Organic Syntheses

A Publication
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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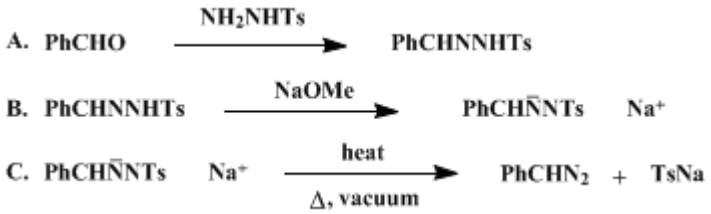
TOSYLHYDRAZONE SALT PYROLYSES: PHENYLDIAZOMETHANES

[Benzenes, diazomethyl-]



Submitted by Xavier Creary[1]
Checked by Weyton W. Tam, Kim F. Albizati, and Robert V. Stevens.

1. Procedure

Caution! Diazo compounds are presumed to be highly toxic and potentially explosive. All manipulations should be carried out in a hood. Although in numerous preparations we have never observed an explosion, all pyrolyses and distillations should routinely be carried out behind a safety shield.

A. *Benzaldehyde tosylhydrazone*. A 14.6-g sample (0.078 mol) of *p*-toluenesulfonylhydrazide (Note 1) was placed in a 125-mL Erlenmeyer flask and 25 mL of absolute methanol was added. The slurry was swirled as 7.50 g (0.071 mol) of freshly distilled benzaldehyde was added rapidly. A mildly exothermic reaction ensued and the *p*-toluenesulfonylhydrazide dissolved. Within a few minutes, the tosylhydrazone began to crystallize. After 15 min the mixture was cooled in an ice bath. The product was collected on a Büchner funnel, washed with a small amount of cold methanol, and dried under an aspirator vacuum. The dry benzaldehyde tosylhydrazone, mp 124–125°C, weighed 16.97–18.19 g (87–93%) and was not purified further.

B. *Phenyldiazomethane (Vacuum pyrolysis method)*. In a 200-mL, single-necked, round-bottomed flask is placed 13.71 g (0.05 mol) of benzaldehyde tosylhydrazone. A 1.0 *M* solution (51 mL) of sodium methoxide in methanol (0.051 mol) (Note 2) is added via syringe and the mixture is swirled until dissolution is complete (Note 3). The methanol is then removed by a rotary evaporator. The last traces of methanol are removed by evacuation of the flask at 0.1 mm for 2 hr. The solid tosylhydrazone salt is broken up with a spatula and the flask is fitted with a vacuum take-off adapter and a 50-mL receiver flask. The system is evacuated at 0.1 mm and the receiver flask is cooled in a dry ice–acetone bath to about −50°C. The flask containing the salt is immersed in an oil bath and the temperature is raised to 90°C. (We recommend the use of a safety shield.) At this temperature, red phenyldiazomethane first begins to collect in the receiver flask. The temperature is raised to 220°C over a 1-hr period (Note 4). During this time red phenyldiazomethane collects in the receiver flask (Note 5). The pressure increases to 0.35 mm over the course of the pyrolysis. On completion of the pyrolysis the pressure drops to less than 0.1 mm.

The apparatus is disconnected and the 50-mL receiver flask that contains the crude phenyldiazomethane is fitted with a water-cooled short-path distillation head and a receiver flask cooled to about −50°C in a dry ice–acetone bath. The pressure is lowered to 1.5 mm and a trace of methanol collects in the receiver. A new receiver flask is connected and cooled to −50°C and the pressure is lowered to less than 0.2 mm. Red phenyldiazomethane distills below room temperature (Note 6). The yield of phenyldiazomethane, which is a liquid above −30°C, is 4.50–4.70 g (76–80%). The product should be used immediately or stored at a low temperature (−20 to −80°C) under nitrogen or argon (Note 7),(Note 8),(Note 9),(Note 10),(Note 11); it is explosive at room temperature.

