Diazo Compounds | Hot Paper

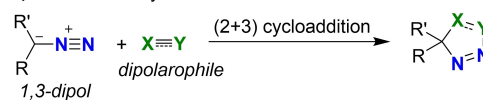# Head-to-Tail Dimerization of N-Heterocyclic Diazoolefins

Paul Varava, Tak Hin Wong, Zhaowen Dong, Anastasia Yu. Gitlina, Andrzej Sienkiewicz, Wolfram Feuerstein, Rosario Scopelliti, Farzaneh Fadaei-Tirani, and Kay Severin*

Abstract: The head-to-tail dimerization of N-heterocyclic diazoolefins is described. The products of these formal (3+3) cycloaddition reactions are strongly reducing quinoidal tetrazines. Oxidation of the tetrazines occurs in a stepwise fashion, and we were able to isolate a stable radical cation and diamagnetic dications. The latter are also accessible by oxidative dimerization of diazoolefins.
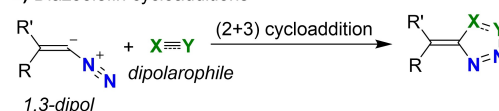
Diazoalkanes undergo (2+3) cycloaddition reactions with a large variety of dipolarophiles (Scheme 1a).[1] First evidence for such a transformation was provided in 1888 by Buchner.[2] He noted that the reaction of methyl diazoacetate with dimethyl fumaric acid gives a well-defined addition product. Soon after, von Pechmann investigated similar reactions with diazomethane.[3] Today, 1,3-dipolar cycloaddition reactions (Huisgen reactions)[4] between diazoalkanes and dipolarophiles represent an indispensable tool in heterocyclic chemistry.[1]

In contrast to the rich chemistry of diazoalkanes, there are only limited studies with diazoolefins.[5–9] A key problem for experimental work is the low stability of most diazoolefins, as they tend to lose dinitrogen, even at low temperatures. However, it could be established that diazoolefins are also able to undergo 1,3-dipolar cycloaddition reactions (Scheme 1b).[6, 7]
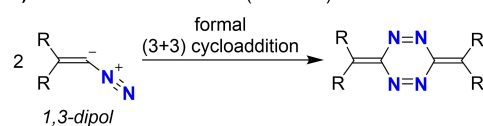
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Scheme 1. 1,3-Diploar cycloaddition reactions of diazoalkanes (**a**) and diazoolefins (**b**). Dimerization reactions of diazoolefins reported herein (**c**).

We have recently reported the synthesis of N-heterocyclic diazoolefins of the general formula (NHC)=C=N₂ (NHC=imidazolylidene).[7,8] These compounds display good thermal stability, allowing handling and reactivity studies at ambient temperature.[7–9] In the course of our investigations, we observed that N-heterocyclic diazoolefins are able to undergo a head-to-tail dimerization, which corresponds to a formal (3+3) cycloaddition reaction (Scheme 1c).[10] The resulting quinoidal tetrazines are strong reducing agents, and they can be oxidized to give an isolable radical cation and dications. Details about these findings are given below.

For our investigations, we have used N-heterocyclic diazoolefins with 2,4,6-$C_6H_2Me_3$ (Mes), 2,6-$C_6H_3Me_2$ (Xyl), and 2,6-$C_6H_3iPr_2$ (Dipp) wingtip groups.[7] Dissolution of these diazoolefins in methanol followed by evaporation of the solvent after 10 minutes resulted in the formation of pink solids. The ¹H NMR spectra of the crude reaction mixtures indicated that a transformation into new products, **1–3**, had occurred (Scheme 2). Washing with small amounts of acetonitrile gave **1–3** in analytically pure form (yields: 72–80%).[11] All three compounds turned out to be highly sensitive, and storage at −40°C under an inert atmosphere was required to avoid decomposition.
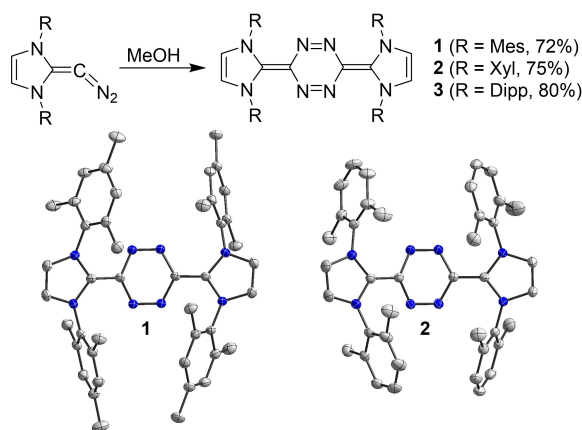
The molecular structures of **1** and **2** in the solid state were established by single-crystal X-ray diffraction (XRD).[12] The results showed that treatment with methanol had induced a head-to-tail dimerization of the diazoolefins via the CN_2 group. The quinoidal character of the products is reflected in the structural parameters of **1** and **2**. The

