Nucleophilic "Addition-Elimination" Displacements on Activated Bicyclobutanes[1]

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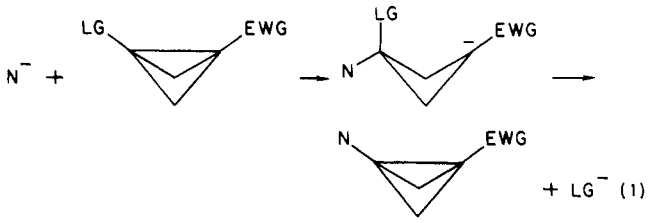
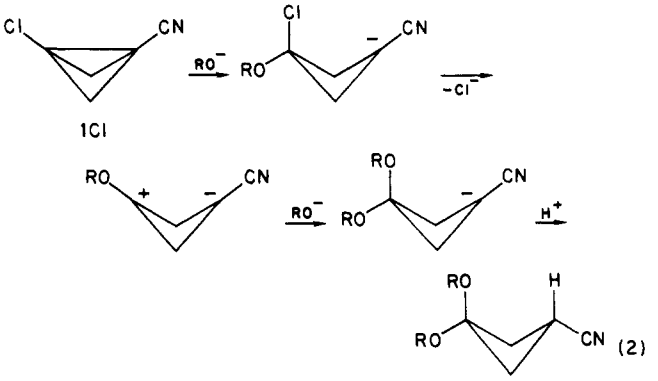
In MeOH CN^- reacts with 3-chlorobicyclobutanecarbonitrile (1Cl) to give both chloride substitution and addition of HCN across the central bond. The bromo derivative (1Br) undergoes only substitution. An addition mechanism is offered for the halide substitution reactions. In Me_2SO with an excess of 1Cl, the major product is 1,3-dicyanobicyclobutane. In the presence of excess CN^-, 1,1,3-tricyanocyclobutane is obtained. With the carbanion NCH_2C^- with HCH = 90° as a model, the barrier for inversion was calculated at a 3-21G$^+$ level to be 2.6 kcal/mol. The relative rates of carbanion inversion, ring flip, protonation, and γ carbanionic halide displacement are discussed.

In light of the demonstrated similarity between the central bond of bicyclobutane and a π bond in olefins,[2] it is surprising that nucleophilic vinylic substitution, a reaction which is typical of activated olefins, has never been reported for bicyclobutanes. The most common mechanism suggested for this reaction in olefins is "addition-elimination".[3] This is a two-step mechanism in which one step is the reversal of the other. When applied to bicyclobutane (eq 1) it is seen that the two major steps of

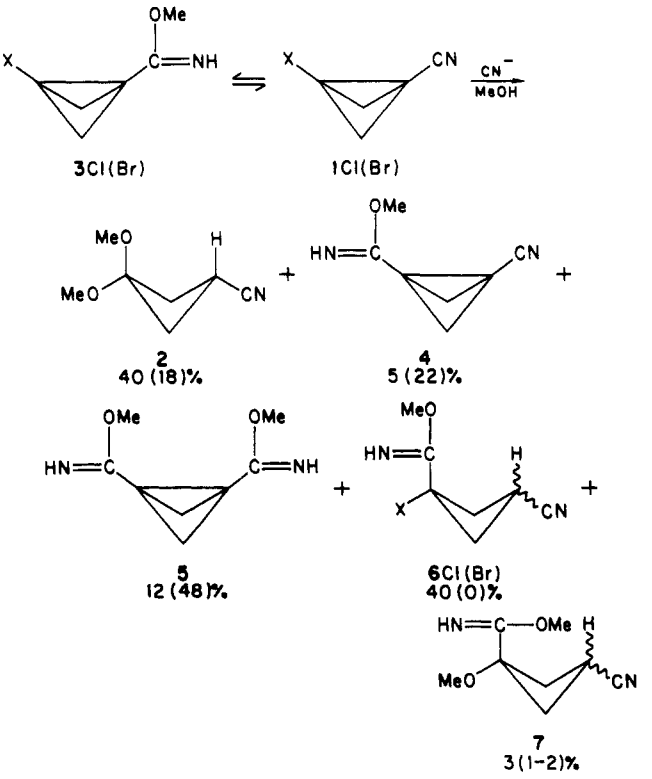


which it consists are in fact well-known processes in bicyclobutane chemistry.[2a,d,4] Nevertheless, in the nucleophilic reactions of alkoxides with 3-chlorobicyclobutanecarbonitrile (1Cl), it was found[5] that the displacement of the leaving group did not occur by this mechanism. Instead, a different mechanism (eq 2) in which an ionic bi-



