Organic Syntheses

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.*

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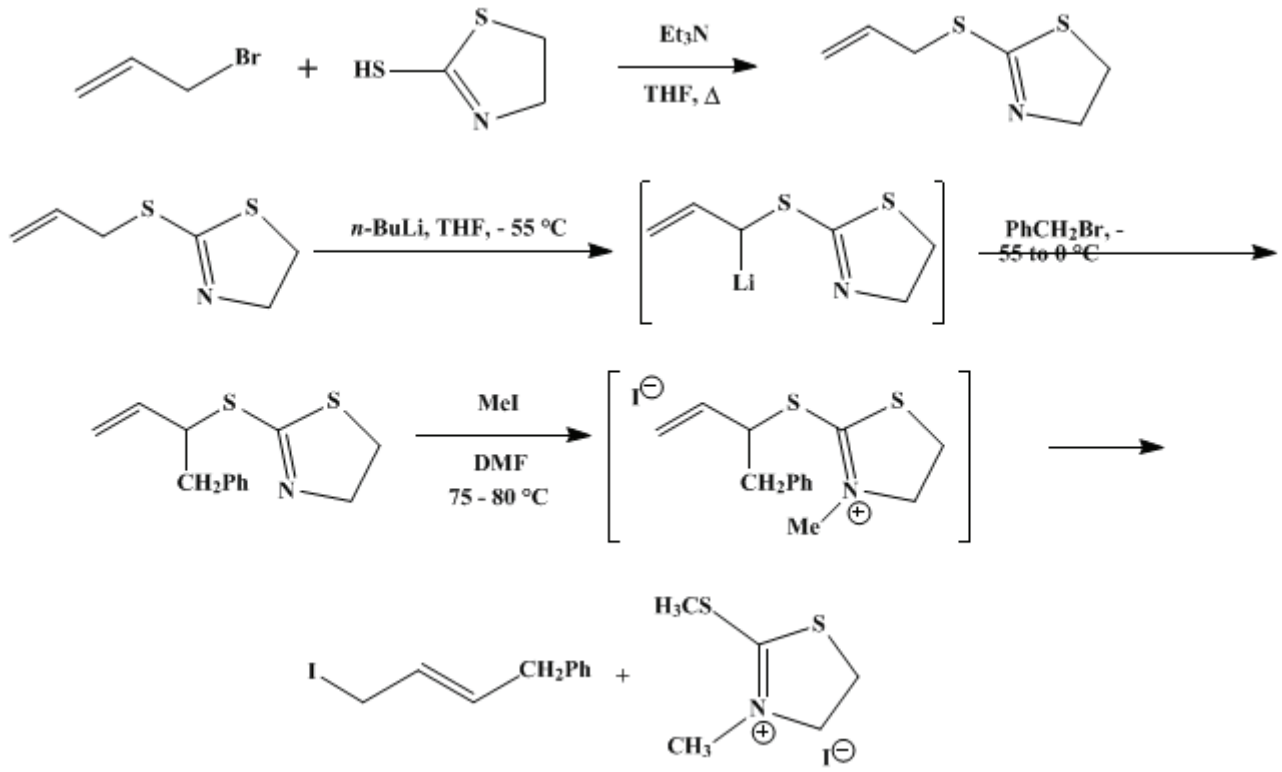
# *trans*-IODOPROPENYLATION OF ALKYL HALIDES: (*E*)-1-IODO-4-PHENYL-2-BUTENE

## [2-Butene, 1-iodo-4-phenyl, (*E*)-]

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## 1. Procedure

*Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*

*Hexamethylphosphoric triamide (HMPA) vapors have been reported to cause cancer in rats.[2] All operations with hexamethylphosphoric triamide should be performed in a good hood, and care should be taken to keep the liquid off the skin.*

