SYNTHESIS OF 3-ARYLPYRROLIDINES BY CYCLOADDITIONS OF *N,N*-BIS(BENZOTRIAZOLYLMETHYL)AMINES TO STYRENES

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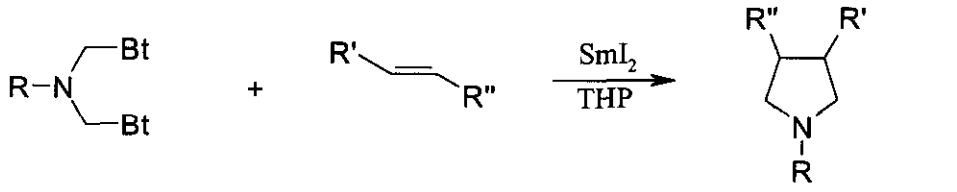
Abstract-A novel synthesis of 3-arylpyrrolidines (**3a-m**) *via* the cycloaddition of bis-benzotriazole derivatives to styrenes is described.

Numerous natural products incorporate pyrrolidine rings. Rapid syntheses of pyrrolidines, especially methods which form more than one ring bond in a single operation, are most desirable.[1] Such reactions generally involve cycloadditions. The 1,3-dipolar cycloaddition of an azomethine ylide to an olefin represents a highly convergent approach for the construction of a pyrrolidine ring,[2] *e.g.* Roussi and Zhang[3] and Laborde[4] utilized nonstabilized azomethine ylides prepared from tertiary amine oxides, and from azidine, respectively. A related, but less developed preparation of pyrrolidines is the cycloaddition of 2-azaallyl anions with alkenes,[1,5] although intramolecular anionic cyclizations have recently become increasingly popular for the preparation of carbocyclic (see 6, 7 for leading references) and heterocyclic ring systems.[8-11]

Extensive investigations in our group have shown that benzotriazole is a useful synthetic auxiliary.[12] Recently we found that C-benzotriazole bonds can be transformed into the corresponding carbanions *via* lithium or samarium(II) iodide.[13-15] Coldham *et al.* also recently found that olefinic aminomethyllithiums, generated by lithium-tin exchange from the corresponding stannane, undergo cyclization with unactivated double bonds to give 3-substituted pyrrolidines.[16,17] Some 3-arylpyrrolidines were previously prepared by 1,3-dipolar cycloaddition of azomethine ylides to styrenes.[3,4] We now report the use of benzotriazole methodology for the generation of anions which subsequently react with alkenes to afford pyrrolidines bearing an aromatic or heteroatom substituent at the C-3 position.

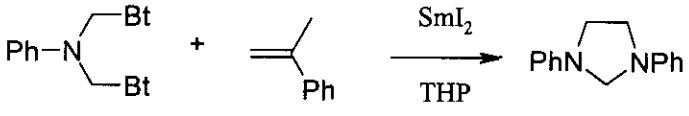


1 **2** **3a-m** (see Table 1)

1a:	R = benzyl	**2a**:	R' = Ph, R" = H
1b:	R = *n*-butyl	**2b**:	R' = 4-fluorophenyl, R" = H
1c:	R = phenyl	**2c**:	R' = 4-methylphenyl, R" = H
1d:	R = cyclohexenyl	**2d**:	R' = trimethylsilyl, R" = H
1e:	R = CH*MePh	**2e**:	R' = Ph, R" = Ph
1f:	R = CHMePh		

Scheme 1

N,N-Bisbenzotriazole derivatives (**1a-f**) were readily prepared from the reaction of 1-hydroxymethylbenzotriazole and the appropriate amine.[18] Addition of compound (**1**) and an alkene to a SmI_2 solution at 0°C with subsequent stirring of the mixture at the same temperature for a few hours, and then at room temperature for two days, afforded the pyrrolidine (**3**) in good yield (Table 1). Performing the reaction of **1a** with **2a** in THF gave **3a** in a low yield (22%, by GC/MS). Probably, this is due to proton abstraction from the solvent by the anion to reform **1a**. Changing the solvent to THP overcame the problem, as we found previously,[14] and this procedure gave **3a** in 84% yield (GC result). However, the reaction of **1a** with *trans*-stilbene still gave *trans*-**3e** in low yield (17%, GC result), probably because the conjugated double bond does not react readily with an anion. Attempts to use **1a** in reactions with α-methylstyrene or *trans*-β-methylstyrene also failed; the major product was *N*-methylbenzylamine from decomposition of starting material. Compound (**1c**) was also reacted with α-methylstyrene; this time compound (**4**) was the major product, according to GC/MS and ^{1}H NMR results.



