A simple synthesis of metallocene aldehydes from lithiometallocenes and *N,N*-dimethylformamide: ferrocene and ruthenocene aldehydes and 1,1'-dialdehydes *

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Abstract

Lithioferrocene, 1,1'-dilithioferrocene, lithioruthenocene and 1,1'-dilithioruthenocene all react with *N,N*-dimethylformamide in diethyl ether to produce the respective aldehydes. The lithiation of the two metallocenes can be steered to maximize the formation of only one of the two aldehydes by choosing either n-butyllithium in the presence of tetramethylethylenediamine (TMEDA) or t-butyllithium (^{t}BuLi) as the metallating reagent: ferrocene mono-aldehydes or 1,1'-dialdehydes are formed with good yields (91% and 85% respectively, based on ferrocene), lower yields (50%) of ruthenocene-1,1'-dialdehyde were obtained under the standard conditions, because the 1,3,1'-trialdehyde also formed in significant (19%) amounts. Monolithiation by ^{n}BuLi and the formation of the ruthenocene monoaldehyde (yield, 66%) are favoured when TMEDA is used in only catalytic amounts; lithiation of ruthenocene by ^{t}BuLi selectively leads to monolithioruthenocene and the mono-aldehyde (yield, 91%). The products are easily purified by column chromatography. The simplicity and the high yield of these reactions make them much more desirable than the previously known multistep procedures.

1. Introduction

The reaction of organolithium compounds with *N,N'*-dimethylformamide (DMF) has long been known in the repertoire of organic syntheses as a desirable method for the preparation of aldehydes [1]. Nevertheless, the low yield Vilsmeier formylation reactions to produce the mono-aldehydes [2] and the very awkward known syntheses of the dialdehydes by oxidation of the diols [3,4] by MnO_2 still seem to be the standard to date for the preparation of metallocene aldehydes. The first (1990) reference known to us for a reaction of a lithio metallocene with DMF is the work of Wright [5], who added DMF to a 1-phosphinyl-1'-lithio-ferrocene in a study of transmetallation reactions. Shortly thereafter, Balvoine *et al.* [6] showed that ferrocene-1,1'-dialdehyde can be prepared from dilithioferrocene and DMF in 70% yield.

As part of our ongoing interest in metallocenophanes, we needed to have easy access to the ferrocene and ruthenocene mono- and dialdehydes 1–4. We therefore undertook a detailed study of the lithiation of ferrocene and ruthenocene, whose effectiveness was measured by the formation of the aldehydes in a subsequent reaction with DMF. We here report the results of this work: effective synthetic methods for each of these lithiated metallocenes and thus their aldehydes are now available.
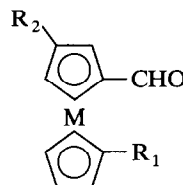
1: M = Fe; $R_1 = R_2 = $ H
2: M = Fe; $R_1 = $ CHO; $R_2 = $ H
3: M = Ru; $R_1 = R_2 = $ H
4: M = Ru; $R_1 = $ CHO; $R_2 = $ H
5: M = Ru; $R_1 = R_2 = $ CHO

1.1. Lithiation of ferrocene: mono- and dilithio-ferrocene

The standard methods to prepare pure monolithioferrocene are either too tedious or not always reproducible. The reaction of ferrocene with butyllithium in ether leads to mixtures of mono- and dilithio-ferro-

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cene, the replacement of bromide in bromoferrocene by butyllithium proceeds cleanly, but the preparation of bromoferrocene is tedious; chloromercuriferrocene can be converted to lithioferrocene, but toxic dialkyl mercury compounds are the byproducts. A major improvement in the monolithiation of ferrocene was documented in the work of Kagan and coworkers [7] through the use of t-butyllithium (^{t}BuLi) in tetrahydrofuran (THF) at 0°C; good yields (up to 70% based on ferrocene) of monosubstituted products were obtained.

The double lithiation of ferrocene by butyllithium in the presence of tetramethylethylenediamine (TMEDA) is not as specific as we might desire [8], but the proper choice of reaction conditions maximizes the yield of the dilithio species at the expense of the mono and oligo-lithio derivatives. We have not been able to (and saw no real need for major efforts to do so) isolate absolutely pure 1,1'-dilithioferrocene. Therefore, in our reactions, the dialdehyde product always is contaminated by a small amount of mono-aldehyde and also some other undefined products. As one chromatographic purification produces a clean separation, the formation of byproducts poses no problem in this case.

