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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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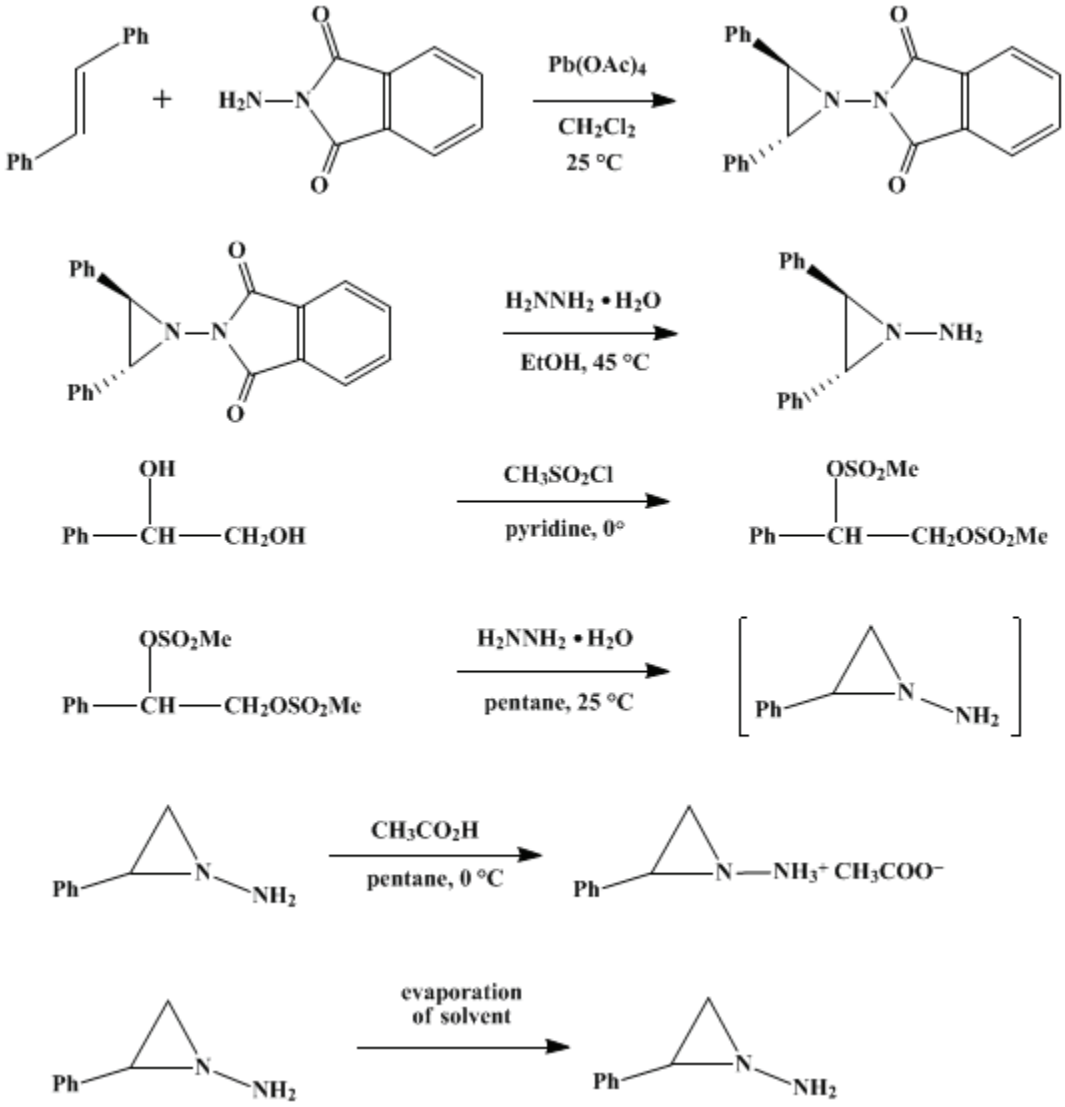
PREPARATION OF *N*-AMINOAZIRIDINES: *trans*-1-AMINO-2,3-DIPHENYLAZIRIDINE, 1-AMINO-2-PHENYLAZIRIDINE, AND 1-AMINO-2-PHENYLAZIRIDINIUM ACETATE

[1-Aziridinamine, *trans*-(±)-2,3-diphenyl-, 1-aziridinamine, (±)-2-phenyl-, and 1-aziridinamine, monoacetate, (±)-2-phenyl-]



Submitted by Robert K. Müller, Renato Joos, Dorothee Felix, Jakob Schreiber, Claude Wintner, and A. Eschenmoser[1].
Checked by Robert E. Ireland, J. Kleckner, and David M. Walba.

