1,4-Disubstituted and 1,4,5-Trisubstituted 2-[(Benzotriazol-1-yl)methyl]pyrroles as Versatile Synthetic Intermediates

Alan R. Katritzky* and Jianqing Li

Center for Heterocyclic compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200

Received October 24, 1995[⊗]

The CH_2Bt substituent, unlike previously used CH_2X substituents, enables (i) the synthetic elaboration of pyrroles with unsubstituted ring positions and (ii) electrophilic as well as nucleophilic substitutions to give pyrroles of type pyrrolyl-2-CHENu. Thus, 1,4-disubstituted (**7**) and 1,4,5-trisubstituted 2-[(benzotriazol-1-yl)methyl]pyrroles (**15**) were easily prepared from the reaction of 5-(benzotriazol-1-yl)-1,2-epoxy-3-pentynes **4** or **14** with primary amines in *i*-PrOH. The 2-(benzotriazol-1-yl)methyl side chains of compounds **7** and **15** were elaborated by nucleophilic substitution and also by initial alkylation followed by replacement or elimination of the benzotriazolyl moiety to afford a variety of 1,2,4-trisubstituted (**6**, **8**−**9**, **11**−**13**) and 1,2,4,5-tetrasubstituted pyrroles (**18**, **20**−**22**).

Introduction

Novel syntheses of pyrroles are of current interest.[1−4] 2-(Functionalized-methyl)pyrroles **1** and 2-alkenylpyrroles **2** are versatile intermediates in organic synthesis, especially for natural products.[1,4−10] Owing to their great synthetic importance, a range of pyrrole intermediates containing 2-CH_2X groups have been studied[1,2,6−11] in which X has varied widely: halogen, hydroxy, alkoxy, alkylthio, amino, cyano, *etc.*, as shown in Chart 1. Among these, halogenomethyl groups have been most frequently employed *inter alia* for the preparation of other CH_2X groups by nucleophilic substitutions.[9,11] However, the use of CH_2-halogen groups is limited to the pyrroles in which all the ring carbons are substituted, otherwise difficulties arise from their instability and sensitivity to rapid intermolecular nucleophilic attack to form polymers.[9,12−15] Quaternary ammonium groups of type $CH_2N^+R_3$ can also be displaced by nucleophiles.[7,11] The other functional groups CH_2X mentioned above are less susceptible to nucleophilic substitution. Base-assisted alkylation has only been achieved for 2-(cyanomethyl)- and 2-[(alkoxycarbonyl)methyl]pyrroles.[9] In particular, neither alkylation and subsequent nucleophilic substitution of CH_2X to give CHENu nor the elimination to form 2-alkenylpyrroles **2** (another class of important compounds) has previously been reported.

Chart 1

1 **2**

X = halogen, OH, OR, SR, NH_2, NR_2, $^+NR_3$, CN, carboxylate, $^+PPh_3$, N_3

We now report a convenient method for the synthesis of 1,4-di- and 1,4,5-trisubstituted 2-[(benzotriazol-1-yl)-methyl]pyrroles **7** and **15** and the transformations of their side-chain 2-(benzotriazol-1-yl)methyl groups by nucleophilic substitution, or by initial alkylation followed by replacement or elimination of the benzotriazolyl group, which allows the preparation of elaborated pyrroles unsubstituted either at the 3- and 5-positions or at the 3-position.

Results and Discussion

Preparation of 1,4-Di- and 1,4,5-Trisubstituted 2-[(Benzotriazol-1-yl)methyl]pyrroles 7 and 15. We have recently described the synthesis of substituted furans by base-catalyzed cyclization of alkynyloxiranes **4** and **14** which were easily prepared from the reaction of 1-propargylbenzotriazole (**3**) with α-bromo ketones.[16] The epoxides of types **4** and **14** have now been further utilized for the preparation of pyrrole systems: refluxing **4** and **14** with primary amines in *i*-PrOH gave 1,4-disubstituted (**7**, Scheme 1) and 1,4,5-trisubstituted 2-[(benzotriazol-1-yl)methyl]pyrroles (**15**, Scheme 3) in good yields. A similar reaction was previously reported for other alkynyloxiranes without using solvents;[17] however, under these reaction conditions our alkynyloxiranes **4** or **14** reacted with amines to give furans as major products.[16] Presumably 1,4-elimination of **4** and **14**

[⊗] Abstract published in *Advance ACS Abstracts,* February 15, 1996.

(1) Kinoshita, H.; Tanaka, S.; Inomata, K. *Chem. Lett.* **1989**, 1107.
(2) Kinoshita, H.; Tanaka, S.; Nishimori, N.; Dejima, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2660.
(3) Danks, T. N.; Velo-Rego, D. *Tetrahedron Lett.* **1994**, *35*, 9443.
(4) Kagabu, S.; Tsuji, H.; Kawai, I.; Ozeki, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 341.
(5) Frydman, B.; Reil, S.; Valasinas, A.; Frydman, R. B.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 2738.
(6) Gonsalves, A. M. d'A. R.; Kenner, G. W.; Smith, K. M. *Tetrahedron Lett.* **1972**, 2203.
(7) Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389.
(8) Wee, A. G. H.; Shu, A. Y. L.; Bunnenberg, E.; Djerassi, C. *J. Org. Chem.* **1984**, *49*, 3327.
(9) Jones, R. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 270.
(10) Jackson, A. H.; Pandey, R. K.; Rao, K. R. N.; Roberts, E. *Tetrahedron Lett.* **1985**, *26*, 793.
(11) Jones, R. A.; Bean, G. P. In *The Chemistry of Pyrroles*; Academic Press: London, 1977; p 355.
(12) Baltazzi, E.; Krimen, L. I. *Chem. Rev.* **1963**, *63*, 511.
(13) Treibs, A.; Grimm, D. *Liebigs Ann. Chem.* **1978**, 2024.
(14) Angelini, G.; Illuminati, G.; Monaci, A.; Sleiter, G.; Speranza, M. *J. Am. Chem. Soc.* **1980**, *102*, 1377.
(15) Angelini, G.; Giancaspro, C.; Illuminati, G.; Sleiter, G. *J. Org. Chem.* **1980**, *45*, 1786.
(16) Katritzky, A. R.; Li, J. *J. Org. Chem.* **1995**, *60*, 638.
(17) Perveev, F. Ya.; Kuznetsova, E. M. *Zh. Obshch. Khim.* **1958**, *28*, 2360; *Chem. Abstr.* **1959**, *52*, 3767g.

