Tandem Inter [4 + 2]/Intra [3 + 2] Cycloadditions. 6. The Bridged Mode†

Scott E. Denmark,* Andreas Stolle, Julie A. Dixon, and Vito Guagnano

Roger Adams Laboratory, Department of Chemistry University of Illinois, Urbana, Illinois 61801

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Tandem pericylic reactions represent a powerful strategy for the construction of complex, polycyclic compounds.[1] In recent years, the tandem [4 + 2]/[3 + 2] chemistry of nitroalkenes and nitronates has been developed in these laboratories as a general approach to functionalized pyrrolidine-containing structures.[2] Within the subclass of inter [4 + 2]/intra [3 + 2] cycloadditions, we have documented the fused mode (β-tether) and spiro mode (α-tether) constructions, Scheme 1. Both of these families are extremely versatile with regard to (1) dienophile, (2) dipolarophile, and (3) length of tether. Moreover, they are highly stereoselective processes and are amenable to asymmetric modification by the use of chiral vinyl ethers.[2b,c] Finally, the nitroso acetals are easily transformed into polycyclic, α-hydroxy pyrrolidinones by hydrogenolysis.

We have now developed a fundamentally new construction called the *bridged mode*, which arises from dipolarophile attachment to the dienophile, Scheme 2. The regiochemical course of the intermolecular [4 + 2] process will determine if the dipolarophile is attached to C(5) or C(6) (shown) of the nitronate. The intramolecular [3 + 2] stage then creates an unusual, bridged tricyclic nitroso acetal which, upon hydrogenolysis, would lead to heavily substituted cyclohexane derivatives. In this communication, we disclose the successful realization of the bridged mode construction and demonstrate the *highly stereoselective synthesis of polysubstituted aminocyclohexanes in three steps from simple nitroalkenes and 1,4-dienes.*

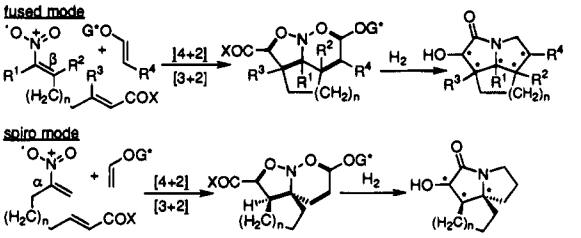
For orienting experiments, we selected (*E*)-2-methyl-2-nitrostyrene (**1a**)[3] as the test nitroalkene and 3,3-dimethyl-1,4-pentadiene[4] (**2a**) as the dienophile/dipolarophile. In no previous study on tandem cycloadditions has a simple vinyl group been successfully employed as a dienophile, though examples of unactivated vinyl dipolarophiles are on record.[5] The preferred protocol utilized $SnCl_4$ as the Lewis acid[6] in a ratio of 1.0/2.0/1.7 for **1a**/**2a**/$SnCl_4$ in CH_2Cl_2 at −15 °C for 36−48 h, Table 1. The stable, crystalline nitronate **3aa** could be isolated in 68% yield as a single stereoisomer. On the basis of previous intermolecular [4 + 2] cycloadditions with simple alkenes and $SnCl_4$,[7] we suspected that **3aa** arose from a preferred exo mode cycloaddition. This was subsequently confirmed by ^1H NMR correlation to a compound whose structure was unambiguously established by X-ray analysis.

Since **3aa** was a stable compound, elevated temperatures were clearly needed to effect the [3 + 2] cycloaddition. We were delighted to find that **3aa** *was cleanly converted to* ***4aa*** *by heating a dilute toluene solution at reflux for 3 h.* The isolation of **4aa** in 79% yield is remarkable testimony to the stability of this strained nitroso acetal. That **4aa** possessed the bridged tricyclic structure shown and not a [3 + 2] regioisomer was easily established by 2D NMR spectroscopy.

