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Programmed Sequential Additions to Halogenated Muconononitriles

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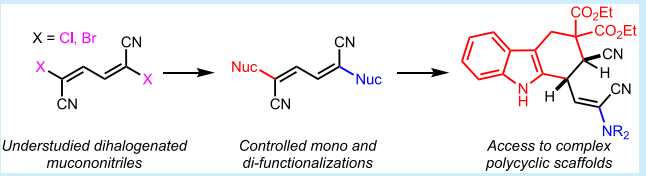
ABSTRACT: Dihalomuconononitriles were synthesized and their reactivity evaluated to assess their ability to function as linchpin reagents. Bis(2-chloroacrylonitrile) and bis(2-bromoacrylonitrile) were synthesized from 2,1,3-benzothiadiazole and undergo conjugate addition/elimination reactions with both nitrogen (40−95% yield) and carbon nucleophiles (72−93% yield). Secondary amines undergo monosubstitutions, while carbon nucleophiles are added twice. The sequence of addition of the nucleophiles could be controlled to give mixed addition products. The multicomponent coupling products could then be converted to natural product like motifs using intramolecular cyclization reactions.



The synthesis of dimeric natural products primarily relies on coupling two similarly sized monomers and often leverages the inherent symmetry of the compound.[1,2] These strategies are efficient but require ready access to the requisite monomer. Moreover, additional postfunctionalization of the monomer is often necessary to access heterodimeric (or unsymmetrical homodimeric) substrates. Thus, linchpin strategies are valuable because they use two different synthetic streams and thus are more convergent.[3−7] Furthermore, these multicomponent[8] strategies are attractive because they only necessitate the synthesis of more synthetically tractable truncated monomeric units. Lastly, these strategies are valuable because of their modularity and divergent[9] nature which lends access to symmetric and nonsymmetric homodimers and heterodimers. Thus, identifying suitable linchpin reagents is desirable and is a contemporary challenge (Figure 1A).

Dienes such as hexa-2,4-dienedinitriles (muconononitriles), **1**, are underexplored motifs that could serve as linchpin reagents because they contain two electron-withdrawing groups at the diene termini. We were intrigued by these substrates because of their bonding and physical organic properties but also because we viewed these substrates as privileged Michael acceptors. We surmised that the incorporation of leaving groups such as halogens at the 1- and 4-position of the muconononitrile would permit programmed sequential additions to the reagent because elimination of the leaving group would regenerate the electron-deficient olefins to be manipulated in a subsequent step. In doing so, the diene would formally be electrophilic at every carbon atom. Additionally, the inert nature of the nitrile group is critical to obtain the desired reactivity because the corresponding succinates and 1,6-diketones are known to undergo cycloaddition[10] and condensation reactions,[11] respectively. Notably, these compounds could also serve as bisketene equivalents, which are of contemporary interest.[12,13] As a part of a research program

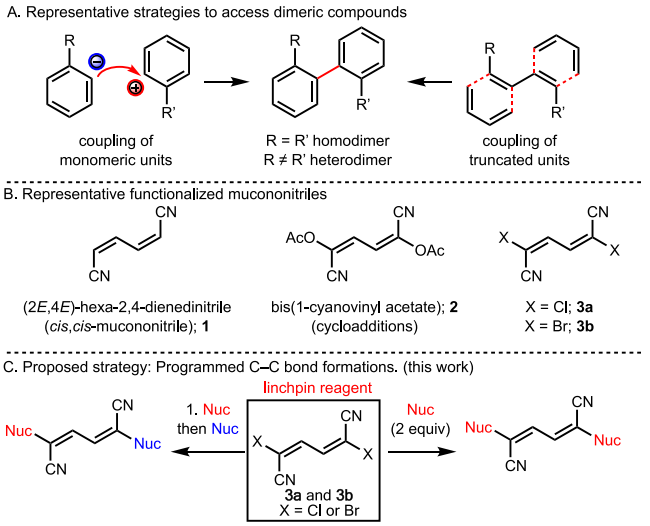


Figure 1. Proposed strategy to use dihalomuconononitriles as linchpin reagents.

directed toward the synthesis of complex dimeric natural products, we envisioned that halogenated muconononitriles would be valuable four carbon atom linchpin molecules that would enable the union of synthetically tractable truncated monomeric units, provided that programmed sequential additions of nucleophiles to these reagents could be achieved.

