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A NOVEL CARBOXYL PROTECTING GROUP
———THE CARBOXAMIDE DERIVED FROM 5,6-DIHYDROPHENANTHRIDINE———

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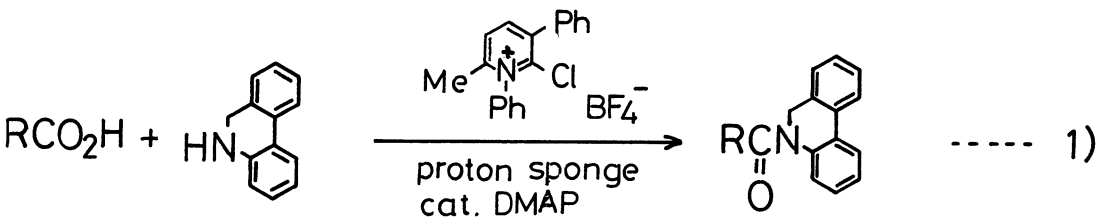
Carboxyl groups protected as the amides derived from 5,6-dihydrophenanthridine are stable under a wide range of conditions and can be selectively deprotected by oxidation on treatment with cerium(IV).

The protection of carboxyl groups is frequently indispensable in the synthesis of multifunctional molecules. A wide variety of methods for the protection of carboxyl function has been utilized. In these methods, ester groups are mostly employed in this role and protection and deprotection are generally carried out under acidic or basic conditions. Recently several useful protecting groups of carboxyl function have been introduced[1], however, there still remains a strong demand to develop new protecting groups which possess greater stability under a wide range of conditions ordinarily encountered in the sequence of synthetic reactions, and capability to be deprotected by a highly specific reagent. We now wish to report a novel carboxyl protecting group, the amide derived from 5,6-dihydrophenanthridine[2], which can be easily converted to the original carboxylic acid by oxidation with cerium(IV).

The amides derived from 5,6-dihydrophenanthridine are readily obtained from various carboxylic acids and the amine by using 2-halopyridinium salts[3] as condensing reagents in acetonitrile, dichloromethane, or 1,2-dichloroethane solution. After repeating experiments employing 2-phenylbutyric acid, we found that the use of 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate[4] and proton sponge as condensing reagent and acid captor, respectively, in the presence of catalytic amount of 4-dimethylaminopyridine (DMAP) gave the best yields of amide(eq. 1). The amides are also obtained from the amine and acyl chlorides, which can be prepared in situ by treating carboxylic acids with oxalyl chloride.[5],[6]



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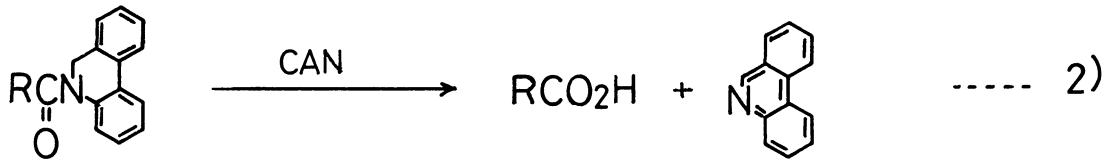
The typical procedure is described for the preparation of the amide of 4-phenylbutyric acid. To 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate (220 mg, 0.60 mmol) of acetonitrile (2.5 ml) solution containing catalytic amount of DMAP was added an acetonitrile solution (9.0 ml) of 4-phenylbutyric acid (82 mg, 0.50 mmol), proton sponge (259 mg, 1.21 mmol), and 5,6-dihydrophenanthridine (101 mg, 0.56 mmol) at room temperature under an argon atmosphere. The resulting mixture was stirred for 1.5 hr at room temperature and then refluxed for 5.5 hr. The reaction mixture was quenched with water, and the product was extracted with ether. The ethereal extract was successively washed with aqueous sodium hydrogencarbonate solution, 1N aqueous HCl solution, and brine, and dried over sodium sulfate. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel to give the amide of 4-phenylbutyric acid (160 mg, 98%).

