

Novel 1,4-Benzodiazepines from Acylnitroso-Derived Hetero-Diels–Alder Cycloadducts

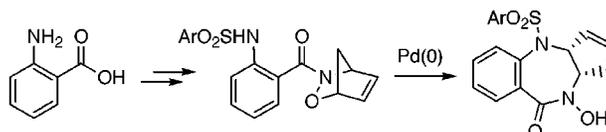
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Received November 12, 2001

ABSTRACT



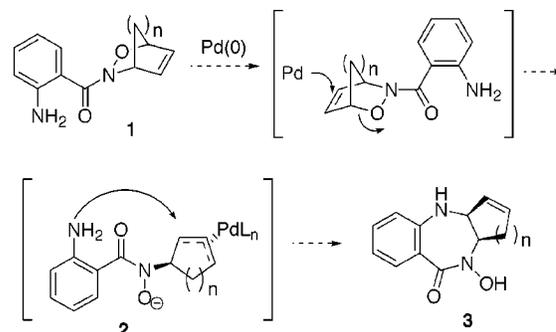
*M*⁴-Hydroxy-1,4-benzodiazepines were synthesized in a single step from synthetically versatile acylnitroso-derived hetero-Diels–Alder cycloadducts. The efficiency of this transformation was found to be dependent on the NH p*K*_a of the cycloadduct sulfonamide.

Compounds containing the 1,4-benzodiazepine core make up an important class of “privileged” structures with a wide range of biological activities and therapeutic uses. In addition to their well-known anxiolytic, anticonvulsant, sedative, and muscle relaxant activities found in therapeutics such as Valium,¹ 1,4-benzodiazepines also demonstrate activities as antibiotics,^{2–4} antiulcer agents,⁵ anti-HIV agents,^{6,7} and ras farnesyltransferase inhibitors.^{8,9} Herein, we wish to report a novel synthetic approach to the important 1,4-benzodiazepine core utilizing synthetically versatile acylnitroso-derived hetero-Diels–Alder cycloadducts.

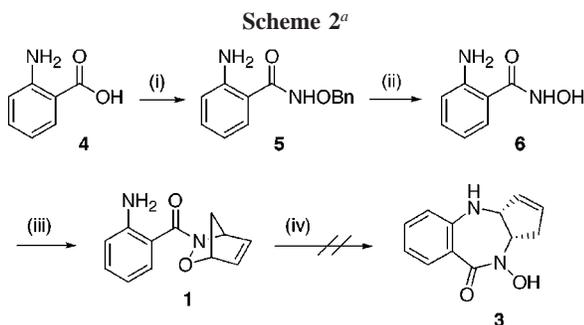
Acylnitroso-derived hetero-Diels–Alder cycloadducts have been shown to be valuable synthetic intermediates in the synthesis of natural products,^{10–12} carbocyclic nucleosides,^{13,14} and other biologically important molecules.¹⁵ We envisioned using an appropriately functionalized cycloadduct to arrive at the 1,4-benzodiazepine core in a *single step*. Treatment of anthranilic acid based cycloadduct **1** with palladium(0) was anticipated to induce a cycloadduct ring opening,^{15–18} followed by an intramolecular nucleophilic attack on the palladium π -allyl complex (**2**) to form the 1,4-benzodiazepine core (**3**) (Scheme 1).

- (1) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1.
- (2) Leimgruber, W.; Stefanovic, V.; Schenker, F.; Karr, A.; Berger, J. *J. Am. Chem. Soc.* **1965**, *87*, 5791.
- (3) Leimgruber, W.; Batcho, A. D.; Schenker, F. *J. Am. Chem. Soc.* **1965**, *87*, 5793.
- (4) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.
- (5) Eberlein, W.; Schmidt, G.; Reuter, A.; Kutter, E. *Arzneim.-Forsch.* **1977**, *27*, 356.
- (6) Kukla, M. J.; Breslin, H. J.; Diamond, C. J.; Grous, P. P.; Ho, C. Y.; Miranda, M.; Rodgers, J. D.; Sherrill, R. G.; De Clercq, E.; Pauwels, R.; Andries, K.; Moens, L. J.; Janssen, M. A. C.; Janssen, P. A. J. *J. Med. Chem.* **1991**, *34*, 3187.
- (7) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97.
- (8) James, G. L.; Goldstein, J. L.; Brown, M. S.; Rawson, T. E.; Somers, T. C.; McDowell, R. S.; Crowley, C. W.; Lucas, B. K.; Levinson, A. D.; Marsters, J. C. *Science* **1993**, *260*, 1937.
- (9) Ding, C. Z.; Batorsky, R.; Bhide, R.; Chao, H. J.; Cho, Y.; Chong, S.; Gullo-Brown, J.; Guo, P.; Kim, S. H.; Lee, F.; Leftheris, K.; Miller, A.; Mitt, T.; Patel, M.; Penhallow, B. A.; Ricca, C.; Rose, W. C.; Schmidt, R.; Slusarchyk, W. A.; Vite, G.; Yan, N.; Manne, V.; Hunt, J. T. *J. Med. Chem.* **1999**, *42*, 5241.