1.2. Lithiation of ruthenocene

The literature [9] indicates that the lithiation of ruthenocene by n-butyllithium (^{n}BuLi) seems to be somewhat complex. Our earlier experience utilizing 1,1'-dilithioruthenocene did confirm this [10]. Although it is possible to minimize the formation of monolithioruthenocene, this can only be done at the expense of the formation of more 1,3,1'-trilithioruthenocene. The addition of this mixture to DMF thus produced the dialdehyde chiefly contaminated by the 1,1',3-trialdehyde. Separation of these aldehydes by column chromatography is even simpler than in the ferrocene case, because their retention times are quite dissimilar.

The monolithiation of ruthenocene does not seem to have been explored in detail. We therefore were prompted to seek specific conditions leading to monolithioruthenocene in the reactions with ^{n}BuLi. One factor was the role of TMEDA in these reactions. TMEDA is necessary to activate ^{n}BuLi (^{n}BuLi does not react with ruthenocene in the absence of TMEDA), but it also appears to stabilize the dilithioruthenocene preferentially because, even in reactions using less than stoichiometric amounts of ^{n}BuLi, significant percentages of 1,1'-dilithio ruthenocene were formed. The use of TMEDA in only catalytic amounts, sufficient to activate ^{n}BuLi but not enough to contribute to the formation of dilithioruthenocene, was thought to favor the formation of monolithioruthenocene. This was confirmed in our experiments; a good yield of the monoaldehyde was obtained.

The reaction of ruthenocene with ^{t}BuLi in THF was also investigated and turned out to be the most effective way of preparing monolithioruthenocene as evidenced by the formation of the mono-aldehyde with a very high yield.

2. Results

2.1. Monolithioferrocene and ferrocene aldehyde (1)

Initial attempts to steer the reactions of ferrocene and ^{n}BuLi (in the presence or absence of TMEDA) in a variety of solvents to produce pure lithioferrocene were not successful, as all further reaction products showed a significant admixture of dilithioferrocene in the intermediate. After several attempts to improve this reaction, we abandoned it in favor of the lithiation by ^{t}BuLi.

Only moderately successful were reactions using a 1:1 ratio of Cp_2Fe:^{t}BuLi under the original lithiation conditions of Kagan and coworkers [7] (reaction in THF at 0°C); we observed (a) only low yields (average, 52%) of the mono-aldehyde, (b) that the formation of products derived from dilithioferrocene was not significant (i.e. 2% of the dialdehyde were isolated), (c) unidentified side products which seemed to stem from reactions between ^{t}BuLi and THF and (d) that a large amount of ferrocene (29%) was found in the reaction product.

This seemed to call for a threefold change in reaction conditions to enhance the monolithiation: (1) the reaction temperature was lowered (to avoid reactions between ^{t}BuLi and THF and the multiple lithiation of ferrocene); (2) a concomitant slightly longer reaction time seemed to be indicated; (3) the use of excess ^{t}BuLi was expected to lead to a more complete conversion of ferrocene to lithioferrocene, but the lower reaction temperature would still avoid the formation of dilithioferrocene.

This indeed turned out to be excellent reaction conditions: lithiation of ferrocene in THF at $-20°C$, using a 1:1.5 molar ratio of the two reagents, followed by addition of DMF at $-10°C$, led, after work-up using dilute HCl, extraction with CH_2Cl_2, and flash chromatography, to ferrocene mono-aldehyde in 91% yield based on ferrocene. Only 5% of ferrocene were recovered, and only a trace of dialdehyde was isolated.

2.2. Formation of dilithioferrocene and 1,1'-ferrocene dialdehyde (2)

Our results agree with those found in the literature [8]; the lithiation of ferrocene by ^{n}BuLi in the presence of TMEDA leads predominantly to 1,1'-dilithioferrocene. However, there are always small amounts of monolithioferrocene and ferrocene in the product.

Therefore the subsequent reaction with DMF does lead to rather good yields (85%) of the 1,1′-dialdehyde, but the byproducts ferrocene and ferrocene mono-aldehyde have to be separated. This is best done by flash chromatography on silica gel.

