Convenient Novel Syntheses of 1,1-Bis(heteroaryl)alkanes

Alan R. Katritzky,* Linghong Xie, and Wei-Qiang Fan

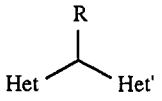
Department of Chemistry, University of Florida, Gainesville, Florida 32611-2046

Received January 8, 1993

A variety of symmetrical 1,1-bis(heteroaryl)alkanes are prepared in excellent yields from the reaction of *N*-(α-benzotriazolylalkyl)carbamate **2** (itself easily available from the condensation of benzotriazole, an aldehyde, and an alkyl carbamate) with an excess of 2-methylthiophene or 2-methylfuran. When methyl *N*-(α-benzotriazolylalkyl)carbamate **2a** is treated with 1 equiv of a heterocycle, the benzotriazolylalkyl-substituted heterocycle is formed. These intermediates react further with other heterocycles to give unsymmetrical 1,1-bis(heteroaryl)alkanes in good yields under mild conditions.

Bis(heterocyclyl)methanes are of interest to the food industry as they are present as natural compounds in food and beverage items such as licorice;[1] for example, difuryl- and dithienylalkanes are flavor agents in coffee.[2,3] Many bis(heterocyclyl)methanes are also of importance in dyestuff chemistry as they are readily oxidized to the corresponding cyanine dyes.[4] Furthermore, 1,1-bis(heterocyclyl)alkanes are important intermediates in the synthesis of various heterocyclic macromolecules;[5] for example, dipyrromethanes have been widely used as synthetic intermediates in total syntheses of porphyrins.[6] The action of dichloromethyl alkyl ether and tin(IV) chloride on (diheteroaryl)methanes is a useful route to polycyclic heteroaromatic systems.[7]

Several synthetic routes to bis(heteroaryl)methanes **1** are known, but none is both general and convenient.



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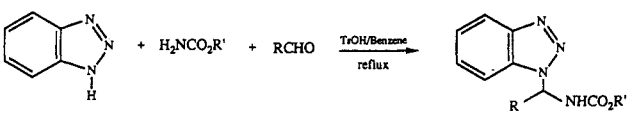
Many are only applicable to the preparation of symmetrical bis(heterocyclyl)methanes. Di-2-furylmethane has been prepared by the reduction of di-2-furyl ketone[8] and also by the interaction of 2-chloromercurifuran and furfuryl chloride.[9] Reduction of the corresponding (diheteroaryl)-methanols also gives (diheteroaryl)methanes.[7] However, most of these methods are limited to the preparation of compounds in which an unsubstituted methylene group links the two heteroaromatic rings (**1**, Het = Het′, R = H), and their utility is further restricted by the inaccessibility of suitable diheteroaryl ketones and methanols. The reaction of a (heteroaryl)lithium with a (heteroaryl)methyl chloride[7] gives a (diheteroaryl)methane, but it requires severe conditions. Thiophenes, furans, and pyrroles with free α-positions are susceptible to electrophilic attack by aldehydes or ketones, and this is a well-known route to (diheteroaryl)methane derivatives.[10] However, this type of condensation generally requires a strong inorganic acid catalyst, such as 75% H_2SO_4[11] or hydrochloric acid.[12] These experimental conditions present the drawback of causing resinification[13] and degradation[14] of the heterocyclic rings of substrates and products. An improvement of this condensation using macroporous ion-exchange resins as catalyst[15] is satisfactory for the preparation of difuryl and dithienyl derivatives.

Unsymmetrical bis(heterocyclyl)methanes are far less explored; in fact, some structurally simple bis(heterocyclyl)methanes, especially with two different heterocyclic ring systems, are not known. The few synthetic procedures available have only led to a limited number of compounds of this class. Perhaps the most important is the reduction of the corresponding alcohols. Sodium borohydride–trifluoroacetic acid reduction of (diheteroaryl)methanols gives (diheteroaryl)methanes in 32–76% yield;[16] however, use of this reduction method has been confined to the methylene derivatives (**1**, R = H). Moreover, the prep-

