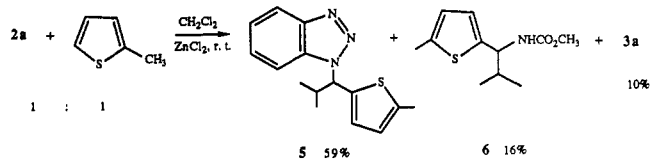
Table V. ^{1}H NMR Data of Symmetrical 1,1-Bis(heteroaryl)alkanes

compd	heteroaryl	5-methyl (S, 6H)	CH	R
3a	6.56 (d, J = 3.3 Hz, 2H), 6.50 (d, J = 3.6 Hz, 2H)	2.38	3.89 (d, J = 9.0 Hz)	2.17 (m, 1H, CHMe$_2$), 0.94 (d, J = 6.7 Hz, 6H)
3b	6.56 (d, J = 3.4 Hz, 2H), 6.54 (d, J = 3.3 Hz, 2H)	2.39	5.66 (s)	7.29 (d, J = 4.2 Hz, 2H), 7.25 (m, 3H)
3c	6.62 (d, J = 3.4 Hz, 2H), 6.54 (d, J = 3.3 Hz, 2H)	2.40	4.16 (s, 2H, CH$_2$)	-
4a	5.96 (s, 2H), 5.85 (s, 2H)	2.24	3.68 (d, J = 8.0 Hz)	2.29 (m, 1H, CHMe$_2$), 0.88 (d, J = 6.8 Hz, 6H)
4b	5.80 (s, 2H), 5.77 (s, 2H)	2.02	5.28 (s)	7.20–7.08 (m, 5H, Ph)

Table VI. ^{13}C NMR Data of Symmetrical 1,1-Bis(heteroaryl)alkanes

compd	heteroaryl	5-methyl	CH	R
3a	145.5, 137.7, 124.2, 124.1	15.2	50.5	35.4 (CH), 21.3 (CH$_3$)
3b	145.1, 138.9, 125.5, 124.4	15.4	47.8	143.6, 128.3, 128.2, 126.8
3c	141.1, 138.4, 124.7, 124.6	15.3	30.5	-
4a	153.2, 150.2, 106.7, 105.8	13.6	46.3	31.2 (CH), 20.7 (CH$_3$)
4b	152.7, 151.2, 108.1, 105.9	13.7	45.1	139.8, 128.3, 128.2, 126.8

Scheme III



utility superior to that of a halogen in many instances.[25] In particular, we have demonstrated the versatility of N-[α-(benzotriazolyl)alkyl]amides in organic synthesis. In common with other frequently used amidoalkylation reagents,[26] they are good precursors of the corresponding acyliminium cation because the benzotriazole anion is a good leaving group. N-[α-(Benzotriazolyl)alkyl]amides have been successfully used in the amidoalkylation of C–H acids[27] and of active aromatic compounds, including heteroaromatics,[28] and further in the synthesis of tri- and tetrasubstituted 4H-1,3-oxazines[29] and N-(α-alkoxyalkyl)-amides.[30] The benzotriazole derivatives of thiophenols have been used in the thioalkylation of aromatics and heteroaromatics.[31] In view of these previous results and the value of benzotriazole as a leaving group, we anticipated that the use of the α-benzotriazolylalkyl-substituted furans, thiophenes, pyrroles and indoles could provide an attractive alternate synthetic route to unsymmetrical 1,1-bis(heteroaryl)alkanes.

Results and Discussion

Condensation of Benzotriazole, Aldehydes, and Carbamates. The Mannich condensation of benzotriazole, an aldehyde, and a carbamate is known to give N-(1-benzotriazol-1-ylalkyl)carbamate in good yield.[32] Thus, the benzotriazole derivatives **2a–d** were prepared by the literature procedures in 84%, 78%, 74%, and 69% yields, respectively (see Table I and Scheme I). The ^{1}H and ^{13}C NMR spectra of these benzotriazolylalkyl carbamates (Tables II and III) indicated that they were all benzotriazol-1-yl isomers; furthermore, no isomerization to the 2-isomer was observed in dimethyl sulfoxide at room temperature. This behavior is similar to that found for N-(1-amidoalkyl)-benzotriazoles.[32]

Preparation of Symmetrical Bis(heteroaryl)alkanes. The methyl N-(α-benzotriazol-1-ylalkyl)carbamates **2a–c** reacted smoothly with an excess amount of 2-methylthiophene or 2-methylfuran in CH_2Cl_2 in the presence of zinc chloride at room temperature to give the corresponding symmetrical 1,1-bis(heteroaryl)alkanes. In this reaction, both benzotriazole and methoxycarbamoyl acted as leaving groups and each was replaced by a heterocycle. 1,1-Bis(5-methylthiophen-2-yl)alkanes **3a–c** and 1,1-bis(5-methylfur-2-yl)alkanes **4a** and **4b** were thus prepared in excellent yields (86–94%) (Table IV) as shown in Scheme II. As expected, the substitution occurred at the free α-positions of furan and thiophene as shown by the ^{1}H NMR spectra of the products.

