ALKENES and CYCLOALKANES FROM TOSYLHYDRAZONES

The Aprotic Bamford-Stevens Reaction and Camphor Tosylhydrazone

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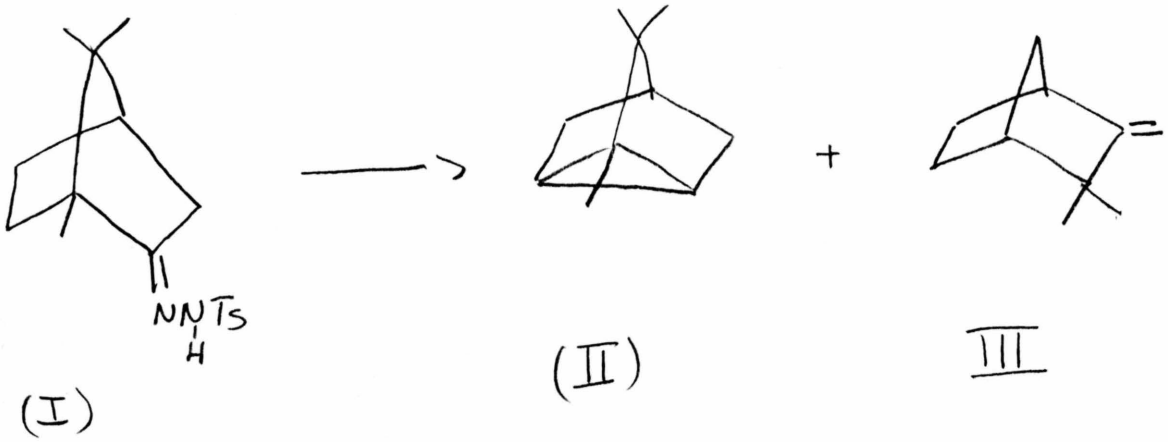
In 1952 Bamford and Stevens discovered that p-toluenesulfonylhydrazones of many different types of ketones decomposed on heating in a base to form alkenes, and cycloalkanes by insertion. In addition to the alkene, molecular nitrogen and p-toluenesulfinate anion are produced.

There are three major reaction types: the protic Bamford-Stevens reaction (base induced decomposition of tosylhydrazones in protic solvents), the aprotic Bamford-Stevens reaction (base induced decomposition of tosylhydrazone in aprotic solvents), and reactions of tosylhydrazones with alkyllithium reagents, called the Shapiro reaction. Our main interest is the aprotic reaction and we will give the protic and alkyllithium reactions little attention. All three are discussed together since all are base induced.

Our main concern with the aprotic reaction is with camphor tosylhydrazone. Camphor tosylhydrazone decomposes to a mixture of camphene and tricyclene when heated in aprotic solvents with sodium methylate (NaOMe) or sodium hydride (NaH). Some aprotic solvents often used are diglyme, decalin, and N,N-dimethylformamide. We employed diglyme and triglyme with NaOMe and an "unreported" aprotic solvent ,dimethyl sulfoxide (DMSO), with NaH.

The major product depends on whether the solvent is protic or aprotic. When the salt(I) decomposes in an aprotic solvent, tricyclene(II) is the major product, with the ratio of tricyclene to camphene changing depending on the particular aprotic solvent used. If the solvent is protic then the major product will be

camphene(III).



Equation 1

The Bamford-Stevens Reaction

The protic reaction is defined as the reaction of a tosylhydrazone with a strong base in a protic solvent. The solvent commonly used is ethylene glycol(EG) but other glycols have been used such as diethylene glycol(DEG). The base is prepared by dissolving metallic sodium in the solvent before the tosylhydrazone is added, or commercial NaOMe may be added to the tosylhydrazone dissolved or suspended in the solvent.

The aprotic reaction employs a solvent with little or no proton donating ability. Diglyme is typical but other high boiling esters have been used with success. Triglyme is one example as we shall show. The most common base employed in the aprotic reaction is NaOMe. NaH has been used with success (as we shall show) but $LiAlH_4$ and sodium amide have been tested and

found to be less satisfactory; the former may cause reductive elimination.[1] Sodium and acetamide were used as well and gave satisfactory results.

Protic and aprotic solvents often produce totally different reaction products. It is not always obvious by inspection of its structure whether a solvent will be "aprotic" or "protic" in a Bamford-Stevens reaction. Solvent effects of the reaction led early workers to the conclusion that under protic conditions a diazonium ion and/or a carbonium ion is an intermediate, but when no important proton source is present, the intermediate is a carbene. These intermediates would lead to the observed products. Later studies, however, revealed that some products thought to have come from carbene intermediates probably came from cationic intermediates.

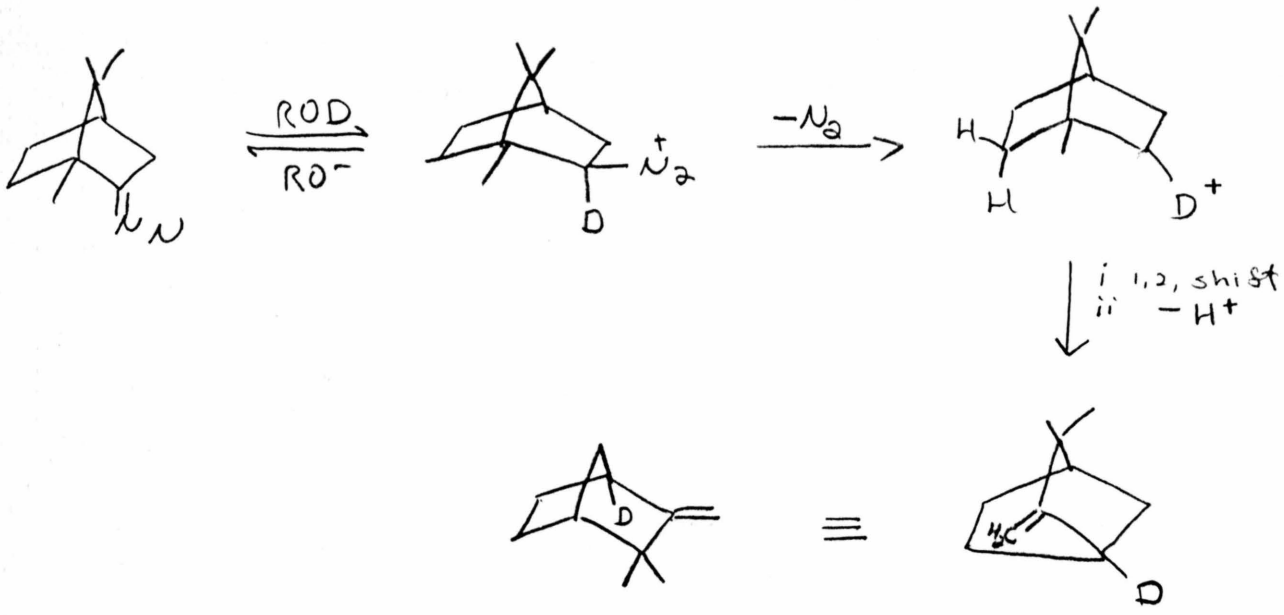
Studies of product ratios reveal a strong solvent dependence. This leads to the generalization that cationic paths are most common in protic media whereas carbenoid intermediates are involved under aprotic conditions. Subsequent investigation uncovered additional complexities and have made it clear that carbenes and energetic cations can behave similarly with respect to carbon skeleton rearrangement, hydride shifts, and the formation of insertion products, and therefore product ratios are not reliable criteria for the existence of carbenoid or cationic precursors.[2]