cyclobutane, namely a bicyclobutane in which the two bridgehead carbons are electrostatically (and not covalently) bound was observed.[5] The major reason for this deviation from the expected course was the ability of the halo ether moiety on C-3 to expel the halide ion before the negatively charged carbon atom (C-1) could react. This was also observed in the reaction of PhS^- in MeOH with 1Cl(Br).[6]

Scheme I



In the present work we report an example in which the system indeed reacts via the expected addition-elimination pathway (eq 1). In order to force the reaction into this route, we have chosen to react 1Cl(Br) with CN^- as a nucleophile.

Results

Reactions of 1Cl with NaCN in MeOH. The reactions were carried out in a thermostated bath at 30 °C. The product distribution and the progress of the reactions were monitored by GC. Due to the relatively high basicity of CN^- in methanol, (pK_a of HCN in MeOH[7] is 13) small amounts of MeO^- are also present in the reaction mixture. As a result, product obtained[5] from the reaction of MeO^- with the starting material as well as with the primary products of the reaction of CN^- with the substrate are

(1) This is part 9 in the series the cyclobutane-bicyclobutane system. For Part 7 see: Hoz, S.; Aurbach, D. *J. Org. Chem.* **1984**, *49*, 3285.
(2) (a) Hoz, S.; Aurbach, D. *Tetrahedron* **1979**, *35*, 881. (b) Pomeranz, M.; Wilke, R. N.; Gruber, G. W.; Roy, U. *J. Am. Chem. Soc.* **1972**, *94*, 2752. (c) Hall, J. K.; Blanchard, E. P.; Cherkofsky, S. C.; Sieja, J. B.; Sheppard, W. A. *J. Am. Chem. Soc.* **1971**, *93*, 110. (d) Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749.
(3) (a) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (b) Modena, G. *Ibid.* **1971**, *4*, 73.
(4) Hoz, S.; Albeck, M.; Livneh, M. *J. Am. Chem. Soc.* **1979**, *101*, 2475.
(5) Hoz, S.; Aurbach, D. *J. Am. Chem. Soc.* **1983**, *105*, 7685.
(6) Hoz, S.; Aurbach, D., unpublished results.
(7) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1971**, *93*, 1589.

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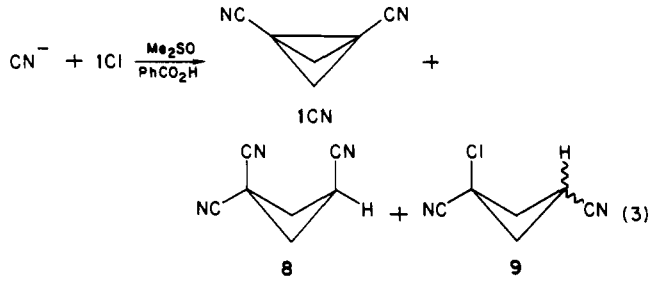
observed. Overall, the reaction is relatively slow. For example, with 0.2 M NaCN and 0.04 M 1Cl, the reaction is completed in ca. three weeks. Product distribution is shown in Scheme I. Some of the primary products of the reaction are converted to their imidates **4**, **5**, **6**, and **7**. The ratio between these final products remains constant during the course of the reaction.

Reaction of 1Br with NaCN in MeOH. The reactions of 1Br were conducted in the same way as those of 1Cl. It is estimated that under the same reaction conditions 1Cl reacts 2–3 times faster than 1Br. With 1Br, only three major products are obtained: **2**, **4**, and **5**. No Br containing product, namely, **6Br** was observed. The numbers in parentheses in Scheme I denote the percents of each of the products obtained in this reaction.

