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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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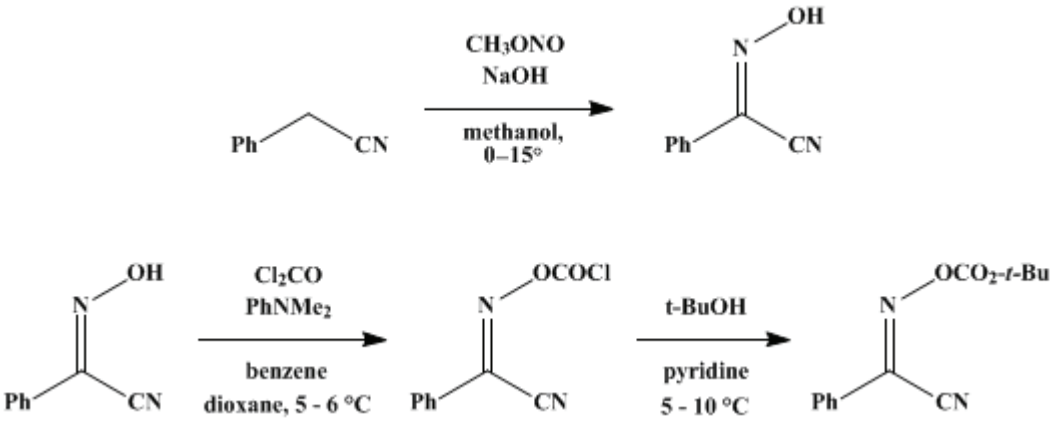
Organic Syntheses, Coll. Vol. 6, p.199 (1988); Vol. 59, p.95 (1979).

A NEW REAGENT FOR *tert*-BUTOXYCARBONYLATION: 2-*tert*-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE

[Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]carbonyl]oxy]imino]-]



Submitted by Masumi Itoh, Daijiro Hagiwara, and Takashi Kamiya[1].
Checked by Hiroyuki Ishitobi, Teruji Tsuji, and Wataru Nagata.

1. Procedure

Caution! Phosgene is highly toxic. Part B should be performed in an efficient hood. Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. 2-*Hydroxyimino*-2-*phenylacetonitrile*. A 1-l., round-bottomed flask fitted with a mechanical stirrer, a calcium chloride drying tube, a thermometer, and a gas-inlet tube is charged with 117 g. (1.00 mole) of benzyl cyanide and a solution of 40.0 g. (1.00 mole) of sodium hydroxide in 300 ml. of methanol (Note 1). The resulting solution is stirred and cooled at 0° as methyl nitrite is introduced through the gas-inlet tube, which extends below the surface of the liquid. The methyl nitrite is generated by dropwise addition of a cold solution of 32 ml. of concentrated sulfuric acid in 65 ml. of water from a 100-ml., pressure-equalizing dropping funnel into a 300-ml. Erlenmeyer flask containing a suspension of 83 g. (1.2 moles) of sodium nitrite in 53 ml. of methanol and 50 ml. of water (Note 2). The rate of generation of methyl nitrite is adjusted so that the reaction temperature does not exceed 15°. After the addition is complete (Note 3), stirring is continued for another 2 hours, and the solvent is removed under reduced pressure with a rotary evaporator. The residue is dissolved in 500 ml. of water, and the resulting solution is washed with two 100-ml. portions of toluene. The aqueous layer is acidified with concentrated hydrochloric acid and cooled in an ice bath. The resulting precipitate is filtered, washed thoroughly with cold water, and dried, yielding 111–120 g. (76–82%) of 2-hydroxyimino-2-phenylacetonitrile, m.p. 119–124° (Note 4). This material is used in Part B without further purification.

B. 2-tert-*Butoxycarbonyloxyimino*-2-*Phenylacetonitrile*. A 200-ml., three-necked, round-bottomed flask equipped with a dropping funnel, a mechanical stirrer, a thermometer, and a calcium chloride drying tube is charged with a solution of 10.9 g. (0.110 mole) of phosgene (Note 5) in 30 ml. of benzene. The contents of the flask are stirred and cooled in an ice bath while a solution of 14.6 g. (0.100 mole) of 2-hydroxyimino-2-phenylacetonitrile and 13.2 g. (0.113 mole) of *N,N*-dimethylaniline in 5 ml. of dioxane and 80 ml. of benzene (Note 6) is added dropwise over 1 hour at 5–6°. Stirring is continued for 6 hours at the same temperature, after which the mixture is allowed to stand overnight in an ice bath. A solution of 11.1 g. (0.150 mole) of *tert*-butyl alcohol and 12.0 ml. (0.150 mole) of pyridine (Note 7) in 30 ml. of benzene (Note 6) is added over 1 hour as the mixture is stirred and cooled at 5–10°. Stirring