Similarly, phenyl N-(α-benzotriazol-1-ylbenzyl)carbamate **2d** also gave α,α-bis(5-methylfur-2-yl)toluene (**4b**) in 65% yield on treatment with an excess of 2-methylfuran in CH_2Cl_2 with zinc bromide as the catalyst; however, the methyl carbamate is a better reagent in light of the yield and the ease of product purification.

The five symmetrical 1,1-bis(heterocyclyl)methanes (**3a–c**, **4a,b**) were all previously unknown and were characterized by elemental analyses or high-resolution mass spectrometry and by ^{1}H and ^{13}C NMR spectra (Tables V and VI).

Preparation of Unsymmetrical Bis(heteroaryl)alkanes. It is clear that the reactions shown in Scheme II proceed stepwise. The departure of either benzotriazole or the alkoxyamido group with the assistance of the Lewis acid led to the formation of a carbocation which was stabilized by the remaining carbamate or benzotriazole group (*via* the iminium ion). This carbocation then attacks the electron-rich heterocycle ring to give a monosubstituted intermediate. This process is repeated if excess of the heterocycle is present in the solution to produce the symmetrical bis-heteroaromatic methane. On the basis of this hypothesis, if only 1 equiv of a heterocycle were to be added, the monosubstituted intermediate should be formed. If it could be isolated it should react further with a different heterocyclic molecule and provide a useful synthetic route to unsymmetrical bis-heterocycles.

Indeed, when methyl N-(α-benzotriazol-1-ylalkyl)carbamate **2a** was treated with 1 equiv of 2-methylthiophene, a mixture was produced in which a benzotriazole derivative **5** predominated, accompanied by methyl N-[1-(thiophen-

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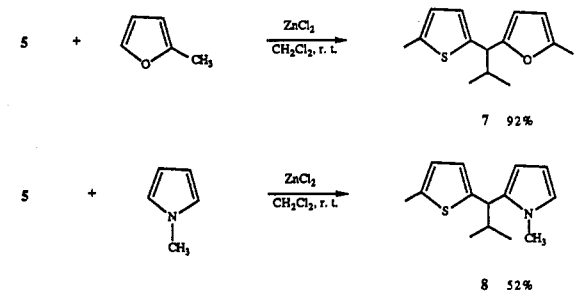
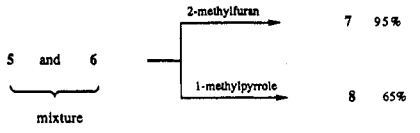
Table VII. Preparation of Unsymmetrical 1,1-Bis(heteroaryl)alkanes

compd	precursor	yield (%)	form	molecular formula	HRMS/analysis found C	found H	found N	required C	required H	required N
7	5	92	oil	$C_{14}H_{18}OS$	234.1071			234.1078		
	5 + 6	95								
8	5	52	oil	$C_{14}H_{19}NS$	233.1221			233.1238		
	5 + 6	65								
11	9 + 10	56	oil	$C_{14}H_{19}NO$	217.1472			217.1467		
13	12	84	oil	$C_{18}H_{21}NO$	267.1624			267.1623		
	one pot	45								
14	12	90	oil	$C_{18}H_{21}NS$	75.95	7.51	4.86	76.28	7.47	4.94