0022-3263/96/1961-1624$12.00/0

Scheme 1

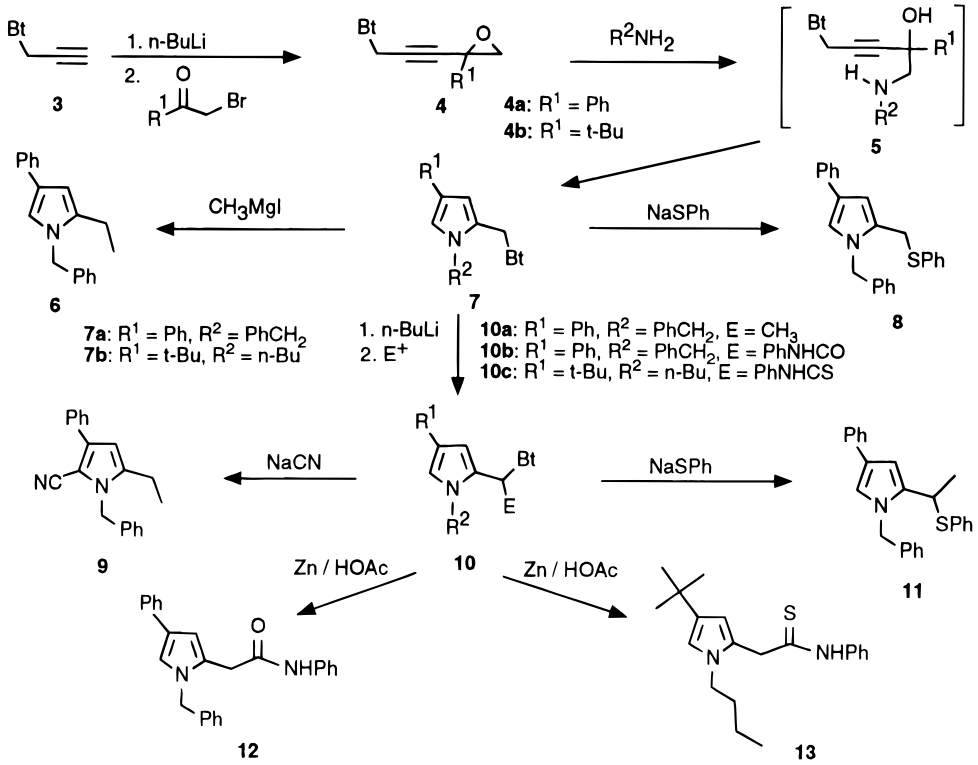


Table 1. Reactions of 1,4-Di- and 1,4,5-Trisubstituted-2-[(benzotriazol-1-yl)alkyl]pyrroles 7, 10, 15, 17, and 19

entry	substr	reagent	solvent	temp (°C)	time (h)	product	yield (%)	mp (°C)	mol form	found (calcd) C	H	N
1	**7a**	CH_3MgI	toluene	reflux	6	**6**	87	oil	$C_{19}H_{19}N$	87.13 (87.31)	7.38 (7.33)	5.40 (5.36)
2	**7a**	NaSPh	DMF	150	24	**8**	65	99−100	$C_{24}H_{21}NS$	80.87 (81.09)	5.96 (5.96)	3.89 (3.94)
3	**10a**	NaCN	DMF	reflux	12	**9**	52	65−66	$C_{20}H_{18}N_2$	84.22 (83.87)	6.57 (6.34)	9.48 (9.79)
4	**10a**	NaSPh	DMF	150	10	**11**	79	96−97	$C_{25}H_{23}NS$	81.03 (81.27)	6.43 (6.28)	3.78 (3.79)
5	**10b**	Zn/HOAc	THF	reflux	12	**12**	73	156−157	$C_{25}H_{22}N_2O$	82.05 (81.93)	6.05 (6.06)	7.67 (7.65)
6	**10c**	Zn/HOAc	THF	reflux	12	**13**	90	oil	$C_{20}H_{28}N_2S$	73.35 (73.13)	8.80 (8.60)	8.52 (8.53)
7	**15a**	PhMgBr	toluene	reflux	3	**18**	91	oil	$C_{17}H_{23}N$	84.93 (84.58)	9.82 (9.61)	5.76 (5.81)
8	**17**	K_2CO_3	DMF	120	12	**20**	57	oil	$C_{19}H_{25}NO$	80.68 (80.51)	9.11 (8.90)	4.87 (4.94)
9	**17**	$NaCH(COOEt)_2$	DMF	140	12	**21**	76	oil	$C_{26}H_{37}NO_5$	70.05 (70.40)	8.51 (8.41)	3.40 (3.16)
10	**19**	NaCN	DMF	reflux	12	**22**	54[a]	oil	$C_{19}H_{22}N_2$	81.65 (81.96)	8.12 (7.97)	10.20 (10.07)

[a] Yield was based on compound **15**.

predominated instead of nucleophilic attack at the epoxide ring. Therefore, for the present reactions, solvent is essential and the yields were better with *i*-PrOH than with DMF.

