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Ring expansion of substituted norbornadienes for the synthesis of mono- and disubstituted 2-azabicyclo[3.2.1]octadienes

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ABSTRACT

We have studied the conversion of substituted norbornadienes into a substituted 2-azabicyclo[3.2.1]-octadiene system via reaction with toluenesulfonyl azide. We have found that both and mono- and disubstituted norbornadienes will undergo the cycloaddition/rearrangement sequence to provide the bicyclooctadiene ring system as a single regioisomer. The 2-azabicyclo[3.2.1]octane ring system can be prepared from the unsaturated 2-azabicyclo[3.2.1]octadiene ring system.

The 2-azabicyclo[3.2.1]octane ring system **1** is found in a number of natural products including nordipertenoid alkaloids such as methyllycaconitine[1–3] as well as himandrine.[4] In addition a number of nonnatural biologically active ring systems contain the 2-azabicyclo[3.2.1]octane ring system.[5,6] The development of new methods for the synthesis of this ring system is important both for natural product synthesis and the preparation of simpler analogues of these natural products. An attractive option for the synthesis of substituted derivatives of **1** would be the functionalization of the readily available *N*-phenylsulfonyl 2-azabicyclo[3.2.1]octadiene **2a**. *N*-phenylsulfonyl 2-azabicyclo[3.2.1]octadiene was first reported in 1965.[7] This unique compound was prepared by the reaction of phenylsulfonyl azide with norbornadiene (**3a**) (Fig. 1). While the yields are only moderate, the reaction is readily scalable and easy to carry out. It has been reported that the reaction proceeds through an initial dipolar cycloaddition of the azide followed by loss of nitrogen to form the fused-ring aziridine. This then undergoes a ring opening reaction to a bicyclo-[3.1.0]hexene imine. This highly strained bicyclic ring system then undegoes a Cope rearrangement to form the observed 2-azabicyclo[3.2.1]octadiene **2a**.[8]

Two options exist for the conversion of **2** into the saturated and substituted ring system **1**. The first is the chemical modification of the parent bicyclo[3.2.1]octadiene ring system. Few examples of such modifications have been reported. These modifications are largely limited to the reduction of one or both double bonds,[9–11] dihyroxylation of the 6,7-olefin[12] and cycloaddition reactions with the 6,7-olefin.[13,14]

Given the limited methods for the functionalization of **2a**, an alternate option for the synthesis of substituted systems such as **1** is the use of substituted norbornadienes **3b** in the addition/rearrangement reaction. The product of this reaction, a substituted 2-azabicyclo[3.2.3]octadiene **2b** could then be further modified via reduction, dihydroxylation, or cycloadditions to provide highly substituted derivatives of **1** (Fig. 1). This strategy has several advantages, including the relative ease with which some substituted norbornadienes can be prepared and the ability to further substitute the products of such an addition/rearrangement process. This would then produce derivatives of **1** with a much wider range of substitution and functionality. A key unknown is the regioselectivity of the cycloaddition/rearrangement process with a substituted norbornadiene.

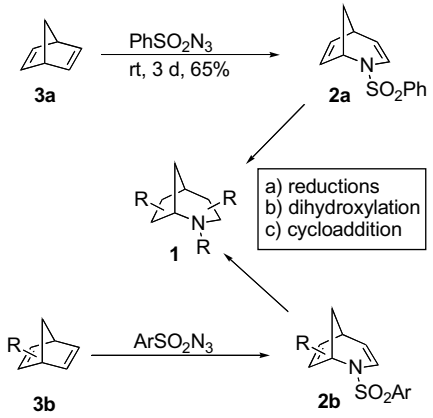

Figure 1. 2-Azabicyclo[3.2.1]octane ring system.