*Methyl iodide, in high concentrations for short periods or in low concentrations for long periods, can cause serious toxic effects in the central nervous system. Accordingly, the American Conference of Governmental Industrial Hygienists[3] has set 5 p.p.m., a level which cannot be detected by smell, as the highest average concentration in air to which workers should be exposed for long periods. The preparation and use of methyl iodide should always be performed in a well-ventilated fume hood. Since the liquid can be absorbed through the skin, care should be taken to prevent contact.*

A. 4,5-*Dihydro*-2-(2-*propenylthio*)*thiazole*. A solution of 11.9 g. (0.100 mole) of 2-mercapto-2-

thiazoline (Note 1) in 60 ml. of tetrahydrofuran is prepared in a 200-ml., one-necked, round-bottomed flask fitted with a 25-ml., pressure-equalizing dropping funnel. Allyl bromide (12.1 g., 8.74 ml., 0.100 mole) is added in one portion at room temperature, and 5 minutes later 10.1 g. (13.9 ml., 0.100 mole) of triethylamine is added dropwise over a 10-minute period. After the dropping funnel has been replaced with a condenser, the mixture is refluxed gently for 4 hours. The resulting slurry is cooled and filtered, removing triethylamine hydrobromide, which is washed with 20 ml. of fresh tetrahydrofuran, and the combined organic solutions are concentrated with a rotary evaporator. The residue is dissolved in 100 ml. of diethyl ether, and this solution is washed with three 20-ml. portions of 5% aqueous potassium hydroxide and two 20-ml. portions of water. After drying over anhydrous magnesium sulfate, the ethereal solution is filtered and concentrated with a rotary evaporator. Vacuum distillation of the residue gives 10.9–11.1 g. (69–70%) of 4,5-dihydro-2-(2-propenylthio)thiazole, b.p. 51–54° (0.02 mm., bath temperature 75–80°, (Note 2)); $n_D^{20}$ 1.5864 (Note 3).

B. 4,5-*Dihydro*-2-[(1-*phenylmethyl*-2-*propenyl*)*thio*]*thiazole*. A dry, 100-ml., four-necked, round-bottomed flask is fitted with a thermometer, a rubber septum, a pressure-equalizing dropping funnel, and a mechanical stirrer (Note 4). A positive pressure of nitrogen, applied either through an adapter inserted in the top of the funnel or through a needle inserted in the septum, is maintained throughout the reaction. A solution of 2.0 g. (0.012 mole) of the thiazole prepared in part A in 24 ml. of dry tetrahydrofuran (Note 5) is placed in the flask, stirred vigorously, and cooled in an acetone–dry ice bath. When the internal temperature reaches −55°, 6.0 ml. (0.013 mole) of a 2.1 *M* solution of *n*-butyllithium in *n*-hexane (Note 6) is added by syringe at a rate such that the temperature remains below −55°; approximately 5 minutes is required. After stirring for an additional 20 minutes at −55° to −60°, a solution of 2.15 g. (0.0125 mole) of benzyl bromide (Note 7) in 2 ml. of dry tetrahydrofuran is added at a rate such that the temperature remains below −55°, which again requires approximately 5 minutes. The solution is stirred for another 50 minutes at −55° to −60°, allowed to warm to 0° over 30 minutes, and poured onto 70 ml. of ice water. The resulting mixture is extracted with three 25-ml. portions of ethyl acetate; the extracts are combined, washed with two 15-ml. portions of saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate.

Removal of solvent from the extracts leaves a residue that is purified by dry-column chromatography.[4] The residue is dissolved in 40 ml. of acetone in a 300-ml., round-bottomed flask, 30 g. of silica gel (Note 8) is added, and the acetone is removed with a rotary evaporator. The resulting solid mixture is placed on top of 360 g. of dry silica gel (Note 8) packed in flexible nylon tubing (Note 9), and the column is developed with 420 ml. of 10:1 (v/v) benzene–acetone. Approximately 150 ml. of solvent drips from the bottom of the column toward the end of development; this eluent is collected in 25-ml. fractions and checked for product by TLC (Note 10). The column itself is then cut into 2-cm. sections, the silica gel in each section is eluted with three 25-ml. portions of ethyl acetate, and the eluent from each section is analyzed by TLC (Note 10). Combination of all the product-containing fractions yields 1.2–1.5 g. (40–47%) of the benzylated compound as an oil, $n_D^{20}$ 1.6083 (Note 11) and (Note 12).

