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2-BENZOYLOXYNITROETHYLENE AS A CIS-2-AMINOETHENOL EQUIVALENT

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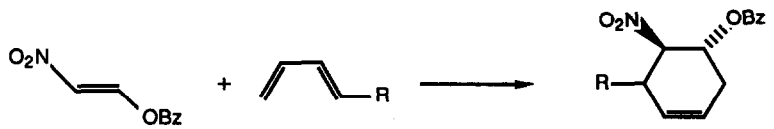
Summary: Nitroester 1 reacts readily with dienes to afford trans-nitroesters which are reduced to cis-aminoalcohols.

Many important natural products contain a 1,2-aminoalcohol subunit. Biologically significant examples include retronecine and many other pyrrolizidine alkaloids,[1] slaframine,[2] daunosamine[3] and sphingosine.[4] Several recent synthetic methods for the synthesis of 1,2 aminoalcohols have been reported,[5] attesting to the high interest in this area and also to the need for additional routes. While advances in the stereocontrolled construction of 1,3-aminoalcohols via cycloaddition reactions continue to be reported,[6] the synthesis of 1,2-aminoalcohols via concerted reactions has received much less attention. One notable advance is the use of N-acetyloxazol-2-one as a cis-2-aminoethenol equivalent.[7] We report herein a method based on the cycloaddition of dienes to 2-benzoyloxy nitroethylene 1. Additionally,



1

the adduct derived from 1 and a diene can be readily aromatized. This makes 1 an efficient synthetic equivalent of nitroacetylene. Although this compound has yet to be prepared, two synthetic equivalents are known.[8]

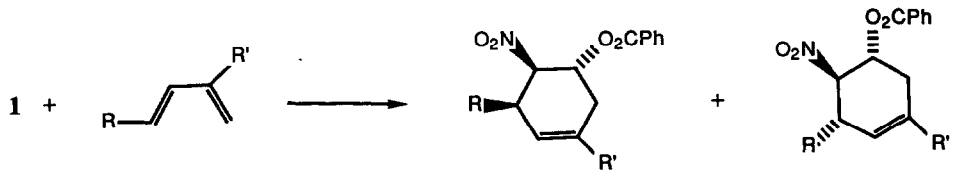
The synthesis of 1 is shown below. The reaction of nitromethane with dimethylaminodimethoxymethane at 70°C affords dimethylaminonitroethylene.[9] Substitution of the dimethylamino group with hydroxide (2 eq KOH, EtOH, 0°C) yields the anion of nitroacetaldehyde as an amorphous solid which without further purification can then be benzoylated using benzoyl chloride and 18-crown-6 in dry methylene chloride. This method is far superior to the analogous phase transfer technique. The overall yield from nitromethane

$$CH_3NO_2 \xrightarrow[\Delta]{Me_2NCH(OMe)_2} \xrightarrow{\ominus OH} \xrightarrow{PhCOCl} 1$$

to 1 (crystallized from hot hexanes) is 34%. Interestingly, a literature search indicated that no nitroalkenes bearing ar alkoxy or acyloxy group had ever been prepared.

The reaction of **1** with representative dienes readily afforded the Diels-Alder adducts **2-9**. The results of our study are listed in Table 1. The reaction of **1** with 2-acetoxyfuran at ambient temperature is significant in that furans are generally poor dienes. Examination

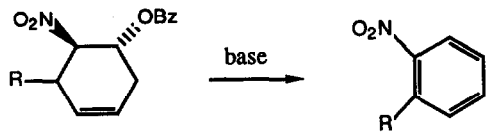
Table 1



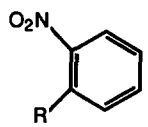
endo exo

Diene R	Diene R'	% yield	endo/exo ratio	
H	$OSiMe_3$	95	---	2
$OSiMe_3$	H	90	6:1	3
H	H	45	---	4
$tBuMe_2SiOCH_2CH_2$	H	57	1:1	5
OCH_3	$OSiMe_3$	95	3:1	6
CH_3	H	62	1:1	7
2-acetoxyfuran		75	6:1	8
2,3-dimethylbutadiene		53	---	9

of the coupling constants of the methine proton alpha to the nitro group confirmed the expected trans relationship between the nitro group and the benzoyloxy group. The reaction conditions were sufficiently mild that the loss of benzoic acid was not observed. However, in



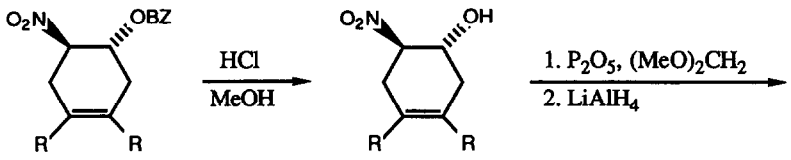
the presence of a slight excess of base the adducts rapidly aromatized to nitrobenzenes. While several bases including potassium acetate provided good yields of aromatic nitro compounds, potassium t-butoxide (1.1 eq, benzene) gave the best results. The aromatization of adducts **4**, **5** and **7** provided nitroarenes **10**, **11** and **12** in 85%, 75% and 95% yields, respectively.