Table I. Preparation of *N*-(1-Benzotriazolylalkyl)carbamates

compd	R	R′	mp (°C)	yield (%)	molecular formula	found (required) C	H	N
2a	iPr	Me	118–120	84	$C_{12}H_{16}N_4O_2$	58.05 (58.05)	6.53 (6.50)	22.44 (22.57)
2b	Ph	Me	123–124	78	$C_{15}H_{14}N_4O_2$	63.87 (63.82)	5.03 (5.00)	19.90 (19.85)
2c	H	Me	155–156	74	$C_9H_{10}N_4O_2$	52.38 (52.42)	4.86 (4.89)	27.45 (27.17)
2d	Ph	Ph	162–164	69	$C_{20}H_{16}N_4O_2$	69.59 (69.76)	4.73 (4.68)	16.27 (16.27)

Scheme I



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2a: R = i-Pr, R'=Me 84%
2b: R = Ph, R'=Me 78%
2c: R=H, R'=Me 74%
2d: R=R'=Ph 69%

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Table II. ^{1}H NMR Data of *N*-(1-Benzotriazolylalkyl)carbamates

	benzotriazole (each H)						
compd	H4	H5	H6	H7	NH (1H)	OMe (3H, s)	other signals
2a	8.10 (d, J = 9.0 Hz)	7.43 (t, J = 7.5 Hz)	7.59 (t, J = 7.6 Hz)	8.08 (d, J = 8.4 Hz)	8.91 (d, J = 8.7 Hz)	5.36	6.15 (t, J = 9.0 Hz, 1H, CH), 2.71 (m, 1H, CHMe$_2$), 1.18 (d, J = 6.6 Hz, 3H, CH_3), 0.57 (d, J = 6.6 Hz, 3H, CH_3)
2b	8.12 (d, J = 8.3 Hz)	7.41 (m, overlapped by PhH)	7.56 (t, J = 7.9 Hz)	7.95 (d, J = 8.4 Hz)	9.47 (d, J = 8.5 Hz)	3.64	7.86 (d, J = 8.6 Hz, 1H, CH), 7.41 (m, 5H, Ph-H)
2c	8.03 (d, J = 8.3 Hz)	7.39 (t, J = 7.6 Hz)	7.52 (t, J = 6.9 Hz)	7.94 (d, J = 8.3 Hz)	6.55 (s)	3.71	6.06 (d, J = 6.8 Hz, 2H, CH_2)
2d	8.12 (d, J = 8.3 Hz)	7.44 (m, overlapped by PhH)	7.44 (m, overlapped by PhH)	7.86 (m, overlapped by PhH)	10.0 (d, J = 8.5 Hz)		7.86 (m, 2H, Ph-H), 7.44 (m, 7H, Ph-H), 7.18 (m, 1H, CH), 7.18 (m, 1H, Ph-H)

Table III. ^{13}C NMR Data of *N*-(1-Benzotriazolylalkyl)carbamates

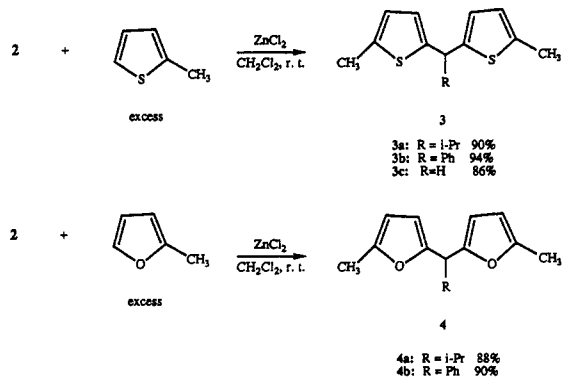
	benzotriazole							
compd	C_4	C_5	C_6	C_7	C_{3a}	C_{7a}	CO	other carbons
2a	119.2	127.2	124.0	111.1	145.2	132.0	156.3	71.9 (CH), 51.7 (OCH_3), 31.4 (CH), 19.1 (CH_3), 18.2 (CH_3)
2b	119.2	127.4	124.1	111.1	145.3	131.5	156.1	135.9 (Ph), 128.7 (Ph), 128.5 (Ph), 126.5 (Ph), 68.2 (CH), 52.1 (OCH_3)
2c	119.4	127.9	124.4	110.8	146.0	132.4	156.8	53.5 (CH_2), 52.8 (OCH_3)
2d	119.4	127.7	124.3	111.2	145.5	131.7	154.2	150.5 (Ph), 135.7 (Ph), 129.4 (Ph), 129.0 (Ph), 128.7 (Ph), 126.9 (Ph), 125.5 (Ph), 121.7 (Ph), 68.1 (CH)

