In order to investigate the deblocking further, we examined the catalytic hydrogenolysis of both ∇^EPhe and ∇^ZPhe derivatives with several palladium catalysts. The results, summarized in Table I, showed that 5% Pd/C deactivated with pyridine selectively removed the benzyloxycarbonyl group from the *E* isomer but was completely nonselective in deblocking the *Z* isomer. Thus, none of the three catalysts selectively removed the benzyloxycarbonyl protecting group.

The (-)- and (+)-∇^EPhe hydrochlorides were obtained from the blocked amino acid enantiomers (1) by hydrogenolysis over 5% Pd/C attenuated with pyridine. Their CD spectra (Figure 1) showed[8] that the (-) isomer of 3 had a large positive Cotton effect at 214 nm while the (+) isomer showed a similar curve opposite in sign, indicating these to be the 2*S* and 2*R* enantiomers, respectively. Potentiometric titration gave average pK_as of 3.11 (CO_2H) and 8.04 (NH_2) in water solution, somewhat different from phenylalanine itself [pK_a[9] 2.58 (CO_2H) and 9.24 (NH_2)].

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. The ^{1}H NMR spectra were recorded on a Varian EM-390 90-MHz NMR spectrometer with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 infrared spectrophotometer with polystyrene as the standard. Elemental analyses were carried out by Atlantic Microlab, Atlanta, GA.

Z-∇^EPhenylalanine (1). A suspension of ∇^Ephenylalanine methyl ester hydrochloride (456 mg, 2 mmol) and carbobenzyloxy chloride (95%, 0.40 g, 2.2 mmol) in 5% $NaHCO_3$ (10 mL) was stirred at room temperature overnight. The reaction mixture was extracted with ethyl acetate (20 mL × 3). The extract was washed with 5% citric acid (20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was suspended in 2 N NaOH (5 mL) and methanol (5 mL) and stirred overnight at room temperature. The reaction mixture was condensed under reduced pressure to one-half its volume, diluted with water (20 mL), and washed with ethyl acetate. The aqueous solution was acidified with 2 N HCl and extracted with ethyl acetate, and this extract was dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was crystallized from ethyl acetate–hexane to give 450 mg (72%) of 1 as colorless needles: mp 124–125 °C; IR (KBr) ν_{max} cm^{-1} 3300 (NH), 3150–2800 (OH), 1700 (C=O); ^{1}H NMR ($CDCl_3$) δ 1.35–1.66 (1 H, br, CH), 1.95–2.20 (1 H, br, CH), 2.73–3.05 (1 H, br, PhCH), 5.20 (2 H, s, $PhCH_2$), 7.00–7.45 (10 H, m, ring H), 10.46 (1 H, s, CO_2H).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.66; H, 5.66; N, 4.51.

Z-∇^ZPhenylalanine. Following the same procedure described above, ∇^Zphenylalanine (1.14 g, 5 mmol), carbobenzyloxy chloride (95%, 0.95 g, 5.5 mmol), and 5% $NaHCO_3$ (20 mL) gave Z-∇^ZPhe·OMe, which was treated with 2 N NaOH (10 mL) and methanol (10 mL) and gave 0.98 g (62%) of Z-∇^ZPhe·OH as a white solid: mp 168–169 °C (ethyl acetate–hexane); IR (KBr) ν_{max} cm^{-1} 3280 (OH), 1695 (C=O); ^{1}H NMR ($CDCl_3$ 20% Me_2SO-d_6) δ 1.63–1.87 (1 H, m, CH), 1.93–2.16 (1 H, m, CH), 3.08 (1 H, t, *J* = 9 Hz, PhCH), 5.07 (2 H, s, $PhCH_2$), 5.97 (1 H, s, NH), 7.33 (10 H, s, ring H).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.41; H, 5.52; N, 4.48.

Resolution of Z-(2*RS*)-∇^EPhenylalanine (1). A solution of 1 (6.22 g, 0.02 mol) and brucine·2H_2O (8.64 g, 0.02 mol) in 100 mL of ethanol–water (1:1) was allowed to stand at room temperature for 4 days. The precipitated crystals were collected by suction and recrystallized twice from ethanol–water (1:1) to give 5.64 g of a brucine salt; $[\alpha]^{20}_D$ -59.3° (*c* 1.03, MeOH). This salt was suspended in 5% NaOH (100 mL), and the suspension was stirred for 10 min. The precipitated crystals were filtered and washed three times with water. The filtrate was acidified with concentrated HCl and extracted with ethyl acetate. After the solution was dried over Na_2SO_4, the extract was evaporated in vacuo and the crystals were recrystallized from ethyl acetate–hexane to give 1.91 g (59.3%) of (-)-1 as colorless leaves: mp 153–154 °C; $[\alpha]^{22}_D$ -120.1° (*c* 1.03, MeOH).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.44; H, 5.53; N, 4.48.

