A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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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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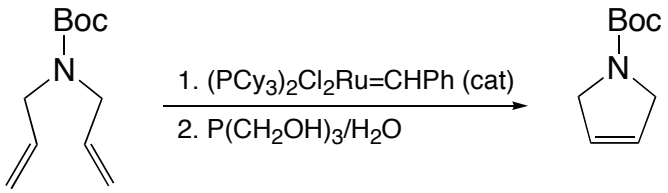
RING-CLOSING METATHESIS SYNTHESIS OF *N*-Boc-3-PYRROLINE [(1*H*-Pyrrole-1-carboxylic acid, 2,5-dihydro-, 1,1-dimethylethyl ester)]



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Checked by Louise M. Stamp and Andrew B. Holmes.
Discussion Addendum: *Org, Synth.* **2012**, *89*, 170.

1. Procedure

N-Boc-3-pyrroline.[3] An oven-dried, 3-L, three-necked, round-bottomed flask equipped with an overhead mechanical stirrer, rubber septum with nitrogen inlet, and condenser with a bubbler-sealed outlet, is charged with 732 mg (0.89 mmol, 0.5 mol%) of bis(tricyclohexyl-phosphine)benzylidine ruthenium dichloride (Note 1) and 445 mL of dry dichloromethane (Note 2). The mixture is stirred under a nitrogen atmosphere to give a burgundy-colored solution. *N*-Boc-diallylamine (38.3 mL, 178 mmol) (Note 3) is transferred to the flask by syringe. After addition of the *N*-Boc-diallylamine, ethylene gas is evolved vigorously and the color of the solution changes from burgundy to dark brown. The solution is heated to reflux with stirring for 2.5 h (Note 4), then cooled to room temperature.

An aqueous methanolic solution of tris(hydroxymethyl)phosphine is prepared (Note 5). This solution is transferred to the flask containing the *N*-Boc-3-pyrroline, using 5 mL of methanol as a rinse. Triethylamine (0.247 mL, 1.78 mmol) is added to the mixture, which is vigorously stirred at room temperature overnight under a nitrogen atmosphere (Note 9).

Deionized water (400 mL) is added to the flask and the mixture is stirred vigorously for 30 min. Using a 2-L separatory funnel, the dichloromethane phase is separated from the aqueous phase, which is discarded. The organic phase is then washed with 350 mL of deionized

water and with 200 mL of 50% v/v water/saturated brine solution. The dichloromethane phase is dried with 10 g of $MgSO_4$, then filtered through a sintered glass funnel. The filtrate is concentrated under reduced pressure by rotary evaporation (water aspirator) using a bath temperature of ca. 40 °C.

The crude product is divided in half and each portion is separately distilled in a Kugelrohr apparatus (50 mL distillation and receiver flasks) (Notes 10, 11) to give a combined yield of 27.2-28.3 g (90-94%) of *N*-Boc-3-pyrroline as a white, crystalline, low-melting solid (Note 12).

2. Notes

1. Bis(tricyclohexylphosphine)benzylidine ruthenium dichloride was obtained from Strem Chemical Company and used as received.

2. Dichloromethane was distilled over calcium hydride before use. The submitters found that identical reaction yields were obtained using commercial amylene-free HPLC-grade dichloromethane.

3. *N*-Boc-diallylamine was obtained from Aldrich Chemical Company, Inc. and used as received.

4. The progress of the reaction can be conveniently monitored by gas chromatography. GC analyses were performed on a Hewlett-Packard 6890 series gas chromatograph equipped with a 6890 series mass selective detector and an HP-5MS 30-m × 0.25-mm × 0.25-μm column under the following conditions: injector temp 180 °C; detector temp 150 °C; oven temp 70 °C, 2 min; ramp 5.75 °C/min; final temp 150 °C; helium gas flow 20.0 mL/min; t_R = 9.73-9.75 min (the submitters observed t_R 9.71 min). Complete conversion was usually observed after 2 h of reflux.

