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A SIMPLE METHOD FOR THE DIRECT BIS-ACYLATION OF THE PRIMARY AMINO GROUPS IN SPERMIDINE AND OTHER LINEAR TRIAMINES

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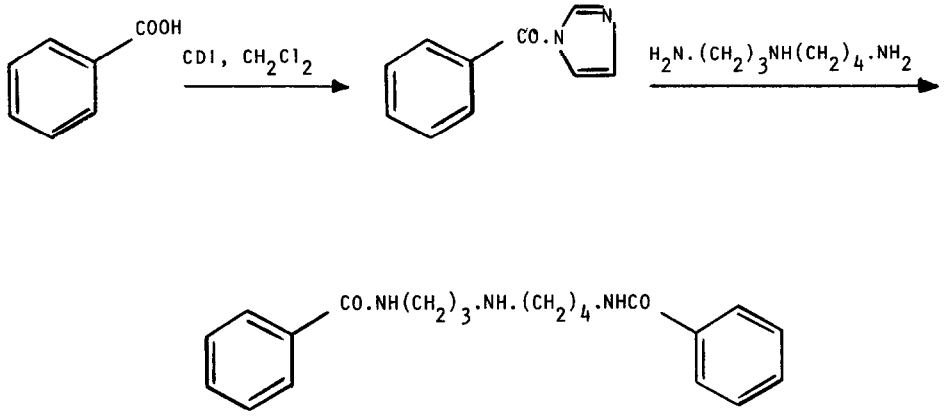
Abstract

A simple and efficient method for the direct symmetrical bis-acylation of spermidine and other linear triamines using acylimidazoles is described. By this procedure, the siderophore natural product N^1,N^8-bis(2,3-dihydroxybenzoyl) spermidine was synthesized in an overall yield of 70% in two steps.

Spermidine (1,8-diamino-4-azaoctane) derivatives are of considerable biological interest because of their potent antibiotic[1,2] and antineoplastic[3] properties and their pronounced effect on the bio-synthesis of macromolecules[4,5]. Another class of compounds which has received widespread attention are the N^1,N^8-bis(2,3-dihydroxybenzoyl) spermidine derivatives. Examples are the siderophores agrobactin and parabactin[6] which because of their strong iron chelating properties show promise in the treatment of Cooley's anemia[7]. In these compounds one often finds different substitution pattern at the primary and secondary amino groups. Therefore any synthetic approach to these important molecules should address the problem of distinguishing between the primary and secondary amino groups and sometimes even between the primary amino groups.

Bergeron and co-workers[8] have reported N^4-benzylspermidine as a useful precursor for siderophores and other structures where the primary amino groups need not be distinguished in the acylation reaction. Ganem et al[9] have developed the "urea and formaldehyde protected spermidines" as useful intermediates in the synthesis of several natural products. But direct selective symmetrical acylation of spermidine proceeds poorly because of the higher nucleophilicity of secondary amines with most electrophilic reagents. On the other hand the primary amino groups of spermidine are more reactive for steric reasons and this important feature has been exploited for the synthesis of maytennine [1,8-bis(trans-cinnamoyl) spermidine] by acylating spermidine with the N-hydroxypiperidine ester of cinnamic acid[10]. There is no other reported method for the direct 1,8-bis-acylation of spermidine. We have found that direct symmetrical bis-acylation of spermidine and other linear triamines can be achieved in good yields using acylimidazoles as acylating agents. Acylimidazoles can be generated easily by treating carboxylic acids with N,N'-carbonyldiimidazole (CDI) in dichloromethane at room temperature for 1-2 hours[11] Addition of the triamine and stirring for 24-48 hours completes the reaction. (Scheme 1). The by-product imidazole can be removed by washing with water and any free carboxylic acid by washing with dilute sodium

Scheme 1



hydroxide. The procedure is simple and efficient. It can be used for a number of carboxylic acids and triamines. The acylimidazole method is widely used for acylating amines[11-13]. A typical experimental procedure is described for spermidine and benzoic acid.

A mixture of benzoic acid (2 mmol) and carbonyldiimidazole (2 mmol) in dichloromethane (3 ml) is stirred (CO_2 evolution) at room temperature for 1 hour. Spermidine (1 mmol) is added and stirring continued for 24 hours. The reaction mixture is diluted with dichloromethane (10 ml) and washed with 5% sodium hydroxide (10 ml), water (10 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo. Crystallization of the residue from ethyl acetate gave 0.250g (78%) of N^1,N^8-bisbenzoylspermidine. M.p. 129-130°. (lit[8]. 130.5-133).

Table 1 summarizes the results we have obtained with three triamines and four carboxylic acids.

The procedure also has certain limitations. The success of the procedure depends upon the steric hindrance at the carbonyl group for the attack of the nucleophile. Thus as the steric hindrance decreases, selectivity is lost and mixtures of products are obtained as is the case with cinnamic acid. Also, the procedure is not applicable to carboxylic acids containing acetoxy groups. For example, reaction of 2,3-diacetoxybenzoylimidazole with spermidine results in an unidentifiable mixture of products presumably because of acetoxy cleavage by the amino groups.

This method should prove useful in the symmetrical bis-acylation of spermidine and other linear triamines where bulky acyl groups, especially aromatic, are involved. Thus reaction of spermidine with 2,3-dibenzyloxybenzoylimidazole (entry 4) and subsequent removal of the benzyl protecting groups (H_2, Pd-C, Methanol-5% acetic acid), gave the siderophore natural product N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine[8] (1) in 70% overall yield in two steps.

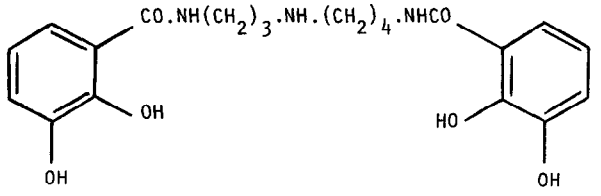
Table 1. Synthesis of Symmetrical Bis-Acylated Triamines[a,b]

No.	Triamine	Carboxylic Acid	Yield %	m.p. (°C)
1	Spermidine	Benzoic	78	129-130
2	Spermidine	Phenylacetic	80	132-133
3	Spermidine	2,3-Dimethoxybenzoic	74	Oil[c]
4	Spermidine	2,3-Dibenzyloxybenzoic	78	Oil[c]
5	Diethylenetriamine	Benzoic	70	108-109
6	Diethylenetriamine	Phenylacetic	75	152-154
7	Diethylenetriamine	2,3-Dimethoxybenzoic	77	Oil[c]
8	Diethylenetriamine	2,3-Dibenzyloxybenzoic	72	Oil[c]
9	3,3-Iminobispropylamine	Benzoic	69	73-74
10	3,3-Iminobispropylamine	Phenylacetic	82	118-119
11	3,3-Iminobispropylamine	2,3-Dimethoxybenzoic	82	Oil[c]
12	3,3-Iminobispropylamine	2,3-Dibenzyloxybenzoic	87	Oil[c]

a. Structure determination was done by ^{1}H-nmr.

b. All new compounds gave satisfactory C,H and N analysis.

c. Purified by chromatography on silica gel and elution with chloroform-20% methanol.



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