In a similar manner, other carboxylic acids with various structural characteristics were converted to the amides and the results are summarized in Table.

The resulting amides are stable under basic or acidic hydrolytic conditions.[7] On the other hand, they can be easily cleaved under relatively mild oxidative conditions to recover the original carboxylic acid along with phenanthridine. After examination of various oxidizing agents, e.g., DDQ, trityl cation, sodium persulfate, and mercuric chloride, we found that ceric ammonium nitrate (CAN) gave the best results(eq. 2).



----- 2)

The typical procedure is as follows: CAN (904 mg, 1.65 mmol) was added at once to an acetonitrile-water solution (7.5 ml, 4:1) of the amide (245 mg, 0.45 mmol) derived from 4-phenylbutyric acid. After being stirred for 15 min, the reaction mixture was diluted with ether. The organic layer was washed successively with 1N aqueous HCl solution and brine, and dried over sodium sulfate. The solvent was removed under reduced pressure to give pure 4-phenylbutyric acid (119 mg, 97%). In this procedure, we carried out the deprotection of the amides and the results are summarized in Table.

It is noted that the amide having ester, keto, or halo group in a same molecule, can be selectively deprotected as shown in Table. Further, the amide are stable enough under normal conditions for acetate saponification and the Grignard reaction. For example, by treatment with lithium hydroxide in THF-MeOH-H_2O solution at room temperature, the amide of 3α-acetoxy-5β-cholan-24-oic acid was converted to the corresponding alcohol in 95% yield, which gave selectively 3α-hydroxy-5β-cholan-24-oic acid in 83% yield upon treatment with CAN. On the other hand, treatment of the amide of terephthalaldehydic acid with methyl-

Table Reactions of carboxylic acids with 5,6-dihydrophenanthridine and the regeneration of carboxylic acids from resulting amides.

Substrate	Yield(%) of the amide[a)]	Yield(%) regeneration of carboxylic acid[a)]
4-Phenylbutyric acid	98	97
Phenylacetic acid	93[b)]	96
2-Phenylbutyric acid	90	94
3α-Acetoxy-5β-cholan-24-oic acid	88[b),c)]	98[d)]
3-Oxo-5β-cholan-24-oic acid	78[b),c)]	95[d)]
11-Bromoundecanoic acid	95[b)]	95
5-Benzoylvaleric acid	96[b),c)]	79[e)]
Terephthalaldehydic acid	94[b),c)]	——

a) Satisfactory spectroscopic data (NMR, IR) were obtained for these substances.
b) The preparation of the amides was carried out in 1,2-dichloroethane solution and in the other cases acetonitrile was used as solvent as described above.
c) The preparation of the amide was carried out at room temperature and in the other cases the reaction mixture was refluxed for several hours.
d) Oxidation with CAN was carried out in acetonitrile-benzene-water solution.
e) Oxidation with CAN was carried out at 0 °C and in the other cases carried out at room temperature.

magnesium iodide in THF-HMPT at -78°C~0°C in the presence of magnesium chloride afforded the expected Grignard product in 89% yield.

The amide derived from 5,6-dihydrophenanthridine combines great stability under a wide range of conditions with the capability to be readily deprotected by oxidizing reagents such as cerium(IV). Further applications of the utility of this protecting group are now in progress.

References

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6) For example, upon treatment of 4-phenylbutyryl chloride prepared in situ according to the procedure of R. Adams et al.,[5] with 5,6-dihydrophenanthridine in the presence of triethylamine and catalytic amount of DMAP in THF solution, the corresponding amide was obtained in 86% yield.
7) The amides were not hydrolyzed upon treatment with hydrochloric acid or potassium hydroxide in THF-MeOH-H_2O solution at 70°C over 10 hr.

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