1c **4**

Scheme 2

The range of R groups employed include aryl, alkyl and cycloalkyl. For the anionophile, styrene itself and styrenes carrying a substituent in the aromatic ring, such as methyl or fluoro, were used to afford 3-aryl substituted pyrrolidines. Vinyltrimethylsilane also was used as the anionophile to give 3-heteroatom substituted pyrrolidines. However, attempts to extend the anionophile to unactived alkenes failed.

Table1. Cyclization of Compounds (**1a-f**) with Anionophiles (**2a-e**).

Product **3**	Starting materials		R	R'	R"	Total GC yield %[a]
a	1a	2a	benzyl	phenyl	H	84 (53)
b	1a	2c	benzyl	4-Me-phenyl	H	54 (49)
c	1a	2b	benzyl	4-F-phenyl	H	52 (50)
d	1a	2d	benzyl	trimethylsilyl	H	78 (70)
e	1a	2e	benzyl	phenyl	Ph	17 (15)
f	1b	2b	*n*-butyl	4-F-phenyl	H	50 (40)
g	1b	2a	*n*-butyl	phenyl	H	70 (59)
h	1b	2c	*n*-butyl	4-Me-phenyl	H	73 (53)
i	1b	2d	*n*-butyl	trimethylsilyl	H	94 (85)
j	1c	2a	phenyl	phenyl	H	69 (60)
k	1d	2d	cyclohexyl	trimethylsilyl	H	60 (52)
l	1e	2a	(*R*)-α-methylbenzyl	phenyl	H	62 (60)
m	1f	2a	α-methylbenzyl	phenyl	H	80 (80)

[a] Isolated yield in parenthesis. All compounds (**3a-m**) are oils.

In conclusion, the present strategy provides an effective synthesis of 1-substituted 3-arylpyrrolidines in a convenient one-pot procedure. The syntheses of compounds (**3a**) and (**3b**) were previously reported:[3,4,19-21] our new procedure has resulted in the preparation of novel analogues (**3c-3m**). Advantages of our methodology include readily available starting material, good yields and general applicability for the synthesis of this type of substituted pyrrolidine.

EXPERIMENTAL

General Comments. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Gemini-300 spectrometer in $CDCl_3$ with TMS or $CDCL_3$, respectively, as the internal reference. Column chromatography was carried out on neutral alumina (Brockman Activity I, 60 - 325 mesh). Tetrahydrofuran was freshly distilled from sodium-benzophenone.

General Procedure for the Synthesis of Compounds (3a-m). Samarium(II) iodide was first prepared from Sm (0.49 g, 3.3 mmol) and I_2 (0.76 g, 3 mmol) in THP (5 mL). Benzotriazole derivative (**1a-f**) (1 mmol) and anionophile (**2a-e**) (0.5 mmol) were added to the freshly prepared SmI_2 solution at 0 °C. The mixture was stirred at the same temperature for a few hours and at rt for two days. The reaction was quenched with water, extracted with ethyl acetate and dried (Na_2SO_4). After evaporation of the solvent, the crude product was subjected to column chromatography using hexanes and ethyl acetate (100 : 1) as eluent to afford the pure product (**3a-m**).

1-Benzyl-3-phenylpyrrolidine (**3a**): ^1H NMR δ: 7.50-7.10 (m, 10H), 3.67 (s, 2H), 3.46-3.28 (m, 1H), 3.04 (t, 1H, J = 8.0 Hz), 2.92-2.78 (m, 1H), 2.77-2.62 (m, 1H), 2.50 (t, 1H, J = 8.0 Hz), 2.43-2.25 (m, 1H), 1.98-1.80 (m, 1H), ^{13}C NMR δ: 145.7, 139.3, 128.8, 128.3, 128.2, 127.3, 126.9, 126.0, 62.3, 60.6, 54.6, 43.3, 33.3. HRMS Calcd for $C_{17}H_{19}N$: 237.1517. Found 237.1498

1-Benzyl-3-(4'-methylphenyl)pyrrolidine (**3b**): ^1H NMR δ: 7.45-7.21 (m, 5H); 7.16 (d, 2H, J = 8.8 Hz), 7.09 (d, 2H, J = 7.9 Hz), 3.66 (s, 2H), 3.43-3.25 (m, 1H), 3.03 (t, 1H, J = 8.0 Hz), 2.83 (q, 1H, J = 6.0 Hz), 2.66 (q, 1H, J = 6.0 Hz), 2.46 (t, 1H, J = 8.1 Hz), 2.31 (s, 3H), 2.30-2.10 (m, 1H), 1.95-1.78 (m, 1H); ^{13}C NMR δ: 142.6, 139.3, 135.5, 129.0, 128.8, 128.2, 127.2, 126.8, 62.4, 60.7, 54.6, 43.0, 33.3, 20.9. Anal Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.81; H, 8.90; N, 5.69.

