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Synthesis and Characterization of Cyanobutadiene Isomers—Molecules of Astrochemical Significance

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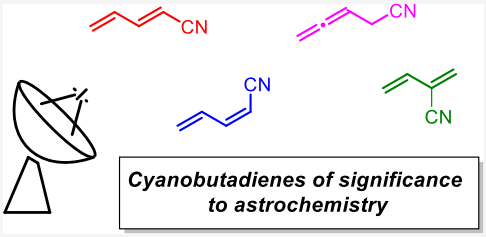
ABSTRACT: Four cyanobutadiene isomers of considerable interest to the organic chemistry, molecular spectroscopy, and astrochemistry communities were synthesized in good yields and isolated as pure compounds: (*E*)-1-cyano-1,3-butadiene (***E*-1**), (*Z*)-1-cyano-1,3-butadiene (***Z*-1**), 4-cyano-1,2-butadiene (**2**), and 2-cyano-1,3-butadiene (**3**). A diastereoselective synthesis was developed to generate (*E*)-1-cyano-1,3-butadiene (**1**) (10:1 *E*/*Z*) *via* tandem S_N2 and E2′ reactions. The potential energy surfaces of the E2′ reactions leading to (*E*)- and (*Z*)-1-cyano-1,3-butadiene (**1**) were analyzed by density functional theory calculations, and the observed diastereoselectivity was rationalized in the context of the Curtin−Hammett principle. The preparation of pure samples of these reactive compounds enables measurement of their laboratory rotational spectra, which are the critical data needed to search for these species in space by radioastronomy.



INTRODUCTION

Over 200 different molecules have been detected in the interstellar medium (ISM) or circumstellar shells[1,2] and are theorized to be involved in complex reaction networks.[3−7] The vast majority of these detections have been made *via* radioastronomy, through observation and assignment of rotational spectra. Because of their large dipole moments,[8−10] which confer intense rotational transitions, and composition of relatively abundant elements, nitriles (R−CN) represent realistic targets for detection by radioastronomy. Approximately 10% of the known interstellar molecules are nitriles, including recently detected benzonitrile,[11] hydroxyacetonitrile,[12] and silyl cyanide.[13] Interstellar nitriles are observed in varying degrees of hydrogenation, from highly unsaturated cyanopolyynes, $RC_{2n+1}N$ (R = H, n = 1−4; R = CH_3, n = 1, 2),[14−20] to vinyl and phenyl derivatives (vinyl cyanide (acrylonitrile),[21] cyanoallene,[22] and benzonitrile[11]), to compounds with fully saturated backbones (acetonitrile,[23] hydroxyacetonitrile,[12] propyl cyanide,[24] and isopropyl cyanide[25]). Spectroscopic data for the organic nitriles described herein—(*E*)-1-cyano-1,3-butadiene (***E*-1**), (*Z*)-1-cyano-1,3-butadiene (***Z*-1**), 4-cyano-1,2-butadiene (**2**), and 2-cyano-1,3-butadiene (**3**) (Figure 1)—would enable radioastronomical searches for these compounds. Each of these nitriles has been proposed as a likely component of the ISM.[26−30] Additionally, these nitriles are acyclic isomers of the aromatic heterocycle, pyridine, which has yet to be identified in the ISM.[31] Detection of any of these nitriles would provide additional motivation to detect pyridine and other aromatic heterocycles. The existence of organic nitriles in the ISM is relevant not only to our understanding of the chemical processes in the ISM but also to our understanding of the origin of amino acids, nucleotides, and other prebiotic compounds that are critical for life on Earth.

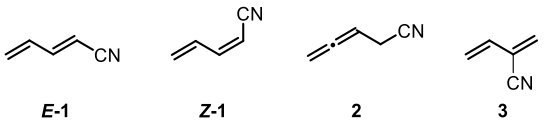


Figure 1. Cyanobutadiene isomers: (*E*)-1-cyano-1,3-butadiene (***E*-1**), (*Z*)-1-cyano-1,3-butadiene (***Z*-1**), 4-cyano-1,2-butadiene (**2**), and 2-cyano-1,3-butadiene (**3**).

Organic nitriles have also been detected in the nitrogen-rich atmosphere of Saturn's largest moon, Titan. Titan has been of interest as a possible analogue to prebiotic Earth[26] and has been visited by the Cassini−Huygens probe.[32] Small organic nitriles (up to four carbon atoms) and their corresponding anions were detected in Titan's atmosphere.[33] Electric discharge experiments performed on various gaseous mixtures (*e.g.* N_2, CH_4, C_2H_6, NH_3, H_2O, and H_2S) simulating the atmosphere of Titan produce a myriad of nitrile-containing small molecules.[3,34,35] It is plausible that the nitriles in Figure 1 are components of Titan's atmosphere.

Despite the sophistication of modern synthetic chemistry, the synthesis, purification, and isolation of the simple organic

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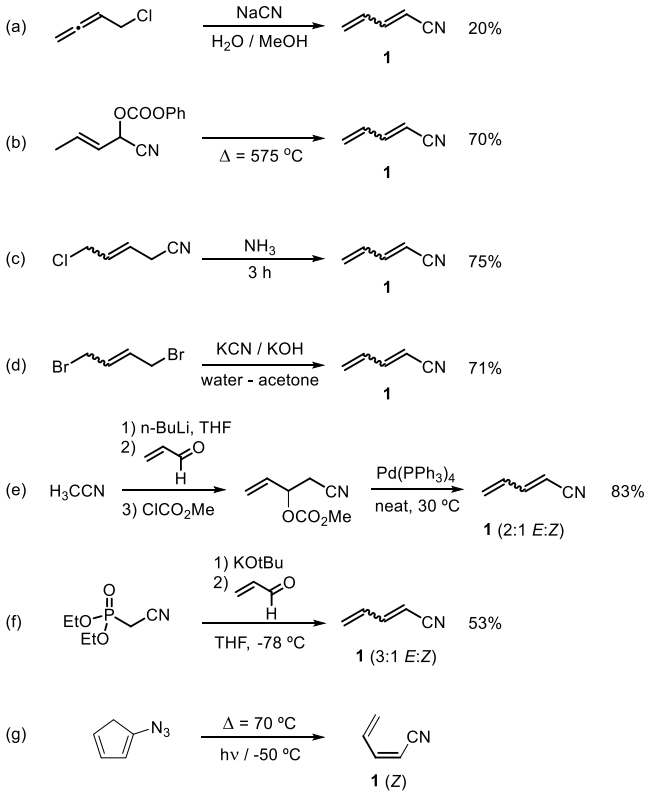
nitriles shown in Figure 1 remain a challenge at the current time. The new procedures reported in this work enable detailed studies of the high-resolution rotational spectroscopy of the four cyanobutadiene isomers (Figure 1).[36] The rotational spectrum of each of these compounds is very complex; having a pure sample, for which spectral features are not obscured by impurities, is critical to achieve a sophisticated analysis of the complex spectrum. In measuring gas-phase spectra, volatile impurities are especially problematic. Our procedures have been designed to minimize, or eliminate, these troubling contaminants. This work provides the foundation for the ultimate detection of nitriles ***E*-1**, ***Z*-1**, **2**, and **3** in extraterrestrial environments. With their relevance in the atmospheric chemistry of Titan and interstellar chemistry, the improved isolation of these nitriles allows new spectroscopic measurements of broad interest to the chemistry community.

BACKGROUND

1-Cyano-1,3-butadiene (2,4-pentadienenitrile) (**1**; mixture of *E* and *Z* isomers) was originally isolated and studied at DuPont as a potential monomer unit by Carothers and co-workers (Scheme 1a).[37−40] Snyder *et al.* prepared **1** by flash vacuum pyrolysis (Scheme 1b), separated the *E* and *Z* isomers by careful fractional distillation,[41] and investigated the reactivity of **1** in trapping, dimerization, and polymerization reactions.[42−44] These early investigations contain a wealth of useful data describing the synthesis and physical properties of ***E*-1** and ***Z*-1**, but the experimental procedures for synthesis, purification, and isolation were designed for a relatively large scale, and these reports predate modern methods for spectroscopic characterization.[45−54]

Scheme 1. Previous Syntheses of 1-Cyano-1,3-butadiene (1)[a]



[a](a) Carothers and Berchet;[38] Coffman.[39] (b) Snyder *et al.*[41] (c) Daessle *et al.*[48] (d) Katagiri *et al.*[53] (e) Braun *et al.*[55] (f) Clary and Back.[56] (g) Banert.[57]

An efficient, selective synthesis of (*E*)-1-cyano-1,3-butadiene (***E*-1**) has not been described, although modern synthetic procedures for producing a mixture of diastereomers (***E*-1** and ***Z*-1**) have been reported (Scheme 1e−g). The preparation reported by Braun *et al.*[55] (Scheme 1e) involves the reaction of the acetonitrile anion with acrolein and subsequent protection/elimination steps to yield diastereomers ***E*-1** and ***Z*-1** in a 2:1 ratio. The procedure described by Clary and Back[56] (Scheme 1f) combines diethylcyanomethyl-phosphonate ylide with acrolein in a Horner−Wadsworth−Emmons olefination to afford diastereomers ***E*-1** and ***Z*-1** in a 3:1 ratio. Banert[57] reported the selective preparation of ***Z*-1** by thermolysis or photolysis of 1-azido-cyclopentadiene (Scheme 1g). These various procedures notwithstanding, details concerning both purification and characterization of ***E*-1** and ***Z*-1** remain incomplete because of the sensitivity and high reactivity of these compounds under a variety of conditions.