2. Notes

1. *p*-Toluenesulfonylhydrazide was obtained from Aldrich Chemical Company, Inc. and used without further purification.
2. The sodium methoxide solution was prepared by dissolving 2.30 g of sodium in absolute methanol and diluting it to 100 mL. If commercial sodium methoxide powder is used, it must be of high quality; otherwise the yield of phenyldiazomethane is lower.
3. Powdered sodium hydroxide can be used in place of sodium methoxide with no appreciable change in yield. Sodium hydroxide dissolves less readily in methanol.
4. When carried out on a small scale, pyrolysis is complete at lower temperatures (160–200°C).
5. Phenyldiazomethane solidifies at dry ice temperature. Care must be taken not to plug the vacuum take-off adapter; this occurs if the temperature of the receiver flask is too low. The receiver bath was maintained manually at about −50°C by addition of small pieces of dry ice to an acetone bath. We prefer to use this procedure rather than a chloroform–dry ice bath, which freezes at −63°C, because of the toxic nature of chloroform and the disposal problems associated with this solvent.
6. Slight warming with an oil bath at 30°C allows distillation to proceed at a reasonable rate. The bath should not be heated above this temperature. Gutsche and Jason[2] report a boiling point of 37–41°C at 1.5 mm. Although we have never experienced any difficulty in numerous distillations, Gutsche and Jason[2] report that phenyldiazomethane "sometimes detonated violently during purification" by distillation. Therefore, we emphatically recommend that distillation be carried out below room temperature, behind a safety shield. On completion of the distillation, only a small amount of nonvolatile residue remained.
7. The checkers reported that a sample that was allowed to stand at room temperature for approximately 1 hr and then exposed to air decomposed violently after 5 min. In numerous preparations, when distilled phenyldiazomethane was immediately stored at −20°C or at −80°C under nitrogen, we never experienced any difficulty. We emphasize the need to keep phenyldiazomethane cold, and under nitrogen.
8. In runs on smaller scales, yields ranged from 84 to 91%.
9. The IR spectrum (CCl_4) shows an intense band at 4.83 μm (2060 cm^{-1}); ^1H NMR (CCl_4) δ: 4.79 (s, 1 H), 6.7–7.6 (m, 5 H).
10. Phenyldiazomethane shows no appreciable change on storage at −80°C for 3 months. Storage at −20°C led to significant decomposition after 2 weeks.
11. Traces of diazo compounds should be destroyed by addition to acetic acid.

3. Discussion

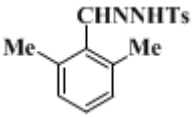
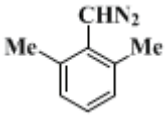
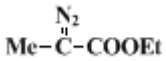
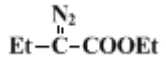
Diazo compounds have previously been prepared by a variety of methods. Some of these methods include hydrazone oxidations,[3] the reaction of diazomethane with acid chlorides,[4] the reaction of activated methylene compounds with tosyl azide,[5] decomposition of *N*-nitroso compounds,[6] diazotization of amines,[7] and pyrolysis of tosylhydrazone salts.[8,9,10,11,12,13] The present procedure for the preparation of phenyldiazomethane illustrates the vacuum pyrolysis method introduced by Shechter[12] for carrying out the Bamford–Stevens reaction.[9]

Phenyldiazomethane has been prepared by reaction of base with ethyl *N*-nitroso-*N*-benzylcarbamate,[13] *N*-nitroso-*N*-benzylurea,[14] and *N*-nitroso-*N*-benzyl-*N*′-nitroguanidine.[15] Staudinger's preparation[16] and that of Gutsche and Jason[2] employed mercuric oxide oxidation of benzaldehyde hydrazone. Yates and Shapiro[17] prepared phenyldiazomethane by basic cleavage of azibenzil. Bamford and Stevens[9] prepared phenyldiazomethane by solution pyrolysis of the salt of benzaldehyde tosylhydrazone. Closs and Moss[10] and Farnum[11] used variations of this solution pyrolysis method for the preparation of phenyldiazomethane. The vacuum pyrolysis method employed by Shechter[12] has also been used to prepare phenyldiazomethane.

The present procedure uses sodium methoxide in methanol for generation of the tosylhydrazone salt. This procedure gives the highest reported yield and, unlike other procedures, also gives pure diazo compounds free from solvents. This vacuum pyrolysis method appears applicable to the formation of relatively volatile aryldiazomethanes from aromatic aldehydes. Table I gives yields of diazo compounds

produced by this vacuum pyrolysis method. The yields have not been optimized. The relatively volatile diazo esters, ethyl α-diazopropionate[18] and ethyl α-diazobutyrate, can also be prepared by this method.

