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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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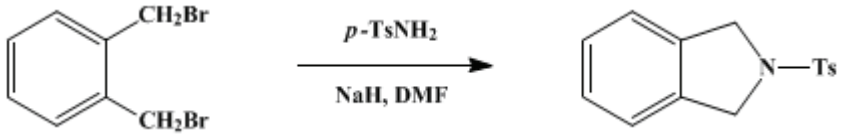
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.047.0110

Organic Syntheses, Coll. Vol. 5, p.1064 (1973); Vol. 47, p.110 (1967).

2-(*p*-TOLYLSULFONYL)DIHYDROISOINDOLE

[Isoindoline, 2-*p*-tolylsulfonyl-]



Submitted by J. Bornstein and J. E. Shields[1].
Checked by Rosetta McKinley and R. E. Benson.

1. Procedure

Caution! This reaction should be carried out in a good hood because hydrogen is evolved and o-xylylene dibromide is a powerful lachrymator (Note 6).

A 1-l. three-necked flask is fitted with an efficient stirrer (Note 1), thermometer, condenser, and a pressure-equalizing dropping funnel that carries an inlet for admission of dry nitrogen. The entire apparatus is dried by warming with a soft flame as a brisk stream of nitrogen is passed through the system. The flow of nitrogen is reduced to a slow stream, and in the cooled flask are placed 18.9 g. (0.42 mole) of 53% sodium hydride dispersed in mineral oil (Note 2) and 60 ml. of purified dimethylformamide (Note 3). The mixture is stirred at room temperature and a solution of 34.2 g. (0.20 mole) of *p*-toluenesulfonamide (Note 4) in 100 ml. of purified dimethylformamide is added dropwise over a period of 1 hour. The resulting suspension is stirred at room temperature for 1 hour and then at 60° for an additional hour (Note 5).

A solution of 52.8 g. (0.20 mole) of *o*-xylylene dibromide (Note 6) in 300 ml. of purified dimethylformamide is added dropwise with stirring at such a rate as to maintain a temperature of 60–70° (Note 7). Subsequently the reaction mixture is stirred at room temperature for 3 hours and then poured into 600 ml. of ice water in a 2-l. Erlenmeyer flask. After standing at room temperature overnight the product is collected by suction filtration, pressed on the funnel, and washed twice with 100-ml. portions of water. The crude product is air-dried on filter paper for 2–3 hours and is then dissolved in 1.2 l. of boiling 95% ethanol. The solution is filtered through a heated funnel, and the filtrate is refrigerated overnight. The crystals are collected on a Buchner funnel and washed on the funnel with 100 ml. of cold 95% ethanol. The product is dried over phosphorus pentoxide in a vacuum desiccator. The yield of white crystals of 2-(*p*-tolylsulfonyl)dihydroisoindole is 41–46 g. (75–84%), m.p. 174–175° (dec.).

2. Notes

1. Either a paddle-type sealed stirrer or a heavy-duty magnetic stirrer is suitable.
2. Sodium hydride was obtained from Metal Hydrides Division of Ventron Corporation, Beverly, Massachusetts.
3. Dimethylformamide, b.p. 152–154°, purchased from Matheson, Coleman and Bell, was stirred for 5 minutes with solid potassium hydroxide, decanted, shaken briefly with lime, filtered, and distilled.
4. Commercial *p*-toluenesulfonamide of high purity was recrystallized from water and dried over phosphorus pentoxide in a vacuum desiccator, m.p. 134–135°.
5. It is necessary to maintain vigorous stirring at this stage to prevent excessive foaming due to the evolution of hydrogen.
6. Precautions to be observed in handling *o*-xylylene dibromide are described in *Org. Syntheses*, Coll. Vol. **4**, 984 (1963). The dibromide was purchased from Eastman Organic Chemicals, recrystallized from 95% ethanol (3 ml./g.), and dried over potassium hydroxide in a vacuum desiccator, m.p. 89–91°.
7. Control of the temperature at this point is critical; a deeply colored product is obtained if the

temperature is allowed to exceed 70°. The addition of the dibromide requires about 1 hour.

3. Discussion

2-(*p*-Tolylsulfonyl)dihydroisoindole has been prepared by alkylation of *p*-toluenesulfonamide with *o*-xylylene dibromide in the presence of sodium methoxide in ethanol.[2,3]

4. Merits of the Preparation

This is the most practical procedure for the preparation of 2-(*p*-tolylsulfonyl)dihydroisoindole. It is superior to earlier ones[2,3] because it is more convenient and affords considerably higher yields (*ca.* 80% versus *ca.* 45%).

The method illustrates the ability of the sodium hydridedimethylformamide system to effect the alkylation of aromatic sulfonamides under mild conditions and in good yield. The method appears to be fairly general. The submitters have prepared N,N-diethyl- and N,N-di-*n*-butyl-*p*-toluenesulfonamide as well as 2-(*p*-tolylsulfonyl)benz[*f*]isoindoline from 2,3-bis-(bromomethyl)naphthalene, and 1-(*p*-tolylsulfonyl)pyrrolidine from 1,4-dichlorobutane; the yield of purified product exceeded 75% in each case.

The reductive cleavage of 2-(*p*-tolylsulfonyl)dihydroisoindole to 1,3-dihydroisoindole constitutes the most convenient synthesis of this heterocyclic compound.[3] The sulfonamide is also useful in the synthesis of isoindole.[4]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 406

References and Notes

1. Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167.
2. G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3295 (1928).
3. J. Bornstein, S. C. Lashua, and A. P. Boisselle, *J. Org. Chem.*, **22**, 1255 (1957).
4. R. Kreher and J. Seubert, *Z. Naturforsch.*, **20b**, 75 (1965).

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

N,N-diethyl- and N,N-di-n-butyl-p-toluenesulfonamide

ethanol (64-17-5)

hydrogen (1333-74-0)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

potassium hydroxide (1310-58-3)

1,4-dichlorobutane (110-56-5)

dimethylformamide (68-12-2)

sodium hydride (7646-69-7)

1,3-Dihydroisoindole (496-12-8)

o-Xylylene dibromide (91-13-4)

2,3-bis-(bromomethyl)naphthalene

isoindole

phosphorus pentoxide (1314-56-3)

p-toluenesulfonamide (70-55-3)

2-(p-Tolylsulfonyl)dihydroisoindole,
Isoindoline, 2-p-tolylsulfonyl- (32372-83-1)

2-(p-tolylsulfonyl)benz[f]isoindoline

1-(p-tolylsulfonyl)pyrrolidine