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1,4-Diamination of Cyclic Dienes via a (4 + 3) Cycloaddition of Diaza-allyl Cationic Intermediates

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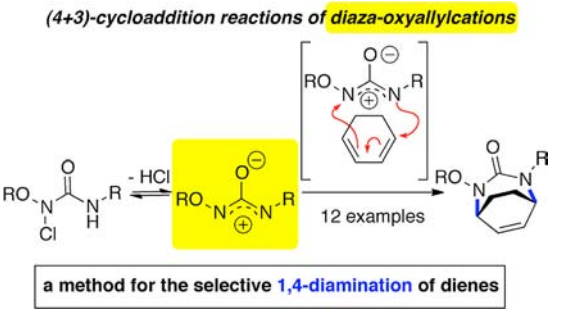
ABSTRACT



Diaza-(4 + 3) cycloadditions of putative diaza-oxyallyl cationic intermediates and cyclic dienes are reported as a method for the 1,4-diamination of cyclic dienes. This reaction was entirely selective for diamination and provided cycloadducts in good to excellent yield.

1,*n*-Diamine (n = 2–5) motifs are found in numerous pharmaceuticals and biologically active natural products, including the anti-HIV molecules cobicistat[1] and DMP-450[2] (Figure 1).[3] Of the methods of diamination of alkenes, the vicinal 1,2-diamination of dienes and alkenes is the most comprehensively investigated reaction type.[4] Despite the importance of 1,4-diamino motifs in biologically active molecules, selective methods for the 1,4-diamination of dienes have not been thoroughly explored.[5] The hetero-Diels–Alder reactions of diazocarboxylates and triazine diones are the most widely used methods for the selective diamination of dienes.[6] Despite numerous applications of this reaction, limitations due to a competitive ene-reaction and the explosion hazard of the diazidocarboxylates have limited their use.

The (4 + 3) cycloaddition reaction of allylic cations and dienes has developed into a powerful method for the synthesis of seven-membered carbocycles.[7] We have recently reported the aza-(4 + 3) cycloaddition of a putative aza-oxyallylcation and a diene as a heteroatomic analog of this reaction.[8] It was envisioned that a related hetero-(4 + 3) type cycloaddition of a diaza-oxyallylcation could deliver cyclic ureas and serve as a method for the chemoselective 1,4-diamination of dienes (Figure 1). This communication describes our work on the aforementioned reaction.

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(2) Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N. *Science* **1994**, *263*, 380.

(3) (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627. (b) Saibabu Kotti, S. R.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

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(5) For examples of methods of 1,4-diamination of conjugated dienes, see: (a) Lishchynskyi, A.; Muñiz, K. *New J. Chem.* **2012**, *18*, 2212. (b) Bäckvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335. (c) Bäckvall, J.-E.; Nyström, J.-E.; Nyström, J.-E. *J. Chem. Soc., Chem. Commun.* **1981**, 59. (d) Akermark, B.; Bäckvall, J.-E.; Löwenborg, A.; Zetterberg, K. *J. Organomet. Chem.* **1979**, *166*, 33.

(6) For a general review of hetero-Diels–Alder reactions, see: (a) *The Diels–Alder Reaction: Selected Practical Methods*; Fringuelli, F., Taticchi, A., Eds.; John Wiley & Sons: New York, 2002. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley–VCH: Weinheim, Germany, 2002; pp 151–209. (c) *Comprehensive Asymmetric Catalysis III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 1237–1254. (d) Gouverneur, V.; Reiter, M. *Chem.—Eur. J.* **2005**, *11*, 5806. (e) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (f) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1.

