PREPARATION OF SUBSTITUTED, ANNULATED BENZIMIDAZOLES VIA BENZYNE MEDIATED CYCLIZATION[1]

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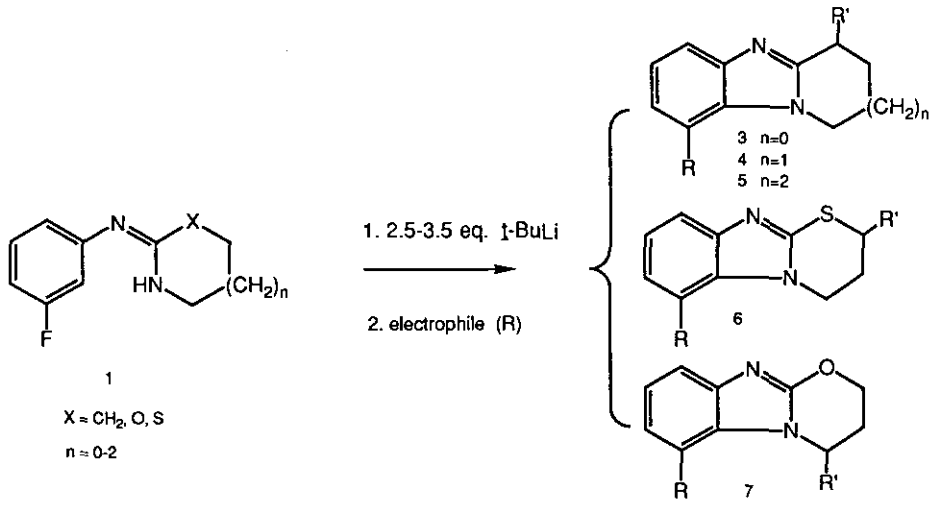
Abstract-The synthesis of 1,2-annulated benzimidazoles via an internal benzyne cyclization is described.

Most syntheses of unsymmetrically substituted benzimidazoles are either not regioselective or are lengthy.[2] However, we have shown that 1,3-benzoxazoles can be regiospecifically and conveniently synthesized from 3-fluoro-t-BOC anilides[3] via an intramolecular trapping of the benzyne resulting from ortho-directed lithiation followed by loss of LiF.[4] Electrophilic trapping of the resulting aromatic lithio species yields substituted benzoxazoles. We now report that a similar reaction occurs to form 1,2-annulated benzimidazoles from easily prepared amidines.[5] Furthermore, these can be regioselectively substituted with electrophiles, via trapping of the resulting anions.

Scheme 1



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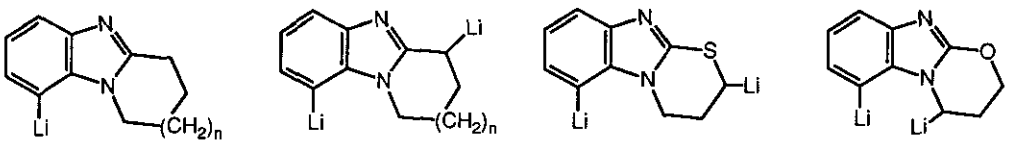
X = CH_2, O, S

n = 0-2

Thus, treatment of amidines (**1**) (Scheme I) with excess t-BuLi (3.3 equiv.) in tetrahydrofuran-hexane solution at -75 °C followed by warming to -25 °C and stirring for 2 hours generated the cyclized lithio species of types **2A-2D** (see Figure 1). Cooling the resulting mixture to -70 °C and quenching with an

Figure 1

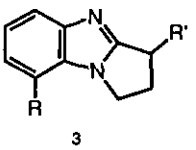


2A 2B 2C 2D

electrophile, followed by pouring into an aqueous buffer and extraction with EtOAc gave 7-substituted ring fused benzimidazoles (**3-7**) (Scheme I). The results of a number of experiments are presented in Table 1. Selective monoalkylation could be achieved on the aromatic ring by limiting the amount of base to about 2 equivalents (entries **11,14,16,17,19** and **20**) as compared to 3.3 equivalents of base which resulted in anions of structures **2B,2C** and **2D** (Figure 1) (entries **4-10,13,18,21** and **24**). The use of excess base coupled with slower warming and excess electrophile occasionally resulted in trisubstituted products (entry **15**). Attempts to achieve selective monoalkylation on the piperidine ring (i.e. structure **2B**) using one equivalent of MeI gave a mixture containing both dialkylated, monoalkylated and nonalkylated materials (by tlc). In the thiazine case, quenching with octyl iodide gave a mixture from which the monoalkylated product (entry **22**) was isolated.