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Scheme 2. Synthesis of the quinoidal tetrazines **1–3**. The structures of **1** and **2** could be confirmed by crystallographic analyses. Thermal ellipsoids are at 40% probability and hydrogen atoms are not depicted.

Scheme 3. The proposed mechanism for the dimerization of N-heterocyclic diazoolefins (**a**), and synthesis of the methylated dimers **4** and **5** (**b**).

compounds show a pronounced bond length alternation in the central C_2N_4 ring, with shortened N–N bonds (1.272(1)–1.277(1) Å) and elongated C–N_2 bonds (1.405(1)–1.407(1) Å). The C–C bonds bridging the heterocycles are longer (1.379(2)–1.387(1) Å) than a standard double bond (≈ 1.34 Å). This elongation is expected for compounds that classify as 'N-heterocyclic olefins'.[13] The imidazole rings in **1** and **2** are nearly planar, but the central C_2N_4 rings display a boat conformation. Such a deviation from planarity was predicted theoretically for the parent quinoidal tetrazine $H_2C=(C_2N_4)=CH_2$.[14]

Density functional calculations (DFT) at the M06-2X/6-311+G(d,p) level of theory were used to investigate the electronic structures of **1** and **2**.[15] The optimized structures match what was found experimentally by XRD analyses (for details, see the Supporting Information, Table S12). The HOMOs of **1** and **2** feature large contributions from the π orbitals of the (NHC)–C and N–N bonds (Supporting Information, Figures S54–S55), and the HOMO-1 orbitals present the σ-bonding orbitals of the C–N bonds in the six-membered C_2N_4 ring. These results further support the quinoidal character of the tetrazines.

So far, experimental data for quinoidal tetrazines are scarce.[16-18] Kotschy and co-workers have reported compounds of the general formula (NHC)=(C_2N_4)=O.[16] These tetrazines are structurally distinct from **1** and **2** since they feature very long (NHC)–C bonds (1.453–1.470 Å), a strong zwitterionic character, and large dipole moments. Furthermore, quinoidal tetrazines were prepared in situ by chemical or electrochemical reduction of tetrazines with alkylpyridinium substituents.[17] Structural data for the products were not reported.

We propose that the formation of **1–3** is initiated by protonation of the diazoolefin at the ylidic exocyclic carbon atom (Scheme 3a). The resulting vinyl diazonium salt **I** reacts with non-protonated diazoolefin to give an intermediate of type **II**. The latter is the dominant species in solution, and conversion into the quinoidal tetrazine occurs upon removal of the solvent under vacuum. The proposition that
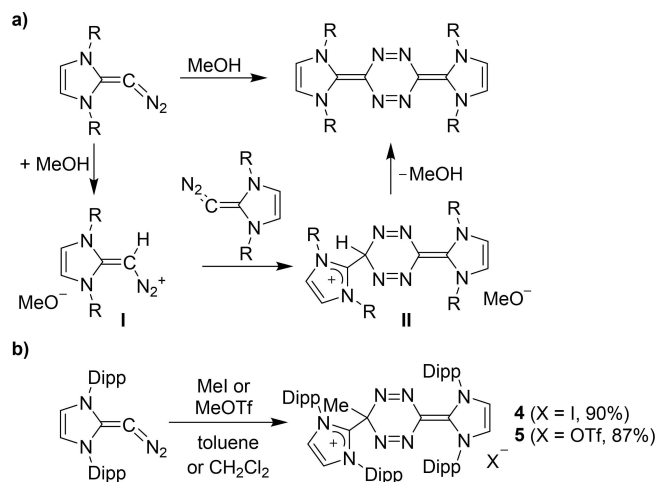
the products are formed during evaporation of the solvent is supported by the following observations: a) the characteristic dark red color of the products developed *after* removal of the solvent and drying under vacuum; b) the ^1H NMR spectra of the solutions of **1–3** in CD_3OD showed the presence of a low-symmetry species, with a double set of signals for the wingtip groups R at the imidazolium rings (Supporting Information, Figures S29–S31). These spectra match what is expected for intermediates of type **II**. Further indirect evidence for the relevance of **II** was obtained by the synthesis of the structural analogs **4** and **5** (Scheme 3b). The compounds were obtained by a reaction of the corresponding diazoolefin with MeI or MeOTf (0.5 equiv), respectively, and their structures were confirmed by single crystal XRD analyses. It is worth noting that **4** and **5** were also formed when an excess of the methylating agent was employed.