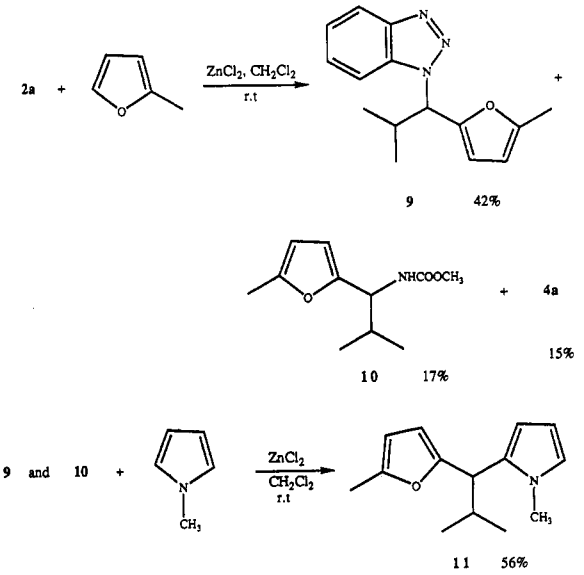
Scheme IV



Scheme V

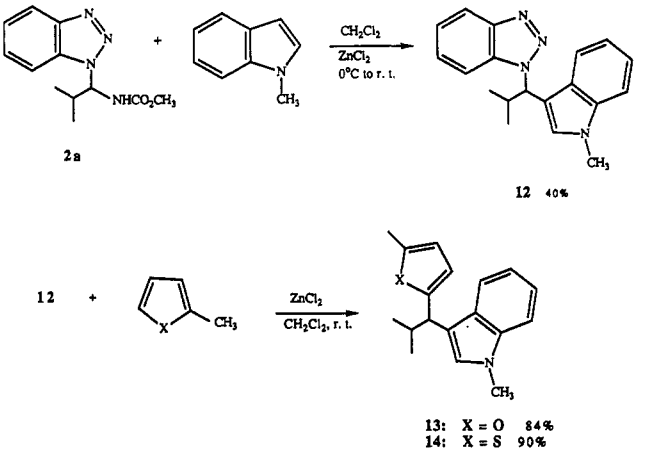


Scheme VI

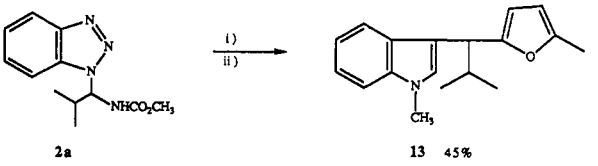


2-yl)-2-methylpropyl]carbamate (**6**), and the dithiophen-2-ylalkane **3a** (Scheme III). 2-Methyl-5-[1-(benzotriazol-1-yl)-2-methylpropyl]thiophene (**5**) could be purified either by column chromatography or by recrystallization from $CHCl_3$/hexane; it reacted readily with 2-methylfuran or with 1-methylpyrrole in CH_2Cl_2 in the presence of zinc chloride at room temperature to give the unsymmetrical bis(heteroaryl)alkanes **7** and **8** in 92% and 52% yields (Table VII), respectively (Scheme IV). In this reaction, the benzotriazole, activated by the thiophene ring, was readily replaced by a molecule of another heterocycle to afford the desired product. On the basis of the results illustrated in Scheme II, the methoxycarbamoyl group is also a suitable leaving group and can also be substituted

Scheme VII



Scheme VIII[a]



[a] Key: (i) 2-methylindole, $ZnCl_2$, CH_2Cl_2, rt; (ii) 2-methylfuran, $ZnCl_2$, CH_2Cl_2, rt.

by a heterocycle; thus, the mixture of compounds **5** and **6** on treatment with 2-methylfuran under the same conditions gave the expected product **7** in 95% yield and with 2-methylpyrrole afforded the compound **8** in 65% yield (Scheme V).

Similarly, when carbamate **2a** was treated with 1 equiv of 2-methylfuran, a mixture of the benzotriazole derivative **9**, methyl *N*-[1-(5-methylfur-2-yl)-2-methylpropyl]carbamate (**10**) and the difur-2-ylalkane **4a** was afforded. Treatment of the mixture of compounds **9** and **10** with 1-methylpyrrole in CH_2Cl_2 in the presence of zinc chloride at room temperature gave 1-(1-methylpyrrol-2-yl)-1-(5-methylfur-2-yl)-2-methylpropane (**11**) in 56% yield (Scheme VI).

The carbamate **2a** reacted with 1-methylindole in a 1:1 ratio in CH_2Cl_2 under the same conditions to give, after recrystallization from $CHCl_3$/hexane, 3-(α-benzotriazol-1-ylalkyl)indole **12** in 40% yield as the only isolated product. Intermediate **12** was then treated further with 2-methylthiophene or with 2-methylfuran at room temperature to afford 3-(α-fur-2-ylalkyl)- (**13**) or 3-(α-thiophen-2-ylalkyl)indole (**14**), respectively, in excellent yields (Scheme VII).

In practice, however, it is not necessary to isolate the intermediates, and unsymmetrical 1,1-bis(heteroaryl)-alkanes can be prepared from **2a** in an one-pot procedure.