In the case of benzyl cyanide quench, only triphenyltriazine[6] was isolated, possibly via an electron transfer process. Valeronitrile quench gave the cyclized but unsubstituted product resulting from α-hydrogen abstraction rather than addition to the nitrile. It is interesting to note that 6 membered rings formed in the highest yield while the formation of 5 and 7 membered rings resulted in lower yields (entries **1-3**). Therefore, it would appear that ring size of the products is an important constraint in this reaction. In the case of other heterocycles, although both oxazines and thiazines underwent the cyclization reaction in good yeild, the 5 membered ring thiazole analog failed to give cyclized material. In the thiazine case (entries **13,15,18,**and **21**), the hydrogen on the carbon adjacent to the sulfur atom was acidic enough that

Table 1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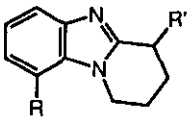
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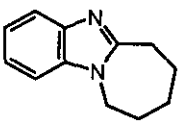
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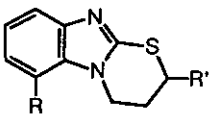
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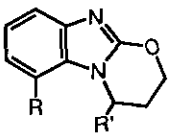
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entry	n(1)	X(1)	electrophile [a]	equiv. base	product [e]	yield(%)[f]	mp °C
1.	0	CH_2	H_2O	2.3	**3a**,R=R'=H	65	110-112[7]
2.	1	CH_2	H_2O	2.3	**4a**,R=R'=H	85	244-245[b]
							99-100[8]
3.	2	CH_2	H_2O	2.3	**5a**,R=R'=H	30	175-180[b]
							120-122[9]
4.	0	CH_2	$(PhS)_2$	3.3	**3b**,R=R'=SPh	23	c.
5.	1	CH_2	$(PhS)_2$	3.3	**4c**,R=R'=SPh	25	95-99
6.	1	CH_2	MeI	3.3	**4b**,R=R'=CH_3	74	>240[b]
7.	1	CH_2	EtI	3.3	**4d**,R=R'=CH_2CH_3	21	178-181[b]
8.	1	CH_2	4-t-Butylcyclo-hexanone	3.3	**4e**,R=R'=$C_{10}H_{20}OH$	27	>220
9.	1	CH_2	PhCHO	3.3	**4f**,R=R'=CH(OH)Ph	39	d.
10.	1	CH_2	TMSCl	3.3	**4g**,R=R'=$Si(CH_3)_3$	32	c.
11.	1	CH_2	TMSCl	2.2	**4h**,R=$Si(CH_3)_3$,R'=H	30	99-102
12.	1	S	H_2O	2.2	**6a**,R=R'=H	62	181-183
13.	1	S	CH_3I	3.3	**6b**,R=R'=CH_3	60	175-177
14.	1	S	$(PhS)_2$	2.2	**6c**,R=SPh,R'=H	23	128-130
15.	1	S	$(PhS)_2$	3.3	**6d**,R=SPh,R'=$(SPh)_2$	26	181-184

16.	1	S	4-t-Butylcyclo-hexanone	2.2	**6e**,R=$CH_{10}H_{20}OH$,R'=H	27	171-173
17.	1	S	PhCHO	2.2	**6f**,R=CH(OH)Ph,R'=H	35	160(decomp.)
18.	1	S	PhCHO	3.3	**6g**,R=R'=CH(OH)Ph	14	c.
19.	1	S	DMF	2.2	**6h**,R=CHO,R'=H	41	160-161
20.	1	S	TMSCl	2.2	**6i**,R=$Si(CH_3)_3$,R'=H	63	127-129
21.	1	S	TMSCl	3.3	**6j**,R=R'=$Si(CH_3)_3$	7	191-193
22.	1	S	$C_8H_{17}I$	2.3	**6k**,R=H,R'=C_8H_{17}	32	171-173
23.	1	O	H_2O	3.3	**7a**,R=R'=H	90	115-118[10]
24.	1	O	CH_3I	3.3	**7b**,R=R'=CH_3	86	112-115

a) The electrophile was always used in excess relative to the base. b) HCl salt. c) oil. d) isomer 4f-I mp 189-193 °C, yield 12%; isomer 4f-II mp 118-122 °C, yield 12%; isomer 4f-III mp178-180 °C, yield 15%. e) Analytical data can be found in reference 11 and Table 2. f) Yields are not optimized.

