



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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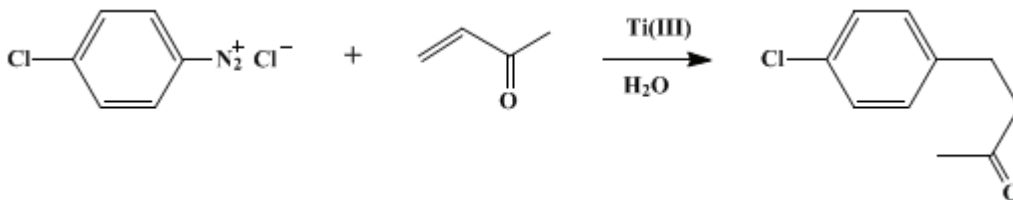
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 7, p.105 (1990); Vol. 62, p.67 (1984).*

## REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS: 4-(4-CHLOROPHENYL)BUTAN-2-ONE

[2-Butanone, 4-(4-chlorophenyl)-]



Submitted by Attilio Citterio

Checked by Robert Haessig, Leo Widler, and Dieter Seebach.

### 1. Procedure

*Caution! Like all vinyl monomers, 3-buten-2-one is toxic and the preparation should be carried out in a well-ventilated hood.*

A 500-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a gas inlet, an externally cooled, pressure-equalizing dropping funnel (Note 1), and a gas bubbler is charged with 15% aqueous titanium trichloride (92 mL, 0.109 mol) (Note 2). *N,N*-Dimethylformamide (Note 3) (70 mL) is added during 45 min with stirring and cooling (ice-bath; 0–5°C) while nitrogen is bubbled through the solution. Freshly distilled 3-buten-2-one (5.7 mL, 0.066 mol) is added at 0–5°C by syringe. The nitrogen flow is stopped, and 4-chlorobenzene diazonium chloride solution (0.044 mol) (Note 4) is added dropwise at 0–5°C from the dropping funnel. After 2–3 min, nitrogen evolution commences, and the rate of addition is adjusted so that 1–2 bubbles per second are vented through the bubbler. Nitrogen evolution continues for 20 min after the addition is complete (1.5 hr). The ice bath is removed and the solution stirred for 1 hr at room temperature. Ether, 50 mL, is added with stirring, and the organic phase is separated. The aqueous phase is extracted with ether (3 × 50 mL) and the combined organic extracts are washed with 3% aqueous  $Na_2CO_3$  (2 × 30 mL) and water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue is distilled to give 5.2–6.0 g (65–75% yield) of 4-(4-chlorophenyl)butan-2-one as a pale-yellow liquid, bp 90–91°C (0.5 mm) (Note 5).

### 2. Notes

- The checkers used a dropping funnel with temperature-control jacket [Normag N 8055, Otto Fritz GmbH, Normschliff-Aufbaugeräte (Normag), D-6238 Hofheim am Taunus].
- The 15% titanium trichloride solution was purchased from Carlo Erba Chemicals or from Merck & Company, Inc., but can also be prepared by dissolving metallic titanium in 20% aqueous hydrochloric acid<sup>1</sup> or by dissolving solid titanium trichloride in 1 M aqueous hydrochloric acid. Titanium(III) sulfate (from BDH Chemicals Ltd.) can also be used. All titanium(III) solutions were titrated with aqueous cerium(IV) sulfate prior to use.
- N,N*-Dimethylformamide from Carlo Erba Chemicals, from Fluka AG or from Merck & Company, Inc. was used as received. Other solvents (e.g., acetone, acetic acid, acetonitrile) can also be used.
- The 4-chlorobenzene diazonium chloride solution is prepared as follows: finely powdered 4-chloroaniline (5.65 g, 0.044 mol) is suspended in 18 mL of 24% aqueous hydrochloric acid and cooled to 0°C. Sodium nitrite (3.2 g, 0.046 mol) in water (7 mL) is added dropwise during 45 min at 0–5°C to give a pale-yellow solution of the diazonium salt.
- The physical properties of the product are as follows:  $n_D^{25}$  1.5251; IR (liquid film)  $cm^{-1}$ : 1715; <sup>1</sup>H NMR ( $CDCl_3$ )  $\delta$ : 2.0 (s, 3 H), 2.6–2.8 (m, 4 H), 6.8–7.3 (m, 4 H); mass spectrum *m/e*: 182 (M); semicarbazone, mp 165°C (164–165.5°C<sup>2</sup>). GLC analysis (glass capillary column, 20 m, pluronic L-64,

