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Murthy R. Akula [a] & George W. Kabalka [a]
[a] Departments of Chemistry and Radiology , The University of Tennessee , Knoxville, TN, 37996—1600, U.S.A.
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A CONVENIENT SYNTHESIS OF HINDERED *N*-ARYL SUBSTITUTED CYCLIC AMINES

Murthy R. Akula and George W. Kabalka*

Departments of Chemistry and Radiology
The University of Tennessee
Knoxville, TN 37996-1600, U.S.A.

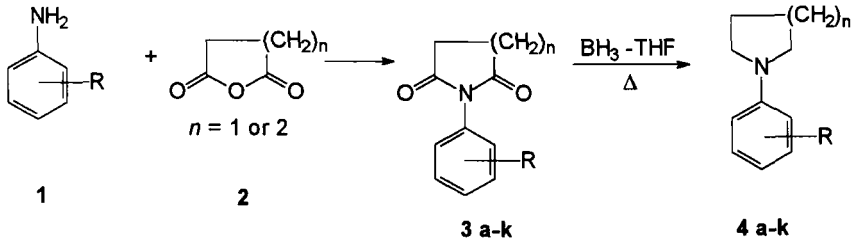
Abstract: An efficient and high yielding synthesis of *N*-substituted pyrrolidines and piperidines is described.

The synthesis of *N*-substituted cyclic amines such as pyrrolidines and piperidines is usually accomplished by the use of cyclization reactions.[1,2,3,4] These reactions are of limited scope owing to difficulties in obtaining the requisite starting materials or to severe reaction conditions. Cyclic amines can also be prepared via the deoxygenation of cyclic lactams or imides to the corresponding amines but lithium aluminum hydride is often used to achieve the reduction and the yields are normally poor.[5] Shim and co-workers have reported a tandem reductive amination-cyclization route to pyrrolidines, but the approach involves the use of potassium tetracarbonyl hydridoferrate and succinaldehyde which readily polymerizes.[6] Venuti and Ort reported the reductive cyclization of *N*-substituted succinamic and

*To whom correspondence should be addressed.

glutaramic esters to the corresponding *N*-substituted pyrrolidines and piperidines using borane-methyl sulfide.[7] However, sterically hindered *N*-2,4,6-trimethylphenyl succinamic and glutaramic esters failed to afford cyclization products. We wish to report a convenient synthesis of hindered *N*-aryl substituted pyrrolidines and piperidines via the reduction of cyclic imides using borane-THF.

N-substituted succinimides or glutarimides were prepared according literature procedures.[8,9] Aniline **1** was treated with succinic anhydride or glutaric anhydride, **2**, to obtain the prerequisite *N*-substituted succinamic acids or glutaramic acids. The crude acids were cyclized to the corresponding imides (Tables 1 and 2) by refluxing them with acetic anhydride in presence of sodium acetate. Reduction of these imides at reflux with borane-THF afforded *N*-substituted pyrrolidines and piperidines (Tables 3 and 4).



1 **2** **3 a-k** **4 a-k**

A variety of 2,6-disubstituted phenyl sucinimides or glutarimides was reduced to the corresponding pyrrolidines and piperidines, respectively, after refluxing with borane-THF complex. Isolated yields are high, ranging from 76-89%. The two most highly hindered imides **3d** and **3j** were also reduced

Table 1. Physical and Spectral Data for *N*-Aryl Succinimides (*n*=1; 3 a-f).

