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Chemoselective Acylation of Primary Amines in the Presence of Secondary Amines with Acyl Cyanides. Highly Efficient Methods for the Synthesis of Spermidine and Spermine Alkaloid†

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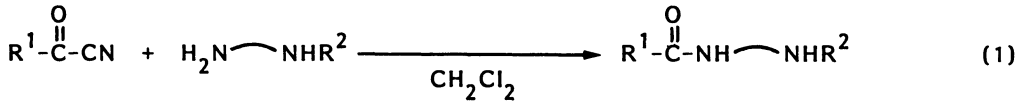
Acyl cyanides are highly useful reagents for the chemoselective acylation of primary amines in the presence of secondary amines. The reaction provides the versatile method for the short-step synthesis of various naturally occurring polyamines.

Naturally occuring polyamines and their derivatives are of interest in view of biological and synthetic aspects because of their potent antibiotic[1] and antineoplastic[2] properties. Therefore, much effort has been devoted for the synthesis of polyamines such as spermidine and spermine alkaloids.[3] The major problem in their synthesis is the selective protection and functionalization of polyamine units. To overcome this difficulty several direct[4] and indirect[3a,3b,5] methods for selective acylation of polyamines have been reported.

We have found that chemoselective N-acylation of primary amines can be performed in the presence of secondary amines upon treatment with acyl cyanides as depicted in Eq.1. The present reaction is advantageous over the previous methods, because the reaction proceeds generally and highly selectively under mild conditions, and the products can be isolated simply without any washing process.



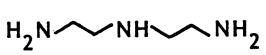
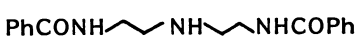
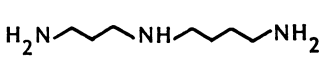
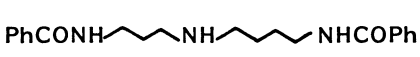
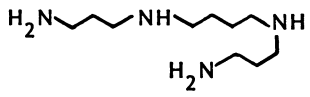
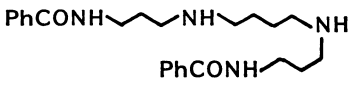
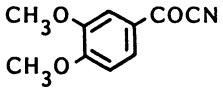
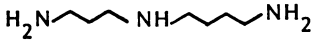
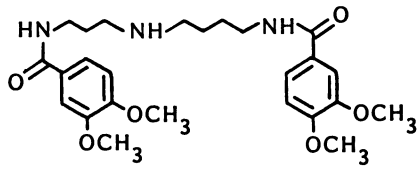
(1)

A variety of acyl cyanides can be readily prepared by either the ruthenium-catalyzed oxidation of cyanohydrins with t-BuOOH[6] or the substitution reaction of acyl halides with metal cyanides or $(CH_3)_3SiCN$.[7]

Table 1 summarizes the representative results of the acylation of polyamines with acyl cyanides. Linear polyamines such as spermidine and spermine are selectively acylated with various acyl cyanides. The reaction proceeds efficiently in an aprotic solvent, such as CH_2Cl_2, CH_3CN, and 1,2-dimethoxyethane. The reaction of spermidine with 3,4-dimethoxybenzoyl cyanide (2.0 equiv.) gave N^1,N^8-bis(3,4-dimethoxybenzoyl)spermidine (Entry 4), which is the precursor of pistillarin [N^1,N^8-bis(3,4-dihydroxybenzoyl)spermidine].[8] The only detectable

†This paper is dedicated to late Professor Ryozo Goto, Kyoto University.

Table 1. Selective Acylation of Polyamines with Acyl Cyanides[a)]

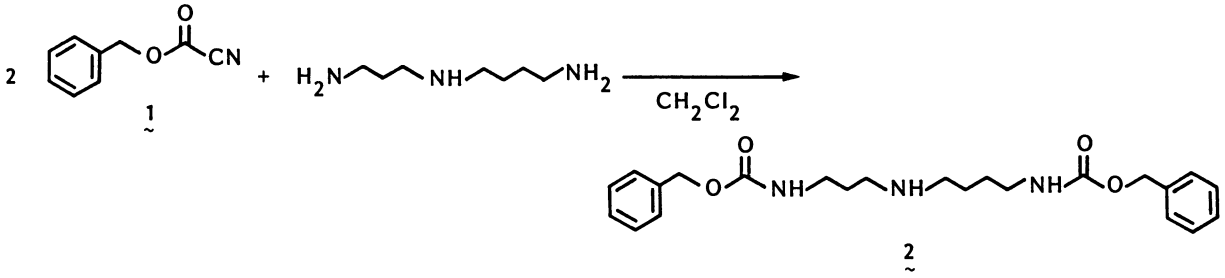
Entry	Acyl Cyanide	Polyamine	Product[b)]	Yield[c)]/%
1	PhCOCN			89
2	PhCOCN			92
3	PhCOCN			91
4				83

a) All reactions were carried out according to the standard procedure described in the text. b) All products gave satisfactory IR and NMR spectral data and elemental analyses. c) Isolated yield.