The proton donating ability of the solvent, or lack of it, is not the only important criterion in determining the reaction

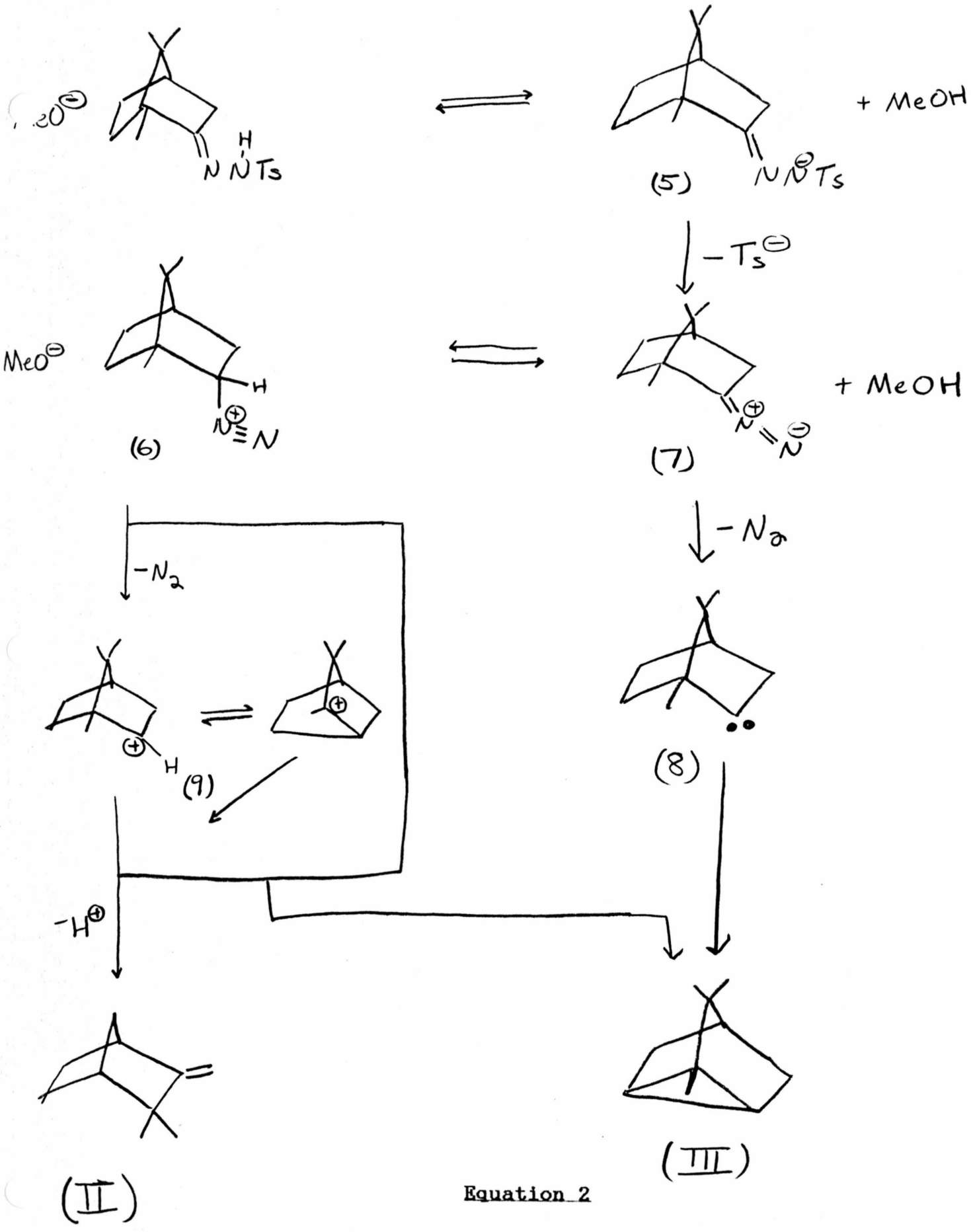
pathway and thus the products. Even under aprotic conditions, products derived from cationic intermediates can predominate when less than one equivalent of base is used. Since the H on nitrogen is fairly acidic, the tosylhydrazone is almost entirely in the form of the salt when one or more equivalents of base are present. With a deficiency of base, the free tosylhydrazone can act as a proton donor leading to cationic products.

The effect of base concentration on the decomposition of camphor tosylhydrazone (I) with NaOMe and NaH in aprotic solvents has been studied and strong evidence has been obtained that the nature of the intermediate which leads mainly to tricyclene (III) is dependent upon the relative amount of base used.

In this base dependence study it was discovered that the relative amount of camphene (II) to tricyclene (III) decreases at higher base concentrations so that tricyclene is found in greater amounts than camphene. Camphor tosylhydrazone was allowed to decompose with 0.75, 2.00, and 4.00 equivalents of NaOMe in diglyme in the presence of deuterium oxide. Tricyclene (III) formation by way of a carbene does not lead to the incorporation of a deuterium atom, and therefore with 0.75 equiv of NaOMe, two thirds of the tricyclene is generated from some other intermediate, whereas at higher concentrations (e.g., 4.00 equiv.) the carbene mechanism appears to predominate. A cationic mechanism is consistent with deuterium incorporation at low base concentration.[3]



