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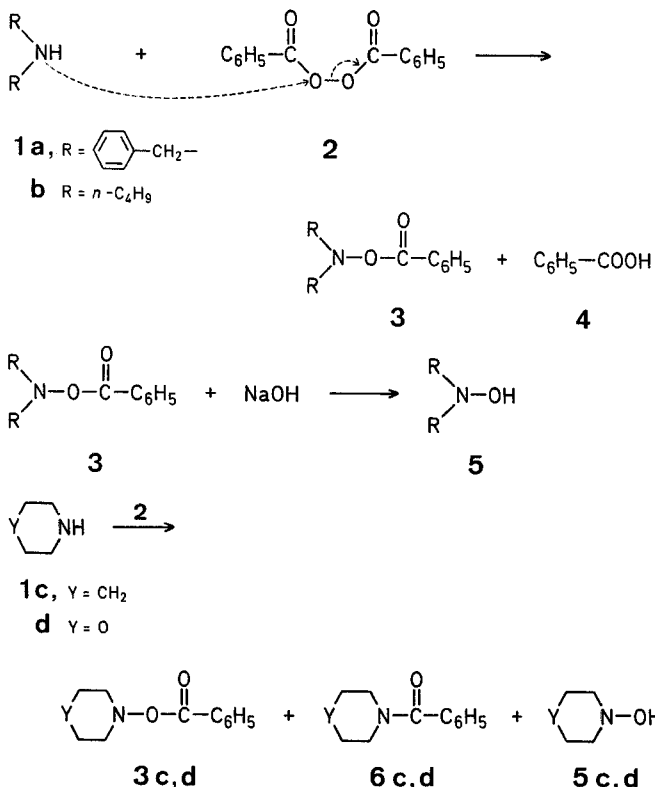
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Improved Oxidation of Amines with Dibenzoyl Peroxide

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The oxidation of secondary amines to *N*-substituted hydroxylamines is a common synthetic transformation for which no generally reliable methodology exists. Perhaps the most widely employed process is due to Gambarjan² and uses dibenzoyl peroxide (**2**) as the oxidant. This two-step procedure involves (a) nucleophilic displacement along the peroxide *O—O* linkage³, and (b) saponification of the intermediate *O*-benzoylhydroxylamine (**3**).



The necessity of using an additional equivalent of starting amine **1** to trap the benzoic acid (**4**) liberated in the first step is a serious shortcoming of this method, nevertheless it has been widely used, especially in the production of important antihypertensive agents⁴. Yields of 27–35%^{4,5,6} have been reported for the first step.

It seemed reasonable to expect that the displacement reaction could be carried out in the presence of an appropriate auxiliary base which would irreversibly remove the benzoic acid (**4**) as it formed. This expectation was realized by employing disodium hydrogen phosphate (Na₂HPO₄) or a crosslinked 4-vinylpyridine copolymer in ethereal solvents. A doubling or tripling of previously reported yields resulted from this strategy. The overall yield of hydroxylamine **5** was further im-

proved^{2b} by utilizing anhydrous potassium methoxide/methanol for the debenzoylation step. The Table summarizes our experimental results.

It should be noted that some product yields are lower because of appreciable water solubility. In certain hydroxylations, amides **6** were also observed, arising from the acylation of amines **1** by dibenzoyl peroxide (**2**) in the first step. Nevertheless, pure hydroxylamines **5** were easy to isolate by partitioning the debenzoylated material between aqueous 5% hydrochloric acid and ether; benzamide byproducts **6** were inert to potassium methoxide and thus remained in the organic phase.

The reaction of benzylamine in tetrahydrofuran with reagent **2** gave only *N*-benzylbenzamide (90%; m.p. 103–105 °C). In contrast to this result, Zinner has reported the successful oxidation of several primary amines in moderate yield using 0.5 mol-equivalents of reagent **2** in benzene⁹. Use of an auxiliary base in this solvent-dependent process can also be expected to improve the yields of primary *N*-hydroxylamines.

Table. Oxidation of Amines **1** with Dibenzoyl Peroxide (**2**)

Amine	Method ^a	Product	Yield [%]	m.p. [°C]	
				found	reported
1a	A	3a	83	96–96.5°	96–96.5° ^{2b}
		5a	90	121–123°	123–124° ^{2b}
1a	B	3a	89	—	—
		5b	98	—	—
1b	A	3b	98	—	—
		5b	69	52.5–53.5°	52–53° ¹⁰
1b	B	3b	100	—	—
		5b	100	—	—
1c	A	3c	75	62.5–63°	62° ²
		6c	9.5	104–105°	—
		5c	38	38–40°	37–40° ¹¹
		3d	66	81–82°	82–84° ¹²
1d	B	6d	30	74–75°	—
		5d	50	—	—
		3d	66	81–82°	82–84° ¹²

^a Method A: 5 equiv poly-4-vinylpyridine in tetrahydrofuran. Method B: 5 equiv Na₂HPO₄ in ether or tetrahydrofuran.

Reaction of Dibenzylamine (**1a**) with Dibenzoyl Peroxide (**2**); Typical Procedures:

Method A: A mixture of poly-4-vinylpyridine (Reilly Chemical Company; 5.9 g, 50 mol-equiv) in tetrahydrofuran (60 ml) is dried by azeotropic distillation (30 ml of solvent removed). Dibenzylamine (**1a**; 1.97 g, 10 mmol) is introduced, then a solution of dibenzoyl peroxide (2.27 g, 11 mmol) in tetrahydrofuran (10 ml) is added dropwise. After 24 h at room temperature the mixture is heated under reflux for 2 h. The cooled mixture is filtered and the polymer washed with dichloromethane (4 × 20 ml). The combined organic phases are evaporated under reduced pressure to leave a viscous yellow residue which is diluted with fresh dichloromethane (35 ml) and washed with 10% aqueous sodium carbonate solution (2 × 10 ml). The organic phase is dried with magnesium sulfate and concentrated to leave an off-white solid (3.11 g, 98%) which is recrystallized from methanol/water to give pure *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**3a**); yield: 2.82 g (89%); m.p. 94–95.5 °C (Ref.^{2b}, m.p. 95–96 °C).

Method B: The same crystalline *O*-benzoate of dibenzylhydroxylamine (**3a**) is obtained by substitution of disodium hydrogen phosphate (7.1 g, 50 mmol) for poly-4-vinylpyridine in the above experiment. Upon completion of addition of dibenzoyl peroxide, the mixture is heated in ether (60 ml) for 15 h at reflux. Workup as above followed by recrystallization affords the product; yield: 2.63 g (83%).

Dibenzylhydroxylamine (5a):

A 0.42 molar solution of potassium methoxide in methanol (4.46 ml, 1.89 mmol) is diluted with methanol (5 ml) and treated dropwise with a solution of **3a** (0.43 g, 1.35 mmol) in ether (13 ml). The mixture is stirred at room temperature for 20 h, concentrated under reduced pressure, and the residual white paste is partitioned between water (5 ml) and ether (20 ml). The organic phase is separated, 5% aqueous hydrochloric acid is added, the white precipitate formed is isolated by suction filtration, and washed with ether (3 × 5 ml). The solid is dissolved in 5% aqueous sodium carbonate solution (10 ml) and extracted with fresh ether (3 × 5 ml). Drying and concentration of the combined ether layers gives **5a**; yield: 0.26 g (90%); m.p. 121–123 °C (Ref.², m.p. 122 °C).

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