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Working with Hazardous Chemicals

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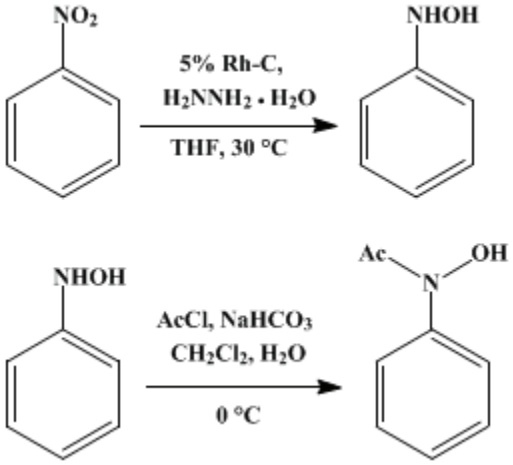
N-ACETYL-*N*-PHENYLHYDROXYLAMINE VIA CATALYTIC TRANSFER HYDROGENATION OF NITROBENZENE USING HYDRAZINE AND RHODIUM ON CARBON

[Acetamide, *N*-hydroxy-*N*-phenyl-]



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1. Procedure

Caution! Nitrobenzene and hydrazine are both toxic. Phenylhydroxylamine and N-acetyl-N-phenylhydroxylamine are both suspected carcinogens.

A. *N-Phenylhydroxylamine.* Wet, 5% rhodium on carbon (1.1 g) (Note 1), tetrahydrofuran (200 ml) (Note 2), and nitrobenzene (41.0 g) (Note 3) are introduced into a 500-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer, a thermometer, and a condenser. The mixture is cooled to 15°C and hydrazine hydrate (17.0 g) (Note 4) is introduced into the reaction mixture from a pressure-equalized addition funnel over 30 min. The temperature of the mixture is maintained at 25–30°C throughout the addition by means of an ice–water bath. After the mixture is stirred for a further 2 hr at 25–30°C, the reaction is complete (Note 5). The mixture is filtered and the catalyst washed with a little tetrahydrofuran. The solution is used immediately in the acylation step (Note 6).

B. *N-Acetyl-N-phenylhydroxylamine.* To the *N*-phenylhydroxylamine solution in a 1000-mL, three-necked, round-bottomed flask fitted with a mechanical stirrer and a thermometer is added a slurry of sodium bicarbonate (42 g) in water (40 mL). The mixture is cooled to −4°C in an ice–salt bath before acetyl chloride (26.0 g) (Note 7) is introduced into the well-stirred mixture over 1 hr (Note 8) while the temperature is maintained below 0°C. Stirring is then continued for 30 min before a solution of sodium hydroxide (20.0 g) in water (200 mL) is added, keeping the temperature below 20°C. The aqueous phase is separated, the tetrahydrofuran phase is diluted with an equal volume of petroleum ether, the aqueous phase is separated again, and the organic phase is extracted with aqueous 10% sodium hydroxide solution (2 × 50 mL). The combined aqueous phases are washed with methylene chloride (200 mL) and then neutralized with concentrated hydrochloric acid (cooling employed). The mixture is extracted with methylene chloride (3 × 100 mL) and the extracts are combined, dried over magnesium sulfate, filtered, and concentrated at reduced pressure (about one-fifth volume) (Note 9). After the solution is cooled to 40°C, 100 mL of petroleum ether (bp 60–80°C) is added. The mixture is stirred at 10°C for 39 min before filtering and washing with additional petroleum ether. The material is dried at room temperature to afford 39.3–40.1 g (79–80%) of *N*-acetyl-*N*-phenylhydroxylamine as a white crystalline solid, mp

66–67°C (lit.[2] mp 67–67.5°C) (Note 10).

