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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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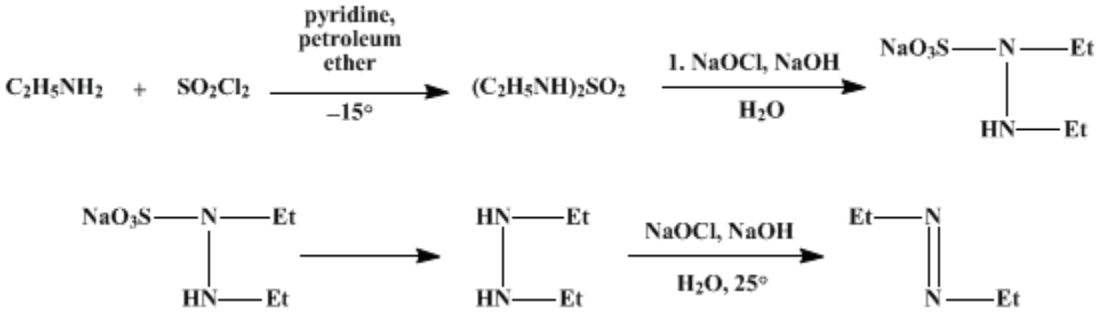
AZOETHANE

[Diazene, diethyl]



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Checked by Harvey W. Taylor and Henry E. Baumgarten.

1. Procedure

Caution! Azoalkanes have been reported to have carcinogenic properties.[2,3] Care should be taken to avoid inhalation of these substances and contact of them with the skin. It is advisable to prepare and handle these compounds in a good fume hood.

A. *N,N′-Diethylsulfamide*. A dry, 2-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel, and protected from atmospheric moisture with calcium chloride drying tubes is charged with 500 ml. of petroleum ether, 100 g. (2.20 moles) of ethylamine, and 140 g. (1.76 moles) of pyridine (Note 1). The stirred mixture is cooled in an acetone–dry ice bath to −30° to −15°; a solution of 120 g. (0.889 mole) of sulfuryl chloride in 220 ml. of petroleum ether is added, dropwise and with stirring, to the reaction flask at such a rate that the temperature remains below −15°. After addition is complete, the reaction mixture is stirred at room temperature for one hour. The petroleum ether layer is separated and discarded. The dark semisolid residue is made acidic by addition of 6 *M* hydrochloric acid, and the acidic mixture is heated under reflux for 2 hours (Note 2). The resulting solution is extracted with diethyl ether in a continuous extractor (Note 3) until all of the diethylsulfamide has dissolved. The ether is evaporated using a rotary evaporator, yielding 58–61 g.. (44–45%) of crude *N,N′*-diethylsulfamide, m.p. 65–67°, (Note 4) which is of sufficient purity for use in the next step.

B. *Azoethane*. A 3-l., three-necked, round-bottomed flask fitted with a mechanical stirrer, a reflux condenser, a thermometer, and a dropping funnel is charged with 500 ml. of an aqueous 2 *M* solution of sodium hydroxide and 152 g. (1.00 mole) of *N,N′*-diethylsulfamide, which is brought into solution by warming the reaction flask. The reaction flask is cooled in a cold water bath before 715 ml. (1.0 mole) of aqueous 1.4 *M* sodium hypochlorite (Note 5) is added dropwise with stirring. After addition is complete, the reaction mixture is stirred for 15 minutes at room temperature. The mixture is brought to pH 1 by addition of 6 *M* hydrochloric acid and stirred for an additional 30 minutes at 60° (Note 6). The mixture is cooled to room temperature, then is brought to pH 14 by addition of aqueous 2 *M* sodium hydroxide (Note 7). Addition of 715 ml. (1.0 mole) of aqueous 1.4 *M* sodium hypochlorite solution causes the separation of azoethane as an oil, having a fruitlike odor. The mixture is extracted with three 100-ml. portions of toluene (Note 8). The combined extracts are dried over anhydrous sodium sulfate and distilled through a 50-cm. packed column, yielding 44–46 g. (51–54%) of azoethane, b.p. 58–59°, n_D^{20} 1.3861 (Note 9).

2. Notes

1. The submitters dried the ethylamine and pyridine by distillation over potassium hydroxide pellets and used 600 ml. of petroleum ether, 113 g. (2.50 moles) of ethylamine, and 158 g. (2.00 moles) of pyridine to which was added 135 g. (1.00 mole) of sulfuryl chloride in 250 ml. of petroleum ether. In the United States ethylamine is sold in 100-g. quantities in sealed-glass vials (Eastman Organic Chemicals) or as the compressed gas in cylinders (Matheson Gas Products). The checkers used the contents of a freshly opened vial (without distillation) for each run, as a matter of convenience, and used either pentane or petroleum ether (b.p. 38–51°). Note that step B requires the product from at least two [submitters' scale *and yield* (Note 4)] or three (checkers' scale) step A runs. Step B can be run at half scale with the same percentage yield.

2. The purpose of this step is to hydrolyze any alkyl imido compound that may have formed from the further reaction of the sulfamide.[4]

3. A convenient continuous extractor has been described earlier in this series.[5]

4. After purification by dissolving the crude product in ether and precipitating with petroleum ether, *N,N′*-diethylsulfamide is obtained as shiny, white leaflets, m.p. 67°. The submitters reported a 54% yield of the purified product.

Under identical conditions using 78 g. (2.5 mole) of methylamine, 71 g. (57%) of *N,N′*-dimethylsulfamide, m.p. 76°, may be obtained as fine, white needles after recrystallization from benzene.