Reactions of 1Cl with NaCN in Me_2SO. The reactions were carried out at room temperature and were followed by GC. The CN^- concentration in the reactions was around 0.1 M and the solutions were homogeneous.[8] The reactions are faster than those in MeOH by at least an order of magnitude and their course is governed by the initial CN^-/1Cl ratio. In reactions where the nucleophile concentration was lower than that of the substrate (0.08 and 0.1 M, respectively), 1,3-dicyanobicyclobutane (1CN) was the major product (80–90%). When the concentration of the nucleophile was larger than that of 1Cl (0.1 and 0.005 M, respectively), the primary product 1CN adds another CN^- to give the tricyano-substituted cyclobutane **8**. This is accompanied by a darkening of the solution (which was not observed in the presence of $PhCO_2H$) which probably results from deprotonation of the solvent followed by side reactions.

One of the reactions in which the solution was saturated with cyanide and benzoic acid (sodium benzoate precipitates) was analyzed by GC–MS combination. In addition to 1CN and **8**, traces of the two isomers of **9Cl** were detected. The reaction is described in eq 3.



Discussion

Reactions in MeOH. The primary products of the reactions are obtained from the nucleophilic attack of both methoxide and cyanide ions on **1**. These are further converted to the corresponding imidates presumably by a methoxide-catalyzed reaction. The major product of the reaction of MeO^- with **1** is the ketal **2**. Most of the other products with the exception of one, as will be shown later, are derived from intermediates obtained in the reaction of **1** with CN^-.

Although 1Br reacts ca. 2.5 times slower than 1Cl, this value of 2.5 can not be taken as an estimate for the element effect of the reaction of CN^- with 1Cl(Br) since it includes a major contribution from the MeO^- element effect. The element effect of the CN^- reaction can be evaluated in the following manner. The relative rates of the reaction of MeO^- and CN^- with 1Cl and 1Br can be evaluated (eq 4 and 5, respectively) from the product distribution (see Scheme I).

$$\frac{k_{Cl}^{MeO}[MeO^-]}{k_{Cl}^{CN}[CN^-]} \approx \frac{40}{60} \quad (4)$$

$$\frac{k_{Br}^{MeO}[MeO^-]}{k_{Br}^{CN}[CN^-]} \approx \frac{20}{80} \quad (5)$$

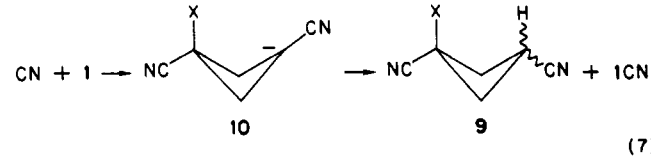
Therefore

$$(k_{Cl}^{MeO}/k_{Br}^{MeO})/(k_{Cl}^{CN}/k_{Br}^{CN}) \approx \frac{8}{3} \quad (6)$$

Since the element effect for MeO^- is 3.7,[9] the element effect for the reaction of CN^- with 1Cl(Br) is ca. 1.4.

In previous work[5] we have shown that the nucleophilic attack is coupled with cleavage of the central bond rather than the displacement of the leaving group. Two experimental observations in this study further support this conclusion. The first is the element effect (k_{Cl}/k_{Br}) of 1.4 for the reaction of CN^- with 1Cl(Br) which indicates[10] that the carbon–halogen bond is not cleaved in the rate-determining step. The second is the formation of **9Cl** which indicates that at least during the major course of the reaction of CN^- with 1Cl, the central bond rather than the carbon–chlorine bond is ruptured.

The mechanism of the reaction involves, therefore, nucleophilic cleavage of the central bond to form the carbanion **10** which can then either γ-eliminate the halide ion to give 1CN or abstract a proton from the solvent to give **9** (eq 7).



These primary products react further to give the corresponding imidates. 1CN → **4** + **5**, **9Cl** → **6Cl**. (As will be shown later, **7** is obtained from a different origin.)