1. Procedure

Caution! Steps B and D should be carried out in a hood behind a safety screen.

A. trans-2,3-*Diphenyl*-1-*phthalimidoaziridine* (Note 1). A 1-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer is charged with a mixture of 19.5 g (0.120 mole) of *N*-

aminophthalimide (Note 2), 108 g. (0.600 mole) of (*E*)-stilbene (Note 3), and 300 ml. of dichloromethane (Note 4). To the resulting suspension is added 60 g. (*ca.* 0.12 mole) of lead tetraäcetate (Note 5) over a period of 10 minutes, at room temperature with *vigorous* stirring. Stirring is continued for an additional 30 minutes, after which time the mixture is filtered through Celite®, which is washed twice with 50-ml. portions of dichloromethane. The combined filtrates are transferred to a 4-l. beaker, and 1.5 l. of pentane is added with gentle stirring and cooling in an ice bath. The yellow precipitate that forms after 15 minutes is suction filtered and redissolved in 200 ml. of dichloromethane. The solution obtained is swirled for 5 minutes with 20 g. of silica gel, filtered through Celite®, which is washed with two 100-ml. portions of dichloromethane. To this dichloromethane solution is added 1.5 l. of pentane, with cooling. The precipitate that forms after 0.5 hour is dried under vacuum (10 mm.) at room temperature for 5 hours, yielding 16–21 g. (39–51%) of product, m.p. 175°, which is of sufficient purity for use in the next step (Note 6).

B. trans-1-*Amino*-2,3-*diphenylaziridine* (Note 7). To a magnetically stirred suspension of 20.4 g. (0.0600 mole) of *trans*-2,3-diphenyl-1-phthalimidoaziridine in 150 ml. of 95% ethanol in a 500-ml., round-bottomed flask at room temperature is added 150 ml. (3 moles) (Note 8) of hydrazine hydrate (Note 9). The mixture is stirred for 40 minutes while maintaining the temperature at 43–45° (Note 10) with a thermostatted oil bath. The resulting cloudy yellow solution (Note 11) is cooled and filtered through Celite®. The filtrate is poured into a 2-l. separatory funnel containing 400 ml. of diethyl ether and 200 g. of ice, and shaken vigorously. The organic phase is separated and washed with three 200-ml. portions of ice-cold water, and the aqueous washings are reextracted with a 250-ml. portion of ether (Note 12). The combined ethereal extracts are dried over anhydrous potassium carbonate, filtered through Celite® if necessary, and concentrated to approximately 300 ml. on a rotary evaporator at room temperature. Addition of 400 ml. of pentane and overnight storage at −20° leads to crystallization of 7.9–9.5 g. (63–75%) of *trans*-1-amino-2,3-diphenylaziridine (Note 13) as colorless crystals, m.p. 93–94° (dec.) (Note 14). An additional 1.2–2.2 g.. (10–17%) is obtained by concentration of the mother liquor to 50–80 ml. and addition of approximately 50 ml. of pentane (Note 7).

C. *Styrene glycol dimesylate* (Note 15). A 300-ml., three-necked, round-bottomed flask equipped with a thermometer, an efficient stirrer (Note 16), and a dropping funnel is charged with a solution of 34.5 g. (0.250 mole) of styrene glycol (Note 17) in 90 ml. of pyridine (Note 18). The solution is cooled to −5° with an ice–salt bath, and 64.7 g. (43.7 ml., 0.560 mole) of methanesulfonyl chloride (Note 19) is added dropwise over a 1-hour period, while maintaining the temperature at or below 0° (Note 20). Stirring is continued for 4 hours at 2–4°, with the flask cooled with an ice-water bath. The reaction mixture is mixed thoroughly with 600 g. of ice, and the dimesylate precipitates. After careful acidification of the mixture with 6 *N* hydrochloric acid to approximately pH 3 (Note 21), the dimesylate is suction filtered, washed twice with 100-ml. portions of ice water, and pressed as dry as possible. This product, which is still moist, is transferred to a separatory funnel and is shaken well with 200 ml. of dichloromethane. The dichloromethane is separated, and the aqueous layer is extracted further with two 20-ml. portions of dichloromethane. The combined dichloromethane layers are dried over anhydrous magnesium sulfate, and 250–300 ml. of pentane is added to the solution, until crystallization just begins. After 2 hours in a deep freeze at −25°, the crystals are collected, washed with two 30-ml. portions of pentane precooled to 0°, and dried to constant weight in a vacuum desiccator (10 mm.) at room temperature, yielding 62–64 g. (84–86%) of white, crystalline dimesylate, m.p. 93–94° (Note 15).

