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Diels-Alder Reactions of *N*-Silyloxy 1-Azadienes

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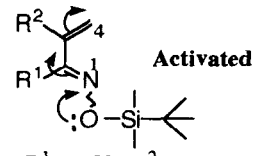
Summary: Novel 1-(*t*-butyldimethylsilyloxy)-1-aza-1,3-butadienes **1** and **2** are prepared by the reaction of *O*-(*t*-butyldimethylsilyloxy)hydroxylamine with methyl vinyl ketone and methacrolein, respectively. Azadienes **1** and **2** through sharing of oxygen nonbonding electrons are activated and thus their Diels-Alder reactions with a number of halobenzoquinones, napthoquinones and *N*-phenylmaleimide regiospecifically give low to good yields of various pyridine heterocycles.

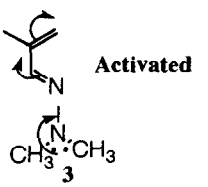
In contrast to the extensive application of the all-carbon Diels-Alder reaction in the synthesis of various organic molecules, the use of hetero Diels-Alder reactions, specifically those of 1-azadienes, have been limited.[1] This has been mainly due to the fact that compared to carbon dienes, 1-azadienes are electron poor and consequently less reactive toward common dienophiles.[1,2] To a limited extent, a number of investigators have been able to improve the yields of the 1-azadiene Diels-Alder reactions either by increasing the reactivity of the dienes through placement of appropriate substituents or by catalysis.

A number of intramolecular Diels-Alder reactions of *in situ* generated 1-azadienes such as *N*-acyl-1-aza-1,3-butadienes,[3] *o*-quinomethide imines[4] or 2-*t*-butyldimethylsilyloxy- and 2-trimethylsilyloxy-1-aza-1,3-butadienes[5] have been reported. Recently Fowler and co-workers have reported that a cyano group at the C-2 position of an *N*-substituted 1-azadienes increases its reactivity and results in relatively high yields of adducts with electron rich or electron deficient dienophiles.[6]

Ghosez has reported that placement of an electron releasing group such as nitrogen or oxygen atoms at position 1 of the 1-azadiene (e.g. **3**) increases its reactivity in a normal electron demand Diels-Alder reaction. He reported fair to good yields of adducts for the cyclization of the methacrollein dimethylhydrazone (**3**) with a number of dienophiles.[7] Avendano and co-workers have reported improved product yields of this azadiene system under ultrasound irridiation and mild conditions.[8] The same investigators have reported that an acylamino group in place of the dimethylamino function in this system slows down the reaction rate but produces similar or higher yields of adducts with quinolinetriones due to the formation of less side products.[9] The first asymmetric Diels-Alder reactions of the nitrogen activated 1-azadienes have recently been reported by Ghosez who obtained high yields of cycloadducts (76 to 98% de) when chiral hydrazones of α,β-unsaturated aldehydes were condensed with activated cyclic dienophiles.[10]



1; $R^1 = CH_3$, $R^2 = H$
2; $R^1 = H$, $R^2 = CH_3$



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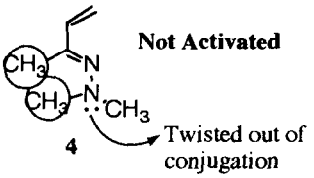
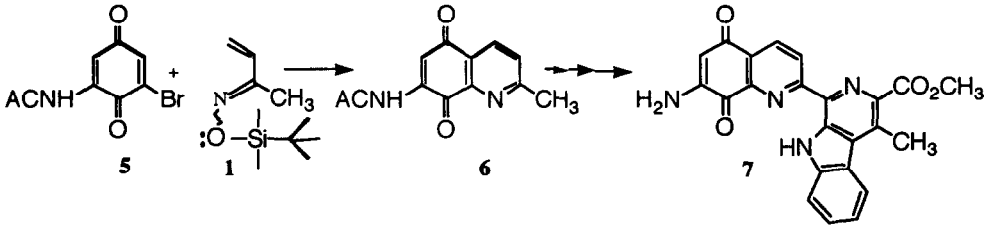


4

It should be noted that placement of an electron withdrawing group such as a sulfonyl function at position 1 of this system as reported by Boger increases the diene reactivity in an inverse electron demand Diels-Alder addition and affords good yields of adducts with electron rich dienophiles.[11] Recently we reported a concise synthesis of the antitumor agent lavendamycin methyl ester (**7**) through the Diels-Alder reaction of the novel silyloxyazadiene **1** with bromoquinone **5** (Scheme 1).[12] This is the first report of a successful intermolecular Diels-Alder reaction of a 2-methylsubstituted 1-azadiene.

