Organic Syntheses

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of Reliable Methods
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.

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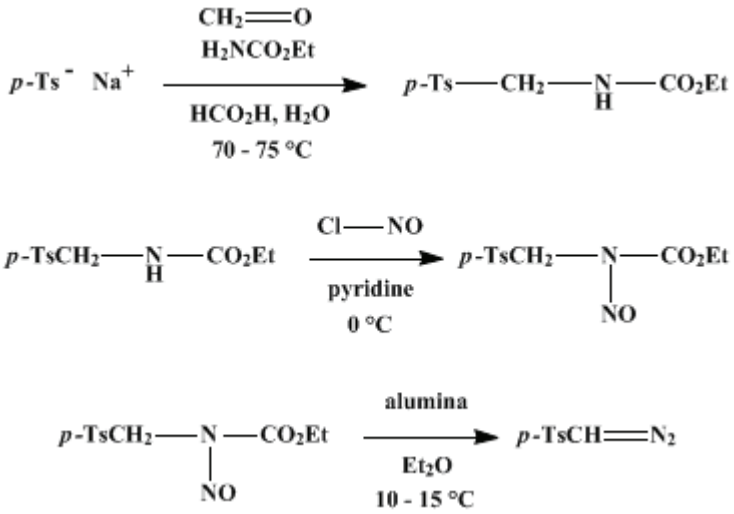
p-TOLYLSULFONYLDIAZOMETHANE

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



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1. Procedure

Caution! Part B must be conducted in a efficient hood to avoid exposure to toxic nitrosyl chloride.

A. *Ethyl* N-(p-*tolylsulfonylmethyl*)*carbamate*. A solution of 178 g. (1.00 mole) of sodium *p*-toluenesulfinate (Note 1) in 1 l. of water is placed in a 3-l., three-necked flask equipped with a condenser, an efficient mechanical stirrer, and a thermometer. After addition of 100 ml. (108 g.) of an aqueous 34–37% solution of formaldehyde (*ca.* 1.2–1.4 moles) (Note 2), 107 g. (1.20 moles) of ethyl carbamate (Note 3), and 250 ml. of formic acid (Note 4), the stirred solution is heated to 70°. Soon after this temperature is reached, the reaction mixture becomes turbid due to separation of the product as oily droplets, which are kept dispersed with vigorous stirring. After heating for 2 hours at 70–75°, the heating mantle is replaced with an ice bath, while stirring is continued. At about 60° the product begins to solidify. Under continued stirring the mixture is cooled further and kept in the ice bath for 2 hours after a temperature of 5° is reached (Note 5). The precipitate is collected by suction filtration and washed three times by stirring efficiently with 400-ml. portions of cold water. After drying at 70° to constant weight, 214–232 g. (83–90%) (see (Note 1)) of white, microcrystalline ethyl *N*-(*p*-toluenesulfonylmethyl)carbamate, m.p. 108–110°, is obtained; it is sufficiently pure for use in the next step of the reaction. Recrystallization from 95% ethanol provides colorless flasks, m.p. 109–111°

B. *Ethyl* N-*nitroso*-N-(p-*tolylsulfonylmethyl*)*carbamate*. A solution of 154 g. (0.599 mole) of the ethyl *N*-(*p*-tolylsulfonylemthyl)carbamate in 600 ml. of pyridine (Note 6) is placed in a 1-l., four-necked flask equipped with a thermometer, a mechanical stirrer, a gas-inlet tube leading into the solution, and a gas outlet leading to the exhaust. The weight of the flask together with its contents is determined, preferably on a balance placed in the same hood. The solution is cooled to 0° in an ice–salt mixture. Gaseous nitrosyl chloride (Note 7) is introduced, *via* a mineral oil bubbler and a trap, into the stirred solution at such a rate that the temperature is kept between 0° and 5°. After 52–65 g. (0.79–0.99 mole) of nitrosyl chloride has been taken up (Note 8), the reaction is completed by stirring for 30 minutes at about 0°, at which point the reaction mixture is poured in a thin stream into a hand-stirred mixture of 4 l. of ice and water, giving a pale-yellow oil that readily solidifies (Note 9). The solid is collected by suction filtration after standing for 1 hour at 0°. Any lumps present are pulverized, and the solid is