Elaboration of the 2-(Benzotriazol-1-yl)methyl Side Chain. Work in our laboratory has demonstrated that benzotriazole is a good synthetic auxiliary.[18] The good leaving ability and the anion-stabilizing capability are two of its advantageous features which have been well recognized. Thus, compound **7a** readily underwent nucleophilic substitution with methylmagnesium iodide and sodium thiophenolate to give the corresponding products **6** and **8**, respectively, in good yields (Scheme 1). The electron-rich pyrrole nucleus assisted the reaction by stabilizing the transient carbocations.

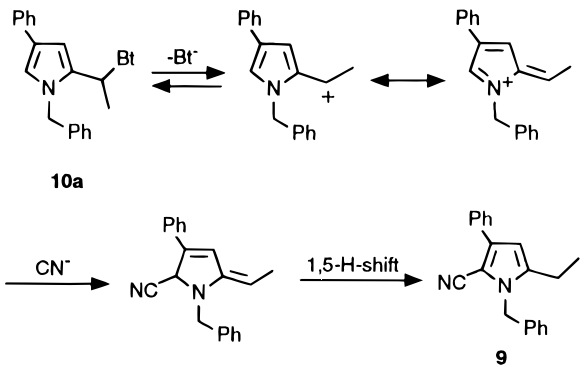
It is well-known that pyrroles smoothly undergo 2-lithiation; however, in the case of compounds **7**, lithiation occurred regiospecifically at the carbon attached to the benzotriazolyl group due to the electron-withdrawing ability of the benzotriazolyl moiety. Accordingly, the 3,5-unsubstituted 2-[(benzotriazol-1-yl)methyl]pyrroles **7a**,**b** were easily converted by lithiation and subsequent quenching with the appropriate electrophile such as methyl iodide, phenyl isocyanate, and phenyl isothiocyanate to give the corresponding products **10a**−**c** in high yields. The nucleophilic substitution of the benzotriazolyl group in the substituted derivatives **10a** with sodium thiophenolate was much faster than that of compound **7a** due to the stabilization of the intermediate carbocation by the directly attached methyl group, and thus the reaction gave the product **11** in higher yield (Table 1). Compounds of type **10b** and **10c** readily underwent reductive elimination of benzotriazole when they were treated with zinc in the presence of acetic acid to generate pyrrol-2-ylacetanilide **12** and -thioacetanilide **13**, respectively.

Interestingly, the reaction of **10a** with sodium cyanide in DMF gave the S_N' type of "abnormal" product **9** in 52% yield; this result supports the S_N1 pathway described by Maryanoff and co-workers.[19] The proposed mechanism is illustrated in Scheme 2. We were unable to isolate the other possible isomers by column chromatography.

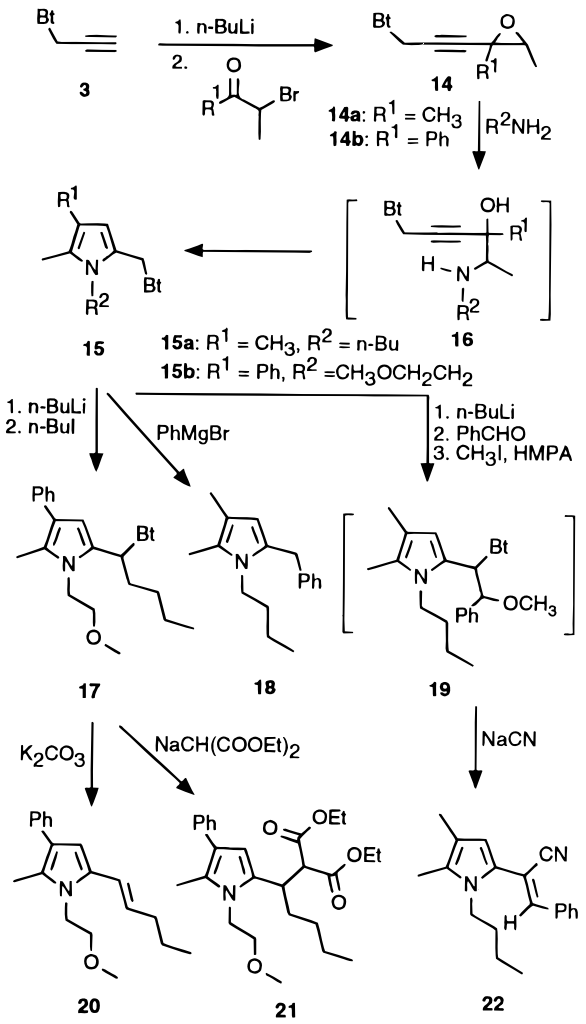
(18) Katritzky, A. R.; Wu, H.; Xie, L.; Rachwal, S.; Rachwal, B.; Jiang, J.; Zhang, G.; Lang, H. *Synthesis* **1995**, 1315.

(19) Carson, J. R.; Hortenstine, J. T.; Maryanoff, B. E.; Molinari, A. J. *J. Org. Chem.* **1977**, *42*, 1096.

