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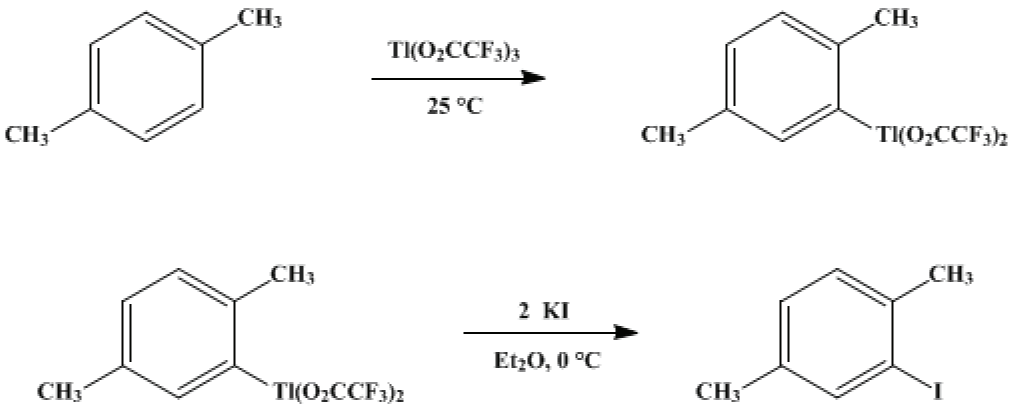
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.055.0070

Organic Syntheses, Coll. Vol. 6, p.709 (1988); Vol. 55, p.70 (1976).

2-IODO-*p*-XYLENE

[Benzene, 2-iodo-1,4-dimethyl]



Submitted by Edward C. Taylor[1], Frank Kienzle[1], and Alexander McKillop[2].
Checked by Gordon S. Bates and S. Masamune.

1. Procedure

Caution! Thallium salts are very toxic. This preparation should be carried out in a well-ventilated hood. The operator should wear rubber gloves. For disposal of thallium wastes, see (Note 1) in Org. Synth., ***Coll. Vol. 6****, 791 (1988).*

A 500-ml., round-bottomed flask equipped with a magnetic stirring bar and a glass stopper is charged with 110 ml. of trifluoroacetic acid (Note 1) and 54.34 g. (0.1008 mole) of solid thallium(III) trifluoroacetate (Note 2). A clear solution is obtained after 30 minutes of vigorous stirring. Upon addition of 10.6 g. (0.100 mole) of *p*-xylene (Note 3), the reaction mixture turns brown (Note 4). After vigorous stirring for 20 minutes, the trifluoroacetic acid is removed on a rotary evaporator with a bath temperature of 35°, and the residue is dissolved in 100 ml. of diethyl ether. The solvent is again evaporated, and the solid residue is dissolved in 100 ml. of ether. With ice cooling (Note 5), a solution of 33.2 g. (0.200 mole) of potassium iodide in 100 ml. of water is added in one portion. After the resulting dark suspension is stirred vigorously for 10 minutes, a solution of 3 g. of sodium bisulfite in 30 ml. of water is added (Note 6). Yellow thallium(I) iodide is removed by filtration after another 10 minutes of vigorous stirring and washed thoroughly with 150 ml. of ether. The aqueous layer is separated and extracted with two 60-ml. portions of ether. The combined ether extracts are washed once with 10% aqueous sodium hydroxide (Note 7) and twice with 20 ml. of water. After being dried over anhydrous magnesium sulfate for 1 hour, the ether is removed on a rotary evaporator. Distillation under reduced pressure yields 18.5–19.6 g. (80–84%) of pure 2-iodo-*p*-xylene, b.p. 110–113° (19 mm.) (Note 8),(Note 9),(Note 10).