the dianion (**2C**) was formed as evidenced by the observed alkylation products. In the oxazine cases, excess base abstracted the proton next to the imidazole ring (dianion **2D**) resulting in the dimethyl compound(**7b**)as the major product (entry **24**). The structure of this compound was determined by nOe experiments.[11] Attempts to obtain this type of product by lithiation of the parent compound **7a**, followed by quenching with MeI gave a complex mixture in which **7b** was not a major product. This would suggest that the aromatic lithio species first formed after cyclization facilitates the second deprotonation to dianion(**2D**).
Thus, this type of internal benzyne cyclization is quite useful in synthesizing ring fused benzimidazoles, with the added feature of allowing a great deal of substitution to be selectively achieved in a single step.

EXPERIMENTAL

Silica gel chromatography was performed using 70-230 mesh (Merck) silica gel. Melting points are uncorrected. ^1H And ^{13}C nmr spectra were measured on a Bruker AM 500 spectrometer in $CDCl_3$ solution referenced to internal tetramethylsilane unless otherwise noted.

TYPICAL PROCEDURE

1,2,3,4-Tetrahydropyrido[1,2-a]benzimidazole (4a)

The starting amidine was prepared following the procedure of Loev, et al. [5] for similiar amidines. Thus, to 20.3 g (0.2 mol) of caprolactam in 40 ml of toluene were added 10 ml of phosphorus oxychloride in 20 ml of toluene. The resulting mixture was stirred at room temperature for 5 h. Then 13.8 ml (16 g, 0.14 mol) of 3-fluoroaniline in 20 ml of toluene were added and the mixture was heated at reflux for 18 h. The mixture was cooled to room temperature and the solvent was decanted. Fresh toluene was added and the mixture was made basic by addition of 20% NaOH. The resulting mixture was stirred at room temperature for 2 h, and then diluted with 30 ml of water. The layers were separated and the aqueous layer was washed with toluene. The organic layer was dried over Na_2SO_4 and solvent was removed in vacuo . The resulting oil was taken up in i-PrOH and a solution of 20% HCl in MeOH was added until the solution was acidic. The hydrochloride salt precipitated upon addition of ethyl ether. The solid was removed by filtration and dried to afford 32.4 g (98%) of the amidine hydrochloride: mp 189-192 °C.

The amidine hydrochloride (1 g, 4.4 mmol) was partitioned between 10 ml of 30% NH_4OH and 100 ml of CH_2Cl_2. The organic layer was evaporated under reduced pressure. Toluene was added and then removed under reduced pressure to remove any residual water. The waxy yellow residue was placed under vacuum for 2 h and was then taken up in 50 ml of freshly distilled THF. The solution was cooled under argon to -75 °C and 7.3 ml of 1.5 M t-BuLi (2.5 equiv.) were added dropwise. The resulting yellow solution was warmed to -30 °C and stirred at that temperature for 2 h. Yellow precipitates formed. The mixture was cooled to -70 °C and 15 ml of H_2O were added rapidly. The mixture was diluted with Et_2O, washed with saturated NH_4Cl solution, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give 0.66 g (87%) of yellow solid. Recrystallization from cyclohexane gave tan crystals, mp 99-100 °C (Lit.7 mp 101-102 °C). ^1H Nmr ($CDCl_3$) δ 2.10 (4H, m, CH_2CH_2), 3.09 (2H, t, J=6.4 Hz), 4.09 (2H, t, J=6.1 Hz, NCH_2), 7.76 (3H,m),7.69 (1H,m); ms(EI) m/z 172(M^+).

4,9-Dimethyl-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (4b)

To 0.9 g (4.3 mmol) of the free base of the amidine prepared above in 50 ml of THF were added slowly 10 ml of 1.6 M t-BuLi (3.6 equiv.) at -70 °C. The yellow solution was allowed to stir at -30 °C for 2 h. The mixture was cooled to -70 °C and 0.8 ml (3 equiv.) of MeI was added. The mixture was allowed to warm to 0 °C and diluted with Et_2O, washed with saturated NH_4Cl solution, dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to give 0.87 g (74%) of yellow oil. Chromatography (30% EtOAc in hexane) gave 850 mg of **4b**, mp 91-94 °C.[11] Conversion to the hydrochloride (i-PrOH, HCl in Et_2O) gave 600 mg of the hydrochloride salt, mp >240 °C.