Scheme 1



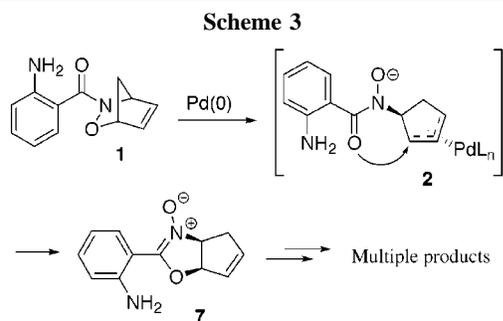
Construction of the appropriately functionalized cycloadduct (**1**) began with a 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) mediated coupling of anthranilic acid (**4**) and *O*-benzyl hydroxylamine (Scheme 2). The desired *O*-benzyl hydroxamate **5** was obtained in



^a Reagents: (i) NH_2OBn , EDC, CH_2Cl_2 , 71%; (ii) H_2 , Pd/C, MeOH, 99%; (iii) cyclopentadiene, NaIO_4 , MeOH, H_2O , 58%; (iv) $\text{Pd}(\text{PPh}_3)_4$, THF.

71% yield without the use of any protecting groups on the anthranilic acid nitrogen. Removal of the benzyl group under hydrogenolysis conditions gave a 99% yield of hydroxamic acid **6**. The hydroxamic acid was oxidized to the transient nitroso species in the presence of cyclopentadiene to give anthranilic acid based cycloadduct **1** in 58% yield. Disappointingly, treatment of cycloadduct **1** with palladium(0) did not provide the desired benzodiazepine (**3**). Instead, a complex mixture of products was observed.

The inability to induce benzodiazepine formation was thought to be due, at least in part, to the competitive nucleophilic attack on the π -allyl complex (**2**) by the hydroxamate carbonyl oxygen (Scheme 3). This would lead



to nitronium **7**, which in the presence of various olefins in the reaction mixture could undergo further reaction to form the observed complex mixture of products.

(10) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.

(11) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089.

(12) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811.

(13) Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602.

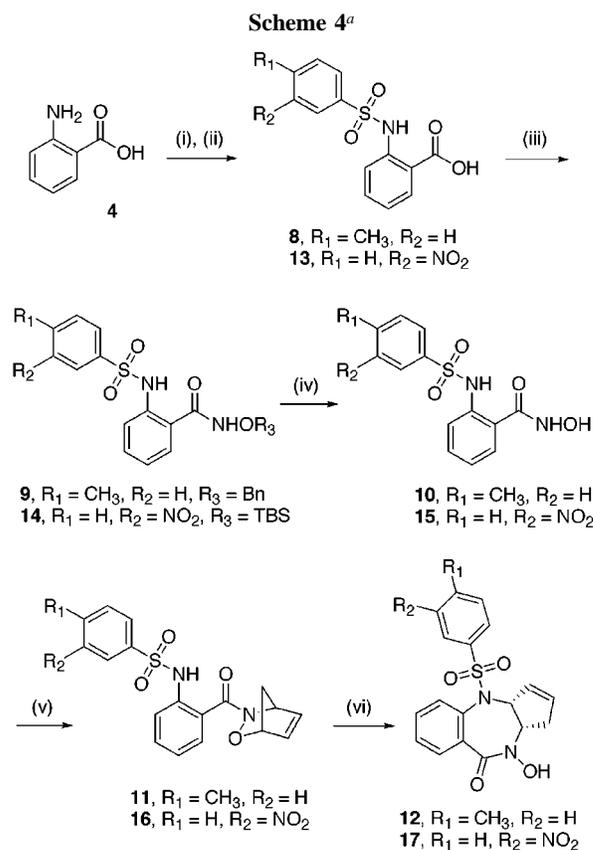
(14) Zhang, D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 755.