Table VIII. ^{1}H NMR Data of Unsymmetrical 1,1-Bis(heteroaryl)alkanes

compd	Het_1	Het_2	CH	iPr
7	5-methylthiophen-2-yl 6.64 (d, J = 3.4 Hz, 1H), 6.53 (d, J = 3.3 Hz, 1H), 2.40 (s, 3H, CH_3)	5-methylfur-2-yl 5.95 (d, J = 3.1 Hz, 1H), 5.83 (d, J = 3.0 Hz, 1H), 2.24 (s, 3H, CH_3)	3.75 (d, J = 8.8 Hz)	2.22 (m, 1H, $CHMe_2$), 0.91 (d, J = 6.6 Hz, 3H, CH_3), 0.89 (d, J = 6.6 Hz, 3H, CH_3)
8	5-methylthiophen-2-yl 6.45 (d, J = 3.3 Hz, 1H), 6.41 (d, J = 3.0 Hz, 1H), 2.32 (s, 3H, CH_3)	1-methylpyrrol-2-yl 6.40 (m, 1H), 6.01 (d, J = 2.1 Hz, 2H), 3.38 (s, 3H, NCH_3)	3.60 (d, J = 9.0 Hz)	2.20 (m, 1H, $CHMe_2$), 0.97 (d, J = 6.7 Hz, 3H, CH_3), 0.86 (d, J = 6.7 Hz, 3H, CH_3)
11	5-methylfur-2-yl 5.81 (s, 2H), 2.23 (s, 3H, CH_3)	1-methylpyrrol-2-yl 6.49 (t, J = 2.3 Hz, 1H), 6.07 (d, J = 2.3 Hz, 2H), 3.48 (s, 3H, NCH_3)	3.60 (d, J = 8.5 Hz)	2.33 (m, 1H, $CHMe_2$), 0.94 (d, J = 6.6 Hz, 3H, CH_3), 0.89 (d, J = 6.8 Hz, 3H, CH_3)
13	5-methylfur-2-yl 5.95 (d, J = 2.9 Hz, 1H), 5.81 (d, J = 3.0 Hz, 1H), 2.24 (s, 3H, CH_3)	1-methylindol-3-yl 7.64 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.96 (s, 1H, H-2), 3.71 (s, 3H, NCH_3)	3.90 (d, J = 8.3 Hz)	2.44 (m, 1H, $CHMe_2$), 0.93 (d, J = 6.6 Hz, 3H, CH_3), 0.89 (d, J = 6.8 Hz, 3H, CH_3)
14	5-methylthiophen-2-yl 6.67 (d, J = 2.9 Hz, 1H), 6.49 (d, J = 2.7 Hz, 1H), 2.37 (s, 3H, CH_3)	1-methylindol-3-yl 7.62 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.93 (s, 1H, H-2), 3.69 (s, 3H, NCH_3)	4.09 (d, J = 8.5 Hz)	2.43 (m, 1H, $CHMe_2$), 0.98 (d, J = 6.7 Hz, 3H, CH_3), 0.95 (d, J = 6.8 Hz, 3H, CH_3)

Table IX. ^{13}C NMR Data of Unsymmetrical 1,1-Bis(heteroaryl)alkanes

compd	Het_1	Het_2	CH	iPr
7	5-methylthiophen-2-yl 143.0, 137.7, 124.5, 124.3, 15.2 (CH_3)	5-methylfur-2-yl 154.8, 150.4, 106.4, 105.8, 13.6 (CH_3)	48.3	33.6, 21.0, 20.9
8	5-methylthiophen-2-yl 145.3, 137.9, 124.0, 123.9, 15.3 (CH_3)	1-methylpyrrol-2-yl 135.2, 121.0, 106.4, 105.2, 22.1 (CH_3)	46.3	33.7, 21.2
11	5-methylfur-2-yl 154.4, 150.1, 106.5, 105.7, 13.7 (CH_3)	1-methylpyrrol-2-yl 132.9, 120.9, 106.4, 106.3, 21.6 (CH_3)	44.2	32.6, 21.0
13	5-methylfur-2-yl 155.9, 149.8, 106.0, 105.6, 13.8 (CH_3)	1-metheylindol-3-yl 136.7, 127.7, 126.7, 121.1, 119.5, 118.4, 115.2, 108.9, 21.4 (CH_3)	43.8	32.7, 21.3
14	5-methylthiophen-2-yl 146.9, 136.9, 124.0, 123.8, 15.4 (CH_3)	1-methylindol-3-yl 136.7, 127.6, 126.2, 121.3, 119.5, 118.5, 117.5, 109.0, 21.7 (CH_3)	45.9	34.2, 21.6

For example, 3-(α-fur-2-ylalkyl)indole **13** was prepared in 45% yield by reacting **2a** with successive molar equivalents of 1-methylindole and 2-methylfuran as illustrated in Scheme VIII.

