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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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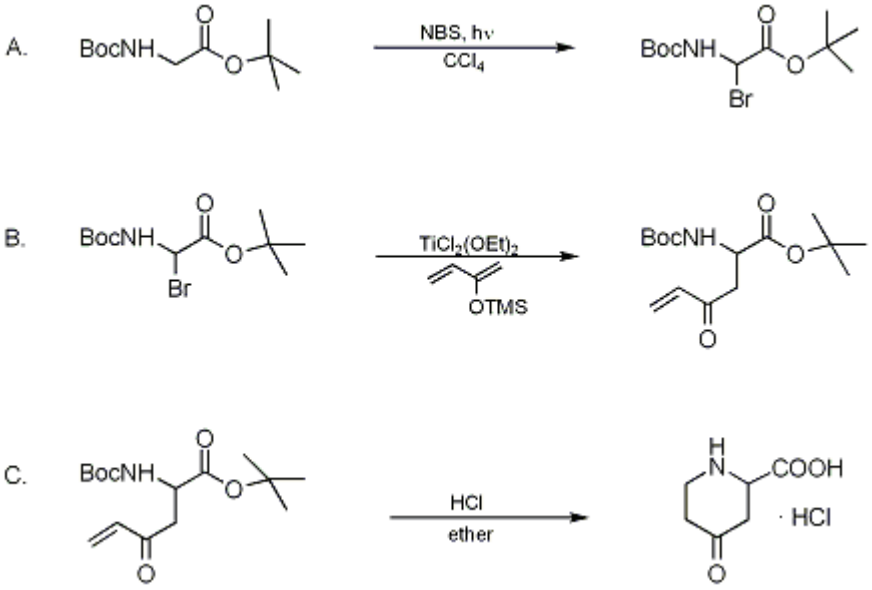
TITANIUM-MEDIATED ADDITION OF SILYL DIENOL ETHERS TO ELECTROPHILIC GLYCINE: 4-KETOPIPECOLIC ACID HYDROCHLORIDE

[Pipecolic acid, 4-oxo-, hydrochloride]



Submitted by Clarisse Mühlemann, Peter Hartmann, and Jean-Pierre Obrecht[1].
Checked by Eugene Ho and David L. Coffen.

1. Procedure

A. *2-Bromo-N-Boc-glycine tert-butyl ester*. In a 1-L, round-bottomed flask are placed 20.0 g (0.0865 mol) of N-Boc-glycine tert-butyl ester (Note 1) and 16.2 g (0.0912 mol) of N-bromosuccinimide (Note 2). Carbon tetrachloride (350 mL, (Note 3)) is added, the flask is connected to a clean rotatory evaporator (Note 4) and the apparatus is flushed with argon. The flask is cooled, while being rotated, by means of a water bath and is irradiated with two 150-W tungsten lamps (Note 5) for 1 hr. The colorless solution becomes dark red and a precipitate forms. The suspension is filtered through a Schlenk tube and the carbon tetrachloride (CCl_4) is evaporated under reduced pressure. The remaining yellowish oil is employed in the next step without purification (Note 6).

B. *tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate*. The crude bromination product from the previous step is taken up in 240 mL of dry tetrahydrofuran (THF) (Note 7) and transferred to a 1000-mL flask equipped with a stirrer, thermometer, dropping funnel, and argon inlet. The solution is cooled to −78°C and a solution of 42 g (0.20 mol) of dichlorodiethoxytitanium [$TiCl_2(OEt)_2$] in 80 mL of dry THF (Note 8) is added at such a rate that the internal temperature does not exceed −72°C. When the addition is complete, the reaction mixture is stirred at −78°C for 10 min and then 24 g (0.170 mol) of 2-trimethylsiloxybutadiene (Note 9) in 100 mL of THF is added dropwise, causing only a slight increase in temperature (−72°C). The reaction mixture is allowed to warm to room temperature overnight and poured into 700 mL of ice-cooled, saturated sodium bicarbonate solution. After filtration through Celite, the aqueous phase is extracted with three 200-mL portions of ether. The combined organic layers are washed twice with water, dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated. The remaining dark oil (29 g) is subjected to flash chromatography (20-cm column diameter, ether/hexane 1:3); 8.44–8.73 g (33–36%) (Note 10) of the product is obtained as a slightly yellowish oil (Note 11).