D. *Hydrazinolysis of styrene glycol dimesylate*. A 1-l., round-bottomed flask equipped with a magnetic stirring bar is charged with 50 ml. (1 mole) of hydrazine hydrate (Note 9). Finely powdered styrene glycol dimesylate (20 g., 0.068 mole), m.p. 93–94°, is then added with gentle stirring at room temperature. To the resulting slurry is slowly added 600 ml. of pentane. The stirring speed should be adjusted in such a manner that the two phases mix somewhat, but the dimesylate–hydrazine hydrate layer is not deposited on the upper walls of the flask. After 20–24 hours of stirring at room temperature two entirely clear layers can be observed upon the cessation of stirring (Note 22), indicating that the reaction is complete. The hydrazine hydrate is separated from the pentane and extracted with two 30-ml. portions of pentane. The combined pentane layers are filtered through cotton, which holds back any remaining droplets of hydrazine hydrate, into a 1-l., round-bottomed flask. At this point *Step E* is followed for 1-amino-2-phenylaziridine, and *Step F* for 1-amino-2-phenylaziridinium acetate.

E. 1-*Amino*-2-*phenylaziridine* (Note 23). If the pentane solution from *Step D* is removed on a rotary evaporator at room temperature, 7.5–7.7 g.. (82–85%) of 1-amino-2-phenylaziridine, suitable for preparative use, is obtained. Kügelrohr distillation of this material on a 1–2 g. scale (0.01 mm./60–65° oven temperature) (Note 24) gives a recovery of over 90% (Note 23) and (Note 25).

F. 1-*Amino*-2-*phenylaziridinium acetate* (Note 23). The pentane solution from *Step D* is stirred with a magnetic stirrer and cooled to 0°, and 3.9 ml. (0.068 mole) of acetic acid is measured. Three drops of acetic acid are added at first, and stirring is continued at 0° until the precipitation of white 1-amino-2-phenylaziridinium acetate begins. If necessary, crystallization is initiated by scratching with a glass rod or by addition of a seed crystal from a previous run. The remainder of the acetic acid is added over a 10-minute period, and stirring is continued for an additional 20 minutes, while maintaining the temperature at 0°. The salt is filtered, washed with 30 ml. of pentane precooled to 0°, and dried in a vacuum desiccator (10 mm.) at room temperature, yielding 10.0–10.5 g. (76–79%) (Note 26) of product, m.p. 69–70° (Note 27) which is suitable for preparative purposes. Recrystallization is possible; however, it must be carefully carried out to avoid the formation of a yellow product, whose melting point is lower than that of the crude product. A solution of 10 g. of 1-amino-2-phenylaziridinium acetate in 40 ml. of dichloromethane is prepared at a maximum temperature of 20–22°. The turbid solution is immediately filtered through Celite®, which is washed with two 10-ml. portions of dichloromethane. The resulting clear solution is treated with 200–250 ml. of pentane until crystallization just begins, and placed in a deep freeze at −25° for 2 hours. Filtration, washing with 30 ml. of pentane precooled to 0°, and drying as before, afford 9.2–9.3 g. of 1-amino-2-phenylaziridinium acetate, m.p. 70–72° (Note 23) and (Note 28).

