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DIASTEREOFACIAL SELECTIVITY IN DIELS-ALDER REACTIONS OF CHIRAL 1,2-DIAZA-1,3-BUTADIENES DERIVED FROM CARBOHYDRATES

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Summary: The synthesis of several 1,2-diaza-1,3-butadienes **1** derived from carbohydrates is described. The reaction of **1**, as chiral dienophiles, with 1,4-benzoquinone, 1,4-naphthoquinone, and diethyl azodicarboxylate occurs with high π-facial stereoselectivity.

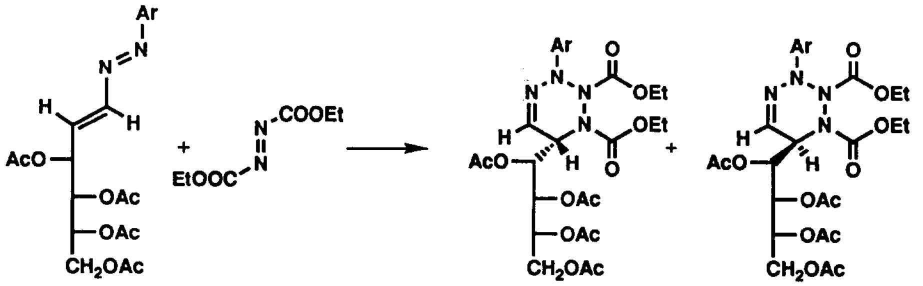
The heterodienes are useful starting materials in the synthesis of heterocyclic compounds[1]. Thus, conjugated azadienes can participate in Diels-Alder reactions as 4π-electron components[2] to provide fundamental skeletons of many important biologically active compounds as azanaphthoquinones, azaanthracyclines and azatetracyclines when quinones are used as dienophiles[3]. To the best of our knowledge, nothing is reported about this reaction with 1,2-diaza-1,3-butadienes (azoalkenes)[4].

Acyclic azoalkenes on carbohydrate templates have received very little attention in the literature[5], although have been postulated as non-isolated intermediates in some highly stereoselective dehydration and nucleophilic substitution processes on sugar hydrazones[6], osazones[7,8] and formazanes[9].

As part of our research on synthesis of optically pure heterocycles, we report here the synthesis of several (*E*,*E*)-1-aryl-4-(1',2',3',4'-tetra-O-acetyl-D-*arabino*-tetritol-1-yl)-1,2-diaza-1,3-butadienes[10] (**1**) and their [4+2] cycloadditions with 1,4-quinones and diethyl azodicarboxylate.

The reaction of D-mannose with arylhydrazones followed by acetylation-elimination (Ac_2O/py, 80°C, 15 min) gave **1a-e** as stable solids in moderate yields (~50%)[11]. The proposed (*E*)-configuration for the C3-C4 double bond was confirmed by the chemical shift of H-3 (~7.32 ppm) and H-4 (~6.75 ppm) and its $J_{3,4}$ value (~13.6 Hz)[12a,b]. The (*E*)-configuration of the N=N bond is in accord with the H-4 chemical shift[12a,13].

The Diels-Alder reaction of **1a-d** (1 mmol) with diethyl azodicarboxylate (1.1 mmol) in anhydrous benzene at room temperature gave quantitatively a diastereomeric mixture of the corresponding 1,2,3,6-tetrahydro-1,2,3,4-tetrazine derivatives **2a-d** and **3a-d**. The ratio of both diastereomers is very high[14] and they could be separated (80-90% isolated yield of **2a-d**) by flash chromatography (1:1 ether-light petroleum). We have assigned the absolute configuration *S* of the new chiral center of the major diastereomers by comparison of their circular dichroism spectra[15] with literature data[16,17].