5. Preparation of tris(hydroxymethyl)phosphine. A 250-mL, three-necked, round-bottomed flask, equipped with a condenser having a bubbler-sealed outlet, rubber septum with nitrogen inlet, and magnetic stir bar, is charged with 43 mL (74.1-79.1 mmol) of a 1.72-1.84M aqueous solution of tetrakis(hydroxymethyl)phosphonium sulfate (Note 6). The flask is immersed in an oil bath. Methanol (25 mL) is added to the flask (Note 7), and the contents are heated to a gentle reflux under a nitrogen atmosphere. Sodium hydroxide pellets (3.1 g, 76.5 mmol) are added to the flask over the course of 30 min, accompanied by the gradual addition of 40 mL of

methanol (Note 8). The mixture is stirred for an additional 10 min, then cooled to room temperature with stirring.

6. Tetrakis(hydroxymethyl)phosphonium sulfate was obtained as a 70-75% w/v (ca. 1.72-1.84M) aqueous solution from Fluka and was not purified before use. The submitters used 30.5 mL (76.5 mmol) of a 2.56M aqueous solution (11% active phosphorus by weight) obtained from Cytec, Inc.

7. Methanol was added to the tetrakis(hydroxymethyl)phosphonium sulfate by syringe through the rubber septum and this resulted in a cloudy, white solution.

8. A white precipitate forms on the bottom of the flask as NaOH is added over the 30 min period, causing the solution to become viscous. Additional methanol is added to enable stirring to be maintained.

9. The brown color of the *N*-Boc-3-pyrroline solution begins to fade immediately upon addition of tris(hydroxymethyl)phosphine. Approximately 45 min later, a viscous, brown substance is observed to adhere to the walls of the flask. This initially insoluble material dissolves after stirring overnight. A pale yellow solution results.

10. The submitters used a Kugelrohr distillation apparatus fitted with 24/40 ground glass joints and the *N*-Boc-3-pyrroline was distilled from a 500-mL, round-bottomed flask directly into a 250-mL receiving flask.

11. The Kugelrohr oven was heated from room temperature to 80 °C over the course of 45 min. The submitters noted that the pressure was 280 mtorr as the residual solvent was removed. As the oven temperature approached 50 °C, an acetone and dry ice bath was placed under the collection bulb. The submitters noted that the system pressure then dropped to 70 mtorr and the product distilled as a clear and colorless liquid that rapidly crystallized. The checkers observed similar results. The distillation was terminated when the distilling flask was nearly empty.

12. The submitters obtained 28.71 g (96%) of *N*-Boc-3-pyrroline. The analytical properties are as follows: mp 36-38 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9 H), 4.10 (s, 4 H), 5.75 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.5, 53.1, 79.2, 125.8, 154.3; IR ($CHCl_3$) cm^{-1} 2937, 1680, 1623, 1522, 1477, 1405, 1208, 1124, 995, 950, 871, 742, 624; MS (EI) *m/z* (rel intensity) 169 (20, M^+), 114 (30), 96 (45), 68 (100); HRMS (ES^+) *m/z*

192.1004 ([M + Na]$^+$, calcd. for $C_9H_{15}NO_2Na$ 192.1000). Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.3. Found C, 63.3; H, 8.8; N, 8.1.

Waste Disposal Information

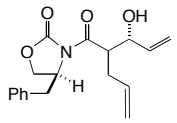
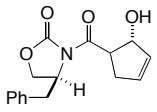
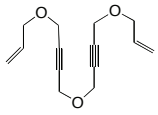
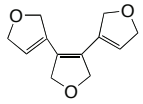
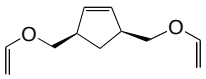
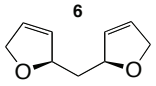
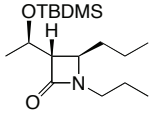
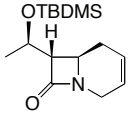
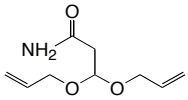
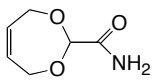
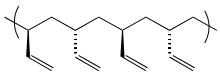
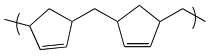
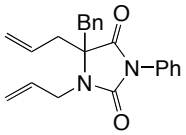
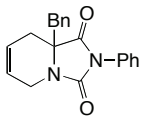
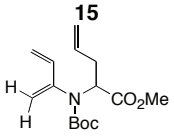
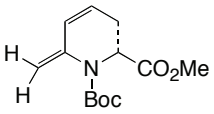
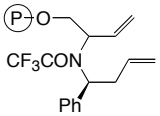
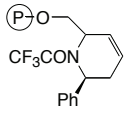
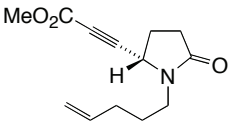
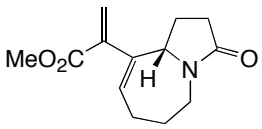
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The preparation of 3-pyrroline was recently reported in *Organic Syntheses*.[4] The protected form, *N*-Boc-3-pyrroline, has been used effectively in Heck arylations for the preparation of various 4-aryl endocyclic enecarbamates.[5] It has also been used in the preparation of regioisomeric 3-hydroxyisoxazolinyl prolines which are medicinally active.6 The catalytic asymmetric hydroformylation of *N*-Boc-pyrroline has been investigated.7 N-Boc-pyrroline has also been utilized in the synthesis of various antibacterial compounds.[8,9,10]

