Preparation, Lithiation and Transformation of *N*-(Benzotriazol-1-ylmethyl) Heterocycles [1]

Alan R. Katritzky*, Malgorzata Drewniak-Deyrup, Xiangfu Lan, and Frederic Brunner

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

Received December 9, 1988

Indole, carbazole, pyrrole, imidazole, benzimidazole, 2-methyl- and 2-phenylbenzimidazole, and 1,2,4-triazole have each been converted into their *N*-(benzotriazol-1-ylmethyl) derivatives. The pyrrole, indole, and carbazole adducts undergo smooth lithiation at the inter-ring methylene group and subsequent reaction there with electrophiles. For the imidazole, benzimidazole, and triazole systems, lithiations at other molecular positions competed.

J. Heterocyclic Chem., **26**, 829 (1989).

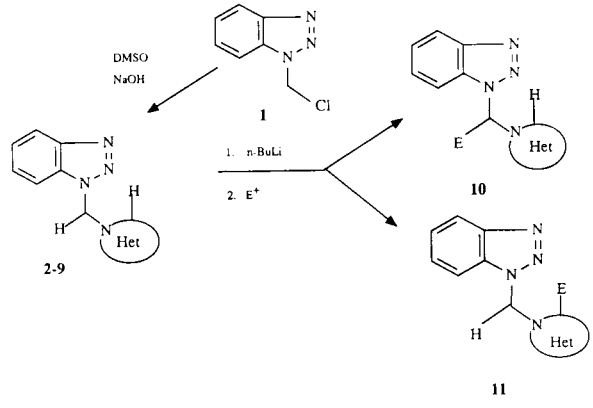
Considerable recent work from our laboratory has been concerned with the elaboration of substituents attached to pyrrole-like nitrogen atoms in heterocycles *via* the intermediate formation of α-lithiated derivatives. In some cases a simple alkyl group has been deprotonated as in *N*-methylpyrazoles [2,3]. More often the α-methylene has carried an activating group such as phenyl in *N*-benzylpyrazole [3], in *N*-benzyl-3,4,5-triphenyl-1,3-dihydroimidazol-2-one [4], or in *N*-benzylimidazole [5,6], or substituted phenyl in *N*-arylmethylimidazoles [7]. Other activating groups include a second nitrogen-linked heterocyclic ring in methylenebispyrazoles [8]; phenylthio in 1-(phenylthiomethyl)benzimidazole [9], in 9-(phenylthiomethyl)carbazole [10], and in 1-(phenylthiomethyl)benzotriazole [11], or trimethylsilyl in 1-trimethylsilylbenzotriazole [12].

In the present paper we have explored the use of a benzotriazol-1-ylmethyl group in the context of our recent demonstration of the synthetic versatility of benzotriazole as a good protecting and activating auxiliary during the *N*-alkylation of amines [13], of amides [14], of thioamides [15], and of other nitrogen functionalities [16]. We considered that *N*-(benzotriazol-1-ylmethyl) heterocycles could open new routes for synthetic transformations: in particular, the benzotriazole moiety should increase the acidity of the α-methylene protons, because of its electron withdrawing character, and thus facilitate metallation on the α-carbon.

Heterocyclic aminals, in which a methylene group links two pyrrole-like heterocyclic nitrogen atoms, are not easily accessible by previously available synthetic methods. In 1982, Elguero and co-workers reported [17] the nmr study of several aminals of this type in which the two heterocyclic rings were identical, prepared by the reactions of azoles with methylene chloride under phase transfer catalysis conditions in yields of 22 to 88%. Further transformations of these products were not reported at that time.

We prepared *N*-(benzotriazol-1-ylmethyl) heterocycles in good yields by heating the NH-heterocycles in dimethyl sulfoxide with powdered sodium hydroxide and 1-chloromethylbenzotriazole [18] (Scheme 1, Table I). Alternatively, the sodium salt of the NH-heterocycle is formed with sodium ethanolate. The structures of all adducts were determined by their spectral properties and supported by analytical data. The ^{13}C nmr spectra showed the characteristic pattern for a 1-substituted benzotriazole [20] and heterocycle. The most indicative chemical shift was the one corresponding to the methylene carbon between two heterocycles. This peak appeared in the region δ 58.0-48.7 ppm.

Scheme 1



Cpd Heterocycle

2	Indol-1-yl
3	Carbazol-9-yl
4	Pyrrol-1-yl
5	Benzimidazol-1-yl
6	(2-Methyl)benzimidazol-1-yl
7	(2-Phenyl)benzimidazol-1-yl
8	Imidazol-1-yl
9	1,2,4-Triazol-1-yl

Adducts of indole **2**, carbazole **3**, pyrrole **4**, benzimidazole **5**, 2-methylbenzimidazole **6**, 2-phenylbenzimidazole **7**, imidazole **8**, and 1,2,4-triazole **9** (Scheme 1) were examined for facility of metallation at the α-carbon and subsequent introduction of substituents by reaction with electrophiles.

Table I

Preparation of *N*-(Benzotriazol-1-ylmethyl) Heterocycles [a]

No	Method	Yield (%)	MP (°C)	Recrystallizing solvent	Crystal form	Molecular formula	Required (%) C	H	N	Found (%) C	H	N
2	A	84	176-178	Ethanol	Needles	$C_{15}H_{12}N_4$	72.6	4.9	22.6	72.2	4.7	22.6
3	A	87	195-197	Benzene	Prisms	$C_{19}H_{14}N_4$	76.5	4.7	18.8	76.6	4.7	18.8
4	A	61	141-143	Hexane/EtOAc	Plates	$C_{11}H_{10}N_4$	66.7	5.1	28.3	66.4	5.0	28.4
5	B	80	198-199	Ethanol	Needles	$C_{14}H_{11}N_5$	67.5	4.5	28.1	67.4	4.4	28.5
6	A	78	182-184	Methanol	Prisms	$C_{15}H_{13}N_5$	68.4	5.0	26.6	68.0	4.9	26.9
7	B	89	191-192	MeOH/Acetone	Prisms	$C_{20}H_{15}N_5$	73.8	4.7	21.5	74.1	4.7	21.9
8	A	62	108-112	EtOAc	Prisms	$C_{10}H_9N_5$	60.3	4.5	35.2	60.2	4.3	35.2
9	B	82	137-138	Ethanol	Prisms	$C_9H_8N_6$	54.0	4.0	42.0	54.0	4.0	42.0

[a] Method A uses sodium hydroxide/DMSO; method B uses sodium/ethanol.

