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

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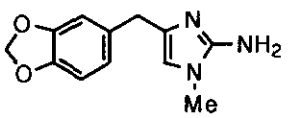
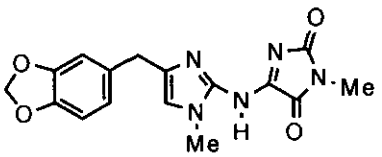
Abstract - Procedures for the preparation of 2-amino- and 2-arylaminobenzimidazoles were developed, and one of the efficient procedure was applied to the synthesis of preclathridine A, a marine imidazole alkaloid isolated from a sponge.

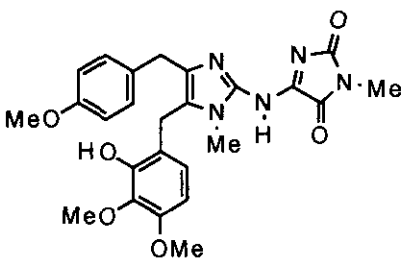
Several methods for the preparation of 2-aminoimidazole compound have been reported, and they are reactions of 2-chloroimidazole with ammonium hydroxide,[1] imidazole with sodium amide,[2] and substitution of 2-lithioimidazole with vinyl azide followed by hydrolysis.[3] But these procedures are



preclathridine A
1



clathridine
3

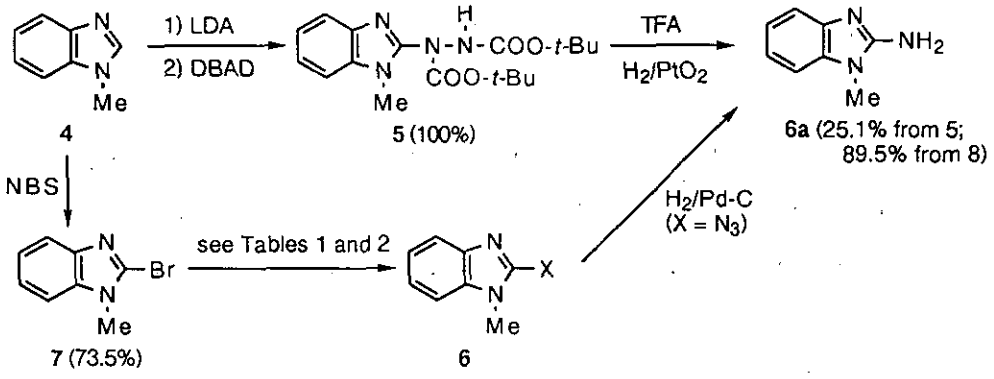


pyronaamidine
2

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-arylaminobenzimidazoles 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=NH_2) 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=NMe_2) in 91.4%

Table 1. Substitution Reaction of the Bromide(**7**)

Entry	Reagent	Solvent	X	Yield (%)
1	28% NH_4OH	—[a]	NH_2	**6a**[b]: 30.6
2	28% NH_4OH	DMF[a]	NMe_2	**6b**[c]: 91.4
3	28% NH_4OH	$HCONH_2$[a]	OH	**6c** : 70.9
4	28% NH_4OH	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.

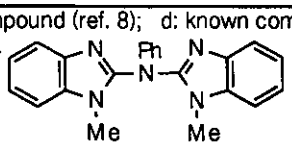
yield (Entry 2), but the reaction with an excess of *N,N*-dialkylamine gave poor results (Entries 5 and 6).

