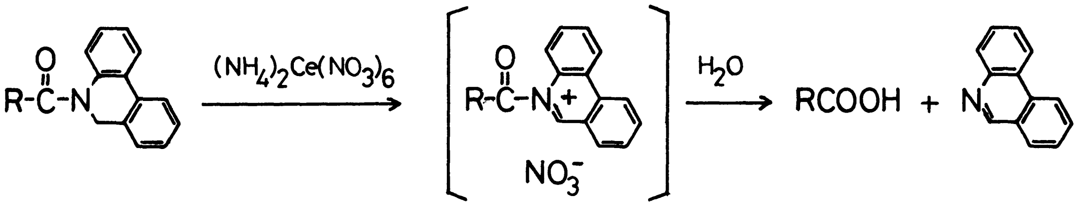
CHEMISTRY LETTERS, pp. 991-992, 1982.

# 5,6-DIHYDROPHENANTHRIDIN-5-YL AS AN ACTIVATABLE PROTECTING GROUP OF CARBOXYLIC ACID — A DIRECT PREPARATION OF AMIDES FROM 5-ACYL-5,6-DIHYDROPHENANTHRIDINE

Koichi NARASAKA*, Takuji HIROSE, Tadafumi UCHIMARU, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyoku, Tokyo 113

Various amides are directly prepared from the protected carboxylic acids, 5-acyl-5,6-dihydrophenanthridines, by the reaction with primary amines in the presence of ceric pyridinium chloride and cupric oxide.

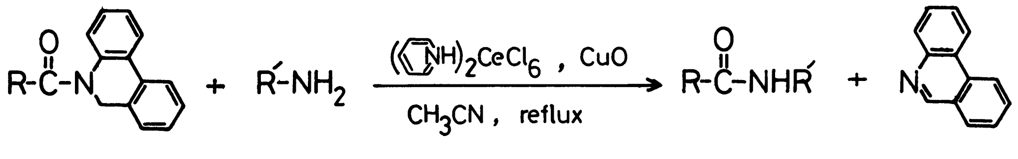
Previously we reported a useful method for the protection of carboxyl group as the carboxamide, 5-acyl-5,6-dihydrophenanthridine.1) This amide is stable under acidic and basic conditions, and the deprotection proceeds specifically by oxidative hydrolysis with ceric ammonium nitrate. In the reaction, it is considered that the amide is oxidized to the 5-acylphenanthridinium salt, which is subsequently hydrolyzed to give the carboxylic acid.

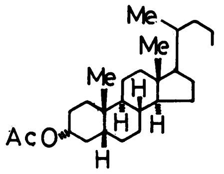
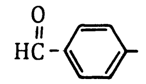


Instead of regeneration of carboxylic acid by treatment with water, it is expected that when the reaction is carried out in the presence of amine, the corresponding carboxamide should be formed. According to this procedure, the concept of an activatable protecting group would be realized, and the protected carboxylic acid would be transformed directly to the amide without regeneration of carboxylic acid.

Based on this assumption, we examined the amide formation utilizing various oxidizing agents in the presence of some acid captors, such as tertiary amine, 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one, and metal oxide. And we found that the combination of ceric pyridinium chloride2) and cupric oxide gave the best results.

A typical experimental procedure is described for the reaction of 5-(4-phenylbutyryl)-5,6-dihydrophenanthridine with phenethylamine; to an acetonitrile (10 ml) solution of 5-(4-phenylbutyryl)-5,6-dihydrophenanthridine (0.41 mmol) and phenethylamine (0.47 mmol) were added ceric pyridinium chloride (1.39 mmol) and cupric oxide (0.45 mmol). After the solution was heated at reflux for 8 h, it was diluted with ether and then the reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were successively washed with 1 N HCl solution and brine, and dried over sodium sulfate. After removal of the solvent under reduced pressure, N-phenethyl-4-phenybutylamide was isolated by thin layer chromatography on silica gel (82%). According to this procedure, various 5-acyl-5,6-dihydrophenanthridines were readily converted to the corresponding amides, and the results are summarized in the table.



| R | R'[a)] | Yield(%)[b)] |
|---|---|---|
| $Ph(CH_2)_3$- | $Ph(CH_2)_2$- | 82 |
| $Ph(CH_2)_3$- | $\underset{\mathrm{Ph}}{\mathrm{CH_3CH}}$- | 85 |
| Ph- | L-Leu-OEt | 94[c)] |
|  | $Ph(CH_2)_2$- | 84[d)] |
| $\underset{\mathrm{Ph}}{\mathrm{CH_3CH_2CH}}$- | $Ph(CH_2)_2$- | 79 |
| $\underset{\mathrm{Ph}}{\mathrm{CH_3CH_2CH}}$- | $\underset{\mathrm{Ph}}{\mathrm{CH_3CH}}$- | 70 |
| Br-$(CH_2)_{10}$- | $Ph(CH_2)_2$- | 85 |
|  | $Ph(CH_2)_2$- | 76 |

a) From primary amines, the corresponding amides were prepared in high yields. On the other hand, employment of secondary amines did not give satisfactory results.

b) Satisfactory spectroscopic data (NMR, IR) were obtained for these amides.

c) The optical purity was determined by specific rotation of N-benzyl-L-leucinol which was obtained by the reduction of N-benzoyl-L-leucine ethyl ester as in the literature.[3)] $[\alpha]_D^{21}$+23.63 (c1.174, benzene) (literature $[\alpha]_D^{26}$+23.44 (c 1.024, benzene)).

d) The reaction was carried out in a mixture of 1,2-dichloroethane and acetonitrile.

It should be noted that, according to the present method based on the concept of an activatable protecting group, various amides are directly prepared from 5-acyl-5,6-dihydrophenanthridines, and 5-acyl-5,6-dihydrophenanthridines having functional groups such as ester, carbonyl, or halo group in the same molecule, are also converted to the corresponding amides in high yields. Further, the benzoylation of L-leucine ethyl ester proceeds without racemization.

References

1) T. Ushimaru, K. Narasaka, and T. Mukaiyama, Chem. Lett., 1981, 1551.
2) D. C. Bradley, A. K. Chatterjee, and W. Wardlaw, J. Chem. Soc., 1956, 2260.
When ceric ammonium nitrate was used instead of ceric pyridinium chloride, amides were obtained only in trace amounts.
3) S. Tsuboyama, Bull. Chem. Soc. Jpn., 39, 698 (1966).

(Received March 31, 1982)