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Regiospecific Synthesis of 3-Substituted Imidazo[1,2-a]pyridines, Imidazo[1,2-a]pyrimidines, and Imidazo[1,2-c]pyrimidine

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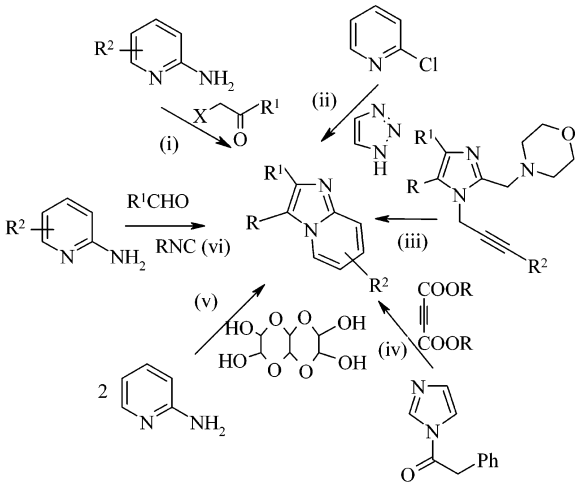
Abstract: 3-Substituted imidazo[1,2-a]pyridines, imidazo-[1,2-a]pyrimidines, and imidazo[1,2-c]pyrimidine were obtained regiospecifically in yields of 35−92% in one pot by reaction of 2-aminopyridines or 2-(or 4-)aminopyrimidines, respectively, with 1,2-bis(benzotriazolyl)-1,2-(dialkylamino)-ethanes.

Imidazo[1,2-a]pyridines show anticytomegalo−zoster and antivaricella−zoster virus,[1a−e] antibacterial,[2] anti-inflammatory, analgesic, antipyretic,[3a−c] hypnoselective and anxioselective activities.[4] They are β-amyloid formation inhibitors[5] and constitute a novel class of orally active nonpeptide bradykinin B_2 receptor antagonists.[6] Several imidazo[1,2-a]pyridines already on the market include zolimidine (an antiulcer drug),[3c] zolpidem (a hypnotic drug), and alpidem (a nonsedative anxiolytic).[7] Imidazo[1,2-a]pyrimidine structural moieties are also important as benzodiazepine receptor agonists,[8] antiviral agents,[1a] antibacterials,[9] antifungal agents,[10] and calcium channel blockers.[11]

SCHEME 1



Syntheses of the imidazo[1,2-a]pyridine ring system include: (i) coupling reactions of 2-aminopyridines with α-halocarbonyl compounds;[1a,b,12a−e] (ii) reactions of 2-chloropyridine with 1,2,3-triazoles and subsequent elimination of nitrogens;[13] (iii) cyclizations of 1-(2-alkynyl)-2-aminomethylimidazoles, which are obtained from substituted imidazoles via six steps;[14] (iv) reactions of (arylacetyl)imidazoles with acetylenedicarboxylic esters;[15] (v) condensation of 2-aminopyridine with glyoxal trimer dihydrate in aqueous $NaHSO_3$;[16] and (vi) one-pot condensations of aldehydes, isonitriles, and 2-aminopyridines (Scheme 1).[17] Moreover, methods i and vi are also used for the preparation of imidazo[1,2-a]pyrimidines.[17−19]

Method i is popular for the synthesis of both imidazo-[1,2-a]pyridines and imidazo[1,2-a]pyrimidines, since a variety of starting materials are either commercially available or can be easily synthesized, and severe reac-

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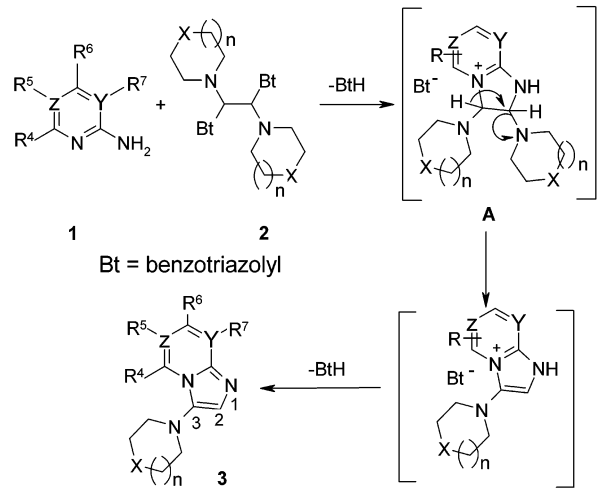
tion conditions are avoided. However, the synthesis of 3-monosubstituted imidazo[1,2-a]pyridines and imidazo-[1,2-a]pyrimidines would require a correspondingly substituted α-haloacetaldehyde. Significantly, no syntheses of 3-amino monosubstituted imidazo[1,2-a]pyridines or imidazo[1,2-a]pyrimidines using method i were found in the literature. In fact, only two 3-amino monosubstituted imidazo[1,2-a]pyridines have been made by ring synthesis: 3-aminoimidazo[1,2-a]pyridine (from condensation of potassium cyanide, formaldehyde, and 2-aminopyridine[20]) and 3-(*N*-2-pyridinylamino)imidazo[1,2-a]pyridine (from method v[16]). Some 3-amino-imidazo[1,2-a]pyridines[21,22] were prepared using 2-(2-pyridinylamino)acetonitrile as a key starting material, which was synthesized via reaction of sodium cyanide, formaldehyde, and 2-aminopyridine. Many others have been obtained by further reactions of 3-amino-imidazo[1,2-a]pyridines with electrophiles.[23−25] We now present a novel regiospecific benzotriazole-mediated one-pot approach to 3-amino monosubstituted imidazo[1,2-a]pyridines **3a**−**g**, imidazo-[1,2-a]pyrimidines **3h**,**i**, and imidazo[1,2-c]pyrimidine **3j** in moderate to excellent yields.

