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SYNTHETIC TRANSFORMATIONS USING ARENESULFONYLOXY GROUPS, FIRST AS ELECTROPHILES, THEN AS LEAVING GROUPS

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1 Introduction

A pervasive method for the formation of new bonds is to react an electron rich reagent (nucleophile) with a substrate (electrophile) containing an electronegative atom or group (leaving group) Formation of the new nucleophile-substrate bond by electron pair donation from the nucleophile to the substrate is made possible by breakage of the substrate-leaving group bond In order to conserve valence octets, the leaving group retains the electron pair formerly shared with the substrate Figure 1 shows the process in cartoon fashion

Figure 1

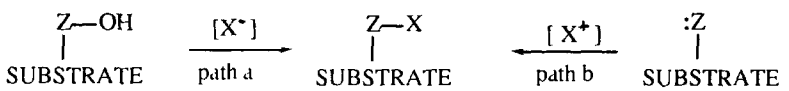
This process of substitution of one group for another is attractive synthetically since there are many possible variations on the theme A wide range of electron donors can be used as nucleophiles,

different elements (Z=C, N, S, P, Si, Se, Sn among others) can serve as the electrophilic center in the substrate, and many leaving groups (X= halide, sulfonate, phosphate among others) can be employed

One invariant feature of the process, regardless of the nucleophile or the electrophilic element Z, is that the leaving group is converted from a covalently bonded atom or group to an anion (for uncharged substrates) In order to accept negative charge readily, the leaving atom or group must be stable as an anion, and thus must be able to stabilize negative charge either by electronegativity and/or resonance Halides and sulfonate esters are commonly used as leaving groups for this reason

A covalently attached leaving group imparts the same oxidation level to the electrophilic atom Z as does a hydroxyl group, thus it is not surprising that hydroxyl substituted substrates are important starting materials for the preparation of substrates with leaving groups attached (Fig 2, path a) A conceptually different approach for attaching leaving groups to substrates is to oxidize the substrate with an oxidant that delivers the leaving group directly to the future electrophilic atom Z (Fig 2, path b)

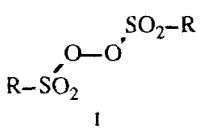
Figure 2



Both **path a** and **path b** can be used to attach halogen leaving groups Sulfonate leaving groups on the other hand, are better leaving groups than halides, but are normally introduced by converting the hydroxyl group to a sulfonate group with a sulfonylating agent (path a) [1] In some instances the sulfonylation of hydroxyl groups is problematic since the sulfonate products are reactive compounds that may not survive the conditions of their formation Until recently there were no methods available for the oxidative introduction of sulfonate groups into substrate molecules Were such methods available, substitution chemistry using excellent sulfonate leaving groups could be extended to include new substrates, and thus new synthetic methodologies could result

Consideration of Figure 2 suggests that a synthetic equivalent of RSO_2O^+ could react with an electron pair of the substrate and thus oxidatively attach a sulfonate leaving group to the substrate Sulfonyl peroxides, RSO_2OOO_2SR, **1**, reacting as pseudohalogen electrophiles would provide the desired synthetic equivalent

1 1 Arenesulfonyl Peroxides as Electrophiles Sulfonyl peroxides, **1**, are derivatives of hydrogen



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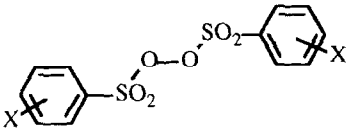
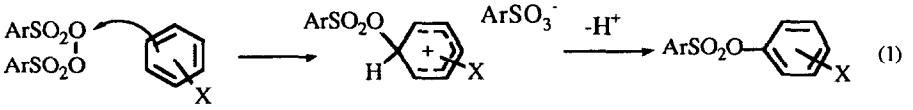


2 a X=H
b X=p-NO_2
c X=m-NO_2
d X= o NO_2
e X= m-CF_3
f X= 3,5-$(CF_3)_2$
g X=p-Br
h X=p-Cl
i X=p-CH_3

peroxide in which the O-O bond is flanked by sulfonyl groups While sulfonyl peroxides with both alkyl[2] and aryl groups[3] attached to sulfur have been reported, the largest group of compounds are those with aromatic groups attached to sulfur, i e bis-(arenesulfonyl) peroxides, **2** Bis-(arenesulfonyl) peroxides with a variety of aryl substituents have been prepared [4]

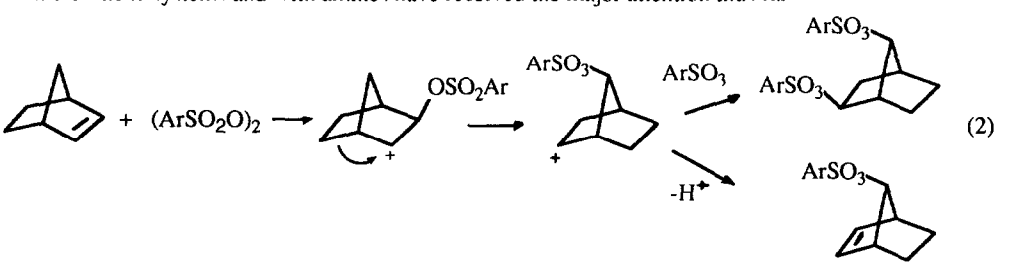
The electrophilic properties of sulfonyl peroxides **2b**, **2c**, and **2e** have been convincingly demonstrated in their reactions with aromatic compounds Extensive studies of aromatic substitution by arenesulfonyl peroxides carried out by Dannley and coworkers[5-10] showed that arenesulfonyl peroxides give aromatic substitution by an electrophilic mechanism Electron donation from the aromatic substrate to the peroxide yields a Wheland intermediate and thence product by proton loss (Eqn 1) A wide variety of mechanistic tools, summarized elsewhere,[3] were used to confirm the mechanism Others have supported the electrophilic mechanism of aromatic substitution [11]