C. (E)-1-*Iodo*-4-*phenyl*-2-*butene*. A 20-ml., round-bottomed flask is charged with 2.0 g. (0.008 mole) of the thiazole prepared in Part B, 5 ml. of methyl iodide, and 2 ml. of *N,N*-dimethylformamide. The resulting solution is heated at 75–80° for 2.5 hours under a nitrogen atmosphere (Note 13), cooled, and poured into 10 ml. of water. Extraction with three 12-ml. portions of ether separates the product from water-soluble by-products. The extracts are combined, washed with 8 ml. of 1% aqueous sodium thiosulfate and two 8-ml. portions of water, dried over anhydrous magnesium sulfate, and filtered. Removal of ether by distillation at 30° (100 mm.) leaves 1.5–1.7 g. (74–82%) of (*E*)-1-iodo-4-phenyl-2-butene (Note 14) and (Note 15).

## 2. Notes

1. This product was purchased from the Aldrich Chemical Company, Inc., and used without further purification.
2. Rapid distillation is required to avoid a [3,3]-sigmatropic rearrangement, which gives *N*-allylthiazolidine-2-thione.
3. IR (neat) cm.$^{-1}$: 1570, 995, 965, 920; $^1$H NMR ($CDCl_3$), (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.39 (t, *J* = 7, 2H, ring C*H*$_2$), 3.75 (d, *J* = 6, 2H, allylic C*H*$_2$), 4.20 (t, *J*

= 7, 2H, ring C$H_2$), 5.0–5.4 (m, 2H, CH=C$H_2$), 5.6–6.3 (m, 1H, C$H$=C$H_2$).
4. A three-necked flask may be used if magnetic stirring is substituted for mechanical stirring or if benzyl bromide is added with a syringe instead of a dropping funnel.
5. Tetrahydrofuran was distilled from lithium aluminum hydride immediately prior to use. See *Org. Synth.*, **Coll. Vol. 5**, 976 (1973) for precautions.
6. This product was purchased from Sankyo Kasei, Inc., Tokyo (submitters) and Ventron Corporation (checkers).
7. This product was purchased from the Aldrich Chemical Company, Inc., and distilled prior to use, b.p. 126–128° (80 mm.).
8. Woelm silica gel for dry-column chromatography, activity III/30 mm. (according to Brockmann and Schodder,[5]) was supplied by M. Woelm, Eschwege, Germany.
9. Woelm nylon column DCC-5 was used, giving a packed column 66–67 cm. high and 32 mm. in diameter.
10. Merck precoated silica gel $F_{254}$ plates, layer thickness 0.25 mm., were used. Developed with 10:1 (v/v) benzene–acetone and visualized with UV light, the product appears at $R_f$ 0.58–0.67. Normally the product is found in the lower third of the column, and occasionally some is found in the last fractions of eluent collected during development. However, since the exact position of this material on the column depends critically on the way in which the column is packed, a thorough check of all fractions is advisable.
11. IR (neat) cm.$^{-1}$: 1570, 995, 965, 920, 740, 700; $^1$H NMR ($CDCl_3$), δ (multiplicity, coupling constant $J$ in Hz., number of protons, assignment): 2.9–3.4 (m, 4H, ring C$H_2$ and $C_6H_5CH_2$), 4.14 (t, $J$ = 8, 2H, ring C$H_2$), 4.3–4.7 (m, 1H, allylic C$H$), 4.9–5.3 (m, 2H, C$H_2$=CH), 5.5–6.2 (m, 1H, $CH_2$=C$H$), 7.23 (broad s, 5H, $C_6H_5$).
12. The submitters also tried to purify the crude product by distillation (130–145° at 0.005 mm.), but under these conditions decomposition occurred. It is possible to substitute thick-layer chromatography for the dry column. Using Merck silica gel $F_{254}$ precoated plates, layer thickness 2 mm., and developing with 10:1 (v/v) benzene–acetone, the submitters report a 73% yield of pure product.
13. *N*-Methyl-2-methylthiothiazolium iodide (m.p. 132°) usually precipitates as the reaction proceeds.
14. (*E*)-1-Iodo-4-phenyl-2-butene is reported to decompose on attempted distillation at 4 mm.[6] The crude product, which is suitable for subsequent reactions (see (Note 15)), may be purified by thick-layer chromatography. Using the plates described in (Note 10) and developing with hexane, the product is found at $R_f$ 0.5 as an oil, $n_D^{20}$ 1.5940; IR (neat) cm.$^{-1}$: 1655 weak, 1600 medium, 1460 strong, 1150 strong, 960 strong (*trans*-CH=CH-), 740 strong, 690 strong; $^1$H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 3.2–3.5 (m, 2H, $C_6H_5CH_2$), 3.7–4.0 (m, 2H, C$H_2$I), 5.6–5.9 (m, 2H, vinylic C$H$), 7.23 (broad s, 5H, $C_6H_5$).
15. This material may be converted directly to a phosphonium salt: 1.40 g. (0.00545 mole) of the crude iodide is dissolved in 20 ml. of benzene, and 1.42 g. (0.00542 mole) of triphenylphosphine is added. On standing, 2.5 g. (77%) of the triphenylphosphonium salt precipitates as a colorless 1:1 complex with benzene, m.p. 135–137°. Recrystallization from methanol–benzene raises the melting point to 140–142°. Analysis calculated for $C_{28}H_{29}PI{\cdot}C_6H_6$: C, 68.23; H, 5.39. Found: C, 68.15; H, 5.28.

