Radical Cyclization/Fragmentation Reactions of Dicyanocyclopropanes to Enaminonitriles. A Radical Alternative to the Thorpe-Ziegler Reaction

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Abstract: Radical cyclizations to dicyanocyclopropanes provide cyclic enaminonitriles by a series of radical reactions that features radical cyclization to a nitrile and cyclopropane cleavage. The direction of cyclopropane cleavage—and hence the ring size of the final product—depends on the nature of the ring formed in the initial cyclization to the nitrile.

Keywords: radical cascade, nitrile, Thorpe-Ziegler, ring expansion, cyclopropane

The qualitative analogy between reactions of double bonds to those of cyclopropanes is well established in many areas of organic chemistry.[1] However, in radical chemistry, additions to carbon-carbon double bonds are widespread[2] while analogous homolytic substitution reactions of cyclopropanes are rare.[3] In an attempt to discover substituent effects that would promote homolytic substitution, we studied the radical reactions of a series of dicyanocyclopropanes (Figure 1). However, in no case was homolytic substitution observed. Instead, the reactions evolve through initial cyclization to one of the nitriles[2b,4] followed by a series of steps that ultimately provides enaminonitriles. This newly discovered radical sequence complements the traditional method to make enaminonitriles—the Thorpe-Ziegler reaction[5]—both by starting from different types of precursors and by providing access to products that are difficult or impossible to make by the traditional route.

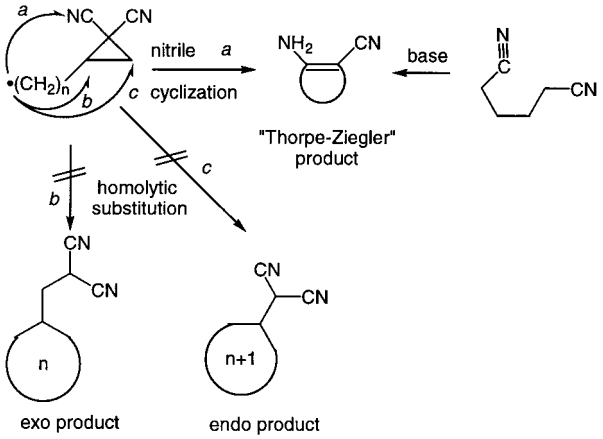
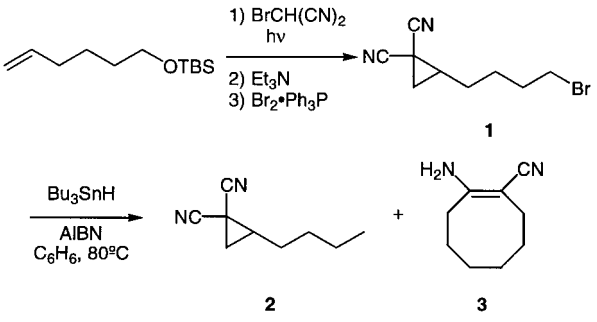


Figure 1. Radical Cyclizations of Dicyanocyclopropanes

We first investigated the radical cyclization of bromodinitrile **1**, which has options for 7-*endo* cyclization to a nitrile and 6-*endo* or 5-*exo* homolytic substitution reactions (Scheme 1). This system was viewed as the most favorable for homolytic substitution relative to nitrile cyclization. The synthesis of **1** follows a straightforward series of steps from the TBS-ether of hex-5-en-1-ol and bromomalonodinitrile that features an atom transfer addition/1,3-elimination reaction[6] to form the cyclopropane.



method	equiv Bu_3SnH	%2	%3
0.1M	1.5	76%	---
0.01M	1.5	56%	---
syringe pump	1.5	33%	43%
syringe pump	2.5	trace	56%

Scheme 1

Cyclization of **1** with 1.5 equiv of tributyltin hydride at both 0.1 and 0.01M provided only the product **2** of simple reductive debromination. However, syringe pump addition of tin hydride provided **2** (33%) along with the enaminonitrile **3** (43%) and some starting material. The mechanism for formation of **3**[7,8] (see below) suggested that 2 equiv of tin hydride was required for complete reaction, and the reaction was repeated with slower syringe pumping and now using 2.5 equiv of tin hydride. This gave mainly **3** alongside a trace amount of **2**; product **3** was isolated in 56% yield after flash chromatography. In no experiment did we see evidence for any of the possible homolytic substitution products.

