Programmed Sequential Additions to Halogenated Mucononitriles

Adam J. Zahara[†], Elsa Hindst[†], Andrew L. Nguyen, and Sidney M. Wilkerson-Hill*

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Dihalomucononitriles 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 2,13-benzothiadiazole and shown to undergo conjugate addition reactions with both nitrogen (40–95% yield) and carbon nucleophiles (72–93% yield). Secondary amines were found to undergo monoadditions while carbon nucleophiles added twice. The sequence of addition of the nucleophiles could be controlled giving 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 post-functionalization 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.^{3-4,5,6,7} Furthermore, these multicomponent⁸ 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 divergent⁹ nature which lends access to symmetric and nonsymmetric homodimers and heterodimers. Thus, identifying suitable linchpin reagents is desirable and is a contemporary challenge (Figure 1, A).

A. Representative strategies to access dimeric compounds

B. Representative functionalized mucononitriles

C. Proposed strategy: Programmed C–C bond formations. (this work)

Figure 1: Proposed strategy to use dihalomucononitriles as linchpin reagents.

Dienes such as hexa-2,4-dienedinitriles (mucononitriles), 1, are underexplored motifs that could serve as linchpin reagents because they contain two electron-withdrawing groups at the diene terminus. 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 mucononitrile 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 cycloaddition¹⁰ and condensation reactions¹¹ respectively. Notably, these compounds could also serve as bisketene equivalents, which

Department of Chemistry, The University of North Carolina at Chapel Hill,
Chapel Hill, North Carolina, 27599-3290, United States.

Email: smwhill@email.unc.edu

[†] The authors contributed equally to this work.

Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

are of contemporary interest.^{12,13} As a part of a research program directed toward the synthesis of complex dimeric natural products, we envisioned halogenated mucononitriles 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.

To our knowledge, functionalized mucononitriles have not been thoroughly investigated. Mucononitriles are accessed through the oxidative degradation of *ortho*-phenylenediamines using sodium periodate,¹⁴ bis(acetoxy)iodobenzene,¹⁵ O₂ and CuCl₂,¹⁶ or NiO₂.¹⁷ Mucononitriles containing acetoxy groups such as bis(1-cyanovinylacetate) (**2**) can be obtained from the corresponding succinyl chloride and were reported by Oku¹⁸ and coworkers 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 mucononitriles such as **3a** and **3b** have been reported, but the reactivity of these compounds remains unexplored (Figure 1, B).²⁰

Central to our goal of developing a reagent-based linchpin strategy, we needed to demonstrate that mucononitrile 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 *non-symmetrical 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 mucononitriles, 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 accessing *ortho*-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 product, 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 *ortho*-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 Common chlorinating reagents as *N*-chlorosuccinimide and bleach provided monochlorination products in low yield by ¹H NMR analysis of the crude reaction mixture. Reagents such as Palau'chlor,²⁵ and iodobenzene dichloride were also ineffective for this transformation. Ultimately, we found that 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) in H₂SO₄ at 45 °C for 12 h provided high conversion of heterocycle **4** to the desired product **5a** (Equation 1).²⁶

4,7-Dibromobenzothiadiazole (**5b**) is available through known procedures and commercially.²⁷ With ample quantities of heterocycles **5a** and **5b** in hand, we then obtained dienes **3a** and **3b** as bench-stable crystalline solids using a two-step procedure involving reduction of the benzothiadiazole unit with NaBH₄, followed by an oxidative degradation of the resulting *ortho*-phenylenediamine **6** with lead tetraacetate (Equation 2). 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 towards 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 (Chart 1). 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** (98% and 93% 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). Presumably, the dienamines arise from a 1,6-conjugate addition reaction into the electron-deficient mucononitrile 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. 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.

Chart 1. Reaction scope with amine nucleophiles^a

The 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 Cs₂CO₃. A ^c 50% probability level shown.

Additionally, 2-substituted malonates were discovered to be competent carbon-based nucleophiles in the conjugate addition reactions with diene **3b**. We were able to react mucononitrile **3b** with excess (3.0 equiv) of

monosubstituted malonates to afford products resulting from double conjugate addition/elimination (Chart 2). The reactions proceeded in THF at 23 °C and were tolerant of *p*-substituted aryl groups to give products **20a–20e** (84–93% yield). Aliphatic groups such as diethyl 2-methylmalonate gave 72% yield. Heteroaromatic malonates containing a 2-furyl and 3-indolyl group gave adducts **24** and **25** in 74 and 83% yield respectively.

Chart 2. Reaction scope with malonate component^a

^a The standard conditions: 0.10 mmol **3b** with 3.0 NaH, 3.0 equiv. malonate, 0.1 M THF.

^b E = CO₂Et

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 adduct **26** in 84% yield after the one-pot two-step operation (Equation 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 (Equation 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 non-symmetrical dimeric natural product motifs.