Table II

^{13}C NMR Chemical Shifts for Benzotriazole, Heterocyclic Ring Carbons and Methylene Group [a]

No	C-3a	C-7a	C-4	C-5	C-6	C-7	C-2' [b]	C-3'	C-4'	C-5'	C-6'	C-7'	C-3a'	C-7a'	CH_2
2	145.3	132.1	119.3	124.4	128.9	110.6	127.9	102.9	120.5	122.0	120.2	110.4	128.6	135.4	56.8
3	143.9	130.4	117.7	122.4	126.1	108.7	108.6	124.6	118.6	118.7	121.4	137.9	-	-	53.0
4	146.2	132.0	120.0	124.3	128.1	109.0	110.3	120.7	-	-	-	-	-	-	59.9
5	145.3	132.0	119.3	124.3	128.0	110.7	144.0	-	110.2	123.1	122.3	118.3	143.4	132.7	54.8
6	145.1	131.9	118.4	124.0	127.8	109.5	151.5	-	109.4	122.2	122.1	119.7	141.9	134.2	53.9
7	145.7	131.8	119.9	124.3	128.1	110.0	153.1	-	108.6	123.9	123.5	120.0	142.8	134.4	55.3
8	145.8	132.4	119.5	124.7	128.4	110.6	138.0	-	119.7	129.8	-	-	-	-	56.5
9	145.2	132.7	119.3	124.4	128.0	110.6	-	145.1	-	152.5	-	-	-	-	58.0

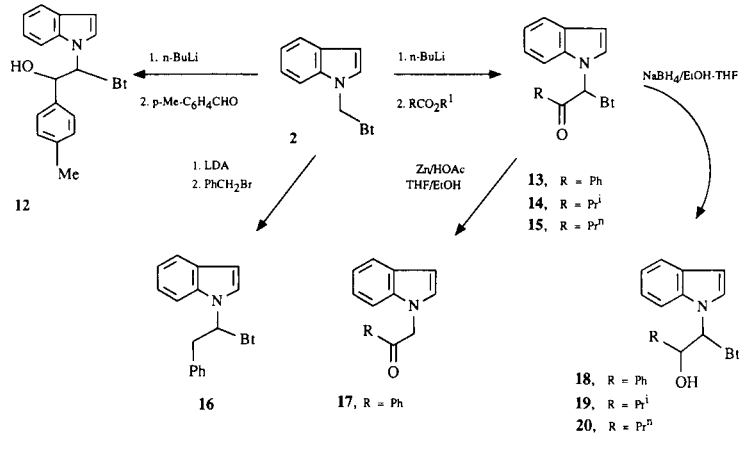
[a] All ^{13}C nmr spectra were made on 50 MHz FT Varian XL-200 in dimethyl sulfoxide-d_6, for the compound **4** in deuteriochloroform. [b] C-1' for compound **3**.

Lithiation of the Indole and Carbazole Adducts and Reactions with Electrophiles.

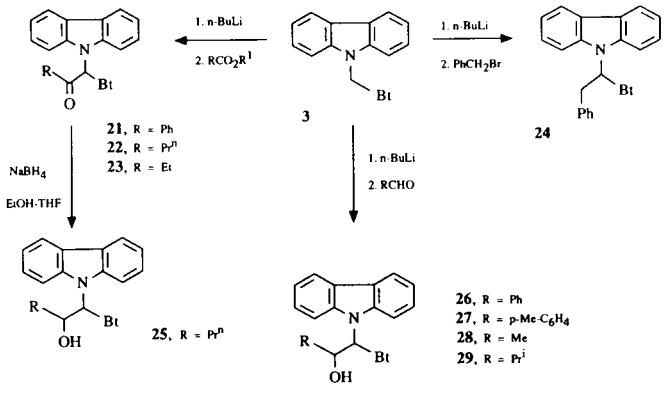
The indole **2** and carbazole adducts **3** underwent smooth lithiation with *n*-butyllithium in tetrahydrofuran at -78° to form deeply colored carbanions. Electrophiles were added at -78° and the mixture was allowed to warm up overnight. Esters of the carboxylic acids (aliphatic and aromatic) reacted readily with the lithium anions of both the indole **2** and the carbazole adducts **3** giving products **13-15** and **21-23** in which acyl or aroyl groups had been substituted at the methylene bridge carbon in good yields.

Similarly, the addition of aliphatic and aromatic aldehydes formed the hydroxy compounds **12** and **26-29**, and benzyl bromide gave **16** and **24** (Scheme 2,3). Structures of all synthesized products were confirmed by their spectral and analytical properties. The ^{13}C nmr spectra

Scheme 2



Scheme 3

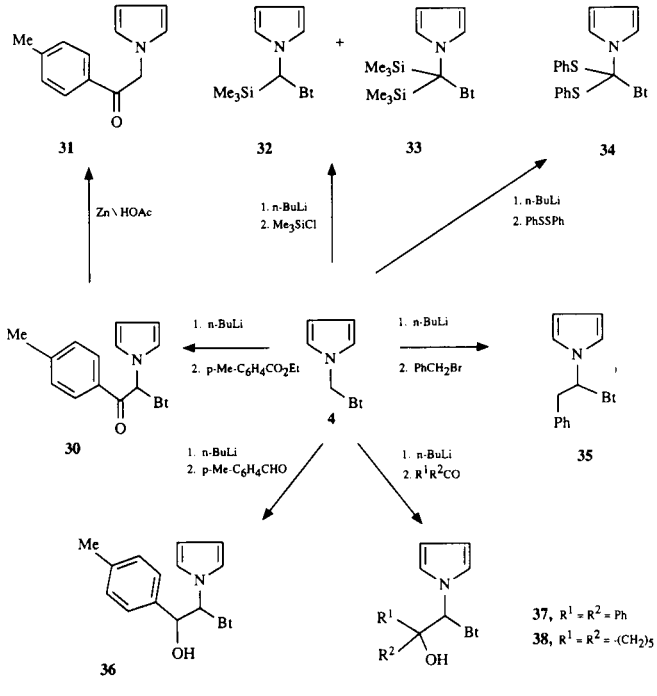


revealed new features that allowed structure assignment (Table IV). The acyl and aroyl adducts had chemical shifts for the carbonyl carbon in the region of δ 202.9-187.5 ppm. The methine carbon alpha to both heterocyclic nitrogens was observed downfield at 71.3-69.4 ppm. Product **13** was reduced with zinc powder in acetic acid and ethanol using the ultrasonic bath to give the *N*-benzoylmethylindole **17**.

