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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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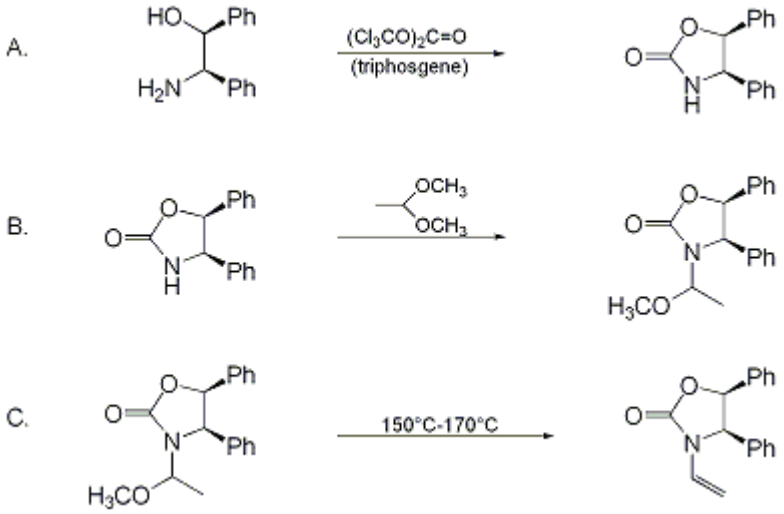
(4R,5S)-4,5-DIPHENYL-3-VINYL-2-OXAZOLIDINONE

[2-Oxazolidinone, 3-ethenyl-4,5-diphenyl-, (4R-cis)-]



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1. Procedure

Caution! Step A should be performed with gloves in an efficient hood in order to avoid contact with the toxic phosgene derivative.

A. (4R,5S)-4,5-Diphenyl-2-oxazolidinone . A 1-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer, reflux condenser, and a dropping funnel is charged with (1S,2R)-(+)-2-amino-1,2-diphenylethanol (20.0 g, 94 mmol) (Note 1) and dichloromethane, CH_2Cl_2, (140 mL), and cooled in an ice-water bath. After addition of triethylamine (28.4 mL, 204 mmol), a solution of triphosgene [bis (trichloromethyl) carbonate] (9.8 g, 33 mmol) (Note 2) in dichloromethane (20 mL) is added dropwise with a dropping funnel over 1 hr, keeping the temperature below 10°C (Note 3). After the addition is over, the mixture is stirred for 2 hr at the same temperature (Note 4). Water (40 mL) and methanol (20 mL) are added to the resulting suspension, and the mixture is stirred for 30 min. The mixture is concentrated under reduced pressure on a rotary evaporator. Water (100 mL) is poured onto the residue and the suspension is stirred vigorously for several minutes. The resulting precipitate is collected by filtration, and washed with 1 M hydrochloric acid (10 mL) and water (50 mL) to give (4R,5S)-4,5-diphenyl-2-oxazolidinone as colorless crystals (Note 5). The combined organic extracts are washed with brine , then evaporated under reduced pressure. A small amount of water is added to the residue, and the precipitate is collected by filtration and washed with a small amount of water to obtain additional (4R,5S)-4,5-diphenyl-2-oxazolidinone as colorless crystals. The two lots of crystals are air-dried, then completely dried in a desiccator over phosphorus pentoxide (P_2O_5) under reduced pressure for 24 hr. The (4R,5S)-4,5-diphenyl-2-oxazolidinone (22.3 g, 99.2%) (Note 6) obtained is used for the next step without further purification.

B. (4R,5S)-3-(1-Methoxyethyl)-4,5-diphenyl-2-oxazolidinone . A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer, and a reflux condenser is charged with (4R,5S)-4,5-diphenyl-2-oxazolidinone (20.0 g, 84 mmol), (±)-10-camphorsulfonic acid (9.7 g, 42 mmol) (Note 7), and acetaldehyde dimethyl acetal (700 mL) (Note 8). The mixture is heated at gentle reflux in an oil bath (bath temperature 80°C) for 5 hr (Note 9). The mixture is allowed to cool to ambient temperature, then concentrated under reduced pressure on a rotary evaporator (Note 10). Ethyl acetate (100 mL) is

added to the residue, and the ethyl acetate solution is transferred to a beaker. The solution is neutralized with saturated sodium bicarbonate solution (100 mL) (Note 11), and transferred into a separatory funnel. The two layers are separated, and the lower aqueous layer is extracted with ethyl acetate (100 mL). The organic layers are combined, washed with brine, dried over anhydrous sodium sulfate , filtered, then concentrated under reduced pressure on a rotary evaporator. The residue is stirred with 2-propanol-hexane (1 : 1, 60 mL) for several minutes. The solid product is collected by filtration. The filtrate is concentrated on a rotary evaporator, and the residue is again stirred with 2-propanol-hexane (1 : 1, 5 mL). The precipitate is collected by filtration. The two lots of the products are dried in a desiccator over phosphorus pentoxide (P_2O_5) under reduced pressure for 12 hr. (4R,5S)-3-(Methoxyethyl)-4,5-diphenyl-2-oxazolidinone (22.2 g, 89.3%) (Note 12) is obtained as a diastereomeric mixture. In some runs, small amounts of impurities remained after trituration. These impurities can be carried through the next step without a problem although final yields will be reduced.