While this scheme faithfully describes the reaction of 1Cl it is only partly correct for the reaction of 1Br, since, when 1Br reacts with CN^-, no **9Br** or its imidate derivative is observed. Instead, the carbanion **10** exclusively displaces the bromine atom at the γ-position without undergoing protonation to a measurable extent. This is highly consistent with the greater nucleofugality of Br as compared to Cl in direct nucleophilic displacements.[11]

As we have mentioned before **4**, **5**, and **6** are obtained from 1CN and **9Cl**, respectively. The other product **7** could not be obtained from either **4** or **5** since the product ratio remains constant during the reaction. In addition 1CN can not be the precursor of **7** since if it were to undergo attack by MeO^- it would necessarily give rise to relatively large quantities of **8** and its derivatives which were not observed in MeOH. The other alternative which is indeed the most reasonable one is that **7** is obtained by incorporation of CN^- into the intermediate ionic bicyclobutane (**11**) obtained in the reaction of 1Cl(Br) with MeO^-.

We would like to comment briefly on the kinetic and mechanistic aspects of the reaction of CN^- with **11**. Three

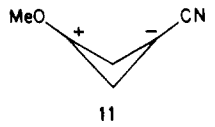
(8) Low solubility of NaCN in Me_2SO was reported by Ritchie (Ritchie, C. D.; Skinner, G. A.; Badding, V. G. *J. Am. Chem. Soc.* **1967**, *89*, 2063). It is possible that the presence of traces of water in our system increased the solubility of NaCN in this medium.

(9) This value was determined at 25 °C (ref 5) and is assumed not to be largely different at 30 °C.

(10) Bunnett, J. F.; Gabrisch, E. W., Jr.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385. Bartsch, R. A.; Bunnett, J. F. *Ibid.* **1968**, *90*, 408.

(11) Bunnett, J. F. *Tech. Chem. (N.Y.)* **1974**, *6*, 367.

(12) This may be further complicated by a general base catalyzed reaction.



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possibilities exist: (a) The reaction of CN^- and MeO^- with **11** are diffusion controlled. (b) The rate-determining step is the transition from solvent separated to intimate ion pairs. (c) The combination itself is rate determining. Using the p*K*a values of HCN[7] (13) and MeOH[13] (18.2) in MeOH one can calculate the concentration of the two nucleophiles CN^- and MeO^-. For a 0.2 M solution of NaCN the initial concentrations of CN^- and MeO^- are 0.195 and 0.005 M, respectively. Since the products ratio **7**/**2** is far from 0.195/0.005 it is clear that the additions is not diffusion controlled. The Ritchie equation[14] (eq 8)

$$\log \frac{k}{k_0} = N_+ \tag{8}$$

can be used only in cases where the anion–cation combination itself is rate determining. In cases where the transition from solvent separated to intimate ion pair is rate determining, no correlation will be obtained. This can be used to distinguish between possibilities b and c.

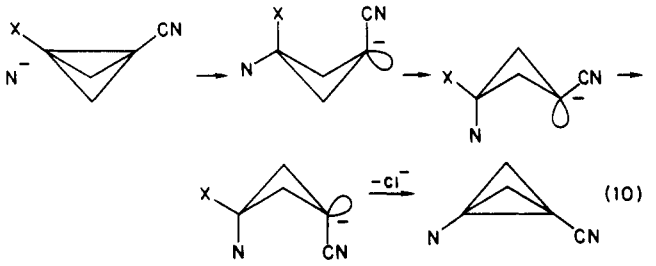
When applied to our case, eq 8 will take the following form

$$\log \frac{k_{MeO}}{k_{CN}} = N_+^{MeO} - N_+^{CN} \tag{9}$$

Using the original value of Ritchie for N_+^{MeO} (7.68) or the one that we have redetermined[15] (6.27) leads to a **7**/**2** ratio of ca. 1 or 20, respectively. (Inclusion of an S_+ parameter[15] of 1.25 will further increase this ratio.) Since it is observed that **7**/**2** $\ll$ 1, it is clear that the system does not correlate with the Ritchie equation and therefore case b seems to be more consistent with our findings.