1,2-Bis(benzotriazolyl)-1,2-(dialkylamino)ethanes **2**, previously synthesized in our group via double condensation of glyoxal, benzotriazole, and amines,[26] are readily available 1,2-bis-electrophiles. In the present paper, [3 + 2] cyclizations of 2-aminopyridines or 2-(or 4-)aminopyrimidines (as 1,3-bisnucleophiles) with compounds **2** formed the imidazole ring to give the titled compounds in one-pot reactions (Scheme 2).

Synthesis. The cyclizations proceeded in dichloromethane or in 1,2-dichloroethane. Reactions of 2-aminopyridines **1** with compounds **2** were carried out in refluxing 1,2-dichloroethane to shorten the reaction time. Reactions of 2-(or 4-)aminopyrimidines with **2** in refluxing dichloromethane (or 1,2-dichloroethane) were done in the presence of zinc bromide as Lewis acid to promote the leaving ability of the benzotriazole group. Products **3** were obtained in moderate to excellent yields after refluxing for 1.5−4.5 h (Scheme 2). The reaction works smoothly when compounds **1** with various functional groups (such as amino, benzyoxyl and methyl) are used as starting materials. NOE experiments have shown that all products are 3-substituted derivatives. No 2-substituted or 2,3-disubstituted products were observed. This fact is well explained via the proposed mechanism (next paragraph). Structures **3** were characterized by ^{1}H and ^{13}C NMR and microanalysis. However, compound **3j** was unstable under normal conditions. In the ^{1}H NMR, one distinct singlet, usually near 7.19−7.48 ppm, was ascribed to the proton at the 2-position in the imidazole ring. A new tertiary carbon in the aromatic region, as

SCHEME 2



3	R^4	R^5	R^6	R^7	X	Y	Z	n	yields,%
a	H	H	H	H	O	C	C	1	86
b	H	H	H	$PhCH_2O$	O	C	C	1	90
c	H	H	H	$PhCH_2O$	CH_2	C	C	1	85
d	CH_3	H	CH_3	H	O	C	C	1	87
e	H	H	H	$PhCH_2O$	CH_2	C	C	0	78
f	H	Cl	H	H	O	C	C	1	92
g	NH_2	H	H	H	O	C	C	1	64
h	H	H	H		O	N	C	1	35
i	CH_3	H	CH_3		O	N	C	1	62
j	CH_3		CH_3	H	O	C	N	1	40

determined by APT spectra for **3**, further supported the successful outcome of the [3 + 2] cyclization.

Although reactions were successful using aliphatic amines **2** as 1,2-biselectrophile synthons, the expected imidazo[1,2-a]pyridines of type **3** were not obtained using reagents **2** derived from aromatic amines in these reactions: reactions attempted with phenyl and with benzyl derivatives (**2**, Ph_2N, $PhCH_2N$) did not give the desired products.

Regioselectivity and the Proposed Reaction Mechanism. The position of substituents in imidazo[1,2-a]-pyridines **3a**−**g**, imidazo[1,2-a]pyrimidines **3h**,**i**, and imidazo[1,2-c]pyrimidine **3j** was determined by NOE experiments. In all products, when the proton in the imidazole ring (a singlet around 7.19−7.48 ppm) was irradiated, no NOE effect for the proton(s) of R^4 (H, NH_2, CH_3) in the pyridine and pyrimidine rings was observed and vice versa. Positive NOE effects were, however, obtained between protons in R^4 and certain protons in morpholine and piperidine moieties. The detailed results listed in Table 1 demonstrate that the substituents in the imidazole ring are at the 3-position in each of these imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrimidines, and imidazo[1,2-c]pyrimidine **3a**−**j**. The NOE effects for compounds **3d**−**j** are given in Supporting Information as Table 2.

