



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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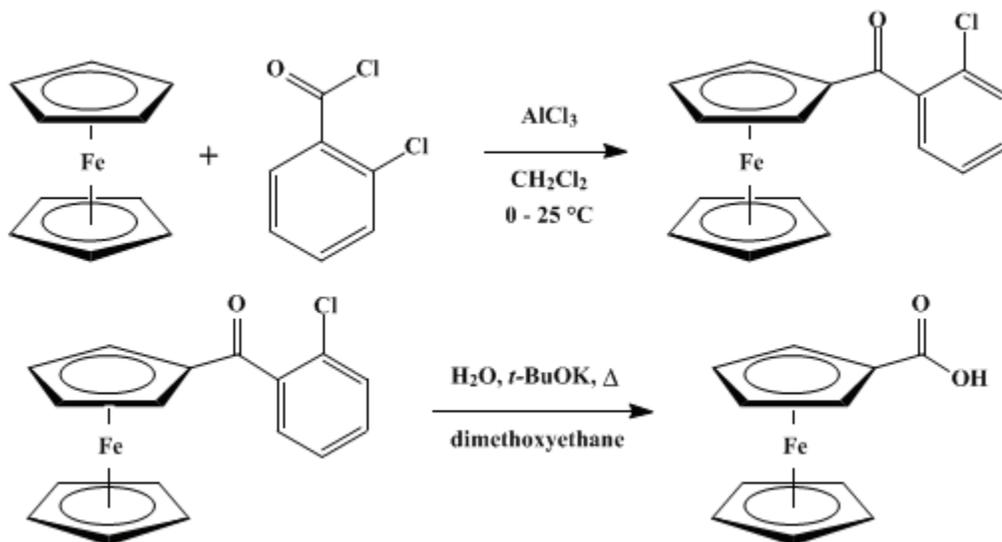
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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CARBOXYLATION OF AROMATIC COMPOUNDS: FERROCENECARBOXYLIC ACID

[Ferrocene, carboxy-]



Submitted by Perry C. Reeves¹

Checked by J. J. Mrowca, M. M. Borecki, and William A. Sheppard.

1. Procedure

A. *(2-Chlorobenzoyl)ferrocene*. A thoroughly dried, 1-l., three-necked, round-bottomed flask is equipped with a mechanical stirrer, a funnel for the addition of air-sensitive solids (Note 1), and a two-necked adapter holding a thermometer and a gas-inlet tube. Throughout the ensuing reaction the system is maintained under positive pressure of dry nitrogen. The flask is charged with 18.6 g. (0.100 mole) of ferrocene (Note 2), 17.5 g. (0.100 mole) of 2-chlorobenzoyl chloride (Note 3), and 200 ml. of dichloromethane, and the addition funnel contains 14.0 g. (0.105 mole) of anhydrous aluminum chloride. Stirring is begun, and the flask is immersed in an ice bath. When the solution has been chilled thoroughly, the aluminum chloride is added in small portions at such a rate that the reaction mixture remains below 5° . The appearance of a deep blue color indicates that the reaction is occurring. This addition requires about 20 minutes, and after its completion stirring is continued for 30 minutes with ice cooling and for 2 hours at room temperature.

The reaction mixture is cooled again in ice, 200 ml. of water is added cautiously, and the resulting two-phase mixture is stirred vigorously for 30 minutes. After transferring the mixture to a separatory funnel, the layers are separated, and the aqueous layer is extracted with two 50-ml. portions of dichloromethane. The combined dichloromethane solutions are washed once with 50 ml. of water, twice with 50-ml. portions of 10% aqueous sodium hydroxide, and dried over magnesium sulfate, filtered and evaporated to dryness at reduced pressure, yielding 30.4–30.9 g. (94–96%) of (2-chlorobenzoyl)ferrocene as a viscous, red liquid, which gradually solidifies (Note 4).

B. *Ferrocenecarboxylic acid*. A dry, 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser topped with a nitrogen-inlet tube is charged with 250 ml. of 1,2-dimethoxyethane (Note 5) and 46.0 g. (0.411 mole) of potassium *tert*-butoxide (Note 6). A nitrogen atmosphere is established in the system, and 2.2 ml. (0.12 mole) of water (Note 6) is added with stirring, producing a slurry, to which the crude (2-chlorobenzoyl)ferrocene is added. The red solution is stirred and refluxed under nitrogen. As the reaction proceeds the color fades to tan, and after 1 hour at reflux the reaction mixture is cooled and poured into 1 l. of water. The resulting solution is washed with three

150-ml. portions of **diethyl ether**, which are combined and back-extracted with two 50-ml. portions of 10% aqueous **sodium hydroxide**. The aqueous phases are then combined and acidified with concentrated **hydrochloric acid**. The precipitate is collected by filtration and air dried, yielding 17.0–19.2 g. (74–83% from ferrocene) of ferrocenecarboxylic acid as an air-stable yellow powder, m.p. 214–216° (dec., (Note 7)).