Reactions in Me_2SO. As expected these reactions are faster in Me_2SO than in MeOH. In the first step of the reaction the carbanion **10** is irreversibly formed and in the absence of a good proton donor it γ-eliminates the chloride on C-3 to give 1CN. The rate of the latter process is apparently very fast since even in the presence of benzoic acid (partly converted to HCN), only traces of the protonation product **9** were observed. In the presence of excess CN^-, 1CN adds another cyanide ion to give after protonation the tricyano derivative **8**.

General Comment on the Elimination Step. The second and in fact final step of the reaction is an internal displacement of the leaving group positioned across the ring. Since equatorial approach is the preferred mode for nucleophilic attack on bicyclobutane,[2a,16] by microscopic reversibility, equatorial expulsion of the leaving group will be favored over an axial one. However, since during the course of the nucleophilic attack the leaving group is pushed to an axial position, two probably uncoupled processes must take place before the favored elimination geometry is achieved. The first (not necessarily in chronological sense) is a flip of the ring, the second is inversion of the carbanion α to the activating group (eq 10). In the event that there is a very good leaving group, departure from an axial position[4] could be faster than the other two



(10)

skeletal changes. Using a leaving group of smaller nucleofugality may render one of these steps rate determining. The energy needed for a ring flip of an unsubstituted cyclobutane is estimated to be 1.4–1.5 kcal/mol.[17] This barrier is not expected to be significantly larger for substituted cyclobutanes. The activation energy for the inversion of a cyano-stabilized carbanion (as a model for the second skeletal change) was calculated to be very low since in the ground state the cyanomethide anion is almost planar.[18] However, contraction of the angle between the two substituents will increase the pyramidalization in the ground state and therefore is likely to give rise to a higher inversion barrier. In the absence of relevant data we have calculated at a 3-21G+ level[19] the barrier for inversion in H_2C^-–CN in which the HCH angles was set equal to 90° in order to mimic the cyclobutane ring. Indeed, in the ground-state geometry, the deviation from planarity (defined as the angle between the C–CN bond and the plane determined by H_2C) was found to be 51.3°. The activation energy for the inversion, i.e., the difference between the energy of the optimized ground state (−130.574760 au) and the optimized planar geometry (−130.570553 au) is 2.6 kcal/mol.[20] Thus in cases where the leaving group is of high nucleofugality and does not depart from an axial position, carbanion inversion could be the rate-determining step for the elimination part of the reaction.

Summary and Conclusions

We have demonstrated here that when a nucleophile such as CN^-, which does not possess a dominant positive mesomeric effect, reacts with a suitably substituted bicyclobutane, the reaction mechanism is similar to nucleophilic vinylic substitution observed in olefins. The major difference between the two systems is the life span of the intermediate carbanion. While evidence for its existence in nucleophilic vinylic substitution is mainly indirect,[3] in the reaction of 1Cl with CN^-, the isolation of the two isomers of **6** derived from **9** provides unambiguous proof for its existence.

The intermediate carbanion **10** can react via two different pathways: (a) protonation and (b) ejection of the leaving group on C-3. In the case of Cl as a leaving group, the protonation rate is ca. 2-fold faster than elimination. However, when the reaction is carried out in the absence of proton donor (Me_2SO) only the elimination product is observed. When Br is used as a leaving group of higher nucleofugality (compared with Cl), only elimination is

(13) Koskikallio, J. *Suom. Kemistil. B* **1957**, *30B*, 111, 155.
(14) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348.
(15) Hoz, S.; Speizman, D. *J. Org. Chem.* **1983**, *48*, 2904.
(16) This is also concluded from an ab initio study at a 4-31G level of the preferred approach of H^- to bicyclobutane. Hoz, S., unpublished results.
(17) Malloy, T. B., Jr.; Lafferty, W. J. *J. Mol. Spectrosc.* **1975**, *54*, 20. Malloy, T. B., Jr.; Bauman, L. E. *Top. Stereochem.* **1979**, *11*, 97.
(18) Moffat, J. B. *Int. J. Quantum Chem.* **1982**, *22*, 299. Hopkinson, A. C.; Lien, M. H. *Ibid.* **1980**, *18*, 1371. Mezey, P. G.; Robb, M. A.; Yates, K.; Csizmadia, I. G. *Theor. Chim. Acta* **1978**, *49*, 277.
(19) (a) Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B. Topiol, S.; Kahn, L. R.; Pople, J. A. Gaussian 80, Carnegi-Mellon University, 1980. (b) Clark, T.; Chandrasekhav, J.; Spitznagel, G. W.; von Schleyer, P. R. *J. Comput. Chem.* **1983**, *4*, 294.
(20) Bond length in the pyramidal geometry: C–H, 1.10; C–C, 1.402; C–N, 1.163 Å. In the planar geometry (transition state): C–H, 1.087; C–C, 1.351; C–N, 1.172.

