

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

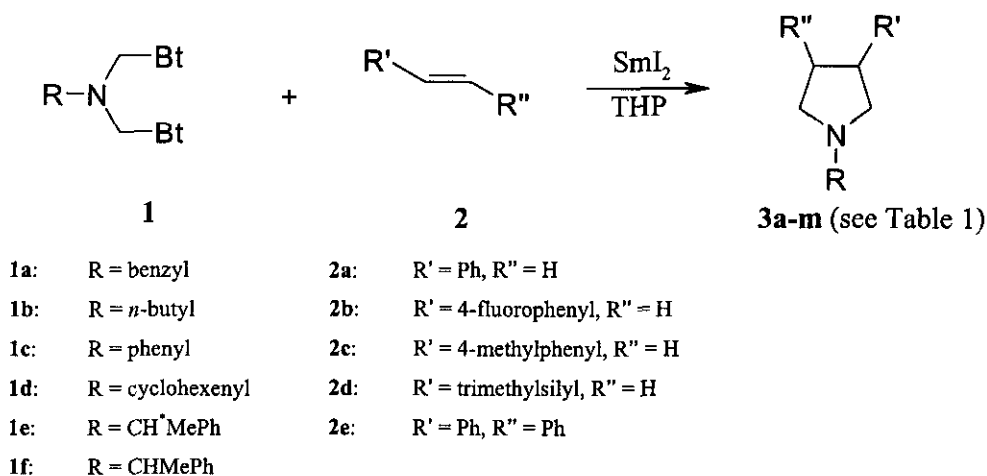
Alan R. Katritzky,* Yunfeng Fang, Ming Qi, and Daming Feng

Center for Heterocyclic Compounds, Department of Chemistry, University of
Florida, Gainesville, FL 32611-7200, USA

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

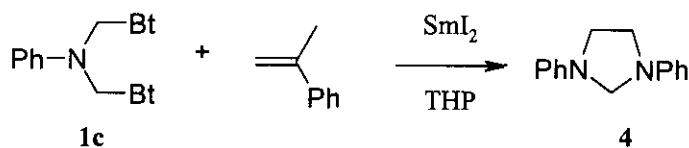
Numerous natural products incorporate pyrrolidine rings. Rapid syntheses of pyrrolidines, especially methods which form more than one ring bond in a single operation, are most desirable.¹ Such reactions generally involve cycloadditions. The 1,3-dipolar cycloaddition of an azomethine ylide to an olefin represents a highly convergent approach for the construction of a pyrrolidine ring,² *e.g.* Roussi and Zhang³ and Laborde⁴ 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 aminomethylolithiums, 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.



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 SmI₂ 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 ¹H NMR results.



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 unactivated alkenes failed.

Table 1. 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	<i>n</i> -butyl	4-F-phenyl	H	50 (40)
g	1b 2a	<i>n</i> -butyl	phenyl	H	70 (59)
h	1b 2c	<i>n</i> -butyl	4-Me-phenyl	H	73 (53)
i	1b 2d	<i>n</i> -butyl	trimethylsilyl	H	94 (85)
j	1c 2a	phenyl	phenyl	H	69 (60)
k	1d 2d	cyclohexyl	trimethylsilyl	H	60 (52)
l	1e 2a	(<i>R</i>)- 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 $\text{C}_{17}\text{H}_{19}\text{N}$: 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 $\text{C}_{18}\text{H}_{21}\text{N}$: 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 $\text{C}_{17}\text{H}_{18}\text{NF}$: 255.1423. Found: 255.1372.

1-Benzyl-3-trimethylsilylpyrrolidine (**3d**): ^1H 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 $\text{C}_{14}\text{H}_{23}\text{NSi}$: 233.1600. Found: (M^+ +1) 234.1661.

1-Benzyl-3,4-diphenylpyrrolidine (**3e**): ^1H 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 $\text{C}_{23}\text{H}_{23}\text{N}$: 313.1830. Found: 313.1738.

1-Benzyl-3-(4'-fluorophenyl)pyrrolidine (**3f**): ^1H 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 $\text{C}_{14}\text{H}_{20}\text{NF}$: 221.1580. Found: 221.1481.

1-Butyl-3-phenylpyrrolidine (**3g**): ^1H 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 $\text{C}_{14}\text{H}_{21}\text{N}$: 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**): ^1H 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 $\text{C}_{15}\text{H}_{23}\text{N}$: C, 82.89; H, 10.66. Found: C, 82.55; H, 11.10.

1-Butyl-3-trimethylsilylpyrrolidine (**3i**): ^1H 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 $\text{C}_{11}\text{H}_{25}\text{NSi}$: 199.1756. Found: (M^+ +1) 200.1784.

1,3-Diphenylpyrrolidine (**3j**): ^1H 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**): 1H 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**): 1H 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**): 1H 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**): 1H 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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