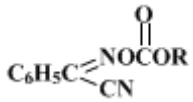
is continued for an additional 6 hours while the reaction temperature is allowed to rise to room temperature. The reaction mixture is allowed to stand overnight (Note 8) and is then mixed with 50 ml. of water and 50 ml. of benzene. The organic layer is separated and washed successively with three 30-ml. portions of cold 1 *N* hydrochloric acid, 30 ml. of water, two 30-ml. portions of 5% sodium hydrogen carbonate solution, and two 30-ml. portions of water. Each of the aqueous washings is extracted with 30 ml. of benzene. The organic layers are combined, dried with magnesium sulfate, and concentrated to dryness under reduced pressure at a temperature lower than 35°. The crystalline residue is triturated with 20 ml. of aqueous 90% methanol. The solid is filtered, washed with 30 ml. of aqueous 90% methanol, and dried, giving 15.8–17.0 g. of crude product, m.p. 84–86° (Note 9). Recrystallization from methanol (Note 10) affords 14.6–15.7 g. (59–64%) of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile as white needles or plates, m.p. 84–86° (Note 11).

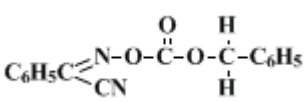
2. Notes

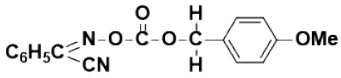
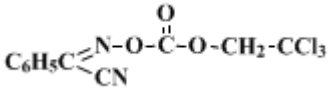
1. The submitters used reagent grade solvents and reagents without further purification. The yield of 2-hydroxyimino-2-phenylacetonitrile was 76% when the checkers used technical grade benzyl cyanide purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan. The yield was improved to 81% with distilled material, b.p. 75–77° (3 mm.). Benzyl cyanide is also available from Aldrich Chemical Company, Inc.
2. This method for the preparation of methyl nitrite is described in *Org. Synth.*, **Coll. Vol. 2**, 363 (1943).
3. The addition of sulfuric acid requires *ca.* 1 hour. Occasional swirling of the Erlenmeyer flask is recommended for smooth generation of methyl nitrite.
4. Material of this quality is satisfactory for most purposes; however, if further purification is necessary, it may be recrystallized from hot water, giving a solid that melts at 126–128°. The checkers obtained product melting at 104–116° and 104–117° in the first and second runs, respectively. Evidently the product is a mixture of *syn* and *anti* isomers, the ratio of which was different in the material obtained by the submitters and the checkers. This difference in the isomer ratio might be attributed to a slight variation of experimental conditions. The submitters later informed the checkers that the methanol was evaporated at 70–80°; the checkers removed the solvent at 35–40°. On partial recrystallization from hot water, the checkers isolated both the less soluble *anti* isomer, m.p. 127.5–129°, and the more soluble *syn* isomer, m.p. 97–99°. The melting points given in the literature for the *syn* and *anti* isomers are 129° and 99°, respectively.[2] The UV spectra (95% C_2H_5OH) of the *syn* and *anti* isomers show maxima at 274 nm. (log ε, 3.99) and 260 nm. (log ε, 4.05), respectively.
5. Phosgene may be replaced by a 0.5 molar equivalent of trichloromethyl chloroformate. This reagent may be purchased from Hodogaya Chemical Company, Ltd., Tokyo, Japan, or prepared by the procedure in *Org. Synth.*, **Coll. Vol. 6**, 715 (1988).
6. *N,N*-Dimethylaniline, pyridine, *tert*-butyl alcohol, and the solvents were dried with Linde type 3A molecular sieves.
7. The use of a 0.5 molar excess of pyridine and *tert*-butyl alcohol is necessary in this case to obtain a satisfactory yield. However, when this procedure is applied to the preparation of other alkoxycarbonates (Table II), excess alcohol should be avoided since it may contaminate the product.

TABLE II

OTHER ALKOXYCARBONYLATING REAGENTS PREPARED FROM 2-HYDROXYIMINO-2-PHENYLACETONITRILE



R	Solvent for Recrystallization	M.p. (°)	Yield (%)
	ethyl acetate-hexane	73–75	62
$C_6H_5CH_2$-			

 4-$CH_3OC_6H_4CH_2$-	ethyl acetate-hexane	112–113	36
 Cl_3CCH_2-	methanol	82–84	87