No	R	Yield %	mp °C	^{1}H NMR	^{13}C NMR
3a	2,4,6-tri-methyl	89	151-153	2.35 (*s*, 6H), 2.58 (*s*, 3H), 3.40 (*s*, 4H), 7.24 (*s*, 2H)	16.25, 19.63, 27.15, 127.89, 133.86, 137.892, 174.77
3b	2,6-diethyl	85	125-127	1.33 (*t*, 6H), 2.36 (*q*, 4H), 2.89 (*s*, 4H), 7.18 (*d*, 2H, *J* = 7.5 Hz), 7.30 (*m*, 1H)	14.89, 25.06, 29.35, 127.37, 130.58, 142.01, 177.31
3c	2-*iso*-propyl	88	126-127	1.24 (*d*, 6H, *J* = 7 Hz), 2.36 (*m*, 1H), 2.95 (*s*, 4H), 6.98 (*d*, 1H, *J* = 7.8 Hz), 7.29 (*m*, 1H), 7.44 (*m*, 2H)	23.04, 28.02, 126.12, 126.27, 127.62, 129.24, 129.40, 145.65, 176.10
3d	2,6-*diiso*-propyl	93	162-163	1.16 (*d*, 12H, *J* = 7.4 Hz), 2.57 (*m*, 2H), 2.85 (*s*, 4H), 7.24 (*d*, 2H, *J* = 7.5 Hz), 7.37 - 7.43 (*m*, 1H)	23.32,28.02, 28.66, 123.46, 126.82, 129.60, 145.42, 176.32
3e	2-*tert*-butyl	98	131-132	1.34 (*s*, 9H), 2.93 (*s*, 4H), 6.91 (*d*, 1H, *J* = 7.8 Hz), 7.29 - 7.36 (*m*, 1H), 7.40 - 7.47 (*m*, 1H), 7.61 - 7.65 (*m*, 1H)	26.86, 31.20, 35.42, 126.79, 128.57, 129.13, 130.60, 136.59, 145.72, 172.88
3f	2,6-dichloro	82	152-153	3.05 (*s*, 4H), 7.35-7.42 (*m*, 1H), 7.45-7.55 (*m*, 2H)	18.66, 128.55, 128.79, 131.12, 134.26, 174.28

Table 2. Physical and Spectral Data for *N*-Aryl Glutarimides (*n* - 2, 3g-k)

No	R	Yield %	mp °C	^{1}H NMR	^{13}C NMR
3g	2,4,6-tri-methyl	98	125-127	2.00 (*s*, 6H), 2.04 - 2.27 (*m*, 2H), 2.27 (*s*, 3H), 2.81 (*t*, 4H), 6.91 (*s*, 2H)	16.47, 20.07, 32.06, 128.28, 133.67, 137.44, 159.60, 161.22, 170.86
3h	2,6-diethyl	93	92-93	1.18, (*t*, 6H), 2.10 - 2.23 (*m*, 2H), 2.25 - 2.43 (*q*, 4H), 2.85 (*t*, 4H), 7.25 (*d*, 2H, *J* = 7.5 Hz), 7.25 - 7.39 (*m*, 1H)	13.38, 16.85, 23.50, 32.51, 125.79, 126.49, 131.63, 140.03, 171.86
3i	2-*iso*-propyl	82	127-129	1.22 (*d*, 6H, *J* = 6 Hz), 2.05 - 2.22 (*t*, 2H), 2.52 - 2.70 (*m*, 1H), 2.85 (*t*, 4H), 6.95 (*d*, 1H, *J* = 7.5 Hz, 7.20 - 7.30 (*m*, 2H), 7.40 - 7.50 (*m*, 1H)	24.32 , 26.70, 54.75, 120.34, 123.86, 125.41, 126.01, 126.09, 144.55, 152.13
3j	2,6-*diiso*-propyl	70	169-170	1.15 (*d*, 2H, *J* = 7.5 Hz), 2.00 - 2.15 (*m*, 2H), 2.55 - 2.65 (*q*, 2 H), 2.85 (*t*, 4H), 7.25 (*d*, 2H, *J* = 7.8 Hz), 7.30 - 7.41 (*m*, 1H)	17.28, 23.74, 28.86, 32.87, 123.69, 129.55, 145.14, 172.43
3k	2-*tert*-butyl	81	135-137	1.24 (*t*, 9H), 2.05 - 2.20 (*m*, 2H), 2.85 (*t*, 4H), 7.80 (*d*, 1H, *J* = 7.5 Hz), 7.20 - 7.45 (*m*, 2H), 7.60 (*d*, 1H, *J* = 7.5 Hz)	16.88, 31.62, 33.30, 35.72, 127.09, 128.88, 130.91, 133.16, 146.62, 173.09