A possible mechanism is that the lone electron pairs on the nitrogen atoms in the pyridine ring and the amino group could attack both BtCHN carbon atoms in **2** to form intermediate **A** with the elimination of both benzotriazole

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TABLE 1. NOE Effects in Compounds 3a−c

compd	irradiation peaks δ/ppm	observed NOE effects δ/ppm
3a	3.05 ($N(CH_2)_2$, morpholine ring)	3.90 ($O(CH_2)_2$, morpholine ring)
		7.31 (H-2, imidazole ring)
		8.00 (R^4, pyridine ring)
	8.00 (R^4, pyridine ring)	3.05 ($N(CH_2)_2$, morpholine ring)
		6.81 (R^5, pyridine ring)
3b	3.05 ($N(CH_2)_2$, morpholine ring)	3.89 ($O(CH_2)_2$, morpholine ring)
		7.26 (H-2, imidazole ring)
		7.63 (R^4, pyridine ring)
	7.63 (R^4, pyridine ring)	6.64 (R^5, pyridine ring)
		3.05 ($N(CH_2)_2$, morpholine ring)
3c	2.99−3.11 ($N(CH_2)_2$, morpholine ring)	7.35 (H-2, imidazole ring)
		3.74 ($O(CH_2)_2$, morpholine ring)
		3.90 ($O(CH_2)_2$, morpholine ring)
	2.86 (R^4, pyridine ring)	6.30 (R^5, pyridine ring)
		3.74 ($O(CH_2)_2$, morpholine ring)
		3.90 ($O(CH_2)_2$, morpholine ring)

moieties, which are good leaving groups.[27] Although in theory both the amino moieties at 2- and 3-positions could be eliminated, the elimination from the 2-position is more favorable than that from the 3-position because of the greater acidity of the proton adjacent to the positively charged nitrogen. Intermediate **B** is formed by elimination of an amine moiety from the favorable 2-position to give 3-substituted imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrimidines, and imidazo[1,2-c]pyrimidine **3** (Scheme 2).

In summary, we have developed an efficient and simple approach to 3-substituted imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrimidines, and imidazo[1,2-c]pyrimidine with excellent regioselectivity. The reaction conditions are mild, and reactions were completed in 1.5−4.5 h. A mechanism was also proposed and discussed on the basis of experimental results.

Experimental Section

1,2-Dichloroethane, 2-aminopyridines, and 2-(or 4-)aminopyrimidines were used as received without further purification. Dichloromethane was distilled before use. Column chromatography was performed on silica gel unless otherwise noted. All of the reactions were carried out under N_2.

General Procedure for the Synthesis of 3-Substituted Imidazo[1,2-a]pyridines 3a−g. The corresponding compounds **2** (1 mmol) and substituted 2-aminopyridines **1** (1 mmol) were refluxed in 1,2-dichloroethane (10 mL) for 1.5−2.5 h. All reactions were monitored by TLC, which showed the disappearances of the starting materials. The reaction mixture was then cooled to room temperature. Potassium hydroxide powder (0.22 g, 3.3 mmol, 86%) was added to the solution and stirred for 0.5 h. Then, the solid was filtered out and washed with chloroform. After removal of the solvent, the residue was separated by column chromatography on silica gel using a mixture of EtOAC/methanol (from 100/0.5 to 100/10) as an eluent.

3-Morpholinoimidazo[1,2-a]pyridine (3a): brown prisms (acetone), mp 78−80 °C; ^{1}H NMR δ 8.00 (d, J = 6.9 Hz, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.31 (s, 1H), 7.16−7.11 (m, 1H), 6.81 (t, J = 6.3 Hz, 1H), 3.90 (t, J = 4.7 Hz, 4H), 3.05 (t, J = 4.7 Hz, 4H); ^{13}C NMR δ 142.1, 134.9, 123.5, 122.1, 121.6, 118.0, 111.7, 67.1, 52.2. Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.98; H, 6.69; N, 20.78.

General Procedure for the Synthesis of 3-Substituted Imidazo[1,2-a]pyrimidines and Imidazo[1,2-c]pyrimidine 3h−j. The corresponding compounds **2** (1 mmol), substituted 2-(or 4-)aminopyrimidines **1**(1 mmol), and zinc bromide (1 mmol) were refluxed in dry dichloromethane for about 4.5 h until the TLC showed the disappearance of compounds **2**. The solid was then filtered out and washed with chloroform. The filtrate was washed with 2 N NaOH solution and dried with sodium sulfate. After removal of the solvent, the residue was separated by column chromatography on silica gel using a mixture of EtOAC/methanol (from 100/0.5 to 100/15) as an eluent.

3-Morpholinoimidazo[1,2-a]pyrimidine (3h): yellow prisms (acetone), mp 157−158 °C; ^{1}H NMR δ 8.53 (br s,1H), 8.31 (dd, J = 6.7, 1.9 Hz, 1H), 7.48 (s, 1H), 6.87 (dd, J = 6.7, 4.1 Hz, 1H), 3.91 (t, J = 4.5 Hz, 4H), 3.07 (t, J = 4.7 Hz, 4H); ^{13}C NMR δ 149.0, 145.0, 133.2, 129.8, 123.4, 108.1, 67.0, 52.1. Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 59.06; H, 6.32; N, 27.29.

Supporting Information Available: Characterization data for compounds **3b−g** and **3i**,**j** and NOE effects for compounds **3d−j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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