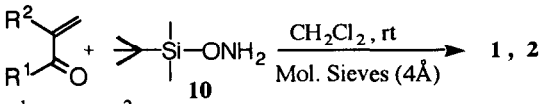
Scheme 1



We report a detailed study of the Diels-Alder reaction of this novel class of dienes (**1** and **2**) with a number of active dienophiles. These cycloaddditions offer alternate routes to the synthesis of a number of substituted pyridines, quinolinediones and azaanthraquinones. In contrast to the known azadiene **4** in which the steric interference of the methyl groups at the N and C-2 positions does not allow the conjugation of the nitrogen electron pair, silyloxyazadiene **1** is free of this steric strain and activated through sharing of its oxygen nonbonding electrons. Thus, azadiene **1** successfully undergoes the normal electron demand Diels-Alder reaction with quinone **5** to produce **6**, while diene **4** fails in the analogous reaction and gives unstable products which may be the result of nucleophilic reactions of the dimethylamino function at one or more sites of the bromoquinone system. This method allows the placement of a methyl group at the C-2 position of a pyridine ring which if desired can be converted to other functionalities as exemplified by our work in the total synthesis of lavendamycin methyl ester.[12] Silyloxyazadiene **2** is similar in chemical behavior to that of Ghosez's diene **3**. Although the Diels-Alder reaction yields of dienes **1** and **2** range from low to good, the advantages of this method are the ease of azadiene preparation, the potential and simple extension of the method to the preparation and use of other substituted silyloxyazadienes, and most importantly, its application to the synthesis of a variety of pyridines and quinolinediones, specifically those with C-2 substitution. It should be noted that quinolinediones are a well-known class of compounds with a wide spectrum of important biological activity.[13]

Azadienes **1** and **2** were prepared (Scheme 2), respectively, by treatment of methyl vinyl ketone (**8**) or methacrolein (**9**) with commercially available silyloxyhydroxylamine **10** in dry dichloromethane at room temperature in the presence of molecular sieves (4Å).[14] Removal of the molecular sieves, solvent evaporation and the purification of the products either by silica gel chromatography or vacuum distillation gave the desired dienes.[15] Diene **1** was obtained as an E/Z (7/3) mixture in 71% yield and diene **2** was obtained as an E/Z (4/1) mixture in 70% yield, and both were used as obtained in the Diels-Alder reactions. The E/Z ratios were determined by pmr and gas liquid chromatography.[16]