10: R = H
11: R = CH_2CH_2OTBS
12: R = CH_3

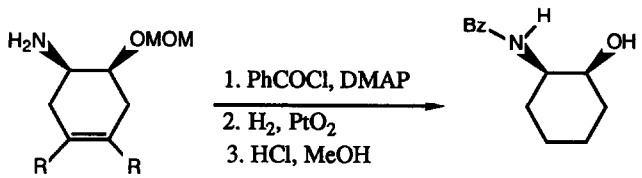
The reduction of the Diels-Alder adducts **4** and **9** was next examined. Unexpectedly, catalytic hydrogenation conditions (Pt/C or Pd/C) which were known to furnish high yields of aminocyclitols from their nitro precursors[10] afforded products in which only the double bond had been reduced. Hydrolysis of the benzoate with anhydrous HCl in hot methanol provided a 60% yield of nitroalcohol **13**. The reduction of this compound with either Pt/C or $LiAlH_4$[11] also proved futile. However, protection of **13** as a methoxymethyl ether (dimethoxymethane and P_2O_5)[12] and reduction with $LiAlH_4$ in ether at ambient temperature produced amine **14** in 70% yield from adduct **13**. Similarly, amine **16** was generated in 71% yield from **15**.

At this point we had assumed that the protected aminoalcohols **14** and **16** were trans compounds. However, decoupling of the allylic methylene groups in **16** gave a vicinal coupling constant of less than 3 Hz. A coupling constant of this magnitude is not consistent with a trans relationship unless both the amide and hydroxyl groups are axial. In order to secure the structure of **14**, the benzamide derivative **17** was prepared. The melting point of **17** was 184-185°C, in good agreement with that of the authentic cis isomer (189-190°C) but different from that of the authentic trans isomer (175-176°C).[13] As a final proof, the structure of **17** was determined by X-ray crystallography.[14] This confirmed that the benzamide and alcohol groups were cis. It seems unlikely that epimerization occurred during the debenzoylation or



4 : R = H
9 : R = CH_3

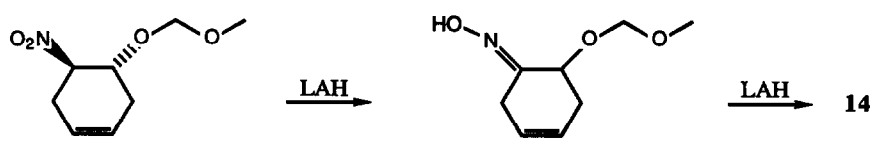
13 : R = H
15 : R = CH_3



14 : R = H
16 : R = CH_3

17

protection steps. We, therefore, postulate that the nitro group was first reduced to an oxime. The oxime could then be reduced to the cis alkoxyamine, possibly via a chelated Cram transition state.



The chemistry described above demonstrates the utility of **1** as both a 2-aminoethenol equivalent and as a nitroacetylene equivalent. Given the many biologically active natural products which contain vicinal aminoalcohols, compound **1** should become a useful complement to

existing methodology. We will continue to examine applications of 1 and related nitro compounds in organic synthesis.[15]

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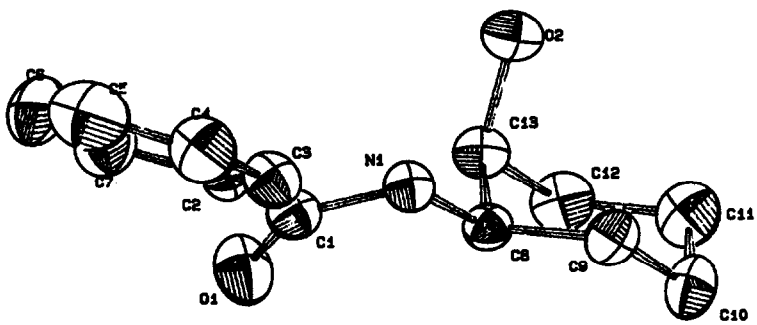

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