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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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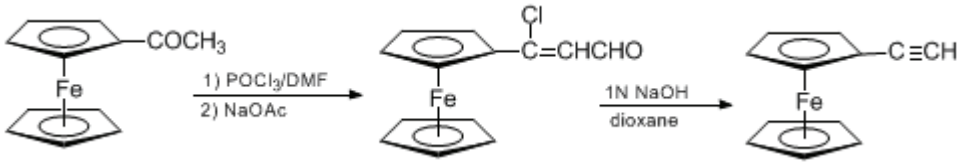
# CONVERSION OF METHYL KETONES INTO TERMINAL ACETYLENES: ETHYNYLFERROCENE

## [Ferrocene, ethynyl]

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Checked by Bruce Anderson and Stephen F. Martin.

## 1. Procedure

*(2-Formyl-1-chlorovinyl)ferrocene*: A dry, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, an inlet valve for inert gas, a pressure-equalizing addition funnel, and an outlet valve vented through a mercury bubbler, is charged with 22.8 g (0.1 mol) of acetylferrocene (Note 1) and 25 mL (0.32 mol) of N,N-dimethylformamide (DMF) (Note 2). The system is flushed with argon, cooled to 0°C by means of an ice bath, and the brown reaction mixture is stirred well for several minutes (Note 3). Separately, a dry, 100-mL, graduated cylinder bearing a standard taper ground joint with an argon inlet/outlet, is purged with nitrogen and charged with 25 mL (0.32 mol) of DMF. The DMF is cooled in crushed ice and agitated by hand during the cautious addition of 25 mL (0.27 mol) of phosphorus oxychloride (Note 4). The resulting viscous, red complex is transferred to the dropping funnel and added to the magnetically stirred mixture of acetylferrocene and DMF dropwise over 30 min (Note 5). Complete addition is assured by washing the addition funnel and walls of the flask with a small amount of DMF using a pipette. The mixture is stirred at 0°C for 2 hr during which time the color of the reaction mixture changes from dark brown to olive and ultimately to deep blue. Prior to neutralization, the dropping funnel is replaced by a reflux condenser (Note 6). A 75-mL portion of diethyl ether is added, and the viscous mixture is stirred vigorously for several minutes (Note 7).

Under a positive pressure of argon with continued ice cooling, 116 g (0.85 mol) of sodium acetate trihydrate is cautiously added to the reaction mixture in one portion through a powder funnel followed by cautious addition of 10 mL of water with vigorous stirring (Note 8). The ice bath is removed whereupon the organic layer undergoes a striking color change from colorless to ruby red indicating the formation of the formyl derivative. After 1 hr, an additional 10 mL of ether is added, and stirring is continued for 3 hr at room temperature to ensure complete quenching. The reaction mixture is transferred to a 2-L separatory funnel with ether and water and mixed thoroughly, and the organic phase is separated. The aqueous phase is extracted several times with 100-mL portions of ether (Note 9). The combined organic phases are carefully washed twice with 100-mL portions of saturated aqueous sodium bicarbonate solution (*CAUTION: gas evolution*) and then with 100 mL of water (Note 10). The organic phase is dried over sodium sulfate, filtered, and concentrated using a rotary evaporator affording 23.4–25.6 g (85–93%) of (2-formyl-1-chlorovinyl)ferrocene (homogeneous by TLC analysis) as deep purple crystals (mp 76–77°C) after drying under high vacuum (Note 11).

*Ethynylferrocene*: A dry, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, reflux condenser, and inlet/outlet valves for maintenance of an inert atmosphere as described above, is flushed with argon, charged with 26.0 g (95.0 mmol) of (2-formyl-1-chlorovinyl) ferrocene and 300 mL of anhydrous 1,4-dioxane (Note 12), and the apparatus is placed in an oil bath. The reaction mixture is heated to reflux and after 5 min at reflux, 250 mL of a boiling 1 N solution of sodium hydroxide (a 2.5-fold excess) is cautiously added as rapidly as possible in one portion (Note 13), and the mixture is heated at reflux for another 25 min (Note 14). The oil bath is removed and the reaction mixture is allowed to cool to room temperature.