For sulfamides with larger alkyl groups (C_3 to C_6) the following procedure is preferred. A solution of 316 g. (4.00 moles) of pyridine in 400 ml. of chloroform is added dropwise, with cooling to −10° to −5°, to a stirred mixture of 135 g. (1.00 mole) of sulfuryl chloride and 500 ml. of chloroform. Maintaining a temperature of −5° to 0°, a solution of 2.5 moles of alkylamine in 600 ml. of chloroform is added to the reaction. After addition is complete the mixture is stirred for 30 minutes at room temperature, evaporated under reduced pressure to a thick brown liquid, and treated with 2 *M* hydrochloric acid until the pyridine dissolves. Cooling the acidic solution, the crystalline sulfamide precipitates and is filtered. Any dissolved sulfamide may be recovered by extraction of the filtrate with ether. The crude product may be purified by recrystallization from 50% ethanol.

The pyridine used in the submitters' procedures apparently reacts with the sulfuryl chloride to form an intermediate, quaternary pyridinium complex which undergoes aminolysis, yielding the sulfamide.[6] However, in many instances the pyridine may be replaced by an equivalent quantity of the primary alkylamine being used.[4,7] Using this variation the checkers obtained a 78% yield of *N,N′*-dicyclohexylsulfamide (compare with Table I). Moreover, in the reaction of 4-aminospiro(cyclohexane-1,9'-fluorene) with sulfuryl chloride no sulfamide could be isolated from reactions run in the presence of pyridine (or triethylamine); however, a 54% (purified) yield of *N,N′*-dispiro(cyclohexane-1,9'-fluorene)-4-ylsulfamide was obtained when 2.7 *equivalents* of the amine (relative to sulfuryl chloride) were used. Probably the failure of the mixed pyridine-alkylamine technique was the result of combined bulk of the pyridinium complex and the amine.

TABLE I

PREPARATION OF AZOALKANES

R	$RNHSO_2NHR$		$R\text{-}N{=}N\text{-}R$	
	m.p.	Yield, %	b.p.	Yield, %
n-C_3H_7	118°	69	113–115°	54
n-C_4H_9	126°	66	59–60° (18 mm.)	54
tert-C_4H_9	140–142°	68	109–110°	84
cyclo-C_6H_{11}	154°	59	m.p. 33–34°	80
4-NO_2-C_6H_4	197°	58	m.p. 216°	31

5. The sodium hypochlorite solution was prepared by passing chlorine, with stirring and cooling to 0–5°, into 1.5 l. of aqueous 1.4 *M* sodium hydroxide solution.

In some small-scale preparations of this type the checkers used commercial household bleach (Chlorox®, 5.25% NaOCl) and followed the course of the reaction by TLC. The yields appear to be somewhat lower than those obtained with sodium hypochlorite prepared as described above. The

obvious attractive alternative, preparation of potassium hypochlorite as described elsewhere in this series,[8] apparently has not been tried.
6. In the preparation of 2,2'-azoisobutane and azocyclohexane the acid hydrolysis step is not necessary and the two moles of sodium hypochlorite may be added in one step.
7. In the preparation of azomethane a gas-inlet tube is used to pass nitrogen slowly through the reaction mixture, during the second oxidation stage while the temperature is raised to 60°. The reflux condenser is fitted with a drying tube filled with potassium hydroxide pellets connected via rubber hose to two dry ice-cooled cold traps connected in series and terminated with a second drying tube filled with potassium hydroxide pellets. The azomethane collects in the cold traps. Redistillation gives a 39% yield of azomethane, b.p. 1°.
8. For the homologous azoalkanes ether, pentane, or petroleum ether may be used for extraction. The extraction solvent may be added before the addition of hypochlorite.[6]
9. The checkers used a 60-cm. Vigreux column. Their product gave the following ^{1}H NMR spectrum ($CDCl_3$): δ 1.17 (q, J = 7 Hz., 2H, CH_2), 3.77 (t, J = 7Hz., 3H, CH_3).

3. Discussion

Azoalkanes have been prepared by oxidation of *N,N'*-dialkylhydrazines with copper(II) chloride[9] or with yellow mercury(II) oxide.[10,11] The dialkyl hydrazines are obtained by alkylation of *N,N'*-diformylhydrazine and subsequent hydrolysis,[9] by reduction of the corresponding azine with lithium aluminum hydride,[11] or by catalytic hydrogenation of the azine over a platinum catalyst.[10]

The present procedure may be used for the preparation of azoalkanes with alkyl, cycloalkyl, or aromatic substituents (Table I). Azoalkanes have been used as radical sources for inducing of radical reactions (*e.g.*, polymerization). The present procedure may also be used for the preparation of *N,N'*-dialkylhydrazines.[6] For this purpose only one equivalent of sodium hypochlorite solution is employed and the reaction mixture is worked up after its addition (yields: 60–95%).

References and Notes

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

petroleum ether

Diazene, diethyl

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

mercury(II) oxide (21908-53-2)

platinum (7440-06-4)

sulfuryl chloride (7791-25-5)

pyridine (110-86-1)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

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

Pentane (109-66-0)

sodium hypochlorite (7681-52-9)

methylamine (74-89-5)

potassium hypochlorite

lithium aluminum hydride (16853-85-3)

triethylamine (121-44-8)

ethylamine (75-04-7)

Azoethane (38534-43-9)

diethylsulfamide

azocyclohexane

azomethane

N,N'-diformylhydrazine

N,N'-Diethylsulfamide (6104-21-8)

N,N'-dimethylsulfamide

N,N'-dicyclohexylsulfamide

4-aminospiro(cyclohexane-1,9'-fluorene)

N,N'-dispiro(cyclohexane-1,9'-fluorene)-4-ylsulfamide

2,2'-azoisobutane