

## A New Simple Method for the Synthesis of Cyclobutyl Cyanide

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**Abstract:** A clean and efficient intramolecular cyclization of  $\delta$ -halovaleronitrile to cyclobutyl cyanide was achieved using NaOH and phase-transfer catalysts in a solid-liquid system at 70 °C.  
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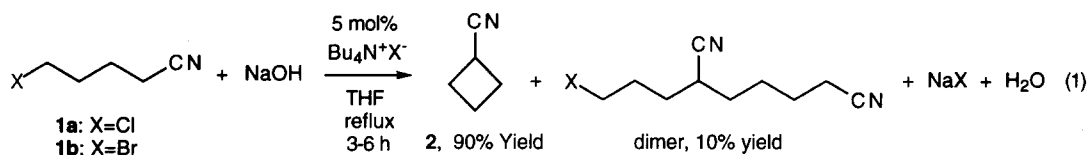
Cyclization of 4-membered rings is an arduous task compared to that of 3-, 5- or 6-membered ones.<sup>1,2</sup> In particular, very few methods for the synthesis of cyclobutyl cyanide **2** have been published. The state of the art offers 3 pathways: 2+2 cycloaddition of ethylene to acrylonitrile,<sup>3</sup> alkylation of chloroacetonitrile *via* a sulfur-stabilized carbanion intermediate,<sup>4</sup> and intramolecular cyclization of chloronitriles.<sup>5</sup> These methods, however, demand extreme conditions and/or expensive, and environmentally unacceptable reagents.

Several applications of NaOH under solid-liquid phase-transfer conditions have been documented.<sup>6-9</sup> The rate of C-alkylation reactions using OH<sup>-</sup> under phase-transfer conditions was found to be critically dependent on the concentration of the base. An order of 5.3 was reported for the effect of [OH<sup>-</sup>] on the rate of phenylacetonitrile alkylation.<sup>10</sup> Similar rate dependence was found in the OH<sup>-</sup> initiated isomerization of allyl benzene.<sup>11</sup> Solid NaOH pellets, applied in the absence of water, are expected to function as an extremely strong base in various alkylation reactions.<sup>12</sup> Following this line of thought, we investigated the cyclization of 4-membered rings under NaOH/PTC conditions. No reaction was observed in the absence of the catalyst, or when 50% NaOH/water was used as base. However, a combination of solid NaOH and 5 mol% of Bu<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup> afforded high yields of **2** (eq 1).<sup>13</sup> At moderate conversions (table 1) **2** was the only product. At 100% conversion, however, the intermolecular by-product, 1-Chloro,4,8-dicyanooctane, was observed (ca. 10%). The pure cyclobutyl cyanide was easily isolated by distillation. The only inorganic by-products of the reaction were water and NaCl.

Table 1 Examples of  $\delta$ -halovaleronitrile Cyclizations

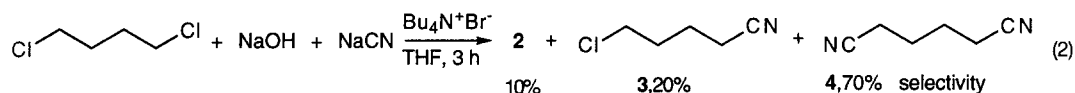
Entry	Substrate	Solvent	Conversion %	Selectivity %
1	<b>1a</b>	THF	60	100
2	<b>1b</b>	THF	24	100
3	<b>1a</b>	THF <sup>a</sup>	100	90
4	<b>1a</b>	Xylene	55	60
5	<b>1a</b>	Xylene <sup>b</sup>	55	60
6	<b>1a</b>	DMF	90	60

Conditions: 6 mmol substrate, 10 ml solvent, 70 °C (67 °C in THF), NaOH contains 5% W/W water, 3 h, 5 mol% Bu<sub>4</sub>N<sup>+</sup>X<sup>-</sup>, GC conversions and selectivities. <sup>a</sup> 6 h, 90 mmol substrate, 100 ml solvent, 90% isolated yield. <sup>b</sup> NaOH contains 15% W/W water.