Table IV. Preparation of Symmetrical 1,1-Bis(heteroaryl)alkanes

						HRMS/analysis			
						found		required	
compd	heteroaryl	R	mp (°C)	yield (%)	molecular form	C	H	C	H
3a	5-methylthiophen-2-yl	iPr	45–46	90	$C_{14}H_{18}S_2$	67.07	7.26	67.15	7.25
3b	5-methylthiophen-2-yl	Ph	oil	94	$C_{17}H_{16}S_2$	284.0717		284.0694	
3c	5-methylthiophen-2-yl	H	oil	86	$C_{11}H_{12}S_2$	208.0370		208.0380	
4a	5-methylfur-2-yl	iPr	oil	88	$C_{14}H_{18}O_2$	218.1304		218.1307	
4b	5-methylfur-2-yl	Ph	oil	90 (65)[a]	$C_{17}H_{16}O_2$	252.1167		252.1150	

[a] From phenyl *N*-(1-benzotriazol-1-yl)carbamate (**2d**).

Scheme II



aration of (diheteroaryl)methanols usually requires lithiation under severe conditions. Alkyl α-methoxy- and α-hydroxypyrrylacetates interact with *N*-methylindole in the presence of Lewis acids to give diarylacetic esters,[17] but the starting materials are not easily available and this method is not general. Condensation of an α-(acetoxymethyl)pyrrole with an appropriately substituted pyrrole with a free α-position in acetic acid,[18] in the presence of toluene *p*-sulfonic acid[19] or Montmorillonite clay,[20] produces unsymmetrical dipyrrolylmethanes. However, the isolation of the product from tarry reaction byproducts is tedious.[20] Symmetrical pyrrolylmethanes are often formed as byproducts by self-condensation of the (acetoxymethyl)-pyrrole,[21,22] and the method is useful only for the fully substituted dipyrrolylmethanes in order to avoid polymerization. Unsymmetrical difurylmethanes are obtained from the reaction of [(5-methylfuryl)phosphinyl]carbinol and furan followed by a Wittig–Horner reaction,[23] but this method is not general. Alkylation of furan, thiophene, and pyrrole with furfuryl alcohol in the presence of the strongly acidic Amberlyst 15 cation-exchange resin affords the respective (2-furylheteroaryl)methanes;[24] however, the yields are low and purification is difficult (preparative GLC) because of the formation of difurylmethyl ether and resinous byproducts.

We now report a general and convenient method for the preparation of both symmetrical and unsymmetrical bis-heterocyclic alkanes using benzotriazole as a synthetic auxiliary. Recent work in our laboratory has shown the utility of the benzotriazole anion as a leaving group, with

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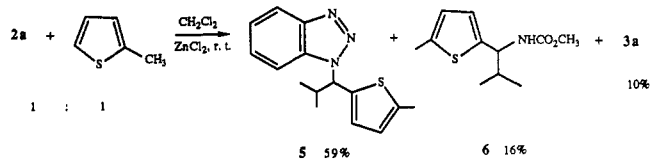
Table V. ^{1}H NMR Data of Symmetrical 1,1-Bis(heteroaryl)alkanes

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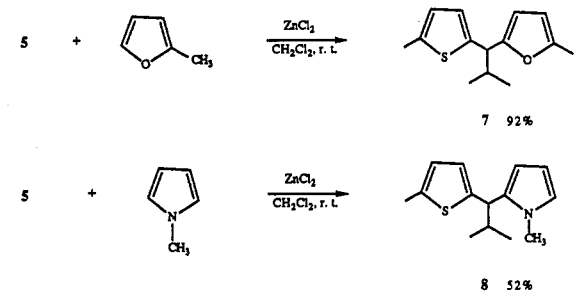
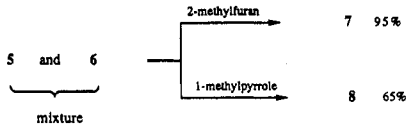
Table VII. Preparation of Unsymmetrical 1,1-Bis(heteroaryl)alkanes