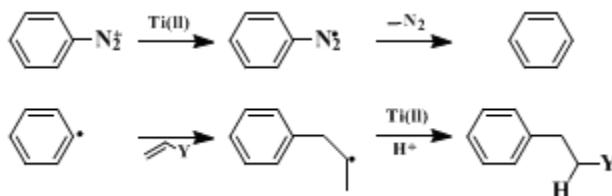
program: 120–200°C at 5°C/min): >99% pure.

### 3. Discussion

This synthesis is only one example of a wide range of reactions that involve aryl (or alkyl) radical addition to electron-deficient double bonds resulting in reduction.<sup>3,4,5</sup> The corresponding oxidative reaction using aryl radicals is the well-known Meerwein reaction,<sup>6</sup> which uses copper(II) salts.

General arylation reactions are summarized by the following equations and some specific examples are presented in Table I.

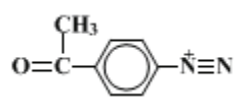
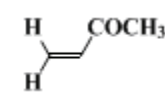
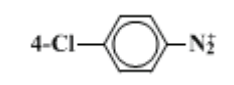
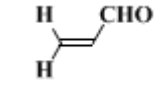
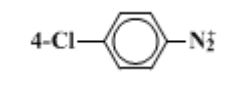
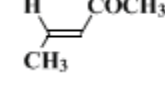
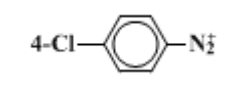
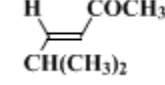
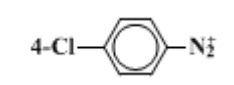
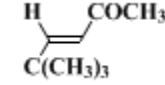
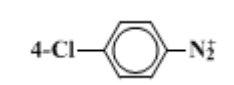
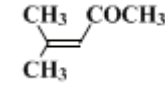
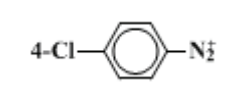
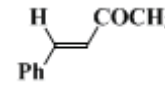
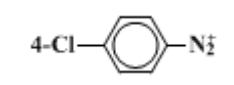
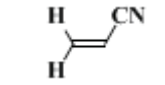
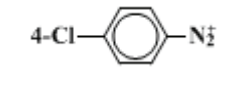
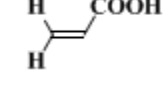
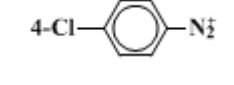
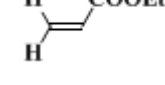
Homolytic cleavage of diazonium salts to produce aryl radicals is induced by titanium(III) salt, which is also effective in reducing the  $\alpha$ -carbonylalkyl radical adduct to olefins, telomerization of methyl vinyl ketone, and dimerization of the adduct radicals. The reaction can be used with other electron-deficient olefins, but telomerization or dimerization are important side reactions.



Other limitations of the reaction are related to the regioselectivity of the aryl radical addition to double bond, which is determined mainly by steric and radical delocalization effects.<sup>7</sup> Thus, methyl vinyl ketone gives the best results, and lower yields are observed when bulky substituents are present in the  $\beta$ -position of the alkene. However, the method represents complete positional selectivity because only the  $\beta$ -adduct radicals give reductive arylation products whereas the  $\alpha$ -adduct radicals add to diazonium salts, because of the different nucleophilic character of the alkyl radical adduct.<sup>7,8</sup>

TABLE I  
REDUCTIVE ARYLATION OF ELECTRON-DEFICIENT OLEFINS BY ARENEDIAZONIUM SALTS INDUCED BY TITANIUM(III) SALTS

	R	R'	Y	Yield (%) <sup>a</sup>
	H	H		65
4-OCH <sub>3</sub>			COCH <sub>3</sub>	
	H	H		75
H			COCH <sub>3</sub>	
	H	H		68
4-Br			COCH <sub>3</sub>	