To rationalize the formation of **3**, we suggest that (Figure 2) initial radical **4** undergoes a slow ($< 10^4$ $M^{-1}s^{-1}$) cyclization to one of the nitriles (probably the one which is cis-disposed) in preference to either homolytic substitution option. Reduction of **5** by tin hydride provides an imine **6** and consumes the first equiv of tin hydride. This

imine **6** is then subject to addition of the tin radical, cyclopropane cleavage and hydrogen transfer in a sequence (**6** → **7** → **8** → **9**) that consumes the second equivalent of tin hydride. Hydrolytic workup then provides the enaminonitrile **3**. A number of features of this cascade merit amplification. Cyclizations to nitriles are relatively slow and can be reversible.[2b,4] In this case, the rigid cyclopropane ring must facilitate the 7-*exo* cyclization of **4**. Fragmentation of the iminyl radical **5** does not occur in preference to reduction to **6** since only the starting primary radical or a cyano-substituted cyclopropyl radical could be formed. The sequence of **6** →→ **9** appears to be new, but it has precedent in related reactions of ketocyclopropanes and related molecules.[9,10] Cleavage of the transannular bond is the expected outcome with a cyclopropyl-fused cyclohexyl radical, although the results do not exclude reversible cleavage of the lateral bond.[8] The overall transformation in Scheme 1 represents a straightforward route from an acyclic precursor to a functionalized cyclooctane ring, and it features radical reactions for all the key C–C bond forming steps.

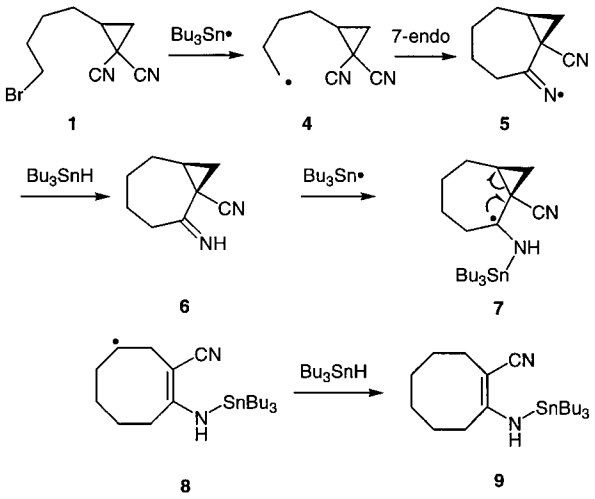
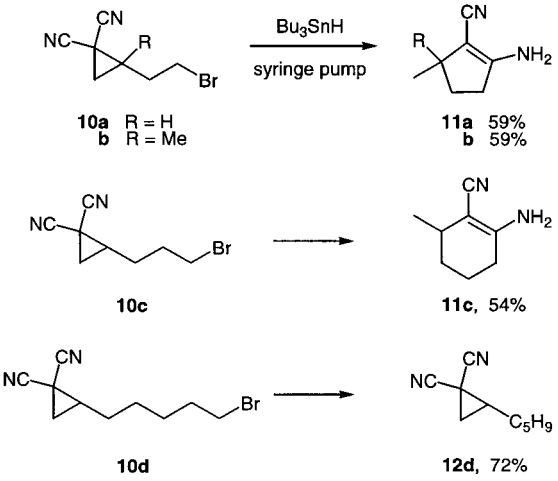


