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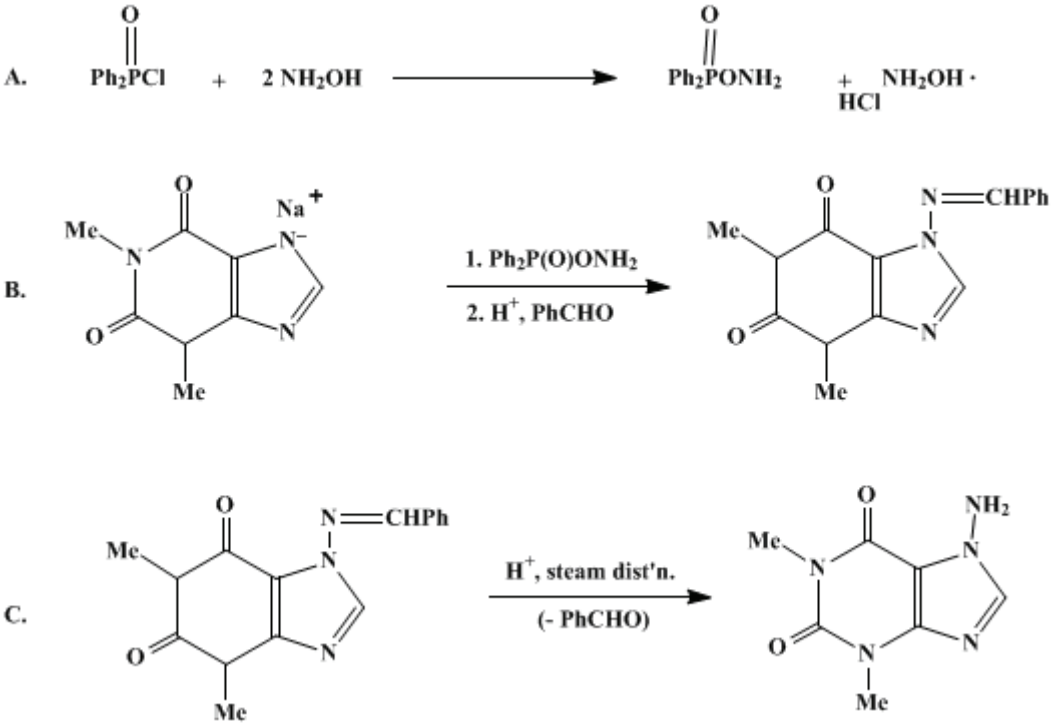
ELECTROPHILIC *N*-AMINATION OF IMIDE SODIUM SALTS WITH *O*-DIPHENYLPHOSPHINYLHYDROXYLAMINE (DPH): 7-AMINOTHEOPHYLLINE

[1*H*-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl-]



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1. Procedure

A. *O-Diphenylphosphinylhydroxylamine*.[2] A 500-mL, round-bottomed flask, equipped with a reflux condenser, drying tube, an efficient mechanical stirrer, a dropping funnel, and a nitrogen-inlet tube, is charged with 300 mL of anhydrous methylene chloride, 16.5 g (0.5 mol) of hydroxylamine base (Note 1), and 1.0 g of dry sodium bicarbonate. While the suspension is stirred vigorously at −30°C (bath temperature), a solution of 52.06 g (0.22 mol) of diphenylphosphinyl chloride (Note 2) in 70 mL of anhydrous methylene chloride is added under a nitrogen atmosphere at a constant rate within 30 min. The resulting thick suspension is stirred at −30°C for 2 hr and for an additional 2 hr after the cooling bath is removed. The reaction mixture is filtered through a sintered-glass funnel (porosity 3) and the residue is washed with two 80-mL portions of methylene chloride. The methylene chloride is removed from the colorless solid by a stream of air for 2 hr. The dry solid, still on the funnel, is then mixed thoroughly with 200 mL of deionized water. The water is removed by suction. The same operation is performed sequentially with 150 mL of 5% aqueous sodium bicarbonate solution and then with two 150-mL portions of water. This solid, which retains water tenaciously, is dried by suction and by pressing down on the funnel for several hours, followed by drying in a phosphorus pentoxide-charged vacuum desiccator until its weight is constant (24 hr) to give 36 g (70%) of impure *O*-diphenylphosphinylhydroxylamine, mp 120–135°C, with decomposition.