Given a unique substituted norbornadiene **4** (Fig. 2), the reaction with a sulfonyl azide could produce four possible products when $R^1 \neq R^2$ (or two when $R^1 = R^2$). Reaction on the opposite side of the substitution would provide regioisomeric products **5** and **6**, while reaction on the same side would provide regioisomers **7** and

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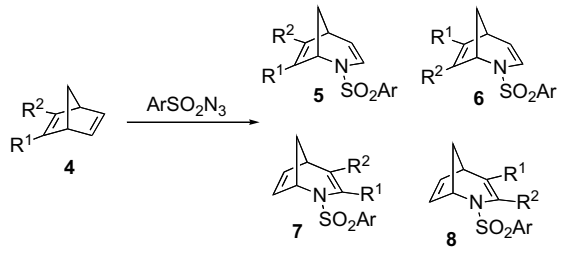


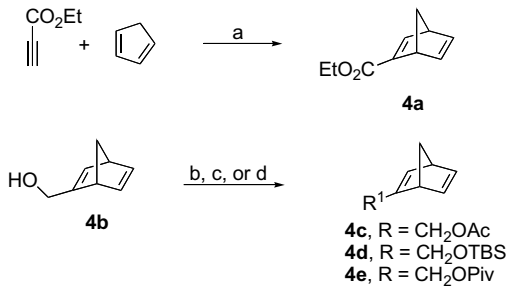
Figure 2. Possible products derived from the reaction of a substituted norbornadiene with a sulfonyl azide.

8. One report has briefly examined this reaction.[15] Treatment of a compound where $R^1 = R^2 = CN$ or $R^1 = R^2 = CO_2Me$ provides largely a single product **5**, where the addition of the phenylsulfonyl azide occurred distal to the substitution. We wished to determine if other functional groups, where $R^1 = R^2$, would provide the same level of regiocontrol. More interestingly would be an examination of the reaction of **4**, where $R^1 \neq R^2$. Such compounds would likely provide only **4** and **5** but a priori it is not obvious which of these two regioisomers will be formed.

In order to begin to address these questions several monosubstituted norbornadienes were prepared as outlined in Scheme 1. The Diels–Alder cycloaddition of ethyl propiolate with cyclopentadiene provided monosubstituted norbornadiene **4a** in 83% yield.[16] While the Diels–Alder method provides an excellent route for the synthesis of norbornadienes with electron withdrawing substituents, an alternate approach was needed for the synthesis of non-electron withdrawing substituted norbornadienes. Alcohol **4b** can be readily prepared via metallation and reaction of norbornadiene with formaldehyde.[17] The resulting alcohol was acylated or silylated to provide monosubstituted norbornadienes **4c**,[18] **4d**, and **4e**.

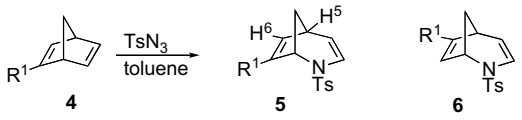
With a group of monosubstituted norbornadienes in hand, their reaction with tosyl azide was investigated (Table 1). Based on previous studies,[15] it was expected that addition would occur distal to the substitution. In concert with the original reaction conditions and in contrast to the report by Umano et al.,[15] all reactions were carried out at room temperature.[19]

The reaction of **4a** with tosyl azide resulted in only a 6% yield of an 85:15 mixture of **5a** and **6a**. This reaction provided multiple products. The reaction of the acetate provided a significantly better yield of the product in a 94:6 mixture of **5c**/**6c**. Changing the ester to a silyl ether (**4d**) lowered the yield somewhat, but dramatically improved the product ratio yielding only the 7-substituted product **5d**. Suspecting that this moderate change in regioisomer ratio might be due to the size of the group on the oxygen, the pivalate ester **4e** was prepared. The yield returned to the moderate yield observed with the acetate and retained the improved ratio of regioisomers. Clearly the substitution of these monosubstituted



Scheme 1. Reagents and conditions: (a) CH_2Cl_2, reflux, 18 h, 83%. (b) CH_2Cl_2, AcCl, pyridine, DMAP, 98%. (c) CH_2Cl_2, $Me_2tBuSiCl$, Et_3N, DMAP, 98%. (d) CH_2Cl_2, pivaloyl chloride, Et_3N, DMAP, 98%.

