phosphate buffer (μ = 1.0, KCl) was added 708 mg of Fremy's salt. The mixture was stirred at room temperature for 1 h, during which time red *syn*-**2b** crystallized from solution. Filtration, washing the solids with a small volume of water, and then drying afforded *syn*-**2b** as a fiberous red solid: 61 mg (36%) yield. The filtrate was extracted with 2 × 50 mL of chloroform. Evaporation of the dried extracts ($MgSO_4$) to a residue and then trituration with acetone afforded yellow *anti*-**2b** (21 mg (12%) yield).

Physical properties of *syn*-**2b**: mp 312 °C dec; TLC (acetone) R_f = 0.57; IR (KBr pellet) 3340, 1745, 1625, 1601, 1380, 1238 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 9.34 and 6.68 (2 H, 2 br s, imine protons), 5.99 (1 H, m, C(3) proton), 4.24 (2 H, m, C(1) diastereomeric methylene), 3.04 and ~2.5 (2 H, 2 m, C(2) diastereomeric methylene), 2.07 (3 H, s, 7-methyl), 1.74 and 1.54 (6 H, 2 s, acetate and acetamido methyls); ^{13}C NMR (dimethyl sulfoxide-d_6) 176.2, 169.6, 154.7, 154.1, 149.8, 138.7, 130, 110.6, 96.8, 65.5, 43.3, 34.1, 25.5, 20.6, 8.7 cps; mass spectrum (EI mode), m/z 316 (P^+). Anal. Calcd for $C_{15}H_{16}N_4O_4 \cdot 0.25H_2O$: C, 56.15; H, 5.18; N, 17.45. Found: C, 55.94; H, 5.19; N, 17.18.

Physical properties of *anti*-**2b**: mp 304 °C dec; TLC (same as *syn*-**2b**); IR (KBr pellet) 3188, 1740, 1714, 1644, 1627, 1487, 1376, 1310, 1230 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 11.65 (1 H, s, amide proton), 9.64 (1 H, s, imine proton), 6.06 (1 H, dd, J = 8 Hz, J = 3.8 Hz, C(3) proton), 4.29 (2 H, m, C(1) diastereomeric methylene), 3.06 and ~2.6 (2 H, 2 m, C(2) diastereomeric methylene), 2.08 (6 H, 2 s), and 1.8 (3 H, s), 7-methyl, acetamido, and acetate methyls, no assignments made; mass spectrum (same as *syn*-**2a**).

6-Acetamido-5-amino-8-hydroxy-7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (19). A solution of 25 mg (0.09 mmol) of *syn*-**2a** in 5 mL of methanol was shaken under 50 psi of H_2 in the presence of 5 mg of 5% Pd on charcoal. The catalyst was then removed by filtering through Celite, and the filtrate immediately concentrated to a solid. Dissolution of the solid in 5 mL of chloroform/methanol (1:4) and adding hexane resulted in precipitation of **19**: 20 mg (79%) yield; TLC (chloroform/methanol [6:4]) R_f = 0.4; IR (KBr pellet) 3322, 3210, 3140, 1660, 1640, 1505 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 9.19 (1 H, s, amide proton), 8.68 (1 H, s, 8-hydroxyl), 4.14 (2 H, t, J = 7.1 Hz, C(1) methylene), 3.20 (2 H, t, J = 7.5 Hz, C(3) methylene), 2.72 (2 H, m, C(2) methylene), 2.07 and 2.04 (6 H, 2 s, 7-methyl and acetamido methyl); mass spectrum (EI mode), m/z 260 (P^+), 242 ($P^+ - H_2O$), 217 (P^+ – acetyl).

6-Acetamido-5,6-dihydroxy-7-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (20). A solution of 30 mg (0.11 mmol) of **1a** in 10 mL of methanol was shaken under 50 psi of H_2 for 25 min in the presence of 8 mg of 5% Pd on charcoal. After addition of 3 drops of concentrated HCl to the reaction, the catalyst was removed by filtering through Celite, and the filtrate was concentrated to a solid. Recrystallization of the solid by dissolution in a minimal amount of methanol followed by addition of ethyl acetate afford **20** as the HCl salt: 32 mg (97%) yield; TLC (chloroform/methanol [6:4]) R_f = 0.57; IR (KBr pellet) 3337, 3150, 1650, 1505, 1299 cm^{-1}; ^1H NMR (dimethyl sulfoxide-d_6) δ 9.39 (2 H, s, 5,8-dihydroxy), 9.03 (1 H, s, amide proton), 4.45 (2 H, t, J = 6.9 Hz, C(1) methylene), 3.22 (2 H, t, J = 7.5 Hz, C(3) methylene), 2.72 (2 H, quintet, J = 7.6 Hz, C(2) methylene), 2.10 and 2.08 (6 H, 2 s, 7-methyl and acetamido methyl); mass spectrum (EI mode), m/z 261 (P^+), 243 ($P^+ - H_2O$), 219 (P^+ – ketene).