Scheme 2



Scheme 3



Similarly, the benzotriazolyl group of the 3-unsubstituted 2-[(benzotriazol-1-yl)methyl]pyrrole **15a** was readily replaced by phenylmagnesium bromide to give compound **18** (Scheme 3). Compound **15b** was treated with 1.1 equiv of *n*-BuLi at −78 °C for 1 h followed by reaction with *n*-butyl iodide to yield product **17**. Upon treatment with potassium carbonate in DMF under reflux, compound **17** underwent base-catalyzed elimination of benzotriazole to form alkenylpyrrole **20** which is stable and can be isolated by column chromatography as a 3:1 *E*:*Z* mixture. When compound **17** was refluxed with sodium malonate in DMF for 12 h, the substituted product of type **21** was obtained in 76% yield. Treatment of compound **15a** with 1.1 equiv of *n*-butyllithium followed by quenching of the reaction with benzaldehyde generated the alkylated anion which was trapped by addition of methyl iodide and HMPA to give the intermediate **19**. **19** was treated with sodium cyanide without purification to undergo initially nucleophilic substitution of the benzotriazolyl group by cyanide and then elimination of methanol to afford vinylpyrrole **22**.

In conclusion, 1,4-di- and 1,4,5-trisubstituted 2-[(benzotriazol-1-yl)methyl]pyrroles **7** and **15**, derived from the reaction of alkynyloxiranes **4** and **14** with α-bromo ketones, readily underwent nucleophilic replacement of the benzotriazolyl group with Grignard reagents and sodium thiophenolate. Compounds **7** and **15** were alkylated *via* lithiation and subsequent quenching with the appropriate electrophile to give intermediates **10**, **17** and **19** in which the benzotriazolyl group could either be replaced by a variety of nucleophiles or eliminated in the presence of a base. Compounds **10b**,**c** were reduced by zinc in acetic acid to afford the corresponding products **12** and **13**. The above benzotriazole-mediated transformations should find general use in synthesis; the transformation should be applicable to any alkyl or aryl substituents at C-4 and C-5.

Experimental Section

General. Melting points were determined on a hot-stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer using TMS as the internal standard and $CDCl_3$ as the solvent. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument with the solvent peak ($CDCl_3$) as the reference. Elemental analyses (C, H, N) were carried out within the department.

1-Propargylbenzotriazole (**3**) was prepared according to the procedure described in the literature.[20] All α-bromo ketones were purchased neat and used without further purification. The preparation of compound **14a** was reported in a previous paper.[16]

General Procedure for the Preparation of Epoxides 4a,b and 14b. To a stirred solution of 1-propargylbenzotriazole (**3**) (1.57 g, 10 mmol) in THF (50 mL) was added at −78 °C a solution of *n*-BuLi (5.5 mL, 11 mmol, 2.0 M in cyclohexane). The mixture was stirred at this temperature for 1 h, and α-bromo ketone (indicated in Schemes 1 and 3) (10 mmol) in THF (5 mL) was added slowly. After stirring at −78 °C for 5 to 8 h, diethyl ether (100 mL) and water (100 mL) were added and the organic phase was separated, washed with a saturated NH_4Cl solution (3 × 100 mL), and dried ($MgSO_4$). Evaporation of the solvent gave the crude product which was purified by column chromatography using EtOAc/hexane (1:4) as the eluent to afford the pure product.

5-(Benzotriazol-1-yl)-1,2-epoxy-2-phenyl-3-pentyne (4a): yellow oil, yield 76%; ^{1}H NMR δ 8.05 (d, J = 8.4 Hz, 1 H), 7.69 (d, J = 8.3 Hz, 1 H), 7.46−7.52 (m, 1 H), 7.28−7.41 (m, 6 H), 5.55 (s, 2 H), 3.35 (d, J = 6.0 Hz, 1 H), 2.97 (d, J = 6.0 Hz, 1 H); ^{13}C NMR δ 145.9, 135.9, 132.2, 128.3, 128.2 (2C), 127.5, 125.1 (2C), 124.0, 119.8, 109.5, 84.1, 75.9, 58.6, 50.5, 38.0. Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.15; H, 4.76; N, 15.27. Found: C, 74.03; H, 4.77; N, 15.37.

5-(Benzotriazol-1-yl)-1,2-epoxy-2-*tert*-butyl-3-pentyne (4b): white solid, yield 76%; mp 49−50 °C; ^{1}H NMR δ 8.09 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 8.3 Hz, 1 H), 7.51−7.57 (m, 1 H), 7.30−7.44 (m, 1 H), 5.51 (s, 2 H), 2.93 (d, J = 5.2 Hz, 1 H), 2.86 (d, J = 5.2 Hz, 1 H), 0.97 (s, 9 H); ^{13}C NMR δ 146.2, 132.4, 127.6, 124.1, 120.1, 109.6, 85.4, 74.5, 57.1, 51.5, 38.2, 33.2, 25.4. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.55; H, 6.72; N, 16.47. Found: C, 70.22; H, 6.69; N, 16.77.

5-(Benzotriazol-1-yl)-1,2-epoxy-1-methyl-2-phenyl-3-pentyne (14b): yellow oil, yield 67%; ^{1}H NMR δ 8.05 (d, J =

(20) Katritzky, A. R.; Li, J.; Malhotra, N. *Liebigs Ann. Chem.* **1992**, 843.

8.3 Hz, 1 H), 7.66 (d, J = 8.3 Hz, 1 H), 7.46−7.51 (m, 1 H), 7.30−7.42 (m, 6 H), 5.51 (s, 2 H), 3.53 (q, J = 5.4 Hz, 1 H), 1.01 (d, J = 5.5 Hz, 3 H); ^{13}C NMR δ 146.0, 134.3, 132.3, 128.1, 128.0 (2C), 127.5, 126.7 (2C), 124.0, 119.9, 109.6, 86.2, 74.5, 62.7, 55.2, 38.1, 12.9. Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.71; H, 5.23; N, 14.53. Found: C, 74.37; H, 5.24; N, 14.73.