washed thoroughly in a beaker with four 500-ml. portions of cold water, removing pyridine. The moist product is dissolved in sufficient dichloromethane (*ca.* 1.5 l.) and the water layer is removed. The dichloromethane solution is dried over anhydrous magnesium sulfate and concentrated to dryness under reduced pressure, giving 157–171 g. (92–100%) of crude ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl) carbamate, m.p. 86–89° (slight dec.). The crude nitroso compound can be used without purification in the next step of the reaction, provided that it is free of starting material (Note 10).

If the nitrosocarbamate is to be stored (preferably at −20°) for periods longer than a month, it should be recrystallized once from 1:2 dichloromethane-diethyl ether (Note 11), m.p. 87–89°. In this purified form it can be stored for several months at −20° without noticeable decomposition.

C. p-*Tolylsulfonyldiazomethane*. *Warning! α-Diazosulfones slowly decompose under the influence of light. Exposure to light should therefore be kept at a minimum in all stages of the reaction.* A 3-l., three-necked, round-bottomed flask equipped with a condenser, an efficient mechanical stirrer, and a stopper, is charged with 570 g. of alumina (Note 12). The flask is wrapped with aluminum foil or covered with dark cloth or black paper. With stirring, 1.5 l. of ether (Note 13) is added. The mixture is cooled to 10–15° with a water–ice bath, and a solution of 57.3 g. (0.200 mole) of ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl)carbamate in 150 ml. of dichloromethane (Note 14) is added in one portion. Stirring is continued for 2 hours at 10–15° (Note 15); during this time the ether solution soon develops the bright-yellow color of *p*-tolylsulfonyldiazomethane. The ether solution is decanted from the alumina. The alumina is extracted thoroughly by stirring for periods of 5 minutes with two portions of 500 ml. and three portions of 250 ml. of ether. The combined ether solutions are filtered through coarse filter paper and concentration is a vacuum rotary flash evaporator. The temperature of the water bath must not exceed 25°. When the volume is reduced to about 200 ml., the water bath is removed entirely and concentration is continued until the cold residue crystallizes spontaneously (Note 16). The crystal mass is stirred for about 2 minutes in 50 ml. of ice-cold petroleum ether (40–60°). The crystals are collected on a sintered-glass filter and washed on the filter with two 25-ml. portions of cold petroleum ether. Drying overnight at 0° in a vacuum desiccator over anhydrous calcium chloride, yields 26–30 g. (66–76%) of yellow *p*-tolylsulfonyldiazomethane, m.p. 35–38° (slight dec.) (Note 17). Recrystallization from anhydrous ether-pentane (Note 18) will raise the melting point to 36–38° (slight dec.) at the expense of 5–10% of material. *p*-Tolylsulfonyldiazomethane should be stored at or below 0° in the absence of light in an *unsealed* container (Note 19).