2.3. Monolithioruthenocene and ruthenocene aldehyde (3)

In the absence of TMEDA, ruthenocene does not react with ^{n}BuLi in hexane. Using a Cp_2Ru : BuLi : TMEDA ratio of 1 : 1 : 1 leads to dilithioruthenocene as the main product. Decreasing the amount of TMEDA increases the proportion of the monoaldehyde. The use of TMEDA in only catalytic amounts was the key in steering this reaction toward the monolithio derivative. When a Cp_2Ru : BuLi : TMEDA ratio of 1 : 1 : < 0.1 was used, the monoaldehyde formed in 66% yield, although the product still contained 30% of the dialdehyde. No trialdehyde was observed.

The reaction between Cp_2Ru and ^{t}BuLi in THF at 0°C for 20 min, as specified by Kagan and coworkers [7] for the lithiation of ferrocene followed by the addition of DMF, aqueous work-up and chromatography, led to the recovery of 30% Cp_2Ru, a 49% yield of ruthenocene monoaldehyde and a trace amount of the dialdehyde. A drastic improvement in this reaction was seen when a 1 : 1.5 ratio of Cp_2Ru : ^{t}BuLi was used, the yield of the monoaldehyde jumped to 90.5%, ohly 4% of the starting ruthenocene were recovered, and only 3% of the trialdehyde were formed.

2.4. Dilithioruthenocene and 1,1′-ruthenocene dialdehyde (4)

Using an excess of ^{n}BuLi and a 1 : 1 ratio of Cp_2Ru : TMEDA, the 1,1′-dilithio derivative is the main product, but a significant amount of the 1,3,1′-trilithio derivative also forms. The best synthesis of the 1,1′-ruthenocene dialdehyde involves a Cp_2Ru : BuLi : TMEDA ratio of 1 : 4 : 1.5 and leads to 2–3% mono-aldehyde, 49.5% dialdehyde and 19.2% trialdehyde. The reaction products can easily be separated by column chromatography.

3. Summary and discussion

The double lithiation of ferrocene and ruthenocene by ^{n}BuLi in hexane and in the presence of TMEDA is a good method for preparing the 1,1′-dilithio derivatives and products derived from them. In the case of ruthenocene, however, the formation of the trilithio derivative appears unavoidable.

The monolithiation of these two metallocenes using ^{n}BuLi is much more difficult. Even when a large excess

of ferrocene is used, the formation of dilithioferrocene cannot be suppressed. Similarly, monolithiation of ruthenocene using ^{n}BuLi in conjunction with TMEDA increases when the amounts of ^{n}BuLi and TMEDA are decreased. Using only a catalytic amount of TMEDA to activate ^{n}BuLi produces a good yield of monosubstituted products, but the 1,1′-disubstituted derivatives are still a significant part of the products.

Successful monolithiation of ferrocene has been achieved by using excess ^{t}BuLi in THF. We found that ruthenocene reacts in an identical manner. This reaction does not require activation by TMEDA, and the double lithiation is essentially excluded. For our syntheses, in which the presence of excess ^{t}BuLi is of no consequence, we found this reaction to be much cleaner when the reaction temperature was lowered to −20°C. Under these conditions, even the excess of ^{t}BuLi did not cause a significant amount of the 1,1′-dilithio derivative to be formed.

We think that the above results can best be understood when the role of TMEDA in the activation of ^{n}BuLi and in the stabilization of dilithiometallocenes relative to the monolithiometallocenes is considered. Ferrocene is more reactive than ruthenocene and therefore can be lithiated by ^{n}BuLi without TMEDA. However, the reaction in ether at room temperature does not stop at the monolithio derivative and significant amounts of dilithioferrocene are formed as well. On the contrary, no reaction occurs between ruthenocene and ^{n}BuLi in the absence of TMEDA. We therefore need this reagent, but it also seems to be detrimental when monolithiation of ruthenocene is desired, because even in the presence of excess ruthenocene the dilithio derivative is formed in significant proportions. This indicates a stabilization of the dilithio derivatives by TMEDA, whereas no stabilization is given to the monolithio derivative.