A 500-mL, two-necked flask, equipped with a reflux condenser and a drying tube, is charged with 240 mL of anhydrous ethanol. The solvent is preheated to 70°C and a 12-g portion of this finely

powdered dry product is added all at once. The resulting suspension is refluxed for 2–3 min when almost all of the solid has dissolved. The hot solution is filtered as quickly as possible through a sintered-glass funnel (porosity 3) and the filtrate is chilled to 0°C for 30 min. Isolation of the crystalline deposit and washing with 20 mL of ether provides 7.8 g of pure product. Recrystallization of three 12-g portions furnishes 23.4 g (44%) of *O*-diphenylphosphinylhydroxylamine, mp >140°C, with decomposition (Note 3).

B. *7-Benzylideneaminotheophylline*. A 2000-mL, round-bottomed flask, equipped with an efficient mechanical stirrer, thermometer, and drying tube, is charged with 600 mL of anhydrous *N*-methylpyrrolidone (Note 4) and 20.2 g (0.1 mol) of anhydrous theophylline sodium salt (Note 5). The flask is cooled with an ice–salt bath to 0°C (internal temperature). Then 23.4 g (0.1 mol) of *O*-diphenylphosphinylhydroxylamine is added in three equal portions while the suspension is stirred vigorously. After the ice–salt bath is removed, the resulting viscous suspension is stirred for 6 hr at 20°C.

After the solution is diluted with 1200 mL of water, the pH is adjusted to 1–2 with concentrated hydrochloric acid and the mixture stirred at 5°C for 1 hr. The precipitated diphenylphosphinic acid is isolated by filtration and washed with 50 mL of water (Note 6). The filtrate is placed in a 2000-mL, round-bottomed flask, equipped with a reflux condenser and an efficient mechanical stirrer. A solution of 20 mL of benzaldehyde in 50 mL of ether is added and the mixture is stirred vigorously for 20 min. The precipitate that forms is isolated by filtration and washed sequentially with 50 mL of water and 50 mL of ether to yield 19.6 g (69%) of 7-benzylideneaminotheophylline, mp 207–209°C.[3] An analytical sample may be prepared by recrystallization from ethanol (mp 209°C).

C. *7-Aminotheophylline*. The reaction flask of a steam distillation apparatus is charged with 19.6 g (0.069 mol) of 7-benzylideneaminotheophylline and 100 mL (0.1 mol) of 1 *N* hydrochloric acid. The suspension is steam-distilled until no more benzaldehyde is detected in the distillate (Note 7). The resulting clear solution in the reaction flask is concentrated by rotary evaporation to a volume of 30 mL, adjusted to pH 10 with concentrated ammonium hydroxide, transferred to a separatory funnel, and extracted with five 60-mL portions of chloroform. The combined chloroform extracts are dried with anhydrous sodium sulfate, filtered, and concentrated to dryness by rotary evaporation. The residue is recrystallized from 75 mL of water to afford 11.3 g (84%) of 7-aminotheophylline, mp 222°C.[3]

2. Notes

1. Hydroxylamine base has been prepared by the method of Lecher and Hofmann.[4] The free base can be stored in a tightly stoppered flask at −20°C for several days. The checkers found it expedient to prepare free hydroxylamine by a modification of the Lecher–Hofmann procedure in which a Schlenk tube under dry N_2 was used to filter the NaCl precipitate and the NH_2OH base was crystallized from the filtrate at −30°C, then isolated by inverting the Schlenk apparatus and filtering the product (74% yield from the hydrochloride).
2. Diphenylphosphinyl chloride can be purchased from Aldrich Chemical Company, Inc. or from EGA-Chemie, D-7924 Steinheim, West Germany (an Aldrich Chemical Company). Diphenylphosphinyl chloride can also be prepared by oxygen-mediated oxidation of diphenylchlorophosphine[5] (purchased from Fluka AG, CH-9470 Buchs, Switzerland).
3. The recrystallization should be performed as quickly as possible in portions below 15 g. Prolonged heating in ethanolic solution causes substantial losses. The pure, dry compound can be stored in a tightly stoppered flask at 0°C for at least 6 months without loss of aminating capacity. The submitters report that the pure compound showed no signs of spontaneous decomposition during 4 years of use, except when heated to >140°C, where the compound decomposes with effervescence.
4. *N*-Methylpyrrolidone (purum grade) was purchased from Fluka AG, CH-9470 Buchs, Switzerland, dried over calcium hydride, and vacuum-distilled [bp 78–79°C (12 mm)].
5. The sodium salt of theophylline was obtained as follows: to a solution of 36.34 g (0.2 mol) of theophylline in 120 mL of 50% aqueous ethanol at 80°C was added 50 mL (0.2 mol) of aqueous 4 *N* sodium hydroxide. Chilling to 0°C, filtration of the precipitate, washing with 50 mL of 96% ethanol, then with 100 mL of ether, and drying in a vacuum desiccator over phosphorus pentoxide provides 28.0 g of the anhydrous salt.