General Procedure for the Preparation of 1,4-Di- and 1,4,5-Trisubstituted 2-[(Benzotriazol-1-yl)methyl]pyrroles 7 and 15. A solution of epoxide **4** or **14** (20 mmol) and the appropriate primary amine (40 mmol) (see Schemes 1 and 3) in *i*-PrOH (100 mL) was refluxed for 24−48 h. After cooling, the solvent was removed under reduced pressure to give an oil was purified by short column chromatography using EtOAc/hexane as the eluent to afford the corresponding product.

***N*-Benzyl-2-[(benzotriazol-1-yl)methyl]-4-phenylpyrrole (7a)**: white needles, yield 82%; mp 157−158 °C; ^{1}H NMR δ 7.97 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 7.2 Hz, 2 H), 7.16−7.44 (m, 9 H), 7.02 (d, J = 1.9 Hz, 1 H), 6.90−6.93 (m, 2 H), 6.76 (d, J = 1.9 Hz, 1 H), 5.74 (s, 2 H), 5.08 (s, 2 H); ^{13}C NMR δ 146.3, 136.8, 135.0, 132.7, 128.7 (2C), 128.6 (2C), 127.6, 127.3, 126.3 (2C), 125.8, 125.6, 124.9 (2C), 124.0, 123.9, 120.9, 119.9, 110.1, 109.8, 50.9, 44.9. Anal. Calcd for $C_{24}H_{20}N_4$: C, 79.08; H, 5.53; N, 15.38. Found: C, 78.81; H, 5.46; N, 15.35.

***N*-*n*-Butyl-2-[(benzotriazol-1-yl)methyl]-4-*tert*-butylpyrrole (7b)**: white solid, yield 63%; mp 69−70 °C; ^{1}H NMR δ 8.01 (d, J = 8.2 Hz, 1 H), 7.26−7.37 (m, 3 H), 6.44 (d, J = 2.0 Hz, 1 H), 6.31 (d, J = 2.0 Hz, 1 H), 5.79 (s, 2 H), 3.73 (t, J = 7.4 Hz, 2 H), 1.02−1.40 (m, 4 H), 1.25 (s, 9 H), 0.79 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 146.2, 134.5, 132.7, 127.0, 123.6, 123.2, 119.6, 117.7, 110.2, 108.8, 46.3, 45.1, 33.2, 31.6, 30.3, 19.7, 13.5. Anal. Calcd for $C_{19}H_{26}N_4$: C, 73.50; H, 8.45; N, 18.06. Found: C, 73.86; H, 8.57; N, 18.16.

***N*-*n*-Butyl-2-[(benzotriazol-1-yl)methyl]-4,5-dimethylpyrrole (15a)**: white solid, yield 62%; mp 86−87 °C; ^{1}H NMR δ 7.99 (d, J = 8.2 Hz, 1 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.24−7.37 (m, 2 H), 6.17 (s, 1 H), 5.76 (s, 2 H), 3.74 (t, J = 7.8 Hz, 2 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 1.10−1.28 (m, 4 H), 0.81 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 146.1, 132.5, 126.9, 126.6, 123.5, 121.3, 119.4, 113.8, 111.5, 110.3, 45.1, 43.7, 32.9, 19.7, 13.5, 10.9, 9.5. Anal. Calcd for $C_{17}H_{22}N_4$: C, 72.29; H, 7.86; N, 19.85. Found: C, 72.60; H, 7.88; N, 19.92.

***N*-(2-Methoxyethyl)-2-[(benzotriazol-1-yl)methyl]-4-phenyl-5-methylpyrrole (15b)**: brown oil, yield 57%; ^{1}H NMR δ 8.02 (d, J = 8.3 Hz, 1 H), 7.53 (d, J = 8.2 Hz, 1 H), 7.26−7.38 (m, 6 H), 7.17−7.21 (m, 1 H), 6.46 (s, 1 H), 5.91 (s, 2 H), 4.09 (t, J = 5.4 Hz, 2 H), 3.33 (t, J = 5.4 Hz, 2 H), 3.21 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR δ 146.2, 136.6, 132.7, 128.2 (2C), 127.9 (2C), 127.1, 127.0, 125.2, 123.9, 123.7, 121.4, 119.6, 110.5, 110.2, 71.8, 58.9, 45.0, 43.8, 10.9. Anal. Calcd for $C_{21}H_{22}N_4O$: C, 72.79; H, 6.40; N, 16.18. Found: C, 73.12; H, 6.57; N, 16.11.

Alkylation of 1,4-Di- and 1,4,5-Trisubstituted-2-[(benzotriazol-1-yl)methyl]pyrroles 7 and 15. To a solution of compound **7** or **15** (5 mmol) in THF (80 mL) at −78 °C was added a solution of *n*-BuLi (5.5 mmol, 2.75 mL, 2.0 M in cyclohexane). The reaction mixture was stirred at −78 °C for 1 h, and then a solution of an appropriate electrophile (5 mmol) in THF (5 mL) such as methyl iodide, phenyl isocyanate, phenyl isothiocyanate, and butyl iodide was added. After the reaction solution was stirred for another hour, water (100 mL) was poured into the solution and the mixture was extracted with ethyl acetate (100 mL), washed with water (3 × 100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product which was purified either by recrystallization or column chromatography to afford the corresponding product in pure state.