Table 1
Reaction of monosubstituted norbornadienes[a,b]



R^1	Yield (%)	Ratio **5**:**6**
4a, CO_2Et	6	85:15 **5a**:**6a**
4c, CH_2OAc	50	94:6, **5c**:**6c**
4d, CH_2OTBS	30	Only **5d**
4e, CH_2OPiv	50	Only **5e**

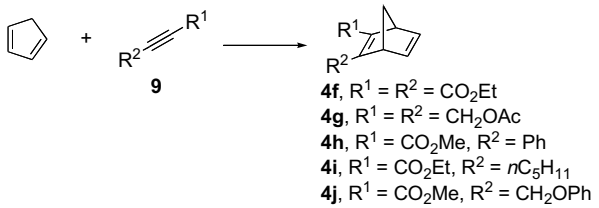
[a] When $R^2 = H$, R^2 is not shown for clarity.
[b] The regiochemistry of products **5a**–**e** was determined by the observation of coupling between H5 (δ 2.62–3.01) and H6 (δ 5.93–6.09) as determined via COSY experiments.

norbornadienes is of paramount importance. Electron withdrawing substitution provides little to no product while the substituted hydroxymethyl derivatives provided a moderate yield of a single regioisomer.

In order to investigate regioselectivity in the reaction of disubstituted norbornadienes, a series of disubstituted norbornadienes were prepared via the Diels–Alder reaction of cyclopentadiene with substituted alkynes (Scheme 2). The reaction of diethyl acetylene dicarboxylate with cyclopentadiene provided norbornadiene **4f** in 97% yield. Reaction of the diacetate of butyne diol with cyclopentadiene required microwave heating of the reaction to 220 °C in DMF and provided **4g**[20] in 50% yield.

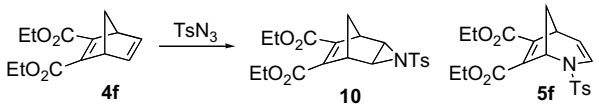
In order to prepare norbornadienes where $R^1 \neq R^2$, cyclopentadiene was heated with several substituted propiolate esters in a sealed tube at 160 °C. Norbornadiene **4h**[21] was obtained in an almost quantitative yield. Compounds **4i** and **4j** were prepared in moderate yield; however, they could not be completely purified due to contamination with ~40% of an unidentified non-polar impurity that could not be readily removed.

The ring expansion of symmetrically disubstituted norbornadiene **4f** was examined first (Scheme 3). Following the reaction conditions that worked well for norbornadiene itself as well as the monosubstituted norbornadienes provided only a 4:1 mixture of aziridine **10** and rearrangement product **5f**. Heating the reaction to 80 °C for 18 h provides the same mixture of aziridine and rearrangement product. Increasing the temperature to 110 °C (reflux-



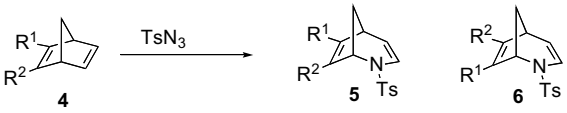
4f, $R^1 = R^2 = CO_2Et$
4g, $R^1 = R^2 = CH_2OAc$
4h, $R^1 = CO_2Me$, $R^2 = Ph$
4i, $R^1 = CO_2Et$, $R^2 = nC_5H_{11}$
4j, $R^1 = CO_2Me$, $R^2 = CH_2OPh$

Scheme 2. Reagents and conditions: **4f**, $R^1 = COOEt$, $R^2 = COOEt$, toluene, reflux, 18 h, 97%. **4g**, $R^1 = CH_2OAc$, $R^2 = CH_2OAc$, DMF, microwave, 220 °C, 2 h, 50%. **4 h**, $R^1 = Ph$, $R^2 = COOMe$, toluene, sealed tube, 160 °C, 42 h, 99%. **4i**, $R^1 = nC_5H_{11}$, $R^2 = COOEt$, toluene, sealed tube, 160 °C, 60 h, 56%*. **4j**, $R^1 = CH_2OPh$, $R^2 = COOMe$, toluene, sealed tube, 160 °C, 60 h, 56%.