(15) Surman, M. D.; Miller, M. J. *Org. Lett.* **2001**, *3*, 519.

(16) Mulvihill, M. J.; Surman, M. D.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 4874.

To overcome this competitive nucleophile problem, we envisioned altering the $\text{p}K_a$ of the anthranilate NH to facilitate a proton transfer from the amine to the hydroxamate at the π -allyl complex (**2**) stage. This would increase the nucleophilicity of the anthranilate nitrogen and hopefully lead to benzodiazepine formation. As a way of lowering the NH $\text{p}K_a$, we envisioned replacing the amine with a sulfonamide.

Thus, *N*-tosyl cycloadduct **11** was chosen as a second generation test compound to be used in the pursuit of benzodiazepine formation. Cycloadduct **11** was synthesized, once again, from anthranilic acid (**4**). The tosyl group was introduced by reacting **4** with *p*-toluenesulfonyl chloride and sodium carbonate, to give *N*-tosyl anthranilic acid **8** in 69% yield (Scheme 4, A). An EDC coupling of acid **8** and



^a Reagents: **A** (i) TsCl , Na_2CO_3 , H_2O , Δ ; (ii) HCl , 69% (two steps); (iii) NH_2OBn , EDC, CH_2Cl_2 , 81%; (iv) H_2 , Pd/C, MeOH, 99%; (v) cyclopentadiene, NaIO_4 , MeOH, H_2O , 79%; (vi) $\text{Pd}(\text{PPh}_3)_4$, THF, Δ , 20%. **B** (i) 3-nitrobenzenesulfonyl chloride, Na_2CO_3 , H_2O , Δ ; (ii) HCl , 64% (two steps); (iii) NH_2OTBS , EDC, CH_2Cl_2 ; (iv) 1 M HCl , MeOH; (v) cyclopentadiene, NaIO_4 , MeOH, H_2O , 81% (three steps); (vi) $\text{Pd}(\text{PPh}_3)_4$, THF, Δ , 38%.

O-benzyl hydroxylamine provided *O*-benzyl hydroxamate **9** in 81% yield. Removal of the benzyl group under hydrogenolysis conditions gave hydroxamic acid **10** in 99% yield. Oxidation of **10** in the presence of cyclopentadiene induced

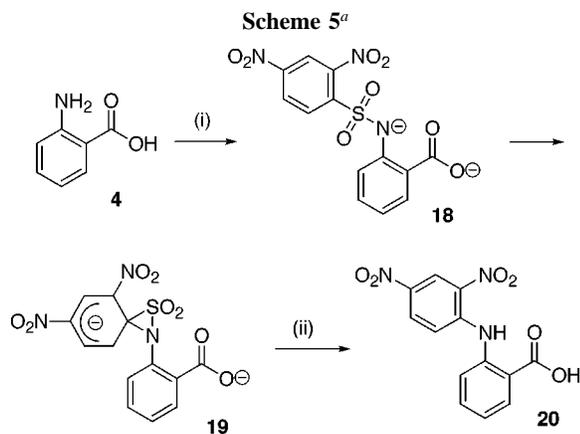
(17) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1043.

(18) Cowart, M.; Bennett, M. J.; Kerwin, J. F., Jr. *J. Org. Chem.* **1999**, *64*, 2240.

the acylnitroso hetero-Diels–Alder reaction to give a 79% yield of the desired *N*-tosyl cycloadduct **11**. Encouragingly, treatment of cycloadduct **11** with palladium(0) provided the targeted benzodiazepine **12**. While the yield was quite modest (20%), the concept of lowering the pK_a of the nucleophile to induce benzodiazepine formation had been demonstrated.

To increase the yield of benzodiazepine formation, the pK_a was lowered further by incorporating a nitro group onto the sulfonamide. Once again, starting from anthranilic acid (**4**), the 3-nitrobenzenesulfonamide **13** was produced in 64% yield (Scheme 4, **B**). Coupling of acid **13** with *O*-*tert*-butyldimethylsilyl hydroxylamine,¹⁹ followed by removal of the silyl protecting group, provided hydroxamic acid **15**. Oxidation of the hydroxamic acid in the presence of cyclopentadiene gave the desired cycloadduct **16** in 81% yield from acid **13**. Treatment of cycloadduct **16** with palladium(0) provided benzodiazepine **17** in 38% yield. Thus, by lowering the pK_a of the sulfonamide through the inclusion of a nitro group, the yield of benzodiazepine formation nearly doubled.