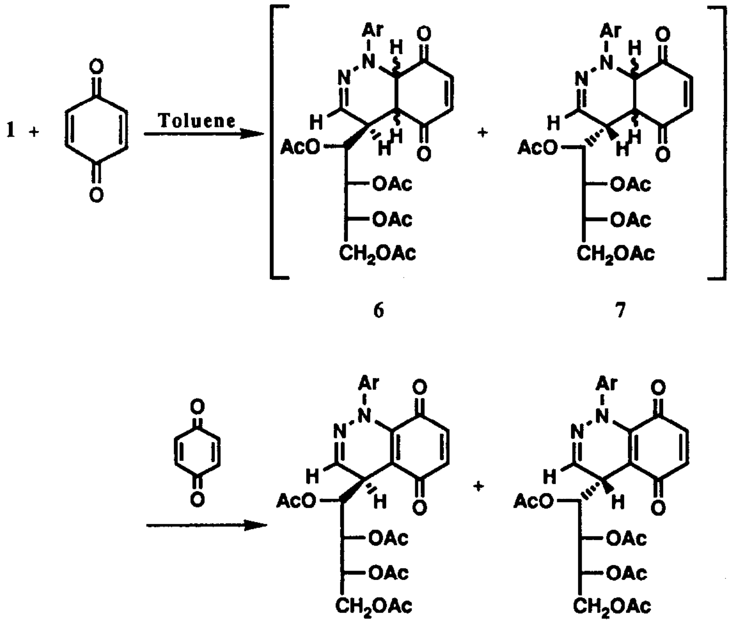


1a-e **2a-d** **3a-d**

a, Ar=C_6H_5; b, Ar=4-$CH_3OC_6H_4$; c, Ar=4-$CH_3C_6H_4$

d, Ar=4-ClC_6H_4; e, Ar=4-BrC_6H_4

On the other hand, 1,4-benzoquinone (2 mmol) reacts with **1a-d** (1 mmol) in refluxing toluene (24 h) to give the diastereomeric mixture of **4a-d** and **5a-d**. Again, a very high diastereomeric ratio was observed and the major isomers **4a-d** were isolated (20-30% yield), as described above for **2a-d**, as dark violet amorphous solids[11,20].

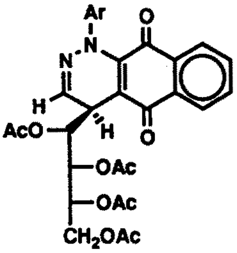


6 **7**

4a-d **5a-d**

The reaction, probably occurs *via* the non-isolated intermediates **6** and **7**, which are oxidized by the excess of quinone to give **4** and **5**, respectively.

In a similar way, the 1,4-dihydro-1,2-diazaantraquinone **8b** (20%) was prepared by reaction of **1b** with 1,4-naphthoquinone[21].



8b

In these reactions an important amount of 1,2-diaza-1,3-butadiene does not react, but the 1,4-quinone disappears completely as shown by t.l.c. analysis[22].

In conclusion, we have showed that the readily available acyclic 1,2-diaza-1,3-butadienes derived from carbohydrates react with diethyl azodicarboxylate and 1,4-quinones in high diastereofacial way. The cycloaddition reactions of **1** with other dienophiles and heterodienophiles in order to the preparation of optically active heterocycles are under progress in our laboratory.

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10. Only three compounds of this type have been reported (see ref. 5).
11. Satisfactory NMR data and mass spectra or elemental analyses were obtained for all new compounds.
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13. It has been reported that both (Z)-olefinic[12a,b] and (Z)-arylazo[12c] compounds are unstable and isomerize to the corresponding (*E,E*)-compounds.
14. For example, compounds **2d** and **3d** showed a diastereomeric ratio of 85:15 (^{1}H-NMR).
15. For example, compound **2b** showed CD (MeCN): 204 ($\Delta\varepsilon$ –26.3), 234 ($\Delta\varepsilon$ –27.3), and 272 nm ($\Delta\varepsilon$ +33.5).
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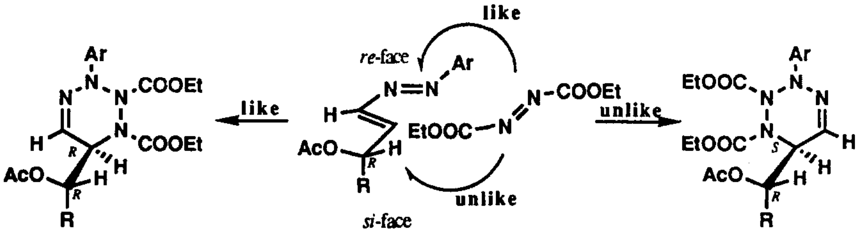
17. The *S*-configuration results from the unlike[18] attack to the *si*-face of the *s-cis*-conformer of **1**. The generation of the *S*-configuration in the new chiral center is in agreement with the Franck's results[19] for diastereofacial selectivity in Diels-Alder reaction of chiral 1,3-butadienes.



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20. Similar yields have been reported for analogous reactions, see ref. 3a.
21. The *R*-configuration for compounds **4a-d** and **8b** was tentatively assigned on the basis of a preferential like[18] attack as reported[19] for reactions of chiral 1,3-butadienes with maleic anhydride or *N*-phenylmaleimide.
22. A black and intractable solid, insoluble in most organic solvents, is also isolated in high proportion. The structure of this polymeric compound remains unknown. Studies to elucidate it are under current investigation.

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