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Preparation of $N(\pi)$-alkyl- histamine and histidine derivatives through efficient alkylation followed by deprotection using activated silica gel

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Abstract

Efficient $N(\pi)$-alkylation of L-histidine and histamine derivatives through employment of $N(\tau)$-trityl-protection was achieved and regioselective removal of the $N(\tau)$-trityl group in the presence of either Boc- or trityl-protected primary amine was effected based on a mild hydrolysis mediated by activated silica gel with 0.1–0.2% trifluoroacetic acid. © 2000 Elsevier Science Ltd. All rights reserved.

Substituted histamine and histidine derivatives are often core constituents in biologically active compounds.[1–3] Both histidine and histamine have two common functional groups, i.e. an imidazole ring and a primary amine. The imidazole ring can be used as a useful scaffold for the construction of compounds possessing a conformational constraint such as a turn or extended structural motif, thus selective introduction of $N(\tau)$- or $N(\pi)$-substituent in the imidazole ring is of considerable importance in preparing peptidomimetic structures. However, methods for general and efficient construction of $N(\pi)$-alkylated histamine or histidine derivatives have not been widely available. Some of the known methods of alkylation have been limited to the purpose of installing a blocking group which protects the $N(\pi)$-position against racemization of histidine at the α-carbon center in peptide synthesis.[4] During the course of a solution-phase combinatorial library synthesis of histidine and histamine derivatives, we needed a general and highly efficient alkylation method at the $N(\pi)$-position and selective removal of the $N(\tau)$-protection in the presence of *N*-(*tert*-butyloxycarbonyl)- (Boc-) or *N*-triphenylmethyl- (Trt-) protected primary amine. Herein we wish to report such alkylation through employment of $N(\tau)$-Trt-protected histamine or histidine derivatives and regioselective removal of $N(\tau)$-trityl group in the presence of either Boc- or trityl-protected primary amine based on a mild hydrolysis mediated by activated silica gel.

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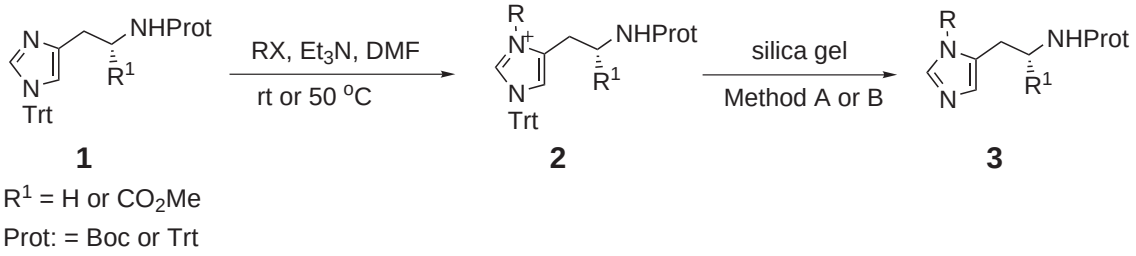
Introduction of various alkyl groups such as phenylacyl-, *t*-butoxymethyl-, benzyloxymethyl-, or benzyl groups at the $N(\pi)$-position of histidine derivatives equipped with Boc-, Cbz-, Trt-, or Fmoc-protecting groups at the $N(\tau)$-position of the imidazole ring and primary amine has been reported.[5–9] However, several drawbacks have been associated with some of these methods. Bis-acylated histidines at the $N(\tau)$- and primary amine positions have low nucleophilicity towards alkylating agents. On the other hand, $N(\tau)$-trityl histidine derivatives with the primary amine protected with Boc, Cbz, or Trt group exhibited higher nucleophilicity and allowed for the use of a wide variety of alkylating agents. However, various basic and acidic deprotecting conditions for the trityl group from the imidazolium salt intermediate afforded only moderate yields of the desired products. Also, selective removal of Boc and Trt groups at the $N(\tau)$-position in the presence of those at the primary amine-position of histidine derivatives under acidic conditions has been troublesome.[4] In particular, selective deprotection the $N(\tau)$-trityl group of histidine and histamine intermediate salts (**2**) with Boc or Trt group at the primary amine under acidic conditions has not been reported. In this communication we disclose an easy and convenient strategy for the synthesis of $N(\pi)$-alkylated histidine and histamine derivatives protected at the primary amine position with Boc or Trt group under extremely mild conditions (Scheme 1).



