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CONTROL OF REGIOSELECTIVITY IN THE INTRAMOLECULAR CYCLOADDITION REACTION OF AN OLEFINIC TOSYLHYDRAZONE

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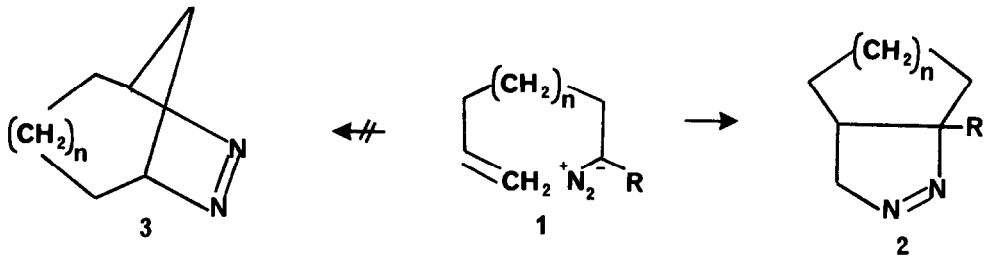
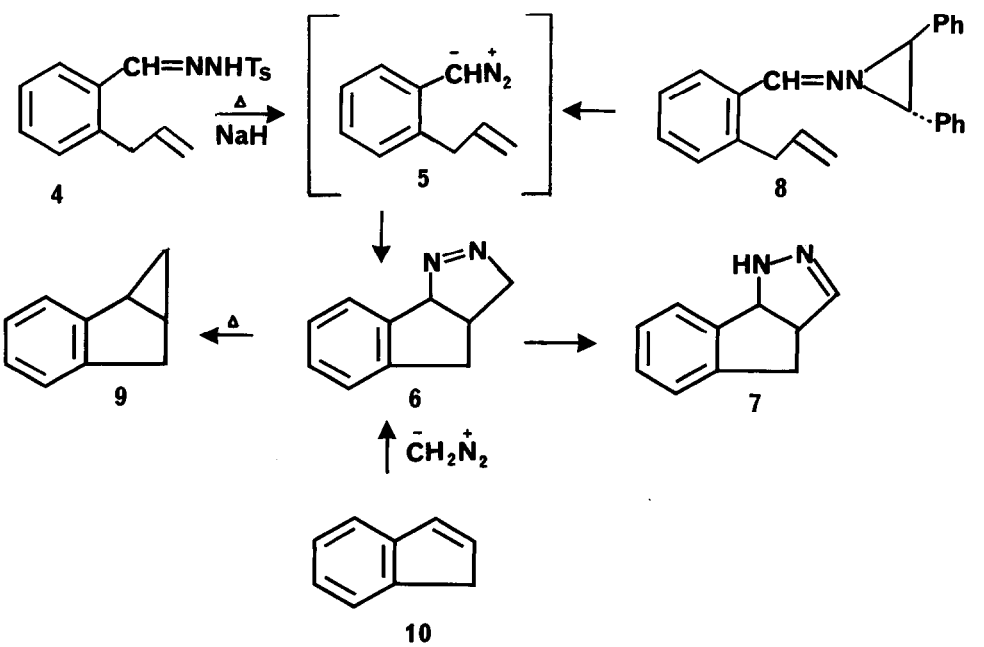
Abstract: The regioselectivity of the internal cycloaddition of o-allylbenzaldehyde N-tosylhydrazone has been found to be markedly dependent on the experimental conditions employed.

Although 1,3-dipolar cycloadditions have been successfully employed by chemists for decades[1-3], it is only within the last few years that a fundamental understanding of the reactivity, stereoselectivity and regioselectivity phenomena of the reaction has begun to emerge[4-6]. The additions of diazoalkanes to olefins are amongst the most thoroughly studied 1,3-dipolar cycloadditions[1,7]. Tosylhydrazones are commonly used as precursors to generate diazoalkanes. The cycloadditions are HO(1,3-dipole) -LU(dipolarophile) controlled[5,6]. Both conjugating and electron attracting groups accelerate reactions of dipolarophiles with diazoalkanes as compared to ethylene. With these dipolarophiles, 3-substituted Δ^1-pyrazolines are favored; a result of union of the larger diazoalkane HO coefficient on carbon with that of the larger dipolarophile LU coefficient on the unsubstituted carbon[5]. Simple diazoalkanes and alkylethylenes, on the other hand, give rise to the 4-substituted pyrazoline isomer[5,8].

In spite of the copious literature dealing with bimolecular cycloaddition reactions of diazoalkanes, intramolecular examples have received only a minimum of attention[9]. Previous workers have found that the internal dipolar cycloaddition of diazoalkenes 1 generally leads to bicyclo[n.3.0] adducts (2) rather than bicyclo[n.2.1]azoalkanes (3)[10]. Moreover, these reactions require polar or strained alkenes in order to proceed in satisfactory yield[7]. In this communication we wish to report that the regioselectivity of the intramolecular cycloaddition of an olefinic tosylhydrazone can be controlled by the experimental conditions used.

