

HIGHLY EFFECTIVE PROCEDURE FOR INTRODUCTION OF AMINO GROUP INTO THE 2-POSITION OF IMIDAZOLE RING

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Abstract - Procedures for the preparation of 2-amino- and 2-arylaminobenzimidazoles were developed, and one of the efficient procedure was applied to the synthesis of preclathridine A, a marine imidazole alkaloid isolated from a sponge.

Several methods for the preparation of 2-aminoimidazole compound have been reported, and they are reactions of 2-chloroimidazole with ammonium hydroxide,¹ imidazole with sodium amide,² and substitution of 2-lithioimidazole with vinyl azide followed by hydrolysis.³ But these procedures are

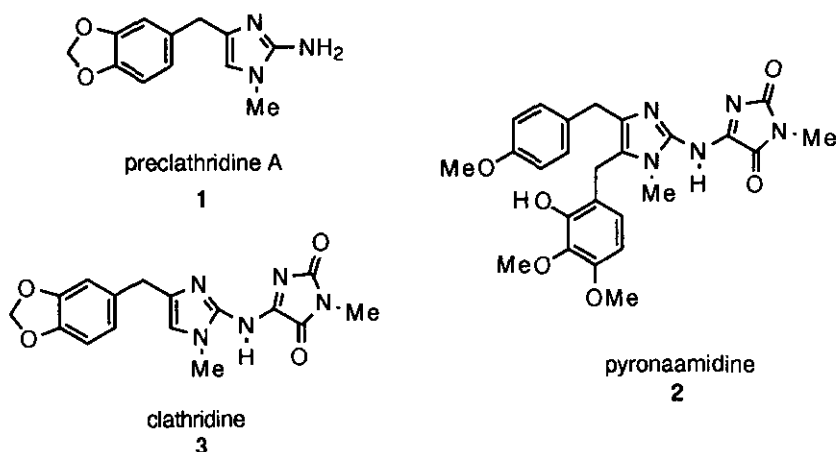
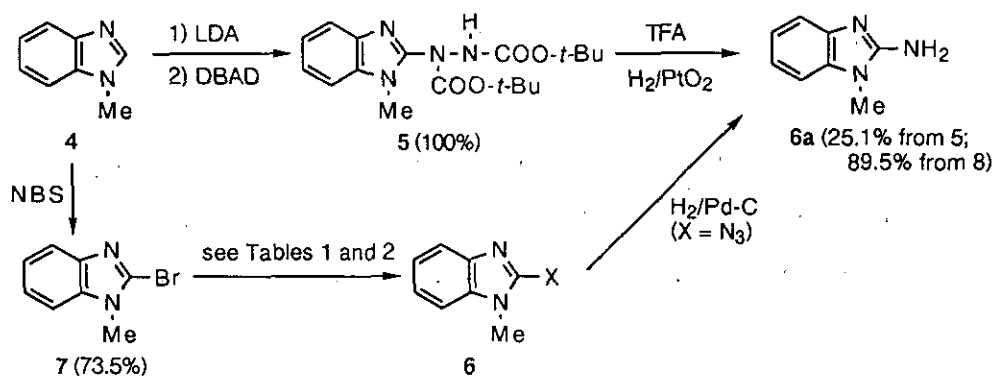


Figure 1

of low yield and require some severe reaction conditions. On the other hand, several marine alkaloids such as 1-3 containing primary amino or substituted amino group at the 2-position of imidazole ring were recently isolated from sponges.⁴ We have hitherto investigated synthesis of imidazole compounds,⁵ and in this communication we would like to report several improved procedures, proceed in good yields and under mild conditions, for the preparation of 2-amino and 2-arylamino benzimidazoles and the first total synthesis of preclathridine A (1).