The critical unmasking transformation in all of these tandem cycloadditions is a hydrogenolysis (Raney nickel/MeOH/1 atm/room temperature) which should afford a highly polar amino diol. Isolation of the product is facilitated by acetylation after removal of catalyst and methanol to afford the triacetate **5aa** in 59% yield as a single stereoisomer. The full structure of **5aa** was confirmed by correlation (vide infra).

The initial reason for selecting **2a** was to prevent isomerization to a 1,3-diene in the presence of $SnCl_4$. This concern was unfounded as 1,4-pentadiene (**2b**) was shown to be a superior partner in this transformation (Table 1, entry 2). The oily, red nitronate **3ab** was formed in 91% yield using 5 equiv of **2b** at 0 °C. The [3 + 2] cycloaddition and subsequent hydrogenolysis/acetylation proceeded analogously but in higher yield than in the prior example. The full stereostructure of **5ab** was established by X-ray crystallographic analysis which, in turn, confirms the basic structures of **3a** and **4**. In particular, the cis relationship between the phenyl and acetoxy groups confirms the exo mode [4 + 2] cycloaddition of **1** and **2**. The generality of this sequence was also demonstrated by the reactions of other substituted nitroalkenes **1b** and **1c** (entries 3 and 4). The overall yields are comparable, though a slight erosion in the [4 + 2]

Scheme 1



Scheme 2

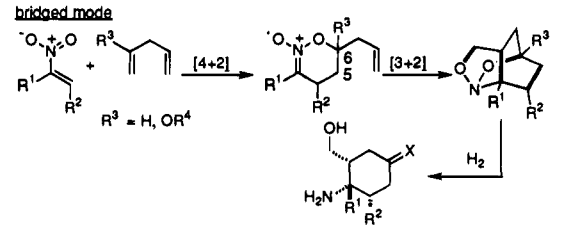
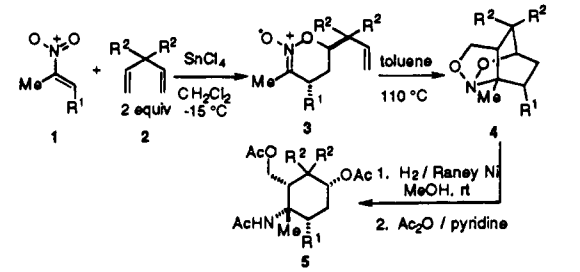


Table 1. Yields of Intermediates in Tandem [4 + 2]/[3 + 2] Cycloadditions[a]



entry	1 (R^1)	2 (R^2)	3 (yield, %)	4 (yield, %)	5 (yield, %)
1	**1a** (Ph)	**2a** (Me)	**3aa** (68)	**4aa** (79)	**5aa** (59)
2	**1a** (Ph)	**2b** (H)	**3ab** (91)[b]	**4ab** (84)	**5ab** (78)
3	**1b** (c-Hex)	**2b** (H)	**3bb** (62)[b]	**4bb** (100)	**5bb** (74)
4	**1c** (*n*-Pent)	**2b** (H)	**3cb** (55)[b]	**4cb** (100)	**5cb** (67)

[a] Yields of analytically pure material. [b] Chromatographically homogeneous, nondistillable oil.

† For part 5, see ref 2b.

(1) For recent reviews, see: (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Ziegler, F. E. In *Comprehensive Organic Synthesis, Combining C-C π-Bonds*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.3. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131.

(2) (a) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1994**, *59*, 4576. (b) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859. (c) Denmark, S. E.; Senanayake, C. B. W.; Ho, G.-D. *Tetrahedron* **1990**, *46*, 4857. (d) Denmark, S. E.; Moon, Y.-C.; Senanayake, C. B. W. *J. Am. Chem. Soc.* **1990**, *112*, 311. (e) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853. (f) Denmark, S. E.; Schnute, M. E.; Thorarensen, A.; Middleton, D. S.; Stolle, A. *Pure Appl. Chem.* **1994**, *66*, 2041.

(3) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912.

(4) Eilbracht, P.; Acker, M.; Trotzauer, W. *Chem. Ber.* **1983**, *116*, 238.