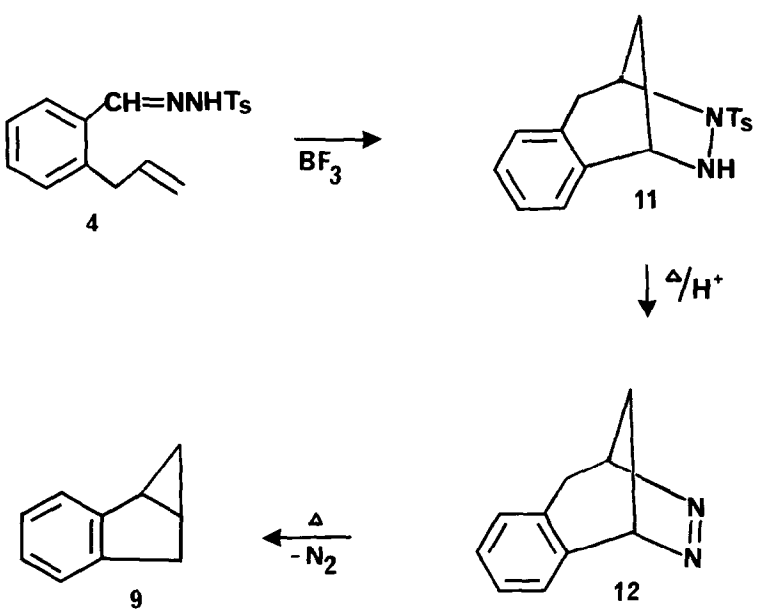


Thermolysis of the sodium salt of o-allylbenzaldehyde N-tosylhydrazone (4) at 120° gave cis-1,3a,4,8b-tetrahydroindeno[1,2-c]pyrazole (7) in high yield. Dihydropyrazole 7 is apparently formed by intramolecular dipolar cycloaddition of the initially generated diazoalkene 5 followed by a proton transfer reaction of the transient cycloadduct 6. Photolysis of the tosylhydrazone salt of 4 gave benzobicyclohexane 9, thus supporting the intermediacy of cycloadduct 6. Further support for the above sequence of reactions was obtained by thermolyzing aziridinamine 8. Eschenmoser and his coworkers[11] have used aziridinyl imines as masked diazo compounds; these have the advantage over other diazoalkane precursors, such as tosylhydrazones, that they are cleaved thermally without the introduction of an external base, and, being soluble in organic solvents, they allow homogeneous reactions to occur.



Thermolysis of 8 at 80° resulted in the isolation of 3,3a,4,8b-tetrahydroindeno[1,2-c]pyrazole 6 in 75% yield. The structure of 6 was unambiguously established by comparison with an independently synthesized sample prepared by treating indene 10 with diazomethane. In the presence of a base, structure 6 was readily converted to the isomeric 1H-dihydropyrazole 7 when heated at 100°C. Upon photolysis or thermolysis, cycloadduct 6 readily loses nitrogen to give 9.

In contrast to the above results, treatment of tosylhydrazone 4 with boron trifluoride etherate followed by silica gel chromatography gave 4,5-dihydro-1,4-methano-1H-2,3-benzodiazepine (12) as the exclusive product (97%); NMR ($CDCl_3$, 100 MHz) δ 1.92 (m 2H), 2.80-3.20 (m, 2H), 5.20 (broad s, 1H), 5.60 (broad s, 1H), 7.0-7.4 (m, 4H). Addition of Eu(fod)$_3$ to the solution resulted in the separation of the multiplet at δ 1.92 into a doublet at δ 2.84 (1H, J=12.0 Hz) and a multiplet at 3.10 (1H). The multiplet at 2.80-3.20 separated into a distinct AB pattern at 3.60 (dd, 1H, J=18.0 and 2.0 Hz) and 3.94 (d, 1H, J=18.0 Hz). Heating a sample of 12 produced benzobicyclohexane 9 in quantitative yield. Examination of the crude reaction mixture before column chromatography clearly showed the presence of 11 as an isolable itermediate (90%); NMR ($CDCl_3$, 100 MHz) δ 1.20 (m, 1H), 1.66 (d, 1H, J=10.0 Hz), 2.40 (s, 3H), 3.16 (m, 2H), 4.08 (d, 1H, J=5.0), 4.40 (m, 1H) and 6.8-7.8 (m, 8H).



The results reported here clearly show that the mode of internal cycloaddition of tosylhydrazone 4 is markedly dependent on the experimental conditions employed. The orientation observed under basic conditions can readily be accounted for on the basis of frontier orbital theory of diazoalkane cycloadditions[5]. The regioselectivity encountered under acidic conditions, on the other hand, is probably the consequence of the carbocation pathway involved in the cycloaddition. The intramolecular addition of tosylhydrazones to olefins under acidic conditions potentially provides for a versatile new type of carbon-carbon bond forming reaction which may complement the extensive work that has been done with tosylhydrazones under basic conditions[12]. Similar findings have recently been reported by Wilson and Rekers[13].

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