



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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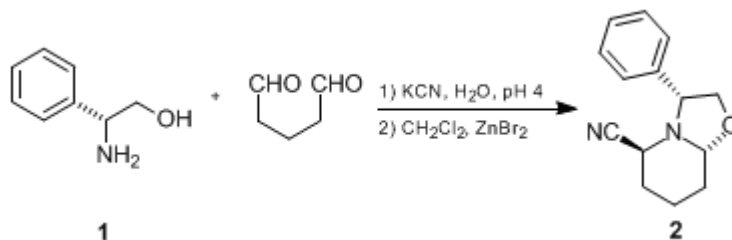
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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A STABLE CHIRAL 1,4-DIHYDROPYRIDINE EQUIVALENT FOR THE ASYMMETRIC SYNTHESIS OF SUBSTITUTED PIPERIDINES: 2-CYANO-6-PHENYLOXAZOLOPIPERIDINE

[5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-, [3R-(3 α ,5 β ,8 α)]]



Submitted by Martine Bonin, David S. Grierson, Jacques Royer, and Henri-Philippe Husson¹.
Checked by Gilbert Rishton and Larry E. Overman.

1. Procedure

CAUTION! Aqueous potassium cyanide is used in this procedure. All operations should be conducted in a well-ventilated hood and rubber gloves should be worn.

2-Cyano-6-phenyloxazolopiperidine. A 2-L, round-bottomed flask is charged with 10 g (0.073 mol) of (–)-phenylglycinol (Note 1) and 40 g of citric acid in 1 L of distilled water. The mixture is stirred magnetically until complete dissolution is achieved and is then cooled to 0–5°C (ice-water bath). The flask is equipped with a dropping funnel and 45 mL of an aqueous 24% glutaraldehyde solution (0.11 mol) is added dropwise over 20 min and the resultant cloudy solution is stirred for an additional 30 min at 0°C. The cooling bath is removed and a solution of 7.15 g (0.11 mol) of potassium cyanide in 20 mL of water is carefully added in one portion followed by 200 mL of methylene chloride. The resulting two-phase reaction system is stirred for 3 hr at room temperature, then the aqueous phase is neutralized (Note 2) by addition of sodium bicarbonate and the two layers are separated. The water layer is extracted with three 200-mL portions of methylene chloride (Note 3) and the combined methylene chloride layers are dried over sodium sulfate and concentrated on a rotary evaporator to a volume of 500 mL. Zinc bromide (2 g) is added in small portions over 5 min to this solution and vigorous stirring under nitrogen is continued for 3 hr (Note 4). The reaction mixture is concentrated to a volume of approximately 150 mL (Note 5) and the resultant mixture is applied to a 10-cm diameter flash chromatography column prepared using hexane-ether (2:1) as the eluant. The desired product is eluted first (Note 6), (Note 7). By recrystallization from hexane, the product [10.8–11.6 g (65–70%)] is obtained analytically pure; mp 79–81°C, $[\alpha]_D^{23}$ –280° (CHCl₃, *c* 1.0) (Note 8).

2. Notes

1. The checkers used (R)-(–)-2-phenylglycinol [98%, $[\alpha]_D^{24}$ –31.7° (1 N HCl, *c* 0.76)] purchased from Aldrich Chemical Company, Inc. The submitters employed material [mp 78°C, $[\alpha]_D^{20}$ –26.5° (MeOH, *c* 0.7)] prepared by lithium aluminum hydride reduction of (–)-phenylglycine and report that the yield of 2-cyano-6-phenyloxazolopiperidine prepared from this material is 75–83%.
2. Extraction at pH greater than 9 led to the formation of by-products (2,6-dicyanopiperidines)² and consequently to a lower yield of the desired product.
3. The aqueous layer containing residual potassium cyanide is destroyed by addition of potassium permanganate.
4. The reaction must be carried out in a well-ventilated hood as hydrogen cyanide may be evolved.
5. Complete evaporation of the solvent gives a viscous oil which is only slightly soluble in either the

elution solvent or [methylene chloride](#). Significant loss of material thus occurs during the purification process.

6. $R_f = 0.6$ (SiO_2 , [hexane-ether](#) : 2–1) for the product.

7. Further elution permits the isolation of a mixture of two other isomers (0.3 g, 3.6%).

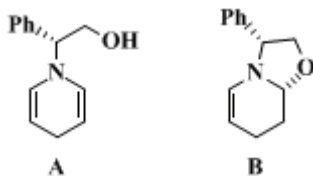
8. The product obtained by this procedure shows the following spectral data: IR (CHCl_3) cm^{-1} : 2100; ^1H NMR (400 MHz, CDCl_3) δ : 1.5–2.0 (m, 5 H), 2.13 (dd, 1 H, $J = 11.5$, $J' = 1.5$), 3.74 (t, 1 H, $J = 7.8$), 3.85 (bd, 1 H, $J = 7.1$), 3.90 (t, 1 H, $J = 8.0$), 4.12 (dd, 1 H, $J = 9.7$, $J' = 2.8$), 4.25 (t, 1 H, $J = 7.9$), 7.4 (m, 5 H); ^{13}C NMR (15 MHz, CDCl_3) δ : 19.3, 28.0, 30.0, 47.4, 63.9, 73.0, 89.9, 116.0, 128.2, 128.6, 129.0, 137.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. See [\(Note 3\)](#).

