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Novel Tri-*n*-butyltin Hydride–Azoisobutyronitrile-induced Intramolecular Ring-closure Reaction: a Convenient Synthesis of Substituted Azetidin-3-ones†,‡

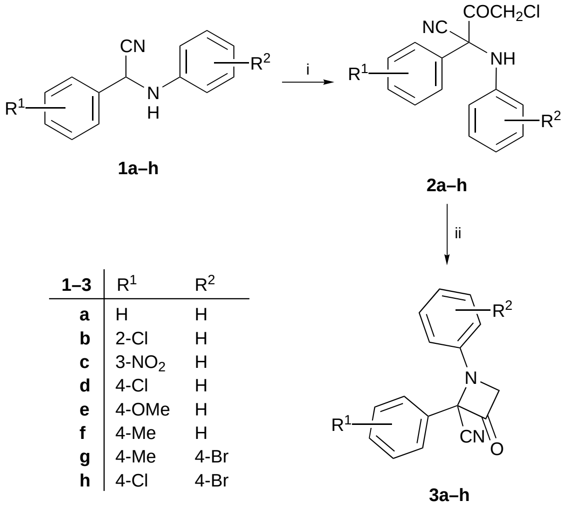
Abhijit Roy Chowdhury, Versha V. Kumar, Raja Roy and A. P. Bhaduri*

Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226 001, India

Tri-*n*-butyltin hydride–azoisobutyronitrile-mediated intramolecular ring-closure reactions yield 2-cyano-1,2-di(phenyl or substituted phenyl)azetidin-3-ones; ^{15}N NMR studies support the assigned structures.

Convenient methods for synthesising four-membered nitrogen-containing heterocycles are extremely limited.[1–5] During the course of our studies on intramolecular ring-closure reactions induced by tri-*n*-butyltin hydride (TBTH)–azoisobutyronitrile (AIBN), novel intramolecular ring closures of α-anilino-α-(chloromethylcarbonyl)phenylacetonitriles leading to the formation of azetidin-3-one derivatives were observed. The details of this first report are presented here.

Addition of HCN to the appropriate Schiff's base[6,7] yielded compounds **1a–h** which reacted with chloroacetyl chloride in the presence of sodium hydrogen carbonate to yield the *C*-acylated products **2a–h** instead of *N*-acetylated products. The *C*-acylation was confirmed on the basis of the disappearance of the methine proton and the presence of a D_2O-exchangeable NH proton between δ_H 6.51 and 6.52 in the ^1H NMR spectra. Reactions of **2a–h** with TBTH in the presence of AIBN gave 2-cyano-1,2-di(phenyl or substituted phenyl)azetidin-3-ones **3a–h** in excellent yields (72–77%) (Scheme 1). Attempted reactions of compounds **2a–h** with TBTH alone did not yield **3a–h**.



1a–h

2a–h

3a–h

1–3	R^1	R^2
a	H	H
b	2-Cl	H
c	3-NO_2	H
d	4-Cl	H
e	4-OMe	H
f	4-Me	H
g	4-Me	4-Br
h	4-Cl	4-Br

Scheme 1 *Reagents and conditions:* i, $ClCOCH_2Cl$, $NaHCO_3$, $CHCl_3$, room temp., 8–10 h; ii, TBTH, AIBN, anhydrous THF, 65 °C, 12–14 h

The N—CH_2 linkage in these four-membered heterocycles was established on the basis of ^{15}N NMR studies carried out with **3d** as the model compound. The nitrogen of the nitrile group appeared at δ_N 149.8 and the trisubstituted ring nitrogen showed up as a broad triplet at δ_N 127.2. The latter in a ^{15}N inverse-gated experiment appeared as a singlet, indicating $^2J_{NH}$ long-range coupling with the methylene protons.[8,9] Long-range HMBC (heteronuclear multiple bond correlation spectroscopy) experiments[10] showed that the carbonyl carbon was coupled with the methylene protons. The presence of the methylene protons adjacent to the trisubstituted nitrogen was further reinforced by phase-sensitive ROESY (rotating-frame Overhauser effect spectroscopy) experiments[11] in which the CH_2 protons between δ_H 3.4 and 4.2 gave NOE cross-peaks with the *ortho* protons of the phenyl group attached to the N-1 position. The outcome of all the spectroscopic results, therefore, unambiguously proves the structure of the azetidinones as **3a–h**.

