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A New Simple Method for the Synthesis of Cyclobutyl Cyanide

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Abstract: A clean and efficient intramolecular cyclization of δ-halovaleronitrile to cyclobutyl cyanide was achieved using NaOH and phase-transfer catalysts in a solid-liquid system at 70 $^{\circ}$C.

Cyclization of 4-membered rings is an arduous task compared to that of 3-,5- or 6-membered ones.[1,2] 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,[3] alkylation of chloroacetonitrile *via* a sulfur-stabilized carbanion intermediate,[4] and intramolecular cyclization of chloronitriles.[5] 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.[6-9] The rate of C-alkylation reactions using OH^- 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 $[OH^-]$ on the rate of phenylacetonitrile alkylation.[10] Similar rate dependence was found in the OH^- initiated isomerization of allyl benzene.[11] Solid NaOH pellets, applied in the absence of water, are expected to function as an extremely strong base in various alkylation reactions.[12] 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 $Bu_4N^+Cl^-$ afforded high yields of **2** (eq 1).[13] 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 δ-halovaleronitrile Cyclizations

Entry	Substrate	Solvent	Conversion %	Selectivity %
1	**1a**	THF	60	100
2	**1b**	THF	24	100
3	**1a**	THF^a	100	90
4	**1a**	Xylene	55	60
5	**1a**	Xylene^b	55	60
6	**1a**	DMF	90	60

Conditions: 6 mmol substrate, 10 ml solvent, 70 $^{\circ}$C (67 $^{\circ}$C in THF), NaOH contains 5% W/W water, 3 h, 5 mol% $Bu_4N^+X^-$, GC conversions and selectivities. ^{a} 6 h, 90 mmol substrate, 100 ml solvent, 90% isolated yield. ^{b} NaOH contains 15% W/W water.

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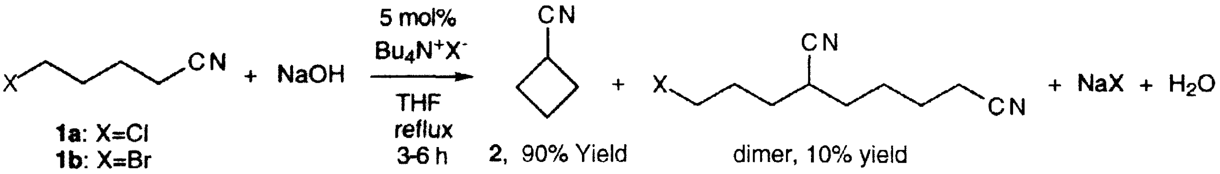
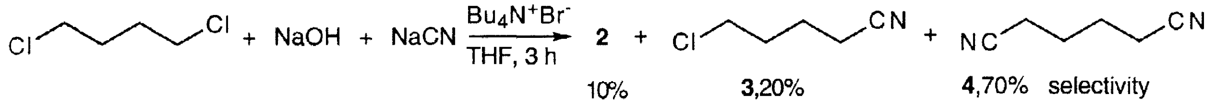


(1)

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

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. [15]



(2)

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13. *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) $Bu_4N^+Cl^-$, 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}H NMR, 2D HH NMR (COSY), and ^{13}C NMR. Proton-decoupled ^{13}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.[16]
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15. *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 $NaOH_{(s)}$, and 0.5 mmol (0.16 gr) $Bu_4N^+Br^-$. 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.
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