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Registry No. **1a**, 123567-03-3; **1b**, 123567-28-2; **1c**, 123567-24-8; **1d**, 123567-25-9; *syn*-**2a**, 123592-95-0; *anti*-**2a**, 123567-29-3; *syn*-**2b**, 123593-07-7; *anti*-**2b**, 123567-30-6; **3**, 123567-04-4; **4**, 123567-05-5; **4** deacetylated derivative, 123567-31-7; **5**, 123567-06-6; **6**, 123567-07-7; **6** deacetylated derivative, 123567-20-4; **6** phenyl carbonate analogue, 123567-21-5; **7c**·2HCl, 123567-08-8; **7d**·2HCl, 123567-22-6; **8**, 123567-09-9; **9c**, 123567-10-2; **9d**, 123567-23-7; **10**, 123567-11-3; **11**, 123567-12-4; **12**, 123567-13-5; **13**, 123567-14-6; **14**, 123567-15-7; **15a**, 123567-16-8; **15b**, 123567-26-0; **16a**, 123567-17-9; **16b**, 123567-27-1; **19**, 123567-18-0; **20**·HCl, 123567-19-1; 3-bromo-4-nitrotoluene, 40385-54-4; pyrrolidine, 123-75-1; ethylenimine, 151-56-4; 5-bromo-2,4-dinitrotoluene, 5411-53-0.

A Novel and Versatile Synthesis of 1-Alkyl-, 1-Aryl-, 1-(Alkylamino)-, or 1-Amido-Substituted and of 1,2,6-Trisubstituted Piperidines from Glutaraldehyde and Primary Amines or Monosubstituted Hydrazines[1]

Alan R. Katritzky* and Wei-Qiang Fan

Department of Chemistry, University of Florida, Gainesville, Florida 32611

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Various primary amines and 1-mono- and 1,1-disubstituted hydrazines were converted into the corresponding N-substituted piperidines in good to excellent yields via the products of double condensations with benzotriazole and glutaraldehyde. Reduction of the 2,6-bis(benzotriazolyl) N-substituted piperidines **4** and **7** with sodium borohydride in tetrahydrofuran afforded N-substituted piperidines. The benzotriazole moieties were also replaced by alkyl groups by reaction with Grignard reagents to produce 1,2,6-trisubstituted piperidines.

Many N-substituted piperidines and their 2,6-dialkyl derivatives are pharmacologically active and form an essential part of the molecular structure for important drugs.[2] For example, the 1-piperidino group is a feature of the antihistaminic agent and the spasmolytic benzhexol,[3] of narcotic analgesics,[4] of postganglionic parasympathetic agonists,[5] and of oral anesthetics.[6] Many 1,2,6-trialkylpiperidine alkaloids have been isolated from both animal and plant species.[7,8]

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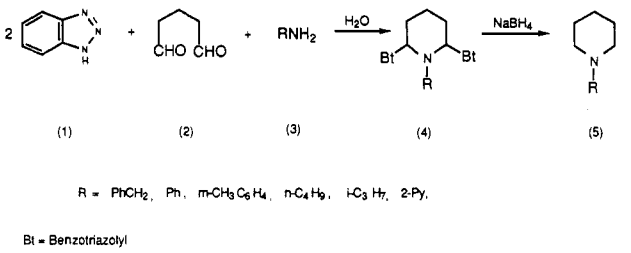
Table I. Preparation of the N-Substituted 2,6-Bis(benzotriazolyl)piperidines

					calcd			found		
no.	N-substituent	solvent	yield (%)	mp (°C)	C	H	N	C	H	N
4a	$PhCH_2$	H_2O	91	61–63	70.42	5.62	23.96	70.74	5.69	23.47
4b	Ph	H_2O	85	155–158	69.87	5.32	24.81	69.52	5.66	24.50
4c	m-$CH_3C_6H_4$	H_2O	80	145–148	70.42	5.62	23.96	70.74	5.87	23.62
4d	n-C_4H_9	H_2O	75	*a*						
4e	i-C_3H_7	H_2O	82	*a*						
4f	2-pyridyl	H_2O–EtOH	79	48–51	66.67	5.05	28.28	66.49	4.97	28.46
7a	PhNH	H_2O–EtOH	86	65–67	67.32	5.37	27.32	67.64	5.19	27.06
7b	$(CH_3)_2N$	H_2O	73	*a*						
7c	PhCONH	EtOH	95	169–171	65.68	5.02	25.47	65.34	5.00	25.08
7d	CH_3CONH	EtOH	86	178–181	60.64	5.32	29.81	60.59	5.48	30.22
7e	$CH_3CH_2O_2CNH$	EtOH	94	183–186	59.11	5.42	27.59	58.98	5.52	27.65
7f	$(CH_3)_3CO_2CNH$	EtOH	97	186–190	60.83	5.99	25.81	61.01	5.82	25.49
7g	$PhCH_2O_2CNH$	EtOH	93	192–195	64.10	5.13	23.93	63.92	5.31	23.65