In conclusion, the present method provides a more convenient route to substituted azetidin-3-ones compared with existing ones. Studies are under way to elucidate the mechanism of this unusual ring-closure reaction.

Experimental

Melting points were determined on a hot-stage apparatus and are uncorrected. IR spectra were recorded on Beckmann Acculab-10 or Perkin-Elmer 881 spectrophotometers. ^1H NMR spectra, ^{15}N NMR spectra and related 2D-NMR experiments were carried out on Bruker 400 FT NMR and Bruker Avance DRX 300 spectrometers. EI mass spectra were recorded on a JEOL JMS-D-300 spectrometer. Elemental analyses were carried out on a Carlo-Erba EA 1108 elemental analyser. Reactions were monitored by TLC on silica gel 60 (E. Merck) of 0.25 mm thickness. Column chromatography carried on Merck silica gel (70–230 mesh).

α-Anilino-α-(chloromethylcarbonyl)phenylacetonitriles: *General Procedure.*—To a solution of **1a–h** (2 mmol) in $CHCl_3$ (25 ml) were added $NaHCO_3$ (0.168 g, 3 mmol) and chloroacetyl chloride (0.239 ml, 2 mmol) in $CHCl_3$ (10 ml) under stirring. The reaction mixture was allowed to stir for 8–10 h. Then, the reaction mixture was neutralised with saturated aqueous $NaHCO_3$ followed by separation of the organic layer which was washed with brine (25 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent led to a crude solid which was recrystallised in EtOH to afford products **2a–h**. **2a**: colourless *crystals*, mp 88 °C (from EtOH), 71% yield (Found: C, 67.58; H, 4.73; N, 9.91. $C_{16}H_{13}ClN_2O$ requires C, 67.49; H, 4.60; N, 9.80%); ν_{max} (KBr)/cm^{-1} 1685 (C=O), 2252 (C≡N), 3122 (NH); δ_H (400 MHz; $CDCl_3$) 3.8 (2 H, s, CH_2), 6.56 (1 H, br, NH, D_2O exchangeable), 7.08 (1 H, m, ArH), 7.30 (4 H, m, ArH), 7.42 (4 H, d, *J* 9 Hz, ArH), 7.52 (1 H, m, ArH); *m*/*z* (EI-MS) 284 (M^+, 2.4%), 248 (34.6). **2b**: colourless *crystals*, mp 121 °C (from EtOH), 72.5% yield (Found: C, 60.46; H, 3.74; N, 8.72. $C_{16}H_{12}Cl_2N_2O$ requires C, 60.20; H, 3.78; N, 8.77%); ν_{max} (KBr)/cm^{-1} 1670 (C=O), 2265 (C≡N), 3085 (NH); δ_H (400 MHz, $CDCl_3$) 3.83 (2 H, s, CH_2), 6.51 (1 H, br, NH, D_2O exchangeable), 7.06 (1 H, m, ArH), 7.14 (2 H, d, *J* 9 Hz, ArH), 7.31 (4 H, m, ArH), 7.43 (2 H, d, *J* 9 Hz, ArH); *m*/*z* (EI-MS) 320 (M^+, 11.1%), 294 (34.3). **2c**: yellow *crystals*, mp 107 °C (from EtOH), 70.5% yield (Found: C, 58.49; H, 3.75; N, 13.24. $C_{16}H_{12}ClN_3O_3$ requires C, 58.28; H, 3.66; N, 12.94); ν_{max} (KBr)/cm^{-1} 1710 (C=O), 2252 (C≡N), 3120 (NH); δ_H (400 MHz, $CDCl_3$) 3.81 (2 H, s, CH_2), 6.51 (1 H, br, NH, D_2O exchangeable), 6.85 (1 H, s, ArH), 7.18 (4 H, s, ArH), 7.35 (1 H, m, ArH), 7.56 (2 H, d, *J* 9 Hz, ArH), 8.18 (1 H, s, ArH); *m*/*z* (EI-MS) 329 (M^+, 4.9%), 253 (100.0). **2d**: colourless *crystals*, mp 98 °C (from EtOH), 74.0% yield (Found: C, 60.52; H, 3.77; N, 8.60. $C_{16}H_{12}Cl_2N_2O$ requires C, 60.20; H, 3.78; N, 8.77%); ν_{max} (KBr)/cm^{-1} 1668 (C=O), 2251 (C≡N), 3180 (NH); δ_H (400 MHz, $CDCl_3$) 3.78 (2 H, s, CH_2), 6.53 (1 H, br, NH, D_2O exchangeable), 7.10 (4 H, s, ArH), 7.25 (2 H, d, *J* 9 Hz, ArH), 7.34 (2 H, d, *J* 9 Hz, ArH); *m*/*z* (EI-MS) 319 (M^+, 2.3%), 283 (39.0). **2e**: colourless *crystals*, mp 88 °C (from EtOH), 71.5% yield (Found: C, 64.72;