Scheme 2

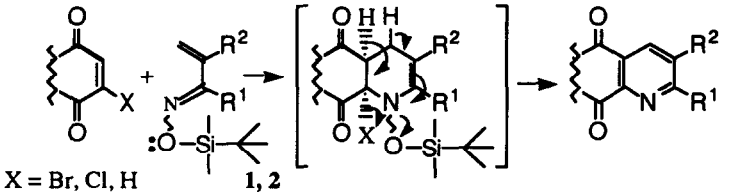


8; $R^1 = CH_3$, $R^2 = H$

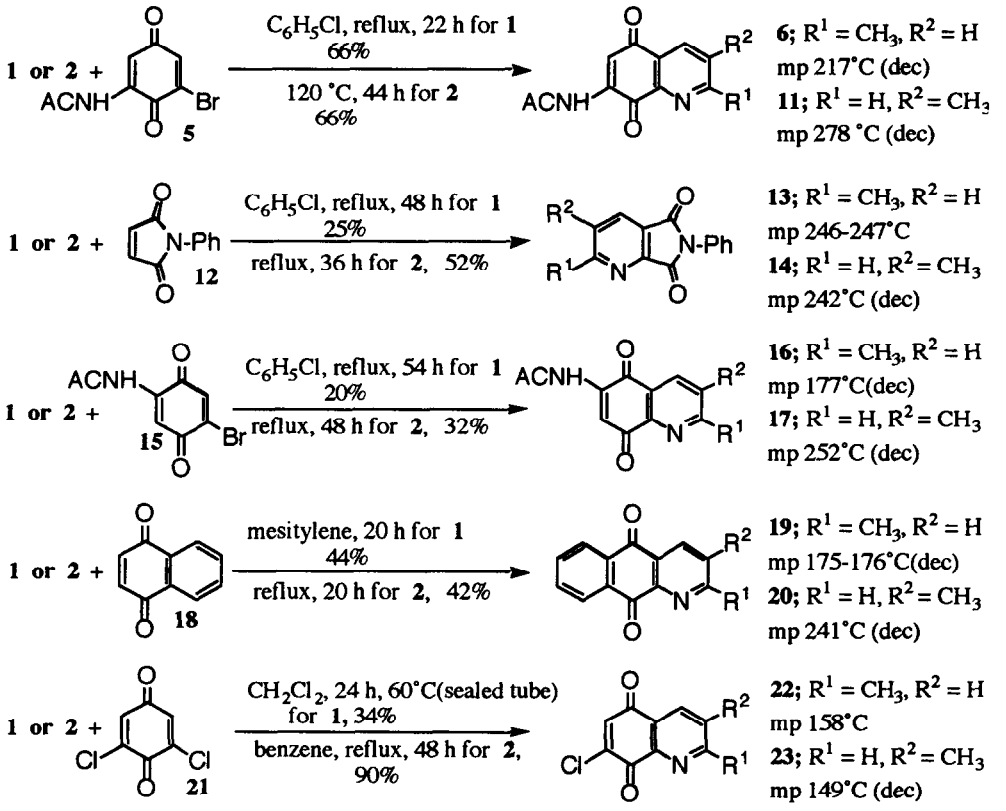
9; $R^1 = H$, $R^2 = CH_3$

Azadienes **1** and **2** were reacted with various dienophiles to produce the corresponding pyridine derivatives (Scheme 4). The cycloadditions are all regiospecific and most probably involve the intermediate shown in Scheme 3. Under the reaction conditions, this intermediate loses silylhydroxide, a molecule of hydrogen halide or hydrogen to produce the adducts.

Scheme 3



The Diels-Alder reactions were carried out in hot chlorobenzene or other solvents. The products were purified by silica gel chromatography and characterized by nmr, mass spectroscopy and/or elemental analyses. Reaction conditions, product yields, melting points and other information are given in Scheme 4.



Scheme 4. For a typical procedure see the preparation of compound **11** below. The ratios of dienophile/diene were 2/1 except for **12** (4/1). Percent yields are based on pure products isolated by silica gel chromatography. All products gave satisfactory NMR, IR and HRMS spectral data. For the preparations of dienophiles **5** and **15** see reference 17 and for **21** see reference 18.

6-Acetamido-3-Methylquinoline-5,8-dione (11): A stirred solution of azadiene **2** (127 mg, 0.64 mmol) and bromoquinone **5** (312 mg, 1.28 mmol) in 20 mL of dry chlorobenzene was heated at 120°C for 44 h under an argon atmosphere. The solvent was removed, the residue was dissolved in 15 mL of acetonitrile and then concentrated to about 3 mL. Flash chromatography of this solution using acetonitrile as the solvent gave 96 mg (66%) of the pure yellow product **11**: mp 278°C (dec); ^{1}H NMR($CDCl_3$) δ 2.30 (s, 3H), 2.52 (s, 3H), 7.90 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 8.41 (br s, 1H), 8.81 (d, J = 2.1 Hz, 1H); HRMS for $C_{12}H_{10}N_2O_3$, Calcd: 230.0691, Found: 230.0675.

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14. Molecular sieves were dried for 48h at 150° under vacuum.
15. Azadiene **2** was prepared according to the method described for **1** in ref. 12. Careful vacuum distillation of the crude product (92-94°/3.5 mm-Hg) gave 70% of **2** in an E/Z ratio of 4/1.^{1}H NMR ($CDCl_3$) (major isomer) δ 0.2 (s,6H), 0.95 (s,9H), 1.9 (s,3H), 5.2 (s,1H), 5.3 (s,1H), 7.85 (s,1H). (minor isomer) δ 0.2 (s,6H), 0.95 (s,9H), 1.9 (s,3H), 5.3 (s,1H), 5.4 (s,1H), 7.06 (s,1H). Compound **2** gave acceptable elemental analyses data.
16. Detailed nmr studies of geometric isomers of azadienes will be the subject of another report.
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