Table 3. Spectral and Physical Data for *N*-Arylpyrrolidines (*n* = 1, 4a-f)

No	R	Yield %	^{1}H NMR	^{13}C NMR	Elemental Analysis
4a	2,4,6-trimethyl	81	1.87 (*t*, 4H), 2.24 (*s*, 6H), 2.26 (*s*, 3H), 3.17 (*t*, 4H), 6.87 (*s*, 2H)	18.41, 20.63, 26.44, 50.05, 129.16, 134.31, 137.96, 142.65	$C_{13}H_{19}$ N requires C, 82.48, H, 10.12, N, 7.40. Found: C, 82.89, H, 10.11, N 7.00
4b	2,6-diethyl	84	1.21 (*t*, 6H), 1.96 (*t*, 4H), 2.61 (*t*, 4H), 3.17 (*q*, 4H), 7.05 (*bs*, 3H)	16.02, 25.10, 27.04, 52.32, 126.25, 127.22, 144.96, 145.59	$C_{14}H_{21}$ N requires C, 82.70, H, 10.41, N, 6.89. Found:C, 82.63, H, 10.40, N, 6.84
4c	2-*iso*-propyl	88	1.24 (*d*, 6H, *J* = 7 Hz), 1.93 (*t*, 4H), 3.09 (*t*, 4H), 3.40-3.46 (*m*, 1H), 6.97-7.14 (*m*, 3H), 7.24-7.27 (*m*, 1H)	23.00, 24.17, 26.86, 52.28, 117.66, 121.88, 125.52, 125.97, 142.07, 147.82	$C_{13}H_{19}N$ requires C, 82.48, H, 10.12, N, 7.40. Found: C,82.86, H, 10.39, N, 7.18
4d	2,6-*diiso*-propyl	76	1.04 (*s*, 12H, *J* = 7 Hz), 1.85 (*t*, 4H), 3.04-3.10 (*m*, 6H), 6.96-7.05 (*m*, 3H)	24.33, 26.35, 27.56, 52.42, 123.58, 125.80, 142.61, 149.80	$C_{16}H_{25}N$ requires C, 83.12, H, 10.82, N, 6.49, Found: C, 83.36, H, 10.86, N, 6.10.
4e	2-*tert*-butyl	85	1.29 (*s*, 9H), 1.77 (*t*, 4H), 2.83 (*t*, 4H), 6.97-7.00 (*m*, 1H), 7.07-7.20 (*m*, 1H), 7.21-7.28 (*m*, 2H)	24.61, 31.02, 35.39, 56.11, 125.43, 126.46, 126.57, 126.93, 149.05, 151.59	$C_{14}H_{21}$ N requires C, 82.70, H, 10.41, N, 6.89. Found: C,82.72, H, 10.38, N, 6.70
4f	2,6-dichloro	77	2.15 (*t*, 4H), 3.35 (*t*, 4H) 7.00 (*t*, 1H) 7.00 (*d*, 2H, *J* = 7.5 Hz).	26.52, 49.86, 126.00, 128.97, 736.70, 143.47	$C_{10}H_{11}NCl_2$ requires C,55.58,H,5.14,N 6.48 Found:C,55.24,H,5.47, N, 6.39

Table 4: Spectral and Physical Data for *N*-Arylpiperidines (*n* = 2, 4g-4k)

