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SYNTHESIS OF 2-DIMETHYLAMINOBENZAZOLES *VIA* A GUANIDINE INTERMEDIATE: REACTION OF 2-SUBSTITUTED ANILINE DERIVATIVES WITH 2-CHLORO-1,1,3,3-TETRAMETHYL-FORMAMIDINIUM CHLORIDE

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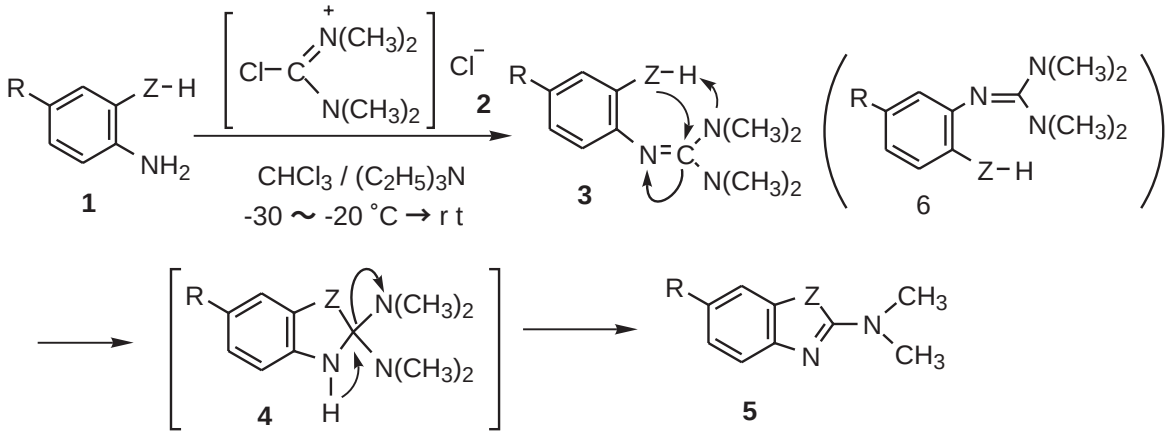
Abstract – Reactions of 2-aminophenols, 2-aminothiophenol and *o*-phenylenediamines with 2-chloro-1,1,3,3-tetramethylformamidinium chloride proceeded easily *via* cyclization of guanidine intermediates to give the corresponding benzazoles having a dimethylamino group at 2-position.

Benzazoles have attracted considerable interest because of their potential biological activities including an antimicrobial activity,[1] and served as one of the pharmacophore in clinical medicines. For example, benzazole derivatives with a basic moiety at 2-position, such as 2-piperazinyl- and 2-piperidinylbenzazoles, have been synthesized in relation to the structure-activity relationships (SAR) studies on the antagonists or agonists for 5-HT receptors [2] and antiallergic agents.[3]

During the course of our study on the chemistry of guanidino group, we found that 2-guanidinophenol cyclized readily to give 2-dimethylaminobenzoxazole. This finding led us to an exploitation of a useful

synthetic method of 2-aminobenzazole derivatives. The general synthetic methods need multi-steps via 2-chloro-[4, 5, 6] or 2-methylsulfone-benzazoles [2, 3] as an intermediate. In this paper we wish to report a facile synthesis of 2-dimethylaminobenzazole by a one-pot reation *via* guanidino intermediates.



Compd	R	Z	Products
1a	H	O	**5a**
1b	NO_2	O	**5b**
1c	H	S	**5c**

Compd	R	Z	Products
1d	H	NH	**5d**
1e	NO_2	NH	**5e**

Scheme 1

First, in order to obtain a guanidino derivative, reation of *o*-aminophenol (**1a**) with 2-chloro-1,1,3,3-tetramethylformamidinium chloride (**2**) in the presence of triethylamine in chloroform was carried out at -30 - -20 °C, and subsequently the reaction mixture was allowed to stand at an ambient temperature for 3 h. A usual basic workup furnished a crude product, the ^{1}H NMR spectrum of which indicated it consisted of three compounds (**3a**, **4a**, and **5a**) in a ratio of 57 : 31 : 12. Since the cyclized product (**5a**) had formed along with the intermediates (**3a**, **4a**), we anticipated that an acid would catalyze the cyclization of these intermediates to yield the corresponding benzazole. Thus, when a chloroform solution of the mixture was stirred in the presence of silica gel for 1.5 h at room temperature, **5a** was obtained in 76% yield. In the similar reaction of 2-aminothiophenol (**1c**) with **2**, the cyclization occurred more readily to give a mixture of an intermediate (**3c**) and the benzothiazole (**5c**), the ratio