2. Notes

1. Commercially available anhydrous sodium *p*-toluenesulfinate, purum, *ca.* 97% (Fluka A G, Busch S. G., Switzerland) was used. Sodium *p*-toluenesulfinate dihydrate can be used equally well. The checkers used anhydrous sodium *p*-toluenesulfinate from Aldrich Chemical Company, Inc., which was determined by titration to be 87% pure and gave lower yields. The yield stated was obtained by using stoichiometric amounts based on calculated purity. Sodium *p*-toluenesulfinate from other suppliers was found less pure and gave considerably lower yields.
Alternatively, sulfinates can be synthesized conveniently by the method of Truce and Roberts,[2] or by that of Oxley and colleagues.[3]
2. Commercial aqueous formaldehyde solution, containing about 8% of methanol, was used.
3. Ethyl carbamate (J. T. Baker Chemical Company), with a reporter melting point of 48–50° (46–49° was found), was used without purification. The solid was added to the reaction mixture.
4. Formic acid (97%) from J. T. Baker Chemical Company was used.
5. By cooling and stirring as described, the product is obtained in a finely divided form, which can be removed from the flask easily and washed efficiently.
6. Commercial pyridine (J. T. Baker Chemical Company) was used without purification.
7. Nitrosyl chloride (Matheson Gas Products) with a purity specified as >97% was used. Occasionally, the needle valve of the nitrosyl chloride tank clogs. After closing the tank, the valve is disconnected and flushed with acetone until the acetone remains colorless. The needle valve is reconnected after being dried with compressed air.
Nitrosyl chloride also can be prepared conveniently from hydrochloric acid and sodium nitrite.[4] Alternatively, the nitrosation can be carried out conveniently with nitrosonium tetrafluoroborate (Aldrich Chemical Company, Inc.). Ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl)carbamate (99%) was

obtained when 0.06 mole of nitrosonium tetrafluoroborate, a hygroscopic solid, was added over 45 minutes, from an Erlenmeyer flask connected to the reaction flask with a piece of Tygon® tubing, to a −10 to 0° solution of ethyl *N*-(*p*-tolylsulfonylmethyl)carbamate (0.05 mole) in 50 ml. of pyridine.

8. The color of the pyridine solution changes rapidly from blue and green to yellow. After roughly I equivalent (0.6 mole) of nitrosyl chloride has been taken up (*ca.* 1 hour), the color of the solution changes to dark red-brown. During the reaction a precipitate of pyridinium chloride is formed; however, it will disappear during the workup with water as described. A large excess of nitrosyl chloride (up to 3 equivalents) has been used occasionally without any disadvantages.

9. Preferably, a few drops of the pyridine solution are rubbed first with a little water, providing seed crystals so that the product will solidify immediately, giving a finely divided material which can be washed more easily.

10. The presence of ethyl *N*-(*p*-tolylsulfonylemthyl)carbamate in the reaction product is most readily detected by the N-H IR absorption band at 3370 $cm.^{-1}$. If the nitrosation is incomplete, the reaction with nitrosyl chloride should be repeated on the mixture of compounds, rather than to try to purify the product by recrystallization.

11. Ether (*ca.* 1.4 l.) is added to a warm, filtered solution of 100 g. of the crude nitroso compound in *ca.* 0.7 l. of dichloromethane until the solution becomes slightly turbid. The nitrosocarbamate is collected after cooling overnight at −20° and dried under reduced pressure at 0°, providing 88–93 g. of yellow crystals with a pink luster, m.p. 87–89.

12. Alumina Number 1076, "aktiv basisch," for chromatography (E. Merck, Darmstadt) was usually employed. Occasionally, when alumina Number 1077, "aktiv neutral," from the same company, was used, a longer reaction time was required (compare (Note 15)).

13. Commercial ether was stored over potassium hydroxide pellets and used without distillation. Because some heat is evolved when the ether is added to the alumina, the flask is equipped with a condenser.

14. Commercial dichloromethane was used without purification.

15. The time necessary for completion of the reaction may vary from 0.5 to 4 hours, depending on the actual activity of the alumina. The progress of conversion should be monitored by IR analysis of a concentrated sample of the solution. Stirring should be continued for 15 minutes after the nitroso band at 1540 $cm.^{-1}$ has disappeared. A strong diazo band at about 2100 $cm.^{-1}$ will then be present. The carbonyl band a 1750 $cm.^{-1}$, initially due to nitrosocarbamate, will usually not disappear completely during the reaction, because some diethyl carbonate is formed in addition to carbon dioxide and ethanol. Diethyl carbonate is removed during the workup procedure.

During the reaction the alumina usually attains a pink color, due to some decomposition of *p*-tolylsulfonyldiazomethane. However, the colored decomposition products adhere strongly to the alumina and will not, therefore, contaminate the final product. If the alumina becomes reddish rather than pink, the type of the alumina in use may be too basic, causing more extensive decomposition of the *p*-tolylsulfonyldiazomethane; the reaction time should then be reduced as much as possible to prevent a considerable decrease in yield.