2. Notes

1. The 5% rhodium on carbon used was purchased dry from Engelhard Industries Ltd. The checkers purchased it from Aldrich Chemical Company, Inc. The catalyst is used wet (40–50% water) to reduce the risk of fire when the solvent is added.
2. Tetrahydrofuran was from a bulk supply purchased from Blagden Campbell. The checkers obtained it from EM Science. The solvent was tested for peroxides prior to use.
3. Nitrobenzene was supplied by BDH Chemicals Ltd., and was used as received. The checkers obtained it from Aldrich Chemical Company, Inc. Nitrobenzene should be handled only with gloves and in an efficient fume hood.
4. Hydrazine hydrate was purchased from FBC Industrial Chemicals and was used as supplied. The checkers obtained it from Aldrich Chemical Company, Inc. Hydrazine is a severe poison and should be handled only with gloves in an efficient fume hood.
5. An HPLC system was used to monitor the reduction and to determine the end of the reaction. The HPLC monitoring was not employed by the checker. However, TLC indicated that the reduction was almost complete after stirring for 2 hr at 25–30°C. If only a slight excess (1.03 equiv) of hydrazine is employed, the reaction is generally complete in 2 hr and excessive overreduction cannot occur.
The HPLC system consisted of a Waters C_{18} μ-Bondapak column, a mobile phase consisting of 15% acetonitrile, 85% 0.05 *M* aqueous ammonium acetate using a flow rate of 2 mL/min and a UV wavelength detector for 235 nm. The relative response factors of nitrobenzene and aniline were 1.75 and 0.66, respectively.
6. *N*-Phenylhydroxylamine, mp 83.5–85°C, can be isolated at this stage in 75–85% yields if desired, but it should be borne in mind that *N*-phenylhydroxylamine is not very stable. The isolation can be carried out by adding an equal volume of methylene chloride to the tetrahydrofuran solution, which is then dried over magnesium sulfate and concentrated to low volume under reduced pressure. Addition of a little petroleum ether precipitates *N*-phenylhydroxylamine, which is then filtered and washed with petroleum ether.
7. Acetyl chloride was obtained from Hoechst and was used as supplied. The checkers obtained it from Fluka Chemical Corporation. The quantity of acetyl chloride used is 1.05 equiv based on the HPLC yield. (The checkers simply used the amount specified.) Acetyl chloride should be handled only with gloves in an efficient fume hood.
8. No vigorous, exothermic reaction is seen during the addition of acetyl chloride, but the addition should be slow because of the heterogeneous nature of the reaction and the need to destroy efficiently hydrogen chloride as it is formed. The product, like *N*-phenylhydroxylamine, is sensitive to acid and undergoes the Bamberger rearrangement.[3]
9. Excessive heating causes decomposition of the product. This method also affords an easily handled crystalline solid of good purity.
10. The following analytical data have been obtained: ^{1}H NMR ($CDCl_3$, 100 MHz) δ: 2.11 (s, 3 H acetylmethyl); 7.40 (m, 5 H, aromatics); 8.90 (board, 0.6 H, NOH); IR (Nujol) cm^{-1}: 3140, 2930, 2860, 1630, 1595, 1460, 1380. Anal. calcd. for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.48; H, 5.99; N, 9.21. Nonaqueous titration (Bu_4NOH), 98.3%.

3. Discussion

This preparation illustrates a convenient reduction of nitrobenzene under catalytic transfer hydrogenation conditions to give *N*-phenylhydroxylamine in high yield and demonstrates a monoacylation method to afford the *N*-acetyl derivative in high yield. Some work has been done in this area by Johnstone et al.[4] A number of other reductive methods described in the literature were tried,[5,6,7] but these were not as good as the procedure described here. Phenylhydroxylamine is thermally unstable, can undergo a Bamberger rearrangement,[3] and deteriorates on storage, so its isolation is undesirable. The material was therefore converted directly, without isolation, to its more stable *N*-acetyl derivative. Other acylation methods led to mixtures of mono and diacylated products.

References and Notes

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

petroleum ether

hydrogen chloride,
hydrochloric acid (7647-01-0)

ammonium acetate (631-61-8)

aniline (62-53-3)

acetonitrile (75-05-8)

sodium hydroxide (1310-73-2)

acetyl chloride (75-36-5)

sodium bicarbonate (144-55-8)

carbon (7782-42-5)

Nitrobenzene (98-95-3)

Phenylhydroxylamine,
N-Phenylhydroxylamine (100-65-2)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

Tetrahydrofuran (109-99-9)

rhodium (7440-16-6)

N-Acetyl-N-phenylhydroxylamine,
Acetamide, N-hydroxy-N-phenyl- (9032-75-1)

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