***N*-Benzyl-2-[1-(benzotriazol-1-yl)ethyl]-4-phenylpyrrole (10a)**: recrystallized from EtOAc/hexane (1:3), white plates, yield 98%; mp 142−143 °C; ^{1}H NMR δ 7.91−7.95 (m, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.37 (t, J = 7.6 Hz, 2 H), 7.18−7.27 (m, 4 H), 7.08−7.13 (m, 3 H), 7.02 (d, J = 1.6 Hz, 1 H), 6.93 (d, J = 1.6 Hz, 1 H), 6.76−6.80 (m, 2 H), 6.24 (q, J = 7.1 Hz, 1 H), 4.83 (d, J = 16.2 Hz, 1 H), 4.69 (d, J = 16.2 Hz, 1 H), 2.01 (d, J = 7.1 Hz, 3 H); ^{13}C NMR δ 148.2, 138.1, 136.7, 133.1, 131.4, 130.4 (2C), 130.1 (2C), 129.1, 128.8, 127.8 (2C), 127.4, 126.5 (2C), 125.4, 125.3, 122.5, 121.5, 112.4, 109.1, 54.1, 52.3, 21.2. Anal. Calcd for $C_{25}H_{22}N_4$: C, 79.34; H, 5.86; N, 14.80. Found: C, 79.34; H, 5.94; N, 14.43.

α-(*N*-Benzyl-4-phenylpyrrol-2-yl)-α-(benzotriazol-1-yl)-acetanilide (10b): recrystallized from EtOAc/hexane (1:3), white solid, yield 87%; mp 104−105 °C; ^{1}H NMR δ 9.70 (s, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.34−7.44 (m, 5 H), 6.92−7.24 (m, 10 H), 6.58−6.74 (m, 4 H), 6.33 (d, J = 7.2 Hz, 2 H), 4.68 (d, J = 16.2 Hz, 1 H), 4.54 (d, J = 16.2 Hz, 1 H); ^{13}C NMR δ 164.5, 145.8, 137.4, 135.8, 134.5, 133.2, 128.9 (2C), 128.6 (2C), 128.1 (2C), 127.8, 127.1, 125.9, 125.7 (2C), 124.8 (2C), 124.7, 124.2, 121.5, 119.9 (2C), 119.0, 112.2, 109.9, 60.6, 50.4. Anal. Calcd for $C_{31}H_{25}N_5O$: C, 77.00; H, 5.21; N, 14.49. Found: C, 77.29; H, 5.24; N, 14.43.

α-(*N*-*n*-Butyl-4-*tert*-butylpyrrol-2-yl)-α-(benzotriazol-1-yl)thioacetanilide (10c): recrystallized from Et_2O, white solid, yield 94%; mp 147−148 °C; ^{1}H NMR δ 10.00 (s, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 7.72 (d, J = 7.7 Hz, 2 H), 7.33−7.48 (m, 5 H), 7.22−7.27 (m, 2 H), 6.54 (d, J = 2.0 Hz, 1 H), 6.48 (d, J = 2.0 Hz, 1 H), 3.59−3.73 (m, 2 H), 1.42−1.54 (m, 1 H), 1.03−1.36 (m, 12 H), 0.72 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 192.8, 145.7, 138.2, 135.3, 133.4, 128.9 (2C), 128.0, 127.0, 124.3, 123.4, 122.9 (2C), 119.9, 119.0, 110.5, 108.5, 68.4, 46.8, 33.1, 31.7, 30.5, 19.8, 13.5. Anal. Calcd for $C_{26}H_{31}N_5S$: C, 70.08; H, 7.01; N, 15.72. Found: C, 70.21; H, 7.08; N, 15.83.

***N*-(2-Methoxyethyl)-2-[α-(benzotriazol-1-yl)pentyl]-4-phenyl-5-methylpyrrole (17)**: purified by column chromatography using EtOAc/hexane (1:4), yellow oil, yield 77%; ^{1}H NMR δ 8.00−8.04 (m, 1 H), 7.50−7.55 (m, 1 H), 7.19−7.44 (m, 7 H), 6.67 (s, 1 H), 6.41 (t, J = 7.6 Hz, 1 H), 3.94−4.04 (m, 1 H), 3.80−3.89 (m, 1 H), 3.15−3.20 (m, 2 H), 3.17 (s, 3 H), 2.45−2.53 (m, 2 H), 2.26 (s, 3 H), 1.26−1.47 (m, 3 H), 1.08−1.18 (m, 1 H), 0.86 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 146.7, 136.9, 131.6, 128.2 (2C), 128.0 (2C), 127.4, 126.9, 126.7, 125.3, 123.7, 121.4, 119.8, 111.1, 108.4, 71.7, 58.9, 56.9, 43.5, 32.6, 28.4, 22.0, 13.7, 11.0. Anal. Calcd for $C_{25}H_{30}N_4O$: C, 74.58; H, 7.52; N, 13.93. Found: C, 74.93; H, 7.55; N, 13.67.

Nucleophilic Substitution of 7a and 15a with Grignard Reagents. To a solution of compound **7a** or **15a** (2 mmol) in toluene (30 mL) was added a freshly prepared solution of CH_3MgI (5 mmol) in Et_2O (5 mL) at room temperature, and the solution was then refluxed for the time indicated in Table 1. After cooling, the solvent was removed under reduced pressure and the residue was extracted with Et_2O (50 mL), washed with water (3 × 50 mL), and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by column chromatography using CH_2Cl_2/hexane (1:4) as eluent to afford product **6** or **18**.

***N*-Benzyl-2-ethyl-4-phenylpyrrole (6)**: see Table 1; ^{1}H NMR δ 7.47−7.50 (m, 2 H), 7.19−7.29 (m, 5 H), 7.06−7.11 (m, 1 H), 6.98 (d, J = 7.0 Hz, 2 H), 6.87 (d, J = 2.0 Hz, 1 H), 6.28 (d, J = 2.0 Hz, 1 H), 4.93 (s, 2 H), 2.43 (q, J = 7.5 Hz, 2 H), 1.19 (t, J = 7.5 Hz, 3 H); ^{13}C NMR δ 138.1, 136.1, 135.9, 128.6 (2C), 128.5 (2C), 127.3, 126.3 (2C), 125.0, 124.7 (2C), 123.5, 117.5, 103.4, 50.2, 19.3, 12.8.