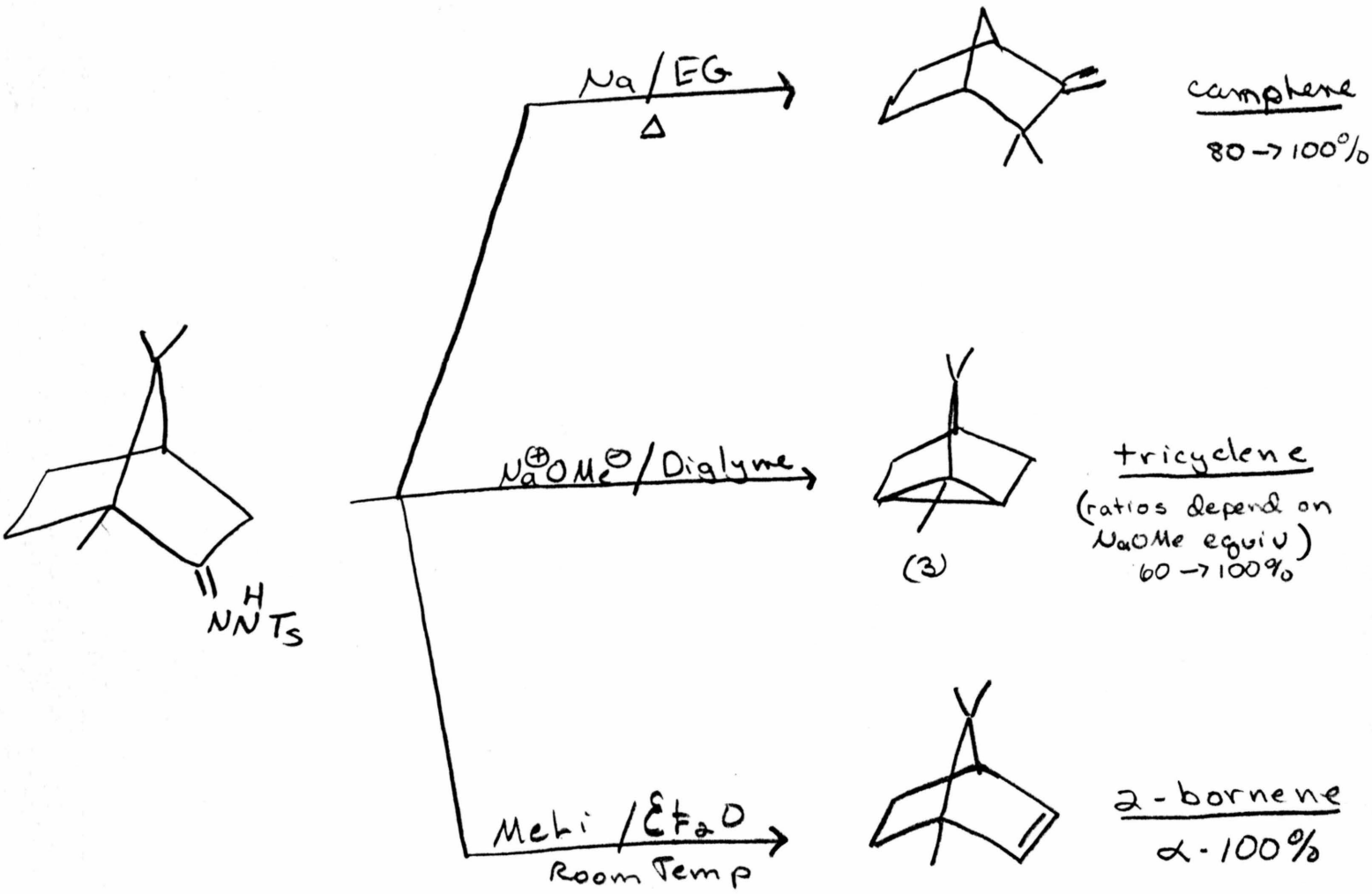
In the base-catalyzed decomposition of camphor tosylhydrazone (I), tricyclene (III) can be formed from one of the two intermediates depending on the concentration of base.



Equation 2

At high concentrations of base (e.g., 4.00 equiv.) the equilibrium between the tosylhydrazone and its conjugate base highly favors the conjugate base(5), which decomposes to diazocamphane(7). The diazocamphane can then take a proton from methanol (formed when MeO- removes the hydrogen from the nitrogen) to set up an equilibrium between methoxide ion and the resulting diazonium ion(6), the methoxide ion being present in large excess. In the presence of large excess of methoxide the diazocamphane should be favored in the equilibrium, and this can then lose nitrogen, giving the carbene intermediate(8). If there is not enough base at the second equilibrium (6&7), then the diazonium ion is favored. This ion loses N_2 and a cationic intermediate(9) is formed which will then lose a hydrogen to form camphene(II).[4]

A different course is followed when a tosylhydrazone bearing an alpha-hydrogen is allowed to react with an alkyllithium reagent. In such reactions an unrearranged, less substituted alkene is almost always the exclusive product. To illustrate the utility of this reaction and to contrast it with the protic and aprotic Bamford-Stevens reactions, the behavior of the camphor tosylhydrazone(1) toward the three sets of reaction conditions is shown in Equation 3.



Equation 3

Clearly the formation of 2-bornene (4) is not consistent with a cationic or carbenic intermediate.[5]

It has also been discovered that sodium amide or NaH can convert tosylhydrazones containing alpha-hydrogen atoms to unrearranged alkenes. NaH, however, appears to be unreliable, since it sometimes leads to carbenic products.[6] But for our work this result is what we are looking to get.

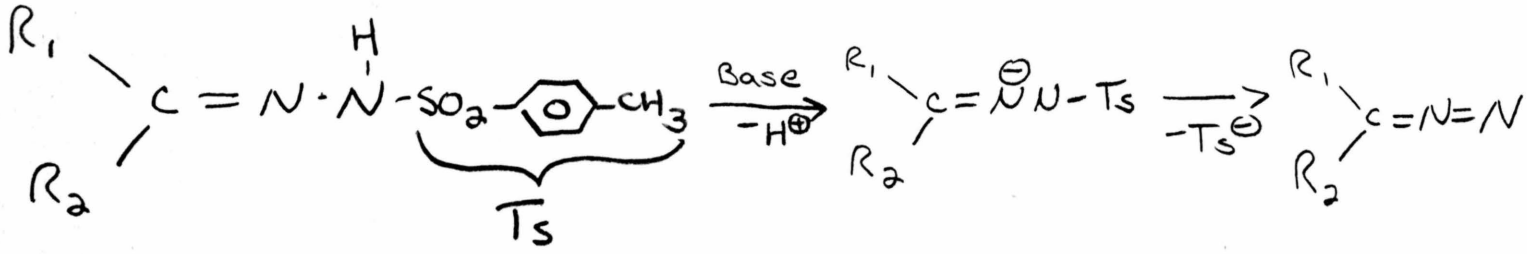
$LiAlH_4$, NaH, and sodium amide possess the ability to direct

tosylhydrazones to unrearranged alkenes, but alkyllithium reagents have replaced them. The alkyllithium reagents are commercially available, easy to handle, induce elimination at low temperatures and proceed virtually without rearrangement. Two or more equivalents of alkyllithium must be used, since the first equivalent is consumed by the acidic hydrogen on nitrogen in the tosylhydrazone.