(5) Senanayake, C. B. W. Ph.D. Thesis, University of Illinois, Urbana, 1991.

(6) Other Lewis acids examined were BF_3·OEt_2, $TiCl_4$, and $AlCl_3$.

(7) (a) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971. (b) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373.

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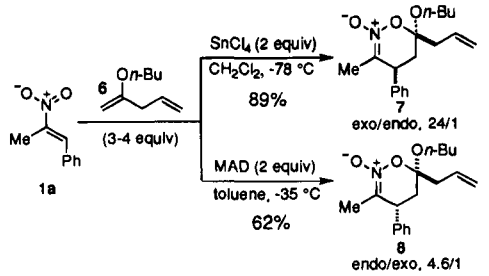
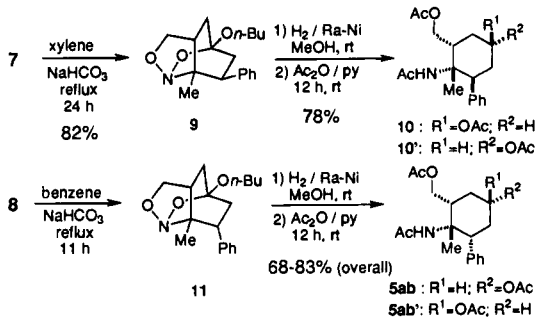
Scheme 3



Scheme 4



cycloaddition rate and selectivity was noted.[8] Interestingly, the [3 + 2] cycloadditions of **3bb** and **3cb** were faster than **3ab**.[9]

While the products **5** of this sequence are formed with high stereoselectivity, there is no obvious opportunity for absolute stereocontrol. In both fused and spiro mode cycloadditions, chiral vinyl ethers served admirably as the carriers of chiral modifier groups.[2b,f] Thus, to show the potential for incorporating stereocontrol elements in this variant, simple enol ether **6**[10] was first tested as a dienophile/dipolarophile. Since the [4 + 2] cycloaddition is an inverse electron demand process, it was certain that the enol ether would function as the dienophile. We were pleased to find that both $SnCl_4$ and MAD[11] promoted the cycloaddition to afford **7** and **8**, respectively, with complementary selectivities, Scheme 3.[12] *These nitronates represent the first examples of C(6)-disubstituted nitronates, and their stability to purification and isolation is noteworthy.*

Both **7** and **8** underwent [3 + 2] cycloaddition at elevated temperatures, though extensive optimization of addition rate, time, and temperature was necessary, Scheme 4. The rates of cycloaddition for the two diastereomers were quite different; whereas **8** was consumed within 11 h in refluxing benzene, **7** required 24 h in refluxing xylene. This difference is easily understood in terms of the steric interactions of the phenyl and methyl groups in the transition state leading to **9**. The product **9** and **11** *are extremely acid sensitive, and it was critical to have solid $NaHCO_3$ present in the reaction vessel* as well as for any manipulations of the isolated nitroso acetals.[13] Hydrogenation of the nitroso acetals proceeded readily, but even at 1 atm the products (after acetylation) were not the expected ketones but rather a mixture of epimeric triacetates (**10/10'**, 1/1.6) which arose from unselective reduction of the ketone. In the case of nitroso acetal **11**, the minor triacetate (**5ab/5ab'**, 1/1.8) was found to be identical in all respects to **5ab**, the product triacetate from the cycloaddition of 1,4-pentadiene. Since the stereostructure of **5ab** is assured by X-ray analysis, the structures of **8** and **11** can be deduced as arising from the endo (butyloxy) [4 + 2] pathway. The stereostructures of **7**, **9**, and **10** follow by analogy.[14]

(8) Observed exo/endo ratios: **3bb**, 90/10; **3cb**, 96/4 (from ^{1}H NMR).

(9) After 14 h at room temperature 5−10% of **4bb** and **4cb** was detected in the NMR solutions of **3bb** and **3cb**.