Figure 2. Suggested Mechanism for Formation of Enaminonitrile **3**

We briefly investigated the scope of this transformation by studying the reactions of cyclopropane dinitriles **10a-d** (Scheme 2). The syntheses of these substrates are not shown; they all started with the corresponding TBS-alkenol and followed an identical sequence of steps to that shown in Scheme 1. The halides were reduced by the syringe pump procedure with 2.5 equiv of tin hydride and then the products were purified by flash chromatography. Not surprisingly, the substrate **10d** capable of 8-*exo* cyclization provided only the product **12d** of reductive debromination. In contrast, substrates capable of 5-*exo* (**10a,b**) or 6-*exo* (**10c**) cyclization to the nitrile underwent a series of reactions similar to that in Figure 2, but cleaved the lateral bond rather than the transannular bond to provide methyl substituted enaminonitriles **11a-c**. This stereoelectronically controlled mode of cleavage is anticipated based on prior results of structurally related radicals.[8]



Scheme 2

Although we have only studied a limited number of examples, the synthetic method introduced in this paper shows good promise for application in diverse and complex settings. The individual steps in the sequence can each be related back to known reactions and their success should be relatively predictable in other analogs. In essence, the method is a strategic alternative to the classical Thorpe-Ziegler condensation of dinitriles, which is the most popular way to make enaminonitriles. However, the radical approach allows access to otherwise difficult or impossible products. For example, cyclooctanes are not easy to form by the Thorpe-Ziegler condensation. And substitution patterns like **11a-c** are difficult to form regioselectively in the traditional Thorpe-Ziegler condensation due to problems with regioisomers. Facile access to these types of enaminonitriles should expand the synthetic utility of this class of molecules.

Acknowledgement

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(8) 2-Aminocyclooct-1-enecarbonitrile (**3**): ^{1}H NMR δ 4.33 (bs, 2 H), 2.28 (t, *J* = 6, 2 H), 2.22 (t, *J* = 6, 2 H), 1.48-1.67(m, 8 H); ^{13}C NMR δ 160.13, 121.54, 75.28, 31.02, 30.31, 28.94, 26.98, 25.95, 25.72; IR 3427, 3350, 3245, 2931, 2854, 2324, 2175, 1638, 1600, 1442, 1194, 1055; MS *m/e* 150, 122, 107, 94, 82, 67, 54. 2-Amino-5-methylcyclopent-1-enecarbonitrile (**11a**): ^{1}H NMR δ 4.50 (bs, 2 H), 2.91 (m, 1 H), 2.44 (t, *J* = 7, 2 H), 2.13 (m, 1 H), 2.13 (d *J* = 7, 3 H), 1.42 (m, 1 H); ^{13}C NMR δ 151.17, 118.71, 81.09, 38.85, 33.55, 31.05, 20.77; IR 3486, 3376, 2979, 2191, 1669, 1396, 1616; MS *m/e* 122, 107, 94, 80, 67, 53. 2-Amino-5,5-dimethylcyclopent-1-enecarbonitrile (**11b**): ^{1}H NMR δ 4.32 (bs, 2 H), 2.48 (t, *J* = 7, 2 H), 1.77 (t, *J* = 7, 2 H), 1.18 (s, 6 H); ^{13}C NMR δ 159.81, 118.14, 86.15, 44.73, 37.91, 32.71, 28.24; IR 3442, 3299, 2950, 2192, 1663, 1345, 1610; MS *m/e* 136, 121, 106, 94, 77, 67. 2-Amino-6-methylcyclohex-1-enecarbonitrile (**11c**): ^{1}H NMR δ 4.22 (bs, 2 H), 2.37 (m, 1 H), 2.14 (m, 2 H), 1.79 (m, 2 H), 1.57 (m, 2 H), 1.18 (d, *J* = 3, 3 H); ^{13}C NMR δ 156.00, 120.31, 81.13, 30.68, 28.95, 28.47, 21.13, 19.90; IR; 3368, 2961, 2182, 1722, 1643, 1466; MS *m/e* 136, 122, 108, 94, 81, 67, 54.
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