The mother liquor, containing the other optical isomer, was evaporated to dryness in vacuo, and the residue was suspended in 5% NaOH (100 mL) and stirred for 10 min. The precipitated crystals were filtered and washed three times with water. The filtrate was acidified with concentrated HCl and extracted with ethyl acetate. After the solution was dried over anhydrous Na_2SO_4, the extract was evaporated in vacuo and the crystalline residue was recrystallized from ethyl acetate–hexane to give 1.22 g (37.9%) of (+)-1 as colorless leaves: mp 153–154 °C; $[\alpha]^{20}_D$ +114.8° (*c* 1.0, MeOH).

Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.52; H, 5.52; N, 4.46.

(-)-(2*S*)-∇^EPhenylalanine (-)-3. A suspension of (-)-1 (3.11 mg, 1 mmol), 5% Pd/C (Engelhard) (30 mg) and pyridine (80 mg, 1 mmol) in absolute EtOH (30 mL) was stirred under hydrogen for 1.5 h at room temperature. The precipitated catalyst and crystals were collected on a filter, washed with ether, and extracted with 20 mL of ethanol–1 N HCl (10:1). The extract was evaporated in vacuo, and the residue was recrystallized from AcOEt–EtOH to give 137 mg (67%) of (-)-3·HCl: mp 219–220 °C dec; $[\alpha]^{25}_D$ -74.6° (*c* 1.0, H_2O).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.29; H, 5.67; N, 6.53. IR and NMR spectra were identical with those previously reported for the racemic compound.

(+)-(2*R*)-∇^EPhenylalanine (+)-3. Following the same procedure, Z-(2*R*)-∇^EPhe (187 mg, 0.6 mmol), 5% Pd/C (20 mg), pyridine (50 mg, 0.6 mmol) and absolute EtOH (20 mL) gave 82 mg (64%) of (+)-3·HCl: mp 221–222 °C dec; $[\alpha]^{25}_D$ +74.4° (*c* 1.0, H_2O).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.28; H, 5.70; N, 6.52.

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Registry No. (±)-*trans*-1, 86014-29-1; (-)-1, 86087-19-6; (+)-1, 86087-20-9; (±)-*trans*-1 methyl ester, 86014-30-4; (±)-*cis*-1, 86014-31-5; (-)-1 brucine salt, 86116-64-5; (-)-3, 86087-21-0; (+)-3, 86087-22-1; (±)-*trans*-3 methyl ester, 82112-05-8; (±)-∇^Z-phenylalanine, 82112-08-1; carbobenzyloxy chloride, 501-53-1; brucine, 357-57-3.

(8) See Yamada et al. (Yamada, S.; Achiwa, K.; Terashima, S.; Mizuno, H.; Takamura, N.; LeGrant, M. *Chem. Pharm. Bull.* **1969**, *17*, 2608) for references to ORD/CD studies on α-methyl amino acids.

(9) "The Merck Index", 9th ed.; Merck: Rahway, NJ, 1976; p 7072.

Base-Catalyzed Conversion of 2,5-Dicarbomethoxy-3,4-diazacyclopentadienone 3,4-Dioxide to 3,5-Dicarbomethoxy-4-hydroxyisoxazole

Jeremiah P. Freeman* and James A. Kassner

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

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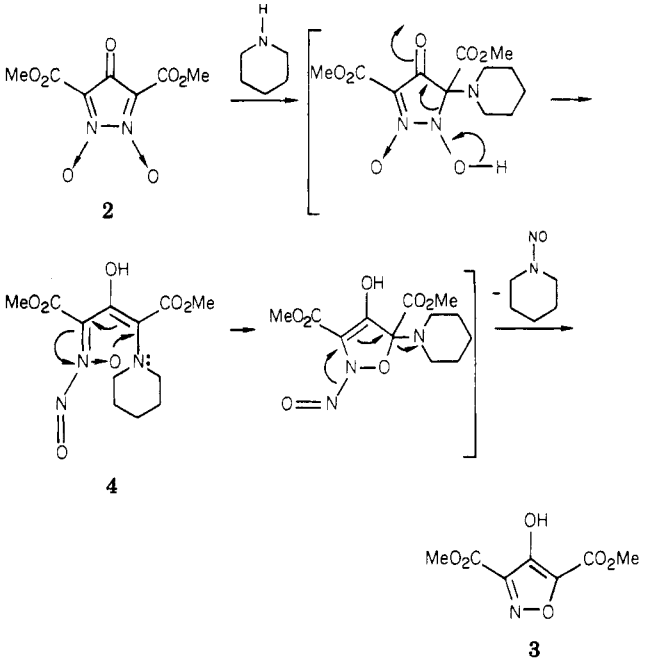
Since the establishment of the structure by Freeman et al. some years ago,[1] abortive efforts have been made to carry out base-catalyzed reactions to functionalize the

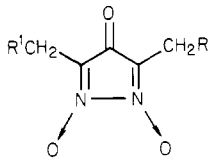
(1) Freeman, J. P.; Gannon, J. J.; Surbey, D. L. *J. Org. Chem.* **1969**, *34*, 187–194.

0022-3263/83/1948-2441$01.50/0

Scheme I



potentially active alkyl substituents of 2- and/or 5-alkyl-3,4-diazocyclopentadienone 3,4-dioxides (1). It was



observed that these bright yellow, orange, or red compounds were bleached in base, but no products could be characterized.