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*To receive any correspondence (*e-mail:* root%cdrilk@sirnetd.ernet.in).

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H, 4.93; N, 8.75. $C_{17}H_{15}ClN_2O_2$ requires C, 64.87; H, 4.80; N, 8.89%); ν_{max} (KBr)/cm^{-1} 1666 ($C=O$), 2334 ($C\equiv N$), 3016 (NH); δ_H (400 MHz, $CDCl_3$) 3.82 (5 H, q, *J* 14 Hz, OCH_3 and CH_2), 6.48 (1 H, br, NH, D_2O exchangeable), 7.26 (4 H, m, ArH), 7.33 (4 H, m, ArH), 7.40 (1 H, q, *J* 18 Hz, ArH); *m/z* (EI-MS) 314 (M^+, 21.0%), 279 (30.1). **2f**: colourless *crystals*, mp 92 °C (from EtOH), 74.5% yield (Found: C, 68.60; H, 5.18; N, 9.30. $C_{17}H_{15}ClN_2O$ requires C, 68.34; H, 5.06; N, 9.37%); ν_{max} (KBr)/cm^{-1} 1670 ($C=O$), 2247 ($C\equiv N$), 3120 (NH); δ_H (400 MHz, $CDCl_3$) 2.35 (3 H, s, CH_3), 3.78 (2 H, s, CH_2), 6.48 (1 H, br, NH, D_2O exchangeable), 6.95 (2 H, d, *J* 9 Hz, ArH), 7.09 (1 H, m, ArH), 7.18 (4 H, m, ArH), 7.24 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 298 (M^+, 3.8%), 262 (32.9). **2g**: colourless *crystals*, mp 129 °C (from EtOH), 70% yield (Found: C, 53.93; H, 3.83; N, 7.17. $C_{17}H_{14}BrClN_2O$ requires C, 54.06; H, 3.73; N, 7.41%); ν_{max} (KBr)/cm^{-1} 1680 ($C=O$), 2258 ($C\equiv N$), 3120 (NH); δ_H (400 MHz, $CDCl_3$) 2.34 (3 H, s, CH_3), 3.78 (2 H, s, CH_2), 6.52 (1 H, br, NH, D_2O exchangeable), 6.79 (2 H, d, *J* 9 Hz, ArH), 7.12 (2 H, m, ArH), 7.18 (2 H, d, *J* 9 Hz, ArH), 7.20 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 377 (M^+, 16.3%), 343 (23.1). **2h**: colourless *crystals*, mp 180 °C (from EtOH), 71% yield (Found: C, 48.51; H, 2.47; N, 7.18. $C_{16}H_{11}BrCl_2N_2O$ requires C, 48.27; H, 2.78; N, 7.03%); ν_{max} (KBr)/cm^{-1} 1666 ($C=O$), 2280 ($C\equiv N$), 3322 (NH); δ_H (400 MHz, $CDCl_3$) 3.75 (2 H, s, CH_2), 6.52 (1 H, br, NH, D_2O exchangeable), 7.14 (1 H, m, ArH), 7.19 (2 H, d, *J* 9 Hz, ArH), 7.21 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 397 (M^+, 12.1%), 249 (34.3).