The proposed structures of the new unsymmetrical bis(heteroaryl)alkanes **5**, **7**, **8**, and **11–14** were confirmed by NMR spectroscopy, elemental analyses, or high-resolution mass spectrometry.

For each of these compounds the α-C*H* group showed a large coupling (J = 8.3–10.4 Hz) to the β-C*H* in the ^{1}H spectra. Similarly, the α-carbons had a characteristic resonance between δ = 43.8 and δ = 66.1 ppm in the ^{13}C NMR spectra. The features of the NMR spectra of the benzotriazolyl-substituted intermediates **5** and **12** indicated that they were the benzotriazol-1-yl regioisomers. For those products containing either the 2-methylthiophene or 2-methylfuran moieties the two doublets ($J \approx$ 3.5 Hz) of the two *ortho*-heteroaromatic protons was strong evidence for α-substitution. Likewise, the 1H singlet at $\delta \approx$ 6.9 ppm in the spectrum of compounds **13** and **14** was indicative of substitution of the 3-position. Detailed assignments of the NMR spectra are listed in Tables VIII and IX and in the Experimental Section.

It is believed that the reaction of α-benzotriazolylalkyl-substituted heterocycles with thiophene, furan, or indole involved electrophilic attack by the carbocation **15** which was stabilized by the heteroatom as shown in Scheme IX. The benzotriazole anion is a good leaving group, and many benzotriazole derivatives exist as mobile equilibria between the 1- and 2-isomers *via* benzotriazolide–iminium ion pairs.[33,34] It follows that the carbocation **15** would be readily prepared in the presence of a Lewis acid.

The ease with which these carbocations can be formed and their smooth reactions with a variety of heteroaromatics has provided a new and significantly more convenient route to the corresponding bis(heteroaryl)alkanes. In addition to affording good to excellent yields, this novel methodology also incorporates the advantage of simple removal of the benzotriazole auxiliary from the product mixture by extraction with dilute base.

Experimental Section

Melting points were determined with a Kofler hot stage apparatus without correction. ^{1}H and ^{13}C NMR spectra were taken at 300 and 75 MHz, respectively. Tetramethylsilane was used as the internal standard for the ^{1}H NMR spectra, and the central line of $CDCl_3$ (δ = 77.0) or DMSO-d_6 (δ = 39.5) was referenced in ^{13}C NMR spectra.

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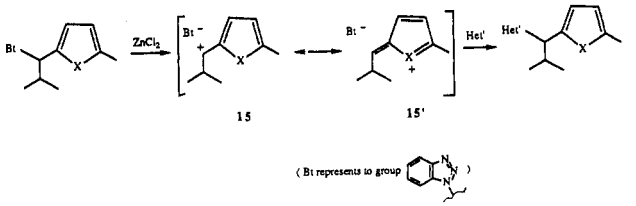
Scheme IX



***N*-(α-Benzotriazolylalkyl)carbamates 2a–d** were prepared by the literature procedure (Table I).[32]

General Procedure for the Preparation of Symmetrical 1,1-Bis(heteroaryl)alkanes 3a–c and 4a,b. A mixture of *N*-(α-benzotriazolylalkyl)carbamate **2** (10 mmol), the heterocycle (22 mmol), and zinc chloride (20 mmol) in dry methylene chloride (50 mmol) was stirred at room temperature overnight and poured into ice–water (50 mL). The water layer was extracted with chloroform (2 × 20 mL). The combined organic layer was washed with NaOH solution (30 mL, 2%) and water (30 mL) and dried over $MgSO_4$ (10 mg). The solvent was evaporated, and the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give the pure product (Table IV).