No	R	Yield %	^{1}H NMR	^{13}C NMR	Elemental Analysis
4g	2,4,6-trimethyl	84	1.45 - 1.65 (*m*, 6H), 2.22 (*s*, 3H), 2.32 (*s*, 6H), 2.94-3.05 (*m*, 4H), 6.78 (*s*, 2H)	17.84, 19.94, 25.56, 28.42, 52.48, 128.94, 134.58, 137.82, 147.52	$C_{14}H_{21}$ N requires C, 82.70, H, 10.41, N, 6.89. Found: C, 82.84, H, 10.34, N, 6.77
4h	2,6-diethyl	81	1.15-2.05 (*t*, 6H), 2.48-2.65 (*m*, 6H), 2.60 (*q*, 4H), 2.90-3.05 (*m*, 4H), 6.90-6.95 (*m*, 2H) 7.35 (*s*, 1H, *J* = 7.5 Hz)	16.19, 25.08, 25.72, 27.58, 52.57, 125.92, 127.00, 127.41, 144.44, 149.21	$C_{15}H_{23}N$ requires C,82.89, H, 10.67, N 6.44. Found: 82.85, H, 10.67, N, 6.37
4i	2-*iso*-propyl	89	1.12 (*d*, 3H, *J* = 7.8 Hz), 1.14(*d*, 3H, *J* = 7.8 Hz), 1.45-1.48 (*m*, 2H), 1.62 (*t*, 4H), 2.72 (*t*, 4H), 3.44 (*q*, 1H), 6.96-7.04 (*m*, 3H), 7.14-7.19 (*m*, 1H)	23.95, 24.32, 26.63, 26.70, 54.75, 120.24, 123.66, 126.01, 126.09, 144.55, 152.13	$C_{14}H_{21}$ N requires C, 82.70, H, 10.41, N, 6.89. Found: C, 82.60, H, 10.42, N, 6.91
4j	2,6-*diiso*-propyl	79	1.21 (*d*, 12H, *J* = 7 Hz), 1.60-1.64 (*m*, 6H), 3.01-3.05 (*m*, 4H), 3.44 (*q*, 2H), 7.04-7.15 (*m*, 3H)	24.32, 24.65, 27.15, 28.20, 52.37, 123.82, 126.12, 147.38, 149.14	$C_{17}H_{27}$ N requires C, 83.20, H, 11.09, N, 5.71. Found: C, 83.01, H, 11.16, N, 5.66
4k	2-*tert*-butyl	87	1.48 (*s*, 9H),1.60-1.80 (*m*, 6H), 2.70-2.90 (*m*, 4H), 7.05-7.20 (*m*, 2H), 7.25-7.40 (*m*,2H)	24.70, 26.72, 31.09, 35.80, 55.87, 125.64, 126.96, 127.06, 147.59, 155.07	$C_{15}H_{23}N$ requires C, 82.89, H, 10.67, N, 6.44. Found: C, 83.04, H, 10.61, N, 6.35

to **4d** and **4j** in good yields (76% and 79%, respectively). The dichloro analogue was reduced to the corresponding cyclic amine without dehalogenation.

The preparation of *N*-2,4,6-trimethylphenylpyrrolidine is representative: *N*-2,4,6-Trimethylphenyl succinimide (1.0 mmol, 0.22 g) is dissolved in anhydrous THF (10 mL). Borane in THF (8.0 mmol, 8.0 mL of a 1.0 N solution) is added dropwise, and the mixture refluxed for 6 h. The reaction is quenched with methanol to decompose excess borane and the solvent removed. (CAUTION: Hydrogen evolved.) The residue is refluxed with 6 N hydrochloric acid (5 ml) for 30 min and then the solution is basified with sodium hydroxide (5 mL of a 6 N solution). The product is extracted into ether (2 x 25 mL), dried over anhydrous sodium sulphate, the solvent evaporated, and the amine isolated by silica gel column chromatography using ethyl acetate:petroleum ether (1:9, v/v) as eluent. 0.15 mg, 81% yield; ^{1}H NMR ($CDCl_3$): δ 1.87 (*t*, 4H), 2.24 (*s*, 6H), 2.26 (*s*, 3H), 3.17 (*t*, 4H), 6.87 (*s*, 2H). ^{13}C NMR ($CDCl_3$): δ 18.41, 20.63, 26.44, 50.04, 129.16, 134.31, 137.96, 142.65. Anal: calcd for $C_{13}H_{19}N$:C, 82.48, H, 10.12, N, 7.40. Found: C, 82.89, H, 10.11, N, 7.00.

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