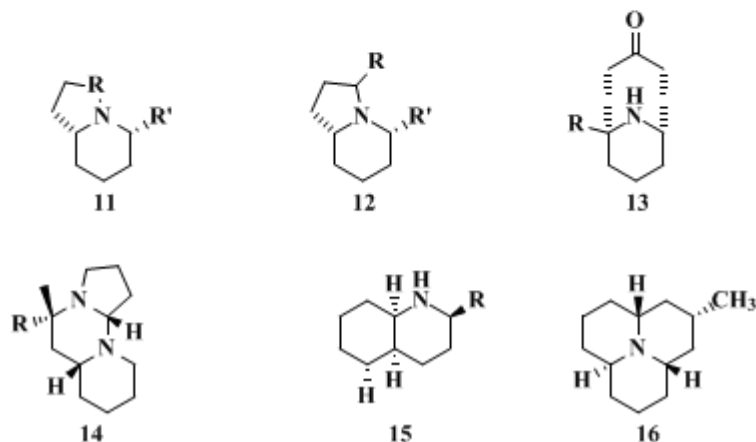
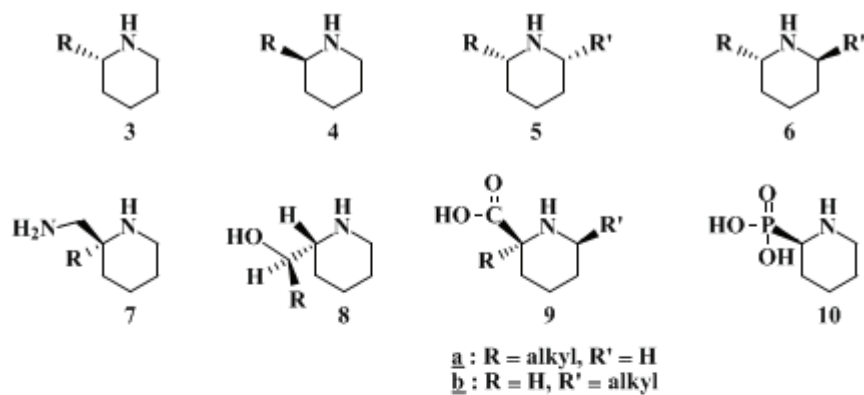
3. Discussion

The preparation described here is an improvement of the previous procedure.³ The double condensation of [glutaraldehyde](#) with the amino group of (R)-(-)-phenylglycinol (related to the Robinson-Schopf condensation) probably leads to the expected product via the formation of an intermediate of type A⁴ and/or B.



Trapping intermediate B with cyanide ion would lead to the final product. Formation of the four possible product isomers has been observed after short reaction periods, and equilibration of this mixture to the described product **2** has been demonstrated. In the original procedure compound **2** was obtained in 50–60% yield after prolonged (72 hr) reaction in water. In the present procedure equilibration of all intermediates and/or product isomers to the observed, thermodynamically more stable form of compound **2** is accelerated and the yield improved considerably through the use of [zinc bromide](#) as a catalyst in an organic medium.

2-Cyano-6-phenyloxazolopiperidine, **2**, is a stable, chiral, [1,4-dihydropyridine](#) equivalent, useful for the asymmetric synthesis of piperidines. Synthon **2** has been used for the asymmetric synthesis of several alkaloids or structural analogs in this laboratory and by others.^{5,6} A sequence of reactions involving alkylation at the α -aminonitrile center (LDA, RX), elimination of the cyano group with concomitant opening of the oxazolidine ring (NaBH_4), and finally debenzoylation (H_2 , Pd/C) permits the preparation of α -alkylated piperidine **3** in 90 % overall yield ($ee \geq 95$ %).⁷ From the same synthon **2**, enantiomeric **4** can also be prepared.⁷ A regio- and chemoselective elimination of the cyano group is also possible giving an oxazolopiperidine intermediate which can further be used to prepare the cis- and trans-2,6-disubstituted piperidines **5**⁷ and **6**.⁸



The possibility to create an R or S chiral center by substituting the CN group in **2** led us to call this methodology the CN(R,S) method, in recognition of the Centre National de la Recherche Scientifique (CNRS) which supported this work.

This methodology was extended to enantiospecific synthesis of generally less accessible or more complex piperidine derivatives :

- 2-(1-aminomethyl)piperidines **7**.⁹
- Amino-alcohols **8**¹⁰ and other β -amino-alcohols reported in the literature.^{5,6}
- Pipecolic acid and 2- or 6-alkylated derivatives **9**.¹¹
- (R)-Enantiomer of piperidin-2-yl phosphonic acid **10**.¹²
- Alkaloids **11**¹³, **12**³, **13**¹⁴, **14**¹⁵, **15**¹⁶, and the symmetric molecule **16**.¹⁷

References and Notes

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

2-Cyano-6-phenyloxazolopiperidine

5H-Oxazolo[3,2-a]pyridine-5-carbonitrile, hexahydro-3-phenyl-, [3R-(3 α ,5 β ,8 $\alpha\beta$)]

(-)-phenylglycinol

(-)-phenylglycine

(R)-(-)-phenylglycinol

HCl (7647-01-0)

ether (60-29-7)

citric acid (77-92-9)

sodium bicarbonate (144-55-8)

potassium permanganate (7722-64-7)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

methylene chloride (75-09-2)

lithium aluminum hydride (16853-85-3)

zinc bromide (7699-45-8)

hexane (110-54-3)

glutaraldehyde (111-30-8)

1,4-DIHYDROPYRIDINE

Pipecolic acid (535-75-1)

piperidin-2-yl phosphonic acid