Lithiation and Reactions with Electrophiles of *N*-(Benzotriazol-1-ylmethyl)pyrrole (**4**).

The pyrrole adduct underwent easy lithiation with *n*-butyllithium in tetrahydrofuran at -78° to form the carbanion which in turn reacted with a variety of electrophiles giving the corresponding *alpha* substituted products (Scheme 4). Using trimethylsilyl chloride as an

Scheme 4

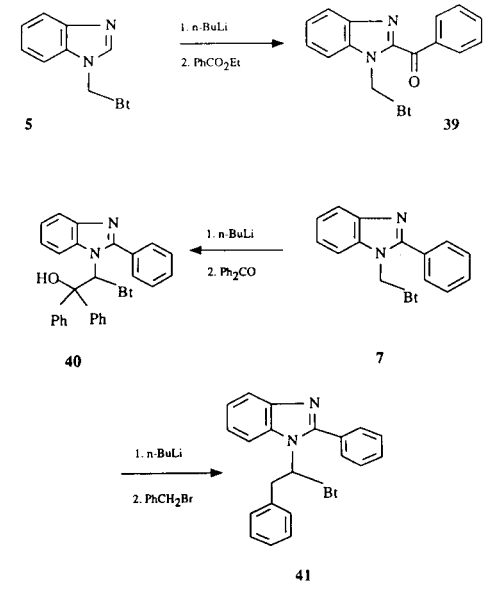


electrophile a mixture of mono- **32** and di-substituted products **33** was obtained. These products were separated by column chromatography using silica gel and hexane-ethyl acetate (8:1) as eluent. The reaction with diphenyl disulfide gave the disubstituted product **34**. Removal of the benzotriazole moiety by zinc in acetic acid was successful for the benzoyl derivative **31**. The structures of all the products **30-38** were confirmed by spectral and analytical data (Tables III and IV).

Lithiation and Reactions with Electrophiles of Benzimidazole and Imidazole Adducts.

Lithiations of 1-substituted imidazoles or benzimidazoles usually occur at the 2-position, if it is free [21-23]. If the 2-position is substituted lithiation normally takes place at the 5-position [24]. Benzimidazole adduct **5** undergoes lithiation with *n*-butyllithium at 2-position and subsequent reaction with ethyl benzoate gives product **39**.

Scheme 5



The 2-methylbenzimidazole derivative **6** in several attempted reactions gave starting material or complicated mixtures. However, the 2-phenylbenzimidazole adduct **7** on lithiation with *n*-butyllithium and subsequent reaction with benzophenone and benzyl bromide gave **40** and **41** (Scheme 5, Table III). In the ^{13}C nmr spectra of both products **40** and **41** the most deshielded carbon was C-2 of the substituted benzimidazole which appeared at δ 153.4 ppm. Additionally, typical patterns for a 1-substituted benzotriazole and a 1,2-disubstituted benzimidazole were observed.

N-(Benzotriazol-1-ylmethyl)imidazole **8**, on lithiation with *n*-butyllithium and treatment with ethyl benzoate gave a mixture of substitution in the methylene group (product **42**) and at the 2-position of the imidazole ring

Table III

Lithiation and Reaction with Electrophiles of *N*-(Benzotriazol-1-ylmethyl) Heterocycles