***N*-*n*-Butyl-2-benzyl-4,5-dimethylpyrrole (18)**: see Table 1; ^{1}H NMR δ 7.11−7.28 (m, 5 H), 5.61 (s, 1 H), 3.87 (s, 2 H), 3.59 (t, J = 7.9 Hz, 2 H), 2.09 (s, 3 H), 1.98 (s, 3 H), 1.34−1.44 (m, 2 H), 1.21−1.30 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 140.0, 128.9, 128.6 (2C), 128.3 (2C), 126.0, 123.9, 113.2, 108.3, 43.7, 33.2, 33.1, 20.1, 13.7, 11.2, 9.7.

Nucleophilic Substitution of 7a and 10a with Sodium Thiophenolate. A solution of compound **7a** or **10a** (1 mmol) and sodium thiophenolate (0.66 g, 5 mmol) in DMF (50 mL) under nitrogen was heated at 150 °C for the time indicated in Table 1. After cooling, water (100 mL) and Et_2O (100 mL) were added. The organic phase was separated, washed with a saturated NaCl solution (3 × 100 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was subjected to column chromatography using CH_2Cl_2/hexane (1:4) as eluent to afford product **8** or **11**.

***N*-Benzyl-2-[(phenylthio)methyl]-4-phenylpyrrole (8)**: see Table 1; ^{1}H NMR δ 7.50 (d, J = 7.2 Hz, 2 H), 7.06−7.34 (m, 13 H), 6.95 (d, J = 1.6 Hz, 1 H), 6.36 (d, J = 1.6 Hz, 1 H), 5.17 (s, 2 H), 4.00 (s, 2 H); ^{13}C NMR δ 137.7, 135.8, 135.5,

130.6 (2C), 128.8 (2C), 128.7 (2C), 128.5 (2C), 128.3, 127.6, 126.7, 126.6 (2C), 125.3, 124.8 (2C), 123.7, 119.5, 108.0, 50.7, 31.1.

***N*-Benzyl-2-[1-(phenylthio)ethyl]-4-phenylpyrrole (11)**: see Table 1; ^{1}H NMR δ 7.38 (dd, J = 8.3 and 1.3 Hz, 2 H), 7.10−7.26 (m, 10 H), 6.97−7.07 (m, 3 H), 6.86 (d, J = 1.7 Hz, 1 H), 6.31 (d, J = 1.7 Hz, 1 H), 5.27 (d, J = 16.2 Hz, 1 H), 5.03 (d, J = 16.2 Hz, 1 H), 4.06 (q, J = 6.9 Hz, 1 H), 1.49 (d, J = 6.9 Hz, 3 H); ^{13}C NMR δ 138.0, 135.6, 133.8, 133.5 (2C), 133.4, 128.8 (2C), 128.7 (2C), 128.5 (2C), 127.6, 127.5, 126.5 (2C), 125.2, 124.7 (2C), 123.5, 119.1, 105.8, 50.5, 39.6, 20.9.

***N*-Benzyl-2-cyano-3-phenyl-5-ethylpyrrole (9).** A solution of compound **10a** (0.76 g, 2 mmol) and NaCN (0.49, 10 mmol) in DMF (25 mL) was refluxed for 12 h. After cooling, water (100 mL) and diethyl ether (100 mL) were added and the organic phase was separated, washed with a saturated NaCl solution (3 × 100 mL), and dried ($MgSO_4$). The solvent was removed to give an oil which was separated by column chromatography using CH_2Cl_2/hexane (1:4) as eluent to afford product **9**: see Table 1; ^{1}H NMR δ 7.73 (d, J = 8.0 Hz, 2 H), 7.24−7.44 (m, 6 H), 7.07 (d, J = 7.2 Hz, 2 H), 6.31 (s, 1 H), 5.23 (s, 2 H), 2.51 (q, J = 7.4 Hz, 2 H), 1.23 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 142.0, 136.2, 134.6, 132.9, 128.9 (2C), 128.8 (2C), 127.8, 127.5, 126.5 (2C), 126.2 (2C), 115.2, 106.3, 100.4, 49.0, 19.8, 12.3.

General Procedure for the Preparation Pyrrol-2-ylacetanilide 12 and -thioacetanilide 13 *via* Reductive Elimination of Benzotriazole. A mixture of compound **10b** or **10c** (2 mmol), acetic acid (10 mL), THF (20 mL), and zinc dust (2.60 g, 40 mmol) was refluxed for 12 h. After cooling, the reaction solution was filtered and extracted with diethyl ether (100 mL). The organic phase was separated, washed with water (3 × 50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the crude product which was purified either by recrystallization or by column chromatography to afford the corresponding product **12** or **13**.

α-(*N*-Benzyl-4-phenylpyrrol-2-yl)acetanilide (12): recrystallized from EtOAc/hexane (1:4), see Table 1; ^{1}H NMR δ 7.53 (d, J = 7.2 Hz, 2 H), 7.17−7.38 (m, 11 H), 7.05−7.10 (m, 4 H), 6.54 (d, J = 1.9 Hz, 1 H), 5.07 (s, 2 H), 3.63 (s, 2 H); ^{13}C NMR δ 167.7, 137.3, 136.9, 135.1, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.6, 127.8, 126.6 (2C), 125.7, 124.8 (2C), 124.5, 124.4, 120.0, 119.8 (2C), 108.2, 51.0, 36.0.

