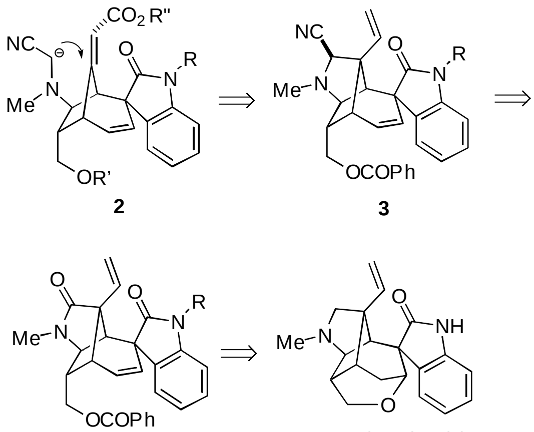
A Novel Oxidative Transformation of α-Aminonitriles to Amides

Satoshi Yokoshima, Tetsuji Kubo, Hidetoshi Tokuyama, and Tohru Fukuyama*
Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033

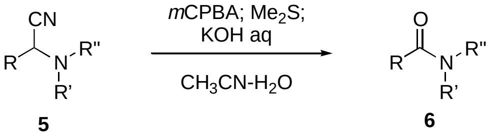
(Received October 31, 2001; CL-011084)

A novel oxidative transformation of α-aminonitriles to amides is reported. Oxidation of α-aminonitriles with peracid, followed by basic treatment affords, amides in good yields. A mechanistic aspect of this transformation is also discussed.

α-Aminonitrile is a valuable functional group since it can be used as an acyl anion equivalent in the umpolung synthesis,[1] a masked hemiaminal functionality,[2] and a precursor of hydroxylamines.[3] In the course of our investigation of total synthesis of gelsemine (**1**),[4] we planned to construct γ-lactam **4** by conjugate addition of α-aminonitrile anion and the subsequent conversion to the lactam. While the expected conjugate addition took place quite smoothly, we confronted a major problem in an efficient conversion of α-aminonitrile **3** into lactam **4**. This transformation could initially be carried out by a two-step procedure, namely, hydrolysis of α-aminonitrile **3** in the presence of silver nitrate in acetonitrile-water followed by oxidation of the resulting hemiaminal with pyridinium dichromate (PDC), albeit in low yield. After extensive investigation, we fortuitously found that this transformation could be executed in one-pot by oxidation with *m*-chloroperbenzoic acid (*m*CPBA) followed by treatment with base (eq 1).[5] In this communication, we describe this novel transformation of α-aminonitriles to amides and its mechanistic aspects as well.

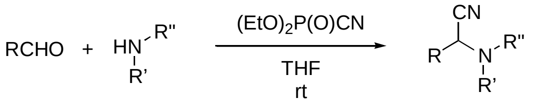


Scheme 1. A Plan for construction of γ-lactam.



(1)

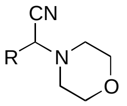
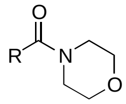
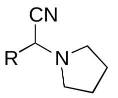
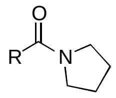
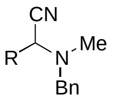
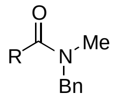
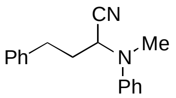
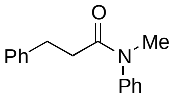
We carried out model studies using α-aminonitriles prepared according to Shioiri's procedure.[6] Thus, aldehydes **7** were condensed with secondary amines **8** by diethyl phosphorocyanidate (DEPC) to yield various α-aminonitriles **5** in 67–88% yields (eq 2). α-Aminonitriles obtained were then subjected to the oxidative transformation according to the following procedure: To a solution of α-aminonitrile **5** in acetonitrile-water (4 : 1) was added *m*CPBA (1.2 equiv) at 0 °C. Upon disappearance of the starting material (10–20 min), the solution was treated with dimethyl sulfide (1.0 equiv).[7] After stirring for 15 min, aqueous potassium hydroxide (3 M, 5.0 equiv) was added and stirring was continued for several hours. Extraction with ethyl acetate and purification by silica gel chromatography afforded the corresponding amide.



(2)

Some representative results are summarized in Table 1. α-Aminonitriles **5a**-**d**, derived from cyclic amines, morpholine or pyrrolidine, with either aliphatic or aromatic aldehyde, could be transformed into the corresponding amides in good yields (entries 1-4). While the reaction of **5e**, prepared from *N*-benzylmethylamine, gave the desired amide in good yield, the corresponding aminonitrile **5f** (R = Ph) afforded amide in low yield. In addition, reaction of the aniline derivative **5g** did not proceed to give any

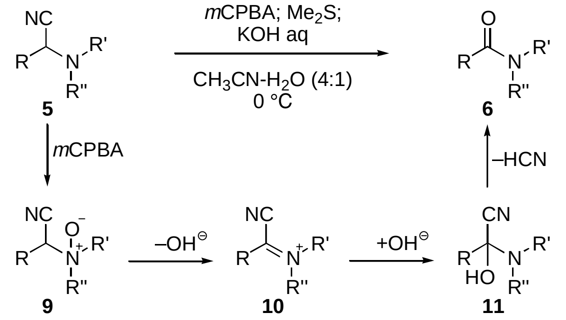
Table 1. Oxidative transformation of aminonitriles