No	Base	Electrophile	Yield (%)	MP (°C)	Recrystallizing solvent	Crystal form	Molecular formula	Required (%) C	H	N	Found (%) C	H	N
12	*n*-BuLi	*p*-Me-PhCHO	68	224-226	Et_2O/P.E.	Needles	$C_{23}H_{20}N_4O$	75.0	5.5	15.2	74.6	5.5	15.5
13	*n*-BuLi	$PhCO_2Et$	81	191-193	Et_2O/P.E.	Prisms	$C_{22}H_{16}N_4O$	75.0	4.6	15.9	74.6	4.6	15.9
14	*n*-BuLi	Me_2CO_2Et	95	138-140	Et_2O/P.E.	Needles	$C_{19}H_{18}N_4O$	71.7	5.7	17.6	71.3	5.7	17.4
15	*n*-BuLi	*n*-$PrCO_2Et$	75	144-146	EtOH	Prisms	$C_{19}H_{18}N_4O$	71.7	5.7	17.6	71.9	5.7	18.0
16	LDA	$PhCH_2Br$	86	107-109	Et_2O/P.E.	Needles	$C_{22}H_{18}N_4$	78.1	5.4	16.6	78.3	5.4	16.2
21	*n*-BuLi	$PhCO_2Et$	88	89-91	Et_2O/P.E.	Plates	$C_{26}H_{18}N_4O$	77.6	4.5	13.9	77.2	4.6	13.6
22	*n*-BuLi	*n*-$PrCO_2Et$	84	189-192	EtOH/Me_2CO	Prisms	$C_{23}H_{20}N_4O$	75.0	5.5	15.2	75.0	5.6	15.2
23	*n*-BuLi	$EtCO_2Me$	68	176-178	EtOH	Needles	$C_{22}H_{18}N_4O$	74.6	5.1	15.8	74.7	5.2	15.7
24	*n*-BuLi	$PhCH_2Br$	81	129-130	[a]	Microcryst	$C_{26}H_{20}N_4$	80.4	5.2	14.4	80.3	5.2	14.0
26	*n*-BuLi	PhCHO	63	225-226	MeOH	Needles	$C_{26}H_{20}N_4O$	77.2	5.0	13.8	77.3	4.8	13.5
27	*n*-BuLi	*p*-Me-PhCHO	71	237-238	MeOH	Microcryst	$C_{27}H_{22}N_4O$	77.2	5.3	13.4	77.7	5.3	13.7
28	*n*-BuLi	MeCHO	45	197-198	MeOH	Microcryst	$C_{21}H_{18}N_4O$	73.7	5.3	16.4	74.0	5.4	16.1
29	*n*-BuLi	Me_2CHCHO	98	155-156	$CHCl_3$/P.E.	Needles	$C_{23}H_{22}N_4O$	74.6	6.0	15.2	74.8	6.3	14.6
30	*n*-BuLi	*p*-Me-$PhCO_2Et$	53	127-129	[a]	Plates	$C_{19}H_{16}N_4O$	72.1	5.1	17.7	71.9	5.1	18.1
32	*n*-BuLi	Me_3SiCl	13	132-134	[a]	Plates	$C_{14}H_{18}N_4Si$	62.2	6.7	20.7	62.4	6.9	20.4
33	*n*-BuLi	Me_3SiCl	36	139-141	[a]	Plates	$C_{17}H_{26}N_4Si_2$	59.6	7.7	16.4	59.7	7.7	16.3
34	*n*-BuLi	PhSSPh	67	163-165	[a]	Prisms	$C_{23}H_{18}N_4S_2$	66.6	4.4	13.5	66.6	4.3	13.7
35	*n*-BuLi	$PhCH_2Br$	47	131-132	[a]	Prisms	$C_{18}H_{16}N_4$	75.0	5.6	19.4	74.9	5.6	19.5
36	*n*-BuLi	*p*-Me-PhCHO	35	187-190	[a]	Needles	$C_{19}H_{18}N_4O$	71.7	5.7	17.6	71.3	5.8	17.5
37	*n*-BuLi	Ph_2CO	72	197-199	[a]	Plates	$C_{24}H_{20}N_4O$	75.8	5.3	14.7	75.4	5.2	14.6
38	*n*-BuLi	$(CH_2)_2CO$	76	173-174.5	[a]	Microcryst	$C_{17}H_{20}N_4O$	68.9	6.8	18.9	68.6	6.8	19.0
39	*n*-BuLi	$PhCO_2Et$	78	137-139	Et_2O/P.E.	Microcryst	$C_{21}H_{15}N_5O$	71.4	4.3	19.8	71.2	4.3	19.8
40	*n*-BuLi	Ph_2CO	79	159-162	Acetone	Prisms	$C_{33}H_{25}N_5O$	78.1	5.0	13.8	78.1	4.9	13.9
41	*n*-BuLi	$PhCH_2Br$	83	176-178	Et_2O/P.E.	Needles	$C_{27}H_{21}N_5$	78.1	5.1	16.9	78.1	5.1	16.7
42	*n*-BuLi	$PhCO_2Et$	53	58-62	Et_2O/Me_2CO	Needles	$C_{17}H_{13}N_5O$	67.3	4.3	23.1	67.0	4.4	23.0
43	*n*-BuLi	$PhCO_2Et$	30	113-114	EtOH	Prisms	$C_{17}H_{13}N_5O$	67.3	4.3	23.1	67.7	4.3	23.4
44	*n*-BuLi	*p*-Me-PhCHO	74	89-91	Et_2O/Me_2CO	Prisms	$C_{18}H_{17}N_5O$	67.7	5.4	21.9	67.4	5.3	22.0

[a] These compounds were purified by column chromatography and submitted for analysis without further recrystallization.

Table IV

^{13}C NMR Chemical Shifts for the Carbons in Compounds **12-16, 21-28, 30-38** and **40-45**