C. *4-Ketopipecolic acid hydrochloride*. tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl] carbamate, 8.73 g (0.0308 mol), is dissolved in 280 mL of an ice-cooled, saturated solution of hydrogen chloride in ether. The solution is kept without stirring at room temperature overnight. The resulting suspension is filtered and the filter cake is immediately washed with dry ether (Note 12). The washing with ether is repeated four times and, after drying under reduced pressure, 5.48 g (99%) of 4-ketopipecolic acid hydrochloride is obtained as a colorless powder, mp 139–142°C dec (Note 13).

2. Notes

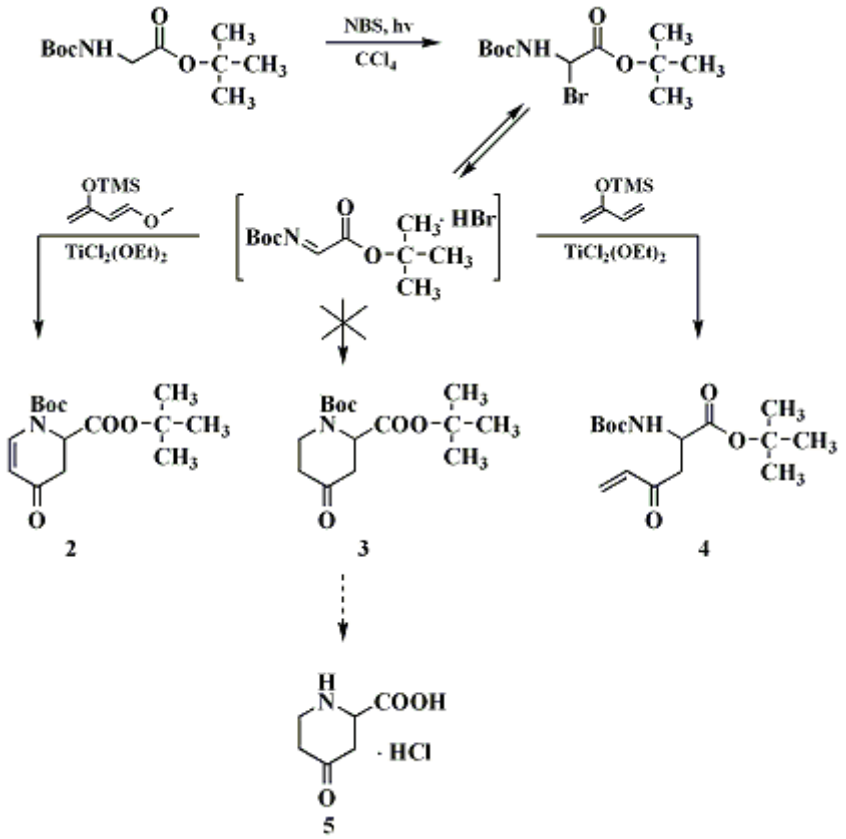
1. Boc-Glycine tert-butyl ester can be prepared by treatment of glycine tert-butyl ester hydrochloride (Aldrich Chemical Company, Inc.) with di-tert-butyl dicarbonate (Fluka Chemical Corporation) and triethylamine in THF.[2]
2. N-Bromosuccinimide was purchased from Fluka Chemical Corporation, recrystallized from water, and dried well in a vacuum desiccator.
3. Carbon tetrachloride is toxic and should only be handled in a well-ventilated hood.
4. The rotatory evaporator was washed with ethanol and ether. Bromination on a smaller scale can be carried out in a three-necked, round-bottomed flask with a thermometer, argon inlet, and stirring bar. External cooling with a water bath to keep the internal temperature between 15° and 20°C is important. The use of more concentrated solutions should be avoided, since dimerization instead of bromination becomes the dominant reaction.
5. The water bath was coated with aluminum foil in order to increase the efficiency of the irradiation.
6. TLC (ethyl acetate/hexane 1:3; vanillin/concd. H_2SO_4/heat) reveals complete consumption of the starting material and only small amounts of impurities. The crude product is stable for several weeks at −20°C under argon.[2]
7. THF was distilled from potassium and benzophenone.
8. Tetraethyl orthotitanate, 22.9 g (0.100 mol), (Fluka Chemical Corporation, bulb-to-bulb-distilled at 110–115°C/0.1 mm) is dissolved in 80 mL of dry THF. Titanium chloride ($TiCl_4$) (Fluka Chemical Corporation), 19.0 g (0.100 mol, distilled at 136°C/atmospheric pressure) was added dropwise while cooling with an acetone/dry ice bath to keep the temperature below 0°C. Alternatively, $TiCl_4$ may be added to a solution of $Ti(OEt)_4$ (obtained from Aldrich Chemical Company, Inc.) in hexane at 0°C; the solvent is evaporated and replaced by THF.[3]
9. Trimethylsiloxybutadiene was purchased from Petrarch Systems, Inc., and employed without further purification. The checkers attempted to use the more stable triethylsiloxybutadiene without success.
10. In an experiment on one tenth the scale, the yield was 57%.[4]
11. The physical properties are as follows: ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 18 H), 3.08 (dd, 1 H, J = 4 and 18), 3.28 (dd, 1 H, J = 4 and 18), 4.45 (m, 1 H), 5.48 (d, 1 H, J = 8, N-H), 5.91 (dd, 1 H, J = 2 and 10), 6.25 (dd, 1 H, J = 2 and 18), 6.34 (dd, 1 H, J = 10 and 18); IR ($CHCl_3$) cm^{-1}: 3430, 3000, 2980, 2930, 1740, 1720, 1710, 1630, 1500.
12. When the filter cake contains hydrogen chloride, it is very hygroscopic. It should therefore be covered immediately with dry ether after the ethereal hydrogen chloride solution has been aspirated.
13. The physical properties are as follows: ^{1}H NMR (MeOD) δ: 3.05 (dt, 2 H, J = 2 and 6), 3.20 (dd, 1 H, J = 7 and 20), 3.29 (dd, 1 H, J = 4 and 20), 3.79 (t, 2 H, J = 6), 4.30 (dd, 1 H, J = 4 and 7); IR (nujol) cm^{-1}: 3300–2300 broad, 3060, 2960, 2920, 2860, 1740, 1725, 1600, 1570.