[a] Sticky oil, used as such in further reactions.

Many alternative methods are available for synthesizing N-substituted piperidines.[9] Cyclization with the formation of a bond between a carbon atom and a heteroatom is the usual heterocyclization that forms a six-membered heterocyclic ring system. Thus, the most familiar approach to piperidines is from a 1-pentanamine derivative with a leaving group on carbon 5.[10] Such methods utilize various 1,5-disubstituted pentanes as the starting materials. The preparation of a suitable starting material is often a major problem that restricts application, particularly in the preparation of 1,2,6-trisubstituted piperidines. *N*-Alkyl-substituted piperidines have also been made by the reduction of *N*-acylpiperidines or N-substituted 2-oxopiperidines,[11] but, once again, this suffers from the limited availability of the starting materials. Double reductive Mannich condensation of a dicarbonyl compound with an amine provided an alternative route for the preparation of N-substituted heterocycles with five- and six-membered rings.[12] Thus, Watanabe reported the synthesis of N-substituted piperidines from the reductive amination of glutaraldehyde and primary amines with tetracarbonylhydridoferrate as a reducing reagent;[13] sodium cyanoborohydride has also been used as the reducing reagent.[14] However, this method is inapplicable to 1,2,6-trisubstituted piperidines or to *N*-(alkylamino)- and *N*-(alkylamido)-piperidines. The reaction of glutaraldehyde with primary amines with sodium hydrogen sulfite followed by potassium cyanide gave *N*-alkyl-2,6-dicyanopiperidines,[15] decyanidation of which by heating with sodium borohydride in isopropyl alcohol afforded the *N*-alkylpiperidines. Reaction of *N*-benzyl-2,6-dicyanopiperidine anions with alkyl halides, and then decyanidation, gave 2-alkyl- and 2,6-dialkyl-*N*-benzylpiperidines.[16] N-Alkylation of C-substituted piperidines, often obtained by the reduction of pyridine derivatives, was an alternative route to 1,2,6-trisubstituted piperidines.[7,17] Other methods previously used have included catalytic or hydride reduction of substituted imines,[18] intramolecular amination of olefins in the presence of mercuric ion,[19] and catalytic reaction of butadiene with Schiff bases by $Pd(NO_3)_2Ph_3P$.[20] These methods are limited by the availability of the starting materials and reagents and sometimes by the severe conditions.

Scheme I



Relatively few *N*-(alkylamino)- and *N*-amido-substituted piperidines have been reported. They were previously prepared by the reduction of *N*-nitrosopiperidines with zinc dust or lithium aluminum hydride[21] to *N*-aminopiperidines, which were then subjected to reductive alkylation with aldehydes and sodium cyanoborohydride[22] or to acylation with an acyl or sulfonyl chloride.[23]

The present paper describes novel syntheses of a variety of *N*-alkyl-, *N*-aryl-, *N*-(alkylamino)-, *N*-(acylamino)-, and *N*-[(alkoxycarbonyl)amino]piperidines and their corresponding 2,6-disubstituted derivatives by double condensations of benzotriazole and glutaraldehyde with primary amines or unsymmetrically substituted hydrazines and subsequent reduction by sodium borohydride or reaction with Grignard reagents.

Recent publications from our laboratory have demonstrated the versatile synthetic utility of benzotriazole.[24–28]

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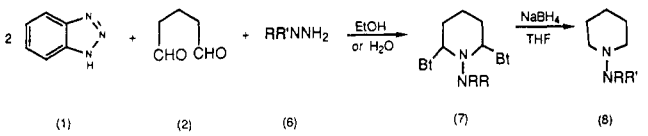
Scheme II



RR'N = PhNH, $(CH_3)_2N$, PhCONH, CH_3CONH, $NHCO_2CH_2CH_3$, $NHCO_2C(CH_3)_3$

The products formed from benzotriazole (1), amines (amides and hydrazines) and aldehydes, have been used as intermediates for the monoalkylation of aromatic and of heteroaromatic amines,[24] for the conversion of secondary aliphatic to tertiary aliphatic amines,[25] and for the alkylation of amides and thioamides[26] and of hydrazines.[27] We now demonstrate the utility of benzotriazole in forming N-substituted piperidines.