An initial kinetic investigation showed that the reaction is of zero order.  $k_{\text{obs}}$  values were  $2.64 \cdot 10^{-3}$  M/min for **1a** and  $8.3 \cdot 10^{-4}$  M/min for **1b**. One possible explanation for this difference is the high lipophilicity of  $\text{Br}^-$  compared to  $\text{Cl}^-$ . The concentration of the active species, QOH, in the organic phase, would be lower for a mixture containing  $\text{Br}^-$  than for that containing  $\text{Cl}^-$  ions, owing to the different  $K^{\text{sel}}$  values.<sup>12, 14</sup>

A further practical improvement of this concept would be a one-pot synthesis of **2** directly from 1,4-dichlorobutane (eq 2). Preliminary, unoptimized runs afforded 90% conversion, but selectivity towards **2** was only 10%. This is partly because dicyanation competes strongly with the cyclization reaction.<sup>15</sup>



## REFERENCES AND NOTES

- Knipe, A. C.; Stirling, C. J. M. *J. Chem. Soc. (B)*, **1968**, 67-71.
- Benedetti, F.; Stirling, C. J. M. *J. Chem. Soc. Perkin Trans. 2*, **1986**, 605-611.
- Hall, H. K. Jr.; Smith, C. D.; Plorde, D. E. *J. Org. Chem.*, **1973**, 38, 2084-2087.
- Yanagawa, M.; Moriya, O.; Watanabe, Y.; Ueno, Y.; Endo, T. *Bull. Chem. Soc. Jpn.*, **1988**, 61, 2203-2204.
- Larcheveque, M.; Mulot, P.; Cuvigny, T. *J. Organometal. Chem.*, **1973**, 57, C33-C35.
- British Patent 1 570 319 (to Ciba-Geigy AG); *Chem. Abstr.* 94:65191y.
- Lukevics, E.; Dirnens, V. V.; Goldberg, Y. S.; Liepinsh, E. E.; Gavars, M. P.; Kalvinsh, I. Ya.; Shimanska, M. V. *Organometallics*, **1985**, 4, 1648-1653.
- Artaud, I.; Seyden-Penne, J.; Viout, P. *Tetrahedron Lett.*, **1980**, 21, 613-616.
- Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*, C & H: NY, **1994**, pp. 325-332.
- Solaro, R.; D'Antone, S.; Chiellini, E.; *J. Org. Chem.*, **1980**, 45, 4179-4183.
- Halpern, M.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.*, **1983**, 48, 1022-1025.
- Sasson, Y.; Arrad, O.; Dermeik, S.; Zahalka, H. A.; Weiss, M.; Wiener, H. *Mol. Cryst. Liq. Cryst. Inc. Nonlin. Opt.*, **1988**, 161, 495-516.
- Cyclobutyl cyanide 2*. to a solution of 90 mmol (10.58 gr) of **1a** in 100 ml dry THF were added 4.5 mmol (1.26 gr)  $\text{Bu}_4\text{N}^+\text{Cl}^-$ , and 180 mmol of solid NaOH (5% water, W/W). The mixture was stirred under reflux for 6 h, cooled and filtered. The solvent was evaporated and the residue was distilled. Pure **2** (6.5 gr, 90 mol% yield relative to **1a**) was obtained at 50 °C and 15 mmHg. The dimer was identified by GCMS. **2** was positively identified using GCMS, FTIR,  $^1\text{H}$  NMR, 2D HH NMR (COSY), and  $^{13}\text{C}$  NMR. Proton-decoupled  $^{13}\text{C}$  NMR showed only 4 peaks (133.89, 116.92, 28.76 and 16.34 ppm), due to molecular symmetry. FTIR analysis was consistent with published data.<sup>16</sup>
- de la Zerda, J.; Sasson, Y. *J. Chem. Soc. Perkin Trans. 2*, **1987**, 1147-1151. See also ref. 5 pp. 24-29.
- Cyclobutyl cyanide 2 (one-pot synthesis, unoptimized)*. to a solution of 5 mmol (0.63 gr) of 1,4-dichlorobutane in 10 ml dry THF were added 10 mmol (0.49 gr) of NaCN, 7.5 mmol (0.30 gr) of  $\text{NaOH}_{(s)}$ , and 0.5 mmol (0.16 gr)  $\text{Bu}_4\text{N}^+\text{Br}^-$ . The mixture was stirred under reflux for 3 h, and analyzed by GC. Analysis showed 90% conversion and 10%, 20%, and 70% selectivity for **2**, **3**, and **4**, respectively.
- Powell, D. L.; Gatial, A.; Klæboe, P.; Nielsen, C. J.; Kondow, A. J.; Boettner, W. A.; Mulichak, A. M. *Act. Chem. Scand.*, **1989**, 49, 441-449.