The literature does not include any reports describing the synthesis of 4-cyano-1,2-butadiene (**2**) or the determination of its physical properties. 2-Cyano-1,3-butadiene (**3**) has been prepared, typically *via* synthetic routes that involve a pyrolysis reaction.[51,58−60] As with the 1-cyano isomers, details concerning both purification and characterization of 2-cyano-1,3-butadiene (**3**) remain incomplete.

RESULTS AND DISCUSSION

1-Cyano-1,3-butadiene (1). From the time of the earliest interest in 1-cyano-1,3-butadiene (**1**) (Scheme 1),[37−44] it has been evident that *generating* this compound has not been the obstacle to further study. Rather, the sensitivity of **1** to undergo reaction (dimerization, polymerization) or degradation (heat, light, strong bases, and silica/alumina gels) greatly complicates the task of purifying and characterizing **1**. Our attempts to replicate the procedure reported by Braun *et al.*[55] (Scheme 1e) failed to produce an isolable amount of the expected mixture of diastereomers. In our hands, the procedure described by Clary and Back[56] (Scheme 1f) afforded ***E*-1** and ***Z*-1** as components in a rather complex mixture of products. Analysis of the crude ^{1}H NMR spectrum revealed the presence of suspected polymeric byproducts generated through addition reactions between ***E*-1**/***Z*-1** and the strong base used to generate the phosphonate ylide. Thus, we sought alternate synthetic strategies to facilitate isolation, purification, and characterization of compound **1**.

We replicated the conditions for the synthesis of 1-cyano-1,3-butadiene (**1**) reported by the DuPont group (Scheme 1a).[38,39] To prepare the requisite starting material, 4-chloro-1,2-butadiene (**7**), we employed the sequence depicted in Scheme 2a. 2-Butyne-1,4-diol (**4**) was monochlorinated with $SOCl_2$ to produce 4-chloro-2-butyn-1-ol (**5**), and subsequent reduction of **5** with $LiAlH_4$ produced 1,2-butadien-4-ol (**6**).[61] Chlorination of **6** with $SOCl_2$ produced 4-chloro-1,2-butadiene (**7**),[62] which was isolated and subjected to the reaction conditions described by Coffman (Scheme 1a).[39] Analysis of the resulting product mixture *via* ^{1}H NMR spectroscopy revealed the presence of both ***E*-1** and ***Z*-1** along with several methoxy-substituted species resulting from the addition of methanol across one (or both) of the double bonds present in **1**, as noted previously.[39] We suspected that the mixed solvent

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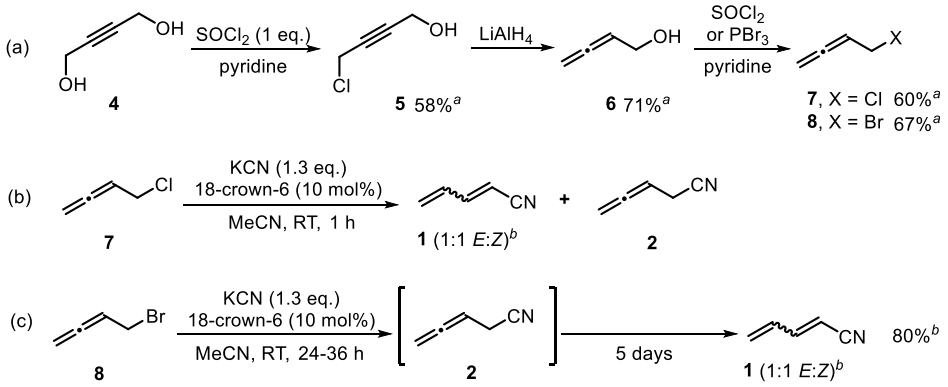
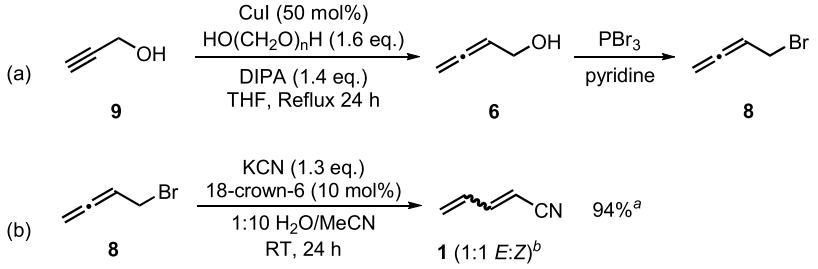
Scheme 2. Initial Synthetic Route to 1-Cyano-1,3-butadiene (1) from 2-Butyne-1,4-diol (4)



[a]Isolated (gravimetric) yield. [b]Yield and diastereomeric ratio determined *via* ^{1}H NMR.

Scheme 3. Improved Synthetic Route to 1-Cyano-1,3-butadiene (Mixture *E*-1 and *Z*-1) from Propargyl Alcohol (9)



[a]Reaction yield determined *via* ^{1}H NMR using phenyltrimethylsilane (Ph-TMS) as an internal standard. [b]Diastereomeric ratio determined *via* ^{1}H NMR.

system (H_2O/MeOH) in Scheme 1a was used in an attempt to optimize the solubility of the ionic and the organic reactants (sodium cyanide and 4-chloro-1,2-butadiene (7), respectively), but the formation of methanol adducts is clearly problematic.

We changed the reaction solvent to acetonitrile, which seemed to be a more appropriate solvent for an S_N2 reaction. The solubility of alkali-metal cyanides in most polar aprotic organic solvents is low, so a crown ether (18-crown-6)[63] was used as a phase-transfer catalyst. Although a solution of KCN and 18-crown-6 in acetonitrile was not completely homogenous, the increased solubility of cyanide was apparently sufficient that the reaction mixture rapidly became a turbid, dark brown color as the reaction progressed (Scheme 2b). The $^{13}C\{^1H\}$NMR spectrum of the crude reaction mixture contained three signals characteristic of an allenic sp-hybridized ^{13}C atom, indicating the presence of alcohol **6**, chloride **7**, and a previously unreported allene derivative. Further analysis *via* two-dimensional NMR spectroscopy (HMBC/HSQC) showed correlation of the new allenic ^{13}C signal to three ^1H signals sharing a very similar coupling pattern as observed in alcohol **6** and chloride **7**, but with different *J*-coupling frequencies and chemical shifts. We suspected that the unassigned ^{13}C signal was due to 4-cyano-1,2-butadiene (**2**), the presumed product of initial S_N2 substitution in chloro compound **7**, prior to rearrangement to 1-cyano-1,3-butadiene (**1**). This suspicion was later confirmed to be true. Details concerning the optimization of reaction conditions, isolation, and spectroscopic characterization of 4-cyano-1,2-butadiene (**2**) are discussed below.

