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Serial double nucleophilic addition of amines to the imidazole nucleus

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Abstract

2-(1-Chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole hydrochloride (**2a**·HCl) was treated with an excess of *N*,*N*-dimethylamine at room temperature to give an abnormal addition product, 4,5-bis(*N*,*N*-dimethylamino)-1-methyl-2-(2,2-dimethylpropyl)-2-imidazoline (**4a**), in 74.2% yield together with a normal S_N2 product, 2-(1-*N*,*N*-dimethylamino-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole (**3a**), in 15.0% yield. The former might be evolved from a serial double nucleophilic addition of the secondary amine molecules to the imidazole nucleus, which has been generally considered as an electron-excessive and stable aromatic ring.

Keywords: imidazoles; nucleophilic addition; imidazolines; amines; S_N2; X-ray crystallography.

Imidazole has been considered as a basic electron-excessive aromatic; therefore, in general, the nucleus is subjected to ordinary electrophilic reactions, imidazolium salt formation and the nucleophilic substitutions of lithioimidazoles.[1,2] Nucleophilic reactions on the imidazole ring with no directly linked electron-withdrawing group such as halogen atom(s) are quite rare† and have been commonly performed by the activation of imidazole rings by quaternization.[1,4] This communication deals with a stereoselective double nucleophilic addition of the secondary amine molecules into the 4- and 5-positions of the imidazole ring under mild conditions without quaternization.

In the course of our investigations on the synthesis of imidazole chiral bidentate ligands for transition metals,‡ we planned the preparation of 2-(1-amino-2,2-dimethylpropyl)-1-methyl-1*H*-

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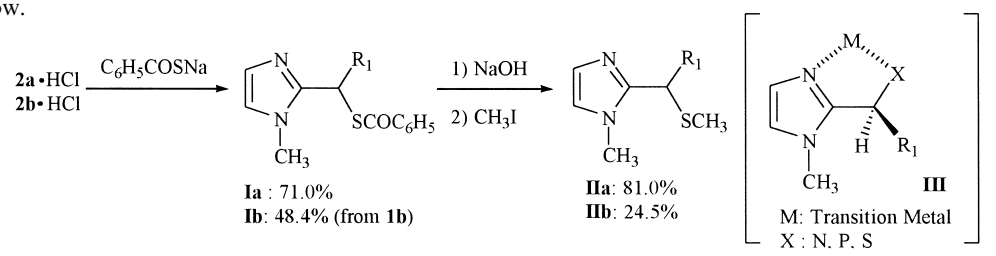
† For example: an oxidative addition of methanol and benzylalcohol into 2-aminoimidazole derivatives in the presence of NCS has been known[3].

‡ For example, expecting formation of complex **III**, the sulfides (**IIa**, **IIb**) were initially prepared by the reactions as shown below.



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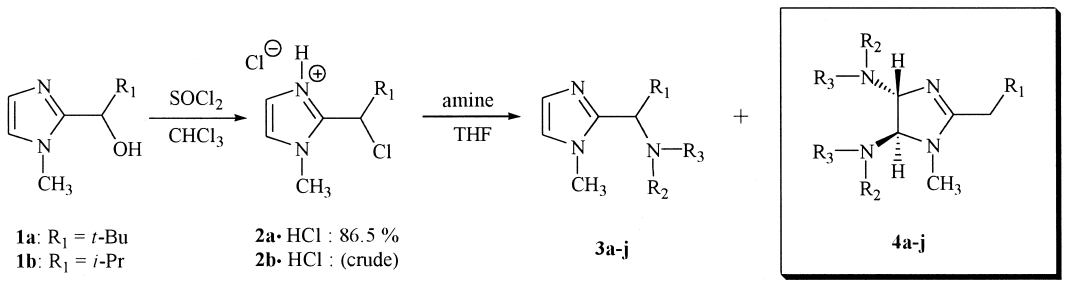
imidazoles (**3**), which would be easily derived by an S_N2 reaction of amine with 2-(1-chloro-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole (**2a**). Thus, 2-(1-hydroxy-2,2-dimethyl-propyl)-1-methyl-1*H*-imidazole (**1a**)[§] was chlorinated with thionyl chloride in chloroform to give **2a**·HCl as colorless crystals. In order to prepare 2-(1-*N*,*N*-dimethylamino-2,2-dimethylpropyl)-1-methyl-1*H*-imidazole (**3a**), **2a**·HCl was treated with an excess of *N*,*N*-dimethylamine. However, the expected normal S_N2 product (**3a**) was obtained in only 15.0% yield, and the unexpected addition product (**4a**) was obtained in 74.2% yield (Scheme 1).



Scheme 1.