Azetidin-3-*ones*: *Typical Procedure*.—To a solution of **2a–h** (2 mmol) in anhydrous THF (25 ml) was added a catalytic amount of AIBN and the reaction mixture was allowed to stir at 65 °C for 30 min under N_2 atmosphere. Thereafter, the reaction mixture was cooled to room temperature (25 °C), followed by the addition of 0.87 ml (3.0 mmol) of TBTH in anhydrous THF and then refluxing at 65 °C for the next 12–14 h under a N_2 atmosphere. The excess of solvent was distilled off *in vacuo* and the residue was extracted with EtOAc (3 × 20 ml). Usual work-up of the organic layer furnished an oily residue which was purified by column chromatography. Elution with hexane–$CHCl_3$ (75:25, v/v) furnished a crude solid which was recrystallised in MeOH–EtOAc to afford compounds **3a–h**. **3a**: colourless *crystals*, mp 79 °C (from MeOH–EtOAc), 77.2% yield (Found: 77.16; H, 4.97; N, 11.69. $C_{16}H_{12}N_2O$ requires C, 77.40; H, 4.87; N, 11.28%); ν_{max} (KBr)/cm^{-1} 1770 ($C=O$), 2264 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 3.35 (1 H, d, *J* 15 Hz, H of CH_2), 3.92 (1 H, d, *J* 15 Hz, H of CH_2), 7.13 (1 H, m, ArH), 7.34 (4 H, m, ArH), 7.48 (4 H, d, *J* 9 Hz, ArH), 7.58 (1 H, m, ArH); *m/z* (EI-MS) 248 (M^+, 7.8%). **3b**: colourless *crystals*, mp 122 °C (from MeOH–EtOAc), 72.5% yield (Found: C, 68.21; H, 3.57; N, 9.48. $C_{16}H_{11}ClN_2O$ requires C, 67.97; H, 3.92; N, 9.90%); ν_{max} (KBr)/cm^{-1} 1780 ($C=O$), 2265 ($C\equiv N$; δ_H (400 MHz, $CDCl_3$) 3.45 (1 H, d, *J* 15 Hz, H of CH_2), 4.14 (1 H, d, *J* 15 Hz, H of CH_2), 7.24 (1 H, m, ArH), 7.28 (1 H, d, *J* 9 Hz, ArH), 7.41 (4 H, m, ArH), 7.55 (2 H, d, *J* 9 Hz, ArH), 7.58 (1 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 283 (M^+, 19.5%), 214 (21.1). **3c**: yellow *crystals*, mp 152 °C (from MeOH–EtOAc), 77.44% yield (Found: C, 65.82; H, 3.96; N, 14.71. $C_{16}H_{11}N_3O_3$ requires C, 65.52; H, 3.78; N, 14.32%); ν_{max} (KBr)/cm^{-1} 1782 ($C=O$), 2270 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 3.45 (1 H, d, *J* 15 Hz, H of CH_2), 4.12 (1 H, d, *J* 15 Hz, H of CH_2), 7.18 (1 H, m, ArH), 7.38 (4 H, s, ArH), 7.71 (1 H, m, ArH), 7.35 (1 H, d, *J* 9 Hz, ArH), 7.95 (1 H, d, *J* 9 Hz, ArH), 8.51 (1 H, s, ArH); *m/z* (EI-MS) 293 (M^+, 35.5%). **3d**: colourless *crystals*, mp 96 °C (from MeOH–EtOAc), 75.2% yield (Found: C, 67.78; H, 4.23; N, 9.76. $C_{16}H_{11}ClN_2O$ requires C, 