Along with 4-cyano-1,2-butadiene (**2**), smaller amounts of 1-cyano-1,3-butadiene (***E*-1** and ***Z*-1**) were formed in this reaction, and the product mixture also included a large amount of unreacted starting material **7**. Extending the reaction time to 4 h resulted in the formation of a polymeric material and complete loss of both ***E*-1** and ***Z*-1**—yet, there was still unreacted **7** present (evident *via* NMR). The same reaction sequence employing the corresponding 4-bromo-1,2-butadiene (**8**) afforded a better result. 4-Bromo-1,2-butadiene (**8**) was prepared in two steps from propargyl alcohol (**9**) (Scheme 3a).[61,64] When treated with the same reaction conditions as allenic chloride **7**, allenic bromide **8** reacted in a more controlled, clean manner, yielding significantly less of the brown polymeric material. The reaction of allenic bromide **8** to form **2** and the subsequent isomerization of **2** to **1** were unexpectedly slow; at room temperature and under anhydrous conditions, isomerization of 4-cyano-1,2-butadiene (**2**) to 1-cyano-1,3-butadiene (**1**) took 5 days (80% yield; approximately 1:1 mixture of ***E*-1** and ***Z*-1**) (Scheme 2c). Despite the use of a phase-transfer catalyst, the reaction in acetonitrile was not homogenous. The addition of water (~10% v/v) to the reaction mixture increased the solubility of KCN and decreased the reaction time to approximately 24 h (Scheme 3b). The optimal conditions for producing a 1:1 mixture of ***E*-1** and ***Z*-1** with minimal byproducts are reported in Scheme 3b. Even though the reaction efficiently produced ***E*-1** and ***Z*-1**, we were confounded in our efforts to separate, purify, and isolate these isomers, as prepared using this procedure. Difficulties included the inability to remove small amounts of acetonitrile and propensity for dimerization and/or polymerization. Requiring pure, neat materials in order to obtain their rotational spectra, we turned to other synthetic strategies that might afford a measure of selectivity in the preparation of ***E*-1** and ***Z*-1**.

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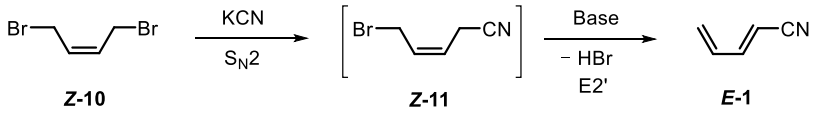
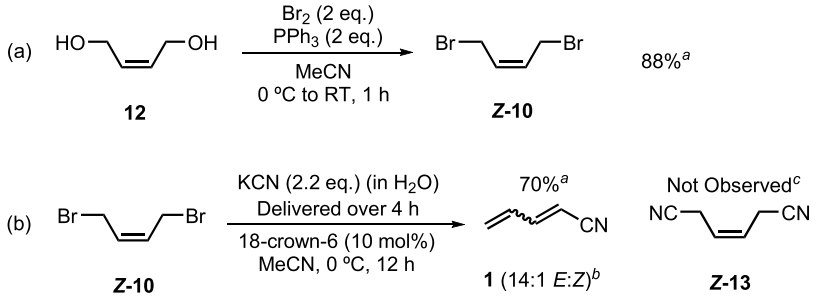
Scheme 4. Strategy for Diastereoselective Synthesis of (*E*)-1-Cyano-1,3-butadiene (*E*-1)



Scheme 5. Diastereoselective Synthesis of (*E*)-1-Cyano-1,3-butadiene (*E*-1) from (*Z*)-1,2-Dibromo-2-butene (*Z*-10)



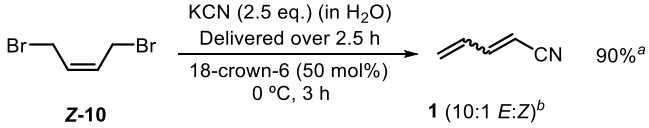
[a]Isolated (gravimetric) yield. [b]Diastereomeric ratio determined *via* ^{1}H NMR. [c]1,4-Dicyano-2-butene (**Z-13**) not observed *via* ^{1}H NMR.

*(E)-1-Cyano-1,3-butadiene (**E-1**).* Daessle *et al.* demonstrated that 1-cyano-1,3-butadiene (**1**) can be accessed *via* an E2′ (1,4-elimination) reaction of a mixture of 1-chloro-4-cyano-2-butenes with anhydrous ammonia (Scheme 1c).[48] Katagiri *et al.* demonstrated that **1** can be produced in a one-pot synthesis involving the treatment of a mixture of 1,4-dibromo-2-butenes (**10**) with alkali-metal cyanides under basic conditions (Scheme 1d).[53] Although the diastereoselectivity of these reactions was not previously investigated, we saw an opportunity to influence the diastereoselectivity of the reaction to favor the formation of ***E*-1** over ***Z*-1** *via* the stereochemistry of the 1,4-dibromo-2-butene precursor ***Z*-10** or ***E*-10** (Scheme 4). Consistent with similar precedents,[65−67] we hypothesized that E2′ reaction of (*Z*)-1-bromo-4-cyano-2-butene (***Z*-11**) would favor the formation of ***E*-1** over ***Z*-1** because of a steric preference for the cyano group to be rotated away from the *cis* $-CH_2Br$ group in the transition state for the elimination reaction. In fact, selectivity in favor of ***E*-1** was observed, and a computational analysis of the basis for the selectivity is described later in this article.

(*Z*)-1,4-Dibromo-2-butene (***Z*-10**), prepared from (*Z*)-2-buten-1,4-diol (**12**) *via* Appel conditions,[68] readily reacts with two equivalents of KCN through tandem S_N2/E2′ reactions to form 1-cyano-1,3-butadiene (**1**; *E*/*Z* ratio 14:1) without the addition of an exogenous base (Scheme 5). The best results were observed using binary acetonitrile/water solvent systems. Reactions performed in pure acetonitrile (*via* the addition of solid KCN to the stirring reaction) proceeded slowly and never to full conversion—likely because of the low solubility of KCN in acetonitrile. Several other polar aprotic solvents were investigated for use in these reactions [dimethylformamide (DMF), tetrahydrofuran (THF), glyme, diethyl ether, polyethylene glycol (PEG), and dimethyl sulfoxide (DMSO)], although the cleanest reactions were observed with the acetonitrile/water solvent system. DMF and DMSO accelerated the reaction to the point of a rapid exotherm, which resulted in degradation of the product, likely because of the high concentration of cyanide in these solvents. We found that the best diastereoselectivity was observed (with near-complete conversion) in experiments where aqueous KCN was added slowly to a solution of ***Z*-10** and 18-crown-6 in acetonitrile at 0 °C. Evaluation of the reaction progress *via* ^{1}H NMR spectroscopy showed the rapid formation of ***E*-1**/***Z*-1** upon the addition of KCN to ***Z*-10**. Signals corresponding to (*Z*)-1-bromo-4-cyano-2-butene (***Z*-11**) or (*Z*)-1,4-dicyano-2-butene (***Z*-13**), a potential byproduct resulting from a second S_N2 displacement in ***Z*-11**, were not observed in the ^{1}H NMR spectrum as the reaction progressed. The rapid formation of ***E*-1**/***Z*-1** and the absence of observable ***Z*-11** and ***Z*-13** signals in the ^{1}H NMR evaluation suggest that the product-forming E2′ reaction occurs more rapidly than either of these competing reactions. The drawback of this procedure was the difficulty of removing the residual acetonitrile solvent from the product ***E*-1**.

The following procedure was developed with the goal of optimizing the isolation and purification of the target compound (*E*)-1-cyano-1,3-butadiene (***E*-1**). The addition of ***Z*-10** to 50 mol % of 18-crown-6 resulted in a eutectic mixture, which remained a liquid when cooled to 0 °C. Slow addition of aqueous KCN to a rapidly stirring eutectic mixture of ***Z*-10**/18-crown-6 at 0 °C proceeded to full conversion, while retaining good diastereoselectivity to produce ***E*-1**. Subsequent extraction with diethyl ether and fractional distillation of the product mixture yielded 1-cyano-1,3-butadiene (**1**) in 90% isolated yield (*E*/*Z* ratio 10:1) (Scheme 6).

Scheme 6. Modified Reaction Conditions for Efficient Synthesis and Purification of (*E*)-1-Cyano-1,3-butadiene (*E*-1)[a]



[a]Isolated (gravimetric) yield. [b]Diastereomeric ratio determined *via* ^{1}H NMR.