The major compound (**4a**) has the molecular formula $C_{13}H_{28}N_4$ on the basis of high-resolution MS (HRMS) and micro-elemental analysis data of its crystalline picrate (**4a·dipicrate**), and its ^{1}H NMR spectrum indicated the presence of two dimethylamino groups and the absence of the olefinic 4- and 5-position protons of the imidazole ring. Finally, the structure of **4a** was determined by X-ray crystallographic analysis of its picrate (**4a·dipicrate**) as shown in Fig. 1.**

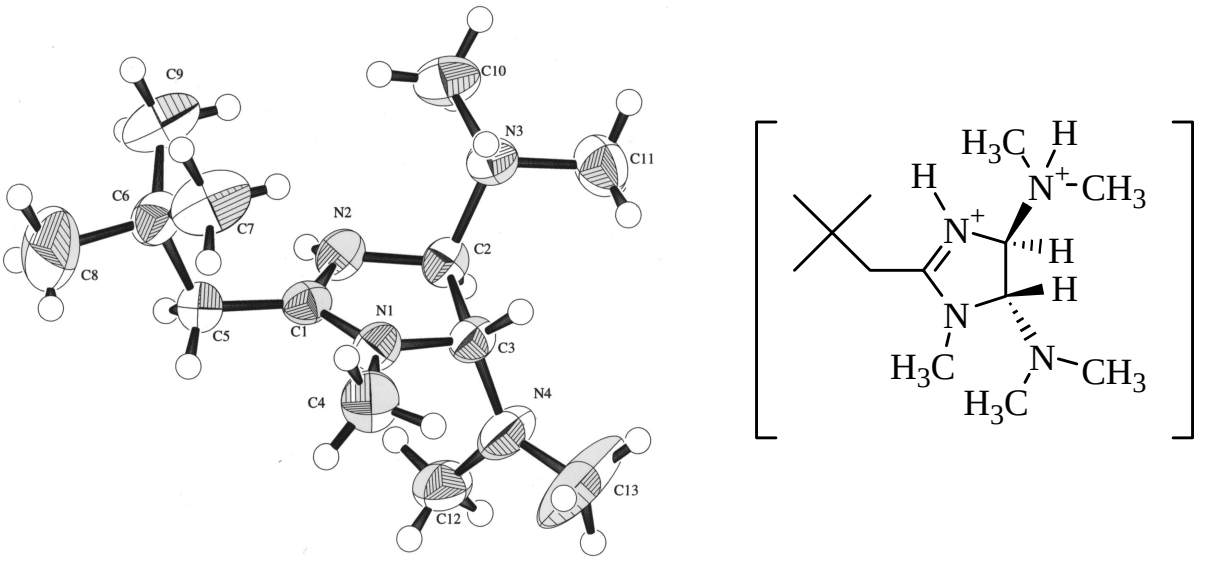
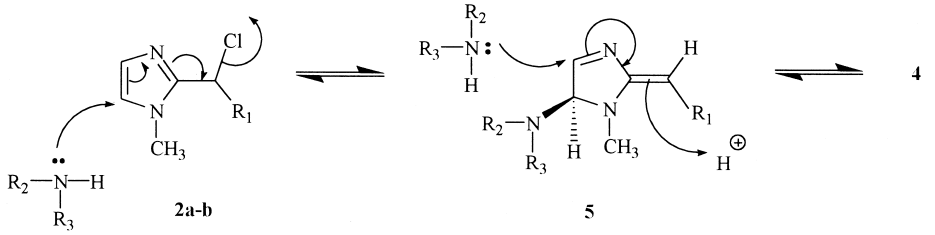


Figure 1. ORTEP view of **4a·dipicrate**. (The trinitrophenoxide portions are omitted)

[§] The alcohols **1a** and **1b** were prepared by treatment of 2-lithio-1-methyl-1*H*-imidazole with pivalaldehyde and isobutyraldehyde in THF at −78°C, respectively.

[**] Detailed data of the X-ray analysis were sent to Cambridge Crystal Data Centre (UK).

The adduct (**4a**) might be produced, interestingly, through a double nucleophilic addition of dimethylamine molecules to the electron-rich imidazole ring of **2a**, and the plausible reaction mechanism is given in Scheme 2. The addition probably proceeded because of the steric hindrance around the –CHCl– moiety of **2** and the instability of the intermediate (**5**).



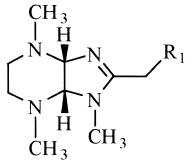
Scheme 2. Plausible reaction mechanism

The reaction of **2a** and **2b** with various amines was examined, and the results are listed in Table 1. The addition products (**4**) were obtained in 28.7–78.2% yields except for the case of benzylamine, a primary amine (entries 1–10). In the cases of benzylamine (entries 4, 9) the corresponding addition products were not isolated, and in the case of *N*,*N*′-dimethylethylenediamine (entries 5, 10), the cyclic products (**4e** and **4j**) were obtained in variable yields.