Results and Discussion

Glutaraldehyde and Amine Double Condensation with Benzotriazole. The preparation of condensation products from aldehydes, benzotriazole, and primary or secondary amines has usually been carried out in ethanolic solution[29] or by the Dean–Stark method.[25] Recently, we reported that benzotriazole reacts with various amines and formaldehyde or acetaldehyde in water at 20 °C, to afford the condensation products in high yield.[30] We have now found that this simple procedure can be easily applied to glutaraldehyde. Thus, benzotriazole (1) was first mixed with water, and the appropriate primary amine (3) and was stirred for 10 min at 20 °C. When aqueous glutaraldehyde (2) (25%) was slowly added, a solid began to form immediately. The essentially pure product was obtained after filtration and washing with water. A variety of both aromatic and aliphatic primary amines were employed; the 2,6-bis(benzotriazolyl) N-substituted piperidines (4) were produced in excellent yields (Scheme I). The results are listed in Table I.

When monosubstituted and unsymmetrically disubstituted hydrazines (phenylhydrazine (**6a**) and *N,N*-dimethylhydrazine (**6b**)) were used as the amine component, the *N*-(alkylamino)piperidine derivatives **7a** and **7b** were obtained. This method can also be applied to acylhydrazines (benzoylhydrazine (**6c**) and acetylhydrazine (**6d**)) and alkyl carbazates (ethyl carbazate (**6e**), *tert*-butyl carbazate (**6f**), and benzyl carbazate (**6g**)) to prepare the corresponding *N*-(acylamino)- or *N*-[(alkoxycarbonyl)amino]piperidine derivatives **7c–g**. For the three alkyl carbazates, ethanol was used as the solvent for the condensation instead of water. The yields of the expected 2,6-bis(benzotriazolyl)-N-(acylamino)- or -[(alkoxycarbonyl)amino]-substituted piperidines were excellent under mild conditions (Scheme II). The results are summarized in Table I. These double condensations can be carried out on a large scale, and the procedure is very simple.

The novel bis(benzotriazole)-substituted piperidines 4 and 7 prepared by double condensation were characterized by elemental analyses. Their spectra (both ^1H and ^{13}C NMR), however, are too complicated to be assigned due to the many possible isomers. *N*-(Aminoalkyl)benzotriazoles generally exist as two isomers[31] (i.e., 1-benzotriazolyl and 2-benzotriazolyl) together with the cis and trans forms of 2,6-disubstituted piperidines. This allows six possible forms of N-substituted 2,6-bis(benzotriazolyl)piperidines. Their ^1H and ^{13}C NMR spectra are correspondingly complex (one example is given in the Experimental Section).

Table II. Preparation of the N-Substituted Piperidines by Reduction

no.	N-substituent	yield (%)	mp (bp), °C/pressure, mm Hg: exptl	mp (bp), °C/pressure, mm Hg: lit.	ref
5a	$PhCH_2$	78	oil	49/0.1	13
5b	Ph	80	oil	99/0.2	13
5c	m-$CH_3C_6H_4$	68	oil	*a*	32
5d	n-C_4H_9	59	80/10	70/34	13
5e	i-C_3H_7	55	145–148/760	149–150/756	33
5f	2-pyridyl	64	oil[b]	138–139/4	34
8a	PhNH	87	oil	*c*	
8b	$(CH_3)N$	79	oil	*d*	22
8c	PhCONH	82	193–195	195–197	23
8d	CH_3CONH	84	105–106	107–108	23
8e	$CH_3CH_2O_2CNH$	88	79–80	*e*	
8f	$(CH_3)_3CO_2CNH$	85	80–81	*f*	
8g	$PhCH_2O_2CNH$	90	101–102	*g*	

[a] Hydrochloride: mp 202–204 °C (lit.[32] mp 206–206.5 °C). [b] Picrate: mp 134–136 °C (lit.[34] mp 136–137 °C). [c] Anal. Calcd for $C_{11}H_{16}N_2$: C, 75.00; H, 9.09; N, 16.91. Found: C, 74.67; H, 8.89; N, 16.98. [d] No boiling point was given. [e] Anal. Calcd for $C_8H_{16}N_2O_2$: C, 55.81; H, 9.30; N, 16.28. Found: C, 55.85; H, 9.45; N, 16.73. [f] Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 60.00; H, 10.00; N, 14.00. Found: C, 60.29; H, 9.72; N, 14.58. [g] Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.67; H, 7.69; N, 11.97. Found: C, 66.79; H, 7.85; N, 11.64.