*(Z)-1-Cyano-1,3-butadiene (**Z-1**).* A selective route to produce (*Z*)-1-cyano-1,3-butadiene (***Z*-1**) has been reported,[57] although details of the experimental procedure and spectroscopic properties are not readily available. Multiple studies describe the separation, isolation, and physical properties of ***Z*-1**.[41,69] As a counterpart to our development of a selective process for the preparation of ***E*-1** from *Z*-1,4-dibromo-2-

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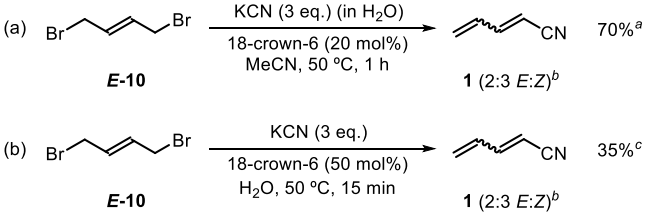
butene (*Z*-**10**), we observed that subjecting *E*-**10** to the reaction conditions shown in Scheme 7 resulted in a mildly

Scheme 7. Modified Reaction Conditions for Semi-selective Preparation of (*Z*)-1-Cyano-1,3-butadiene (*Z*-1) from (*E*)-1,4-Dibromo-2-butene (*E*-10)



[a]Reaction yield determined *via* ^{1}H NMR. [b]Diastereomeric ratio determined *via* ^{1}H NMR. [c]Isolated (gravimetric) yield.

selective formation of *Z*-**1**. Although this procedure utilizes acetonitrile as the solvent, which was problematic in the isolation and purification of *E*-**1**, the slightly higher volatility of *Z*-**1** enables its separation from *E*-**1** and acetonitrile in a straightforward fashion. Iterative fractional distillation of the product mixture increased the relative concentration of *Z*-**1** in the distillate, resulting in a reasonably pure sample of *Z*-**1** after three distillations. Purity was sufficient that the ratio of *E* to *Z* by rotational spectroscopy was observed to be approximately 1:8 (*E*-**1**/*Z*-**1**).

*Computational Analysis of Diastereoselectivity in the Formation of 1-Cyano-1,3-butadiene (**E-1/Z-1**).* The reaction to form (*E*)-1-cyano-1,3-butadiene (*E*-**1**) from (*Z*)-1,4-dibromo-2-butene (*Z*-**10**) is hypothesized to proceed through (*Z*)-1-bromo-4-cyano-2-butene (*Z*-**11**), which, once formed, reacts with another equivalent of cyanide to eliminate HBr in a concerted 1,4-elimination mechanism (E2′ mechanism). Given that the *E* and *Z* diastereomers of 1-cyano-1,3-butadiene (**1**) are predicted to be very similar in energy (within 1 kcal/mol) and the reactions of different precursor stereoisomers lead to different product ratios, it is clear that a kinetically controlled reaction is responsible for the observed diastereoselectivity. Thus, the E2′ transition state barriers leading to each diastereomer of **10** must be responsible for the selectivity, or lack thereof, in the formation of *E*-**1** and *Z*-**1**.

The proposed E2′ substrates, (*Z*)- and (*E*)-1-bromo-4-cyano-2-butene (**11**), exhibit multiple conformational isomers, which are analyzed in detail (see Supporting Information). The isomerization barriers for all conformations of both diastereomers are less than 6 kcal/mol. Contour plots and the detailed analysis of the complete conformational potential energy surfaces of *Z*-**11** and *E*-**11** are provided in the Supporting Information. For the reaction of each diastereomer (*Z*-**11** or *E*-**11**) with cyanide ion, calculations predict two pairs of E2′ transition states leading to products (*E*-**1** and *Z*-**1**) (Figures 2 and 3). In each of the transition state geometries, an acidic hydrogen atom at C-4 is perpendicular to the plane of the adjacent alkene unit. The bromide leaving group at C-1 can be in an *anti* or *syn* orientation with respect to the acidic hydrogen atom at C-4. The cyano substituent at C-4 may occupy a *syn*-periplanar conformation relative to the alkene moiety, which leads to the formation of (*Z*)-1-cyano-1,3-butadiene (*Z*-**1**), or an antiperiplanar conformation, which leads to the formation of (*E*)-1-cyano-1,3-butadiene (*E*-**1**). Each transition state was verified to connect one diastereomer

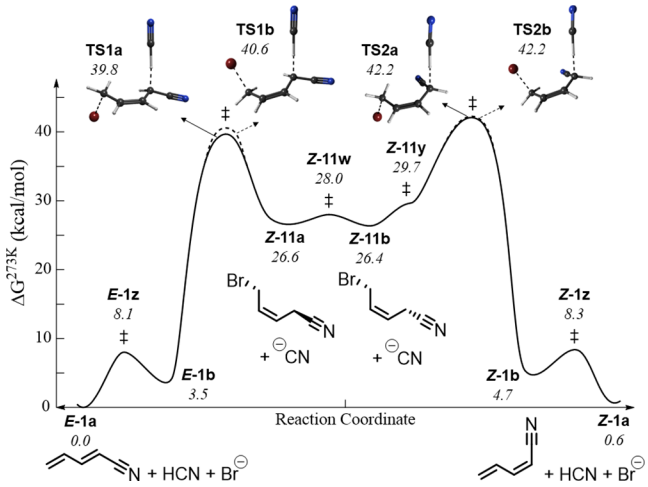


Figure 2. Computed reaction coordinate diagram for E2′ reaction of (*Z*)-1-bromo-4-cyano-2-butene (*Z*-**11**) with cyanide in water. Gibbs free energies at B3LYP/cc-pVTZ with the polarized continuum model for the solvent (H_2O) at 273 K (0 °C). Solid line: lower energy transition state. Dashed line: higher energy transition state.

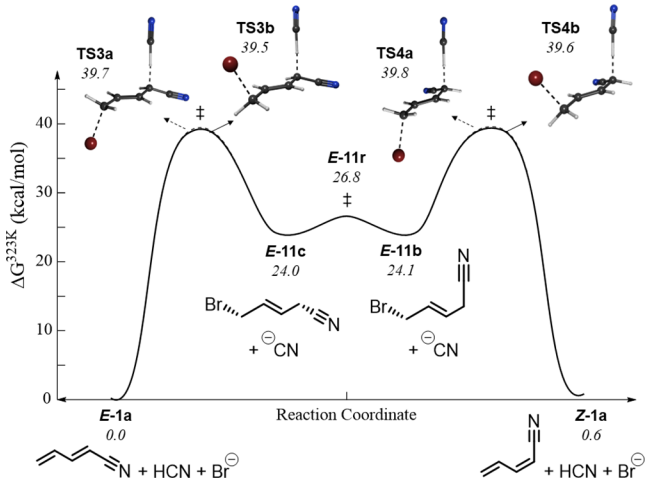


Figure 3. Computed reaction coordinate diagram for E2′ reaction of (*E*)-1-bromo-4-cyano-2-butene (*E*-**11**) with cyanide in water. Gibbs free energies at B3LYP/cc-pVTZ with the polarized continuum model for the solvent (H_2O) at 323 K (50 °C). Solid line: lower energy transition state. Dashed line: higher energy transition state.

of the starting material (**11**) to one diastereomer of the product (**1**), using an intrinsic reaction coordinate (IRC) calculation. Attempts to explore a stepwise pathway beginning with deprotonation of *Z*-**11** or *E*-**11** failed to obtain an anionic intermediate as a stationary point. Therefore, a stepwise mechanism was not considered further.

For either diastereomer of 1-bromo-4-cyano-2-butene (*E*-**11** or *Z*-**11**), the computed activation barriers of the E2′ transition states are significantly higher (by 7−14 kcal/mol) than the activation barriers for conformational interconversion. Thus, the diasteroselectivity in the elimination reaction is interpreted in terms of the Curtin−Hammett principle.[70] Product selectivity is governed by the difference in energy between the competing product-forming transition states ($\Delta\Delta G^{\ddagger}$); conformational equilibrium in the starting materials is rapid and does not govern the composition of products. As such, the potential energy surfaces for the E2′ reactions shown in Figures 2 and 3 contain a simplified surface for the

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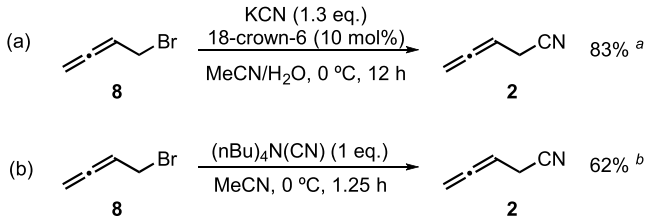
conformational isomerization of each 1-bromo-4-cyano-2-butene (***E*-11** or ***Z*-11**).