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 chloride (or bromide) group served as a handle for a Suzuki–Miyaura or Sonogashira cross-coupling reactions.²⁹ 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.

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). 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). 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 dihalomucononitriles. 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 various dimeric natural products is ongoing in our laboratory and will be reported in due time.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We are grateful for UNC Chapel Hill for funding, the Alexanian, Crimmins, Johnson, Meek, Nicewicz and Aubé lab for chemicals, equipment and helpful discussions used for this study. We thank the University of North Carolina's Department of Chemistry NMR Core Laboratory for the use of their NMR spectrometers. This material is based upon work supported by the National Science Foundation under Grant No.'s CHE-0922858 and CHE-1828183. We thank the University of North Carolina's Department of Chemistry Mass Spectrometry Core Laboratory, for their assistance with mass spectrometry analysis. This material is based upon work supported by the National Science Foundation under Grant No. CHE-1726291.

Notes and references

- 1 E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, 1st Ed.; Wiley: New York, 1989.
- 2 M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193–3207. "Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling."
- 3 A. B. Smith III and C. M. Adams, *Acc. Chem. Res.*, 2004, **37**, 365–377. "Evolution of dithiane-based strategies for the construction of architecturally complex natural products."
- 4 J. Cornil, A. Guérinot and J. Cossy, *Org. Biomol. Chem.*, 2015, **13**, 4129–4142. "Linchpin Dienes: Key building-blocks in the synthesis of polyenic frameworks."
- 5 A. B. Smith III and Y. Deng, *Acc. Chem. Res.*, 2020, **53**, 988–1000. "Evolution of anion relay chemistry: construction of architecturally complex natural products."
- 6 S. E. Denmark and J. H.-C. Liu, *Angew. Chem. Int. Ed.*, 2010, **49**, 2978–2986. "Silicon-based cross-coupling reactions in the total synthesis of natural products."