16. If crystallization does not occur, it can be induced readily by scratching.

17. Spectral data of *p*-tolylsulfonyldiazomethane; IR (Nujol) $cm.^{-1}$: 2125 (C=N=N), 1330 (SO_2), 1150 (SO_2); ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 2.46 (s, 3H, CH_3), 5.36 (s, 1H, C*H*), 7.30, 7.43, 7.73, 7.87 (AB q, 4H, C_6H_4); visible (40% dioxane-water) nm. max. (log ε): 394 (1.8).

18. *p*-Tolylsulfonyldiazomethane tends to separate as an oil when pentane is in excess of an ether to pentane ratio of 2:1. The *p*-tolylsulfonyldiazomethane is dissolved at room temperature in anhydrous ether (about 20 ml. per 10 g. of *p*-tolylsulfonyldiazomethane), and pentane (about 7 ml. per 10 g.) is added, followed by seeding. The solution is cooled first at 0°, then at −20°, before the crystals are collected.

19. *p*-Tolylsulfonyldiazomethane is insensitive to impact detonation; however, it decomposes on warming, evolving significant quantities of nitrogen at temperature as low as 32°. It should never be stored for any length of time in a sealed container and should be stored at or below 0° if not used immediately.

3. Discussion

p-Tolylsulfonyldiazomethane represents a class of compounds called α-diazosulfones, which was discovered in 1961 by the submitters. Besides being useful synthetic intermediates, α-diazosulfones are the only known source of α-sulfonylcarbenes.[5]

Several new trisubstituted methane derivatives have been prepared by replacing the diazo group of α-diazosulfones.[5] For example, *p*-tolylsulfonyldiazomethane (RSO_2CHN_2, R = *p*-tolyl throughout) reacts with *p*-toluenesulfenyl chloride,[6] giving chloro-*p*-tolylsulfonyl-*p*-tolylthiomethane [$RSO_2CH(Cl)SR$] in 83% yield;[7] with nitrosyl chloride yielding the previously unknown *N*-hydroxy-1-(*p*-tolysulfonyl)methanimidoyl chloride [$RSO_2C(Cl)=NOH$] in 28% yield,[8] with 70% perchloric acid in dichloromethane, giving the isolable covalent perchlorate ($RSO_2CH_2OClO_3$) in 49% yield;[9,5] and with *tert*-butyl hypochlorite in *tert*-butyl alcohol, giving 1-(1-*tert*-butoxy-1-chloromethysulfonyl)-4-methylbenzene [$RSO_2CH(Cl)OC(CH_3)_3$] in 62% yield or 1-(1-chloro-1-ethoxymethylsulfonyl)-4-methylbenzene [$RSO_2CH(Cl)OC_2H_5$] in 84% yield when carried out in ethanol.[10]

The photolysis of α-diazosulfones dissolved in alkenes provides sulfonyl-substituted cyclopropanes in high yields.[5] This is exemplified by the preparation of 1-(4-methoxyphenylsulfonyl)-2,2,3,3-tetramethylcyclopropane in 75% yield from 4-methoxybenzenesulfonyldiazomethane and 2,3-dimethyl-2-butene. A similar addition to *trans*-2-butene gives (*d,l*)-1-(4-methoxyphenylsulfonyl)-*trans*-2,3-dimethylcyclopropane in 79% yield, resulting from a stereospecific *cis*- addition, indicating a singlet sulfonylcarbene intermediate.[11]

Originally, *p*-tolylsulfonyldiazomethane was prepared by passing an ethereal solution of its precursor, ethyl *N*-nitroso-*N*-(*p*-tolylsulfonylmethyl)carbamate, slowly through a column of alumina.[12] This procedure, which results in yields about 10% higher, is convenient only for small-scale preparations, up to a maximum of 5 g. of *p*-tolylsulfonyldiazomethane. The present modification is that of Middelbos.[13]

The conversion of nitrosocarbamates into α-diazosulfones is also effected with certain bases, notably with aqueous potassium hydroxide.[12] Potassium hydroxide, however, causes rapid decomposition of *p*-tolylsulfonyldiazomethane. Alumina is thought to act as a solid base and does not cause significant decomposition.