2. Notes

1. If such a funnel is not available, an Erlenmeyer flask connected to the reaction flask by a length of thin-walled rubber tubing (Gooch tubing) may be substituted. In this case, the reaction mixture must not be stirred so vigorously that liquid is splashed up into the neck of the flask, which would cause **aluminum chloride** to cake there and prevent it from falling into the flask.
 2. Ferrocene was purchased from Strem Chemicals Incorporated, Danvers, Massachusetts.
 3. **2-Chlorobenzoyl chloride** was purchased from Aldrich Chemical Company, Inc., and used as received with a stated purity of 95%.
 4. The crude material contains approximately 5% of unreacted ferrocene. Recrystallization from **heptane** affords pure (2-chlorobenzoyl)ferrocene as scarlet needles, m.p. 99–100°; however, the crude material may be used without purification for Part B.
 5. **1,2-Dimethoxyethane** was distilled from **calcium hydride** immediately prior to use.
 6. **Potassium tert-butoxide** was purchased from Columbia Organic Chemicals Company, Columbia, South Carolina. The molar ratio of **potassium tert-butoxide** to water is critical, and the amounts specified represent optimum quantities for cleavage of 0.10 mole of ketone.^{2,3}
 7. The decomposition point was obtained in a sealed capillary tube and not corrected. As the solid is heated, it first changes from yellow to brownish red and then decomposes to a dark red liquid. The decomposition temperature of this compound has been reported to be 208.5°,⁴ 224–225°,⁵ and 225–230°.⁶
- The crude product is suitable for most purposes. It may be recrystallized from **toluene** (1 g. in 15–20 ml. of solvent, 80% recovery in the first crop), giving material melting at 220–222° (dec.).

3. Discussion

The carboxylic acids of organometallic systems, important synthetic intermediates, have been prepared by many different synthetic methods. Ferrocenecarboxylic acid has been studied the most extensively,⁷ and the best laboratory syntheses previously reported involve hydrolyses of cyanoferrocene⁸ or *S*-methylferrocenethiocarbonate.⁹

The present synthesis¹⁰ consists of two simple steps, uses readily available and inexpensive starting materials, and produces pure material in high overall yield. It is based on two observations: that nonenolizable ketones may be cleaved to carboxylic acids by **potassium tert-butoxide**–water,² and that aryl 2-chlorophenyl ketones may be cleaved with loss of the 2-chlorophenyl group, giving only one of the two possible acids.¹¹ Other compounds prepared by this route include **carboxycyclopentadienyltricarbonylmanganese** (79%)¹⁰ and several substituted benzoic acids:¹¹ **biphenyl-4-carboxylic acid** (64%), **3,4-dimethylbenzoic acid** (57%), **2,4,6-trimethylbenzoic acid** (59%), **3,4-dimethoxybenzoic acid** (73%), and **2,4-dimethoxybenzoic acid** (60%). In cases where the cleavage reaction proceeds in low yield, substitution of **2,6-dichlorobenzoyl chloride** for **2-chlorobenzoyl chloride** may be helpful. With **thiophene**, for example, the yield of carboxylic acid was increased from 10% to 72% by this modification.¹¹

References and Notes

1. Department of Chemistry, Southern Methodist University, Dallas, Texas 75275. [Present address: Abilene Christian University, Abilene, Texas 79601.] This work was supported by the Robert A. Welch Foundation.
2. G. A. Swan, *J. Chem. Soc.*, 1408 (1948).
3. P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Am. Chem. Soc.*, **89**, 946 (1967).
4. K. L. Rinehart, K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1957).

5. R. L. Schaaf, *J. Org. Chem.*, **27**, 107 (1962).
 6. V. Weinmayr, *J. Am. Chem. Soc.*, **77**, 3009 (1955).
 7. D. E. Bublitz and K. L. Rinehart, *Org. React.*, **17**, 1 (1969).
 8. A. N. Nesmeyanov, E. G. Perevalova, and L. P. Jaryeva, *Chem. Ber.*, **93**, 2729 (1960).
 9. D. E. Bublitz and G. H. Harris, *J. Organomet. Chem.*, **4**, 404 (1965).
 10. E. R. Biehl and P. C. Reeves, *Synthesis*, 360 (1973).
 11. M. Derenberg and P. Hodge, *Tetrahedron Lett.*, 3825 (1971).
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Ferrocene

(2-Chlorobenzoyl)ferrocene

Ferrocenecarboxylic acid

Ferrocene, carboxy-

S-methylferrocenethiocarbonate

hydrochloric acid (7647-01-0)

diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitrogen (7727-37-9)

aluminum chloride (3495-54-3)

toluene (108-88-3)

dichloromethane (75-09-2)

Thiophene (110-02-1)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

2,4,6-trimethylbenzoic acid (480-63-7)

calcium hydride (7789-78-8)

1,2-dimethoxyethane (110-71-4)

2-chlorobenzoyl chloride (609-65-4)

carboxycyclopentadienyltricarbonylmanganese

biphenyl-4-carboxylic acid (92-92-2)

3,4-dimethylbenzoic acid (619-04-5)

3,4-dimethoxybenzoic acid (93-07-2)

2,4-dimethoxybenzoic acid (91-52-1)

2,6-dichlorobenzoyl chloride (4659-45-4)

potassium tert-butoxide (865-47-4)