Based on our previous experience with azo-bridged N-heterocyclic olefins,[19] we suspected that **1–3** should act as reducing agents. In fact, reactions with AgOTf (2.1 equiv) in THF at room temperature resulted in two-fold oxidation to give the dicationic tetrazines **6–8** in good yields (Scheme 4). The compounds were characterized comprehensively, including single crystal XRD analyses for all three compounds (Scheme 4 and Figures S50 and S51). The structural data suggest that the compounds are best described as aromatic tetrazines with two imidazolium groups as substituents. The imidazole and the tetrazine heterocycles are tilted with respect to each other (α=25–59°), and the C–C bonds connecting the heterocycles have the length of a C–C single bond (1.457(2)–1.470(3) Å).

The redox chemistry of the tetrazines was evaluated by cyclic voltammetry measurements using solutions of **6–8** in CH_3CN in presence of 0.1 M $TBAPF_6$. All three compounds showed two reversible one-electron transitions, and the voltammogram of compound **8** is depicted as a representative example in Figure 1. The transition at $E_{1/2}=-0.29$ V versus Fc/Fc$^+$ can be attributed to the reduction of **8** to the radical cation, and the transition at $E_{1/2}=-1.58$ V corre-
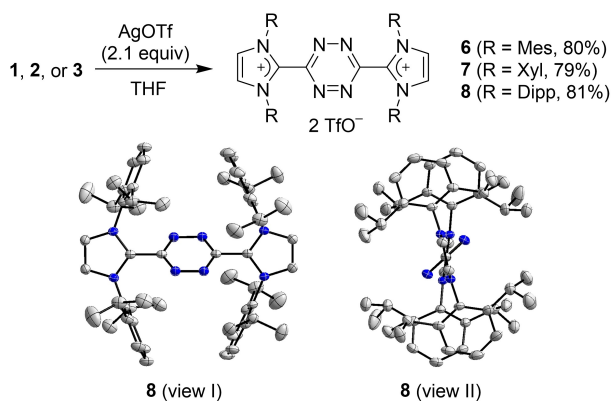
Scheme 4. Synthesis of the dicationic tetrazines **6–8**. The structure of **8** is based on a crystallographic analysis. Thermal ellipsoids are at 40% probability. Triflate anions and hydrogen atoms are not depicted.
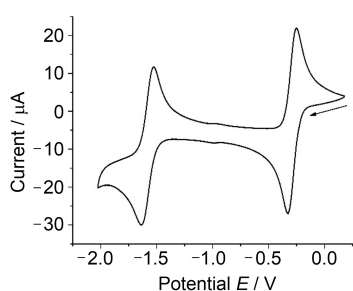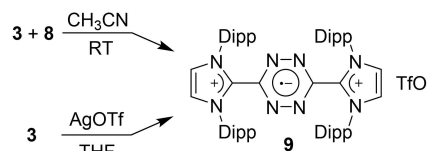

Figure 1. Cyclic voltammogram of **8** vs Fc/Fc$^+$ (0.1 M TBAPF$_6$ in MeCN, 100 mV s^{-1}). Reversible redox transitions are observed at $E_{1/2} = -0.29$ V and $E_{1/2} = -1.58$ V.

sponds to the formation of the neutral tetrazine. The first reduction of **6** and **7** occurred at ca. 0.26 V and the radical cation/quinoidal tetrazine transitions were observed at slightly higher values (**6**: −1.42 V, **7**: −1.40 V). The data show that quinoidal tetrazines are very powerful organic reducing agents.[20]