Other syntheses of *p*-tolylsulfonyldiazomethane have been worked out. Reaction of 4-carboxybenzenesulfonyl azide and ammonia with *p*-tolylsulfonylacetaldehyde hemihydrate or *p*-tolylsulfonylacetaldehyde enol acetate gives *p*-tolylsulfonyldiazomethane in yields of 73 and 58%, respectively.[14] Furthermore, *p*-tolylsulfonyldiazomethane is obtained in 60% yield by reaction of *p*-tolylsulfonylmethylenetriphenylphosphorane and either *p*-tolylsulfonyl azide or 4-carboxybenzenesulfonyl azide.[14] A method similar to the first of these syntheses has been used for preparation of (alkyl- or arylsulfonyl)phenyldiazomethanes; however, the present procedure has the advantages of being simple and easily scaled-up, and uses readily available, inexpensive starting materials.

An alternative to the synthesis of arylsulfonylmethylcarbamates by the Mannich condensation as described here,[15] is the Curtius rearrangement of the hydrazides of arylsulfonylacetic acids.[16]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 987

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

alumina

petroleum ether

N-(p-tolylsulfonylemthyl)carbamate

J. T. Baker Chemical Company

ethyl N-(p-tolylsulfonylemthyl)carbamate

N-hydroxy-1-(p-tolysulfonyl)methanimidoyl chloride

1-(1-tert-butoxy-1-chloromethysulfonyl)-4-methylbenzene

p-tolylsulfonylacetaldehyde hemihydrate

ethanol (64-17-5)

calcium chloride (10043-52-4)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

formaldehyde (50-00-0)

ethyl (2025-56-1)

formic acid (64-18-6)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

sulfur (7704-34-9)

aluminum (7429-90-5)

carbon dioxide (124-38-9)

acetone (67-64-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Pentane (109-66-0)

dichloromethane (75-09-2)

nitrosyl chloride (2696-92-6)

2,3-dimethyl-2-butene (563-79-1)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

ethyl carbamate (51-79-6)

diethyl carbonate (105-58-8)

tert-butyl alcohol (75-65-0)

perchloric acid (7601-90-3)

Benzene, 1-[(diazomethyl)sulfonyl]-4-methyl-,
p-Tolylsulfonyldiazomethane (1538-98-3)

nitrosonium tetrafluoroborate (14635-75-7)

pyridinium chloride (628-13-7)

1-(1-chloro-1-ethoxymethylsulfonyl)-4-methylbenzene

1-(4-methoxyphenylsulfonyl)-2,2,3,3-tetramethylcyclopropane

4-methoxybenzenesulfonyldiazomethane

4-carboxybenzenesulfonyl azide (17202-49-2)

p-tolylsulfonyl azide (941-55-9)

Sodium p-toluenesulfinate

tert-Butyl hypochlorite (507-40-4)

p-Toluenesulfenyl chloride (933-00-6)

sodium p-toluenesulfinate dihydrate (7257-26-3)

trans-2-Butene (624-64-6)

ethyl N-(p-toluenesulfonylmethyl)carbamate,
ethyl N-(p-tolylsulfonylmethyl)carbamate (2850-26-2)

Ethyl N-nitroso-N-(p-tolylsulfonylmethyl)carbamate (2951-53-3)

chloro-p-tolylsulfonyl-p-tolylthiomethane

(d,l)-1-(4-methoxyphenylsulfonyl)-trans-2,3-dimethylcyclopropane

p-tolylsulfonylacetaldehyde enol acetate

p-tolylsulfonylmethylenetriphenylphosphorane

N-nitroso-N-(p-tolylsulfonylmethyl)carbamate