2-Methyl-5-[1-(benzotriazol-1-yl)-2-methylpropyl]thiophene (5). It was prepared by the procedure described above for symmetrical 1,1-bis(heteroaryl)alkanes from methyl *N*-[1-(benzotriazol-1-yl)-2-methylpropyl]carbamate (2.5 g, 10 mmol), 2-methylthiophene (0.98 g, 10 mmol), and zinc chloride (1.36 g, 10 mmol). It was purified by recrystallization from $CHCl_3$/hexane (yield 56%): mp 90–91 °C; ^1H NMR ($CDCl_3$) δ 7.94 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.34 (t, J = 8.1 Hz, 1H), 7.22 (t, J = 8.2 Hz, 1H), 6.85 (d, J = 3.4 Hz, 1H), 6.45 (d, J = 3.4 Hz, 1H), 5.50 (d, J = 10.4 Hz, 1H, CH), 2.96 (m, 1H, C*H*Me_2), 2.28 (s, 3H, CH_3), 1.01 (d, J = 6.6 Hz, 3H, CH_3), 0.72 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR δ 145.8, 140.3, 138.3, 132.4, 126.9, 126.6, 124.4, 123.6, 119.9, 109.7, 66.1 (CH), 33.7, 20.6, 20.5, 19.9. Anal. Calcd for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48. Found: C, 66.47; H, 6.38; N, 15.77. If the crude mixture was separated by column chromatography (silica gel, CH_2Cl_2), it gave **3a** (10%) and a mixture of **5** and **6** (59% and 16%, respectively).

1-Methyl-3-[1-benzotriazol-1-yl-2-methylpropyl]indole (12). 1-Methylindole (10 mmol) was added to a mixture of **2a** (10 mmol) and $ZnCl_2$ (15 mmol) in dry CH_2Cl_2 (40 mL) at 0 °C. The solution was stirred at 0 °C for 2 h and then allowed to warm to room temperature and stirring continued overnight. After workup as above, the product was purified by column chromatography (silica gel, CH_2Cl_2): mp 147–148 °C; ^1H NMR ($CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.38–7.22 (m, 3H), 7.18 (t, J = 6.7 Hz, 1H), 7.08 (t, J = 7.9 Hz, 1H), 5.80 (d, J = 10.2 Hz, 1H, CH), 3.72 (s, 3H, CH_3), 3.23 (m, 1H, C*H*Me_2), 1.12 (d, J = 6.6 Hz, 3H, CH_3), 0.85 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR δ 145.8, 136.6, 132.8, 127.6, 127.5, 126.9, 123.5, 121.9, 119.8, 119.6, 118.9, 111.9, 109.9, 109.3, 62.9, 32.9, 32.8, 20.9, 20.1. Anal. Calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 75.03; H, 6.67; N, 18.40.

General Preparation of Unsymmetrical 1,1-Bis(heteroaryl)alkanes 7, 8, 11, 13, and 14. Example: 1-(5-Methylfur-2-yl)-1-(5-methylthiophen-2-yl)-2-methylpropane (7). To a solution of either compound **5** (2.6 g, 10 mmol) or a mixture of **5** + **6** (10 mmol) in dry methylene chloride was added 2-methylfuran (0.82 g, 10 mmol) and zinc chloride (1.4 g, 10 mmol). The mixture was stirred at room temperature overnight and worked up as for the symmetrical derivatives. Using the same procedure, compound **8** was prepared from 1-methylpyrrole and either **5** or the mixture **5** + **6**; similarly, compound **11** was prepared from 2-methylfuran and **9** + **10**, compound **13** from 2-methylfuran and **12**, and compound **14** from 2-methylthiophene and **12** (Table VII).

One-Pot Preparation of 1-(5-Methylfur-2-yl)-1-(1-methylindol-3-yl)-2-methylpropane (13). A mixture of **2a** (10 mmol), 1-methylindole (10 mmol), and zinc chloride (10 mmol) in dry methylene chloride was stirred at room temperature overnight. 2-Methylfuran (10 mmol) and zinc chloride (10 mmol) were added, and the solution was stirred at the same temperature for an additional 10 h. The workup procedure was as described above.

Supplementary Material Available: Carbon and proton NMR spectra for **3b**, **3c**, **4a**, **4b**, **7**, **8**, **11**, and **13** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis of ω-(Bromomethyl)bipyridines and Related ω-(Bromomethyl)pyridinoheteroaromatics: Useful Functional Tools for Ligands in Host Molecules

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Pyridines and 2,2'-bipyridines have been employed as useful ligands in molecular recognition chemistries. Halomethyl-substituted bipyridine or oligopyridine derivatives were required for the assembly of bipyridine or oligopyridine units with a supporting mother functional part in artificial biofunctional molecules. A series of ω-(bromomethyl)bipyridines and related ω-(bromomethyl)-pyridinoheteroaromatic compounds (types I–III) were synthesized in this paper. Preparation of oligopyridines and pyridinoheteroaromatic compounds have been carried out by either intermolecular ligand coupling of alkyl heteroaryl sulfoxide with pyridyllithium or intramolecular ligand coupling of pyridyl heteroaryl sulfoxide with methylmagnesium bromide for the type I compounds. The type II and III compounds were synthesized by addition of pyridyllithium to pyridinecarboxaldehyde. The ω-bromo group was introduced by radical bromination reaction of methylpyridyl group using NBS and BPO (dibenzoyl peroxide) or bromination of ω-(hydroxymethyl)pyridine using a combination of CBr_4 and Ph_3P.