2. Notes

1. This chemical is available from Aldrich Chemical Company, Inc., Halocarbon Products Corporation, Allied Chemical Corporation, or Eastman Organic Chemicals.
2. Both the submitters and the checkers used thallium(III) trifluoroacetate prepared from thallium(III) oxide and trifluoroacetic acid.[3] Although this material may be purchased from Aldrich Chemical Company, Inc., and Eastman Organic Chemicals, the submitters recommend that the reagent be prepared immediately prior to use.
3. This reagent is obtainable from major chemical suppliers.
4. The submitters report that *p*-xylylthallium bis(trifluoroacetate) precipitates after 5 minutes. The

checkers did not obtain this precipitate until the bulk of the solvent had been evaporated.
5. The reaction of aqueous potassium iodide and *p*-xylylthallium bis(trifluoroacetate) is exothermic and the ether boils off unless the reaction mixture is cooled.
6. The sodium bisulfite is added to reduce any free iodine formed in this reaction. Due to the presence of trifluoroacetic acid in the reaction mixture, sulfur dioxide evolves upon addition of the bisulfite. If not added in small portions, this operation may cause overflow of the reaction mixture.
7. The sodium hydroxide solution should be added slowly, since the reaction with the acidic ether extract is exothermic and may cause the ether to boil. The ether extract should be washed with aqueous sodium hydroxide until the aqueous layer remains basic to litmus. This extraction is self-indicating; the ether turns from a bright yellow to a light brown and color appears in the aqueous phase.
8. There is usually a lower boiling fraction of 0.1–0.3 g. consisting mainly of unreacted *p*-xylene, along with 1.0–1.6 g. of a dark brown residue.
9. The purity of the product may be checked by GC. The submitters used a 10-m. column with 30% QF-1 on 45/60 Chrom W. The checkers used a 2-m. column of 10% UCW-98 on WAW DMCS operated at 150°.
10. The overall time needed for this preparation is less than 5 hours. The product decomposes slowly and should be refrigerated in the dark.

3. Discussion

This procedure for the synthesis of 2-iodo-*p*-xylene is slightly modified from that of Taylor and McKillop.[3] The reaction is generally applicable to a wide range of aromatic substrates,[3,4] and, with some modifications, to thiophenes. A critical feature of this synthesis is that the entering iodine substituent always replaces thallium at the same position on the aromatic ring. The great preference of the thallium electrophile for the *para*-position in activated aromatic substrates leads, therefore, to iodo-compounds of high isomeric purity. With substituents capable of chelating with the thallium(III) electrophile, thallation may occur by an intramolecular delivery route, resulting in exclusive *ortho*-substitution in optimum cases. Furthermore, aromatic electrophilic thallation is reversible, and under conditions of thermodynamic rather than kinetic control, *meta*-substitution often predominates. The preparation of aromatic iodo-compounds *via* arylthallium bis(trifluoroacetate) intermediates thus possesses the additional advantage of potential orientation control.[4]

2-Iodo-*p*-xylene has been prepared by the action of potassium iodide on diazotized *p*-xylidine (2,5-dimethylaniline) (21% yield),[5] from the reaction of *p*-xylene with molecular iodine in concentrated nitric acid (50% yield)[6] or in ethanol–sulfuric acid in the presence of hydrogen peroxide (64% yield),[7] and with molecular iodine in glacial acetic acid–sulfuric acid in the presence of iodic acid as a catalyst (85% yield).[8]

References and Notes

1. Department of Chemistry, Princeton University, Princeton, New Jersey 08540.
2. School of Chemical Sciences, University of East Anglia, Norwich, Norfolk NR4 7TJ, England.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);

(Registry Number)

ethanol (64-17-5)

sulfuric acid (7664-93-9)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

nitric acid (7697-37-2)

sulfur dioxide (7446-09-5)

potassium iodide (7681-11-0)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

hydrogen peroxide (7722-84-1)

p-xylene (106-42-3)

iodic acid (7782-68-5)

bisulfite (7782-99-2)

magnesium sulfate (7487-88-9)

trifluoroacetic acid (76-05-1)

2,5-dimethylaniline,
p-xylidine (95-78-3)

Thallium (7440-28-0)

thallium(I) iodide

thallium(III)

Benzene, 2-iodo-1,4-dimethyl,
2-Iodo-p-xylene (1122-42-5)

thallium(III) trifluoroacetate (23586-53-0)

thallium(III) oxide (1314-32-5)

p-xylylthallium bis(trifluoroacetate)