It is interesting to compare the potentials of **8** with what was reported by Ghadwal and co-workers for the structurally related compound [(NHC)=(C$_6$H$_4$)=(NHC)]Br$_2$ (NHC = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene).[21] The first reduction of the phenylene-bridged dimer occurred at $E_{1/2} = -1.04$ V and the second reduction at $E_{1/2} = -1.29$ V (vs. Fc/Fc$^+$). With $\Delta E_{1/2} = 0.25$ V, the difference between the two redox transitions is significantly smaller than the $\Delta E_{1/2}$ of 1.29 V observed for **8**. The higher oxidation power of **8** when compared to [(NHC)=(C$_6$H$_4$)=NHC)]Br$_2$ can be attributed to the more facile reduction of the tetrazine linker.[22]

The CV data of **6–8** implied that radical cations should be accessible by comproportionation of the quinoidal tetrazines with the oxidized dications. Indeed, paramagnetic tetrazine **9** could be obtained in 85% yield by mixing **3** with **8** in acetonitrile (Scheme 5). Alternatively, **9** can be synthesized by mono-oxidation of **3** with AgOTf in THF (yield: 74%). When kept under an N$_2$ atmosphere, solutions of **9** in benzene are stable for several hours. Upon exposure to air,

the compound slowly degrades (Supporting Information, Figure S44).

DFT calculations imply that most of the spin density is found on the central C$_2$N$_4$ ring (Figure 2a and Supporting Information, Table S13). Accordingly, the EPR spectrum of **9** (benzene, RT) features a singlet with hyperfine splitting due to coupling to four ^{14}N nuclei (Figure 2b). The spectrum can be simulated by using the following parameters: $g = 2.0039$, $A_N = 5.185$ G (for details, see the Supporting Information). The data suggest that **9** is best described as a tetrazine radical anion[22] with two cationic imidazolium substituents.

During our studies with N-heterocyclic diazoolefins, we noticed that a head-to-tail dimerization can also be achieved by oxidation. For example, the diazoolefin with Dipp wing-tip groups is converted into the tetrazine salts **10** or **11** by reaction with either tris(4-bromophenyl)ammoniumyl hexachloroantimonate ('magic blue') or NOBF$_4$ (Scheme 6). In line with this observation, we found that the electrochemical oxidation of diazoolefins is irreversible (for details, see the Supporting Information).

To summarize: we have shown that N-heterocyclic diazoolefins are able to undergo methanol-mediated head-to-tail dimerizations to give quinoidal tetrazines. To the best
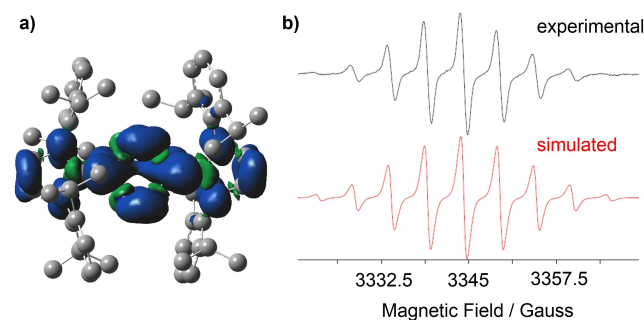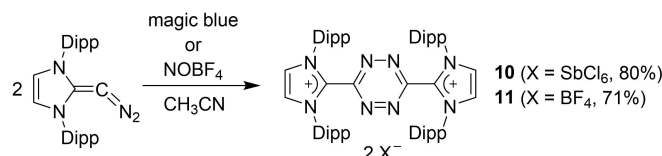

Scheme 5. Synthesis of the paramagnetic tetrazine **9**.

Figure 2. a) Calculated spin density of the radical **9** (isovalue = 0.004; calculated at the M06-2X/6-311+G(d,p) level of theory). b) Experimental (benzene, RT) and simulated EPR spectra of the radical **9**.

Scheme 6. Oxidative dimerization of diazoolefin **3** with tris(4-bromophenyl)ammoniumyl hexachloroantimonate ('magic blue') or NOBF$_4$.

of our knowledge, these reactions are first examples of formal (3+3) cycloadditions of diazoolefins. The quinoidal tetrazines are strong organic reducing agents with first oxidation potentials between -1.40 V and -1.58 V (vs. Fc/Fc$^+$). These values are lower than what is found for common organic reducing agents such as tetraazafulvalene derivatives.[20] With respect to potential applications, one should note that strongly reducing tetrazines could be generated on demand by a quick treatment of stable diazoolefins with methanol. The oxidation of quinoidal tetrazines proceeds in a step-wise fashion, and the initial radical cation is stable over a large potential range. The final oxidation products are tetrazines with two imidazolium substituents. These compounds can also be prepared by direct oxidation of diazoolefins. The high propensity of diazoolefins to undergo head-to-tail dimerizations should be taken into account for future studies with this new compound class.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

[1] G. Mass in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, p. 539–621.