Preparation of N-Substituted Piperidines by Reduction. We have already reported[24,25] that benzotriazole moieties in various reaction products of benzotriazole and aldehyde with an amine or an amide can be replaced smoothly by a hydrogen atom from sodium borohydride. We now demonstrate that 2,6-bis(benzotriazolyl) N-substituted piperidines 4 and 7, derived from the double condensations described above, are smoothly reduced to N-substituted piperidines 5 and 8 by sodium borohydride under mild conditions (Schemes I and II). The benzotriazole formed during the reduction is easily separated by extraction with alkali. Thus, our sequence, double condensation of benzotriazole, glutaraldehyde with amines or hydrazines, and then subsequent reduction by sodium borohydride, provides a novel synthetic route to piperidines with a variety of N-substituents.

The results listed in Table II indicate that the benzotriazole products 7, which contain an *N*-amino or *N*-amido group, are generally reduced even more easily and in higher yields than adducts 4, reflecting the facilitation of departure of the benzotriazole moiety by electron-donating α-effect of the *N*-amino group. Therefore, our present method is particularly suitable for the preparation of the *N*-(alkylamino)- and *N*-(acylamino)piperidines. The simple procedure and mild reaction conditions of both the double condensation and reduction afford excellent yields. The previously available methods usually need at least three steps from piperidine (nitrosation, reduction, and then alkylation or acylation) and give lower overall yields.

The N-substituted piperidines were characterized by their ^1H and ^{13}C NMR (Tables III and IV) and by com-

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Table III. ^{1}H NMR Spectral Data of the N-Substituted Piperidines ($CDCl_3$, δ)

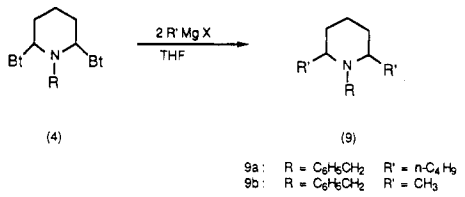
no.	2,6-CH_2 (4 H, t)	3,5-CH_2 (4 H, m)	4-CH_2 (2 H, m)	N-substituent
5a	2.46	1.70	1.55	7.42 (s, 5 H), 3.55 (s, 2 H)
5b	2.85	1.60	1.45	6.35–7.15 (m, 5 H)
5c	3.10	1.68	1.55	7.0–7.20 (m, 1 H), 6.40–6.80 (m, 3 H), 2.32 (s, 3 H, CH_3)
5d	2.50	*a*	*a*	2.40 (t), 1.70–1.40 (m, 10 H), 0.90 (t, J = 7 Hz, 3 H, CH_3)
5e	2.80	1.80	1.55	3.50 (m, 1 H), 1.00 (d, J = 7 Hz, 6 H, CH_3)
5f	3.60	1.80	1.58	8.30 (d, J = 5 Hz, 1 H), 7.52 (m, 1 H), 6.55–6.95 (m, 2 H)
8a	2.32	1.85	1.45	7.05–7.43 (m, 2 H), 6.60–7.00 (m, 3 H), 4.18 (s, 1 H, NH)
8b	2.75	1.68	1.40	2.58 (s, 6 H, CH_3)
8c	2.85	1.78	1.45	7.80 (d, J = 8 Hz, 2 H), 7.35–7.55 (m, 3 H), 7.03 (s, 1 H, NH)
8d	2.70	1.70	1.55	6.65 (s, 1 H, NH), 2.05 (s, 3 H, CH_3)
8e	2.78	1.70	1.40	5.95 (s, 1 H, NH), 4.15 (q, J = 6.5 Hz, 2 H, CH_2), 1.25 (t, 3 H, CH_3)
8f	2.70	1.68	1.40	5.60 (s, 1 H, NH), 1.45 (s, 9 H, t-Bu)
8g	2.73	1.68	1.38	7.34 (s, 5 H, C_6H_5), 5.78 (s, 1 H, NH), 5.12 (s, 2 H, CH_2)

[a] Overlapped by the N-substituent signal.