8. The yield was reduced to 46% in a run in which the product was isolated without the additional overnight reaction time.
9. The checkers obtained 12.8–13.0 g. (52–53%), m.p. 84–86°, in the first crop and 2.7–3.4 g. (11–14%), m.p. 52–62°, in the second crop. Recrystallization of the former from methanol gave 11.5 g. of crystals, m.p. 84–86°, suggesting that the first crop is a pure single isomer. A ^{1}H NMR spectrum ($CDCl_3$) of the second crop shows two singlets at δ 1.62 and 1.64 for the *tert*-butyl groups. Thus, this material is a mixture of *syn* and *anti* isomers. Both the first and second crops proved equally useful for *tert*-butoxycarbonylation of an amino acid.
10. Recrystallization from boiling methanol should be avoided owing to the thermal instability of the product.
11. IR (Nujol) cm.$^{-1}$: 1785 (C=O); ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.62 (s, 9H, 3CH_3), 7.2–8.2 (m, 5H, C_6H_5). A TLC on silica gel (Merck precoated plate, 60 F_{254}) using UV detection and 10% methanol in chloroform as the developing solvent showed a major and a minor spot at an R_f value of 0.74 and 0.50, respectively. The minor spot arises from 2-hydroxyimino-2-phenylacetonitrile formed by partial hydrolysis of the product on the silica gel.
The submitters recommend that the product be stored in a stoppered brown bottle in a refrigerator. Although the material can be kept at room temperature for several weeks without noticeable decomposition, gradual evolution of carbon dioxide occurs over a period of several months, with the attendant risk of explosion. However, storage in the presence of a small amount of silica gel as a drying agent extends the shelf life of the material to more than a year.

3. Discussion

2-Hydroxyimino-2-phenylacetonitrile has been prepared from benzyl cyanide by reaction with nitrous acid,[3] with isoamyl nitrite and sodium ethoxide,[4] and with butyl nitrite and hydrogen chloride.[2]

The *tert*-butoxycarbonyl group is one of the most important amino protecting groups in peptide synthesis. Many *tert*-butoxycarbonylating reagents[5,6] have been prepared as substitutes for *tert*-butyl azidoformate,[7] which is toxic, shock-sensitive, and relatively unreactive.[8] 2-*tert*-Butoxycarbonyloxyimino-2-phenylacetonitrile,[9,10] one such reagent, possesses the following advantages: (1) it is stable, highly reactive, and ready for use; (2) *tert*-butoxycarbonylation of an amino acid is usually complete within 4–5 hours at room temperature in the presence of a 0.5 molar excess of triethylamine in 50% aqueous dioxane (Table I); and (3) the by-product, 2-hydroxyimino-2-phenylacetonitrile, is easily and completely removed by extraction into an organic solvent, leaving the *tert*-butoxycarbonylamino acid salt in the aqueous phase. The present procedure is also applicable to preparation of other amino-protecting reagents (Table II).

TABLE I
PREPARATION OF *N*-*tert*-BUTOXYCARBONYL-PROTECTED AMINO ACIDS WITH 2-*tert*-BUTOXYCARBONYLOXYIMINO-2-PHENYLACETONITRILE[a]

Amino Acid	Solvent[b]	Time (hours)	Yield (%)
Glycine	A	2	87

Alanine	B	4	80
S-Benzyl cysteine	A	3	94
Glutamic acid	A	3	78
Leucine	A	3	72
Methione	A	3	82
Phenylalanine	A	2	65
Proline	C	1.5	88
Threonine	A	3	100
Asparagine	A	20	86

a The reactions were carried out with 0.010 mole of the amino acid, 0.011 mole of 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile, and 0.015 mole of triethylamine at 20–25°.
b The solvents were as follows: A, aqueous dioxane; B, aqueous acetone; C, methanol–dioxane–water, 15:5:10.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 203
- Org. Syn. Coll. Vol. 6, 715

References and Notes

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

silica gel

Benzeneacetonitrile, α-[[[(1,1-dimethylethoxy)carbonyl]carbonyl]oxy]imino]-

Methione

sulfuric acid (7664-93-9)

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

Benzene (71-43-2)

methanol (67-56-1)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

alanine (56-41-7)

sodium nitrite (7632-00-0)

nitrous acid (7782-77-6)

carbon dioxide (124-38-9)

acetone (67-64-1)

pyridine (110-86-1)

toluene (108-88-3)

phosgene (75-44-5)

sodium ethoxide (141-52-6)

Benzyl cyanide (140-29-4)

Butyl nitrite (544-16-1)

N,N-dimethylaniline (121-69-7)

Glutamic Acid (56-86-0)

Glycine (513-29-1)

methyl nitrite (624-91-9)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

Isoamyl nitrite (110-46-3)

phenylalanine (63-91-2)

proline (147-85-3)

asparagine (70-47-3)

leucine (61-90-5)

threonine (72-19-5)

triethylamine (121-44-8)

tert-butyl alcohol (75-65-0)

2-hydroxyimino-2-phenylacetonitrile (825-52-5)

Trichloromethyl chloroformate (503-38-8)

ethyl acetate-hexane (2639-63-6)

tert-Butyl azidoformate (1070-19-5)

2-tert-Butoxycarbonyloxyimino-2-phenylacetonitrile (58632-95-4)

S-Benzyl cysteine