observed even in MeOH. Thus, the protonation rate is assumed not to be affected by the substituents on C-3, the rate of the various processes decreases in the order: elimination of Br > protonation[21] > elimination of Cl.

The favored mode of elimination is an equatorial departure of the leaving group. However in order to obtain the geometry needed for this process, ring flip as well as inversion at the carbanion center must first take place. These two processes are of relatively low activation energy. For unsubstituted bicyclobutane the energy of the first process is ca. 1.4 kcal/mol.[17] The inversion barrier for a model compound H_2C^-–CN (∠HCH 90°) was calculated in this work and found to be ca. 2.6 kcal/mol. Therefore it is clear that in the case of the chloro derivative 1Cl, where both elimination and protonation of 10Cl are observed, the population of the various conformers will not play (according to the Curtin–Hammett principle[22]) a determinitive role in governing the course of the reaction. On the other hand in the case of 1Br where only elimination was observed, inversion of the carbanion could be of higher activation energy than elimination thus dictating an axial expulsion of the leaving group or equatorial departure if the activation energies are in the order: axial expulsion > inversion > equatorial expulsion.

Experimental Section

General Methods. ^1H NMR (in $CDCl_3$) spectra were recorded on a Varian EM 360A spectrometer. Mass spectra were taken with a Finnigan 4021 mass spectrometer. For analytical purposes a Packard Model 878 (FI dector) gas chromatograph was used, whereas for preparative separations a Varian 920 gas chromatograph was employed. In both cases, the column was 3–5% Xe60 on chromosorb W.

Solvents and Starting Materials. Methanol (Frutarom-analytical) was dried by the magnesium method.[23] Me_2SO (Merck) was vacuum distilled (70 °C (10 mmHg)) after standing for 24 h over CaH_2. Sodium cyanide (Merck analytical) was used without further purification. 3-Chlorobicyclobutane (1Cl) was prepared according to published procedures.[2c] Its bromo derivative, 1Br, was prepared by reacting 1Cl with NaBr in DMF.[5]

Product Preparation. 1,3-Dicyanobicyclobutane (1CN). To a stirred solution of 1Cl (300 mg, 2.6 mmol) in 10 mL of Me_2SO was gradually added a solution of NaCN (150 mg, 2.6 mmol) in 10 mL of Me_2SO. The reaction mixture was treated with 50 mL of ether and 50 mL of H_2O. The aqueous phase was extracted twice more with ether. The combined ethereal phase was washed with water and dried over $MgSO_4$ and the ether was evaporated to give 1CN (75% yield—VPC). The needed quantities were purified by preparative gas chromatography. The product was identified by comparison of its spectral data (MS, NMR, and IR) with the literature data.[2c]

1,1,3-Tricyanocyclobutane (8). A solution of NaCN (0.3 g, 6 mmol) and benzoic acid (0.39 g, 3.2 mmol) in 40 mL of Me_2SO was allowed to react at room temperature with 1Cl (0.23 g, 2 mmol). After 6 h the reaction mixture was treated with H_2O–$CHCl_3$. The organic layer was washed and dried over $MgSO_4$ and the solvent was partially evaporated. The product 8 precipitated as a white solid (0.2 g, 75% yield): mp 115 °C; ^1H NMR δ 3.2 (m, 1 H), 3.1–2.7 (m, 4 H); ^{13}C NMR (acetone-d_6) 19.72 (d, J = 155 Hz, CCN), 37.59 (t, J = 150 Hz, CH_2); IR (neat) 2230 cm^{-1}; MS (EI), m/e 131 (M), 130, 105, 104, 79, 78. Satisfactory C, H, N analysis was obtained.