1-Benzyl-3-(4'-fluorophenyl)pyrrolidine (**3c**): ^1H NMR δ: 7.40-7.12 (m, 7H), 6.99-6.90 (m, 2H), 3.67 (s, 2H), 3.41-3.27 (m, 1H), 3.00-2.90 (m, 1H), 2.86-2.65 (m, 2H), 2.50-2.40 (m, 1H), 2.40-2.25 (m, 1H), 1.90-1.75 (m, 1H); ^{13}C NMR δ: 161.3 (J = 240.0 Hz), 141.2, 138.9, 128.8, 128.6 (J = 7.5 Hz), 128.3, 127.0, 115.1 (J = 20.7 Hz), 62.2, 60.5, 54.5, 42.6, 33.4. HRMS Calcd for $C_{17}H_{18}NF$: 255.1423. Found: 255.1372.

1-Benzyl-3-trimethylsilylpyrrolidine (**3d**): ^{1}H NMR δ: 7.40-7.20 (m, 5H), 3.64 (s, 2H), 2.92-2.80 (m, 2H), 2.31-2.20 (m, 1H), 2.28-2.08 (m, 1H), 2.04-1.88 (m, 1H), 1.70-1.58 (m, 1H), 1.47-1.28 (m, 1H), 0.00 (s, 9H); ^{13}C NMR δ: 138.4, 128.8, 128.2, 126.9, 60.7, 56.3, 54.9, 25.3, 24.1, -3.0. HRMS Calcd for $C_{14}H_{23}NSi$: 233.1600. Found: (M^++1) 234.1661.

1-Benzyl-3,4-diphenylpyrrolidine (**3e**): ^{1}H NMR δ: 7.60-7.52 (m, 2H), 7.50-7.20 (m, 13H), 3.84, 3.75 (AB, 2H, J = 15.0 Hz), 3.50-3.38 (m, 2H), 3.28-3.17 (m, 2H), 2.98-2.88 (m, 2H); ^{13}C NMR δ: 144.2, 139.2, 137.3, 128.7, 128.4, 128.3, 127.6, 127.4, 126.9, 126.5, 126.2, 62.6, 60.5, 53.2. HRMS Calcd for $C_{23}H_{23}N$: 313.1830. Found: 313.1738.

1-Benzyl-3-(4'-fluorophenyl)pyrrolidine (**3f**): ^{1}H NMR δ: 7.32-7.20 (m, 2H), 7.08-6.94 (m, 2H), 3.40-3.30 (m, 1H), 3.10-3.00 (m, 1H), 2.90-2.80 (m, 1H), 2.70-2.60 (m, 1H), 2.58-2.28 (m, 4H), 1.92-1.78 (m, 1H), 1.60-1.48 (m, 2H), 1.48-1.30 (m, 2H), 0.96 (t, 3H, J = 7.4 Hz); ^{13}C NMR δ: 161.3 (J = 240.0 Hz), 141.3, 128.6 (J = 7.5 Hz), 115.1 (J = 22.5 Hz), 62.5, 56.3, 54.7, 42.7, 39.4, 31.1, 20.8, 14.1. HRMS Calcd for $C_{14}H_{20}NF$: 221.1580. Found: 221.1481.

1-Butyl-3-phenylpyrrolidine (**3g**): ^{1}H NMR δ: 7.38-7.18 (m, 5H), 3.48-3.30 (m, 1H), 3.15-3.06 (m, 1H), 2.95-2.85 (m, 1H), 2.70-2.30 (m, 5H), 2.00-1.82 (m, 1H), 1.69-1.50 (m, 2H), 1.48-1.30 (m, 2H), 0.96 (t, 3H, J=7.2 Hz); ^{13}C NMR δ: 145.5, 128.3, 127.2, 125.9, 62.4, 56.4, 54.8, 43.4, 33.2, 31.1, 20.8, 14.0. Anal Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.28; H, 10.57; N, 7.18.