C. (4R,5S)-4,5-Diphenyl-3-vinyl-2-oxazolidinone . A 500-mL filter flask is charged with (4R,5S)-3-(1-methoxyethyl)-4,5-diphenyl-2-oxazolidinone (8.9 g, 30 mmol) and solid ammonium chloride, NH_4Cl (0.32 g, 6.0 mmol). The flask is stoppered and heated behind a blast shield in a sand bath to 150°C - 170°C under reduced pressure via a water aspirator (ca. 11 mm) for 3 hr. The crude material is dissolved in CH_2Cl_2 and run through silica gel with CH_2Cl_2 (40 g of SiO_2 , 250 mL of CH_2Cl_2) to afford the product as a white solid (6.68 g, 84.2%) (Note 13). (A second treatment with silica is sometimes required to give completely clean product.)

2. Notes

1. (1S,2R)-(+)-2-Amino-1,2-diphenylethanol and its enantiomer were purchased from Aldrich Chemical Company, Inc. These compounds are also available from Tokyo Kasei Kogyo Co., Ltd.
2. Triphosgene[4] was purchased from Tokyo Kasei Kogyo Co., Ltd. This is also available from Aldrich Chemical Company, Inc. The submitters recommend the use of triphosgene which is more convenient to handle than diphosgene (trichloromethyl chloroformate).
3. This is an extremely exothermic reaction.
4. TLC analysis on Merck silica gel 60 F254 plates (dichloromethane : methanol 10 : 1) showed formation of the product, Rf 0.63 (visualized with phosphomolybdic acid in ethanol). If starting material (Rf 0.36) remains, further amounts of triethylamine (2.7 mL) and triphosgene (0.98 g) are added.
5. The submitters extracted the combined filtrates with CH_2Cl_2 ; the checkers omitted this operation after finding it made less than 1% difference in the yield of final product.
6. A pure sample can be obtained by recrystallization (toluene). The spectral and physical properties are as follows: mp 232.5-233.5°C; $[\alpha]_D^{20}$ +60.6° (MeOH, *c* 0.86); IR ($CHCl_3$) cm^{-1}: 3580, 1765, 1540 ; ^1H NMR ($CDCl_3$): 5.20 (d, 1 H, J = 8.0), 5.85 (br, 1 H), 5.96 (d, 1 H, J = 8.0), 6.8-7.6 (m, 10 H) ; MS (m/z): 239 (M^+), 108, 107 . Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.86. Found: C, 75.09; H, 5.38; N, 5.86.
7. (±)-10-Camphorsulfonic acid was purchased from Tokyo Kasei Kogyo Co., Ltd. (±)-10-Camphorsulfonic acid could be reduced to 0.1 equiv of the starting material with prolonged reaction time. The checkers used (±)-10-camphorsulfonic acid purchased from Aldrich Chemical Company, Inc.
8. Acetaldehyde dimethyl acetal was purchased from Tokyo Kasei Kogyo Co., Ltd. It is also available from Aldrich Chemical Company, Inc.
9. TLC analysis on Merck silica gel 60 F254 plates (hexane : ethyl acetate 1 : 1) showed clean formation of the diastereomeric products, Rf 0.69, and Rf 0.61 (cf. the starting material, Rf 0.45, visualized with phosphomolybdic acid in ethanol). The checkers found Rf 0.32 for the oxazolidinone starting material and Rf 0.50 and 0.61 for the diastereomeric products in 1:1 ethyl acetate:hexane.
10. Excess acetaldehyde dimethyl acetal can be recovered by distillation.
11. The pH of the aqueous layer was 7-8. Care should be taken because of foaming on neutralization.
12. The spectral properties of the diastereomeric mixture are as follows: IR ($CHCl_3$) cm^{-1}: 3000, 1750, 1410, 1100, 1055 ; ^1H NMR ($CDCl_3$) δ: 0.96 (d, 3 H × 2/3, J = 6.2), 1.46 (d, 3 H × 1/3, J = 6.2), 3.25 (s, 3 H × 1/3), 3.46 (s, 3 H × 2/3), 5.0-6.1 (m, 3 H), 6.6-7.5 (m, 10 H) ; MS (m/z): 297 (M^+), 238, 222, 165, 59 .
13. A pure sample can be obtained by vacuum distillation or recrystallization (hexane-ethyl acetate), but some decomposition occurs under drastic conditions. The spectral and physical properties are as