[2] E. Buchner, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 2637–2647.

[3] H. von Pechmann, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 855–861.

[4] a) M. Breugst, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2020**, *59*, 12293–12307; b) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565–598.

[5] For reviews, see: a) R. Knorr, *Chem. Rev.* **2004**, *104*, 3795–3849; b) W. Kirmse, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1164–1170; c) D. Bourissou, G. Bertrand, *C. R. Acad. Sci. Ser. IIb* **1996**, 489–506.

[6] a) J. Kerth, T. Jikyo, G. Maas, *Eur. J. Org. Chem.* **2003**, 1894–1903; b) B. Manz, G. Maas, *Tetrahedron* **1996**, *52*, 10053–10072; c) R. Munschauer, G. Maas, *Chem. Ber.* **1992**, *125*, 1227–1234;

d) R. Munschauer, G. Maas, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 306–308; e) K. Bott, *Chem. Ber.* **1987**, *120*, 1867–1871; f) K. Bott, *Tetrahedron Lett.* **1985**, *26*, 3199–3202; g) W. Ando, T. Furuhata, T. Takata, *Tetrahedron Lett.* **1985**, *26*, 4499–4500; h) P. M. Lahti, J. A. Berson, *J. Am. Chem. Soc.* **1981**, *103*, 7011–7012.

[7] P. Varava, Z. Dong, R. Scopelliti, F. Fadaei-Tirani, K. Severin, *Nat. Chem.* **2021**, *13*, 1055–1060.

[8] Structurally related diazoolefins containing mesoionic heterocycles were described by Hansmann and co-workers: a) P. W. Antoni, J. Reitz, M. M. Hansmann, *J. Am. Chem. Soc.* **2021**, *143*, 12878–12885; b) P. W. Antoni, C. Golz, J. J. Holstein, D. A. Pantazis, M. M. Hansmann, *Nat. Chem.* **2021**, *13*, 587–593.

[9] a) B. Kooij, P. Varava, F. Fadaei-Tirani, R. Scopelliti, D. A. Pantazis, G. P. Van Trieste III, D. C. Powers, K. Severin, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214899; b) B. Kooij, Z. Dong, P. Varava, F. Fadaei-Tirani, R. Scopelliti, L. Piveteau, K. Severin, *Chem. Commun.* **2022**, *58*, 4204–4207; c) Y. Kutin, J. Reitz, P. W. Antoni, S. Savitsky, D. A. Pantazis, M. Kasanmascheff, M. M. Hansmann, *J. Am. Chem. Soc.* **2021**, *143*, 21410–21415.

[10] Dihydro-s-tetrazines can be obtained in reactions of diazo compounds with base. For examples, see: a) D. L. Boger, R. S. Coleman, J. S. Panek, *J. Org. Chem.* **1985**, *50*, 5377–5379; b) P. Yates, R. G. F. Giles, D. G. Farnum, *Can. J. Chem.* **1969**, *47*, 3997–4004; c) P. Yates, O. Meresz, *Tetrahedron Lett.* **1967**, *8*, 77–81; d) T. Curtius, A. Darapsky, E. Müller, *Chem. Ber.* **1908**, *41*, 3161–3172; e) A. Hantzsch, O. Silberrad, *Chem. Ber.* **1900**, *33*, 58–89; f) T. Curtius, J. Lang, *J. Prakt. Chem.* **1888**, *38*, 531–558.

[11] The yields refer to small-scale syntheses (20 mg). A larger-scale synthesis is possible, albeit with a slightly lower yield (see Supporting Information).

[12] Deposition numbers 2241141 (**1**), 2241140 (**2**), 2218605 (**4**), 2241135 (**5**), 2241133 (6), 2241134 (**7**), 2241132 (**8**), and 2109150 (**10**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[13] a) Q. Liang, D. Song, *Dalton Trans.* **2022**, *51*, 9191–9198; b) S. Naumann, *Chem. Commun.* **2019**, *55*, 11658–11670; c) M. M. D. Roy, E. Rivard, *Acc. Chem. Res.* **2017**, *50*, 2017–2025.

[14] A. Skancke, J. F. Liebman, *J. Org. Chem.* **1999**, *64*, 6361–6365.