TABLE I
FORMATION OF DIAZO COMPOUNDS BY VACUUM PYROLYSIS OF SODIUM SALTS OF TOSYLHYDRAZONES

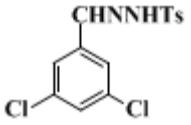
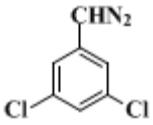
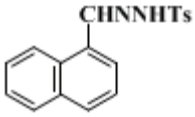
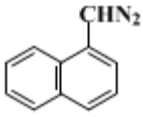
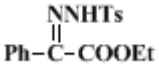
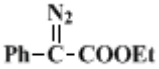
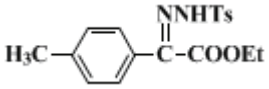
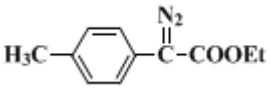
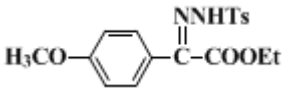
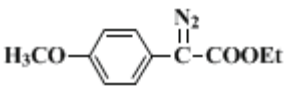
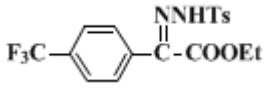
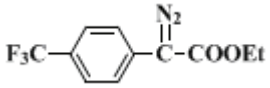
Tosylhydrazone	Product	Yield (%)
p-$MeC_6H_4CHNNHTs$	p-$MeC_6H_4CHN_2$	52
m-$MeC_6H_4CHNNHTs$	m-$MeC_6H_4CHN_2$	55
		69
p-$FC_6H_4CHNNHTs$	p-$FC_6H_4CHN_2$	69
m-$FC_6H_4CHNNHTs$	m-$FC_6H_4CHN_2$	59
		87
		65

The major limitation of the vacuum pyrolysis method appears to be thermal decomposition of less volatile diazo compounds during the pyrolysis. The vacuum pyrolysis method was unsuccessful for the preparation of 1-naphthyldiazomethane and 3,5-dichlorophenyldiazomethane. However, such diazo compounds could be prepared from the corresponding tosylhydrazone salts by pyrolysis in ethylene glycol and extraction of the aryldiazomethane into hexane or ether. This procedure, as described by Goh,[19] permits the periodic extraction of the potentially labile diazo compound into an organic solvent while leaving the unreacted tosylhydrazone salt dissolved in the immiscible ethylene glycol phase. This solution pyrolysis method can also be used to prepare aryl diazo esters in high yields. This method is quite useful since the starting keto esters can be readily prepared in large quantities by reaction of the corresponding arylmagnesium bromides with diethyl oxalate.[20]

In a typical procedure, 0.14 g of sodium was dissolved in 10 mL of ethylene glycol by heating to 70°C and 0.0041 mol of tosylhydrazone was added. After heating with vigorous stirring for 5 min at 70–80°C, the mixture was cooled to about 35°C and 15 mL of hexane or ether was added with continued stirring. The organic extract was removed by pipette and the procedure was repeated a total of 5 times. The combined organic extracts were washed with 30 mL of 5% sodium hydroxide solution, with a saturated sodium chloride solution, and dried over magnesium sulfate. After filtration, the solvent was removed on a rotary evaporator to leave the diazo compound. Table II gives yields of diazo compounds prepared by this solution pyrolysis method.

TABLE II
FORMATION OF DIAZO COMPOUNDS BY PYROLYSIS OF SODIUM SALTS OF TOSYLHYDRAZONES IN ETHYLENE GLYCOL

Tosylhydrazone	Temperature (°C)	Product	Yield (%)
	70[a]		90

			
	80[a]		77
	70[b]		86
	70[b]		88
	70[b]		76
	70[b]		94

[a] The salt in ethylene glycol was heated at this temperature, cooled, and extracted periodically with hexane.
[b] Ether extraction.
[c] This product was further purified by distillation at less than 0.1 mm. The other products were *not* distilled.

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

PHENYLDIAZOMETHANES

Benzenes, diazomethyl-

salt of benzaldehyde tosylhydrazone

SODIUM SALTS OF TOSYLHYDRAZONES

p-$MeC_6H_4CHNNHTs$

p-MeC_6H_4

m-$MeC_6H_4CHNNHTs$

m-$MeC_6H_4CHN_2$

p-$FC_6H_4CHNNHTs$

p-$FC_6H_4CHN_2$

m-$FC_6H_4CHNNHTs$

m-$FC_6H_4CHN_2$

tosylhydrazone

SODIUM SALTS OF TOSYLHYDRAZONES IN ETHYLENE GLYCOL

acetic acid (64-19-7)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

mercuric oxide (21908-53-2)

benzaldehyde (100-52-7)

sodium methoxide (124-41-4)

sodium (13966-32-0)

ethylene glycol (107-21-1)

magnesium sulfate (7487-88-9)

Diazomethane (334-88-3)

hexane (110-54-3)

diethyl oxalate (95-92-1)

argon (7440-37-1)

Ethyl N-nitroso-N-benzylcarbamate (6558-76-5)

phenyldiazomethane (766-91-6)

ethyl α-diazopropionate

tosyl azide (941-55-9)

Benzaldehyde tosylhydrazone (1666-17-7)

benzaldehyde hydrazone

ethyl α-diazobutyrate

1-naphthyldiazomethane

3,5-dichlorophenyldiazomethane

p-Toluenesulfonylhydrazide (1576-35-8)

N-nitroso-N-benzylurea

N-nitroso-N-benzyl-N'-nitroguanidine