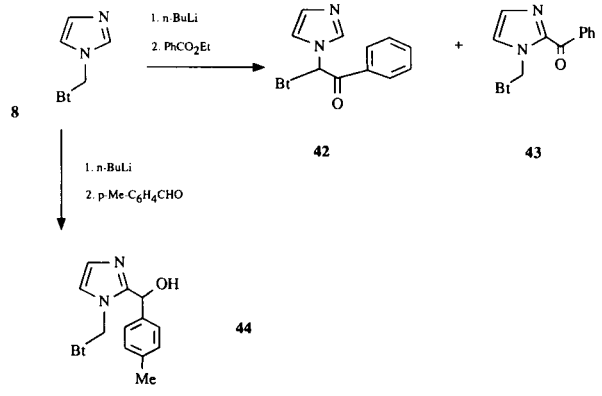
No	C=O	C-3a	C-7a	C-3a' (C-8a')	C-7a' (C-9a')	C-3'	C-α	C-β	Other carbons
12	-	144.9	133.3	128.6	135.8	103.3	72.5	71.3	137.6, 137.1, 127.8, 127.6, 127.4, 126.8, 124.2, 121.9, 120.4, 120.1, 119.1, 111.3, 111.1, 109.9, 20.7
13	188.9	145.7	132.3	128.0	135.7	104.0	69.9	-	134.1, 133.5, 128.6, 128.4, 127.4, 124.3, 122.3, 120.7, 120.6, 119.3, 110.6, 110.3
14	202.9	146.3	132.2	128.9	136.2	105.2	70.7	-	128.3, 125.7, 124.4, 123.2, 121.5, 121.3, 120.2, 110.3, 109.0, 38.8, 13.5, 18.0
15	199.2	144.9	132.5	128.0	135.8	103.8	71.3	-	127.8, 127.7, 124.0, 122.0, 120.5, 120.3, 119.2, 109.9, 40.5, 13.1
16	-	145.9	132.0	128.6	135.4	103.9	70.1	39.4	134.6, 128.7, 128.4, 127.6, 127.1, 124.4, 124.0, 122.4, 121.1, 120.4, 119.8, 109.1
21	187.5	146.2	133.5	122.3	139.3	-	71.3	-	135.0, 134.8, 129.1, 128.4, 128.6, 128.2 126.8, 124.2, 121.3, 120.6, 120.2, 110.5, 110.1
22	198.3	143.3	131.7	122.7	137.9	-	69.4	-	126.4, 124.6, 124.5, 121.8, 119.1, 118.7, 117.9, 109.2, 108.7, 39.2, 14.9, 11.8
23	199.5	143.8	132.2	122.4	138.3	-	69.9	-	126.9, 125.0, 123.2, 119.6, 119.0, 118.3 109.4, 109.0, 31.5, 6.3
24	-	146.1	133.0	123.7	139.0	-	70.0	37.4	135.5, 129.3, 128.6, 128.0, 127.4, 126.4, 124.5, 120.6, 120.4, 120.1, 109.7
26	-	144.8	133.4	122.7	138.8	-	71.0	-	137.1, 136.9, 128.3, 127.6, 126.9, 126.1, 126.0, 124.3, 120.0, 119.9, 119.5, 111.0, 110.7, 20.5
27	-	144.9	133.3	122.7	138.8	-	73.0	71.9	140.0, 127.9, 127.8, 127.6, 126.9, 126.0, 124.3, 122.7, 120.0, 119.2, 110.9, 110.7
28	-	144.8	133.4	122.9	139.0	-	72.1	63.0	127.6, 125.3, 124.2, 120.2, 119.1, 110.8, 110.4, 19.7
29	-	144.8	133.4	122.9	138.8	-	71.9	70.9	127.6, 126.4, 124.2, 123.0, 122.9, 120.3, 119.1, 111.1, 111.0, 110.8, 28.8, 20.4, 14.8
30	187.4	146.2	132.3	-	-	-	73.1	-	146.5, 130.8, 129.9, 128.8, 128.3, 128.4, 121.1, 120.1, 111.0, 110.8
32	-	145.9	133.2	-	-	-	66.0	-	127.7, 124.2, 120.5, 120.0, 109.6, 109.3, -2.1
33	-	146.0	132.9	-	-	-	72.4	-	126.3, 123.9, 120.9, 119.6, 113.0, 108.3, 0.16.
34	-	146.3	132.2	-	-	-	94.2	-	137.1, 130.5, 128.5, 127.8, 124.4, 120.6, 119.9, 112.2, 110.1
35	-	145.9	130.3	-	-	-	72.9	40.6	134.9, 128.9, 128.8, 128.6, 128.2, 128.1, 127.9, 127.3, 124.2, 120.1, 109.1, 109.2
36	-	144.8	133.2	-	-	-	73.9	72.7	137.5, 136.8, 128.4, 127.5, 127.2, 124.2, 120.2, 119.1, 110.9, 108.6, 20.7
37	-	144.8	133.0	-	-	-	74.9	81.7	143.9, 141.8, 128.9, 128.5, 128.0, 127.5, 125.8, 125.2, 121.0, 120.4, 108.9
38	-	145.3	133.8	-	-	-	75.3	78.0	128.8, 125.0, 121.5, 120.5, 109.9, 109.4, 35.8, 34.2, 25.7, 21.9, 21.7
39	186.9	145.9	132.2	141.7	135.4	-	55.5	-	144.8, 136.4, 133.9, 131.3, 128.3, 127.1, 124.6, 124.3, 122.1, 119.9, 112.1, 110.7
40	-	144.6	132.9	143.1	133.8	-	73.0	83.4	153.9, 143.7, 143.0, 140.7, 132.3, 130.2, 129.8, 128.9, 128.6, 128.5, 127.8, 127.5, 125.2, 124.8, 123.6, 120.5, 119.8, 114.9, 109.0
41	-	145.6	132.2	143.2	132.5	-	69.8	38.1	153.4, 134.6, 130.2, 129.8, 129.3, 128.9, 127.8, 127.7, 124.3, 123.7, 123.2, 120.2, 120.0, 112.7, 108.8

Table IV (continued)

No	C=O	C-3a	C-7a	C-3a' (C-8a')	C-7a' (C-9a')	C-3'	C-α	C-β	Other carbons
42	186.6	146.2	132.8	-	-	-	69.6	-	137.0, 134.9, 131.7, 129.9, 129.1, 128.6, 125.0, 120.5, 119.0, 109.5
43	184.8	145.8	132.1	-	-	-	56.9	-	141.7, 136.6, 133.2, 130.9, 130.6, 128.5, 128.1, 125.2, 124.5, 119.9, 109.9
44	-	145.7	132.1	-	-	-	56.3	-	149.2, 137.6, 137.4, 129.5, 127.2, 125.5, 124.3, 119.9, 119.6, 109.7, 68.7, 20.0

(product **43**). Treatment of **8** with *n*-butyllithium followed by *p*-methylbenzaldehyde yielded only the 2-substituted product **44** (Scheme 6). The two isomeric products **42** and **43** were separated by column chromatography and characterized on the basis of their spectral and analytical data. The chemical shift of the methylene carbon in **43** appeared at 56.9 ppm while the methine carbon in **42** was at 69.6 ppm. APT experiments supported the assigned structures. There was a significant difference in the melting points of the two products.

Scheme 6



Complex mixtures were obtained from the 1,2,4-triazole adduct **9** after attempted lithiation and reaction with electrophiles.

Orientation of Lithiation.

N-Dialkylaminomethyl aminals of imidazole, benzimidazole and pyrazole undergo lithiation at the 2-, 2-, and 3-positions respectively [25], and analogous carbazole and benzocarbazole aminals at the aromatic methine nearest to the nitrogen atom [26]. In this work, the dialkylaminomethyl function served as a protecting group for the heterocyclic nitrogen atom and simultaneously activated a ring methine to lithiation.

The lithiation of the *N*-(benzotriazol-1-ylmethyl) heterocycle can occur at the methylene group (*cf* **10**) or at a ring position (*cf* **11**) depending on the relative acidity of the protons in question. We encountered both orientations. The benzotriazol-1-ylmethyl group is clearly much more activating towards α-proton loss than a dialkylamino group, and in some, but not all, cases changes the orientation of lithiation.

Reductions of Acyl and Aroyl Derivatives of Indole and Carbazole with Sodium Borohydride.

The reduction of indole derivatives **13-15** with sodium borohydride in ethanol-tetrahydrofuran gave mixtures of the corresponding diastereoisomeric alcohols **18-20** (Scheme 2). The ratio of two isomers was determined on the basis of the ^{1}H nmr spectra of crude reaction mixtures. The crude mixture of products **18** was separated on the basis of differing solubility in diethyl ether. The alcohols **20** were separated by column chromatography using silica gel and chloroform as eluent. The spectral and analytical data indicated that they were indeed the corresponding diastereoisomers. There was a significant difference in their melting points and proton spectra (see experimental for details). The carbazole derivative **22** under these conditions yielded predominantly (9:1 ratio) one product **25**.