being 3 to 97, which on standing at room temperature for 4.5 h without silica gel afforded **5c** in 84% yield. In the case of *o*-phenylenediamine (**1d**), we presumed that the cyclization of an intermediate (**3d**) would be less facile than the oxygen counterpart since an intramolecular acid-base catalysis by a proximate effect as depicted in Scheme 1 should decrease. Therefore, the isolated crude product (**3d**) was heated under reflux in xylene in the presence of catalytic acetic acid for 4 h to give the benzimidazole (**5d**) in 84% yield.

Thus, it was indicated that the C-N double bond in guanidino group was electrophilic enough to allow the nucleophilic attack of a lone pair of hetero atoms at *ortho*-position, and a dimethylamino group served as a leaving group as shown in Scheme 1.

Next, one pot reaction of **1a** with **2** was examined to yield the benzazole (**5a**) without isolation of intermediates (**3a** and **4a**). After reacting at -30 ~ -20°C for 3 h, the reaction mixture was allowed to stir overnight in the presence of silica gel at room temperature. Filtration of the silica gel followed by workup as described above afforded **5a** in 78% yield.

Finally, in order to investigate the effect of a nitro group on the formation of azole rings, the reaction of 2-amino-5-nitrophenol (**1b**) with **2** was examined. After standing for 3.5 h at room temperature, **5b** was obtained in 91% yield. Similar reaction of 4-nitrophenylenediamine (**1e**) gave **5e** in 85% yield. In this case, however, it seems likely that the cyclization did not take place *via* **3e** (2-amino-4-nitrophenylguanidine intermediate), but *via* **6e** (2-amino-5-nitrophenylguanidine intermediate). It was shown that the introduction of a nitro group on benzene ring accelerated the formation of azole ring.

Thus, 2-chloro-1,1,3,3-tetramethylformamidinium chloride (**2**) was applied in the heterocyclic synthesis for the first time. The present reaction may serve as a convenient and useful method for the synthesis of 2-dimethylaminobenzazoles.

EXPERIMENTAL

All melting points were determined on a Yamato melting point apparatus (Yanaco MP-J3) and are uncorrected. NMR spectra were recorded on JEOL JNM-FX 90Q spectrometer. MS spectra were

determined with a Shimadzu GC MS-9100-MS gas chromatograph-mass spectrometer with a direct inlet system.

2-Chloro-1,1,3,3-tetramethylformamidinium chloride (2) [7]

A mixture of *N,N,N',N'*-tetramethylurea (22.6 g, 0.195 mol) and oxalyl chloride (37.0 g, 0.92 mol) in anhydrous chloroform (100 mL) was refluxed over night. After evaporating chloroform, the residual solids were washed with dry ether (3 x 100 mL) to give formamidinium chloride (**2**) (32.6 g, 98% yield), mp 111-113℃ (lit.,[7] mp 110-112℃), light gray needles. The chloride was used in the next step without further purification.

Preparation of 2-dimethylaminobenzazoles (1a-e): General Procedure

A solution of 2-substituted aniline derivatives (**1a-e**) (30 mmol), 2-chloro-1,1,3,3-tetramethyl-formamidinium chloride (31.5 mmol), and triethylamine (60 mmol) in chloroform (30 mL) was stirred at -30 ~ -20 °C for 3.5 ~ 5 h. The reaction mixture was poured into 10% Na_2CO_3 solution, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to dryness to give the crude mixture. Then silica gel (ca. equivalent weight to the reation mixture; Kieselgel 60, Merck) was added to the mixture dissolved in chloroform, and the resulting mixture was stirred at rt for 2 ~ 3 h. Filtration of the silica gel followed by evaporation of the solvent in vacuo gave the benzazoles (**5a-e**). In the one-pot reaction of **1a** and **2**, the reaction mixture was treated directly with silica gel without isolation of intermediates (**3a**) and (**4a**) to afford benzoxazole (**5a**). In the case of *o*-phenylenediamine (**1d**), after workup, a mixture of products was chromatographed on aluminum oxide 90 using $CHCl_3$-MeOH (97:3, v/v) as an eluent to give the amino-guanidine (**3d**) (85%). A solution of **3d** in xylene was refluxed in the presence of acetic acid for 4 h to give benzimidazole (**5d**).