2. Notes

1. *trans*-2,3-Diphenyl-1-phthalimidoaziridine is available from Fluka AG, CH-9470 Buchs.
2. *N*-Aminophthalimide is available from Fluka AG or may be prepared from phthalimide and hydrazine.[2] The quality is important; the m.p. should be 199–202° with subsequent resolidification of the melt due to thermal reaction. Recrystallization, if necessary, can be carried out in ethanol. The checkers observed that with one batch of recrystallized material, the solid never really did melt, but seemed to sinter at ~200°.
3. Technical grade (*E*)-stilbene obtained from Fluka AG gives satisfactory results, although a better grade is preferable. The checkers used reagent grade material obtained from Aldrich Chemical Company, Inc.
4. This was distilled over phosphorus pentoxide.
5. "Purum" grade lead tetraäcetate, 85–90%, moistened with acetic acid, obtained from Fluka AG was used. The checkers used reagent grade material, moistened with acetic acid, purchased from Matheson, Coleman and Bell.
6. The yield of the reaction, while always at least 39%, is subject to fluctuation. The product may be contaminated with small amounts of (*E*)-stilbene and/or lead salts. The presence of (*E*)-stilbene can easily be monitored by TLC, using ready-prepared Silica Gel F_{254} plates available from E. Merck & Company, Darmstadt, Germany. The plates are developed with dichloromethane, and the spots detected under UV light. In runs of smaller scale, or if product of higher purity is desired, column chromatography on silica gel may replace the work-up described; the reaction mixture is filtered through Celite®, and the resulting solution is concentrated on a rotary evaporator. The residue is then chromatographed on 570 g. of silica gel. Eluting with dichloromethane gives the stilbene first, then small amounts of unidentified impurities, and finally the desired adduct in 70–73% yield.
7. *trans*-1-Amino-2,3-diphenylaziridine decomposes thermally, largely to (*E*)-stilbene and nitrogen. In the crystalline state it is stable for several hours at room temperature, and for several weeks (probably for several months) at −20°. It decomposes within 3 days at room temperature in aprotic solvents and much more rapidly in protic solvents.[3] Decomposition is still faster in the presence of traces of acids. The work-up described should be completed as quickly and as *precisely* as possible, and the product should be stored in a deep freeze if it is not to be used immediately. For the use of this reagent in the α,β-epoxyketone fragmentation, see references [3] and [4].
8. Use of lesser amounts of hydrazine hydrate or ethanol causes precipitation of the product as a pasty mass that dissolves only slowly in ether, thereby making the work-up difficult.
9. "Purum" grade hydrazine hydrate obtained from Fluka AG was used. The checkers used 99–100%