N-Alkyl heterocycles are generally synthesized by alkylation of the anion generated by sodamide [28], potassium hydroxide in dimethyl sulfoxide [29,30], under phase transfer catalysis [31], or with use of thallium salts [32]. Nitrogen heterocycles have been *N*-alkylated with dialkyl oxalates and potassium alkoxides [33]. In all these methods, alkylation of the heterocyclic nitrogen proceeds by formation of the C-N bond. The work described in the present paper offers an alternative method for elaborating the substituents at heterocyclic nitrogen atoms.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope, and are uncorrected. The ^{1}H nmr spectra were obtained on Varian XL200 (200 MHz, FT mode) or Varian XL300 (300 MHz, FT mode) spectrometers, with tetramethylsilane as internal standard. The ^{13}C nmr spectra were obtained on Varian XL200 (50 MHz) and XL300 (75 MHz) spectrometers.

General Procedure for Preparation of Adducts **2-9**. Method A.

Heterocycle (40 mmoles) was dissolved in 20 ml of dimethyl sulfoxide and sodium hydroxide powdered was added (3.2 g, 80 mmoles). The suspension was heated at 60° and then *N*-chloromethylbenzotriazole (6.7 g, 40 mmoles) was added at once. After 1 hour heating at the same temperature, the mixture was cooled down and poured onto 100 g of ice with rapid stirring. The precipitate appeared. After cooling the solid was filtered off, washed thoroughly with cold water (3 x 100 ml) and dried. Then each crude product was recrystallized from the appropriate solvent (see Table I).

Method B.

Sodium metal (0.92 g, 40 mmoles) was dissolved in absolute ethanol (250 ml). After exothermic reaction subsided, heterocycle (40 mmoles) was added. When the compound dissolved the *N*-chloromethylbenzotriazole was added at once; refluxing the solution for half an hour yielded white precipitate. The solvent was removed under the vacuum (35°/25 mm Hg). Water (100 ml) was added to the residue and the mixture was extracted with diethyl ether (3 x 100 ml). The organic layer was dried with magnesium sulfate (20 g) and the solvent removed under vacuum (20°/25 mm Hg) yielding the crude product, which was recrystallized from the appropriate solvent (see Table I).

General Procedure for Lithiation and Reaction with Electrophile.

A solution of *N*-(benzotriazol-1-methyl) heterocycle (4 mmoles) in dry tetrahydrofuran (100 ml) in a Shlenk type reactor under an argon atmosphere was cooled to -78° in a dry ice-acetone bath. *n*-Butyllithium (1.63 ml of 2.5 *M* solution in hexanes, 4.8 mmoles) was added dropwise, very slowly. The mixture developed intense dark color. It was kept at this temperature for 1 hour and then electrophile (5 mmoles) was added slowly (neat or in case of benzophenone in 2 ml of tetrahydrofuran). The color of the solution faded to light brown. The solution was allowed to warm up to the room temperature over a period of 12 hours. Then 100 ml of the saturated solution of ammonium chloride was added with vigorous stirring and 25 ml of water to dissolve the solid formed (lithium chloride). The mixture was extracted with diethyl ether (3 x 150 ml). The organic layer was washed with water (150 ml) and dried with magnesium sulfate (30 g). Removal of the solvent under vacuum (25°/25 mm Hg) yielded crude product which was either purified by column chromatography or precipitated with a mixture of diethyl ether-petroleum ether and then recrystallized from the appropriate solvent (see Table II).

Reduction of **13** and **30** with Zinc in Acetic Acid.

N-(Benzoylmethyl)indole (**17**).

The benzotriazole adduct (2 mmoles) was dissolved in the mixture of absolute ethanol (10 ml) and tetrahydrofuran (10 ml) and acetic acid was added (2 ml). Then zinc powder was added at once (0.33 g, 10 mmoles). The mixture was kept in the ultrasonic bath for 24 hours. Then 10 ml of ethanol was added and the suspension was filtered through celite 545. The filtrate was evaporated to dryness and the residue was treated with 50 ml of water and extracted with chloroform (3 x 50 ml). The organic layer was washed with water (50 ml), dried with magnesium sulfate (5 g). Removal of solvent gave solid (43% yield) that was recrystallized from ethanol, mp 134-135.5° (needles); ^{1}H nmr (300 MHz, dimethyl sulfoxide-d_6): 5.56 (s, 2H), 6.53 (d, J = 3 Hz, 1H), 7.06-7.15 (m, 4H), 7.51-7.64 (m, 4H); ^{13}C nmr (75 MHz, dimethyl sulfoxide-d_6): 51.4, 100.9, 108.3, 118.6, 119.9, 120.7, 127.1, 128.0, 128.2, 133.0, 133.7, 135.7, 192.5.

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.7; H, 5.6; N, 6.0. Found: C, 82.0; H, 5.6; N, 6.0.

N-(4-Methylbenzoylmethyl)pyrrole (**31**).

The adduct **30** (0.63 g, 2 mmoles) was dissolved in ethanol (50 ml) and acetic acid (15 ml) and activated zinc was added (2.6 g, 40 mmoles). The mixture was stirred at room temperature for 23 hours and then additional 50 ml of ethanol was added. The suspension was filtered to remove unsoluble material and the solvent was evaporated. Purification by column chromatography on silica gel using hexane-ethyl acetate (2:1) gave product (50% yield), mp 144-146° (microcrystals, ethanol); ^{1}H nmr (300 MHz, deuteriochloroform): 2.43 (s, 3H), 5.28 (s, 2H), 6.25-6.24 (m, 2H), 6.67-6.66 (m, 2H), 7.36-7.25 (m, 2H), 7.85 (d, J = 8 Hz, 2H); ^{13}C nmr (75 MHz, deuteriochloroform): 21.7, 55.3, 108.9, 121.9, 128.1, 129.6, 132.2, 144.9, 192.9.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 77.9; H, 6.6; N, 6.9.