α-(*N*-n-Butyl-4-*tert*-butylpyrrol-2-yl)thioacetanilide (13): purified by column chromatography using EtOAc/hexane (1:4) as the eluent, see Table 1; ^{1}H NMR δ 8.94 (s, 1 H), 7.62−7.65 (m, 2 H), 7.35−7.40 (m, 2 H), 7.23−7.26 (m, 1 H), 6.52 (d, J = 2.1 Hz, 1 H), 6.12 (d, J = 2.1 Hz, 1 H), 4.20 (s, 2 H), 3.75 (t, J = 7.4 Hz, 2 H), 1.60−1.70 (m, 2 H), 1.28 (s, 9H), 1.18−1.34 (m, 2 H), 0.89 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 199.1, 138.4, 135.1, 128.8 (2C), 126.6, 124.2, 122.6 (2C), 118.0, 108.1, 46.6, 46.5, 33.4, 31.8, 31.7, 30.5, 19.9, 13.6.

***N*-(2-Methoxyethyl)-2-*trans*-1-pentenyl-4-phenyl-5-methylpyrrole (20).** A solution of compound **17** (0.80 g, 2 mmol) and K_2CO_3 (0.84 g, 4 mmol) in DMF (30 mL) was heated at 120 °C for 12 h. After cooling, diethyl ether (100 mL) and water (100 mL) were added and the organic layer was separated, washed with water (3 × 100 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was purified by column chromatography using EtOAc/hexane (1:4) as eluent to give product **20** as a 3:1 *E*:*Z* mixture: see Table 1; ^{1}H NMR δ 7.31−7.39 (m, 4 H), 7.16−7.22 (m, 1 H), 6.37 (s, 1 H), 6.28 (d, J = 16.1 Hz, 1 H), 5.99−6.06 (m, 1 H), 4.05 (t, J = 6.5 Hz, 2 H), 3.57 (t, J = 6.5 Hz, 2 H), 3.33 (s, 3 H), 2.34 (s, 3 H), 2.13−2.20 (m, 2 H), 1.44−1.54 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 137.4, 131.0, 129.4, 128.2 (2C), 128.1 (2C), 125.4, 125.2, 125.1, 122.0, 118.8, 104.8, 72.0, 59.1, 43.3, 35.3, 22.7, 13.6, 11.1. (Peaks quoted refer to *trans* isomer; minor product for *cis* isomer was also detected.)

Preparation of 1-(2-Methoxyethyl)-2-methyl-3-phenyl-5-[1-[bis(ethoxycarbonyl)methyl]pentyl]pyrrole (21). To a solution of diethyl malonate (0.34 g, 2 mmol) in DMF (30 mL) was added sodium hydride (0.08 g, 2 mmol, 60% dispersion in mineral oil) at room temperature. After the mixture was stirred for 30 min, compound **17** (0.40 g, 1 mmol) in DMF (5 mL) was added and the reaction solution was heated at 120 °C for 12 h. After cooling, diethyl ether (50 mL) and water (50 mL) were added and the organic phase was separated, washed with water (3 × 50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an oil which was separated by column chromatography using CH_2Cl_2/hexane (1:4) as eluent to afford product **21**: see Table 1; ^{1}H NMR δ 7.33−7.34 (m, 4 H), 7.15−7.19 (m, 1 H), 6.02 (s, 1 H), 4.16−4.27 (m, 3 H), 3.94−4.04 (m, 3 H), 3.52−3.67 (m, 4 H), 3.35 (s, 3 H), 2.34 (s, 3 H), 1.63−1.66 (m, 2 H), 1.22−1.31 (m, 7 H), 1.03 (t, J = 7.1 Hz, 3 H), 0.82−0.87 (m, 3 H); ^{13}C NMR δ 168.6, 168.3, 137.7, 131.8, 128.2 (2C), 127.9 (2C), 124.8, 124.2, 121.2, 105.6, 72.0, 61.4, 61.2, 59.0, 58.4, 43.0, 36.2, 34.5, 28.9, 22.8, 14.1, 13.9, 13.8, 11.3.

Preparation of *N*-*n*-Butyl-2-(1-cyano-2-phenylvinyl)-4,5-dimethylpyrrole (22). To a solution of compound **15** (1.41 g, 5 mmol) in THF (80 mL) was added a solution of *n*-BuLi (2.75 mL, 5.5 mmol, 2.0 M in cyclohexane) at −78 °C, and the resulting solution was stirred for 1 h. Benzaldehyde (0.53 g, 5 mmol) in THF (5 mL) was added, and the reaction mixture was stirred at −78 °C for another hour. Methyl iodide (2.84 g, 20 mmol) in HMPA (10 mL) was added, and the mixture was allowed to warm to room temperature overnight. Water (100 mL) and diethyl ether (100 mL) were poured into the reaction mixture, and the organic layer was separated, washed with water (3 × 100 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to give oil **19** which was not further purified.

The above oil was dissolved in DMF (50 mL) and treated with NaCN (0.98 g, 20 mmol). The mixture was refluxed for 12 h. Water (100 mL) and diethyl ether (100 mL) were poured into the solution, and the organic layer was separated, washed with NaOH (2 N, 2 × 50 mL) and water (3 × 100 mL), and dried ($MgSO_4$). After removal of the solvent, the residue was subjected to column chromatography using EtOAc/hexane as the eluent to afford the product **22**: see Table 1; ^{1}H NMR δ 7.52−7.56 (m, 2 H), 7.22−7.40 (m, 5 H), 3.89 (t, J = 7.5 Hz, 2 H), 2.18 (s, 3 H), 2.05 (s, 3 H), 1.56−1.64 (m, 2 H), 1.32−1.39 (m, 2 H), 0.95 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 135.6, 131.9, 128.8 (2C), 128.2, 127.3, 125.8, 124.8 (2C), 119.7, 118.4, 114.7, 100.1, 43.2, 33.6, 20.0, 13.7, 11.2, 10.3.

JO951894M