Entry	Substrate	Product	Time/h[a]	%Yield
				
1	**5a** R = CH_2CH_2Ph	**6a** R = CH_2CH_2Ph	3	82
2	**5b** R = Ph	**6b** R = Ph	1.5	73
				
3	**5c** R = CH_2CH_2Ph	**6c** R = CH_2CH_2Ph	5	89
4	**5d** R = Ph	**6d** R = Ph	2	78
				
5	**5e** R = CH_2CH_2Ph	**6e** R = CH_2CH_2Ph	7	89
6	**5f** R = Ph	**6f** R = Ph	3	33
7	 **5g**	 **6g**	–	0

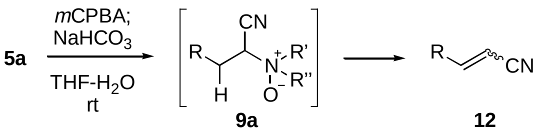
[a]Reaction time for basic treatment.

desired amide.

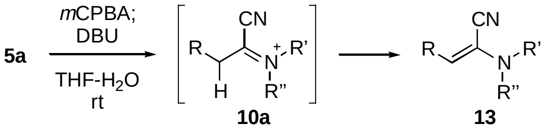
A proposed mechanism of the reaction is shown in Scheme 2. *m*-Chloroperbenzoic acid oxidation of α-aminonitrile **5** is expected to give *N*-oxide **9**. Subsequent base treatment would cause a Polonovsky-type elimination[8] to afford a cyanoiminium ion **10**,[9] which should undergo hydrolysis *via* cyanohydrin **11** to yield amide **6**. During the optimization of the reaction conditions, we observed some side reactions that support the intermediacies of **9**, **10**, and **11**. The reaction of α-aminonitrile **5a** using sodium bicarbonate in THF-water afforded α,β-unsaturated nitrile **12** (eq 3), which might have been generated via Cope elimination of *N*-oxide **5a**. In contrast, the reaction using DBU as base in THF-water yielded enamine **13** (eq 4), which would be derived from cyanoiminium ion **10a**. When excess amount of *m*CPBA was not quenched with dimethyl sulfide, hydroxylamine **15** and methyl ester **16** were obtained (eq 5). Further oxidation of hemiaminal **11e**, followed by fragmentation of the resulting *N*-oxide **14**, would give the hydroxylamine **15**. Methyl ester **16** would be derived from the corresponding acylcyanide by methanolysis.



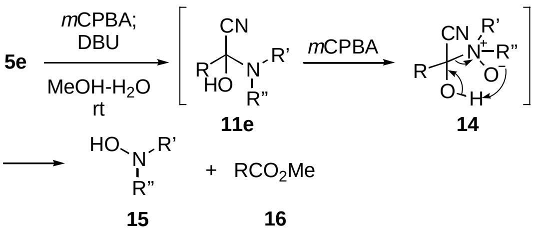
Scheme 2. A proposed reaction mechanism.



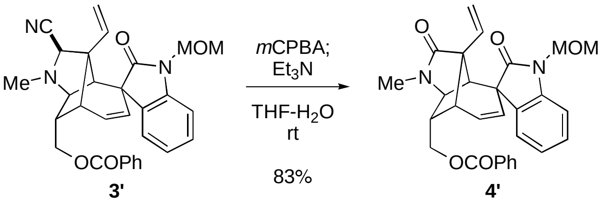
(3)



(4)



(5)



(6)

Having obtained the basic information on the desired transformation with model compounds, we then applied the reaction conditions to the highly functionalized α-aminonitrile **3′** (eq 6). Gratifyingly, the desired transformation proceeded quite smoothly to afford the lactam **4′** in 83% yield, which could be converted to (+)-gelsemine in several steps.[4]

In summary, we have developed a novel oxidative transformation of α-aminonitriles into amides. Because of the ready availability of α-aminonitriles from aldehydes, the present method would serve as a versatile amide formation reaction.

The present work is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

1 D. J. Ager, "Formyl and Acyl Anions," in "Umpoled Synthons," ed. by T. A. Hase, Wiely, New York (1987).

2 For an example in total synthesis of natural products, see: T. Fukuyama and J. J. Nunes, *J. Am. Chem. Soc.*, **110**, 5196 (1988).

3 H. Tokuyama, T. Kuboyama, A. Amano, T. Yamashita, and T. Fukuyama, *Synthesis*, **2000**, 1299.

4 S. Yokoshima, H. Tokuyama, and T. Fukuyama, *Angew. Chem., Int. Ed.*, **39**, 4073 (2000).

5 Although several oxidative transformations of α-aminonitriles to amides have been reported, they need harsh conditions or are lack of generality, see; a) T.-H. Chuang, C.-C. Yang, C.-J. Chang, and J.-M. Fang, *Synlett*, **1990**, 733. b) C.-C. Yang, H.-M. Tai, and P.-J. Sun, *Synlett*, **1997**, 812.

6 S. Harusawa, Y. Hamada, and T. Shioiri, *Tetrahedron Lett.*, **1979**, 4663.

7 It was necessary to quench excess *m*CPBA with dimethyl sulfide because undesired oxidation of an intermediate in the later step lowered the yields.

8 For a review of Polonovski reaction, see: D. Grierson, *Org. React.*, **39**, 85 (1990), and references therein.

9 The elimination occurred with complete regioselectivity because of higher acidity of the α-proton of the nitrile group.