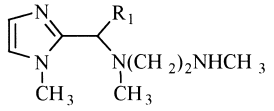
Table 1
Reaction of **2a**·HCl and **2b**·HCl with various amines

Entry	R^1 of **2**	Amine			Yield of **4** (%)	Yield of **3** (%)
			R^2	R^3		
1	*t*-Bu	*N*,*N*-Dimethylamine	CH_3	CH_3	**4a**: 74.2[a]	**3a**: 15.0[a]
2	*t*-Bu	Pyrrolidine	$-(CH_2)_4-$		**4b**: 67.9[a]	**3b**: 4.8[a]
3	*t*-Bu	Piperidine	$-(CH_2)_5-$		**4c**: 60.8[a]	**3c**: 13.4[a]
4	*t*-Bu	Benzylamine	$C_6H_5CH_2$	H	–[c]	**3d**: 67.5[a]
5	*t*-Bu	$CH_3NH(CH_2)_2NHCH_3$	CH_3	$-(CH_2)_2NHCH_3$	**4e**[d]: 78.2[a]	–[e]
6	*i*-Pr	*N*,*N*-Dimethylamine	CH_3	CH_3	**4f**: 63.9[b]	**3f**: 17.1[b]
7	*i*-Pr	Pyrrolidine	$-(CH_2)_4-$		**4g**: 57.5[b]	**3f**: 7.0[b]
8	*i*-Pr	Piperidine	$-(CH_2)_5-$		**4h**: 61.1[b]	**3h**: 17.3[b]
9	*i*-Pr	Benzylamine	$C_6H_5CH_2$	H	–[c]	**3i**[b]: 36.2
10	*i*-Pr	$CH_3NH(CH_2)_2NHCH_3$	CH_3	$-(CH_2)_2NHCH_3$	**4j**[d]: 28.7[b]	–[e]

[a] Isolated yield from **2a**·HCl.
[b] Isolated yield from **1b**.
[c] The expected product **4d** (entry 4) or **4i** (entry 9) was not isolated.
[d] Product



[e] Expected product



Preparation of a C_2-symmetry chiral ligand from **4a** may be an interesting subject for investigation and we are now examining an application of the present addition to carbanion-type nucleophiles and other azoles.[††]

Reaction of 2a with *N,N*-dimethylamine (typical procedure). Aq 50% Me_2NH (3 ml) was added to a solution of **2a** (3 mmol) in THF (3 ml) at 0°C. Stirring was continued for 3 h at 0°C. Water (1.5 ml) was added, and the mixture was extracted with AcOEt (20 ml×3). The organic layer was dried over Na_2SO_4 and evaporated to give an oily residue, which was purified by column chromatography (activated alumina) to give **3a** (AcOEt/*n*-hexane = 1/1, 88 mg, 15.0%) as the first fraction and **4a** (AcOEt, 535 mg, 74.2%) as the second fraction. **3a**: oily product. ^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.06 (s, 9H, $-C(CH_3)_3$), 2.34 (s, 6H, $-N(CH_3)_2$), 3.38 (s, 1H, $-CHN(CH_3)_2$), 3.64 (s, 3H, NCH_3), 6.81 (d, 1H, J = 1.3 Hz, Im–H), 7.05 (d, 1H, J = 1.3 Hz, Im–H). IR ($CHCl_3$): 2926, 1476 cm^{-1}. LR-EIMS m/z (relative intensity): 195 [M$^+$, 5.5], 138 (100). HR-EIMS m/z: calcd for $C_{11}H_{21}N_3$, 195.1735. Found: 195.1732. **4a**: oily product. ^{1}H NMR (400 MHz, in $CDCl_3$) δ 1.08 (s, 9H, $-C(CH_3)_3$), 2.21 (d, 1H, J = 13.6 Hz, $-CH_2C(CH_3)_3$), 2.24 (s, 6H, $-N(CH_3)_2$), 2.26 (d, 1H, J = 13.7 Hz, $-CH_2C(CH_3)_3$), 2.30 (s, 6H, $-N(CH_3)_2$), 2.90 (s, 3H, $-NCH_3$), 3.96 (d, 1H, J = 3.8 Hz, $-CHN(CH_3)_2$), 4.25 (d, 1H, J = 3.8 Hz, $-CHN(CH_3)_2$). IR ($CHCl_3$): 2920, 1585 cm^{-1}. LR-EIMS m/z (relative intensity): 240 [M$^+$, 1.7], 138 (100). HR-EIMS m/z: calcd for $C_{13}H_{28}N_4$, 240.2314. Found: 240.2309. **4a·dipicrate**, mp 147.0–150.0°C (recrystallized from MeOH). Anal. calcd for $C_{25}H_{34}N_{10}N_{14}$: C, 42.98; H, 4.91; N, 20.05. Found: C, 43.13; H, 4.95; N, 19.34. X-ray crystallographic data, triclinic; P-1(#2); a = 12.2412(8), b = 13.3569(8), c = 10.9801(4) Å, α = 92.526(4), β = 94.827(4), γ = 65.166(5)°; V = 1623.4(2) Å^3; Z = 2; D_{calc} = 1.429 g/cm^3; λ(Cu Kα) = 1.54178 Å; μ(Cu Kα) = 10.20 cm^{-1}; F(000) = 732.00; T = 296 K; R = 0.061 (R_w = 0.102) for 3505 observations.

Acknowledgements

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[††] New compounds reported in this communication were fully characterized by HRMS (oily compounds), micro-elemental analysis (crystalline compounds), ^{1}H NMR, IR, and LRMS.