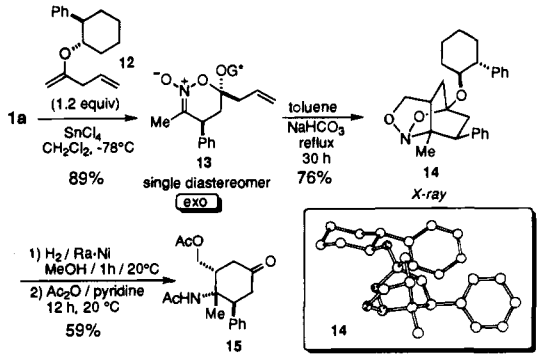
(10) This compound was prepared by modification of the procedure for the methoxy analog: Santiago, R.; Soderquist, J. A. *J. Org. Chem.* **1992**, *57*, 5844. See supplementary material.

(11) Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide). Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

(12) Post facto epimerization of either **7** or **8** has not been ruled out.

(13) Other bases were less satisfactory: $CaCO_3$, $CsHCO_3$, Cs_2CO_3, 2,6-lutidine.

Scheme 5



The ability to control the absolute stereochemical course of the bridged-mode cycloaddition for the construction of enantiomerically enriched aminocyclohexanones (Scheme 2, X=O) requires the use of chiral 2-alkoxy 1,4-dienes as the dienophile/dipolarophile components. Foregoing studies in these laboratories have successfully employed chiral vinyl or propenyl ethers although no α-substituted enol ethers have been examined. We selected (±)-**12** to assay the enantioface selectivity of a chiral 2-alkoxy 1,4-diene. Preparation of (±)-**12** was readily accomplished by the allylcupration[15] of the chiral acetylenic ether.[2b]

As in the previous cases, considerable optimization was required, but ultimately the tandem process became extremely high yielding and selective, Scheme 5. Tin tetrachloride was found to be the Lewis acid of choice, and as little as 1.2 equiv of (±)-**12** could be used for complete consumption of **1a**. Under these conditions nitronate **13** (arising from an exo cycloaddition, vide infra) could be obtained as a *single diastereomer* (^{1}H NMR analysis) in 89% yield. The intramolecular [3 + 2] cycloaddition required heating in refluxing toluene in the presence of $NaHCO_3$ to afford the nitroso acetal **14** quantitatively, again as a single stereoisomer.[16] The full stereostructure of **14** from X-ray crystallographic analysis confirmed the original assignment of **13** as having arisen from an exo [4 + 2] cycloaddition and also established the sense of asymmetric induction from the chiral auxiliary. Interestingly, the sense of induction is opposite to that previously observed in that the vinyl ether reacted via an s-cis conformation.[2b] The unmasking of **14** could be stopped at the ketone stage by hydrogenation (Raney Ni/1 atm) for only 1 h, followed by acetylation to afford **15** in 59% yield (unoptimized) along with an 85% recovery of *trans*-2-phenylcyclohexyl acetate.

In summary we have documented the feasibility of a bridged-mode variant of the tandem [4 + 2]/[3 + 2]cycloaddition. We have shown that unactivated 1,4-dienes and 2-alkoxy 1,4-dienes participate in the process, affording nitronates and nitroso acetals in good to excellent yields and selectivities. Hydrogenolysis of these nitroso acetals reveals highly functionalized cyclohexane derivatives. Extension of the method to incorporate divinyl ethers and heterosubstituted nitroalkenes as well as application to synthesis is in progress.

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Supplementary Material Available: General and experimental procedures as well as complete ^{1}H NMR, ^{13}C NMR, IR, MS, and microanalytical data for all characterized compounds along with a tabular listing of the fractional coordinates for **5ab** and **14** (41 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(14) The assignment of configuration of the acetoxy group in **10** and **10'** was by analysis of ^{1}H NMR coupling patterns. We thank Professor Peter Petillo for assistance.

(15) Wijkens, P.; Vermeer, P. *J. Organomet. Chem.* **1986**, *301*, 247.

(16) In line with earlier studies, both **13** and **14** were considerably more stable than the *n*-butyloxy analogs **7** and **9**.