 <chem>CC(=O)c1ccc([N+]#N)cc1</chem> 4-COCH <sub>3</sub>	H	H	 <chem>CC(=C)C(=O)C</chem> COCH <sub>3</sub>	72
 <chem>Clc1ccc([N+]#N)cc1</chem> 4-Cl	H	H	 <chem>O=C/C=C</chem> CHO	63
 <chem>CC1=CC(Cl)=CC([N+]#N)=C1</chem> 4-Cl	CH <sub>3</sub>	H	 <chem>CC(=C)C(=O)C</chem> COCH <sub>3</sub>	44
 <chem>CC(C)C1=CC(Cl)=CC([N+]#N)=C1</chem> 4-Cl	CH(CH <sub>3</sub> ) <sub>2</sub>	H	 <chem>CC(C)C(=C)C(=O)C</chem> COCH <sub>3</sub>	28
 <chem>CC(C)(C)C1=CC(Cl)=CC([N+]#N)=C1</chem> 4-Cl	C(CH <sub>3</sub> ) <sub>3</sub>	H	 <chem>CC(C)(C)C(=C)C(=O)C</chem> COCH <sub>3</sub>	14
 <chem>CC1=C(C)C(Cl)=CC([N+]#N)=C1</chem> 4-Cl	CH <sub>3</sub>	CH <sub>3</sub>	 <chem>CC(=C)C(=O)C</chem> COCH <sub>3</sub>	12
 <chem>Clc1ccc([N+]#N)cc1</chem> 4-Cl	Ph	H	 <chem>c1ccc(cc1)/C=C/C(=O)C</chem> COCH <sub>3</sub>	18
 <chem>Clc1ccc([N+]#N)cc1</chem> 4-Cl	H	H	 <chem>N#CC=C</chem> CN	25 <sup>b</sup>
 <chem>Clc1ccc([N+]#N)cc1</chem> 4-Cl	H	H	 <chem>OC(=O)/C=C</chem> COOH	33 <sup>b</sup>
 <chem>Clc1ccc([N+]#N)cc1</chem> 4-Cl	H	H	 <chem>CCOC(=O)/C=C</chem> COOEt	32 <sup>b</sup>

<sup>a</sup> From the diazonium salt.

<sup>b</sup> Telomers are formed; the reactions are carried out with twice the amount of titanium(III) salt.

The product described here, 4-(4-chlorophenyl)butan-2-one, was previously prepared in the following ways: (a) by reduction of the corresponding benzalacetone,<sup>9</sup> (b) by catalyzed decarbonylation of 4-chlorophenylacetaldehyde by HFe(CO)<sub>4</sub> in the presence of 2,4-pentanedione,<sup>10</sup> (c) by reaction of 4-chlorobenzyl chloride with 2,4-pentanedione under basic catalysis (K<sub>2</sub>CO<sub>3</sub> in EtOH),<sup>2</sup> (d) by reaction of 4-chlorobenzyl chloride with ethyl 3-oxobutanoate under basic catalysis (LiOH),<sup>11</sup> and (e) by reaction of 3-(4-chlorophenyl)-propanoic acid with methyllithium.<sup>12</sup>

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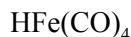
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13. Istituto di Chimica del Politecnico, Piazza L. da Vinci 32, I-20133 Milano, Italy.

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## Appendix

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



hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether (60-29-7)

acetonitrile (75-05-8)

Na<sub>2</sub>CO<sub>3</sub> (497-19-8)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

acetone (67-64-1)

ethyl 3-oxobutanoate (141-97-9)

magnesium sulfate (7487-88-9)

2,4-pentanedione (123-54-6)

N,N-dimethylformamide (68-12-2)

methyl vinyl ketone,  
3-buten-2-one (78-94-4)

Methylithium (917-54-4)

cerium(IV) sulfate (13590-82-4)

4-Chloroaniline (106-47-8)

titanium(III)

titanium (7440-32-6)

titanium trichloride (7705-07-9)

4-(4-Chlorophenyl)butan-2-one,  
2-Butanone, 4-(4-chlorophenyl)- (3506-75-0)

4-chlorobenzenediazonium chloride

Titanium(III) sulfate

4-chlorophenylacetaldehyde

4-chlorobenzyl chloride (104-83-6)

3-(4-chlorophenyl)-propanoic acid (2019-34-3)