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 $PdCl_2(PPh_3)_2$ 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 $PdCl_2[P(o\text{-tol})_3]_2$ 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] $NHBn_2$	$PdCl_2[P(o\text{-tol})_3]_2$	1 h	toluene / a, b	-NBn_2 (**6e**)	47.8
2	NaN_3	$Pd(PPh_3)_4$	2 d	THF-H_2O (2:1) / 70	-N_3 (**6f**)[c]	42.8
3	NaN_3	$PdCl_2(PPh_3)_2$	2 d	THF-H_2O (2:1) / 60	-N_3 (**6f**)	80.9
4	NaN_3	$PdCl_2[P(o\text{-tol})_3]_2$	2 d	THF-H_2O (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	$C_6H_5NH_2$ NaH	$PdCl_2(PPh_3)_2$	4 h	THF / room temperature	-NHC_6H_5 (**6g**)[d]	12.0[f]
7	$C_6H_5NH_2$ NaH	$Pd(PPh_3)_4$	4 h	THF / room temperature	-NHC_6H_5 (**6g**)	55.3
8	$C_6H_5NH_2$ $LiN(TMS)_2$	$PdCl_2(PPh_3)_2$	4 h	toluene / 110	-NHC_6H_5 (**6g**)	44.8
9	$C_6H_5NH_2$ $LiN(TMS)_2$	$PdCl_2[P(o\text{-tol})_3]_2$	1 h	toluene / 110	-NHC_6H_5 (**6g**)	95.7
10	4-$MeOC_6H_5NH_2$ $LiN(TMS)_2$	$PdCl_2[P(o\text{-tol})_3]_2$	1 h	toluene / 110	-NH-C_6H_4-OMe (**6h**)	94.5
11	2-aminopyridine $LiN(TMS)_2$	$PdCl_2[P(o\text{-tol})_3]_2$	12 h	toluene / 110	-NH-2-pyridyl (**6i**)	91.6
12	2-aminopyrimidine $LiN(TMS)_2$	$PdCl_2[P(o\text{-tol})_3]_2$	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%).



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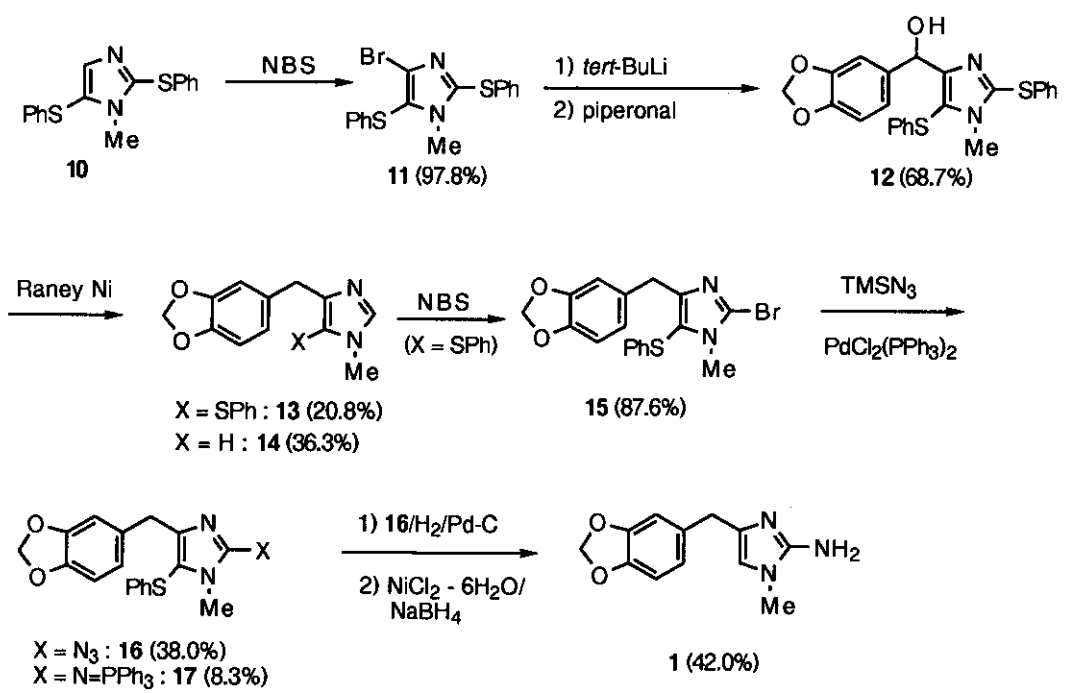
Preclathridine A (**1**) was synthesized by the following way. 1-Methyl-2,5-diphenylthio-1*H*-imidazole (**10**)[5a] was brominated with NBS to give **11** quantitatively, which was treated with *tert*-butyllithium followed by treatment with piperonal to give the alcohol (**12**) in 68.7% yield. The 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 $PdCl_2(PPh_3)_2$ 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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