A procedure to remove colored ruthenium impurities using lead tetraacetate oxidation followed by filtration through a silica gel plug has been described.[11]

Table 1. Examples of RCM using Grubb's Catalyst, **1**

Entry	Substrate	Conditions (yield)	Product	Reference
1	 **3**	1 mol% **1**, 30 min, 25 °C, CH_2Cl_2 (97%)	 **4**	12
2	 **5**	8 mol% **1**, 4 h, 45 °C, C_6H_6, (60%)	 **6**	13
3	 **7**	5 mol% **1**, 2 h, 60 °C, C_6,H_6, (90%)	 **8**	14
4	 **9**	5 mol% **1**, 6 h, 25 °C, CH_2Cl_2, (78%)	 **10**	15
5	 **11**	5 mol% **1**, 21 h, 25 °C, CH_2Cl_2, (83%)	 **12**	16
6	 **13**	2 mol% **1**, 21 h, 35 °C, CH_2Cl_2, (>97%)	 **14**	17
7	 **15**	10 mol% **1**, overnight, reflux, CH_2Cl_2, (>95%)	 **16**	18
8	 **17**	5 mol% **1**, 30 min, reflux, CH_2Cl_2, (93%)	 **18**	19
9	 **19**	13 mol% **1**, 12 h, reflux, CH_2Cl_2, (70%) (tritylpolystyrol resin)	 **20**	20
10	 **21**	4 mol% **1**, 5 h, 25 °C, CH_2Cl_2, (87%)	 **22**	21

An efficient large-scale preparation of *N*-Boc-3-pyrroline using 0.1 mol% bis(tricyclohexylphosphine)ethylidene ruthenium dichloride was published[22] during the time that this procedure was in press. For this particular transformation, even lower catalyst loadings could likely be realized by use of the more active and more stable *N*-heterocyclic carbene-based ruthenium catalysts (e.g., the second-generation Grubbs catalyst).[23, 24]

Newer methods for the removal of ruthenium-derived by-products have also been disclosed, including the use of a polar isocyanide,[25] supercritical CO_2,[26] functionalized silicates,[27] polymer-bound triphenylphosphine oxide/DMSO,[28] polymer bound chelating phosphines,[29] and silica gel/activated carbon.[30]

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3. For the original reports from which this procedure was adapted, see: (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856; (b) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137.

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

N-Boc-3-pyrroline: 1*H*-Pyrrole-1-carboxylic acid, 2,5-dihydro-, 1,1-dimethylethyl ester (9); (73286-70-1)

Bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride: Ruthenium, dichloro(phenylmethylene)bis(tricyclohexylphosphine)-, (SP-5-31)- (9); (172222-30-9)

Boc-diallylamine: Carbamic acid, di-2-propenyl-, 1,1-dimethylethyl ester (9); (151259-38-0)

Tetrakis(hydroxymethyl)phosphonium sulfate ("Pyroset-TKOW"): Phosphonium, tetrakis(hydroxymethyl)-, sulfate (2:1) (9); (55566-30-8)

Tris(hydroxymethyl)phosphine: Methanol, phosphinidynetris- (9); (2767-80-8)

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