Dilithioferrocene seems to form TMEDA adducts of different stoichiometries, depending on the solvent used in its preparation [11]. An adduct $[(LiCp)_2Fe]_2$-$[TMEDA]_3$, which has been structurally characterized [11], was obtained in ether. The reaction in hexanes, however, leads to a TMEDA adduct of unknown structure and with conflicting reports as to its stoichiometry [12]. Not much is known about the TMEDA adducts of the monolithiometallocenes or of dilithioruthenocene.

If indeed the complex formation between TMEDA and the dilithio derivatives is preferred, this would explain our failures to obtain clean monolithiometallocenes in all reactions using the ^{n}BuLi–TMEDA adduct. It also explains the extremely clean monolithiation by the more reactive ^{t}BuLi, which does not require the presence of TMEDA and which can be carried out at low temperature.

4. Experimental details

4.1. General comments

Commercial reagents were used without further purification unless stated otherwise. THF and hexane were dried and distilled from sodium. TMEDA was dried over KOH and was distilled. Column chromatography was done using silica (mesh size 35–70). The ^{1}H NMR spectra were recorded on a 270 MHz Bruker spectrometer with TMS as internal standard. The mass spectra were recorded on either a Hewlett–Packard GC-MS or a Kratos MS 50 RF double focusing magnetic sector spectrometer. The melting points are uncorrected. All the following reactions were conducted in an atmosphere of pure nitrogen.

4.2. Preparation of monolithioferrocene and ferrocene aldehyde

In a nitrogen-flushed three-necked flask with addition funnel, stirrer and reflux condenser, ferrocene (2.0 g, 10.8 mmol) was dissolved in 30 ml of dry THF and the solution was cooled to $-20°C$ in an ice–methanol bath. Over a period of 15 min, 9.2 ml (16.1 mmol) of 1.76 M ^{t}BuLi in heptane were added. After the addition was complete, the mixture was stirred for 30 min and allowed to warm to $-10°C$. The addition of DMF (1.7 ml, 21.5 mmol) produced a yellow precipitate during several minutes. Dilute HCl was then added, which caused the reaction mixture to turn to deep red. The aldehyde was extracted with several portions of CH_2Cl_2 and the combined extracts were dried over $MgSO_4$. Chromatography over a short column of SiO_2 (deactivated by addition of 4% water) with CH_2Cl_2 as eluent led to the clean aldehyde.

The yields, based on ferrocene were as follows: ferrocene aldehyde, 2.1 g (91%); ferrocene, 110 mg (5%); 1,1'-dialdehyde, 30 mg (1%). The melting point (m.p.) was 121°C (123–123.5°C [13]). ^{1}H NMR ($CDCl_3$): δ 4.81 (2H, t, Cp), 4.6 (2H, t, Cp), 4.29 (5H, Cp), 9.95 (1H, s, CHO) ppm. MS: m/e 214 (M^+), 186 ($M - CO^+$), 121 ($CpFe^+$), 56 (Fe^+).

4.3. Preparation of 1,1'-ferrocenedialdehyde

In a nitrogen-flushed three-necked 500 ml flask with addition funnel, stirrer and reflux condenser, 8.0 g (0.043 mol) of ferrocene were dissolved in 150 ml of hexane and 16 ml (0.106 mol) of TMEDA were added. The mixture was stirred while 60 ml of 1.6 M (0.096 mol) ^{n}BuLi were added dropwise through the addition funnel. This produced a homogeneous solution which was stirred overnight under nitrogen at room temperature. An orange solid formed during this period. The hexane supernatant containing excess TMEDA, ^{n}BuLi and unreacted Cp_2Fe was removed through a cannula

by a positive pressure of nitrogen. Fresh hexane was added to the orange solid, the mixture was stirred and then allowed to settle, and the solvent was removed as above. This washing procedure was repeated once more.

In another three-necked 500 ml flask with reflux condenser and stirrer, 7.2 ml (0.091 mol) of DMF were dissolved in 30 ml of dry ether. By using the same cannula, the orange solid, suspended by stirring in 100 ml of hexane, was transferred into the flask containing DMF and the mixture was stirred for about 10 min.

The addition of 120 ml (14%) of HCl to this solution produced a red solid, which was filtered and washed with hexane. The water layer was extracted with methylene chloride, and the organic solution was dried and evaporated.