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

N-Boc-2-Bromoglycine tert-butyl ester (**1**), introduced by Steglich and co-workers, is a versatile synthon for electrophilic glycine,[5] an important tool in the synthesis of non-proteinogenic amino acids.



Elimination of HBr leads to an acylimino acetate that should be able to undergo an aza-Diels–Alder reaction with dienes to give pipecolic acid derivatives not readily accessible by other methods. Indeed, **1**, in the presence of $TiCl_2(OEt)_2$, reacts with Danishefsky's diene between −78°C and room temperature to give the cyclic compound **2** in 72% yield. In a thermal reaction of 2-trimethylsiloxybutadiene with another electrophilic glycine equivalent, Jung and co-workers[6] isolated a cyclic product of type **3**. Under the reaction conditions described here, the reaction product is not **3** but the enone **4**, which by itself is an interesting bifunctional intermediate. However, upon deprotection the anticipated ring closure takes place in a very clean fashion. Pure 4-ketopipecolic acid hydrochloride crystallizes out of the ethereal hydrogen chloride solution in quantitative yield, which illustrates the advantage of the use of **1** in amino acid synthesis, i.e., the ease of deprotection, often a critical step.

References and Notes

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

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium bicarbonate (144-55-8)

carbon tetrachloride (56-23-5)

aluminum (7429-90-5)

Benzophenone (119-61-9)

potassium (7440-09-7)

Glycine (513-29-1)

magnesium sulfate (7487-88-9)

vanillin (121-33-5)

Tetrahydrofuran (109-99-9)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

titanium chloride (7550-45-0)

triethylamine (121-44-8)

argon (7440-37-1)

2-trimethylsiloxybutadiene (38053-91-7)

Di-tert-butyl dicarbonate (24424-99-5)

4-Ketopipecolic acid hydrochloride,
Pipecolic acid, 4-oxo-, hydrochloride (99979-55-2)

2-Bromo-N-Boc-glycine tert-butyl ester,
N-Boc-2-Bromoglycine tert-butyl ester

N-Boc-glycine tert-butyl ester,

Boc-Glycine tert-butyl ester (111652-20-1)

tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate (117833-62-2)

dichlorodiethoxytitanium (3582-00-1)

glycine tert-butyl ester hydrochloride (27532-96-3)

Tetraethyl orthotitanate (3087-36-3)

Trimethylsiloxybutadiene

triethylsiloxybutadiene