenes was recrystallized from ethanol, it was hot filtered to remove any insoluble iron salt residue.

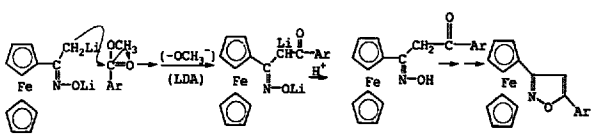


1 – 11 (3)

During the initial condensation of the dilithiated oxime with methyl 3,4,5-trimethoxybenzoate, C-acylated oxime **12** (Table 1, footnote c) was isolated rather than isoxazole **8** when 3 N acetic acid was used instead of 3 N hydrochloric acid. When the procedure was repeated with careful stirring following the addition of aqueous hydrochloric acid, the desired isoxazolyl-ferrocene **8** was isolated. Surprisingly, when the dilithiated oxime was condensed with methyl 3,4-dimethoxybenzoate followed by cyclization, a mixture of isoxazolyl-ferrocene **7** and C-acylated oxime resulted. Completed cyclization to **7** occurred in 46% yield upon recrystallization of the mixture.

3. Discussion

Some of the mechanistic details (Scheme 1) for this three-step one-pot process can be envisioned as O- and



Scheme 1.

Table 2
^{1}H NMR data for (5-aryl-3-isoxazolyl)-ferrocenes illustrated in Eq. (3): δ ppm TMS reference [a]

Prod. no.	(s, C_5H_5)	(t, C_5H_4) [b]	(s, C_4-H)	Other
1	4.23	4.52, 4.93	6.73	7.68–8.05 (m, ArH)
2	4.18	4.53, 4.93	6.63	2.45 (s, $ArCH_3$); 7.40 (d, ArH_b, $J = 8$) and 7.80 (d, ArH_a, $J = 8$)
3	4.25	4.52, 4.90	6.73	2.50 (s, $ArCH_3$); 7.42–7.97 (m, ArH)
4	4.23	4.48, 4.88	6.70	2.47 (s, $ArCH_3$); 7.25 (s, ArH at C_4); 7.62 (s, ArH at C_2-H and C_6-H)
5	4.23	4.50, 4.90	6.73	1.40 (s, $C(CH_3)_3$); 7.74 (d, ArH_b, $J = 8$) and 8.04 (d, ArH_a, $J = 8$)
6	4.15	4.36, 4.78	6.50	3.88 (s, $ArOCH_3$); 7.10 (d, ArH_b, $J = 8$) and 7.85 (d, ArH_a, $J = 8$)
7	4.15	4.46, 4.78	6.50	3.88, 3.97 (s, $ArOCH_3$); 7.50–7.80 (m, ArH)
8	4.23	4.50, 4.83	6.67	3.98, 4.05 (s, $ArOCH_3$); 7.23 (s, ArH)
9	4.20	4.47, 4.83	6.68	7.33–8.00 (m, ArH)
10	4.15	4.55, 4.90	6.65	7.22–8.08 (m, ArH)
11	4.25	4.55, 4.90	6.83	7.42–9.42 (m, C_5H_4N)

[a] $CDCl_3$ solvent for all compounds.
[b] Two sets of apparent triplets, $J \approx 1$–2 Hz.

C-dilithiation of oxime with LDA, followed by a Claisen condensation of the C(α)-carbanion-type center with the carbomethoxy carbon of the ester, with expulsion of the methoxide ion. The extra LDA reacts with one of the more acidic methylene hydrogens of the C-acylated intermediate to give another dilithiated intermediate [12] that is quenched with acid, and the resulting C-acylated ferrocenyl oxime is cyclodehydrated to the heteroaromatic isoxazolyl-ferrocene product. This last transformation from C-acylated oximes to products results from the formation of a single bond.

Isoxazolyl-ferrocene **1** is the only known compound in this series, and it was isolated in 53% yield (m.p. 179–181 °C, lit. 178 °C) [1]. Its ^{1}H NMR spectrum was very similar to that reported. In this study C_4-H was observed at δ 6.73 ppm (Table 2), and the literature indicated that it was located at δ 6.57 ppm. Usually, the C_4-H appears for appropriate isoxazoles and related heteroaromatic azoles as a distinct singlet upfield from the normal aromatic resonance absorptions [4,9].