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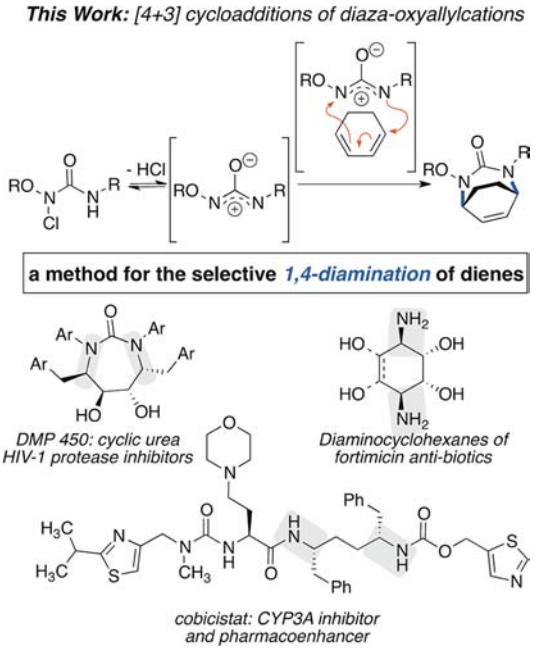
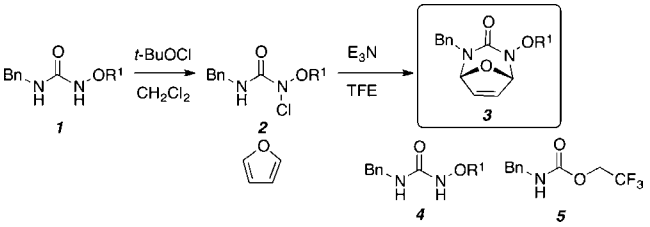


Figure 1. Aza-(4 + 3) cycloaddition of aza-oxyallyl cations with dienes.

In our previous studies the proposed aza-allyl cationic intermediate was generated via a dehydrohalogenation of α-halohydroxamates. Likewise, *N*-chloroureas **2** could dehydrohalogenate to the diazaallyl cationic intermediate, which then could react with a diene to provide a seven-membered urea **3** (Scheme 1). To study this hypothesis, we prepared *N*,*N*′-dibenzyl, dialkyl, and diaryl ureas and attempted their *N*-chlorination. Initial efforts to chlorinate these urea derivatives provided complex mixtures of products. *N*-Alkoxy ureas **1** can be efficiently chlorinated at the *N*-alkoxy position by *tert*-butyl hypochlorite.[9] *N*-Methoxy, *N*-ethoxy, and *N*-benzyloxy benzyl ureas rapidly underwent chlorination to provide the solid *N*-chlorourea products **2** that were isolable via silica gel column chromatography in good to excellent yield.

Scheme 1. Preliminary Experiments[a]



[a] R^1 = Bn, Me, or Et; TFE = 2,2,2-trifluoroethanol.

With the *N*-chlorourea **2** in hand the cycloaddition reaction with furan was evaluated. Treatment of the *N*-chlorourea **2** under Fölisch conditions (CF_3CH_2OH, Et_3N) with furan provided the cycloadduct **3** along with significant products **4** and **5**.[10] The nature of the substituents (R^1 = Bn, Et, Me) had little effect on the yield of the cycloadduct.[11] The choice of base, however, had a significant effect on the yield of the cycloadduct **3**. Using the sodium alkoxide of 2,2,3,3-tetrafluoropropanol (TFP/TFP-Na) provided the highest yield (74%) of the cycloadduct **3** with minimal formation of the solvolysis product **5**.[12] The yield of the desired product **3** was significantly improved when a solution of *N*-chlorourea in CH_3CN was added over 3 h to the mixture of diene and base at 0 °C.[13] Although it is common that (4 + 3) reactions are run in an excess of the diene (> 10 equiv),[6] we found that the yield of the furan adduct **3** was not very sensitive to the ratio of substrate to diene, even when the reaction was conducted with 1.1 equiv of diene (87% using 1.1 equiv vs 95% using 5−25 equiv)!

The scope of this reaction with respect to diene was explored. Cyclopentadiene and *N*-Boc pyrrole underwent the reaction to provide the cycloadducts in similar yield to that with furan (Table 1, entries 2−4). 2,5-Disubstituted (Table 1, entry 5) and 3,4-disubstituted furans (Table 1, entry 6) provided the cycloadduct in good to excellent yields. However, furans with electron-deficient substituents (2-carboethoxy) and acyclic dienes (isoprene and 2,3-dimethyl-1,4-butadiene) provided only solvolysis products and recovered starting material after workup.[14] 6,6-Dimethyl fulvene (Table 1, entry 8) and [2.2.2]-spiro-heptadiene (Table 1, entry 7) both reacted in the desired manner providing the cycloadduct in good to excellent yields. We found that 1,3-cyclohexadiene also provided the cycloadduct in fair yield (entry 9).