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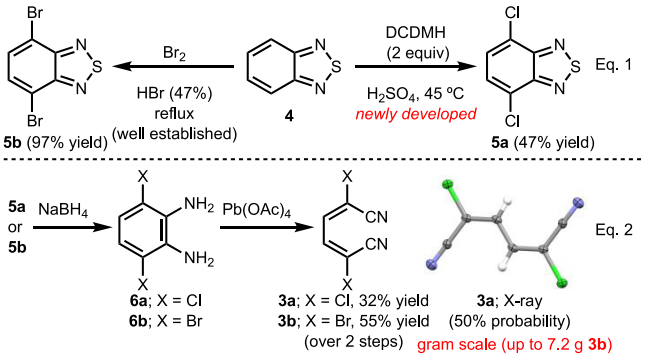
To our knowledge, functionalized muconononitriles have not been thoroughly investigated. Muconononitriles are accessed through the oxidative degradation of *o*-phenylenediamines using sodium periodate,[14] bis(acetoxy)iodobenzene,[15] O_2 and $CuCl_2$,[16] or NiO_2.[17] Muconononitriles containing acetoxy groups such as bis(1-cyanovinylacetate) (**2**) can be obtained from the corresponding succinyl chloride and were reported by Oku[18] and co-workers in 1992; however, outside of the reported photoisomerization and photocycloaddition reactivity, substrates in this class of compounds are only known to undergo tandem intramolecular cyclization/formal [5 + 2]-cycloaddition reactions to give complex [3.2.1]-oxabicyclooctenones.[19] The synthesis of halogenated muconononitriles such as **3a** and **3b** have been reported, but the reactivity of these compounds remains unexplored (Figure 1B).[20]

Central to our goal of developing a reagent-based linchpin strategy, we needed to demonstrate that muconononitrile substrates could be synthesized and these dienes could be appropriately functionalized at *both* the terminal and internal positions in a stepwise fashion to afford annulated products. Furthermore, it was imperative that we were able to select for mono- versus double additions of various nucleophiles to afford both the *symmetrical dimers* and *nonsymmetrical adducts* as well. Dimers of chloroacrylonitrile and bromoacrylonitrile **3a** and **3b** seemed to be attractive starting points, because the most likely reactivity of these dienes would be conjugate addition reactions of soft *C*- and *N*- nucleophiles, which would be in accord with the reactivity of muconate ester derivatives.[21] This strategy would be distinct from other coupling approaches because it could permit access to diverse chemical space surrounding nonsymmetrical homodimers and potentially heterodimers in a convergent fashion. Given the lack of knowledge surrounding halogenated muconononitriles, we undertook a study to systematically synthesize and document the reactivity of this class of substrates.

We first turned our attention to (2*E*,4*E*)-2,5-dichlorohexa-2,4-dienedinitrile (bis(2-chloroacrylonitrile), **3a**) and its bromo congener (bis(2-bromoacrylonitrile), **3b**), which are dimeric versions of commercially available 2-chloroacrylonitrile and 2-bromoacrylonitrile and arise from diamines **6a** and **6b**, respectively. One of the challenges obtaining *o*-phenylenediamine **6** needed in this study is accessing its 1,2,3,4-substitution pattern. Direct halogenation of protected 1,2-phenylenediamines, for instance, results in the undesired 1,2,4,5-dihaloisomers as the major products, which is in line with the known *ortho/para* directing ability of the electron-donating amine substituents.[22] Furthermore, these highly electron-rich arenes are susceptible to oxidation to afford undesired *o*-quinone imines.[23]

To overcome this challenge, we leveraged the ability of 2,1,3-benzothiadiazole to be selectively halogenated at the 4- and 7-positions of this heterocycle to obtain the desired 1,2,3,4-substitution pattern. Thus, we began our studies by evaluating the efficacy of various chlorinating reagents to react with **4**.[24] Ultimately, we found that 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) in H_2SO_4 at 45 °C for 12 h provided high conversion of heterocycle **4** to the desired product **5a** (eq 1).[25]