Isoxazolyl-ferrocenes **2**–**11** are new, and C_4-H absorptions for them were noted as singlets ranging from δ 6.50–6.83 ppm. Other singlet pendant group absorptions were noted for $ArC(CH_3)_3$ δ 1.40 ppm in **3**; $ArCH_3$ δ 2.45–2.50 ppm in **2**, **4**, and **5**; $ArOCH_3$ δ 3.98–4.15 ppm in **6**–**8**; and δ 4.15–4.25 ppm for the unsubstituted cyclopentadienyl in all products. Also, two sets of doublet of doublets for the monosubstituted ferrocenyl ring were displayed as apparent triplets from δ 4.36–4.55 and 4.78–4.93 ppm. Infrared spectra were obtained from starting materials and products, and they routinely distinguished between the two compounds. Additional support for structures **2**–**11** and **12** also resulted from combustion analysis (for C, H, and N).

The yields of isoxazolyl-ferrocenes **1**–**11** ranged from 20–76%, which indicates that the general experimental procedure is usually satisfactory for the expedient preparation of 1.0–2.0 g of the desired products, that can be easily purified by recrystallization from a routine solvent, ethanol. The yields reported may not necessarily represent the optimum conditions for the preparation of an individual compound.

4. Summary

Multi-gram quantities of isoxazolyl-ferrocenes can be prepared from acetylferrocene oxime and aromatic esters. Acetylferrocene oxime can be dilithiated with excess LDA, and the resulting C(α),O-dilithiated oxime can undergo a Claisen-type C-acylation with aromatic esters. The resulting intermediates can be acid-cyclized to (5-aryl-3-isoxazolyl)-ferrocenes. Several additional points are noted: (1) the products are prepared from readily available starting materials; (2) a single product is isolable following crystallization and recrystallization from a routine solvent; (3) the experimental procedure is straightforward so that someone not necessarily familiar with strong-base procedures can be successful with the reactions.

5. Experimental section

^{1}H NMR spectra were obtained with a Varian Associates EM 360L nuclear magnetic resonance spectrometer (60 MHz) and chemical shifts are recorded in δ ppm downfield from an internal tetramethylsilane (TMS) standard. Infrared spectra were obtained with a Mattson Polaris FT-IR spectrometer or a Nicolet Impact 410 C FT-IR spectrometer. Mass spectral measurement for **1** was performed on a Jeol HX110/HX110 Tandem Mass Spectrometer. Combustion analyses for C, H, and N were performed by Quantitative Technologies, Inc., PO Box 470, Salem Industrial Park, Bldg. 5, Whitehouse, NJ 08888, USA. Melting points were obtained with a Mel-Temp melting point apparatus in open capillary tubes and are uncorrected. THF was dried and distilled

from sodium (benzophenone ketyl). ^{n}BuLi (1.6 M in hexane) and other chemicals were purchased from Aldrich Chemical Co., USA. All glassware was dried in an oven (ca., 140 °C), cooled, and kept under a dry nitrogen atmosphere.

5.1. General procedure for the preparation of isoxazolyl-ferrocenes 1–11

In a typical preparation, a syringe was used to add *n*-butyllithium (0.032 mol) to a three-necked round-bottomed flask (ca., 500 ml), which was fitted with a side-arm addition funnel (ca. 125 ml) and nitrogen inlet tube. After cooling the flask in an ice–water bath, a sample of diisopropylamine (0.032 mol) taken up in 25 ml of dry THF was added to the stirred *n*-butyllithium at a fast dropwise rate (5–7 min). The resulting LDA was stirred at 0 °C for an additional 10–15 min before adding a 0.010 mol sample of acetylferrocene oxime dissolved in 30–40 ml of dry THF (5–7 min). Dilithiation, 45–60 min (0 °C, N_2) was followed by addition of a 0.0105 mol sample of ester dissolved in 30–40 ml of dry THF over 5 min. The condensation times varied and depended on the ester used (e.g. methyl 4-chlorobenzoate, 45–60 min; methyl 4-methoxybenzoate and methyl 3,4,5-trimethoxybenzoate, 75–90 min), (oxime:LDA:ester = 1:3:1). Condensation was followed by neutralization and cyclodehydration. Acidification was accomplished by directly adding 100 ml of 3 N hydrochloric acid, and the mixture was well stirred overnight. The stirred two-phase mixture was then heated just to reflux, and poured into a large flask containing ice (ca. 150 g), and 100 ml of solvent-grade ether was added. The resulting mixture was neutralized with solid sodium bicarbonate, followed by separation of organic and aqueous phases. The aqueous layer was extracted with ether (2 × 75 ml); the organic components were combined, filtered several times through a Büchner funnel, and evaporated. A drying agent was unnecessary. The oil or solid residue that resulted was crystallized and recrystallized from ethanol. It was necessary to filter a hot solution of the product through a Büchner funnel prior to recrystallization.

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