MECHANISM

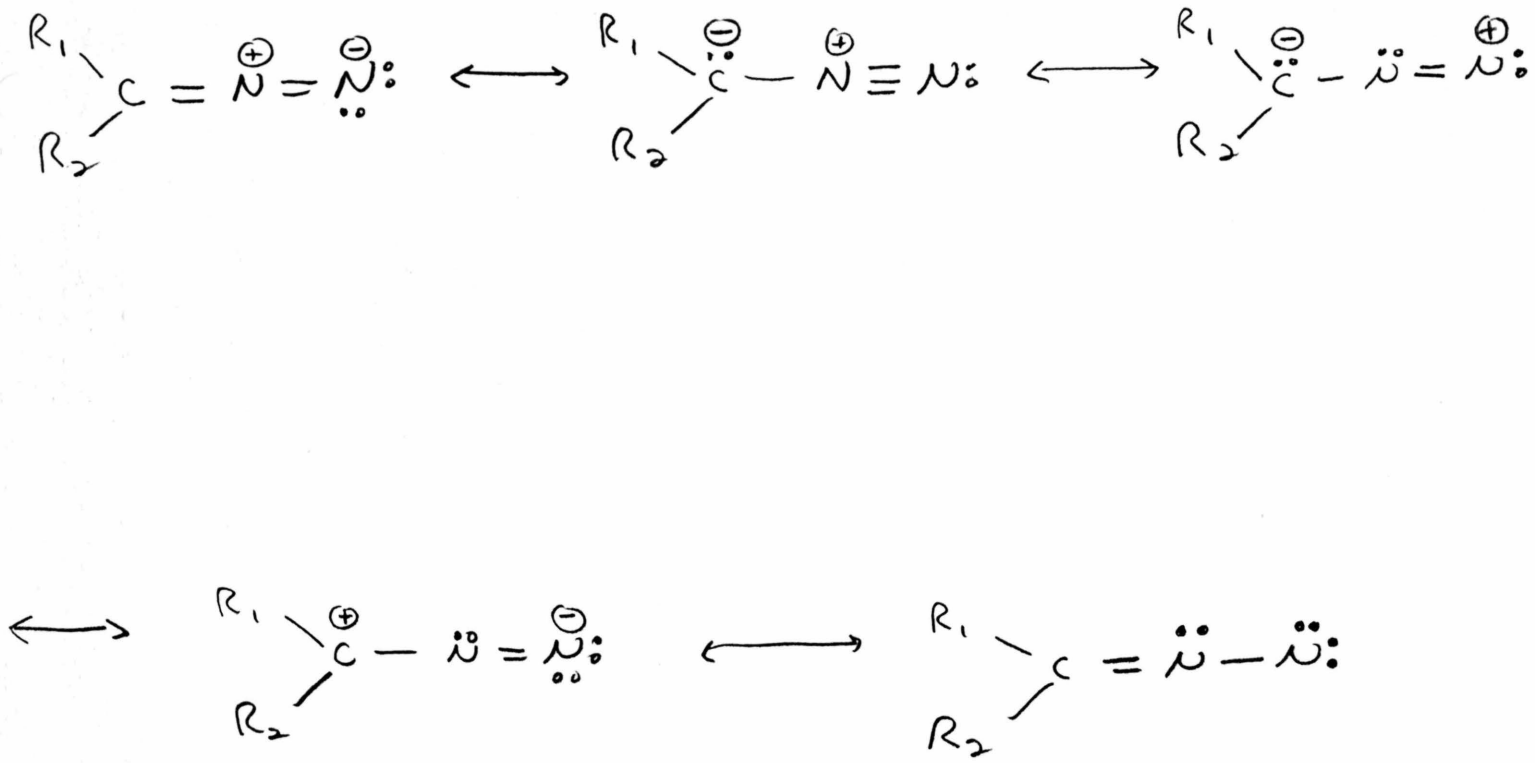
Bamford-Stevens Reaction

The mechanism of the Bamford-Stevens reaction is believed to involve initial proton abstraction by base and subsequent rate-determining thermal elimination of p-toluenesulfinyl anion to give a diazo compound. The net result of the two steps is alpha-elimination of p-toluenesulfinic acid. In alpha elimination, A carbon loses a group without its electron pair, usually a proton, and then a group with its pair.[15] The fact that the diazo compounds can be isolated under some circumstances supports this mechanism. (Equation 4)



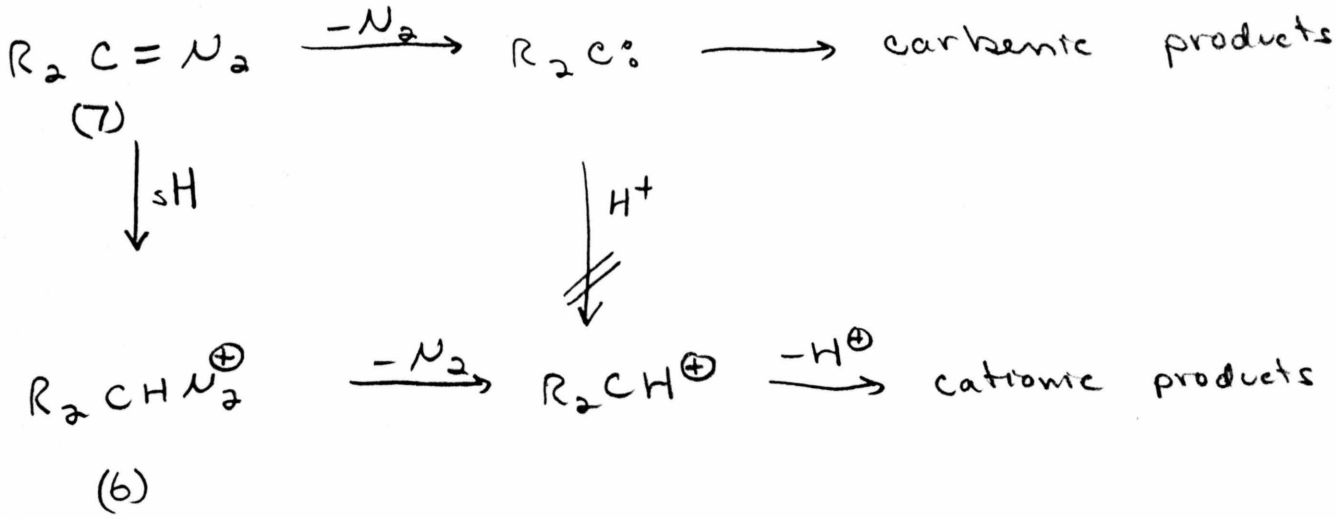
Equation 4

Diazoalkanes are prepared from the alkali-metal salt of the toluene-p-sulfonylhydrazone (tosylhydrazone) because it is the stable precursor since in some instances the diazoalkane itself is too thermally labile to be isolated and characterized. Nevertheless, because they are readily prepared and can be induced fairly easily to lose a molecule of nitrogen with heat or irradiation, diazoalkanes ($R_1R_2CN_2$) shown in their canonical form below (Equation 5) are widely used as sources of carbenes and carbenoids.[7]