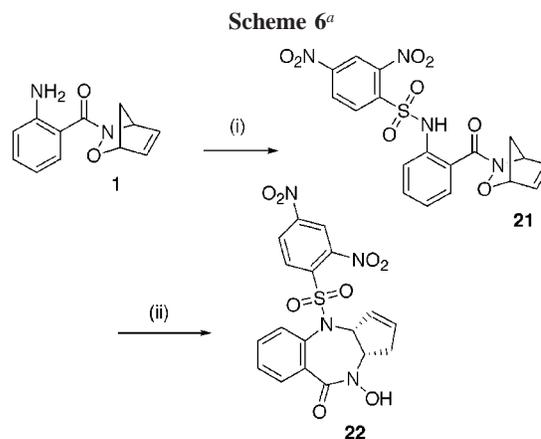
Continuing the trend of lowering the sulfonamide pK_a , 2,4-dinitrobenzenesulfonamide cycloadduct **21** was targeted. Initially, an attempt was made to construct cycloadduct **21** from anthranilic acid (**4**). Treatment of anthranilic acid (**4**) with 2,4-dinitrobenzenesulfonyl chloride and sodium carbonate did not give the desired sulfonamide, however. Instead, 2,4-dinitroaniline **20** was obtained, presumably through the intramolecular Meisenheimer complex **19** (Scheme 5).²⁰



^a Reagents: (i) 2,4-dinitrobenzenesulfonyl chloride, Na_2CO_3 , H_2O , Δ ; (ii) HCl .

Attempts to modify the reaction conditions to provide the desired 2,4-dinitrobenzenesulfonamide were unsuccessful, so an alternative synthetic approach was taken.

The reactivity of the 2,4-dinitrobenzenesulfonamide suggested a late stage introduction of this group would be prudent. Therefore, cycloadduct **21** was obtained through the treatment of cycloadduct **1** with 2,4-dinitrobenzenesulfonyl chloride and pyridine (Scheme 6). When cycloadduct **21** was



^a Reagents: (i) 2,4-dinitrobenzenesulfonyl chloride, pyridine, CH_2Cl_2 , 56%; (ii) $\text{Pd}(\text{PPh}_3)_4$, THF, Δ , 56%.

exposed to palladium(0), a gratifying 56% yield of the desired benzodiazepine **22** was obtained. The structure of **22** was confirmed by analysis of the X-ray crystal structure (see Supporting Information). The increased yield of benzodiazepine **22** demonstrated a clear trend between the pK_a of the nucleophilic sulfonamide and the yield of benzodiazepine formation.

In conclusion, the biologically important 1,4-benzodiazepine template was shown to be accessible from acylnitroso hetero-Diels–Alder cycloadducts in a single synthetic transformation. Furthermore, a trend was observed between the pK_a ²¹ of the cycloadduct sulfonamide and the yield of benzodiazepine formation. As the pK_a of the sulfonamide decreased, the yield of the reaction increased. An intriguing feature of the benzodiazepines formed from the cycloadduct rearrangement is the presence of a hydroxamic acid in the benzodiazepine ring system. This presents the possibility of metal binding and so makes these benzodiazepines interesting potential substrates for and inhibitors of metalloenzymes such as the zinc containing ras farnesyltransferase.⁹ Biological testing against ras farnesyltransferase, as well as broad screen testing of the hydroxamic acid containing benzodiazepines, is currently under consideration.

Acknowledgment. We gratefully acknowledge the NIH for partial financial support of this research, the University of Notre Dame for support in the form of a J. Peter Grace fellowship, the Lizzadro Magnetic Resonance Research Center at Notre Dame for NMR facilities, Dr. W. Boggess and N. Sevova for mass spectrometry facilities, Dr. A. Beatty for X-ray crystal determination, and Maureen Metcalf for assistance with the manuscript.

Supporting Information Available: Experimental procedures and characterization data for products **1**, **5**, **8**, **9**, **11**–**13**, **16**, **17**, **21**, and **22**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL017036W

(19) West, R.; Boudjouk, P. *J. Am. Chem. Soc.* **1973**, *95*, 3987.
(20) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831.

(21) Dauphin, G.; Kergomard, A. *Bull. Soc. Chim. Fr.* **1961**, *3*, 486.