4,7-Dibromobenzothiadiazole (**5b**) is available through known procedures and commercially.[26] With ample quantities of heterocycles **5a** and **5b** in hand, we then obtained dienes **3a** and **3b** as bench-stable crystalline solids on a gram scale (up to 7.2 g of **3b**) using a two-step procedure involving reduction of



the benzothiadiazole unit with $NaBH_4$ in EtOH at 23 °C, followed by an oxidative degradation of the resulting *o*-phenylenediamine **6** with 2.0 equiv of $Pb(OAc)_4$ at 60 °C for 2 h (eq 2). The configurations of the double bonds of **3a** were confirmed in solution using an ^1H coupled ^{13}C NMR spectroscopy experiment and simulating the second order AA′X coupling pattern of the nitrile resonance (δ ($CDCl_3$) = 112.5 ppm, $^3J_{C-H}$ = 13 Hz) using SpinWorks online software.[27] Additionally, the olefin geometry in **3a** was determined to be *E,E*- by X-ray crystallographic analysis.

With ample quantities of dienes **3a** and **3b** in hand, we then began to investigate their reactivity toward nucleophilic partners and quickly identified that secondary amines were viable nucleophiles for these dienes, resulting in the stereoselective formation (>20:1 in all cases) of *E,E*-dienamine products (Figure 2). Cyclic amines such as pyrrolidine, piperidine, and azepane were tolerated and gave products **7**−**9** in excellent yield (92%, 95%, and 92%, respectively, for X = Cl and 88%, 93%, and 92% for X = Br). Heteroatom-containing substrates also produced products **10**−**13** in excellent yields. Notably, using 1-methylpiperazine produced **12** in 98% yield, demonstrating chemoselectivity for different amine groups. Reactions with L-proline methyl ester hydrochloride produced substrates **15a** and **15b** (47% and 40% yield, respectively) bearing introduced chirality when reacted with **3a** and **3b**. Acyclic secondary amines were also reactive producing products **16**−**19** in excellent yield (86−94% for X = Cl and 85−89% for X = Br). Sterically demanding amines such as diisoproylamine failed to react with **3a** or **3b**. Reactions with diallylamine and dibenzylamine also did not produce product. Presumably, the dienamines arise from a 1,6-conjugate addition reaction into the electron-deficient muconononitrile motif followed by ejection of the halide leaving group.[28] Single crystal X-ray crystallographic analysis of compound **19a** confirmed that the addition is stereoretentive and produces the thermodynamically favored *E,E* isomer.[29] Comparison of **3a** and **3b** showed that they performed similarly in most cases, so studies with other soft nucleophiles were performed with **3b** due to its accessibility.

Additionally, 2-substituted malonates were discovered to be competent carbon-based nucleophiles in the conjugate addition/elimination reactions with diene **3b**. We were able to react muconononitrile **3b** with excess (3.0 equiv) of monosubstituted malonates to afford products resulting from double-conjugate addition/elimination (Figure 3). The reactions proceeded in THF at 23 °C and were tolerant of *para*-substituted aryl groups to give products **20a**−**20e** (84−93% yield). Aliphatic groups such as diethyl 2-methylmalonate gave **21** in 72% yield. Heteroaromatic malonates containing a 2-

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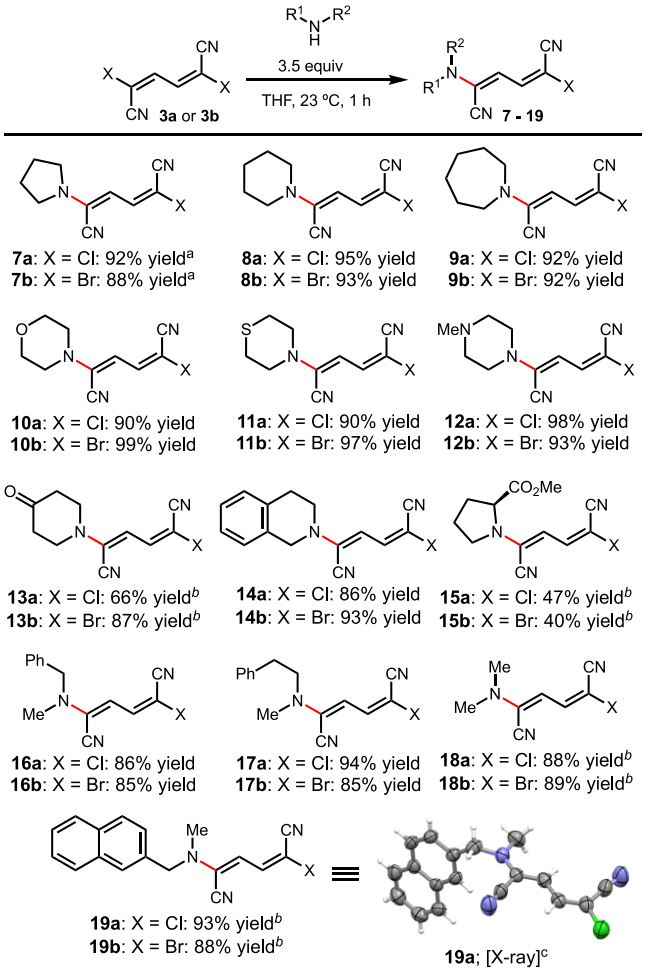