hydrazine hydrate purchased from Matheson, Coleman and Bell.
10. The reaction temperature must be carefully controlled. At temperatures above 48° the yield is markedly reduced by decomposition of the product, and below 43° the reaction time is greatly lengthened.
11. The submitters report that if very pure *trans*-2,3-diphenyl-1-phthalimidoaziridine is used, no insoluble matter is present at this point, and filtration through Celite® is not necessary.
12. Before working up the reaction mixture, it is recommended to test whether the reaction is complete by TLC (Note 6). If (*E*)-stilbene is observed, the reaction should be interrupted immediately. The checkers found that the work-up was complicated by formation of emulsions; small quantities of brine were used to aid separation of the phases.
13. IR ($CHCl_3$) cm.$^{-1}$: 3340, 1603, 1495, 1450, 1085, 1070, 1030 (a weak band at 960 cm.$^{-1}$ is due to (*E*)-stilbene, as there is always some decomposition of the *trans*-1-amino-2,3-diphenylaziridine during the recording of the spectrum) (Note 7); ^{1}H NMR ($CDCl_3$), δ (multiplicity, coupling constant *J* in Hz., number of protons, assignment): 3.10 (broad m, 2H, NH_2), 3.22 and 3.36 (AB q, 2H, *J* = 5), 7.1–7.6 (m, 10H). The nonequivalence of the two methine protons is due to slow inversion at nitrogen, and confirms the *trans*-2,3-substitution.
14. The melting-point tube is placed in the bath at 85° and heated rapidly.
15. A second crystallization from dichloromethane–pentane is sometimes necessary to achieve material having this melting point. Styrene glycol dimesylate must be stored in a refrigerator, since slow decomposition takes place at room temperature.
16. Toward the end of the reaction, the mixture becomes quite viscous. Unless the stirring assembly is capable of mixing material at the flask walls, homogeneous temperature control cannot be guaranteed.
17. Styrene glycol is available from Aldrich Chemical Company, Inc., or from Eastman Organic Chemicals. Alternatively, it may be prepared by hydrolysis of styrene oxide.[3] If the glycol melts at lower than 63°, it should be recrystallized before use.
18. Dried over potassium hydroxide and distilled.
19. "Purum" grade methanesulfonyl chloride supplied by Fluka AG or 98% pure material supplied by Eastman Organic Chemicals was used.
20. The addition rate is about 30 drops/minute. After about half of the methanesulfonyl chloride has been added, white crystals of pyridine hydrochloride begin to precipitate, and the solution becomes viscous (Note 16).
21. About 110–120 ml. of 6 *N* hydrochloric acid is needed. The temperature should not be allowed to rise above 5°.
22. The rate of the reaction is influenced by the speed of stirring. At slow speeds, 30 hours may be required for completion without any decrease in the final yield. The role of pentane is to continuously remove newly formed product from the hydrazine solvent.
23. 1-Amino-2-phenylaziridine decomposes at temperatures over 0°, and must therefore be stored in a deep freeze at −25°, at which temperature it is crystalline. 1-Amino-2-phenylaziridinium acetate is somewhat more stable, but it too decomposes within 2 days at room temperature. It can be kept unchanged in a deep freeze for months. For the use of these two reagents in the α,β-epoxyketone fragmentation, see references [3] and [4].
24. In order to minimize decomposition, the distillation should be carried out on small portions at the lowest possible temperature and pressure.
25. The distilled product has the following ^{1}H NMR spectrum ($CDCl_3$), δ (number of protons, assignment): 1.91, 1.98, and 2.06 (2H, AB part of ABX), 2.50, 2.58, 2.64, and 2.72 (1H, X part of ABX), 3.60 (2H, NH_2), 7.25 (5H). Undistilled material shows substantially the same spectrum.
26. By the addition of two further drops of acetic acid to the mother liquor, and overnight cooling at −25°, an additional 0.3–0.4 g. (2–3%) of product, m.p. 60–62°, can be isolated.
27. For the melting point determination the capillary is placed in the apparatus at 60°, and the temperature is raised 4°/minute.
28. Recrystallized 1-amino-2-phenylaziridinium acetate has the following ^{1}H NMR spectrum ($CDCl_3$), δ (number of protons, assignment): 1.95–2.20 (5H, AB part of ABX and CH_3 at δ 2.02), 2.67–2.95 (1H, X part of ABX), 6.50–6.70 (3H, NH_3) 7.0–7.4 (5H).

3. Discussion

trans-1-Amino-2,3-diphenylaziridine and 1-amino-2-phenylaziridine are reagents for the α,β-

epoxyketone → alkynone fragmentation,[3] an example of which is given in this volume.[4] An alternative preparation of 1-amino-2-phenylaziridine is the hydrazinolysis of 2-phenyl-1-phthalimidoaziridine.[3]

The lead tetraäcetate reaction between *N*-aminophthalimide and (*E*)-stilbene was first described by Rees,[5] and the hydrazinolysis of the addition product by Carpino.[6] The procedures described here incorporate their methods, with improvements. The dimesylate–hydrazine reaction was first described by Paulsen[7] in the carbohydrate series.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 679

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

silica gel

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

nitrogen (7727-37-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

Phthalimide (85-41-6)

hydrazine hydrate (7803-57-8)

Pentane (109-66-0)

hydrazine (302-01-2)

dichloromethane (75-09-2)

Styrene oxide (96-09-3)

magnesium sulfate (7487-88-9)

pyridine hydrochloride (628-13-7)

stilbene

Methanesulfonyl chloride (124-63-0)

1-Amino-2-phenylaziridinium acetate (37079-43-9)

styrene glycol

Styrene glycol dimesylate (32837-95-9)

1-Amino-2-phenylaziridine,
1-aziridinamine, (±)-2-phenyl- (19615-20-4)

2-phenyl-1-phthalimidoaziridine

phosphorus pentoxide (1314-56-3)

(E)-stilbene (103-30-0)

trans-2,3-Diphenyl-1-phthalimidoaziridine (37079-32-6)

N-aminophthalimide (1875-48-5)

trans-1-Amino-2,3-diphenylaziridine,
1-Aziridinamine, trans-(±)-2,3-diphenyl- (28161-60-6)

lead tetraacetate (546-67-8)

1-aziridinamine, monoacetate, (±)-2-phenyl-