Scheme 1. Alkylation and deprotection of histamine or histidine derivatives

The histidine and histamine derivatives protected at the $N(\tau)$- and the primary amine with Trt or Boc group were synthesized by following the literature procedure.[10,11] Products obtained through this procedure exhibited purities higher than 95% according to HPLC analyses. Alkylation at the nitrogen of the $N(\pi)$-position of histidine and histamine derivatives (**1**) proceeded smoothly with many commercially available aryl bromides (room temperature), allyl bromide or *n*-hexyl iodide (5.0 equiv., 50°C) in DMF over a period of 24–48 h (Table 1). It is noteworthy that the introduction of *n*-hexyl group was accomplished in high yields under these conditions. Benzyl or alkyl chloride was found to be unreactive towards the $N(\tau)$-Trt histidine and histamine derivatives, which is consistent with the literature report.[9]

In the course of removing excess alkylating agents, we found that the resulting trityl group of the imidazolium salt intermediates was partially cleaved when eluted with 5% methanolic dichloromethane on silica gel columns to give a small amount of $N(\pi)$-alkylated derivatives (**3**). Recently it was also reported that $N(\tau)$- and amino-Boc histidine was selectively removed on pre-activated silica gel.[12] On the basis of these results, we tested deprotection of $N(\tau)$-trityl group on the salt intermediates using activated silica gel. The salt intermediates of histidine and histamine after alkylation were adsorbed onto silica gel which had been activated under reduced pressure at 50°C for 12 h, and a 5% methanolic methylene chloride solution (2 mL g^{-1} of silica gel) was added to the silica gel. The silica gel slurry was allowed to stir slowly for a period of 3 days at room temperature, when complete deprotection was observed by TLC (*Method A*). In

Table 1
Preparation of $N(\pi)$-alkylated histidine and histamine derivatives

Entry	R^1	Prot	RX	Alkylation		Deprotection		Yield (%) [a]
				Time (h)	Temp. (°C)	Method	Time (h)	
1			4-NO_2-$C_6H_4CH_2Br$	24	Rt	A	72	90
2			4-Br-$C_6H_4CH_2Br$	24	Rt	A	72	88
3			4-CN-$C_6H_4CH_2Br$	24	Rt	A	72	95
4			3-CH_3-$C_6H_4CH_2Br$	24	Rt	A	72	95
5		Boc	$C_6H_5CH_2Br$	24	Rt	A	72	94
6			4-NO_2-$C_6H_4CH_2Br$	24	Rt	B	24	90
7			4-CN-$C_6H_4CH_2Br$	24	Rt	B	24	88
8	H		n-$C_6H_{11}I$	18	50	B	24	97
9			Allyl bromide	24	50	B	24	92
10			4-CN-$C_6H_4CH_2Br$	24	Rt	A	72	88
11			4-NO_2-$C_6H_4CH_2Br$	24	Rt	A	72	87
12		Trt	4-CN-$C_6H_4CH_2Br$	24	Rt	B	24	89
13			4-NO_2-$C_6H_4CH_2Br$	24	Rt	B	24	87
14			n-$C_6H_{11}I$	24	50	B	24	93
15			Allyl bromide	24	50	B	24	83
16			4-NO_2-$C_6H_4CH_2Br$	48	Rt	B	24	95
17		Boc	n-$C_6H_{11}I$	48	50	B	24	91
18			Allyl bromide	48	50	B	24	83
19	CO_2Me		4-NO_2-$C_6H_4CH_2Br$	36	Rt	B	24	83
20			n-$C_6H_{11}I$	24	50	B	24	85
21		Trt	Allyl bromide	48	50	B	24	82
22			Benzyl bromide	24	50	B	12	80