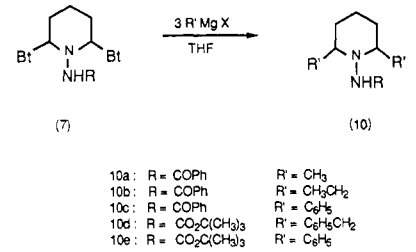
Table IV. ^{13}C NMR Spectral Data of the N-Substituted Piperidines ($CDCl_3$, δ)

no.	2,6-C	3,5-C	4-C	N substitutent
5a	54.2	25.7	24.2	138.4, 128.9, 127.8, 126.6, 63.6 (CH_2)
5b	53.7	25.4	23.9	141.1, 128.9, 128.3, 126.5
5c	50.5	26.3	24.5	138.1, 128.9, 128.5, 119.9, 117.2, 113.5, 21.8
5d	48.3	23.7	22.8	44.5 (CH_2), 25.1, 22.5, 17.5
5e	48.9	23.3	22.3	51.1 (CH), 18.1 (CH_3)
5f	44.7	23.9	23.1	158.1, 146.3, 135.7, 110.8, 105.5
8a	57.2	26.5	23.9	148.0, 128.8, 119.2, 113.5
8b	48.0	25.6	24.0	38.6 (CH_3)
8c	57.0	25.3	22.2	165.2 (CO), 134.0, 131.3, 128.4, 127.0
8d	55.1	25.7	22.6	168.0 (CO), 28.9 (CH_3)
8e	57.0	25.1	22.7	155.0 (CO), 60.3 (CH_2), 14.5 (CH_3)
8f	56.8	25.2	23.0	155.0 (CO), 80.0 (C), 28.5 (CH_3)
8g	57.4	25.3	23.0	155.2 (CO), 136.2, 128.4, 128.3, 128.0, 66.6 (CH_2)

Scheme III



Scheme IV



parison with data of authentic specimens (Table II).

Preparation of 1,2,6-Trisubstituted Piperidines by Grignard Reaction. Reaction of 2,6-bis(benzotriazolyl)-*N*-benzylpiperidine (**4a**) with 2.2 equiv of Grignard reagent in a mixture of tetrahydrofuran and diethyl ether gave the 2,6-dialkyl-*N*-benzylpiperidines (**9a** and **9b**) in moderate yields (Scheme III). This procedure should be potentially applicable to other benzotriazole adducts. The configurations of **9a** and **9b** were examined by ^{1}H NMR. In the trans isomer, the benzyl methylene protons are nonequivalent because the trans isomer (even when rapidly ring interconverting) is chiral and should be an AB system. By contrast, the corresponding equivalent CH_2 protons of the cis isomer will appear as a singlet.[16,17,35] In our reaction, only a singlet benzyl methylene signal at δ 3.70 is observed for both **9a** and **9b**. Accordingly, we consider the product to have the cis configuration.

Once again, similar to the reduction, the Grignard reactions of the *N*-amino- or *N*-amido-substituted benzotriazole adducts **7** are easier than those of the *N*-alkyl or *N*-aryl analogues **4**. Thus, reactions of compounds **7c**, **7e**, and **7f** with 3.3 equiv of Grignard reagents proceeded smoothly, leading to the corresponding symmetrical 2,6-disubstituted *N*-amidopiperidines **10a–f**, respectively. The yields were generally good, and no products of partial reaction were detected in these transformations (Scheme IV). The results, show that this two-step reaction sequence, double condensation and subsequent Grignard reaction, is widely applicable for the preparation of 2,6-disubstituted *N*-amido-substituted piperidines. Benzotriazole, the side product, was easily removed by washing with aqueous alkali in a simple workup.

The 1,2,6-trisubstituted piperidines **10** were characterized by their ^{1}H and ^{13}C NMR spectra and by analyses (Experimental Section). Examination of the NMR (particularly ^{13}C NMR) spectra of products **10** shows that only one of the two possible cis/trans isomers is isolated after recrystallization from aqueous ethanol. Presumably, the other isomer either is formed in smaller amount and remains in solution or is not produced at all, just as with the 2,6-dialkyl-*N*-benzylpiperidines.

Conclusions

The present work demonstrates the synthetic utility of benzotriazole in building up a piperidine ring, the ease of double addition of benzotriazole and glutaraldehyde with amines or hydrazines, and the ease by which the benzotriazole moiety is replaced by a hydrogen atom or by an alkyl group. This method possesses the advantages of simple procedure, mild conditions, easy availability of starting materials, and good yields. It is particularly useful in preparing *N*-(alkylamino)- and *N*-(acylamino)-

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piperidines and their relatively inaccessible 2,6-disubstituted derivatives.

Experimental Section

Melting points were determined on a Kofler hot-state apparatus and are uncorrected. The ^{1}H NMR (300-MHz) spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as the internal standard. ^{13}C NMR spectra were taken on Varian VXR-300 (75-MHz) and JEOL JNM FX-100 (25-MHz) instruments. Elemental analyses were carried out in this department. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone immediately before use.