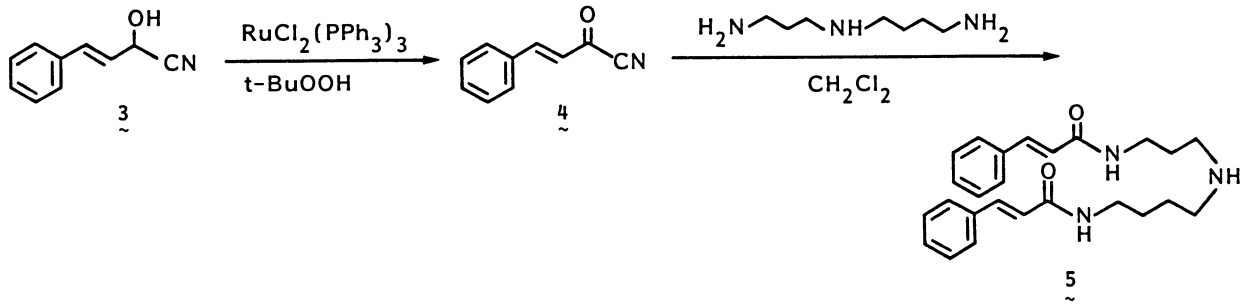
by-product in these reactions is a trace amount (0-3%) of triacyl compounds, which can be readily removed by recrystallization or column chromatography.[9)]

A typical example for the selective N-acylation of polyamines is as follows: To a solution of spermidine (0.436 g, 3.00 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise a solution of benzoyl cyanide (0.787 g, 6.00 mmol) in dry CH_2Cl_2 (10 mL) over a period of 3 h at 20 °C. Hydrogen cyanide generated during the reaction was carefully introduced to a solution of sodium hydroxide in water, and then the solution was treated with antiformin (NaClO). After removal of the organic solvent the residue was subjected to column chromatography (SiO_2). Elution with a mixture of $CHCl_3$ and methanol (2:1) gave N^1,N^8-bisbenzoylspermidine (0.975 g, 92%). Mp 129.5-130.5 °C.

It is noteworthy that carbobenzyloxy group can be introduced chemoselectively into polyamines by the reaction of benzyl cyanoformate (1).[10)] Typically, the reaction of spermidine with benzyl cyanoformate (2.0 equiv.) in dry CH_2Cl_2 gave N^1,N^8-bis(carbobenzyloxy)spermidine (2) in 99% yield. Since carbobenzyloxy protecting groups can be readily removed under mild conditions,[11)] the selective functionalization of secondary amino groups of polyamines can be performed by using the present acylation and deprotection.

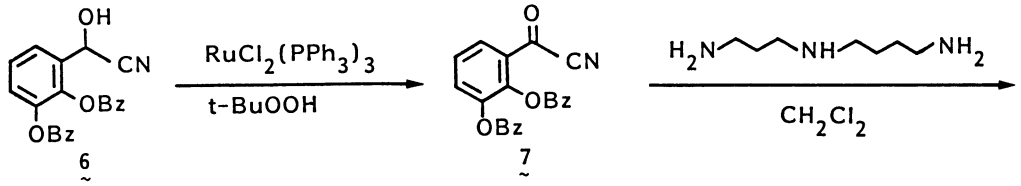


The efficiency of the present reaction is illustrated by the short-step synthesis of the maytenine [N^1,N^8-bis(trans-cinnamoyl)spermidine (5)][12] isolated from Maytenus chuchuhuasha. Thus, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of trans-cinnamaldehyde cyanohydrin (3) with t-BuOOH gave trans-cinnamoyl cyanide (4) in 92% yield. The reaction of spermidine with two equivalents of 4 in dry CH_2Cl_2 at room temperature gave 5 in 92% yield. Although maytenine had been synthesized by several methods,[3a,4a,4e,12] this seems to be the best method because of its easy operation, high selectivity, and mildness of the reaction conditions.



3 4 5

Most importantly, the present method is useful for the synthesis of spermidine siderophores, which are a biologically important class of microbially produced iron transport compounds.[13] A typical example is the synthesis of siderophore, N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine[14] (9) which has been isolated from Micrococcus denitrificans and is an important precursor of the spermidine catecholamides such as agrobactin[15] and parabactin.[16] The reaction of spermidine with two equivalents of 2,3-dibenzyloxybenzoyl cyanide (7) derived from cyanohydrin 6 gave the corresponding bisbenzoylspermidine 8 in 87% yield. Removal of the benzyl groups by catalytic hydrogenation over Pd/C in MeOH-5% AcOH gave siderophore 9 in 95% yield.



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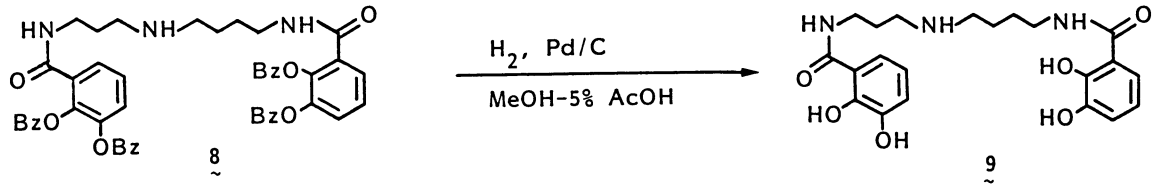

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Acyl cyanides are mild and versatile reagents for selective acylation of polyamines. Quite recently we found that the ruthenium-catalyzed acylation of primary amines with nitriles in the presence of water proceeds chemoselectively in the presence of secondary amines.[17] The present reaction is more practical for the synthesis of thermally unstable polyamines.

Further work is currently in progress on the extension of this reaction to the other system and application to the synthesis of biologically active nitrogen containing natural products.

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