67.97; H, 3.92; N, 9.90%); ν_{max} (KBr)/cm^{-1} 1768 ($C=O$), 2284 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 3.38 (1 H, d, *J* 15 Hz, H of CH_2), 3.02 (1 H, d, *J* 15 Hz, *J* 15 Hz, H of CH_2), 7.16 (1 H, m, ArH), 7.34 (4 H, s, ArH), 7.45 (2 H, d, *J* 9 Hz, ArH), 7.53 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 282 (M^+, 6.7%), 280 (15.1). **3e**: colourless *crystals*, mp 86 °C (from MeOH–EtOAc), 74.56% yield (Found: C, 73.40; H, 4.99; N, 10.50. $C_{17}H_{14}N_2O_2$ requires C, 73.36; H, 5.07; N, 10.06%); ν_{max} (KBr)/cm^{-1} 1780 ($C=O$), 2265 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 3.32 (1 H, d, *J* 15 Hz, H of CH_2), 3.75 (3 H, s, OCH_3), 3.92 (1 H, d, *J* 15 Hz, H of CH_2), 7.14 (1 H, s, ArH), 7.32 (4 H, s, ArH), 7.48 (2 H, d, *J* 9 Hz, ArH), 7.54 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 278 (M^+, 5.1%), 210 (10.7). **3f**: colourless *crystals*, mp 91 °C (from MeOH–EtOAc), 74.5% yield (Found: C, 77.90; H, 5.22; N, 10.52. $C_{17}H_{14}N_2O$ requires C, 77.84; H, 5.36; N, 10.67%); ν_{max} (KBr)/cm^{-1} 1775 ($C=O$), 2262 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 2.37 (3 H, s, CH_3), 3.38 (1 H, d, *J* 15 Hz, H of CH_2), 3.98 (1 H, d, *J* 15 Hz, H of CH_2), 7.14 (1 H, m, ArH), 7.28 (4 H, q, *J* 9 Hz, ArH), 7.35 (2 H, d, *J* 9 Hz, ArH), 7.47 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 262 (M^+, 16.9%), 144 (25.8). **3g**: colourless *crystals*, mp 78 °C (from MeOH–EtOAc), 76.87% yield (Found: C, 59.84; H, 4.70; N, 9.80. $C_{17}H_{13}BrN_2O$ requires C, 59.84; H, 3.84; N, 8.20%); ν_{max} (KBr)/cm^{-1} 1765 ($C=O$), 2271 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 3.38 (1 H, d, *J* 15 Hz, H of CH_2), 3.82 (3 H, s, CH_3), 3.91 (1 H, d, *J* 15 Hz, H of CH_2), 6.98 (2 H, d, *J* 9 Hz, ArH), 7.21 (2 H, m, ArH), 7.38 (2 H, d, *J* 9 Hz, ArH), 7.40 (2 H, d, *J* 9 Hz, ArH); *m/z* (EI-MS) 341 (M^+, 1.8%), 314 (14.1). **3h**: yellow *crystals*, mp 81 °C (from MeOH–EtOAc), 74.84% yield (Found: C, 53.38; H, 3.09; N, 7.59. $C_{16}H_{10}BrClN_2O$ requires C, 53.14; H, 2.78; N, 7.74%); ν_{max} (KBr)/cm^{-1} 1772 ($C=O$), 2265 ($C\equiv N$); δ_H (400 MHz, $CDCl_3$) 3.38 (1 H, d, *J* 15 Hz, H of CH_2), 3.81 (1 H, d, *J* 15 Hz, H of CH_2), 6.95 (2 H, d, *J* 9 Hz, ArH), 7.23 (2 H, m, ArH), 7.43 (4 H, q, *J* 9 Hz, ArH); *m/z* (EI-MS) 361 (M^+, 4.1%).

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