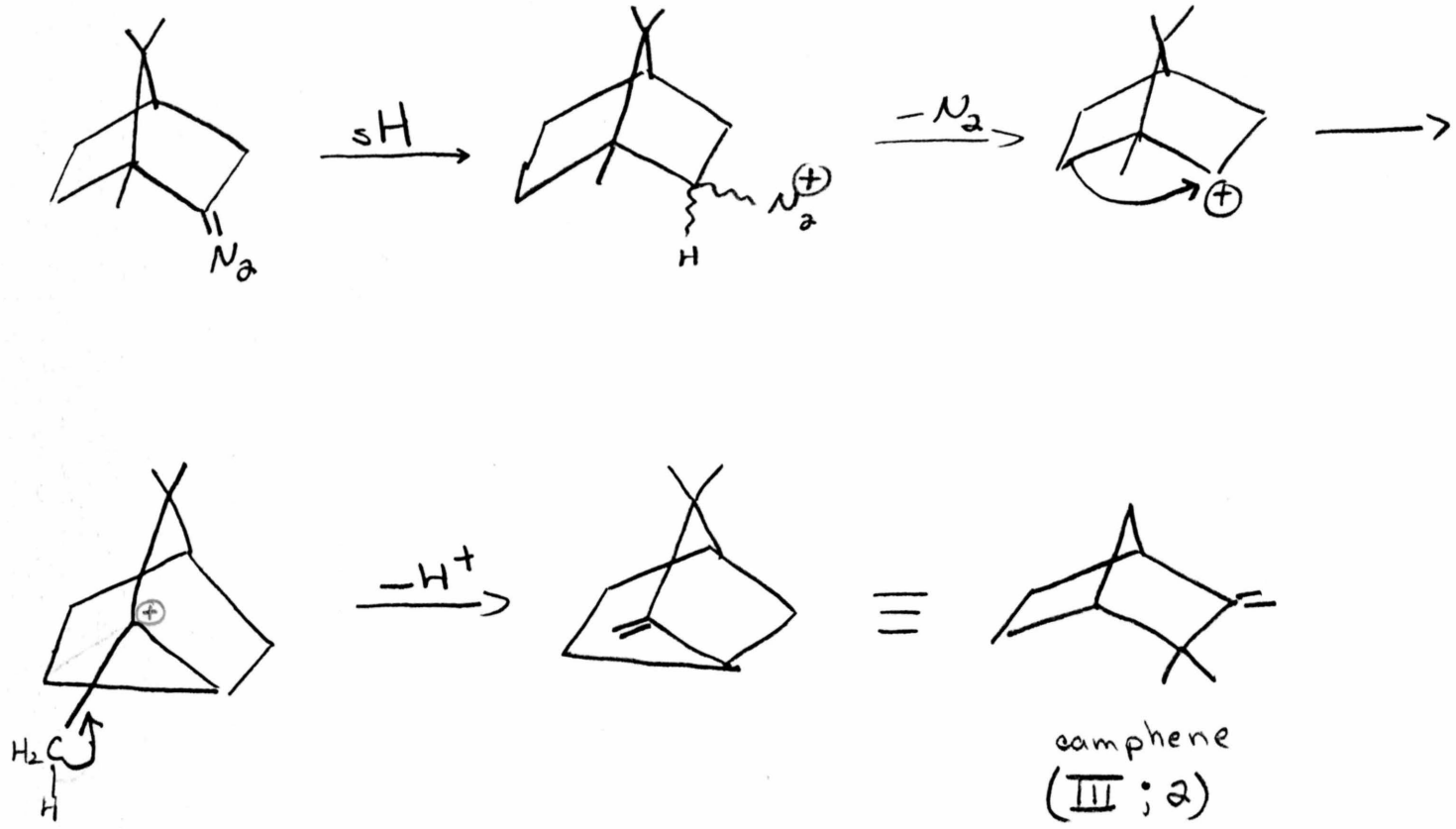
Equation 5

The nature of the solvent dictates what will happen to the diazo compound in the presence of excess base. If no proton source is available, or if available proton sources react too slowly with the diazo intermediate, molecular nitrogen will be eliminated and a carbene generated. If, however, proton donation is faster than nitrogen elimination, a diazonium ion is formed. The diazonium ion can lose nitrogen, giving a carbonium ion, which expels a proton with or without previous rearrangement. Protonation of the carbene is not thought to be an important route.[8]



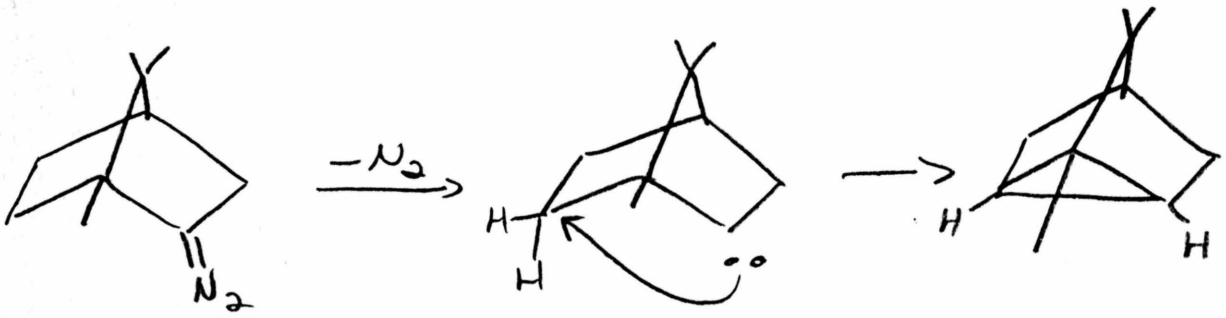
Equation 6

Many of the important mechanistic studies of the Bamford-Stevens reaction have been conducted on the tosylhydrazones of camphor (I,1). Camphor gives different products under protic and aprotic reaction conditions. Camphor tosylhydrazone yields camphene (III,2) under protic conditions and tricyclene (II,3) under aprotic conditions. The formation of camphene (III,2) from camphor tosylhydrazone (I,1) is an example of a bornyl cation undergoing rearrangement followed by the loss of a proton. The proton source effecting the conversion of the diazo compound(7) to a diazonium ion(6) is the solvent.