The reaction mixture is cautiously poured into ice and neutralized with 1 N hydrochloric acid. After transfer to a 1-L separatory funnel, the aqueous mixture is extracted five times with 100 mL of hexane (Note 15). After the combined organic extracts are successively washed twice with 100-mL portions of saturated aqueous sodium bicarbonate solution and water, the organic phase is dried over sodium sulfate, filtered, and concentrated using a rotary evaporator affording an orange residue of crude ethynylferrocene. The crude product is purified by flash chromatography (Silica G-60, 5 × 15 cm column) with elution by hexane (Note 16). Concentration of the fractions containing the product and drying under high vacuum affords 14.8–15.0 g (74–75%) of pure ethynylferrocene which crystallizes as an orange solid, mp 53°C (lit.[2] 52–53.5°C) upon seeding (Note 17).

## 2. Notes

1. Acetylferrocene, $C_{12}H_{12}FeO$, 95% (FW (228.07), mp 85–86°C) is available from Aldrich Chemical Company, Inc. or Lancaster Synthesis Ltd., and is used without further purification (*CAUTION: highly toxic*). Acetylferrocene should be carefully triturated before use. The analytical data are as follows: $^1$H NMR (100 MHz, $CCl_4$) δ: 2.25 (s, 3 H), 4.08 (s, 5 H), 4.30 (s, 2 H), 4.61 (s, 2 H); $^{13}$C NMR (22.6 MHz) δ: 26.9, 69.2, 69.5, 71.8, 79.3, 200.1; IR ($CCl_4$) cm$^{-1}$: 3100, 1675.
2. N,N-Dimethylformamide (DMF), 99% ($C_3H_7NO$, FW (73.10), mp −61°C, bp 153°C, d = 0.944, $n_D^{20}$ 1.4305) was purchased from Fluka Chemie AG, and used without further purification. *CAUTION: DMF is a cancer suspect agent*.
3. The best results were obtained in an argon atmosphere, although from the stability of the product it seems most likely that an inert gas atmosphere is not essential. Care must be taken to stir the entire system, particularly for large-scale syntheses.
4. Phosphorus oxychloride ($POCl_3$), 99% (FW 153.33, mp 1.25°C, bp 105.8°C, d = 1.645) available from Fluka Chemie AG, was used as purchased. $POCl_3$ is highly toxic and moisture sensitive.
5. *CAUTION: The formation of the complex is highly exothermic! Be aware of the hazards of phosphorus oxychloride*.
6. This is a safety measure in case the neutralization should become too exothermic.
7. If the ethereal layer turns orange, it is removed and replaced with 75 mL of fresh ether. This procedure removes any traces of unreacted acetylferrocene or ferrocene impurities. The use of a pipette is recommended to replace the organic layer, if necessary.
8. Sodium acetate trihydrate ($CH_3CO_2Na \cdot 3\ H_2O$) 99%, available from Fluka Chemie AG, was used. Anhydrous sodium acetate ($CH_3CO_2Na$) 99% is only appropriate, if sufficient amounts of water are present.
9. Initially the phase separation is hard to discern. Extraction is continued until the organic phase is nearly colorless.
10. Additional sodium acetate trihydrate is added to the combined aqueous phases, which after some time, affords a small amount of additional product upon ether extraction. Careful extraction and washing of the organic phases prevents undesired polymerization. The yield and quality of the product obtained are largely dependent on the care taken in the extraction procedure.
11. (2-Formyl-1-chlorovinyl)ferrocene ($C_{13}H_{11}ClFeO$) has the following spectroscopic characteristics: $^1$H NMR (300 MHz, $CDCl_3$) δ: 4.24 (s, 5 H), 4.57 (s, 2 H), 4.75 (s, 2 H), 6.40 (d, 1 H, J = 6.7), 10.09 (d, 1 H, J = 6.7); IR ($CCl_4$) cm$^{-1}$: 2851, 1671.
12. 1,4-Dioxane, 99% ($C_4H_8O_2$, FW (88.11), mp 11.8°C, bp 100–102°C, $n_D^{20}$ 1.4225, d = 1.034) was purchased from Aldrich Chemical Company, Inc. and distilled from sodium benzophenone ketyl before use. *CAUTION: dioxane is a cancer suspect agent and a flammable liquid*. Attempts to use other solvents failed, and despite subsequent addition of aqueous sodium hydroxide, prior distillation of the dioxane from sodium benzophenone ketyl seems to be essential.
13. A solution of aqueous sodium hydroxide is prepared by dissolving 10 g of sodium hydroxide pellets, 97% (Fluka Chemie AG) in 250 mL of water. The solution is heated to boiling before addition.
14. After this time, TLC analysis (hexane as eluent) indicates essentially complete conversion to ethynylferrocene and an impurity with an $R_f$ value near zero.
15. A pH of 6–7 should be maintained. The phase boundary of the organic and aqueous phases is often difficult to discern, but separation is most satisfactory if the organic/aqueous mixture is filtered through a pad of Celite to remove an oily third phase prior to separation of the aqueous and organic layers. After the final extraction, the organic layer should be nearly colorless.
16. Silica Gel 60741 from Fluka Chemie AG was used. The impurities remain at the top of the 5 × 15-