(7) (a) Lohse, A. G.; Hsung, R. P. *Chem.—Eur. J.* **2011**, *17*, 3812–3822. (b) Harmata, M. *Chem. Commun.* **2010**, 8904–8922. (c) Harmata, M. *Chem. Commun.* **2010**, 8886–8903. (d) Huan, J.; Hsung, R. P. *ChemTracts* **2005**, *18*, 207–214. (e) Harmata, M. *Adv. Synth. Catal.* **2006**, 2297–2306. (f) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595–605. (g) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, *2*, 217–232. (h) Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Grennwich, 1997; Vol. 4, pp 41−86. (i) West, F. G. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Grennwich, CT, 1997; Vol. 4, pp 1−40. (j) Harmata, M. *Tetrahedron* **1997**, *53*, 6235–6280. (k) Padwa, A.; Schoffstall, A. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 1−89. (l) Harmata, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 523–535. (m) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351–478. (n) Mann, J. *Tetrahedron* **1986**, *42*, 4611–4659. (o) Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1984**, *23*, 1–19. (p) Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **1973**, *12*, 819–835.

(8) Jeffrey, C. S.; Barnes, K. L.; Eickhoff, J. A.; Carson, C. R. *J. Am. Chem. Soc.* **2011**, *133*, 7688–7691.

(9) Shtamburg, V. G.; Shishkin, O. V.; Zubatyuk, R. I.; Kravchenko, S. V.; Tsygankov, A. V.; Mazepa, A. V.; Klots, E. A.; Kostyanovsky, R. G. *Mendeleev Commun.* **2006**, *16*, 323–325.

(10) Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem., Int. Ed.* **1982**, 137.

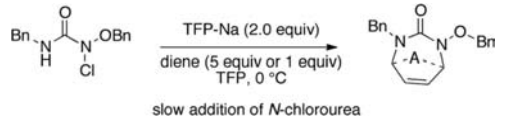
(11) Although the yield was not significantly affected by the nature of the R^1, it was our finding that the ethyl and benzyl substituted substitute hydroxy ureas were easier to handle due to their solubility and chromatographic characteristics.

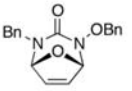
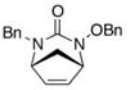
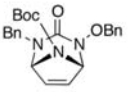
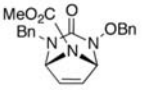
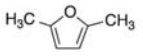
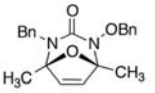
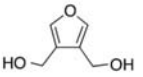
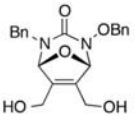
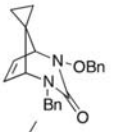
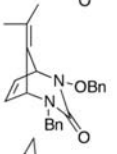
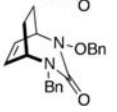
(12) 2,2,3,3-Tetrafluoropropanol is an inexpensive solvent. This solvent base combination has been previously demonstrated to have substantial benefits in the (4 + 3) cycloaddition reaction; see: Föhlisch, B.; Gehrlach, E.; Geywitz, B. *Chem. Ber.* **1987**, *120*, 1815.

(13) The order and rate of addition were found to dramatically affect the yield of the cycloaddition of electron-rich dienes. For example, the yield of the cycloadduct of 2,5-dimethyl furan improved from 35% to 65% yield when the *N*-chlorourea was added over 3 h.

(14) Generally electron-deficient and acyclic dienes do not react efficiently with oxyallylic cations; see refs 6b and 6c.

Table 1. Scope of the Diaza-(4 + 3) Cycloaddition of **2** with Cyclic Dienes[a]



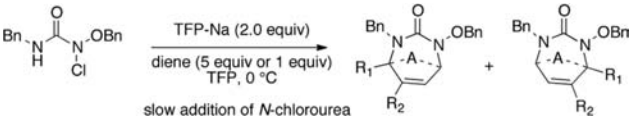
entry	diene	product	yield[b]
1			A: 93% B: 87%
2			A: 92% B: 95%
3			A: 82%
4			A: 90%
5			A: 73% B: 75%
6			A: 69%
7			A: 88% B: 82%
8			A: 85% B: 73%
9			A: 58% B: 43%

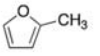
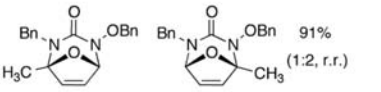
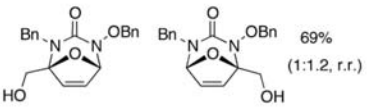
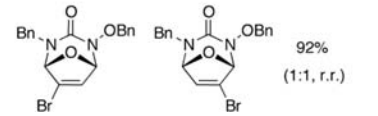
[a] Conditions: *N*-Chlorourea **2** in CH_3CN was added to a solution of the diene [5 equiv (condition A) or 1.1 equiv (condition B)] and TFP-Na (2.0 equiv) in TFP (0.25 M). [b] Isolated yield of the cycloadduct **13**.