[15] a) The Gaussian09 program was used. M. Frisch, et al., Gaussian09, Revision D.01; Gaussian, Inc.: Wallingford, CT, **2010**; b) for a detailed description, see the Supporting Information.

[16] a) A. C. Bényei, A. Stirling, B. Bostai, K. Lőrincz, A. Kotschy, *RSC Adv.* **2014**, *4*, 47762–47768; b) B. Bostai, Z. Novák, A. C. Bényei, A. Kotschy, *Org. Lett.* **2007**, *9*, 3437–3439.

[17] a) Q.-H. Guo, J. Zhou, H. Mao, Y. Qiu, M. T. Nguyen, Y. Feng, J. Liang, D. Shen, P. Li, Z. Liu, M. R. Wasielewski, J. F. Stoddart, *J. Am. Chem. Soc.* **2020**, *142*, 5419; b) E. Waldhör, M. M. Zulu, S. Zalis, W. Kaim, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1197–1204.

[18] The compound Ph$_2$C=(C$_2$N$_4$)=CPh$_2$ is mentioned in an article by Battiste and co-workers, but a synthetic procedure or analytical data are not provided: H. Malkus, M. A. Battiste, R. M. White, *Chem. Commun.* **1970**, 479–480.

[19] L. Eymann, P. Varava, A. M. Shved, B. F. E. Curchod, Y. Liu, O. M. Planes, A. Sienkiewicz, R. Scopelliti, F. Fadaei Tirani, K. Severin, *J. Am. Chem. Soc.* **2019**, *141*, 17112–17116.

[20] For reviews about organic electron donors, see: a) J. Broggi, T. Terme, P. Vanelle, *Angew. Chem. Int. Ed.* **2014**, *53*, 384–413; b) E. Doni, J. A. Murphy, *Chem. Commun.* **2014**, *50*, 6073–6087; c) J. A. Murphy, *J. Org. Chem.* **2014**, *79*, 3731–3746.

[21] D. Rottschäfer, N. K. T. Ho, B. Neumann, H.-G. Stammler, M. van Gastel, D. M. Andrada, R. S. Ghadwal, *Angew. Chem. Int. Ed.* **2018**, *57*, 5838–5842.

[22] For selected publications about tetrazine radical anions, see: a) G. D. DE La Garza, A. P. Kaur, I. A. Shkrob, L. A. Robertson, S. A. Odom, A. J. McNeil, *J. Mater. Chem. A* **2022**, *10*, 18745–18752; b) N. Mavragani, A. A. Kitos, J. L. Brusso, M. Murugesu, *Chem. Eur. J.* **2021**, *27*, 5091–5106; c) C. R. Benson, E. M. Fatila, S. Lee, M. G. Marzo, M. Pink, M. B. Mills, K. E. Preuss, A. H. Flood, *J. Am. Chem. Soc.* **2016**, *138*, 15057–15065; d) B. J. Jordan, M. A. Pollier, L. A. Miller, C. Tiernan, G. Clavier, P. Audebert, V. M. Rotello, *Org. Lett.* **2007**, *9*, 2835–2838; e) P. Audebert, F. Miomandre, G. Clavier, M.-C. Vernières, S. Badré, R. Méallet-Renault, *Chem. Eur. J.* **2005**, *11*, 5667–5673; f) P. Audebert, S. Sadki, F. Miomandre, G. Clavier, M. C. Vernières, M. Saoud, P. Hapiot, *New J. Chem.* **2004**, *28*, 387–392; g) H. Fischer, T. Müller, I. Umminger, F. A. Neugebauer, H. Chandra, M. R. S. Symons, *J. Chem. Soc. Perkin Trans. 2* **1988**, 413–421.
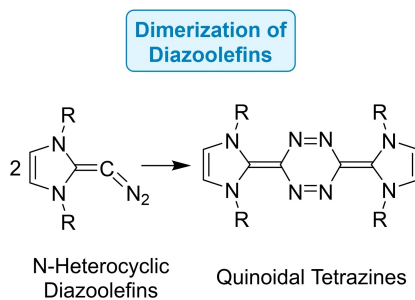
Communications

Diazo Compounds

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Head-to-Tail Dimerization of N-Heterocyclic
Diazoolefins

Dimerization of Diazoolefins

N-Heterocyclic Diazoolefins → Quinoidal Tetrazines

Methanol induces a head-to-tail dimerization of N-heterocyclic diazoolefins. The products of these formal (3+3) cycloaddition reactions, quinoidal tetrazines, are strong organic reducing agents.