cm column when hexane is used as eluent.
17. The spectroscopic data for ethynylferrocene are as follows: $^{1}$H NMR (300 MHz, $CDCl_3$) δ: 2.71 (s, 1 H), 4.19 (m, 2 H), 4.21 (s, 5 H), 4.46 (m, 2 H); $^{13}$C NMR (75 MHz) δ: 63.5, 68.3, 69.6, 71.2; IR ($CCl_4$) $cm^{-1}$: 3311, 2112.

## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

The two-step synthesis of ethynylferrocene described here follows essentially the scale-sensitive route reported by Rosenblum, et al.[2] Although various intermediates have been evaluated,[3,4] (2-formyl-1-chlorovinyl)ferrocene is the most successful precursor in the synthesis of ethynylferrocene. Treatment of acetylferrocene with phosphorus oxychloride in dimethylformamide leads to mixtures of (2-formyl-1-chlorovinyl)ferrocene and the more unstable (1-chlorovinyl)ferrocene, with the ratio of products depending on the stoichiometry.[2] However, production of (1-chlorovinyl)ferrocene can be effectively suppressed by employing an excess of phosphorus oxychloride. Using dimethylformamide as solvent leads to satisfactory results only for small-scale preparations. However, modification of the stoichiometry and experimental conditions led to the above described procedure which is useful for large-scale preparations. Use of conditions employing a comparatively small excess of dimethylformamide and phosphorus oxychloride resulting in a heterogeneous reaction mixture, as well as use of solid sodium acetate trihydrate surmount the problems of scale up and enable the removal of organic impurities. The purity and yield of the intermediate (2-formyl-1-chlorovinyl)ferrocene are substantially improved using the present procedure, and this intermediate is obtained in pure form without need of chromatography .

The procedure for the final elimination reaction is essentially that of Rosenblum, et al.[2] A more detailed procedure is provided which improves reproducibility. Treatment of an ethereal solution of (2-formyl-1-chlorovinyl)ferrocene with sodium amide in liquid ammonia under anhydrous conditions is also an acceptable method,[5] along with the method described which employs base-induced elimination using aqueous sodium hydroxide in dioxane.[2,6] Compounds of the α-haloferrocene type are converted more or less quantitatively into alkynes by dehydrochlorination using potassium tert-butoxide in dimethyl sulfoxide.[7] This alternative method for converting the β-chloroaldehyde might also be useful, but lower yields (15–20% less) make the conventional method[2] more efficient for the synthesis of ethynylferrocene.

With respect to cost and ease of accessibility, the procedure described above is superior to other, more recent synthetic methods.[8,9,10,11,12] However, the most convenient alternative synthesis of ethynylferrocene is that of Doisneau, et al.[11] Some procedures[11,12] also permit the synthesis of 1,1'-diethynylferrocene derivatives. Diethynylmetallocenes represent versatile precursors for the preparation of oligometallocenes.

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## References and Notes


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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

$H_2O$

sodium benzophenone ketyl

Ferrocene

(2-Formyl-1-chlorovinyl)ferrocene

Ethynylferrocene

Ferrocene, ethynyl

acetylferrocene

(1-chlorovinyl)ferrocene

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

sodium acetate (127-09-3)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

dioxane (123-91-1)

sodium amide (7782-92-5)

N,N-dimethylformamide,

dimethylformamide,
DMF (68-12-2)

sodium acetate trihydrate (6131-90-4)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

argon (7440-37-1)

1,4-dioxane (123-91-1)

potassium tert-butoxide (865-47-4)