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Propargyloxycarbonyl and Propargyl Groups for Novel Protection of Amino, Hydroxy, and Carboxy Functions

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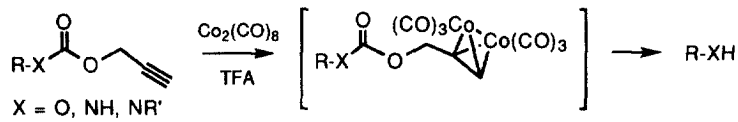
Abstract

The propargyloxycarbonyl group readily introduced to both amino and hydroxy groups by using propargyl chloroformate is stable to neat TFA but is readily cleaved at ambient temperature by treatment with $Co_2(CO)_8$ and TFA in CH_2Cl_2 via formation of an alkyne–Co complex. The propargyl ester similarly serves as a good protecting group for carboxy functions.

Keywords: propargyl; propargyloxycarbonyl; alkyne–Co complex; protecting group

Selective protection and deprotection are of particular importance for the synthesis of complex polyfunctional compounds [1]. In this paper we report new safety-catch protecting groups, i.e., propargyloxycarbonyl (Proc) and propargyl groups, which can be easily cleaved by acids via formation of an alkyne–Co complex by virtue of its strong stabilization of a cationic charge at its α-position [2, 3].



The Proc group was readily introduced to both amino and hydroxy groups by using propargyl chloroformate (**5**) (Table 1, entries 1-3).[1] The propargyl ester **10** was obtained from the acid **4** and propargyl alcohol **6** by the use of DCC and DMAP (Table1, entry 4). The Proc group and the propargyl ester were stable in neat TFA at room temperature for 48 h. The Boc group of **10** was thus selectively removed by TFA in the presence of the propargyl ester. The Proc group of **9** was also stable to Lewis acid-catalyzed ring-opening of the benzylidene function (BH_3•Me_2NH-BF_3•Et_2O) [4].

The alkyne-Co complex of **7** was obtained by the reaction with $Co_2(CO)_8$ in 82% yield after purification by silica-gel column chromatography. Treatment of the complex with 1%

1. Propargyl chloroformate (**5**) : To a solution of triphosgene (25.0 g, 84.2 mmol) in dry CH_2Cl_2 (100 ml) was added dropwise a solution of propargyl alcohol (14.7 ml, 252 mmol) and pyridine (20.4 ml, 252 mmol) in dry CH_2Cl_2 (100 ml) at 0°C for 3 h. The mixture was stirred at r.t. overnight and passed through a short silica-gel column to remove insoluble materials. After the removal of CH_2Cl_2 under reduced pressure, the residue was purified by distillation to give a colorless liquid, bp 58-60°C.

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TFA in CH_2Cl_2 at 0°C for 30 min afforded the free amino compound **1** in a quantitative yield. The Proc group was also removed without isolation of the alkyne-Co complex by successive addition of 5% TFA in CH_2Cl_2 and then $Co_2(CO)_8$ (Table 2, entries 1, 2).[2] However, reverse addition, i.e., excess $Co_2(CO)_8$ and then TFA, gave unidentified byproducts. The propargyl ester was removed by 7% TFA in CH_2Cl_2 and $Co_2(CO)_8$ in a good yield. The Boc group was retained under the cleavage conditions (Table 2, entry 3).

Table 1. Introduction of Proc and propargyl groups

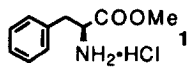
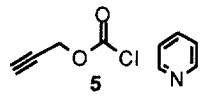
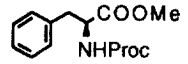
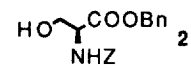
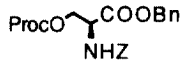
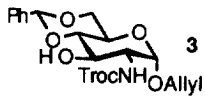
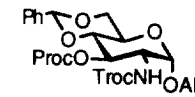
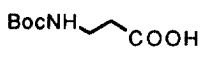
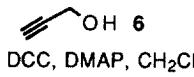
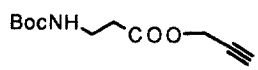
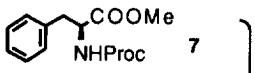
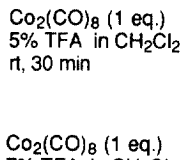
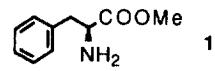
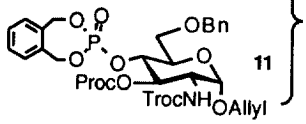
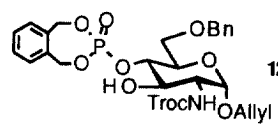
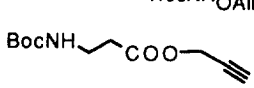
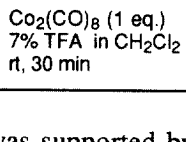
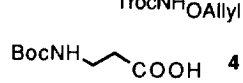
Entry	Starting material	Reagents	Product	Yield
1	 1		 7	quant.
2	 2		 8	quant.
3	 3		 9	quant.
4	 4	 DCC, DMAP, CH_2Cl_2	 10	quant.

Table 2. Cleavage of Proc and propargyl groups

Entry	Starting material	Reagents and conditions	Product	Yield
1	 7		 1	quant.
2	 11		 12	88%
3	 10		 4	99%

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References

[1] Greene TW, Wuts PGM, Editors. Protective Groups in Organic Synthesis, Second Edition. New York: John Wiley, 1991.

[2] Nagasawa T, Taya K, Kitamura M, Suzuki K. J. Am. Chem. Soc. 1996;118:8949.

[3] Nicholas KM. Acc. Chem. Res. 1987;20:207.

[4] Oikawa M, Liu W-C, Nakai Y, Koshida S, Fukase K, Kusumoto S. Synlett 1996:1179.

2. A typical procedure: To a solution of Proc-Phe-OMe (7) (32.9 mg, 126 μmol) in 5% TFA in CH_2Cl_2 was added $Co_2(CO)_8$ (43.0 mg, 126 μmol) under N_2 atmosphere. The mixture was stirred at r.t. for 30 min. A saturated aqueous $NaHCO_3$ solution and ethyl acetate were added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the desired amine 1: Yield 23.6 mg (quant.). The cleaved alkyne-Co complex was removed by evaporation.