1-Butyl-3-(4'-methylphenyl)pyrrolidine (**3h**): ^{1}H NMR δ: 7.20-7.06 (m, 4H), 3.40-3.27 (m, 1H), 3.10-3.00 (m, 1H), 2.91-2.80 (m, 1H), 2.66-2.38 (m, 4H), 2.35-2.22 (m, 4H), 1.90-1.78 (m, 1H), 1.60-1.45 (m, 2H), 1.45-1.30 (m, 2H), 0.93(t, 3H, J = 7.4 Hz); ^{13}C NMR δ: 142.4, 135.4, 129.0, 127.1, 62.5, 56.4, 54.7, 43.0, 33.2, 31.1, 20.9, 20.8, 14.0. Anal Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.66. Found: C, 82.55; H, 11.10.

1-Butyl-3-trimethylsilylpyrrolidine (**3i**): ^{1}H NMR δ: 3.00-2.88 (m, 2H), 2.48-2.40 (M, 2H), 2.20-2.08 (m, 1H), 2.06-1.80 (m, 2H), 1.68-1.45 (M, 3H), 1.42-1.30 (m, 3H), 0.94 (t, 3H, J = 7.4 Hz), 0.01 (s, 9H); ^{13}C NMR δ: 56.4, 56.3, 55.1, 31.4, 25.9, 24.1, 20.9, 14.1, -3.0. HRMS Calcd for $C_{11}H_{25}NSi$: 199.1756. Found: (M^++1) 200.1784.

1,3-Diphenylpyrrolidine (**3j**): ^{1}H NMR δ: 7.35-7.20 (m, 7H); 6.68 (t, 1H, J = 7.3 Hz), 6.58 (d, 2H, J = 8.2 Hz), 3.74-3.68 (m, 1H), 3.53-3.32 (m, 4H), 2.43-2.36 (m, 1H), 2.20-2.08 (m, 1H); ^{13}C NMR δ: 147.6,

142.7, 129.2, 128.6, 127.1, 126.6, 115.7, 111.6, 54.4, 47.6, 44.1, 33.2. HRMS Calcd for $C_{16}H_{17}N$: 223.1361. Found: 223.1360.

1-Cyclohexyl-3-trimethylsilylpyrrolidine (**3k**): ^{1}H NMR δ: 3.18-2.98 (m, 2H), 2.20-2.08 (m, 1H), 2.00-1.82 (m, 5H), 1.80-1.68 (m, 2H), 1.64-1.52 (m, 2H), 1.40-1.10 (m, 6H); ^{13}C NMR δ: 53.7, 52.3, 49.4, 32.4, 32.3, 29.0, 26.1, 25.7, 25.2, 23.8, -3.0. HRMS Calcd for $C_{13}H_{27}NSi$: 225.1913. Found: 225.1881.

1-[(*R*)-α-Methylbenzyl]-3-phenylpyrrolidine (**3l**): ^{1}H NMR δ: ^{1}H NMR δ: 7.40-7.10 (m, 10H), 3.40-3.22 (m 2H), 3.18-3.10+2.78-2.52 (m, 2H), 3.00-2.85 (m, 1H), 2.50-2.40 (m, 1H), 2.40-2.20 (m, 1H), 1.96-1.80 (m, 1H), 1.44 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ: 145.7, 145.6, 128.3, 127.3, 127.1, 126.8, 126.7, 125.9, 65.8, 61.2, 61.0, 53.3, 53.2, 43.3, 33.2, 33.0, 23.3, 23.1. Anal Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 86.14; H, 8.87; N, 5.99.

1-[(*R,S*)-α-Methylbenzyl]-3-phenylpyrrolidine (**3m**): ^{1}H NMR δ: 7.40-7.10 (m, 10H), 3.40-3.22 (m 2H), 3.18-3.10+2.78-2.52 (m, 2H), 3.00-2.85 (m, 1H), 2.50-2.40 (m, 1H), 2.40-2.20 (m, 1H), 1.96-1.80 (m, 1H), 1.44 (d, 3H, J = 6.6 Hz); ^{13}C NMR δ: 145.7, 145.6, 128.3, 127.3, 127.1, 126.8, 126.7, 125.9, 65.8, 61.2, 61.0, 53.3, 53.2, 43.3, 33.2, 33.0, 23.3, 23.1.

1,3-Diphenylimidazolidine (**4**): ^{1}H NMR δ: 7.30 (t, 4H, J = 7.4 Hz), 6.81 (t, 2H, J = 7.3 Hz), 6.66 (d, 4H, J = 7.8 Hz), 4.66 (s, 2H), 3.64 (s, 4H); ^{13}C NMR δ: 146.4, 129.3, 117.6, 112.4, 65.8, 46.4.

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