General Procedure for the Reduction of Acyl and Benzoyl Adducts of Indole and Carbazole with Sodium Borohydride.

The acyl or benzoyl derivative of indole or carbazole (2 mmoles) was dissolved in ethanol (25 ml) and tetrahydrofuran (2 ml). Sodium borohydride (4 mmoles) was then added in one portion. The reaction was monitored by tlc. After 5 minutes there was no starting material left. The solution was treated with 10 ml of water, the mixture concentrated to about ½ its volume, and the organic material extracted with chloroform (3 x 25 ml). The organic layer was then washed with water (20 ml), dried (magnesium sulfate), and the solvent removed under vacuum to give the crude products which were purified accordingly.

1-Phenyl-2-(benzotriazol-1-yl)-2-(indol-1-yl)ethanol (**18**).

Prepared (95%) from **13** as a mixture of two diastereoisomers in (9:4) radio. Solid recrystallized from ethanol with broad melting point 200-222°; ^{1}H nmr (200 MHz, deuteriochloroform): 3.94 (d, J = 3.5 Hz, 1H), 4.17 (d, J = 4 Hz, 1H), 6.26-6.24 (m, 2H), 6.27 (d, J = 3 Hz, 1H), 6.43 (d, J = 4 Hz, 1H), 6.86-7.31 (m, 24H), 7.54-7.59 (m, 4H), 7.89-7.93 (m, 2H); ^{13}C nmr (50 MHz; deuteriochloroform): 72.1, 73.5, 73.9, 74.3, 104.4, 108.8, 109.2, 109.6, 119.7, 120.3, 120.5, 121.1, 121.2, 122.5, 124.2, 124.7, 125.0, 125.8, 126.2, 126.3, 128.0, 128.3, 128.4, 128.5, 128.6, 135.5, 136.6, 137.8, 137.9, 145.0, 145.2.

Anal. Calcd. for $C_{22}H_{18}N_4O$: C, 74.6; H, 5.1; N, 15.8. Found: C, 74.6; H, 5.1; N, 15.9.

3-Methyl-1-(benzotriazol-1-yl)-1-(indol-1-yl)-2-butanol (**19**).

Obtained (87%) as a mixture of two diastereoisomers (ratio 7:4) from **14**. They were separated based on their differing solubility in diethyl ether.

Isomer **1**.

The compound obtained as a solid (56% of the theoretical yield), mp 83-85° (leaflets from ethanol, hygroscopic material); ^{1}H nmr (200 MHz, deuteriochloroform): 1.03 (d, J = 7 Hz, 6H), 2.03-1.70 (m, 1H), 2.06 (s, 1H), 3.97 (d, J = 4 Hz, 1H), 4.87-4.97 (m, 1H), 6.55 (d, J = 4 Hz, 1H), 7.07-7.29 (m, 5H), 7.42-7.59 (m,

2H), 7.75-7.84 (m, 2H); ^{13}C nmr (50 MHz, deuteriochloroform): 16.8, 19.8, 29.8, 69.5, 76.6, 104.2, 108.9, 109.7, 119.6, 120.6, 121.2, 124.3, 127.9, 128.0, 128.3, 132.4, 136.5, 145.3.

Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.2; H, 6.3; N, 17.5. Found: 70.75; H, 6.3; N, 17.3.

Isomer **2**.

The compound insoluble in diethyl ether was obtained as a solid (31% of the theoretical yield), mp 201-203° (prisms from ethanol) (95%); ^{1}H nmr (200 MHz, dimethyl sulfoxide-d_6): 0.71-0.82 (m, 6H), 1.29-1.33 (m, 1H), 3.21 (s, 1H), 4.96-5.00 (m, 1H), 5.32-5.35 (m, 1H), 6.36 (d, J = 3 Hz, 1H), 6.79-7.26 (m, 3H), 7.31 (d, J = 7 Hz, 2H), 7.70-7.85 (m, 3H), 8.10 (d, J = 8 Hz, 1H); ^{13}C nmr (50 MHz, dimethyl sulfoxide-d_6): 14.9, 20.1, 29.1, 70.1, 73.2, 103.6, 110.0, 111.2, 119.1, 120.3, 120.7, 122.3, 124.2, 126.7, 127.5, 128.1, 133.1, 135.6, 145.0.

Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.2; H, 6.3; N, 17.5. Found: C, 70.8; H, 6.3; N, 17.3.

1-(Benzotriazol-1-yl)-1-(indol-1-yl)-2-pentanol (**20**).

Prepared (82%) from **15** as a mixture of two diastereoisomers that were partially separated by column chromatography on silica gel using chloroform.

Isomer **1**.

Prepared (45%) (calculated as a total yield of both pure isomer and from the unseparated mixture) as a hygroscopic solid, mp 79-80° (prisms from ethanol); ^{1}H nmr (200 MHz, deuteriochloroform): 0.86 (t, J = 7 Hz, 3H), 1.26-1.72 (m, 4H), 3.76 (d, J = 4 Hz, 1H), 5.06 (m, 1H), 6.67 (d, J = 3 Hz, 1H), 6.77 (d, J = 8 Hz, 1H), 7.10-7.33 (m, 5H), 7.36-7.62 (m, 3H), 7.89-7.93 (d, J = 9 Hz, 1H); ^{13}C nmr (200 MHz, deuteriochloroform): 13.7, 18.5, 34.4, 71.4, 72.6, 104.7, 108.9, 109.6, 119.8, 120.7, 121.5, 122.9, 124.6, 124.8, 128.3, 133.2, 135.8, 145.7.

Anal. Calcd. for $C_{19}H_{20}N_4O \cdot \frac{1}{2}H_2O$: C, 69.3; H, 6.4; N, 17.0. Found: C, 69.7; H, 6.5; N, 16.8.

Isomer **2**.