## 3. Discussion

(*E*)-1-Iodo-4-phenyl-2-butene has been prepared previously by addition of phenyl and chloro units [generated by decomposition of phenyldiazonium chloride in the presence of a catalytic amount of copper(II) chloride] across the conjugated system of butadiene, followed by treatment with ethanolic potassium iodide.[6]

The present preparation illustrates a general and convenient method for the *trans*-iodopropenylation of an alkyl halide.[7] The iodopropenylated material is not usually stable but is a useful synthetic intermediate. For example, it forms a stable crystalline triphenylphosphonium salt for use in the Wittig reaction, and under Kornblum reaction conditions it gives an (*E*)-α,β-unsaturated aldehyde. In addition to the phosphonium salt described in (Note 15), the following have been prepared: (4-methoxyphenyl-2-butenyl)triphenylphosphonium iodide, m.p. 123–127°; (2-octenyl)triphenylphosphonium iodide, m.p. 98°; and (2-octadecenyl)triphenylphosphonium iodide, m.p. 50°.

The alkylation of 4,5-dihydro-2-(2-propenylthio)thiazole is noteworthy, since in general the

coupling of an alkyllithium and an alkyl halide gives many by-products due to halogen–metal interconversion.[8] In the present case, alkylation α to sulfur occurred cleanly and may be attributed to a five-membered chelating effect.[9,10] In some cases, addition of 1/10–1/20 volume of hexamethylphosphoric triamide to the tetrahydrofuran solution facilitates the alkylation. Representative alkyl halides examined and the yields of products isolated are as follows: (a) amyl bromide, (63%); (b) decyl bromide, (70%); (c) anisyl chloride, (57%); (d) phenethyl bromide, (59%); and (e) cyclohexyl bromide, (52%).[7,9] The same type of alkylation occurred successfully with anions of the 4,5-dihydro derivatives of 2-(methylthio)thiazole, 2-[(3-phenyl-2-propenyl)thio]thiazole, and 2-(phenylmethylthio) thiazole, but attempts to alkylate 4,5-dihydro-2-(ethylthio)thiazole, 2-(methylthio)- or 2-(2-propenylthio)benzo[d]thiazole were unsuccessful.