The products of the reaction of 1Cl with NaCN in MeOH (see Scheme I) were separated by gas chromatography from a reaction mixture containing NaCN (1 g, 2 mmol) and 1Cl (0.7 g, 6.2 mmol) in 50 mL of methanol. The stirred reaction mixture was incubated for a week at 30 °C. Aliquots were periodically removed and analyzed by GC and GC–MS combination. Analysis of the data showed that 3Cl, 1CN, and 9Cl were formed and disappeared in the course of the reaction. After the completion of the reaction, the mixture was extracted with ether which then was washed with water, dried over $MgSO_4$, and evaporated. The products (% GC yield) according to their appearance order on the chromatogram were 3-methoxycyclobuta-2-enecarbonitrile[5] (traces), 3,3-dimethoxycyclobutanecarbonitrile (2) (35%),[5] 1,3-bis(methoxycarbonimidoyl)cyclobutane (5) (10%) [^1H NMR δ 3.75 (s, 6 H), 2.7 (s, 2 H), 1.4 (s, 2 H); MS (CI – CH_4), m/e 169 (M + 1), 153, 137, 105; satisfactory C, H, N analysis was obtained], methyl 3-cyanobicyclobutanecarboximidate (4) (5%) [^1H NMR δ 3.8 (s, 3 H), 2.65 (s, 2 H), 1.55 (s, 2 H); MS (CI – CH_4), m/e 137 (M + 1), 109, 105; satisfactory C, H, N analysis was obtained], methyl 3-cyano-1-methoxycyclobutanecarbonimidate (6, two isomers) (3%) [^1H NMR δ 3.8 (s, 3 H), 3.2 (s, 3 H), 2.7 (m, 5 H); MS (CI – CH_4), m/e 169 (M + 1), 137, 105], and methyl 3-cyano-1-chlorocyclobutanecarbonimidate (6, two isomers) (35%) [^1H NMR δ 3.85 (s, 3 H), 3.15 (m, 5 H); MS (CI – CH_4) 175, 173 (M + 1), 137, 110, 107; satisfactory C, H, N, Cl analysis was obtained].

Reactions of 1Cl and 1Br with NaCN. Procedure and Followup. The reactions were performed in 2-mL volumetric flasks in a thermostated bath. In a typical experiment a 0.2 M solution of NaCN in MeOH was prepared. The substrate was introduced by means of a microsyringe up to a concentration of 0.05 M. Aliquots of 0.1 mL were periodically removed and transferred to a mixture of 1.5 mL of H_2O and 1.5 mL of $CHCl_3$. The organic phase was dried and analyzed by gas chromatography. A similar technique was employed for the reactions in Me_2SO. (The organic phase was repeatedly washed to remove the remainder of Me_2SO which interfered with the GC analysis.)

Acknowledgment. We would like to thank Dr. D. Cohen for her assistance.

Registry No. 1-Cl, 23745-75-7; 1-Br, 87712-20-7; 1 (X = CN), 27184-67-4; 2, 87712-21-8; 4, 91633-47-5; 5, 91633-42-0; *cis*-6 (X = MeO), 91633-43-1; *trans*-6 (X = MeO), 91633-44-2; *cis*-6 (X = Cl), 91633-45-3; *trans*-6 (X = Cl), 91633-46-4; HCN, 74-90-8; CN^-, 57-12-5; MeO^-, 3315-60-4; NCH_2C^-, 21438-99-3; 1,1,3-tricyanocyclobutane, 91633-41-9; benzoic acid, 65-85-0; 3-methoxycyclobut-2-enecarbonitrile, 87712-22-9.

(21) Protonation rates on cyano-stabilized carbanions are in order of 10^8–10^9 M^{-1} s^{-1} (Hibbert, F.; Long, F. A.; Walter, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829; **1972**, *94*, 2647) which is equivalent to ca. 6 kcal/mol.

(22) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(23) Vogel, A. I. "Practical Organic Chemistry", 3rd ed.; Longman: New York, 1964.