Introduction

Bipyridines have been recognized as useful ligands in the fields of inorganic, organometallic, and coordination chemistries. The abilities in coordination with metals or metal cations may be due to the two nitrogen atoms placed in the two adjacent pyridine rings, which may donate their electrons to metals or metal cations in making stable and/or unstable complexes.[1] Bipyridines have been used very commonly as a ligand in a wide range of metal complexes, while recently higher oligopyridines including 2,2':6'2''-terpyridine have also been employed as useful ligands.[2] These heterocycles, such as bipyridines, oligopyridines, and pyridinoheteroaromatic compounds, have been receiving increased attention as a part of artificial functional molecules,[3] in which each pyridine unit plays an important role in catching a metal ion in collaboration with another functional part in the molecule.

A dynamic interaction of metal ions or organoionic compounds associated with functionalized crown ethers bearing pyridine units is one of the recent developments in molecular recognition chemistry.[4] We have been interested in such functionalized crown ethers and designed new pyridinoheteroaromatic double-armed crown ethers, whose structures are described below. These armed crown ethers possess multiple donor heteroatoms in the crown ring as well as on the pyridinoheteroaromatic rings. They are expected to recognize an appropriate guest metal or metal ion specifically. In fact, some of the armed crown ethers have exhibited unique characteristic properties in extraction and transportation experiments of metal ions[5] or of certain amino acid ester salts.[6] For the preparation of such a functional molecules containing pyridinoheteroaromatic units, it is required to assemble a supporting part, e.g., azacrown ethers, and a pyridinoheteroaromatic part.[3,6] In order to couple these two parts, the pyridinoheteroaromatic compound should have an appropriate functional group, such as the ω-(halomethyl) group, on the terminal pyridine unit.

This paper deals with the facile preparation of new (bromomethyl)bipyridines and related (bromomethyl)-pyridinoheteroaromatic compounds categorized into type I (1–5), type II (6 and 7), and type III (8) compounds.

Results and Discussion

Synthesis of ω-(Bromomethyl)bipyridine and Related Heterocycles: Preparation of Type I Compounds. Although metal-catalyzed coupling reaction of bromopyridine was used for symmetrical bipyridine synthesis, no reliable direct coupling reaction of one pyridine ring with other pyridino or quinolino heteromatic rings has been seen in the literature for the preparation of unsymmetrical pyridinoheterocycles.[7] For such preparations, the classic Krohnke method has been employed[8] but is limited in applications to unsymmetrical oligopyridyl or pyridinoheteroaromatic compounds. The ligand coupling reaction of sulfoxide recently developed by Oae[9] is useful in the synthesis of complex heteroaromatic com-

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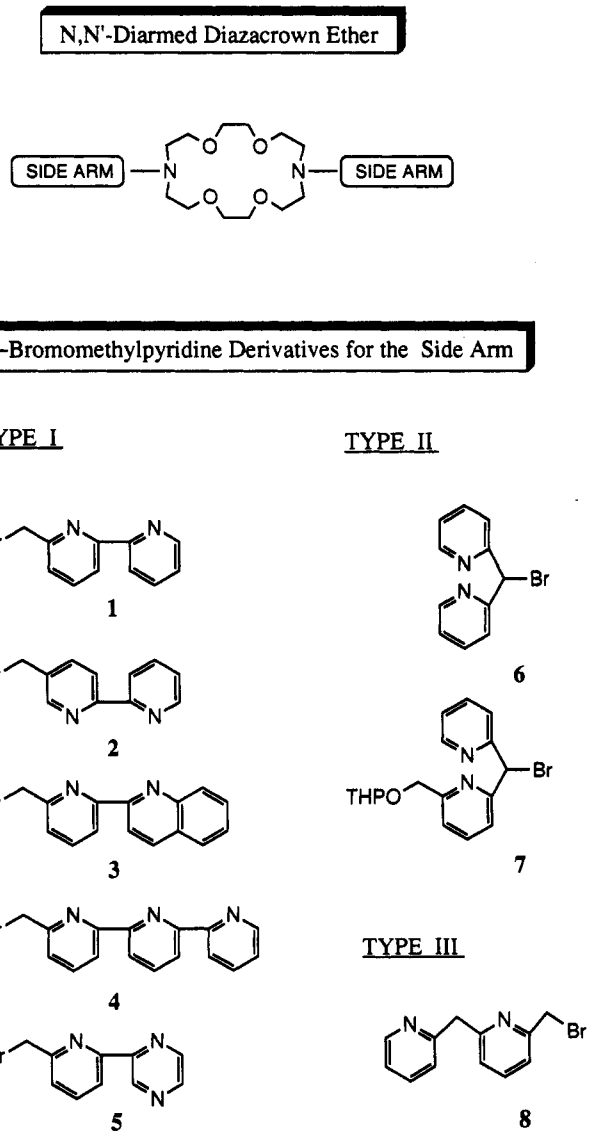
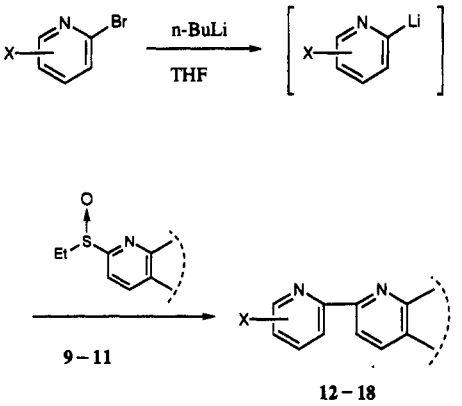