Scheme 3. Time and temperatures studies on **4f**.

Table 2
Reactions of disubstituted norbornadienes[22]



4 5 6

Starting material	R^1	R^2	% Yield,[a] product
4f	CO_2Et	CO_2Et	94, **5f**
4g	CH_2OAc	CH_2OAc	50, **5g**
4h	CO_2Me	Ph	98, **5h**
4i	CO_2Et	nC_5H_{11}	40, **5i**
4j	CO_2Me	CH_2OPh	33, **5j**

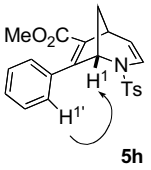
[a] Yields are relative to tosyl azide.

ing toluene) shows a steadily increasing amount of the rearrangement product. After 3 days in refluxing toluene only the rearrangement product was observed.

With a viable procedure in hand, a range of disubstituted norbornadienes were examined (Table 2). The diester **4f** provided **5f** in 94% isolated yield. The yield obtained in refluxing toluene is similar to that obtained by Umano et al. in refluxing 1,2-dichlorobenzene.[15] However the use of toluene provides a somewhat more convenient procedure than using 1,2-dichlorobenzene as the solvent. The diacetate **4g** provided **5g** in 50% yield.

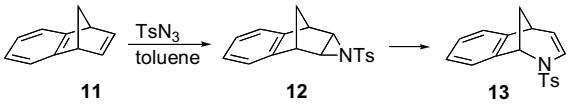
Several nonsymmetrical derivatives were next examined. Our prediction was that the larger of the two groups R^1 or R^2 would end up on the same side of the bicyclic ring as the N–Ts group. A single product, **5h**, was obtained upon treatment of **4h** with tosyl azide. The regiochemistry was determined through NOESY experiments that showed a crosspeak between H1 and H1′ on the phenyl ring. This is consistent with the reactions of the monosubstituted norbornadienes **4a–e** in which the larger group was on the same side of the ring as the N–Ts group. The reaction of unsymmetrically disubstituted norbornadienes **4i** and **4j** provided identical regiochemical results. While the yields of **5i** and **5j** were not as good as **5h**, these were clean reactions providing only a single regioisomer. The regiochemistry of **5i** and **5j** was also assigned by the presence of a similar crosspeak in a NOESY spectrum, between the bridgehead H1 and a methylene proton of the alkyl group at C7 (Fig. 3).

We also wished to examine the reaction of the benzofused norbornadiene **11**[23] with toluenesulfonyl azide (Scheme 4). Reaction of **11** with tosyl azide provided only the aziridine **12**[24] in 77% yield. All attempts to convert **12** to the desired **13** gave either no reaction or complete decomposition. These reaction conditions include heating **12** to over 250 °C, or the addition of a number of Lewis acids with or without heating. In trying to determine the reason for the lack of reaction of **12**, Umano and coworkers determined that *endo-aziridines* (e.g. *endo*-**10**) do not undergo the rearrangement reaction to provide the [3.2.1]bicyclic ring system.[15] We carried out a NOESY experiment with **12** in order to determine the



5h

Figure 3. Observed NOESY crosspeak for product 5 h.



11 12 13

Scheme 4. Attempted reaction of benzonorbornadiene with tosyl azide.

relative stereochemistry of the aziridine. We observed no crosspeaks between the aziridine protons and the bridgehead protons, indicating a likely *exo*-aziridine. Consequently, it may be that the rigidity of the system coupled with the loss of aromaticity in the rearrangement reaction preclude the rearrangement of this system.

In conclusion, we have found that mono- and disubstituted norbornadienes undergo an addition/rearrangement reaction with tosyl azide. The reaction proceeds with excellent levels of regiocontrol in modest to excellent yield. This reaction provides an excellent route for the synthesis of substituted 2-azabicyclo[3.2.1]octadienes. These substituted 2-azabicyclo[3.2.1]octadienes can be readily converted to the reduced bicyclooctane ring system found in a number of natural products and pharmacologically active molecules.

Acknowledgments

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