- 7 J. Pyziak, J. Walkowiak and B. Marciniak *Chem. Eur. J.*, 2017, **23**, 3502–3541. "Recent advances in boron-substituted 1,3-dienes chemistry: synthesis and application."
- 8 For a recent review on multicomponent coupling reactions, see: C. de Graaf, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev.*, 2012, **41**, 3969–4009. "Recent developments in asymmetric multicomponent reactions."
- 9 J. Shimokawa, *Tetrahedron Lett.*, 2014, **55**, 6156–6162. "Divergent strategy in natural product total synthesis."
- 10 a) C. W. Ong, C. M. Chen, L. H. Wang, J. J. Jan and P. C. Shieh, *J. Org. Chem.*, 1998, **63**, 9131–9134. "Efficient synthesis of pyrroles from chemoselective addition of primary amines to 1,6-dioxo-2,4-diene."; b) C. W. Ong, C. M. Chen, L. F. Wang and P. C. Shieh, *Tetrahedron Lett.*, 1998, **39**, 9191–9192. "Convenient synthesis of 2,5-disubstituted thiophene from 1,6-dioxo-2,4-diene."
- 11 a) M. Dai, D. Sarlah, M. Yu, S. J. Danishefsky, G. O. Jones and K. N. Houk, *J. Am. Chem. Soc.*, 2002, **124**, 9676–9677. "Highly selective Diels-Alder reactions of directly connected enyne dienophiles." b) J. H. Rigby, H. S. Ateeq, N. R. Charles, S. V. Cuisiat, M. D. Ferguson, J. A. Hensilwood, A. C. Krueger, C. O. Ogbu, K. M. Short and M. J. Heeg *J. Am. Chem. Soc.*, 1993, **115**, 1382–1396. "Metal-promoted higher-order cycloaddition reactions. Stereochemical, regiochemical, and mechanistic aspects of the [6.pi. + 4.pi.] reaction."; c) B. M. Trost, and D. M. T. Chan, *J. Am. Chem. Soc.*, 1983, **105**, 2315–2325. "Palladium-mediated cycloaddition approach to cyclopentanoids. Introduction and initial studies."
- 12 a) D.-C. Zhao and T. Tidwell, *J. Am. Chem. Soc.*, 1992, **114**, 10980–10981. "A stable and persistent bisketenene: 2,3-bis(trimethylsilyl)-1,3-butadiene-1,4-dione."; b) D.-C. Zhao, A. D. Allen and T. T. Tidwell *J. Am. Chem. Soc.*, 1993, **115**, 10097–10103. "Preparation and reactivity of persistent and stable silyl-substituted bisketenenes."; c) N. H. Werstiuk, J. Ma, M. A. McAllister, T. T. Tidwell and D.-C. Zhao *J. Chem. Soc. Faraday Trans.*, 1994, **90**, 3383–3390. "Conformation properties of buta-1,3-diene-1,4-diones (bisketenenes): computational and photoelectron spectroscopic studies."; d) A. D. Allen, J. Ma, M. A. McAllister, T. T. Tidwell and D.-C. Zhao, *J. Chem. Soc. Perkin. Trans. II*, 1995, **4**, 847–852. "Electrophilic reactivity of bisketenenes: an experimental and theoretical study, and photoinduced hydration."
- 13 I. Dissanayake, J. Hart, E. Becroft, C. Sumbly and C. Newton, *J. Am. Chem. Soc.*, 2020, **142**, 13328–13333. "Masked Bisketenenes as Diels-Alder Dienes."
- 14 V. N. Telvekar and B. S. Takale, *Tetrahedron Lett.*, 2010, **51**, 3940–3943. "Carbon-carbon Cleavage of Aryl Diamines and Quinone Formation using Sodium Periodate: A Novel Application." We were unable to repeat the reported results and different variations of the reported conditions were also ineffective.
- 15 V. N. Telvekar and H. M. Bachhav, *Synlett*, 2010, **14**, 2059–2062. "A Novel Application of (Diacetoxyiodo)benzene for Carbon-Carbon Cleavage of Aryl Diamines and Synthesis of Quinones."
- 16 H. Takahashi, T. Kajimoto and J. Tsuji, *Synthetic Commun.*, 1972, **2**, 181–184. "Organic synthesis by means of metal complexes. X¹ Copper catalyzed Oxidation of o-phenylenediamine to Mucononitrile."
- 17 K. Nakagawa and H. Onoue *Tetrahedron Lett.*, 1965, **20**, 1433–1436. "Oxidation with nickel peroxide. V. The Formation of *cis,cis*-1,4-dicyano-1,3-butadienes in the oxidation of o-phenylenediamines."
- 18 A. Oku, S. Urano, T. Nakaji, G. Qing and M. Abe *J. Org. Chem.*, 1992, **57**, 2263–2266. "Bis(2-acetoxyacrylonitrile) and its Phenylene and Alkylene Bis Homologs. Preparation, Isomerization, and Intramolecular [2+2] Photocycloaddition."
- 19 S. M. Wilkerson-Hill, S. Sawano and R. Sarpong, *J. Org. Chem.*, 2016, **81**, 11132–11144. "Bis(1-cyanovinylacetate) is a Linear Precursor to 3-Oxidopyrlium Ions."
- 20 a) Fisons Ltd. US3644637, 1972, (Chem. Abstr. Vol 76 126427), b) Fisons Pest Control Ltd, ZA6800202, 1967 (Chem Abstr, 1969, vol 70, 87076w)
- 21 Z. Rappoport, Ed.; in *The Chemistry of Functional Groups Vol 2 The chemistry of Dienes and Polyenes 2000*, John Wiley & Sons, Chichester New York.
- 22 S. Chen, F. Raad, M. Ahmida, B. R. Kaafarani and S. H. Eichorn, *Org. Lett.*, 2013, **15**, 558–561. "Columnar Mesomorphism of Fluorescent Board-Shaped Quinoxalinophenanthrophenazine Derivatives with Donor-Acceptor Structure."
- 23 R. Adams and J. W. Way *J. Am. Chem. Soc.*, 1954, **76**, 2763–2769. "Quinone Imides. XXXV. o-Quinonedibenzimides."
- 24 To our knowledge, the only conditions reported to chlorinate 2,1,3-benzothiadiazole use chlorine gas, see: V. G. Pesin, *J. Gen. Chem. USSR (Engl. Transl.)* 1964, **34**, 3063–3069.
- 25 R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 6908–6911. "Palau'chlor: A Practical and Reactive Chlorinating Reagent."
- 26 See Supporting Information for details.
- 27 For a recent example of the bromination of 4, see: N. Huang, P. Wang, M. A. Addicoat, T. Heine and D. Jian, *Angew. Chem. Int. Ed.*, 2017, **56**, 4982–4986. "Ionic Covalent Organic Frameworks: Design of a Charged Interface Aligned on 1D Channel Walls and Its Unusual Electrostatic Functions."
- 28 K. K. Balasubramanian and S. Selvaraj, *J. Org. Chem.* 1980, **45**, 3726–3727. "Novel Reaction of o-Phenolic Mannich Bases with α -chloroacrylonitrile."
- 29 a) Notably, examples of cross-coupling reactions to α -chloroacrylonitriles are limited to the use of the TEDICEP ligand, see: F. Berthiol, H. Doucet and M. Santelli *Synthetic Commun.*, 2006, **36**, 3019–3027. "Suzuki Coupling of 2-Chloroacrylonitrile, Methyl 2-Chloroacrylate, or 2-Chloroprop-1-en-3-ol with Arylboronic Acids Catalyzed by a Palladium-Tetraphosphine Complex."; b) For examples of cross-coupling to 2-chloroacrylonitrile using alkylindium reagents, see: R. Nomura, S.-I. Miyazaki and H. Matsuda, *J. Am. Chem. Soc.*, 1992, **114**, 2738–2740. "New triad alkylation reagent. Cross coupling of indium trialkyls with alkenyl halides."