Figure 2. Reaction scope with amine nucleophiles. Standard conditions: 0.10 mmol **3a** or **3b** with 3.5 equiv amine, 0.3 M THF. [a]Reaction conducted with 1.0 mmol compound **3**. [b]Amine HCl salt was used with 5.0 equiv of Cs_2CO_3. [c]50% probability level shown.

furyl and 3-indolyl group gave products **24** and **25** in 74% and 83% yield, respectively.

We then sought to demonstrate programmed sequential additions of two different nucleophiles to our linchpin reagents. Thus, treating **3b** with 1.25 equiv of diethyl 2-(3-methoxybenzyl)malonate and then excess morpholine afforded diene **26** in 82% yield after the one-pot, two-step operation (eq 3). A malonate containing an *N*-Boc-indolyl group could be used as well to give, after quenching with morpholine, adduct **27** in 71% yield (eq 4). Thus, diene **3b** serves as a useful linchpin reagent to bring together both C and N nucleophiles. The addition reactions serve as a means to desymmetrize these substrates. Notably, the functionalized dienamines are valuable cyclization precursors en route to nonsymmetrical dimeric natural product motifs.

The addition of C-nucleophiles directly to dienamines **7a** or **7b** was unsuccessful, presumably due to the decreased electrophilicity of the dienamine compounds relative to **3a** and **3b**. However, the programmed additions could also be carried out in the reverse order (N- then C-addition), using a different tactic. After addition of the amine to **3a** or **3b**, the *δ*-halo dienamine products **7a** and **7b** are also amenable to a variety of cross-coupling reactions, which permits a greater scope of C-nucleophiles. For example, we found that the vinyl

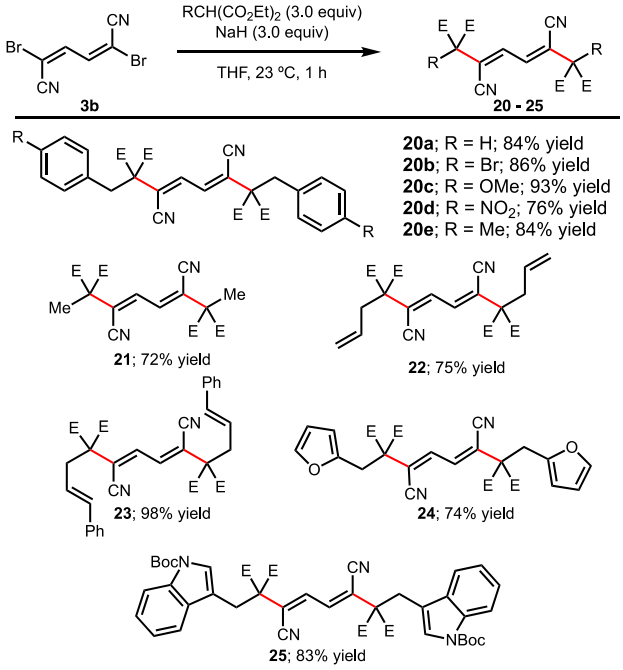
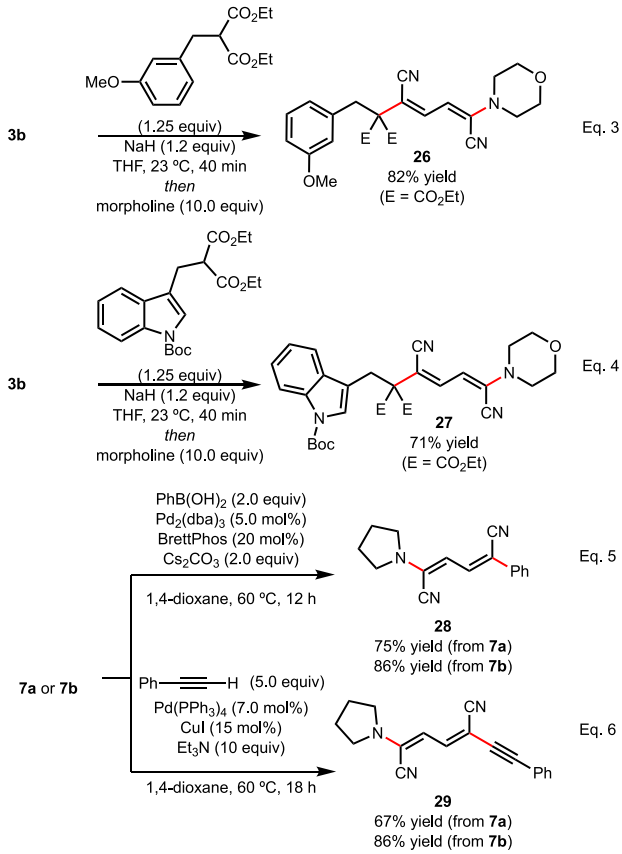