2-Dimethylaminobenzoxazole (5a): Yield, 76%, mp 90-91°C (hexane) (lit.,[4] mp 88-89 °C), reddish orange needles. IR (Nujol): 1650, 1580 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 3.19 (s, 6H, $N(CH_3)_2$), 6.85-7.45 (m,

4H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 37.65, 108.60, 116.08, 120.18, 123.88, 143.72, 149.18, 163.10. MS: m/z 162 (M^+). *Anal*. Calcd for $C_9H_{10}N_2O$: C, 66.65 H, 6.22; N, 17.27. Found: C, 66.57; H, 6.30; N, 17.30.

2-Dimethylamino-6-nitrobenzoxazole (5b): Yield, 91%, mp 174.5-176 °C ($CHCl_3$/MeOH), yellowish orange needles. IR (Nujol): 1665, 1620, 1590, 1380 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 3.27 (s, 6H, $N(CH_3)_2$), 7.29 (dd, *J*=2.5, 8.8 Hz, 1H, C4-H), 8.11 (d, *J*=2.5 Hz, 1H, C7-H), 8.15 (dd, *J*=2.5, 8.8 Hz, 1H, C5-H). ^{13}C NMR ($CDCl_3$) δ: 37.69, 104.80, 114.49, 121.32, 141.09, 148.11, 150.46, 165.61. MS: *m/z* 207 (M^+). *Anal*. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.16; H, 4.48; N, 20.32.

2-Dimethylaminobenzthiazole (5c): Yield, 84%, mp 89-91 °C (hexane/ether) (lit.,[4] mp 86-88 °C), pale yellow needles. IR (Nujol): 1600, 1560, 1550 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.18 (s, 6H, $N(CH_3)_2$), 6.90-7.70 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 40.12, 118.81, 120.57, 120.83, 125.90, 131.17, 153.34, 168.69. MS: *m/z* 178 (M^+). *Anal*. Calcd for $C_9H_{10}N_2S$: C, 60.66; H, 5.66; N, 15.72; S, 17.96. Found: C, 60.59; H, 5.71; N, 15.58; S, 17.92.

2-Dimethylaminobenzimidazole (5d): Yield, 84%, mp > 300 °C ($CHCl_3$) (lit.,[5] mp 312-314 °C), pale yellow needles. IR (Nujol): 1630, 1600, 1575 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 3.03 (s, 6H, $N(CH_3)_2$), 6.75-7.25 (m, 4H, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 38.00, 108.50, 114.90, 119.25, 156.85. MS: *m/z* 161 (M^+). *Anal*. Calcd for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 66.90; H, 6.94; N, 26.08.

2-Dimethylamino-5 (or 6)-nitrobenzimidazole (5e): Yield, 85%, mp 244.5-246 °C (EtOH) (lit.,[6] mp 242-243 °C), yellowish orange needles. IR (Nujol): 1640, 1610, 1590, 1380 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 3.16 (s, 6H, $N(CH_3)_2$), 7.20 (dd, *J*=1.3, 8.8 Hz, 1H, C4-H), 7.89 (dd, *J*=2.5, 8.8 Hz, 1H, C5-H), 7.94 (d, *J*=2.5 Hz, 1H, C7-H). ^{13}C NMR ($CDCl_3$) δ: 37.7, 106.0, 111.3, 116.6, 137.3, 139.8, 147.1. MS: *m/z* 206 (M^+). *Anal*. Calcd for $C_9H_{10}N_4O_2$•1/2H_2O: C, 50.23; H, 5.12; N, 26.04. Found: C, 50.49; H, 5.14; N,

26.33.

Compound 3d: Yield, 84%, mp 50-51°C (hexane), light gray fine needles. IR (Nujol): 3450, 3350, 1610, 1585, 1560 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.68 (s, 12H, 2 x $N(CH_3)_2$), 3.85 (br. s, 2H, NH_2), 6.25-6.85(m,4H, Ar-H). MS: *m/z* 206 (M^+).

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   In this paper, 2-chloro-1,1,3,3-tetramethylformamidinium chloride (**2**) was prepared from tetramethylurea with phosgene ($COCl_2$) in dry THF at reflux in 96 % yield, mp 110-112°C.