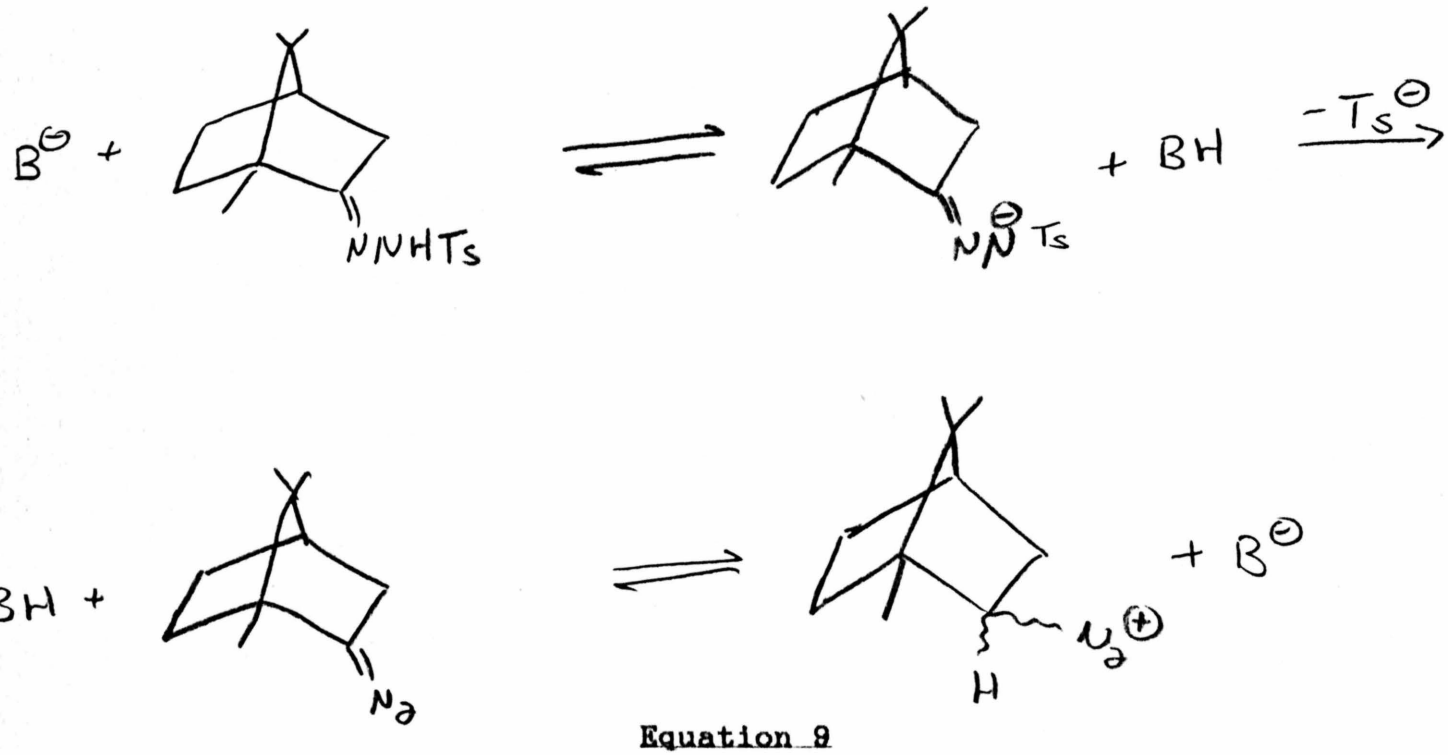
Equation 7

The formation of tricyclene (II,3) appears to result from intramolecular insertion of the carbene (Equation 8). The hydrogen migrates in this reaction.



Equation 8

This information together with that obtained by using various amounts of base led to the mechanism shown in the accompanying scheme (Equation 9). If an equilibrium between the diazo compound and the diazonium ion competes effectively with nitrogen expulsion from either, then a large excess of base (B-) will favor the diazo species and carbenic products. If there is a low concentration of base the diazonium ion and the resulting cationic products will be favored.[9]

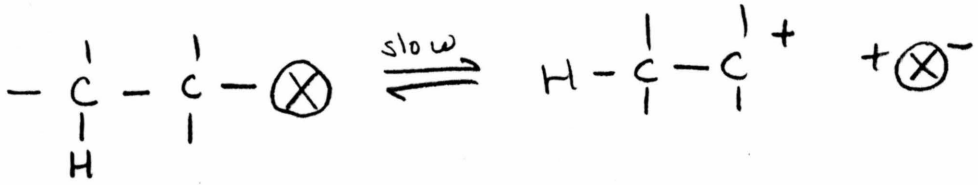


Equation 9

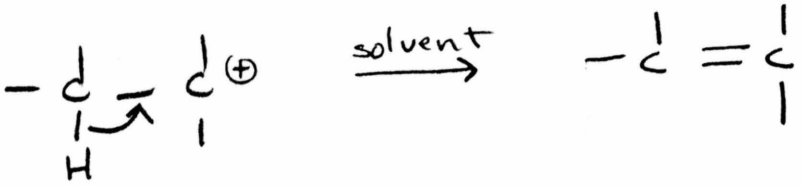
It seems clear, however, that diazonium ion collapse does not always represent a major route to products. For example, studies have revealed that the products obtained in a protic Bamford-Stevens reaction are consistent with an E1 mechanism. The E1 mechanism is a two step process in which the rate determining

step is ionization of the substrate to give a carbocation that rapidly loses a beta-proton to a base, usually the solvent:[16]