Scheme 1



First, 2-lithioimidazole was treated with di-*tert*-butyl azodicarboxylate to give quantitatively the 2-hydrazide (5) (Scheme 1), however, conversion of the product (5) to the 2-aminobenzimidazole (6a; X=NH₂) resulted in low yield (25.1%). On the other hand, aminations of 2-bromobenzimidazole (7) with aqueous ammonium hydroxide in various solvents were examined (Entries 1-6), but the yield of 6a was low (30.6 %) or the 2-hydroxy compound (6c; X=OH) was produced. When DMF was used as the reaction solvent, *N,N*-dimethylamino group was introduced to give 6b (X=NMe₂) in 91.4%

Table 1. Substitution Reaction of the Bromide(7)

Entry	Reagent	Solvent	X	Yield (%)
1	28% NH ₄ OH	— ^a	NH ₂	6a ^b : 30.6
2	28% NH ₄ OH	DMF ^a	NMe ₂	6b ^c : 91.4
3	28% NH ₄ OH	HCONH ₂ ^a	OH	6c : 70.9
4	28% NH ₄ OH	EtOH ^a	OH	6c : trace
5	NHEt ₂	— ^a	NEt ₂	6d : 22.2
6	NHBn ₂	— ^a	—	N.R. ^d

a: bath temperature (100 °C); b: known compound (ref. 6);

c: known compound (ref. 7); d: no reaction.

yield (Entry 2), but the reaction with an excess of *N,N*-dialkylamine gave poor results (Entries 5 and 6).

Next, we tried bromination of 4 followed by substitution reaction of the resulting bromide (7) with *N*-containing reagents such as sodium azide, trimethylsilyl azide and various primary arylamines in the presence of a Pd catalyst, and the results are summarized in Table 2. The best result for the preparation of the azide (6f; 80.8%) was obtained in combination of PdCl₂(PPh₃)₂ with trimethylsilyl azide (Entry 5). The azide (6f) was readily hydrogenated in the presence of Pd-C to give 6a (89.5% yield). In the reaction of 7 with arylamines, the combination of PdCl₂[P(*o*-tol)]₃₂ and LiN(TMS)₂ gave good results (Entries 7-11).