In the E2′ reaction of (*Z*)-1-bromo-4-cyano-2-butene (***Z*-11**) with cyanide in water at 273 K (0 °C) (Figure 2), the transition states **TS2a** and **TS2b** that lead to (*Z*)-1-cyano-1,3-butadiene (***Z*-1**) are higher in energy than the transition states **TS1a** and **TS1b** that lead to (*E*)-1-cyano-1,3-butadiene (***E*-1**). Thus, the computational analysis is in qualitative accordance with the experimental observation of diastereoselectivity favoring the formation of (*E*)-1-cyano-1,3-butadiene (***E*-1**). The difference in transition state energies ($\Delta\Delta G^{\ddagger}$) appears to arise from a steric interaction in the transition states involving the $-CH_2CN$ group. Both transition states leading to ***Z*-1** (**TS2a** and **TS2b**) have a larger interaction between −CN and $-CH_2Br$, relative to the transition states leading to ***E*-1** (**TS1a** and **TS1b**). The small energy difference between the ***E*-1**-forming transition states **TS1a** and **TS1b** (0.8 kcal/mol) is likely due to a subtle difference in electrostatic interactions (repulsion) between the bromo and cyano substituents in the *anti* versus *syn* E2′ elimination pathways. Natural bond orbital (NBO) analysis of each transition state did not reveal any obvious hyperconjugation contribution to the energy differences among **TS1a**, **TS1b**, **TS2a**, and **TS2b**. Assuming that this potential energy surface reasonably models this reaction, the ***E*-1**/***Z*-1** ratio derived from the $\Delta\Delta G^{\ddagger}$ between **TS1a** and **TS2a** (2.4 kcal/mol) is expected to be ca. 60:1. This result is in qualitative agreement with the experimental observation of an ***E*-1**/***Z*-1** ratio of 10:1. This does indicate, however, that the computational prediction of $\Delta\Delta G^{\ddagger}$ is larger than its true value by about 1 kcal/mol.

In a similar fashion, the potential energy surface of the E2′ reaction of (*E*)-1-bromo-4-cyano-2-butene (***E*-11**) with cyanide in water at 323 K (50 °C) is presented in Figure 3. Unlike the reaction of the isomeric system (***Z*-11**), the transition states for the E2′ reaction of ***E*-11** leading to (*E*)- and (*Z*)-1-cyano-1,3-butadiene (**1**) are computed to be virtually isoergic ($\Delta\Delta G^{\ddagger}$ = 0.1 kcal/mol favoring the formation of ***E*-1**). With the $-CH_2CN$ and $-CH_2Br$ groups in a *trans* orientation in the ground state of ***E*-11**, there is no significant preference for the −CN substituent to adopt one conformation over the other. This situation is also manifested in the transition states (**TS3a**, **TS3b**, **TS4a**, and **TS4b**); the relative energies of the transition states reveal no preference for the stereochemical course of the reaction. Thus, the rates of product formation would be expected to afford a diastereomeric ratio of nearly 1:1. This prediction is consistent with the experimentally observed product ratio of ***E*-1**/***Z*-1** (*E*/*Z* ratio 2:3). The deviation of the experimental ratio from 1:1 reveals that there is a slight energetic preference (<1 kcal/mol) for the transition states leading to the *Z* diastereomer. Our computational model is not expected to be of sufficient accuracy to account for such a small energetic difference.

4-Cyano-1,2-butadiene (2). As described earlier, we observed 4-cyano-1,2-butadiene (**2**) as an intermediate during the preparation of 1-cyano-1,3-butadiene (**1**) from 4-halo-1,2-butadienes (**7** or **8**) (Scheme 2). In order to optimize conditions for the preparation and isolation of **2**, it was necessary to avoid the isomerization of **2** to **1**—a process that is typically observed under conditions that utilize both water and cyanide (a weak base) at ambient temperature. When the reaction of 4-bromo-1,2-butadiene (**8**) is performed under anhydrous conditions (dry solvent, vacuum-dried crown ether, and vacuum-dried KCN), bromide **8** undergoes slow S_N2 reaction; minimal isomerization of **2** is observed. The rate of substitution, however, is too slow to be useful. The addition of water to the reaction mixture increases the solubility of cyanide, increases the rate of substitution, and increases the rate of isomerization of **2** to **1**. (Ultimately, the rate becomes very rapid and results in a noticeable exotherm.) At a reaction temperature of 0 °C, the isomerization is slow enough such that 4-cyano-1,2-butadiene (**2**) can be isolated (Scheme 8a). In

Scheme 8. Preparation of 4-Cyano-1,2-butadiene (2)

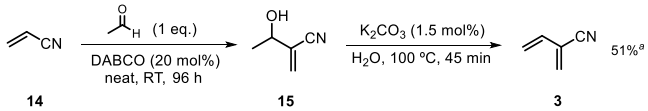


[a]Reaction yield determined *via* ^{1}H NMR. [b]Isolated (gravimetric) yield.

the absence of aqueous acidic or basic conditions, **2** is stable when isolated. The slow addition of an organic-soluble cyanide source [tetrabutylammonium cyanide (TBAC)], under anhydrous conditions, allows for an efficient S_N2 reaction and isolation of pure **2** without significant isomerization (Scheme 8b). Once the cyanide is consumed, exposure to water in the subsequent extraction (to remove the polar aprotic solvent) does not promote significant isomerization of **2**. In fact, neat **2** can be left at ambient conditions for weeks without observable isomerization. Nitrile **2** is sufficiently stable that it can be distilled under a relatively low vacuum (100 Torr) without noticeable degradation. In contrast to the regioselectivity exhibited in the rearrangement of the corresponding allenic halides,[71] the isomerization of allenic nitrile **2** yields exclusively 1-cyano-1,3-butadiene (**1**). 2-Cyano-1,3-butadiene (**3**) is not observed, which is attributable to the absence of cyanide dissociation/recombination previously observed for the corresponding allenic halides.

2-Cyano-1,3-butadiene (3). Although 2-cyano-1,3-butadiene (**3**) has been prepared previously, synthetic routes often involve a pyrolysis reaction as the last step.[51,58−60] Preferring to avoid a pyrolysis reaction, we prepared 2-cyano-1,3-butadiene (**3**) using a combination of literature procedures from Strub *et al.*[72] and Nonaka *et al.*[73−75] (Scheme 9).

Scheme 9. Preparation of 2-Cyano-1,3-butadiene (3)



[a]Isolated (gravimetric) yield.

Morita−Baylis−Hillman addition of acrylonitrile (**14**) and acetaldehyde using catalytic 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded 3-hydroxy-2-methylenebutanenitrile (**15**) in quantitative yield.[72] Subsequent dehydration of **15** was performed using catalytic K_2CO_3. The resulting 2-cyano-1,3-butadiene (**3**) was distilled from the reaction mixture under vacuum and collected as an aqueous emulsion that separated upon cooling. Compound **3** is prone to undergo polymerization, even at −20 °C.

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SUMMARY

We describe the synthesis, isolation, purification, and spectroscopic characterization of four cyano-butadiene isomers: (*E*)-1-cyano-1,3-butadiene (***E*-1**), (*Z*)-1-cyano-1,3-butadiene (***Z*-1**), 4-cyano-1,2-butadiene (**2**), and 2-cyano-1,3-butadiene (**3**). These molecules are of considerable significance to the field of astrochemistry, as possible constituents of both planetary atmospheres and interstellar space. Because of the general experimental difficulties in handling these reactive compounds, the literature data concerning the spectroscopic characterization [NMR, IR, and mass spectrometry (MS)] of these simple organic molecules are remarkably sparse. Our new procedures enable isolation and purification of these compounds, affording high quality NMR, IR, and MS data, for the first time. The preparation of pure samples of these molecules enables the measurement of their laboratory rotational spectra—the critical data needed to search for these species in space by radioastronomy.

COMPUTATIONAL METHODS

Geometry optimizations and harmonic frequency calculations were conducted with density functional theory using the B3LYP functional[76,77] and the cc-pVTZ basis set,[78] correcting for water as a solvent by employing the polarizable continuum model as implemented in Gaussian 16.[79] Thermally corrected Gibbs free energies for all species were obtained from the harmonic frequency calculations at 273, 298, and 323 K and are summarized in the Supporting Information. Conformational analyses of the local minima are included in the Supporting Information along with the Cartesian coordinates of the optimized stationary points. Additional calculations were conducted for the E2′ (1,4-elimination) transition states: IRC calculations verified that each transition state smoothly connects one diastereomer of the starting material to one diastereomer of the product. Natural Bond Orbital (NBO) and Natural Resonance Theory (NRT) calculations[80] were used to analyze the electronic structure, bonding, hyperconjugation, and relative energies of energy minima and transition states on the potential energy surfaces.