Double Condensation. Typical Procedure. Benzotriazole (40 mmol), the appropriate amine or hydrazine (20 mmol), and distilled water (200 mL) were stirred vigorously for 10 min at 20 °C. Glutaraldehyde (20 mmol, 25% aqueous solution; Aldrich) was slowly added to the reaction mixture, and the stirring was continued for 1-2 h at room temperature. The products were filtered off, washed with water, and dried under vacuum.

For acylhydrazines and alkyl carbazates the procedure is similar, except ethanol was used as the solvent instead of water.

2,6-Bis(benzotriazolyl)-*N*-[(ethoxycarbonyl)amino]piperidine (7e): ^{1}H NMR (DMSO-d_6) δ 8.10-8.70 (m), 7.62-7.98 (m), 7.02 (m), 6.30 (m), 4.28 (d), 3.82 (m), 3.05-3.40 (m), 2.85 (d), 2.25-2.75 (m), 1.22-1.60 (m), 0.80-1.00 (m); ^{13}C NMR δ 155.5, 154.6, 145.6, 145.5, 132.3, 127.2, 126.8, 124.0, 123.8, 119.2, 118.9, 117.9, 117.7, 113.0, 111.3, 72.8, 60.0, 58.7, 29.8, 29.5, 20.7, 14.7, 14.5.

Reduction of Benzotriazole Adducts. Typical Procedure. Adduct **4** or **7** (5 mmol) suspended in THF (30 mL) was stirred at room temperature with sodium borohydride (0.6 g, 15 mmol) overnight. The reaction was quenched with water, and the product was extracted with hexane or diethyl ether. The extract was dried ($MgSO_4$), and the solvent evaporated under reduced pressure to obtain N-substituted piperidines. In some cases, the products were purified by column chromatography (silica gel) or recrystallization from aqueous ethanol.

Reaction with Grignard Reagents. Typical Procedure. To the Grignard reagent prepared from magnesium turnings (11 mmol for **4** and 16.5 mmol for **7**) and alkyl or aryl halide in diether ether (30 mL) was added the benzotriazole adduct (**4** or **7**) (5 mmol) in tetrahydrofuran dropwise under nitrogen. After the addition was complete, the reaction mixture was refluxed for 2 h, then poured in ice-water containing NH_4Cl, and extracted with diethyl ether. The organic layer was washed with NaOH (2 × 30 mL, 1 N) and water (2 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude products, which were purified by crystallization or by column chromatography.

2,6-Dibutyl-*N*-benzylpiperidine (9a): oil (45%); ^{1}H NMR ($CDCl_3$) δ 7.20-7.50 (m, 5 H), 3.70 (s, 2 H, $PhCH_2$), 2.85 (m, 2 H, CH), 1.00-1.80 (m, 18 H), 0.82 (t, 6 H, CH_3); ^{13}C NMR δ 143.5, 128.4, 127.7, 125.8, 63.2, 51.6, 34.6, 29.1, 27.8, 23.8, 22.9, 14.0. MS (m/e) for $C_{20}H_{33}N$, calcd 287.4874, found 287.4892.

2,6-Dimethyl-*N*-benzylpiperidine (9b): oil (48%); ^{1}H NMR ($CDCl_3$) δ 7.15-7.45 (m, 5 H), 3.72 (s, 2 H, $PhCH_2$), 2.90 (m, 2 H, CH), 1.75-1.45 (m, 6 H), 0.98 (d, 6 H, CH_3). MS (m/e) for $C_{14}H_{21}N$, calcd 203.1675, found 203.1651.

2,6-Dimethyl-*N*-(benzoylamino)piperidine (10a): 70%; mp 176-178 °C (lit.[23] mp 179-180 °C); ^{1}H NMR ($CDCl_3$) δ 7.75-7.25 (m, 5 H), 7.00 (s, 1 H, NH), 2.95 (m, 2 H, CH), 195-155 (m, 6 H), 1.00 (d, J = 6.5 Hz, 6 H, CH_3).

2,6-Diethyl-*N*-(benzoylamino)piperidine (10b): 72%; mp 152-154 °C; ^{1}H NMR ($CDCl_3$) δ 7.76-7.25 (m, 5 H), 7.00 (s, 1 H, NH), 2.90 (m, 2 H, CH), 1.95-1.05 (m, 10 H), 0.90 (t, 6 H, J = 6 Hz, CH_3); ^{13}C NMR δ 166.7 (CO), 135.1, 130.9, 128.7, 126.8, 66.5 (CH), 26.7, 25.9, 23.0, 17.0. Anal. Calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.75. Found: C, 74.11; H, 9.11; N, 10.48.