[a] Isolated yields after two steps.

order to speed up the reaction, a small amount of trifluoroacetic acid (TFA) was added to the slurry otherwise under the same conditions. Thus by employing 0.1–0.2% of TFA in methanol, the deprotection of the $N(\tau)$-trityl group on the salt intermediate was complete within 24 h to furnish only $N(\pi)$-alkylated histamine and histidine derivatives in excellent yields (*Method B*).[13] However, when more than 0.5% TFA was employed, a partial cleavage of the Boc or Trt group at the primary amine was observed through HPLC analysis.

In order to investigate the stereochemical integrity of the alkylation/selective deprotection process, we have examined the enantiomeric purity of an L-histidine methyl ester derivative by comparing with a racemic derivative. Chiral HPLC analyses of both derivatives (Daicel Chiracel OD column; eluent: hexane/2-propanol 93:7; 0.5 mL min^{-1}) clearly indicated no epimerization at the α-center of the L-histidine derivative.

In summary, a general and efficient alkylation strategy has been developed at the $N(\pi)$-position of the imidazole moiety of histamine or histidine, and selective removal of the $N(\tau)$-trityl group at imidazolium salt intermediate was achieved through the use of a pre-activated silica gel with methanolic methylene chloride solution containing 0.1–0.2% of TFA to give $N(\pi)$-alkylated histamine and histidine derivatives. This method has been successfully exploited in a solution-

phase combinatorial synthesis of biologically active compounds containing the histidine and histamine cores and the result will be reported in due course.

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13. General procedure: To a stirred solution of *N*(α)-Trt-*N*(τ)-Trt-L-histidine methyl ester (0.10 g, 0.15 mmol) in 0.50 mL of DMF was added benzyl bromide (0.13 g, 0.77 mmol). The reaction mixture was allowed to stir for 48 h at 50°C. When the reaction was complete (monitored by HPLC), the solvent was removed under reduced pressure. Excess benzyl bromide was removed by filtering through a pad of silica gel (5% methanol in CH_2Cl_2). The crude product was dissolved in 5% methanol in CH_2Cl_2 (6.0 mL). To the solution was added a 0.01 M TFA solution in CH_2Cl_2 (0.02 mL, 0.15 mol%) and activated silica gel (2.0 g, preactivated under 0.1 mPa at 50°C for 12 h). The slurry was allowed to stir for 24 h at room temperature. The reaction mixture was filtered and washed with 5% methanolic methylene chloride solution (15 mL×5). The combined filtrate was concentrated and purified on silica gel chromatography (from CH_2Cl_2 to CH_2Cl_2:MeOH = 95:5) to give *N*(α)-Trt-*N*(π)-benzyl-L-histidine methyl ester (0.060 g, 0.12 mmol, 80% yield). R_f = 0.60 (CH_2Cl_2:MeOH = 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.22–7.02 (m, 20H), 6.76 (s, 1H), 4.92 (s, 2H), 3.20 (m, 1H), 2.88 (s, 3H), 2.72 (m, 2H), 1.47 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.51, 145.58, 138.11, 136.04, 128.98, 127.95, 127.86, 126.75, 126.54, 126.48, 77.21, 71.03, 56.81, 51.49, 48.49, 30.31; IR (KBr, neat) 3358, 3057, 2927, 1731, 1684, 1599, 1486, 1448, 1373, 1250, 1207, 1169, 1113, 1033, 706 cm^{-1}; LCMS (*m*/*z*) 502.7 $(M+H)^+$ for $C_{33}H_{31}N_3O$; HRFABMS $(M+1)^+$ calcd for $C_{33}H_{31}N_3O_2$ 502.2416, found 502.2478.