Table 2

		Calculated			Observed		
Compound	Formula	C	H	N	C	H	N
3b.	$C_{22}H_{18}N_2S_2 \cdot 0.25H_2O$	69.73	4.92	7.39	69.79	5.08	7.34
4b.	$C_{13}H_{16}N_2$	77.96	8.05	13.98	77.95	8.05	13.69
4c.	$C_{23}H_{20}N_2S_2$	71.12	5.19	7.21	71.53	5.39	6.91
4d.	$C_{15}H_{20}N_2 \cdot HCl \cdot 0.25H_2O$	66.89	8.05	10.40	66.59	7.68	10.59
4e.	$C_{31}H_{48}N_2O_2 \cdot 0.25H_2O$	76.73	10.08	5.77	76.80	9.90	5.61
4f-I.	$C_{25}H_{24}N_2O_2 \cdot 0.25H_2O$	77.19	6.35	7.20	77.20	6.41	6.71
4f-II.	$C_{25}H_{24}N_2O_2 \cdot 1.2H_2O$	73.94	6.55	6.90	73.97	6.28	6.37
4f-III.	$C_{25}H_{24}N_2O_2 \cdot 0.25H_2O$	77.19	6.35	7.20	76.97	6.42	6.84
4g.	$C_{17}H_{28}N_2Si_2 \cdot 1.25H_2O$	60.26	9.06	8.27	60.05	8.77	7.95
4h.	$C_{14}H_{20}N_2Si \cdot 0.25H_2O$	67.55	8.30	11.25	67.53	8.32	10.86
6a.	$C_{10}H_{10}N_2S$	63.14	5.30	14.73	63.75	5.41	14.66
6b.	$C_{12}H_{14}N_2S$	66.03	6.47	12.84	65.69	6.40	12.47
6c.	$C_{16}H_{14}N_2S_2$	64.42	4.73	9.39	64.80	4.84	9.51
6d.	$C_{28}H_{22}N_2S_4$	69.69	4.60	5.81	69.36	4.98	5.62

6e.	$C_{20}H_{28}N_2OS \cdot EtOAc$	69.73	8.19	8.13	66.63	8.38	6.47
6f.	$C_{17}H_{16}N_2OS \cdot H_2O$	64.95	5.77	8.91	65.21	5.89	8.70
6g.	$C_{24}H_{22}N_2O_2S \cdot H_2O$	71.62	5.51	6.96	71.47	5.37	6.59
6h.	$C_{11}H_{10}N_2OS$	60.53	4.62	12.83	60.64	4.90	12.62
6i.	$C_{13}H_{18}N_2SSi$	59.49	6.91	10.67	59.11	6.98	10.92
6j.	$C_{16}H_{26}N_2SSi_2$	57.43	7.83	8.37	57.81	7.92	8.01
6k.	$C_{18}H_{26}N_2S$	71.47	8.66	9.26	71.81	8.27	8.91
7b.	$C_{12}H_{14}N_2O \cdot 0.6H_2O$	67.64	7.19	13.15	67.23	6.89	12.86

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10. Lit. mp 116.5-118.5 °C, J. B. Van Den Berk, L. E. J. Kennis, M. J. M. C. Van Der Au, and A. A. M. T. Van Heertum, Ger. Patent, 2,632,870, (Chem Abstr., *87*, 23274).

11. All new compounds gave ir, ^{1}H nmr (300MHz), mass spectra (ms) consistent with their assigned structures. See Table 2 for combustion analyses. Selected data: **4b**: mp 91-94 °C; ^{1}H nmr (DMSO) δ 1.54 and 1.56 (3 H, d, J=7.03Hz ,2°C$\underline{H}_3$), 1.69 (1H, m), 2.10 (3H, m), 2.77 (3H, s, ArC$\underline{H}_3$), 3.34 (1H, m), 4.60 (2H, m, NC$\underline{H}_2$), 7.27 (1H, m), 7.41 (1H, m), 7.60 (1H, m). Saturation of the H at 2.77 showed nOe effect at 4.60. Ms (EI) m/z 200 (M+).