follows: mp 170-171°C; $[\alpha]_D^{20}$ +21.7° ($CHCl_3$, *c* 0.78); IR ($CHCl_3$) cm^{-1}: 1760, 1640, 1540, 1382, 1364 ; ^1H NMR (C_6D_6): 3.88 (dd, 1 H, J = 1.0 and 16.0), 4.10 (dd, 1 H, J = 1.0 and 9.2), 4.42 (d, 1 H, J = 8.1), 5.08 (d, 1 H, J = 8.1), 6.5-6.9 (m, 10 H), 7.13 (dd, 1 H, J = 9.2 and 16.0) ; MS (m/z): 265 (M^+), 180, 132, 131, 104 . Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.80; H, 5.65; N, 5.25.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Optically active 2-oxazolidinones and 2-thiazolidinones are versatile compounds as chiral auxiliaries.[5] [6] (4R,5S)-4,5-Diphenyl-2-oxazolidinone has been used for the synthesis of optically active amines[7] because of its high stereoselectivity and easy deprotection by hydrogenolysis after the reaction. Compared with several preparations[8] [9] [10] of (4R,5S)-4,5-diphenyl-2-oxazolidinone reported so far, this method, which makes use of triphosgene, seems to have the following advantages: simple and easy procedure, mild reaction conditions, and quantitative chemical yield. This procedure can also be used for preparing 2-oxazolidinones from various 2-aminoethanol derivatives.

Hegedus and co-workers[11] reported the synthesis of (4S,5R)-4,5-diphenyl-3-vinyl-2-oxazolidinone (the enantiomer of the compound prepared here) via the chromium carbene complex in a fair yield. This is an interesting method, but the procedure is complicated (e.g., low temperature, argon atomsphere) and the chromium waste must be disposed of in an appropriate way. On the other hand, this procedure, consisting of transacetalization[12] and pyrolysis,[13] is simple and safe. Optically active 3-vinyl-2-oxazolidinone is also used for the synthesis of (1R,2S)-2-fluorocyclopropylamine [14] [15] that is the key intermediate for novel antibacterial quinolonecarboxylic acids.

References and Notes

1. Chemical Technology Research Laboratories, Daiichi Pharmaceutical Co., Ltd., Kita-Kasai, Edogawa, Tokyo 134, Japan.
2. Faculty of Pharmaceutical Sciences, Takaramachi, Kanazawa, Ishikawa 920-0934, Japan.
3. Sagami Chemical Research Center, Hayakawa, Ayase, Kanagawa 252-1193, Japan.
4. Triphosgene: *Aldrichimica Acta* **1988**, *21*(2), 47.
5. Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, Jr., J. F. *Tetrahedron* **1988**, *44*, 5525;
6. Nagao, Y.; Ochiai, M. *Yuki Gosei Kagaku Kyokaishi* **1990**, *48*, 986 and references cited therein, *Chem. Abstr.* **1991**, *114*, 122087b.
7. Es-Sayed, M.; Gratkowski, C.; Krass, N.; Meyers, A. I.; de Meijere, A. *Tetrahedron Lett.* **1993**, *34*, 289.
8. Stefanovskii, Yu. N.; Spasov, S. L.; Kurtev, B. I.; Balla, M.; Ötvös, L. *Chem. Ber.* **1969**, *102*, 717;
9. Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520;
10. Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc., Chem. Commun.* **1993**, 81.
11. Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255.
12. Böhme, H.; Berg, G. *Chem. Ber.* **1966**, *99*, 2127.
13. Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.-i.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104* , 6697.
14. Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron Lett.* **1992**, *33*, 3487;
15. Akiba, T.; Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Terashima, S. *Tetrahedron* **1994**, *50*, 3905.

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

(4R,5S)-4,5-Diphenyl-3-vinyl-2-oxazolidinone:
2-Oxazolidinone, 3-ethenyl-4,5-diphenyl-, (4R-cis)- (13); (143059-81-8)

(4R,5S)-4,5-Diphenyl-2-oxazolidinone:
2-Oxazolidinone, 4,5-diphenyl-, (4R-cis)- (11); (86286-50-2)

(1S,2R)-(+)-2-Amino-1,2-diphenylethanol:
Ethanol, 2-amino-1,2-diphenyl-, L-erythro-(+)- (8);
Benzeneethanol, β-amino-α-phenyl-, [S-(R*,S*)]- (9); (23364-44-5)

Triethylamine (8);
Ethanamine, N,N-diethyl- (9); (121-44-8)

Triphosgene:
Carbonic acid, bis(trichloromethyl) ester (8,9); (32315-10-9)

(4R,5S)-3-(1-Methoxyethyl)-4,5-diphenyl-2-oxazolidinone:
2-Oxazolidinone, 3-(1-methoxyethyl)-4,5-diphenyl-, [4R-[3(R*),4a,5a]]- (13); 142977-52-4)

Camphorsulfonic acid monohydrate:
Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (±)- (9); (5872-08-2)

Acetaldehyde dimethyl acetal (8);
Ethane, 1,1-dimethoxy- (9); (534-15-6)

Ammonium chloride (8,9); (12125-02-9)

(4S,5R)-4,5-Diphenyl-3-vinyl-2-oxazolidinone:
2-Oxazolidinone, 3-ethenyl-4,5-diphenyl-, (4S-cis)- (12); (128947-27-3)