The combined solids were recrystallized from a mixture of methylene chloride and hexane. The yield of pure product was 8.9 g (85%, based on ferrocene) of red crystals with m.p. 179–180°C (184°C [12]). ^{1}H NMR ($CDCl_3$): 4.67 (4H, t, Cp), 4.89 (4H, t, Cp), 9.88 (2H, s, –CHO) ppm. MS: main assigned peaks at m/e 242 (M^+), 56 (Fe^+).

4.4. Preparation of ruthenocene aldehyde using ^{n}BuLi

The same reaction as above was run with a $Cp_2Ru : n$-BuLi mole ratio of 1:1 and only a few drops of TMEDA. The major product was the monosubstituted ruthenocene (yield 66%) as yellow crystals with m.p. 101–101.5°C (100.2–100.8°C [2b]). ^{1}H NMR ($CDCl_3$): δ 4.58 (5H, s, Cp), 4.79 (2H, t, Cp), 5.02 (2H, t, Cp), 9.66 (1 H, s, –CHO) ppm. MS: main assigned peaks at m/e 260 (M^+), 232 ($M - CO^+$), 167 ($CpRu^+$).

4.5. Preparation of ruthenocene aldehyde using ^{t}BuLi in THF

In a nitrogen-flushed flask, 1.5 g (6.5 mmol) of ruthenocene were suspended in 30 ml of dry THF at 0°C. Over a period of 10 min, 5.5 ml (9.7 mmol) of 1.76 M ^{t}BuLi were added. The Cp_2Ru dissolved during this period, and a pale-yellow solution was obtained. After DMF (1.0 ml, 12.9 mmol) was added, the solution became cloudy. Stirring for an additional 10 min was followed by the addition of dilute HCl and extraction of the product with CH_2Cl_2. The combined CH_2Cl_2 solutions were dried and evaporated. Separation on a SiO_2 column (deactivated with 4% of H_2O) with CH_2Cl_2 led to the clean mono-aldehyde. The yields were as follows: monoaldehyde, 1.52 g (90.5%); ruthenocene, 60 mg (4%); dialdehyde, 55 mg (3%).

4.6. Preparation of 1,1'-ruthenocene dialdehyde

In a three-neck 250 ml flask with addition funnel, stirrer and reflux condenser, 2.31 g (0.01 mol) of

ruthenocene, 150 ml of hexane and 1 ml (0.015 mol) of TMEDA were combined. The mixture was stirred while 30 ml 1.6 M (0.04 mol) of ^{n}BuLi were added dropwise through the addition funnel. The mixture became a homogeneous solution upon heating to 40°C. It was kept at this temperature for 15 min and then was stirred overnight under nitrogen at room temperature. A yellow solid formed during this period. The hexane solution containing excess TMEDA, ^{n}BuLi and unreacted Cp_2Ru was carefully removed through a cannula. The yellow solid was washed twice with hexane, which was removed in the same way.

The yellow solid was suspended in 100 ml of hexane and transferred through a cannula into a three-necked 250 ml flask with reflux condenser and stirrer containing 2 ml (0.02 mol) of DMF dissolved in 25 ml of dry ether. The mixture was stirred for about 10 min, after which 30 ml of 20% HCl were added. A yellow solid formed, which was filtered and washed with hexane. The water layer was extracted with methylene chloride. The organic layer was dried and evaporated. The two solids were combined.

The products were separated by chromatography with a 2:1 solvent mixture of ether: methylene chloride. The first band was 1,1'-ruthenocene dialdehyde and the second band was the 1,3,1'-ruthenocene trialdehyde.

The yield of the dialdehyde was 49.5% and the m.p. 130°C (dec. at 235°C [4b]; we assume that the value in the literature is in error, because our physical data leave no doubt about the structure of our product). ^{1}H NMR ($CDCl_3$): δ 4.93 (4H, t, Cp) 5.18 (4H, t, Cp), 9.71 (2H, s, –CHO) ppm. MS: m/e 288 (M^+), 260 (M – CO^+), 232 (M + $2CO^+$). The yield of the trialdehyde was 19.2% of yellow crystals with m.p. 155°C. ^{1}H NMR ($CDCl_3$): δ 5.03 (2H, t, Cp), 5.29 (2H, t, Cp), 5.45 (2H, t, Cp), 5.70 (1H, d, Cp), 9.69 (1H, s, –CHO), 9.75 (2H, s, –CHO) ppm.

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