4g: mp 99-102 °C; ^{1}H nmr: δ 0.45 (9H, m, Si(C$\underline{H}_3$)$_3$), 2.10 (4H, m, C$\underline{H}_2$-C$\underline{H}_2$), 3.10 (2H, t, J=6.5 Hz, N=C-C$\underline{H}_2$), 4.28 (2H, t, J=6.0 Hz, N-C$\underline{H}_2$), 7.20 (1H, m, Ar-$\underline{H}$), 7.37 (1H, m, Ar-$\underline{H}$), 7.70 (1H, m, Ar-$\underline{H}$). Ms(CI) m/z 229 (M+-CH_3), 244 (M+).

6a: mp 181-183 °C (EtOAc); ^{1}H nmr δ 2.48 (2H, m, C$\underline{H}_2$), 3.23 (2H, t, J=5.9 Hz, C$\underline{H}_2$), 4.19 (2H, t, J=5.9 Hz, C$\underline{H}_2$), 7.23 (3H, m), 7.61 (1H, m); Ms (EI) m/z 190 (M+).

6h: mp 160-161 °C (EtOAc/Hexane); ir sharp 1675 cm^{-1}(-CHO); ^{1}H nmr (CD_3OD) δ 2.00 (2H, m, -C$\underline{H}_2$), 3.05 (2H, t, J=6.1 Hz, -C$\underline{H}_2$), 3.45 (2H, t, J=6.05 Hz, - C$\underline{H}_2$), 6.65 (1H, dt, J=1.90, 5.9 Hz), 7.33 (1H, t, J=5.9 Hz), 7.48 (1H, dd, J=1.9, 5.9 Hz), 10.60 (1H, s, -C$\underline{H}$O). Ms (EI) m/z 219 (M+H)+.

6j: mp 191-193 °C (EtOAc/Hexane); ^{1}H nmr δ 0.20 (9H, s, -Si(C$\underline{H}_3$)$_3$), 0.45 (9H, s, -Si(C$\underline{H}_3$)$_3$), 2.12 (1H, m, -C$\underline{H}_2$-), 2.52 (1H, m, -C$\underline{H}_2$-), 2.77 (1H, dd, J=2.3, 12.4 Hz, -SC$\underline{H}$Si), 4.07 (1H, dt, J=3.4, 12.4 Hz, -C$\underline{H}_2$N), 4.73 (1H, dt, J=2.3, 12.4 Hz, -C$\underline{H}_2$N), 7.17 (1H, dd, J=7.3, 7.9 Hz, Aryl-$\underline{H}$), 7.34 (1H, dd, J=1.3, 7.3, Aryl-$\underline{H}$), 7.75 (1H, dd, J=1.3, 7.9 Hz, Aryl-$\underline{H}$). Ms(EI) m/z 334 (M+).

6k: mp 171-173 °C (hexane); ^{1}H nmr δ 0.89 (3H, t, J=6.8 Hz, C$\underline{H}_3$), 1.25 (14H, m, -(C$\underline{H}_2$)$_7$-), 2.12 (1H, dt, J=6.2, 12.5 Hz, -C$\underline{H}_2$-), 2.51 (1H, m, -C$\underline{H}_2$-), 3.45 (1H, dd, J= 4.7, 6.8 Hz, C$\underline{H}$S), 4.15 (1H, dt, J=2.8, 6.2 Hz, C$\underline{H}_2$N), 4.35 (1H, dt, J=2.8, 6.2 Hz, C$\underline{H}_2$N), 7.21 (3H, m, Aryl-$\underline{H}$), 7.64 (1H, dd, J=5.7, 8.9Hz); Ms(EI) m/z 302(M+).

7b: mp 112-115 °C; ^{1}H nmr δ 1.59 (3H, d, J=6.5 Hz, -C$\underline{H}_3$), 1.95 (1H, dd, J=1.9,14.3 Hz,C$\underline{H}$CH_3),

2.50 (1H, m), 2.63 (3H, s, ArylC$\underline{H}_3$), 4.54 (2H, m), 4.90 (1H, m), 6.85 (1H, d, J=7.4Hz), 7.05 (1H, t,J=7.7 Hz), 7.30 (1H, d, J=7.8 Hz). Irradiation of the signal at 2.63 ppm (the methyl on the aromatic ring) gave an nOe effect at 1.95 ppm (the single proton adjacent to the nitrogen of the imidazole ring as well as the methyl group on the saturated ring. If the methyl group were elsewhere on the saturated ring, one would not expect to observe any nOe effect on irradiation at the aromatic methyl signal. Ms(EI) m/z 202 (M+), 187 (M-CH_3).

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