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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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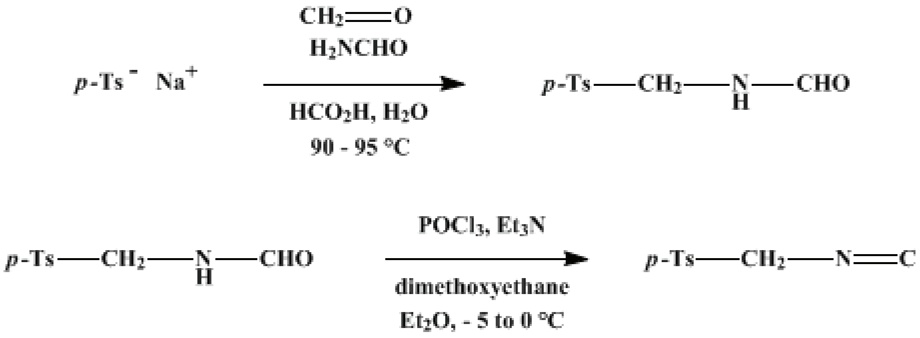
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.057.0102

Organic Syntheses, Coll. Vol. 6, p.987 (1988); Vol. 57, p.102 (1977).

p-TOLYLSULFONYLMETHYL ISOCYANIDE

[Benzene, 1-((isocyanomethyl)sulfonyl)-4-methyl-]



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1. Procedure

Caution! The reaction should be conducted in a well-ventilated fume hood.

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.

A. N-(p-*Tolylsulfonylmethyl)formamide.*[2] A 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a condenser, and a thermometer is charged with 267 g. (1.50 moles) of sodium *p*-toluenesulfinate (Note 1). After addition of 750 ml. of water, 350 ml. (378 g.) of an aqueous 34–37% solution of formaldehyde (*ca.* 4.4 moles) (Note 2), 680 g. (600 ml., 15.5 moles) of formamide (Note 3), and 244 g. (200 ml., 5.30 moles) of formic acid (Note 4), the stirred reaction mixture is heated at 90°. The sodium *p*-toluenesulfinate dissolves during heating, and the clear solution is kept at 90–95° for 2 hours (Note 5). The reaction mixture is cooled to room temperature in an ice–salt bath with continued stirring, then further cooled overnight in a freezer at −20°. The white solid (Note 6) is collected by suction filtration and washed thoroughly in a beaker by stirring with three 250-ml. portions of ice water. The product is dried under reduced pressure over phosphorus pentoxide at 70° (Note 7), yielding 134–150 g. (42–47%) of crude *N*-(*p*-tolylsulfonylmethyl)formamide, m.p. 106–110° (Note 8), which is sufficiently pure for use in the next step.

B. p-*Tolylsulfonylmethyl isocyanide.* A 3-l., four-necked, round-bottomed flask equipped with a mechanical stirrer, a thermometer, a 250-ml. dropping funnel, and a drying tube is charged with 107 g. (0.502 mole) of crude *N*-(*p*-tolylsulfonylmethyl)formamide, 250 ml. of 1,2-dimethoxyethane, 100 ml. of anhydrous diethyl ether, and 255 g. (350 ml., 2.52 moles) of triethylamine (Note 9). The stirred suspension is cooled in an ice–salt bath to −5°. A solution of 84 g. (50 ml., 0.55 mole) of phosphorus oxychloride (Note 10) in 60 ml. of 1,2-dimethoxyethane is added from the dropping funnel at such a rate that the temperature is kept between −5° and 0° (Note 11). During the reaction, the *N*-(*p*-tolylsulfonylmethyl)formamide gradually dissolves and triethylamine salts precipitate. Near the completion of the reaction the white suspension slowly turns brown (Note 12). After stirring for another 30 minutes at 0°, 1.5 l. of ice water is added with continued stirring. The solid material dissolves, giving a clear, dark-brown solution before the product begins to separate as a fine, brown, crystalline solid. After stirring for an additional 30 minutes at 0°, the precipitate is collected by suction filtration and washed with 250 ml. of cold water. The wet product is dissolved in 400 ml. of warm benzene (40–60°), the aqueous layer is removed with a separatory funnel, and the dark-brown benzene solution is dried over anhydrous magnesium sulfate. After removal of the magnesium sulfate, 2 g. of activated carbon (Note 13) is added, and the mixture is heated at about 60° for 5 minutes and filtered (Note 14). One liter of petroleum ether (b.p. 40–60°) is added to the filtrate with thorough swirling. After 30 minutes the precipitate is collected by suction filtration and dried in a vacuum desiccator, yielding 74–82 g. (76–84%) of crude *p*-tolylsulfonylmethyl isocyanide as a light-brown, odorless solid, m.p. 111–114° (dec.) (Note 15), which can be used for synthetic purposes without further purification.

Completely white material is obtained by rapid chromatography through alumina (Note 16). An analytically pure product, m.p. 116–117° (dec.), is obtained after one recrystallization from methanol.