The final step, C-S bond cleavage with allylic rearrangement, incorporates two useful features. First, it is stereospecific, producing only the (*E*)-iodopropenylated product. Second, the sulfur-containing moiety is converted to a water-soluble product; thus, the desired material may be isolated in reasonable purity by a simple water–ether partitioning of the crude reaction mixture. The present procedure represents an improvement over a previous iodomethylation sequence (lithiation of thioanisole, alkylation, and cleavage with methyl iodide and sodium iodide in *N,N*-dimethyl formamide at 75°), in which the product must be separated from thioanisole.[11]

## References and Notes


1. Central Research Laboratories, Sankyo Company Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan.
2. J. A. Zapp, Jr., *Science*, **190**, 422 (1975).
3. American Conference of Governmental Industrial Hygienists (ACGIH), "Documentation of Threshold Limit Values," 3rd ed., Cincinnati, Ohio, 1971, p. 166.
4. B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1965).
5. H. Brockman and H. Schodder, *Ber. Dtsch. Chem. Ges.*, **74B**, 73 (1941).
6. A. V. Dombrovskii and A. P. Terent'ev, *Zh. Obshch. Khim.*, **26**, 2776 (1956) [*Chem. Abstr.* **51**, 7337*d* (1957)].
7. K. Hirai and Y. Kishida, *Tetrahedron Lett.*, 2743 (1972).
8. R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951).
9. K. Hirai, H. Matsuda, and Y. Kishida, *Tetrahedron Lett.*, 4359 (1971);
10. T. Mukaiyama, K. Narasaka, K. Maekawa, and M. Furusato, *Bull. Chem. Soc.*, **44**, 2285 (1971).
11. E. J. Corey and M. Jautelat, *Tetrahedron Lett.*, 5787 (1968).


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

silica gel

2-(methylthio)- or 2-(2-propenylthio)benzo[d]thiazole

Benzene (71-43-2)

ethyl acetate (141-78-6)

methanol (67-56-1)

ether,

diethyl ether (60-29-7)

sodium chloride (7647-14-5)

Allyl bromide (106-95-6)

potassium iodide (7681-11-0)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

phenyldiazonium chloride

sulfur (7704-34-9)

acetone (67-64-1)

potassium hydroxide (1310-58-3)

copper(II) chloride (7758-89-6)

Cyclohexyl bromide (108-85-0)

Methyl iodide (74-88-4)

sodium iodide (7681-82-5)

magnesium sulfate (7487-88-9)

phenethyl bromide (103-63-9)

butadiene (106-99-0)

benzyl bromide (100-39-0)

n-butyllithium (109-72-8)

2-mercapto-2-thiazoline

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

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

hexane,
n-hexane (110-54-3)

triethylamine (121-44-8)

anisyl chloride (623-12-1)

triphenylphosphine (603-35-0)

triethylamine hydrobromide (636-70-4)

hexamethylphosphoric triamide (680-31-9)

thioanisole (100-68-5)

amyl bromide (110-53-2)

4,5-Dihydro-2-(2-propenylthio)thiazole (3571-74-2)

triphenylphosphonium

decyl bromide (112-29-8)

2-(methylthio)thiazole

2-[(3-phenyl-2-propenyl)thio]thiazole

2-(phenylmethylthio)thiazole

4,5-dihydro-2-(ethylthio)thiazole

(E)-1-Iodo-4-phenyl-2-butene,
2-Butene, 1-iodo-4-phenyl, (E)- (52534-83-5)

N-allylthiazolidine-2-thione

N-Methyl-2-methylthiothiazolium iodide

4,5-Dihydro-2-[(1-phenylmethyl-2-propenyl)thio]thiazole (52534-82-4)

(4-methoxyphenyl-2-butenyl)triphenylphosphonium iodide

(2-octenyl)triphenylphosphonium iodide

(2-octadecenyl)triphenylphosphonium iodide