Prepared (37%) (calculated as a total yield of both pure isomer and from the unseparated mixture) as a solid, mp 156-158° (prisms from ethanol); ^{1}H nmr (200 MHz, deuteriochloroform): 0.91 (t, J = 7 Hz, 3H), 1.43-1.64 (m, 5H), 3.78 (d, J = 6 Hz, 1H), 5.15 (m, 1H), 6.55 (d, J = 3 Hz, 1H), 6.84 (d, J = 5 Hz, 1H), 7.05-7.27 (m, 5H), 7.62 (m, 2H), 7.91 (d, J = 9 Hz, 1H); ^{13}C nmr (50 MHz, deuteriochloroform): 13.7, 18.7, 34.6, 71.1, 71.9, 104.3, 108.7, 109.6, 119.8, 120.6, 121.4, 122.6, 124.5, 126.0, 128.3, 128.4, 132.6, 136.6, 145.4.

Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.2; H, 6.3; N, 17.5. Found: C, 71.2; H, 6.3; N, 17.5.

1-(Benzotriazol-1-yl)-1-(carbazol-1-yl)-2-pentanol (**25**).

Prepared (99%) from **22** predominantly as one diastereoisomer (9:1 ratio). Recrystallized from ethanol, mp 176-178° (prisms); ^{1}H nmr (200 MHz, deuteriochloroform): 0.83-0.95 (m, 3H), 1.42-1.74 (m, 4H), 3.18 (m, 1H), 5.63 (m, 1H), 6.88-7.23 (m, 9H), 7.63-7.67 (m, 1H), 7.96-8.03 (m, 3H); ^{13}C nmr (50 MHz, deuteriochloroform): 13.8, 18.7, 35.4, 70.0, 71.5, 109.1, 109.5, 119.8, 119.9, 120.3, 120.4, 120.5, 124.2, 124.5, 126.4, 128.2, 133.1, 139.2, 145.3.

Anal. Calcd. for $C_{22}H_{22}N_4O$: C, 74.6; H, 6.0; N, 15.2. Found: C, 74.4; H, 6.0; N, 15.3.

REFERENCES AND NOTES

[1] A paper in the Series "The Chemistry of Benzotriazole".

[2] D. E. Butler and S. M. Alexander, *J. Org. Chem.*, **37**, 215 (1957).

[3] A. R. Katritzky, C. Jayaram, and S. N. Vassilatos, *Tetrahedron*, 2023 (1983).

[4] A. R. Katritzky, N. E. Grzeskowiak, T. Siddiqui, C. Jayaram, and S. N. Vassilatos, *J. Chem. Res. (S)*, 26 (1982).

[5] D. J. Chadwick and R. I. Ngochindo, *J. Chem. Soc., Perkin Trans. 1*, 481 (1984).

[6] H. Ogura and H. Takahashi, *J. Org. Chem.*, **39**, 1374 (1974).

[7] M. R. Cuberes, M. Moreno-Manas, and A. Trius, *Synthesis*, 302 (1985).

[8] A. R. Katritzky, A. E. Abdel-Rahman, D. E. Leahy, and O. A. Schwarz, *Tetrahedron*, 4133 (1984).

[9] A. R. Katritzky, W. H. Ramer, and J. N. Lam, *J. Chem. Soc., Perkin Trans. 1*, 775 (1987).

[10] A. R. Katritzky, F. Saczewski, and C. M. Marson, *J. Org. Chem.*, **50**, 1351 (1985).

[11] A. R. Katritzky, S. Rachwal, K. C. Caster, (in part) F. Mahni, K. W. Law, and O. Rubio, *J. Chem. Soc., Perkin Trans. 1*, 781 (1987).

[12] A. R. Katritzky and J. N. Lam, manuscript in press.

[13] A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala, and L. Urogdi, *J. Chem. Soc., Perkin Trans. 1*, 225 (1989).

[14] A. R. Katritzky and M. Drewniak, *J. Chem. Soc., Perkin Trans. 1*, 2339 (1988).

[15] A. R. Katritzky and M. Drewniak, *Tetrahedron Letters*, 1755 (1988).

[16] Work concerned with hydroxylamines, hydrazines, and sulfonamides is ongoing in our laboratory.

[17] S. Julia, P. Sala, J. del Mazo, M. Sancho, C. Ochoa, J. Elguero, J. P. Fayet, and M. C. Vertut, *J. Heterocyclic Chem.*, **19**, 1141 (1982).

[18] The literature procedure [19] calls for reflux in large excess of thionyl chloride, these modified conditions were used in our laboratory.

[19] J. H. Burckhalter, V. C. Stephens, and L. A. R. Hall, *J. Am. Chem. Soc.*, **74**, 3868 (1952).

[20] L. Avila, J. Elguero, S. Julia, and J. M. del Mazo, *Heterocycles*, **20**, 1787 (1983).

[21] H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979).

[22] P. W. Alley and D. A. Shirley, *J. Org. Chem.*, **23**, 1791 (1958).

[23] J. V. Hay, D. E. Portlock, and J. F. Wolfe, *J. Org. Chem.*, **38**, 4379 (1973).

[24] B. A. Tertov, V. V. Burykin, and I. D. Sadekov, *Khim. Geterotsikl. Soedin.*, 560 (1969); *Chem. Abstr.*, **71**, 124328y (1969).

[25] A. R. Katritzky, G. W. Rewcastle, and L. M. Vazquez de Miguel, *J. Org. Chem.*, **53**, 794 (1988).

[26] A. R. Katritzky, G. W. Rewcastle, and W. Q. Fan, *J. Org. Chem.*, **53**, 5685 (1988).

[27] R. R. Fraser, T. S. Mansour, and S. Savard, *Can. J. Chem.*, **63**, 3505 (1985).

[28] C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos, and C. A. VanderWerf, *J. Am. Chem. Soc.*, **84**, 43 (1962); K. T. Potts and J. E. Saxton, *Org. Synth. Coll. Vol. V*, 769 (1973).

[29] H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 499 (1973).

[30] Y. Kikugawa, *Synthesis*, 124 (1981); Y. Kikugawa and Y. Miyake, *ibid.*, 461 (1981).

[31] V. Bocchi, G. Casnati, A. Dossena, F. Villani, *Synthesis*, 414 (1976); A. Barco, S. Benetti, and G. P. Pollini, *ibid.*, 124 (1976); E. Santaniello, C. Farachi, and F. Ponti, *ibid.*, 617 (1979).

[32] A. Shafiee and S. Sattari, *Synthesis*, 389 (1981).

[33] J. Bergman and P. Sand, *Tetrahedron Letters*, 1957 (1984).