2. Notes

1. The submitters used anhydrous sodium *p*-toluenesulfinate ("purum" quality, *ca.* 97% from Fluka A G), and the checkers purchased the reagent from Aldrich Chemical Company, Inc. Compare also Note 1 in the preparation of *p*-tolylsulfonyldiazomethane [*Org. Synth.*, **Coll. Vol. 6**, 981 (1988)].
2. Commercial aqueous formaldehyde solution containing 8% methanol was used. Formaldehyde is needed in excess; otherwise the yield is considerably diminished.
3. Commercial formamide (E. Merck, Darmstadt) was used. The use of a large excess of formamide with respect to the sulfinate is required to obtain the yield specified.[2]
4. Commercial 97% formic acid (J. T. Baker Chemical Company) was used.
5. Prolonged heating lowers the yield considerably.
6. When no solid is formed overnight, crystallization may be induced by scratching. In this case the solution should be kept for another 4 hours at −20° before the product is collected.
7. The drying process can be speeded up by dissolving the wet product in dichloromethane, removing the water layer in a separatory funnel, drying the dichloromethane solution over anhydrous magnesium sulfate, and removing the solvent on a rotary evaporator.
8. Recrystallization from 95% ethanol or benzene raised the m.p. to 108–110°.
9. 1,2-Dimethoxyethane and triethylamine, both in "zur Synthese" quality, were purchased from E. Merck, Darmstadt. Ether was distilled from phosphorus pentoxide and stored over sodium wire.
10. Commercial phosphorus oxychloride ("tout pur" from UCB, Belgium) was used without purification.
11. The addition requires about 1 hour. At the beginning of the reaction much heat is evolved, and, therefore, the phosphorus oxychloride solution should initially be added very slowly.
12. The development of a brown color indicates that sufficient phosphorus oxychloride has been added. If the mixture remains colorless, the final product is likely to be contaminated with unreacted *N*-(*p*-tolylsulfonylmethyl)formamide. It is therefore advantageous to add more phosphorus oxychloride and continue stirring until the brown color is obtained.
13. Activated carbon was purchased from J. T. Baker Chemical Company.
14. The color of the solution is lightened only slightly by treatment with activated carbon, but eventually a purer product is obtained.
15. The product has the following spectral properties; IR (Nujol) cm.$^{-1}$: 2150 (N=C), 1320 and 1155 (SO_2); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.5 (s, 3H, CH_3), 4.6 (s, 2H CH_2), 7.7 (q, 4H, C_6H_4).
16. A solution of 50 g. of *p*-tolylsulfonylmethyl isocyanide in 150 ml. of dichloromethane is placed on a 40 × 3 cm. column containing about 100 g. of neutral alumina slurried in dichloromethane. A nearly colorless solution (*ca.* 700 ml.) is collected over about 1 hour. This solution is evaporated to dryness on a rotary evaporator, providing 42–47 g. of white *p*-tolylsulfonylmethyl isocyanide, m.p. 113–114° (dec.).

3. Discussion

p-Tolylsulfonylmethyl isocyanide was originally obtained by irradiation of *p*-tolylsulfonyldiazomethane[3] in liquid hydrogen cyanide.[4] This isocyanide represents a group of sulfonylmethyl isocyanides, most of which have been prepared, as in the present procedure, by dehydration of the corresponding formamides.[4,5] *p*-Tolylsulfonylmethyl isocyanide has also been prepared by reaction of *p*-tolylsulfonyl fluoride with isocyanomethyllithium.[4,6] The advantages of the present dehydration method are twofold: (1) it is a simple procedure using readily available and inexpensive starting materials and (2) the use of the foul-smelling methyl isocyanide is avoided.

p-Tolylsulfonylmethyl isocyanide is a useful and versatile reagent.[7] It has been used for the synthesis of several azole ring systems by base-induced addition of its C-N=C moiety to various C=O, C=N, C=S, C=C, and N=N containing substrates. Thus, oxazoles,[7,8,9,10] imidazoles,[7,8,11,12] thiazoles,[7,13] pyrroles,[7,8] and 1,2,4-triazoles,[7] have been prepared, respectively. Furthermore, *p*-tolylsulfonylmethyl isocyanide has found use in a one-step conversion of ketones and aldehydes to cyanides containing one more carbon atom.[7,14]

Another application is based on the umpolung principle. In this sense *p*-tolylsulfonylmethyl isocyanide is a formaldehyde anion or dianion equivalent,[7,10] which has been used in the synthesis of symmetrical and unsymmetrical ketones,[7,15,16] α-diketones,[7,17] α-hydroxy aldehydes,[7] and α-hydroxy ketones.[7] Under reducing reaction conditions amino, methylamino or β-hydroxy methylamino compounds have been prepared from the same intermediates.[7]

Finally, *p*-tolylsulfonylmethyl isocyanide can be transformed into 1-isocyano-1-tosylalkenes,[7] which are useful synthons in their own right, as appears from their use in the synthesis of imidazoles[12] and pyrroles.[7]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 41

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Appendix

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

petroleum ether

ethanol (64-17-5)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

formamide (75-12-7)

formaldehyde (50-00-0)

hydrogen cyanide (74-90-8)

formic acid (64-18-6)

sulfur (7704-34-9)

carbon (7782-42-5)

Phosphorus Oxychloride (21295-50-1)

sodium wire (13966-32-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

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

Methyl isocyanide (593-75-9)

Benzene, 1-((isocyanomethyl)sulfonyl)-4-methyl-,
p-Tolylsulfonylmethyl isocyanide (36635-61-7)

p-Tolylsulfonyldiazomethane (1538-98-3)

isocyanomethyllithium

phosphorus pentoxide (1314-56-3)

Sodium p-toluenesulfinate

N-(p-tolylsulfonylmethyl)formamide (36635-56-0)

p-tolylsulfonyl fluoride (455-16-3)