6. The recovered and dried diphenylphosphinic acid, 19.6 g (90%), is ready to be recycled to diphenylphosphinyl chloride.[6, 7]
7. Traces of benzaldehyde can be detected with Brady's reagent (2,4-dinitrophenylhydrazine sulfate solution) or by its characteristic smell.

3. Discussion

Electrophilic *N*-aminations of imide salts have been performed with hydroxylamine-*O*-sulfonic acid (HOSA),[8,9,10] *O*-(2,4-dinitrophenyl) hydroxylamine,[11, 12] and *O*-mesitylenesulfonylhydroxylamine (MSH).[11] The use of HOSA is mainly restricted to aqueous reaction media.[8, 9] *O*-(2,4-Dinitrophenyl) hydroxylamine, MSH, and *O*-diphenylphosphinylhydroxylamine (DPH) can be applied in anhydrous or even nonpolar solvents. *O*-(2,4-Dinitrophenyl) hydroxylamine and MSH require *N*-protected hydroxylamine for their preparation.[11, 12] MSH has been found to be explosive.[13, 14] DPH has the advantage of being prepared directly from unprotected hydroxylamine and seems to have no tendency toward spontaneous decomposition. The possibility of recycling diphenylphosphinic acid may be regarded as a further advantage. The advantage of using unprotected hydroxylamine to prepare DPH is partially negated by the required somewhat delicate preparation and handling of the free hydroxylamine base. The large amount of solvent that is sometimes required because of the low solubility of DPH and the resulting diphenylphosphinic acid salt may be regarded as a disadvantage, too.

O-Diphenylphosphinylhydroxylamine has also been used to aminate carbanions,[15, 16] tertiary phosphines, and thio ethers.[2]

TABLE I
N-AMINO COMPOUNDS FROM IMIDE SODIUM SALTS AND DPH[a]

Educt Alkali Salt	Solvent[b]	Product	Yield (%)	Ref.
Imidazole	DMF	1-Aminoimidazole	28	3
2-Nitroimidazole	NMP	1-Amino-2-nitroimi-dazole	40	3
2-Methyl-4(5)-nitroimidazole	NMP	1-Amino-2-methyl-4-nitroimidazole	30	3
Theobromine	DMF	1-Aminotheobromine	71	3
Theophylline	NMP	7-Aminotheophylline	60	3
Phthalimide	DMF	*N*-Aminophthalimide	90	3

[a]DPH = *O*-diphenylphosphinylhydroxylamine.
[b]DMF = anhydrous dimethylformamide; NMP = anhydrous N-methylpyrrolidone.

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

O-DIPHENYLPHOSPHINYLHYDROXYLAMINE (DPH)

1-Amino-2-nitroimi-dazole

2-Methyl-4(5)-nitroimidazole

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

Phthalimide (85-41-6)

ammonium hydroxide (1336-21-6)

hydroxylamine (7803-49-8)

methylene chloride (75-09-2)

dimethylformamide (68-12-2)

Imidazole (288-32-4)

calcium hydride (7789-78-8)

Hydroxylamine-O-sulfonic acid (2950-43-8)

diphenylchlorophosphine (1079-66-9)

N-methylpyrrolidone (872-50-4)

7-Aminotheophylline,
1H-Purine-2,6-dione, 7-amino-3,7-dihydro-1,3-dimethyl- (81281-58-5)

diphenylphosphinyl chloride (1499-21-4)

theophylline sodium salt,
sodium salt of theophylline

diphenylphosphinic acid (1707-03-5)

7-Benzylideneaminotheophylline (81281-59-6)

theophylline (58-55-9)

2,4-dinitrophenylhydrazine sulfate

1-Aminoimidazole

2-Nitroimidazole (527-73-1)

1-Amino-2-methyl-4-nitroimidazole

Theobromine (83-67-0)

1-Aminotheobromine

phosphorus pentoxide (1314-56-3)

N-aminophthalimide (1875-48-5)

O-Mesitylenesulfonylhydroxylamine

O-Diphenylphosphinylhydroxylamine (72804-96-7)

O-(2,4-dinitrophenyl) hydroxylamine