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

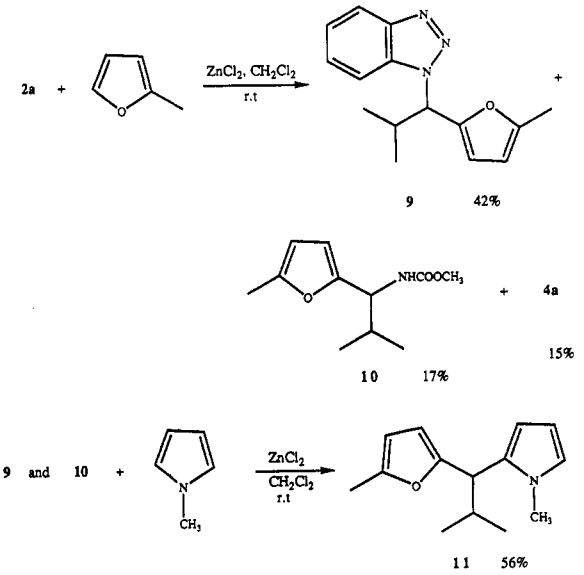
Scheme IV



Scheme V

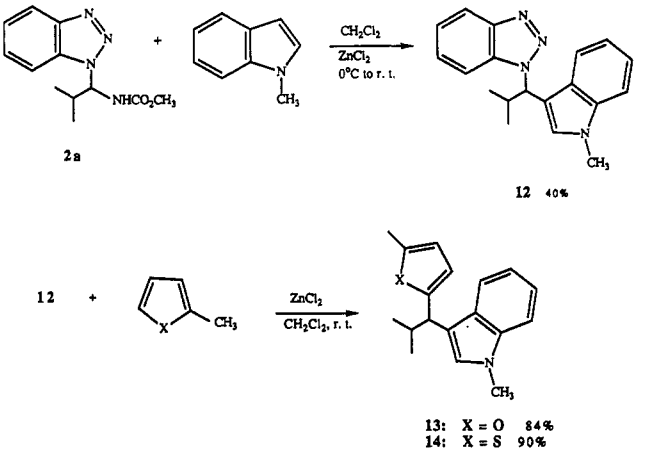


Scheme VI

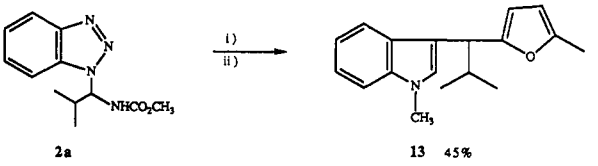


2-yl)-2-methylpropyl]carbamate (**6**), and the dithiophen-2-ylalkane **3a** (Scheme III). 2-Methyl-5-[1-(benzotriazol-1-yl)-2-methylpropyl]thiophene (**5**) could be purified either by column chromatography or by recrystallization from $CHCl_3$/hexane; it reacted readily with 2-methylfuran or with 1-methylpyrrole 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.

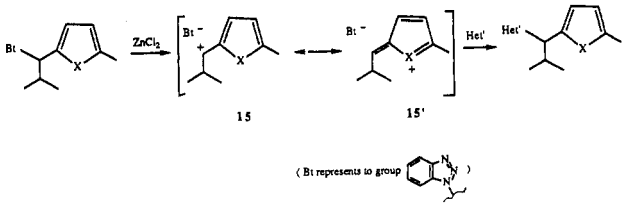
Experimental Section

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.

(33) Katritzky, A. R.; Yannakopoulou, K.; Kuzmierkiewicz, W.; Aurrecoechea, J. M.; Palenik, G. J.; Koziol, A. E.; Szczesniak, M.; Skarjune, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2673.

(34) Katritzky, A. R.; Yannakopoulou, K. *Heterocycles* **1989**, *28*, 1121.

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.