EXPERIMENTAL SECTION

General Experimental Methods. All commercial reagents were purchased from Sigma-Aldrich, Acros, or Oakwood and used as received, unless otherwise noted. ^{1}H NMR spectra (400 or 500 MHz) and ^{13}C{^{1}H}-NMR spectra (100 or 125 MHz) were obtained in $CDCl_3$, CD_3CN, or C_6D_6 on a Bruker 400 MHz AVANCE III or Bruker 500 MHz DCH AVANCE III spectrometer; chemical shifts (δ) are reported as ppm downfield from internal standard $SiMe_4$. Mass spectra were acquired using electrospray ionization (ESI) or the atmospheric solids analysis probe (ASAP)[81] on a Thermo Scientific Q-Exactive Plus mass spectrometer. GC/MS analysis was performed on a Shimadzu GCMS-2010S. IR spectra were obtained on a Bruker TENSOR Fourier transform infrared instrument as neat samples using an attenuated total reflectance accessory (Bruker PLATINUM ATR).

*1-Cyano-1,3-butadiene (**1**).* Our preliminary studies concerning the preparation, isolation, and identification of 1-cyano-1,3-butadiene (**1**) provide some context for the experimental difficulties encountered and detail concerning the spectroscopic assignments.[82]

Following the procedure of Clary and Back:[56] to a suspension of sodium hydride (2.88 g, 120 mmol) in freshly distilled THF (500 mL) was added diethyl cyanomethylphosphonate (8.1 mL, 50.1 mmol) dropwise *via* a syringe at 0 °C. After stirring for 1 h, freshly distilled acrolein (3.6 mL, 53.9 mmol) was added dropwise. The reactants were stirred for 5 h at 0 °C, warmed to room temperature, and quenched with saturated aqueous NH_4Cl solution. The solution was extracted with diethyl ether, washed with saturated aqueous NaCl, and dried over $MgSO_4$. After removal of the drying agent by filtration, ether was removed under reduced pressure at room temperature, and the resulting mixture was fractionally distilled (collection flask cooled to −78 °C and distillation flask cooled to 0 °C). The distillate consisted of a mixture of *E* and *Z* isomers of 1-cyano-1,3-butadiene (**1**) in a ratio of 2:1 in addition to residual THF.

^{1}H NMR (400 MHz, $CDCl_3$): ***E*-isomer** δ 6.31 (ddt, 1H, J = 16, 11, <1 Hz), 5.74 (tt, 1H, J = 10, <1 Hz), 4.94 (dm, 1H, J = 17, <1, <1 Hz), 4.93 (dm, 1H, J = 10, <1, <1 Hz), 4.65 (dd, 1H, J = 16, <1 Hz) ppm; ***Z*-isomer** δ 6.59 (dtd, 1H, J = 17, 10, <1 Hz), 6.03 (tt, 1H, J = 10, <1 Hz), 5.03 (dm, 1H, J = 17, <1, <1 Hz), 5.02 (dm, 1H, J = 10, <1, <1 Hz), 4.55 (dd, 1H, J = 10, <1 Hz). HRMS (ASAP-Q-IT)[81] m/z: $[M + H]^+$ calcd for C_5H_6N, 80.0495; found, 80.0493.

The procedure involves the formation of a phosphonate ylide followed by reaction with acrolein in a Horner−Wadsworth−Emmons-type olefination.[56] Although this reaction appears to be straightforward, the resulting ^{1}H NMR spectrum does not agree with that described in the literature.[56] Upon closer investigation, the previously reported ^{1}H NMR data do not account for all hydrogen atoms in the molecule. Although each isomer (***E*-1** and ***Z*-1**) should have five signals in the spectrum, the *E*-isomer (***E*-1**) has four reported signals and the *Z*-isomer (***Z*-1**) has only three.[56] Additionally, the reaction inherently undergoes a side reaction, and not all signals in the crude spectrum are attributable to **1**. The combination of the two issues combined with challenges encountered in purification created confusion in characterization and complicated the optimization and troubleshooting processes. These issues are discussed in greater detail in the Supporting Information section.

*Isolation of E- and Z-Isomers of 1-Cyano-1,3-butadiene (**1**).* One of the challenges encountered during the isolation of neat ***E*-1**/***Z*-1** originates from its volatility and its tendency to form azeotropes with acetonitrile. The complete removal of acetonitrile was necessary for obtaining accurate spectra and isolated yields of the product. Solvent removal *via* rotary evaporation drastically reduced product yields because of the azeotropic losses. We found that most acetonitrile could be removed through aqueous washes of the crude ethereal extract during reaction workup. Remaining traces of acetonitrile could be fully removed from the products by low-temperature vacuum distillation (∼100−500 mTorr, 0 °C). Attempts to remove acetonitrile *via* careful vacuum fractional distillation were marginally effective, as a small amount of acetonitrile always codistilled with the product diastereomers. We found that highly volatile solvents (such as the diethyl ether used during the biphasic extraction of the reaction mixture) were more easily removed *via* fractional distillation through a packed column under atmospheric pressure without codistilling any ***E*-1** and ***Z*-1**. Additionally, product losses resulting from polymerization of ***E*-1** and ***Z*-1** during the distillation process were minimized *via* the addition of a phenolic polymerization inhibitor. We found that hydroquinone was ideal for our purposes because its high boiling point and extremely low volatility prevented its codistillation with ***E*-1** and ***Z*-1** during the final purification.

*(Z)-1,4-Dibromo-2-butene (**Z*-10).* In a modification of literature procedures,[83−85] 52.55 g (200 mmol) of PPh_3 was added to 300 mL of acetonitrile in a 500 mL round-bottom flask equipped with a 100 mL dropping funnel. The reaction vessel was sealed with a septum and cooled to 0 °C on ice. The reaction vessel and contents were subjected to three vacuum pump/N_2 purge cycles. Br_2 (10.2 mL, 197.8 mmol) was added dropwise to the stirring PPh_3 suspension *via* the dropping funnel. (*Z*)-2-Buten-1,4-diol (**12**) (9.04 g, 103 mmol) was rapidly added to the stirring suspension *via* a syringe. The cooling bath was removed, and the reactants were stirred for 1 h. After the elapsed reaction time, approximately half of the acetonitrile solvent was removed by rotary evaporation. The resulting triphenylphosphine oxide precipitate was removed *via* vacuum filtration. The filtrate was then evaporated to dryness. The resulting orange solids were dissolved in 50 mL of 1:4 EtOAc/*n*-hexane and filtered through a silica plug (5 cm) to remove any remaining triphenylphosphine oxide. The solvent was removed *in vacuo* to yield 18.07 g (88%) of (*Z*)-1,4-dibromo-2-butene (***Z*-10**) as a pale-yellow oil. **CAUTION**: (*Z*)-1,4-Dibromo-2-butene is a potent lachrymator and vesicant and must be handled with caution. Samples of (*Z*)-1,4-dibromo-2-butene will isomerize upon heating and should be stored in a freezer (−20 °C). ^{1}H NMR ($CDCl_3$, 500 MHz):δ (ppm) complex spin system, 5.89 (m,

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2H), 4.02 (m, 4H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 129.9, 24.7.

*(E)-1-Cyano-1,3-butadiene (**E-1**) ((E)-2,4-Pentadienenitrile).* (*Z*)-1,4-Dibromo-2-butene (***Z*-10**; 5.38 g, 25.2 mmol), 3.36 g (12.7 mmol) of 18-crown-6, and 57 mg (0.52 mmol) of hydroquinone were added to a 50 mL single-neck round-bottom flask. The reaction vessel was sealed with a septum and purged with N_2 *via* a syringe needle inlet. The vessel was then cooled to 0 °C on ice. Potassium cyanide (4.09 g, 62.8 mmol) was dissolved in 10 mL of deionized H_2O and delivered to the cooled reaction dropwise *via* a syringe pump over the course of 2 h with vigorous stirring. As the addition completed, the reaction became biphasic with an orange top organic layer and a tan bottom aqueous layer. The reactants were stirred for an additional 15 min at 0 °C after the addition was complete and then allowed to warm to room temperature. The reaction mixture was rinsed into a separatory funnel with 10 mL of diethyl ether and 10 mL of deionized H_2O, the organic layer was separated, and the aqueous layer was extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with 10 mL of saturated aqueous NaCl and dried over anhydrous $CaCl_2$. After removal of the drying agent by gravity filtration, hydroquinone (97 mg) was added to the filtrate and the ethereal solvent was removed by fractional distillation at atmospheric pressure (45 cm Vigreux column). The crude product was cooled to room temperature, and a vacuum of ∼400 Torr was applied to remove residual ether. The remaining yellow concentrate was purified *via* bulb-to-bulb (Kugelrohr) distillation to yield 1.80 g of 1-cyano-1,3-butadiene (**1**) (90%, 10:1 *E*/*Z*) as a colorless oil. Compound ***E*-1** is indefinitely stable as a neat substance at −80 °C or in a dilute solution of diethyl ether with the hydroquinone inhibitor to prevent polymerization. ^1H NMR (C_6D_6, 500 MHz): δ (ppm) ***E*-1**: 6.34 (dd, 1H, J = 16, 10 Hz), 5.79 (dt, 1H, J = 17.1, 10.3 Hz), 5.01 (d, 1H, J = 2.4 Hz), 4.99 (d, 1H, J = 2.7 Hz), 4.69 (d, 1H, J = 16 Hz). $^{13}C\{^1H\}$-NMR (C_6D_6, 125 MHz): δ (ppm) 150.0, 134.3, 125.9, 117.8, 100.2. IR (neat): (cm^{-1}) 3054 (w), 2218 (m), 1629 (w), 1589 (m), 1417 (w), 1292 (w), 1258 (w), 1001 (s), 955 (m), 932 (m), 835 (m), 475 (w). HRMS (ESI) m/z: $[M + H]^+$ calcd for C_5H_6N, 80.0495; found, 80.0494.