Figure 3. Reaction scope with malonate component [a]Standard conditions: 0.10 mmol of **3b** with 3.0 M NaH, 3.0 equiv of malonate, 0.1 M THF. [b]E = CO_2Et.



chloride (or bromide) group served as a handle for Suzuki–Miyaura and Sonogashira cross-coupling reactions (eqs 5–6).[30] Having demonstrated C–C and C–N bond formation at the terminus of the linchpin reagents to effectively desymmetrize them, we then turned our attention to strategies to functionalize the internal positions of the butadiene units.

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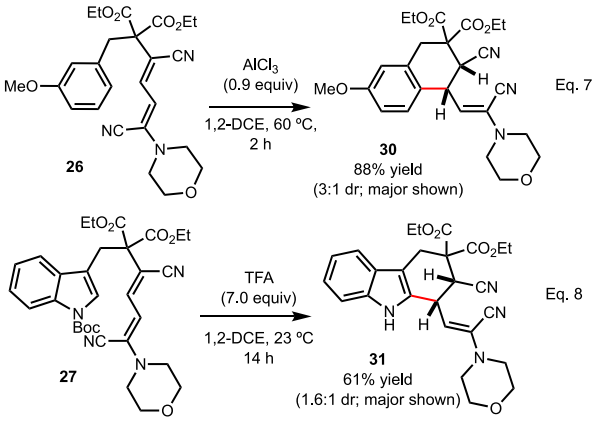
Cyclization reactions of compounds **26** and **27** leverage the nucleophilicity of the embedded dienamines. Reacting anisole **26** with $AlCl_3$ in 1,2-dichloroethane at 25 °C resulted in the clean formation of tetrahydronaphthalene **30** (88% yield, 3:1 dr) (eq 7). Treating indole compound **27** with trifluoroacetic



acid (7.0 equiv) in 1,2-dichloroethane at room temperature for 14 h gave tetrahydrocarbazole **31** (64% yield, 1.6:1 dr) (eq 8). In each instance, the vestige of the dienamine moiety remains as an α-aminoacrylonitrile, which could serve as a handle for further annulation reactions.

In conclusion, we have synthesized and documented the reactivity of two dihalomuconontriles.[30] These compounds readily engage both carbon and nitrogen nucleophiles through conjugate addition/elimination reactions or using cross-coupling strategies. The interrupted addition products can be further processed to afford highly functionalized annulated products. The application of these linchpin reagents to the total synthesis of both symmetrical and nonsymmetrical binary hydroxycarbazole natural products such as bismahanine[31] and bisisomahanine[32] is ongoing in our laboratory and will be reported in due time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03007.

Experimental details; ^1H and ^{13}C NMR spectroscopic data (PDF)

Accession Codes

CCDC 2026766−2026767 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.
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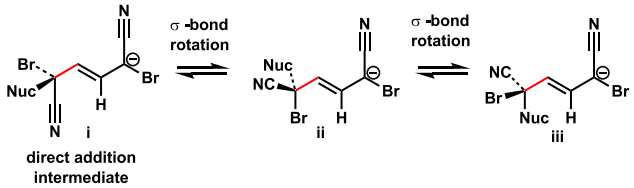

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