Table 2. Introduction of Amino Group into 7 in the Presence of Pd-Catalyst

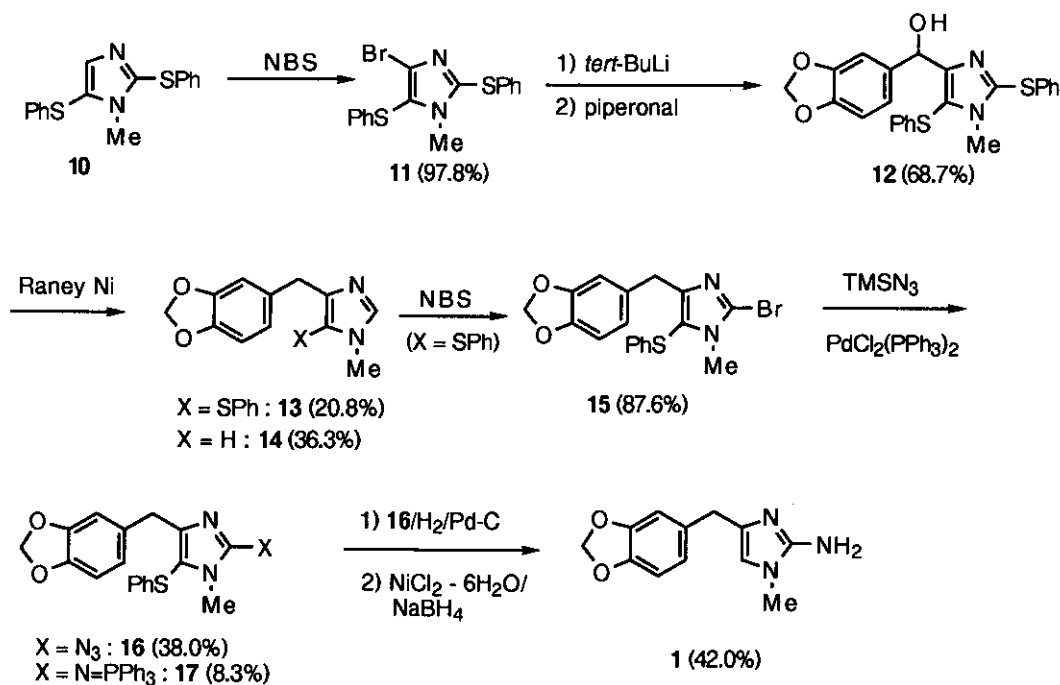
Entry	Reagent(s)	Catalyst (5 mol%)	Time	Solv. / Temp. (°C)	Product	
					X	Yield (%)
1	(1) ^a LiN(TMS) ₂ (2) ^b NHBn ₂	PdCl ₂ [P(<i>o</i> -tol)] ₃ ₂	1 h	toluene / a, b	-NBn ₂ (6e)	47.8
2	NaN ₃	Pd(PPh ₃) ₄	2 d	THF-H ₂ O (2:1) / 70	-N ₃ (6f) ^c	42.8
3	NaN ₃	PdCl ₂ (PPh ₃) ₂	2 d	THF-H ₂ O (2:1) / 60	-N ₃ (6f)	80.9
4	NaN ₃	PdCl ₂ [P(<i>o</i> -tol)] ₃ ₂	2 d	THF-H ₂ O (2:1) / 60	-N ₃ (6f)	N.R. ^e
5	TMSN ₃	PdCl ₂ (PPh ₃) ₂	20 h	THF / 80	-N ₃ (6f)	80.8
6	C ₆ H ₅ NH ₂ NaH	PdCl ₂ (PPh ₃) ₂	4 h	THF / room temperature	-NHC ₆ H ₅ (6g) ^d	12.0 ^f
7	C ₆ H ₅ NH ₂ NaH	Pd(PPh ₃) ₄	4 h	THF / room temperature	-NHC ₆ H ₅ (6g)	55.3
8	C ₆ H ₅ NH ₂ LiN(TMS) ₂	PdCl ₂ (PPh ₃) ₂	4 h	toluene / 110	-NHC ₆ H ₅ (6g)	44.8
9	C ₆ H ₅ NH ₂ LiN(TMS) ₂	PdCl ₂ [P(<i>o</i> -tol)] ₃ ₂	1 h	toluene / 110	-NHC ₆ H ₅ (6g)	95.7
10	4-MeOC ₆ H ₄ NH ₂ LiN(TMS) ₂	PdCl ₂ [P(<i>o</i> -tol)] ₃ ₂	1 h	toluene / 110	-NH-C ₆ H ₄ -OMe (6h)	94.5
11	2-aminopyridine LiN(TMS) ₂	PdCl ₂ [P(<i>o</i> -tol)] ₃ ₂	12 h	toluene / 110	-NH-2-pyridyl (6i)	91.6
12	2-aminopyrimidine LiN(TMS) ₂	PdCl ₂ [P(<i>o</i> -tol)] ₃ ₂	1 d	toluene / 110	-NH-2-pyrimidyl (6j)	38.2

a: (1) -78 °C; b: (2) 110 °C; c: known compound (ref. 8); d: known compound (ref. 9); e: no reaction; f: Compound 9 was also obtained (15.1%).



Preclathridine A (**1**) was synthesized by the following way. 1-Methyl-2,5-diphenylthio-1*H*-imidazole (**10**)^{5a} was brominated with NBS to give **11** quantitatively, which was treated with *tert*-butyllithium followed by treatment with piperonal to give the alcohol (**12**) in 68.7% yield. The alcohol (**12**) was desulfurized with Raney nickel to give a mixture of the sulfide (**13**) (20.8% yield) and the imidazole (**14**) (36.3% yield). The former (**13**) was brominated with NBS to give the bromide (**15**) (87.6% yield), which was treated with trimethylsilyl azide in the presence of PdCl₂(PPh₃)₂ to give the azide (**16**) (38.0% yield) accompanying with the azaphosphorane (**17**) (8.3% yield). The azide (**16**) was hydrogenated in the presence of Pd-C to give preclathridine A (**1**) as an oily product. Spectral data of **1** were all consistent with those of the natural product.^{4a}

Scheme 2



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