*(Z)-1-Cyano-1,3-butadiene (**Z-1**) ((Z)-2,4-Pentadienenitrile).* Potassium cyanide (9.88 g, 152 mmol, 3 equiv) and 18-crown-6 (6.66 g, 25 mmol, 50 mol %) were dissolved in 20 mL of deionized H_2O in a 100 mL three-neck round-bottom flask. Hydroquinone (110 mg, 1 mmol) was added to the flask to inhibit polymerization of the product. The flask was purged with N_2 and sealed with rubber septa. The vessel was heated to 50 °C in an oil bath. Under positive N_2 pressure, one septum was removed from the reaction vessel and solid (*E*)-1,4-dibromo-2-butene (***E*-10**) (10.72 g, 50.1 mmol, 1 equiv) was added in ∼2 g increments to the vigorously stirring KCN/18-crown-6 solution over the course of 15 min. The reaction mixture darkened to a reddish-brown color during the addition of ***E*-10**. The reaction was cooled to room temperature and rinsed into a separatory funnel with 10 mL of diethyl ether and 10 mL of deionized H_2O. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (4 × 25 mL). The combined organic layers were washed with saturated aqueous NaCl (1 × 25 mL) and dried over anhydrous $CaCl_2$. The drying agent was removed by gravity filtration, and the ethereal solvent was removed by fractional distillation at atmospheric pressure (45 cm glass bead packed column). The product was purified by vacuum distillation through the same apparatus to yield 1-cyano-1,3-butadiene (**1**) (34%, 2:3 *E*/*Z*) as a colorless oil (bp 75 °C, 100 Torr). Subsequent fractional distillations through the same apparatus can be performed to further separate ***Z*-1** from ***E*-1**. Compound ***Z*-1** exhibits greater thermal stability than ***E*-1**, presumably because of lower reactivity with respect to dimerization or polymerization. ^1H NMR (C_6D_6, 500 MHz): δ (ppm) ***Z*-1**: 6.58 (dt, 1H, J = 16.8, 10.6 Hz), 5.98 (t, 1H, J = 10.9 Hz), 5.02 (d, 1H, J = 16.8 Hz), 5.0 (d, 1H, J = 10.2 Hz), 4.48 (d, 1H, J = 10.7 Hz). $^{13}C\{^1H\}$-NMR (C_6D_6, 125 MHz): δ (ppm) 148.7, 132.7, 126.2, 115.9, 98.4. IR (neat): (cm^{-1}) 3071 (w), 2216 (m), 1628 (w), 1574 (m), 1428 (w), 1359 (w), 1296 (w), 1229 (w), 1001 (m), 934 (s), 778 (m), 667 (s), 487 (w), 444 (w). HRMS (ESI) m/z: $[M + H]^+$ calcd for C_5H_6N, 80.0495; found, 80.0494.

*4-Chloro-2-butyne-1-ol (**5**).* In a slight modification of literature procedures,[86−89] 59.75 g (0.69 mol, 1 equiv) of 2-butyne-1,4-diol (**4**), 70 mL of dry dichloromethane, and 62 mL (770 mmol, 1.1 equiv) of dry pyridine were added to a 1 L flame-dried three-neck round-bottom flask under a N_2 atmosphere. The stirring reaction vessel was cooled to 0 °C on ice, and 56 mL (92 g, 772 mmol) of $SOCl_2$ was added dropwise over a time of 4 h *via* a pressure-equalizing addition funnel. A white precipitate formed over the course of the $SOCl_2$ addition. The reactants were then poured onto 200 mL of ice water and subsequently extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and saturated aqueous NaCl (1 × 100 mL) and dried over anhydrous Na_2SO_4. After removal of the drying agent by gravity filtration, dichloromethane was removed *in vacuo* to yield a deep red oil. The crude product was purified by vacuum distillation using a short-path apparatus to yield 42.32 g (58%) of colorless 4-chloro-2-butyne-1-ol (**5**), bp 50 °C (0.5 Torr). **CAUTION**: 4-chloro-2-butyne-1-ol is highly explosive and a powerful skin irritant—care must be taken when handling.[90] ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 4.33 (t, 2H, ^5J = 2 Hz), 4.19 (t, 2H, ^5J = 2 Hz). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 84.6, 80.5, 51.1, 30.3. HRMS (ESI) m/z: $[M + H]^+$ calcd for C_4H_5ClO; [^{35}Cl]-isotopologue calcd, 105.0107; found, 105.0102; [^{37}Cl]-isotopologue calcd, 107.0078; found, 107.0072.

*1,2-Butadien-4-ol (**6**). Early Method.*[87,88] Lithium aluminum hydride (6.09 g, 16 mmol) and dry diethyl ether (80 mL) were added to a flame-dried 250 mL three-neck round-bottom flask fitted with a dry ice condenser under a N_2 atmosphere and stirred to generate a slurry. 4-Chloro-2-butyne-1-ol (**5**) (4.19 g, 40 mmol) was diluted with 16 mL of dry diethyl ether and delivered dropwise *via* a syringe to the stirring LAH slurry at a rate sufficient to maintain a gentle reflux. After the addition of **5**, the reactants were stirred for 30 min at 25 °C. The reaction was cooled to 0 °C on ice, and the septa were removed. The reaction was quenched *via* Fieser workup: (slow addition of 6 mL of deionized H_2O, then 6 mL of 15% aqueous NaOH, and finally 18 mL of deionized H_2O). A scoop of anhydrous Na_2SO_4 was added to promote aggregation of the precipitated aluminum salts, and the vessel was stirred overnight at 25 °C. The reaction mixture was filtered, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were then dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The crude product was purified by vacuum distillation using a short-path apparatus to yield 1.99 g (71%) of colorless 1,2-butadien-4-ol (**6**), bp 60 °C (40 Torr).

Primary Method.[64,90] A flame-dried 5 L three-neck round-bottom flask was equipped with a reflux condenser (open to air), thermometer, and mechanical stirrer. To this vessel were added CuI (115.37 g, 605 mmol, 50 mol %), paraformaldehyde (59.53 g, 1.98 mol, 1.6 equiv), and 2.4 L of dry THF. The mechanical stirrer was started, and dry diisopropylamine (240 mL, 1.71 mol, 1.4 equiv) was added—the reaction mixture appeared faint green. Propargyl alcohol (**9**) (74 g, 76 mL, 1.3 mol) was added to the reaction mixture. The addition of propargyl alcohol resulted in an immediate exotherm (increase from 20 to 30 °C), and the reaction color changed to bright orange. The reaction was heated with a mantle to reflux for 24 h. After cooling to 25 °C, most of the THF solvent was removed *via* rotary evaporation. The concentrated reaction mixture was slowly added to a stirred, cooled (0 °C) solution of diethyl ether (1 L) and 12 N HCl (120 mL), resulting in the formation of a viscous brown precipitate. The stirring was stopped, and the mixture was allowed to separate. The supernatant ether was decanted, and the brown precipitate was extracted with diethyl ether (2 × 1 L). The combined ether extracts were filtered through a silica plug (ø = 80 mm × 50 mm), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by vacuum distillation using a short-path apparatus to yield 47.2 g (52%) of colorless 1,2-butadien-4-ol (**6**), bp 60 °C (40 Torr). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) complex spin system,

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5.34 (apparent quint, 1H, J = 6.4 Hz), 4.85 (m, 2H, J = 3 Hz), 4.14 (m, 2H, J = 3 Hz), 2.4 (br s, 1H). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 207.9, 90.8, 77.0, 60.2.