2,6-Diphenyl-*N*-(benzoylamino)piperidine (10c): 49%; mp 126-128 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2 H), 7.45-7.05 (m, 13 H), 4.57 (m, 2 H, CH), 2.00 (m, 4 H), 1.75 (m, 2 H); ^{13}C NMR δ 165.9 (CO), 141.2, 137.1, 130.9, 128.7, 128.0, 127.2, 126.5, 126.2, 36.8, 25.5, 23.7. Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.89; H, 6.74; N, 7.87. Found: C, 81.21; H, 6.43; N, 7.52.

2,6-Dibenzyl-*N*-[(*tert*-butoxycarbonyl)amino]piperidine (10d): 52%; mp 115-117 °C; ^{1}H NMR ($CDCl_3$) δ 7.40-7.15 (m, 10 H), 6.00 (s, 1 H, NH), 3.24 (m, 2 H, CH), 2.75 (d, J = 7 Hz, 4 H, CH_2), 2.05 (m, 4 H), 1.75 (m, 2 H), 1.25 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR 154.6, 137.1, 129.3, 127.5, 126.6, 78.0 (C), 60.2 (CH), 34.2 (CH_2), 28.3, 26.9, 18.5. Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.79; H, 8.42; N, 7.37. Found: C, 75.52; H, 8.71; N, 7.05.

2,6-Diphenyl-*N*-[(*tert*-butoxycarbonyl)amino]piperidine (10e): 75%; mp 168-170 °C; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 8 Hz, 4 H), 7.40-7.20 (m, 6 H), 5.95 (s, 1 H, NH), 4.22 (m, 2 H, CH), 2.00 (m, 4 H, CH_2), 1.78 (m, 2 H), 1.25 (s, 9 H); ^{13}C NMR δ 154.0 (CO), 140.8, 127.4, 127.3, 126.1, 78.3 (C), 62.4 (CH), 28.2, 27.4, 18.8. Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 75.00; H, 7.95; N, 7.95. Found: C, 74.60; H, 8.23; N, 7.91.

Registry No. 1, 95-14-7; **2**, 111-30-8; **3** (R = $PhCH_2$), 100-46-9; **3** (R = Ph), 62-53-3; **3** (R = *n*-$CH_3C_6H_4$), 108-44-1; **3** (R = *n*-C_4H_9), 109-73-9; **3** (R = *i*-C_3H_7), 75-31-0; **3** (R = 2-Py), 504-29-0; **4a**, 126216-53-3; **4b**, 126216-55-5; **4c**, 126216-57-7; **4d**, 126255-29-6; **4e**, 126216-59-9; **4f**, 126216-61-3; **5a**, 2905-56-8; **5b**, 4096-20-2; **5c**, 71982-24-6; **5d**, 4945-48-6; **5e**, 766-79-0; **5f**, 68654-52-4; **6a**, 100-63-0; **6b**, 57-14-7; **6c**, 613-94-5; **6d**, 1068-57-1; **6e**, 4114-31-2; **6f**, 870-46-2; **7a**, 126216-63-5; **7b**, 126216-65-7; **7c**, 126216-67-9; **7d**, 126216-69-1; **7e**, 126216-71-5; **7f**, 126216-73-7; **7g**, 126216-75-9; **8a**, 126216-44-2; **8b**, 49840-60-0; **8c**, 5454-07-9; **8d**, 31507-04-7; **8e**, 4663-84-7; **8f**, 126216-45-3; **8g**, 126216-46-4; **9a**, 126216-47-5; **9b**, 4209-63-6; **10a**, 100875-43-2; 10b, 126216-48-6; **10c**, 126216-49-7; **10d**, 126216-50-0; **10e**, 126216-51-1; $H_2NNHCOOCH_2Ph$, 5331-43-1.

A Novel Method for the Synthesis of Symmetrical Vicinal Tertiary and Secondary Diamines[1]

Alan R. Katritzky,*[§] Wei-Qiang Fan,[§] and Cong Fu[‡]

Department of Chemistry, University of Florida, Gainesville, Florida 32611, and Department of Chemistry, Hangzhou University, Hangzhou, Zhejiang 310028, People's Republic of China

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A variety of symmetrical vicinal tertiary and secondary diamines are readily prepared in good to excellent yields by either Grignard reaction or reduction of the glyoxal bisproducts with benzotriazole and secondary or primary amines.

Vicinal diamino compounds are of importance in medicinal chemistry,[2] in metal chelation,[3] and in polyaza macrocyclic and cryptate chemistry.[4] They are also useful synthetic intermediates, particularly in the formation of heterocyclic rings.[5]

[§] University of Florida.
[‡] Hangzhou University.

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