Step 1

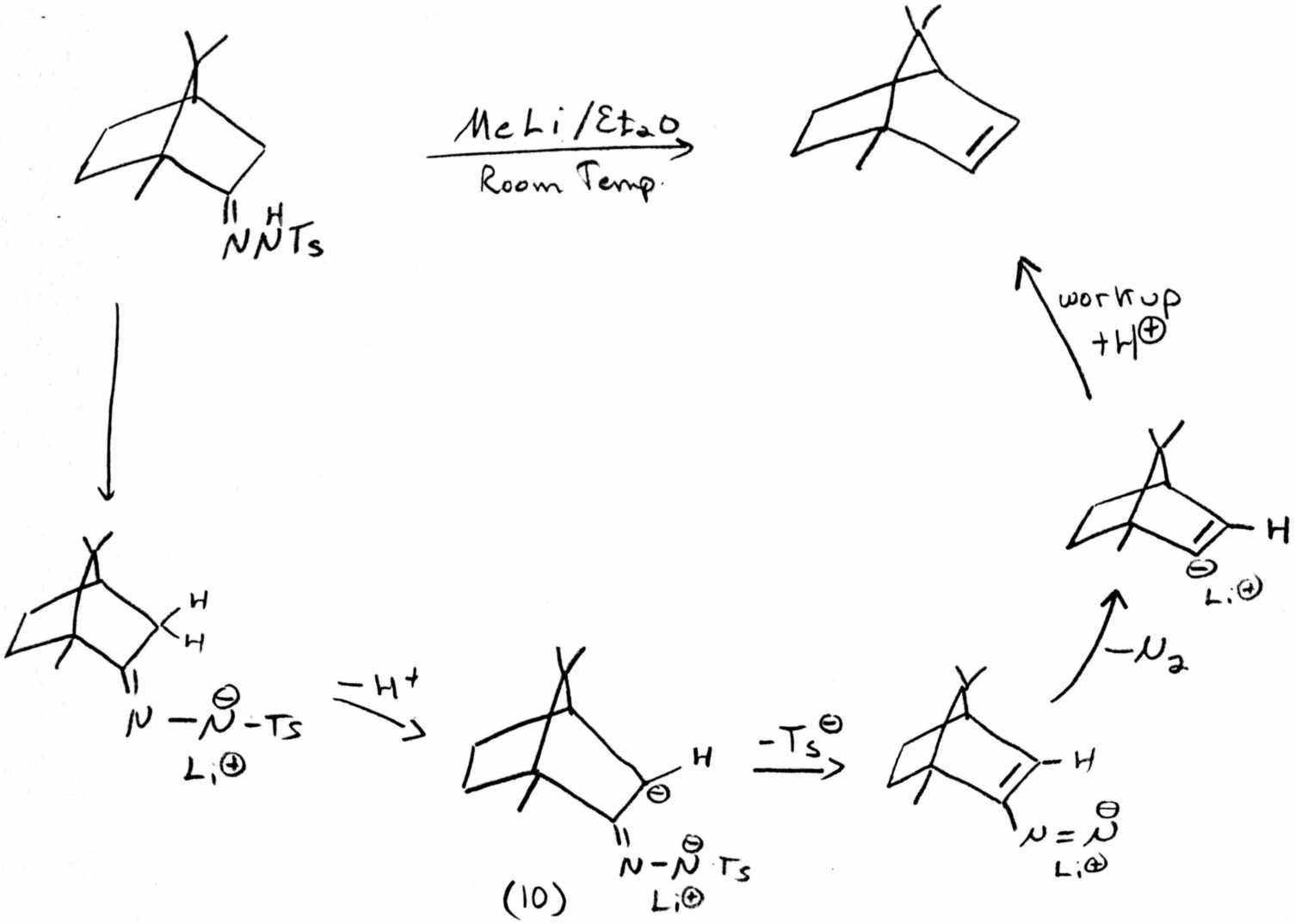


Step 2



These observations are more consistent with carbonium ion intermediate than with diazonium ion undergoing E2 elimination.[10]

In considering the alkyllithium reagents, the first observations on the reactions of tosylhydrazones with alkyllithium reagent were that the less substituted alkene is formed almost exclusively.



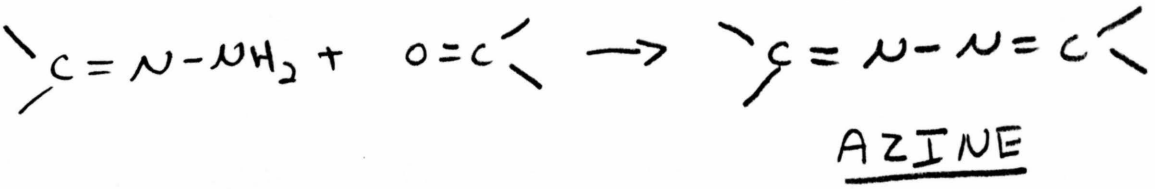
Equation 10

The elimination can be looked at as a two step process in which the alpha-proton is abstracted to give a dianion intermediate(10). Once this is complete the p-toluenesulfinate anion is ejected.[11] Then N2 leaves and H+ is picked up in the workup.

Scope and Limitations

The Protic Reaction

Tosylhydrazones are easily prepared from ketones and are highly crystalline, stable at room temperature and convenient to handle. The intermediates in the protic Bamford-Stevens reaction (diazonium ions and/or poorly solvated carbonium ions) can lead to different product ratios. Also a side reaction with alkene formation sometimes gives azines, a compound formed when the NH2 group of the hydrazine condenses with a second carbonyl compound:[17]



Except for the convenience it offers in some cases, the protic Bamford-Stevens reaction has no clear advantage over other methods of alkene synthesis.

The Aprotic Reaction

The aprotic Bamford-Stevens reaction generates carbene intermediates most conveniently. When the carbene intermediates undergo 1,2-hydride migrations instead of intramolecular insertion, the aprotic Bamford-Stevens reaction gives alkenes in useful yields. Six membered rings which exist in fixed boat conformations such as those in the norbornyl system (Equation 3)

decompose almost exclusively by intramolecular insertion. Hydrogen migration in a carbene intermediate may be somewhat indiscriminate. But in spite of these limitations the aprotic Bamford-Stevens reaction has found numerous applications.[12]

EXPERIMENTAL

We have employed the aprotic reaction in two parts. One part with NaOMe as the base and triglyme as the aprotic solvent and the second part with NaH as the base and dimethyl sulfoxide (DMSO) as the aprotic solvent. The DMSO/NaH system, we predict, should give similar results to the NaOME/triglyme (NaOME/diglyme in the literature).

Diglyme is the preferred solvent for the aprotic reaction but we used triglyme in order to have its peak on the GC further away from the peaks for tricyclene and camphene.

A. p-Toluenesulfonylhydrazine (Tosylhydrazine)

We obtained the tosylhydrazine from a commercial supplier.(Aldrich)

B. Tosylhydrazones

The camphor tosylhydrazone is readily prepared from camphor and tosylhydrazine in an acidic media. Acidified ethanol was employed for the procedure.

The camphor (1 equiv) is dissolved in a minimal amount of EtOH. The tosylhydrazine is also dissolved in a minimal amount of EtOH (forming a slurry). Both are heated to help dissolve the compounds. The camphor solution is heated to boiling and the tosylhydrazine solution is added to it. A drop of concentrated HCl may be added to aid in crystallization but as we discovered

it was not needed. The solution is heated again just until boiling and then is set aside to cool on ice. In about one half hour there will be a 80% - 90% yield of camphor tosylhydrazone. The crystals are filtered and dried. Recrystallization is an option but we did not chose it being that the camphor tosylhydrazone was pure enough to use in the subsequent reactions.

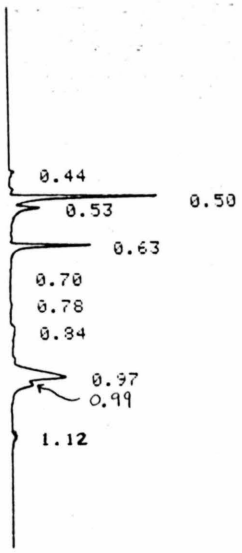
C. Tricyclene/Camphene

1) **NaOMe/triglyme**

In an apparatus equipped for distillation 3.3 grams (.01 mol) of camphor tosylhydrazone is added to 1.7 grams (.03 mol) of NaOMe in 30mL of triglyme. The mixture was heated to 160-170° for 20 minutes during which time a distillate was collected.