4-Chloro-1,2-butadiene (7).[62,86,88] $SOCl_2$ (16.97 g, 10.4 mL, 143 mmol, 1.25 equiv), 11.28 g of dry pyridine (11.5 mL, 143 mmol, 1.25 equiv) and 50 mL of dry diethyl ether were added to a flame-dried, three-neck 500 mL round-bottom flask equipped with a pressure-equalizing addition funnel and reflux condenser under a N_2 atmosphere. The vessel was cooled to 0 °C on an ice bath. A solution of 1,2-butadien-4-ol (**6**) (7.97 g, 114 mmol, 1 equiv) in 70 mL of dry diethyl ether was delivered dropwise to the stirring reaction *via* an addition funnel over 15 min. A white precipitate formed over the course of the addition. The reaction was heated to reflux in an oil bath for 2 h. The reaction was cooled to room temperature and quenched *via* the addition of 15 mL of deionized H_2O. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The ethereal solvent was removed by fractional distillation at atmospheric pressure (45 cm Vigreux column). The fractionating column was removed, and the product was purified by distillation at atmospheric pressure using a short-path apparatus to yield 6.10 g (60%) of 4-chloro-1,2-butadiene (**7**) as a colorless oil. bp 88 °C (760 Torr). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) complex spin system, 5.36 (m, 1H, J = 7.7, 6.6 Hz), 4.91 (dt, 2H, J = 6.6, 2.2 Hz), 4.08 (dt, 2H, J = 7.7, 2.2 Hz). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 209.5, 89.0, 77.5, 66.0.

4-Bromo-1,2-butadiene (8).[88] PBr_3 (21.6 g, 10.4 mL, 80 mmol), 7.89 g of dry pyridine (8 mL, 100 mmol), and 20 mL of dry diethyl ether were added to a flame-dried, single-neck 250 mL round-bottom flask equipped with a pressure-equalizing addition funnel under a N_2 atmosphere. The vessel was cooled to 0 °C on an ice bath. A solution of 1,2-butadien-4-ol (**6**) (14.01 g, 200 mmol, 1 equiv) in 20 mL of dry diethyl ether was delivered dropwise over 15 min to the stirring reaction *via* an addition funnel, and stirring was continued for 24 h. The reaction was allowed to warm to room temperature and quenched with 100 mL of deionized H_2O. The layers were separated, and the aqueous layer was extracted with diethyl ether (4 × 75 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 × 75 mL) and dried over anhydrous Na_2SO_4. After removal of the drying agent by filtration, the solvent was removed *in vacuo*. The crude product was purified by vacuum distillation using a short-path apparatus to yield 17.73 g (67%) of colorless 4-bromo-1,2-butadiene (**8**), bp 62 °C (100 Torr). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) complex spin system, 5.45 (m, 1H, J = 8.1, 6.5 Hz), 4.93 (dt, 2H, J = 6.6, 2.2 Hz), 3.96 (dt, 2H, J = 8.2, 2.0 Hz). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 209.8, 89.5, 77.5, 30.1.

4-Cyano-1,2-butadiene (2) (2,3-Pentadienenitrile). 4-Bromo-1,2-butadiene (**8**; 3.38 g; 25.4 mmol), was added to a flame-dried 100 mL single-neck round-bottom flask. The reaction vessel was then sealed with a septum and purged with N_2 *via* the syringe needle inlet. Dry acetonitrile (10 mL) was added *via* a syringe, and the stirring vessel was cooled to 0 °C on ice. A solution of 6.70 g (24.99 mmol) of tetrabutylammonium cyanide (TBAC) in 15 mL of dry acetonitrile was delivered dropwise to the vigorously stirring reaction over 1 h *via* a syringe pump. The reaction was allowed to stir at 0 °C for 15 min after the TBAC addition had completed. The ^1H NMR spectrum of a reaction aliquot showed complete conversion of **2** with minimal (<2%) isomerization to ***E*-1** and ***Z*-1**. The reaction was then rinsed into a separatory funnel with 50 mL of diethyl ether and 30 mL of cold deionized H_2O (0 °C). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic layers were washed with deionized H_2O (5 × 25 mL) and saturated aqueous NaCl (1 × 25 mL) and dried over anhydrous Na_2SO_4. After removal of the drying agent by gravity filtration, the ethereal solvent was removed by fractional distillation at atmospheric pressure *via* a short-path apparatus. From the resulting concentrate, 4-cyano-1,2-butadiene (**2**) was purified either by flash column chromatography (SiO_2, 3:1 *n*-pentane/Et_2O, R_f = 0.5) or by distillation (bp 94 °C, 100 Torr). Isolated yield: 62%. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) complex spin system; 5.13 (apparent quint, 1H, J = 6.4 Hz), 4.97 (m, 2H, J = 3.3 Hz), 3.09 (m, 2H, J = 3.3 Hz). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 209.0, 117.3, 81.2, 78.6, 17.5. IR (neat): (cm^{-1}) 2252 (w), 1960 (w), 1417 (w), 913 (w), 852 (s), 731 (w), 678 (w), 521 (w), 467 (w). HRMS (ESI) m/z: $[M + H]^+$ calcd for C_5H_6N, 80.0495; found, 80.0495.

3-Hydroxy-2-methylenebutanenitrile (15). Acrylonitrile (**14**) (13.64 g, 257 mmol, 1 equiv), acetaldehyde (11.4 g, 259 mmol, 1 equiv), and 1,4-diazabicyclo[2.2.2]octane (DABCO) (5.64 g, 50 mmol, 20 mol %) were added to a 250 mL single-neck round-bottom flask. The vessel was sealed with a septum and stirred for 96 h. The ^1H NMR spectrum of a reaction aliquot showed complete conversion after 96 h. The crude product was put on a vacuum line (~100 Torr) to remove unreacted acrylonitrile and acetaldehyde, and the crude 3-hydroxy-2-methylenebutanenitrile (**15**) was used in the next synthetic step without further purification (clear amber liquid). ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.0 (d, 1H, J = 1.4 Hz), 5.94 (s, 1H), 4.38 (qt, 1H, J = 6.4, 1.2 Hz), 3.90 (br s, 1H), 1.41 (d, 3H, J = 6.5 Hz). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 128.9, 128.4, 117.3, 68.0, 22.3.

2-Cyano-1,3-butadiene (3). K_2CO_3 (0.19 g, 1.4 mmol, 1.8 mol %) and 1.2 mL of deionized H_2O were added to a 50 mL round-bottom flask containing the crude 3-hydroxy-2-methylene-butanenitrile (**15**) from the preceding synthetic step. Hydroquinone (20 mg) was added to the mixture to inhibit polymerization during the subsequent distillation. The vessel was connected to a short-path distillation apparatus, and a vacuum of 100 Torr was applied to the system. The boiling flask was immersed in an oil bath at 100 °C, and the reactants were stirred vigorously to break the surface tension. The distillation-head temperature increased to 52 °C as the colorless distillate immediately started condensing as a biphasic mixture. A total of 8.6 g of biphasic distillate was collected over 1 h. Over the elapsed collection time, the contents of the boiling flask darkened to a dark red color and the collection rate slowed. The colorless product (the organic layer of the distillate) was separated and dried over anhydrous Na_2SO_4/activated charcoal. The drying and decolorizing agents were removed by filtration through a fine glass frit to yield 3.21 g (51%) of 2-cyano-1,3-butadiene (**3**) as a colorless oil. When stabilized with hydroquinone, **3** can be purified *via* vacuum distillation (bp 55 °C, 100 Torr). Compound **3** is prone to undergo polymerization, even at −20 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 6.35 (dd, 1H, J = 17.2, 10.4 Hz), 5.94 (s, 1H), 5.86 (s, 1H), 5.73 (d, 1H, J = 17.2 Hz), 5.47 (d, 1H, J = 10.4 Hz). $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ (ppm) 132.2, 130.5, 122.5, 120.7, 115.9. IR (neat): (cm^{-1}) 2986 (w), 2233 (w), 1736 (m), 1582 (w), 1378 (m), 1244 (m), 1045 (w), 983 (m), 924 (s), 492 (m). HRMS (ESI) m/z: $[M + H]^+$ calcd for C_5H_6N, 80.0495; found, 80.0494.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03388.

Computational details and ^1H- and $^{13}C\{^1H\}$-NMR, IR, and mass spectra for all compounds (PDF)

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Notes

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