Figure 1.

pounds. The reaction is quite valuable in the construction of a variety of symmetrical and unsymmetrical oligopyridines as well as other heterocyclic compounds. In fact, we have reported preparation of various oligopyridines including 2,2′-bipyridines and 2,2′:6′,6″-terpyridines in moderate yields by the reaction of ethyl pyridyl or ethyl bipyridyl sulfoxide and 2-pyridyllithium.[10] The typical coupling reaction between one pyridine ring and another pyridinoheteroaromatic ring is shown in Scheme I. *Ipso*-substitution of the ethylsulfinyl group by the 2-pyridyl group occurred in the reaction. Lithium–halogen exchange of 2-bromopyridine with n-BuLi was conducted in either THF or ether at −78 to −30 °C to give 2-pyridyllithium, but the best result was obtained in a mixed solvent system of ether/THF/hexane (2:1:1). The lithiopyridine was quenched with ethyl 2-pyridyl sulfoxide (**9**),[11] ethyl 2-quinolyl sulfoxide (**10**),[12] and 6-(2,2′-bipyridyl) ethyl

Scheme I



sulfoxide (**11**) to give oligopyridines **12**–**18**[13–15] in 35–80% yields. The results and the structures are shown in Table I.

Introduction of the ω-(bromomethyl) group at the 2-position in the pyridine ring was commonly achieved by a simple radical bromination of the corresponding 2-methylpyridine derivatives.[16] However, radical halogenation accompanied polyhalogenation as a major problem;[17] for example, Lehn and co-workers reported synthesis of 6,6′-bis(bromomethyl)-2,2′-bipyridine in 32% yield along with mono- and polybrominated products.[18] In fact, polybromination became considerably serious in the cases of the substrates **13**–**15**. When 1–2 equiv of *N*-bromosuccinimide (NBS) and a catalytic amount of BPO (dibenzoyl peroxide) in refluxing benzene was employed in the reaction, three kinds of products were obtained including the desired monobrominated compound, dibrominated compound, and the starting material. These are separable on column chromatography, but the separation is not efficient in the practical sense. We used an excess of NBS (3–5 equiv) and stopped the reaction when the starting material was consumed. The reaction mixture contained only mono and dibromide at this stage (Table II). After rough purification, chemoselective reduction of the dibromomethyl group with DIBALH at −78 °C in methylene chloride by monitoring on TLC gave monobromide exclusively. Pure monobromides **1**–**4** were obtained in 45–60% yields from **12**–**15**, respectively. The results are indicated in Table II.

Alternatively, ω-(bromomethyl)pyridyl derivatives **1**, **3**, and **4** were obtained from 2-bromopyridyl derivatives **16**–**18** *via* 2-(hydroxymethyl)pyridyl intermediates **19**–**21**, shown in Scheme III. Generation of 6-(2,2′-bipyridyl)-lithium by lithium–halogen exchange of 6-bromo-2,2′-bipyridine (**16**) with n-BuLi and subsequent treatment with an excess of *N*,*N*-dimethylformamide at −78 °C gave 6-formyl-2,2′-bipyridine, which was reduced with $NaBH_4$ in one pot at 0 °C in methanol to lead to 6-(hydroxymethyl)-2,2′-bipyridine (**19**) in 63% yield. 6-Hydroxy-2,2′-bipy-

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