Isatogens, which contain a keto nitrone function similar to that in 1, were reported to add ethyl cyanoacetate under Knoevenagel conditions.[2] We decided to attempt a similar reaction with a derivative of 1 containing no base-sensitive alkyl groups. When ester 2[1] was treated with ethyl cyanoacetate in the presence of an equivalent of piperidine, extensive decomposition was observed but no product incorporating ethyl cyanoacetate could be found. Instead, 3,5-dicarbomethoxy-4-hydroxyisoxazole (3) was isolated in low yield. When the reaction was repeated with an excess of piperidine with no ethyl cyanoacetate present, 3 was produced in slightly greater amounts. In addition, *N*-nitrosopiperidine was isolated. Scheme I shows a mechanism to account for these results.

N-Nitroso nitrones similar to 4 have been proposed as the first intermediate in the nitrosation of oximes.[3] They were also proposed to be intermediates in the hydrolysis and thermolysis of pernitrosomesityl oxide.[4] The latter reaction, which leads to an isoxazolone oxime, is particularly similar to the present one.

It appears from the present work and other unpublished work that compounds such as 1 are too sensitive to bases to allow useful reactions to occur.

Experimental Section

2,5-Dicarbomethoxy-3,4-diazacyclopentadienone 3,4-Dioxide and Piperidine. A mixture of 1 g (4.3 mmol) of dioxide 2 and 1.0 mL of piperidine in 50 mL of ethanol was stirred at room temperature for 2 h. The mixture was concentrated to one-half its volume and was placed in a freezer ovenight. The pale yellow crystals that separated were collected on a filter: mp 140 °C dec; yield 0.25–0.3 g (20–25%). This material is the **piperidine salt of 3,5-dicarbomethoxy-4-hydroxyisoxazole.**

Calcd. for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.51; H, 6.59; N, 9.71. This material was identical with an authentic sample prepared from piperidine and 3,5-dicarbomethoxy-4-hydroxyisoxazole.

The salt was dissolved in chloroform, and ethereal HCl was added. Upon cooling, a white solid separated. Recrystallization from hexane–CH_2Cl_2 gave white crystals of **3,5-dicarbomethoxy-4-hydroxyisoxazole,** mp 158–158.5 (lit.[5] 157–158 °C). Its infrared spectrum was identical with an authentic sample prepared by the reaction of dimethyl acetonedicarboxylate with amyl nitrite.[5]

Chromatography of the filtrate from the original reaction misture on silica with CH_2Cl_2 as eluant yielded a yellow oil whose infrared spectrum was identical with that of an authentic sample of *N*-nitrosopiperidine.[6]

Registry No. 2,5-Dicarbomethoxy-3,4-diazacyclopentadienone 3,4-dioxide, 17952-98-6; 3,5-dicarbomethoxy-4-hydroxyisoxazole piperidine salt, 85995-80-8; 3,5-dicarbomethoxy-4-hydroxyisoxazole, 6620-30-0; piperidine, 110-89-4.

(2) Bunney, J. E.; Hooper, M. *Tetrahedron Lett.* **1966**, 3857–3860.
(3) Freeman, J. P. *Chem. Rev.* **1973**, *73*, 283–292.
(4) Freeman, J. P. *J. Org. Chem.* **1962**, *27*, 1309–1314.
(5) Klötzer, W.; Schantl, J. *Monatsh. Chem.* **1964**, *95*, 102–115.
(6) Care is required in the handling of nitrosamines because of their carcinogenicity.

A Novel Furan Synthesis. Menthofuran from 2-Bromo-4-methylcyclohexanone and (α-Formylethylidene)triphenylphosphorane

Michael E. Garst*

Department of Chemistry, D-066, University of California, San Diego, La Jolla, California 92093

Thomas A. Spencer

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

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The widespread occurrence of natural products containing furan rings[1] has stimulated continued interest in the synthesis of this heterocycle with various substitution patterns.[2] The most common type of furan found naturally, exemplified by menthofuran (5) and isomenthofuran (7), has usually been prepared by reduction of a butenolide, as in 6 → 7 in path B of Scheme I.[3,4] We have previously reported a direct synthesis of furans having this substitution pattern from α-hydroxy ketones and (2-ethoxy-1-methylvinyl)triphenylphosphonium bromide,[5] but this synthesis lacked regiospecificity because acyloin isomerization could not be avoided and mixtures of isomeric fu-

(1) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds, Terpenes"; Academic Press: New York, 1972; Vol. II.
(2) (a) Hikino, H.; Konno, C. *Heterocycles* **1976**, *4*, 817–870. (b) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 167–238.
(3) For example, Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542–543.
(4) Gariboldi, P.; Jommi, G.; Sisti, M. *J. Org. Chem.* **1982**, *47*, 1961–1962 and references therein. Gariboldi et al. described a synthesis via β-furanones that could readily be adapted to construction of furans with the substitution pattern of 5 and 7.
(5) Garst, M. E.; Spencer, T. A. *J. Org. Chem.* **1974**, *39*, 584–585.

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