Reactions using monosubstituted dienes provided a mixture of regioisomeric cycloadducts (Table 2). This ratio of regioisomers was close to 1:1 in all cases and remained largely unaffected by the hyrdoxamate substituent.[15] Although using a symmetric dibenzyloxy or methoxy urea would avoid this issue, problems associated with monochlorination of the urea thwarted this approach. Nonetheless, the combined yield of the mixture of regioisomeric products

(15) The regioisomeric ratio was determined by crude ^{1}H NMR analysis. The structures of the regioisomers were assigned from NOSEY correlations of the isolated products.

Table 2. Scope of the Diaza-(4 + 3) Cycloaddition of **2** with Monosubstituted Cyclic Dienes[a]



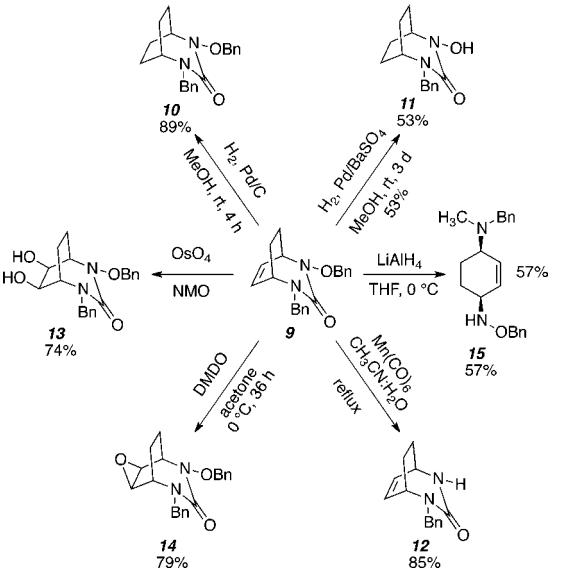
entry	diene	product	yield[b]
1			91% (1:2, r.r.)
2			69% (1:1.2, r.r.)
3			92% (1:1, r.r.)

[a] Conditions: *N*-Chlorourea in CH_3CN was added to a solution of the diene [5 equiv (condition A) or 1.1 equiv (condition B)] and TFP-Na (2.0 equiv) in TFP (0.25 M). [b] Isolated yield of both regioisomers of the cycloadducts **7** and **8**.

remained high with a variety of substituents, including a free alcohol (Table 2, entry 2) and a halide (Table 2, entry 3).

1,4-Diamino moieties are widely represented in a variety of biologically active molecules (Figure 1).[3] The substrates derived from our cycloaddition can serve as useful building blocks for the synthesis of these targets. As an example of this versatility, we treated the [3.2.2] diaza-bicyclononene **9** under a variety of conditions (Scheme 2). Products of these

Scheme 2. Examples of Selective Transformations of the [3.2.2]-Diazabicyclononene **9**



reactions provide useful scaffolds for the synthesis of cyclohexane diamines, such as those found in the fortimicin type antibiotics. Hydrogenation of the alkene could be completed to provide **10** without cleavage of either of the benzyl groups or the N−O bond. Under more strenuous hydrogenation conditions, the *O*-benzyl and *N*-benzyl group were cleaved to provide the hydroxamic acid **11** in good yield. The N−O bond could be chemoselectively reduced using $Mo(CO)_6$ in the presence of the *N*-Bn and alkene to provide **12** in good yield. Oxidation of the alkene to the diol **13** or the epoxide **14** was found to be diastereoselective for the *convex*-face of the diaza-[3.2.2] bicycloadduct. Reductive ring opening of the urea **9** using $LiAlH_4$ provided the *N*-methyl diamine **15** in good yield (ca. 3:1 r.r. based upon crude ^1H NMR analysis). Diaza-allylic cations, generated by the heterolysis of *N*-chloro ureas, reacted with cyclic dienes to provide cyclic urea products in good to excellent yields in a single step. Current efforts are directed toward understanding the mechanism of this transformation, developing new reactions of diaza-allylic cations, and applying this reaction toward the synthesis of various target molecules.

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Supporting Information Available. Experimental procedures, tabulated characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds are provided in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.