The distillate collected was analyzed by gas chromatography using a Hewlett-Packard 5880A GC. The following are the conditions under which the analysis was run:

Oven Temp	100°C
Detector Temp	275°C
Injector Temp	300°C
Attenuation	2^10
Chart Speed	8cm/min



RT	AREA	TYPE	AREA %
0.44	72.09	BP	1.217
0.50	1502.76	BV	25.362
0.53	548.14	VP	9.251
0.63	899.34	BP	15.178
0.70	13.10	PP	0.221
0.78	31.19	PV	0.526
0.84	285.21	VV	4.814
0.97	2407.07	VV	40.624
1.12	166.30	VP	2.807

After running a known of tricyclene(20%) and camphene(80%) it was found that the camphene peak occurs at 1.12 and the tricyclene peak at 0.99. Analyzing the GC peaks for our reaction products, we find that the peak for 1.12 has an area of 166.30 and a peak at 0.99 but this peak has not been labeled. This peak has been lumped with the peak at 0.97 and has been masked.).99 is about one third of the 0.97 peak therefore its area is 802.36. Taking the peaks for camphene and tricyclene, we get a percentage by comparing the area of each peak to the area of the two peaks added together. The tricyclene constitutes 82.8% (13.6% of all the products) and camphene 17.2% (2.8% of all the products). The other peaks are from other reaction products.

2) NaH/DMSO

For the NaH/DMSO system we used 0.5M, 2M, and 5M equivalent amounts of NaH. The NaH is weighed out at twice the amount needed since it is available at approximately 50% (covered in a wax). The NaH is washed three times with a solvent (we used pentane) to remove the wax and the requisite amount is placed in a round bottom flask. DMSO is added (30mL for 0.5M, 45mL for 2M, 70mL for 5M) to the NaH and the flask is fitted with a cork and drying tube($CaSO_4$) to allow the hydrogen gas to escape and to keep moisture out. A mixture of 0.05 mol of NaH and 20-30mL of DMSO requires about 45 minutes for complete reaction and yields a somewhat cloudy, pale yellow-gray solution (a slurry) of the sodium salt.[13] We allowed the reaction at least a day before continuing. In any case the reaction is let go until the evolution of hydrogen gas ceases.

[NOTE:Traces of moisture do not effect the protic reaction but it may produce lower yields in the aprotic reaction.]

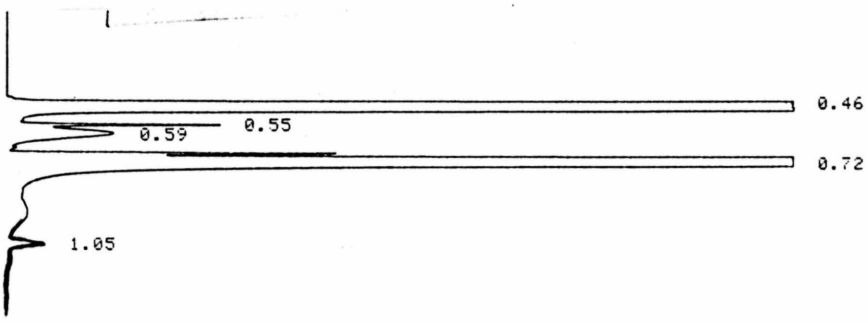
In an apparatus equipped for distillation using a wax bath to control the heat, the requisite amount of camphor tosylhydrazone is added to the NaH/DMSO mixture ($Na^+CH_2SOCH_3^-$).

The wax bath is allowed to reach 195-205°C while the internal mixture is kept below 190°C as to avoid DMSO decomposition. The mixture is heated allowing the nitrogen gas to come off first (small bubbles) and then the distillate is collected and analyzed by gas chromatography as above.

[Methylene chloride is added to the products as in order to cut the smell and to provide an internal standard for the GC analysis.]

The following is for the 5 molar equivalent reaction.

Conditions:		
	Oven Temp	100°C
	Detector Temp	280°C
	Injector Temp	300°C
	Attenuation	2^5
	Chart Speed	8cm/min



[hp] 5880A MANUAL INJECTION @ 17:37 MAR 30, 1988
AREA %

RT	AREA	TYPE	AREA %
0.46	52869.10	BB	89.287
0.55	63.67	BV	0.108
0.59	158.30	VV	0.267
0.72	6099.17	VB	10.300
1.05	22.46	PP	0.038

TOTAL AREA = 59212.70

Running a known of camphene, tricyclene, and methylene chloride the tricyclene peak was at 1.05, the camphene peak at 1.16, and the methylene chloride peak at 0.46. Analyzing the gas chromatograph we find a peak for methylene chloride at 0.46 with an area of 52869.10. There is also a peak at 1.05 showing tricyclene to be present, area being 22.46, but there is no peak for camphene showing that there is 100% tricyclene. The remaining peaks are from the reaction by-products (i.e. CH_3SOCH_2-Na^+, CH_3SOCH_3, CH_3-  -SO_2-Na^+). The reaction byproducts are the same for the 0.5M and 2M equivalent reactions but with these camphene was also present. 0.5M equiv. gave 39% tricyclene and 61% camphene, and 2M equiv. gave 53% tricyclene and 47% camphene.

The following is a summary of the results as well as the results obtained by Shapiro.

Experimental

Using the solvents listed, Shapiro obtained the following results[14]:

Tricyclene found, %

	NaOMe equiv					
Solvent	0.25	0.50	0.75	1.00	1.25	1.50
Diglyme	40	41	43	60	84	97

(eqiv = equivalents of base per mmol of camphortosylhydrazone)

	NaH equiv					
Solvent	0.25	0.50	0.75	1.00	1.25	1.50
Diglyme	37	43	47	61	100	100
Dimethyl formamide	25	25	25	33	95	100
Decalin	54	58	60	88	90	93

From our work:

Tricyclene found, %

	NaOMe equiv
Solvent	3
Triglyme	82.3

	NaH equiv		
Solvent	0.5	2	5
DMSO	39	53	100

ENDNOTES

1 Organic Reactions, Vol.23, pp.407-408

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11 Ibid pp.417-418

12 Ibid pp.420-422

13 Taylor; Wynberg (Ed.), Advances in Organic Chemistry Methods and Results, Vol. 6, 376-377(1969)

14 Shapiro,Duncan,Clopton, J.Am.Chem.Soc., 89, 1443(1967)

15 March,Jerry, Advanced Organic Chemistry, 3rd. Ed. 1985 p.173

16 Ibid p.881

17 Ibid p.804