(1)

A few scattered reports indicate that arenesulfonyl peroxides yield addition products with olefins These were originally thought to be the result of free radical addition reactions [12] However, rearranged products from the reaction of arenesulfonyl peroxides with norbornene suggested that electrophilic addition to the double bond, followed by Wagner-Meerwein rearrangement in the intermediate norbornyl cation, was a more likely explanation (Eqn 2) [13]

Based on these results it appeared that sulfonyl peroxides had potential for use as synthetic equivalents of RSO_2O^+ and thus provide a method for oxidatively introducing arenesulfonate leaving groups into molecules A program of research into the reactions of sulfonyl peroxides with electron donors was initiated to discover if such an approach was feasible, and to investigate new chemistry that might result from this approach The reactions of **2b** with olefinic π-systems and with amines have received the major attention thus far



(2)

1 2 Arenesulfonyl Peroxides as Reagents Most studies have employed p-nitrobenzenesulfonyl peroxide, pNBSP, **2b**, although in some cases m-(trifluoromethyl)benzenesulfonyl peroxide, mTFBSP, **2e**, has been used with equally good results Both are easily prepared by the condensation of the appropriate arenesulfonyl chloride and hydrogen peroxide under alkaline conditions [5,6] The preparation can be carried out on a 20g scale without difficulty so that large amounts are readily available

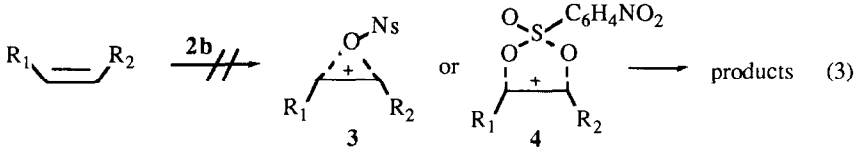
As synthetic reagents, **2b** and **2e** are very easy to handle and safe to use The attachment of sulfonyl groups to the ends of the O-O bond increases the thermal stability of **2b** and **2e** by inductive and/or resonance

withdrawal of electrons from the peroxide bond, thus decreasing electron-electron repulsion The thermal stability is further enhanced by the electron withdrawing substituents attached to the aromatic ring For example **2b** and **2e** are solids that can be recrystallized to high purity (>95%), stored for long periods in the freezer (-20°C) without loss of purity, and handled in the laboratory using normal laboratory procedures and precautions These compounds have relatively high melting points (**2b**, 128°C, **2e**, 82°C), although melting is accompanied by exothermic decomposition The low active oxygen content of these compounds (<5%) precludes violent decomposition Vigorous reaction occurs with neat or very concentrated solutions of good electron donors such as amines, olefins, and alkoxides, but sulfonyl peroxides are relatively stable in the presence of oxygen, water, acids, and a variety of common solvents such as acetone, ethyl acetate, dichloromethane, and acetonitrile For example, the half life for decomposition of **2b** in ethyl acetate solution (0 1M) at room temperature is ≈ 21 hours Most reactions of interest are more rapid, so that competitive decomposition of the peroxide is not usually a significant side reaction

Compound **2b** is also very convenient operationally It can be analyzed by iodometric titration, both as a measure of purity and to monitor the extent of reaction The p-nitrobenzenesulfonate (nosylate) group also has a distinct AA'BB' pmr signal that indicates if the group is ionic or covalent If the higher field doublet of the AA'BB' signal falls below 8 0 ppm, the nosylate group is covalently attached, whereas if it occurs above 8 0 ppm, then the nosylate anion is present Furthermore the nosylate products are often solids that can be recrystallized easily In contrast **2e** is much more soluble in most solvents than **2b**, and the 3-(trifluoromethyl)benzenesulfonate (m-TFBs) products are usually oils

2 Addition of Sulfonyl Peroxides to Simple π-Systems

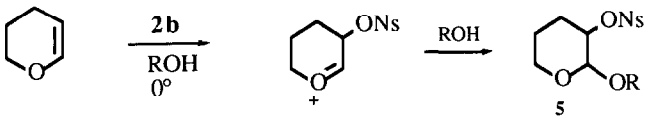
2 1 Simple Olefins Initial experiments with simple olefins demonstrated quickly that **2b** was distinctly different than many other pseudohalogen electrophiles It was anticipated that electrophilic addition to the π-bond of olefins would give an β-sulfonyloxy carbocation that might be bridged Either a three-membered ring (**3**) or five-membered ring (**4**) intermediate, produced by interaction of the lone pairs on the sulfonyloxy oxygen or on the sulfonyl oxygens with the neighboring carbocation could be envisioned (Eqn 3) In the event, addition of **2b** to *cis*- and *trans*-stilbene showed that neighboring group interaction between the sulfonyloxy group and the carbocationic center did not occur [14] Indeed, addition of **2b** to simple olefins gave complex product mixtures reminiscent of product mixtures obtained from the diazotization of amines [15]



Thus the strong inductive electron withdrawing property of the nosylate group[16] renders the first-formed carbocation very unstable and prone to rapid and complex rearrangements and eliminations, even in the presence of nucleophilic solvents [17] In this respect arenesulfonyl peroxides are quite different than halogens and many pseudohalogens, which yield stabilized carbocations due to bridging interactions Arenesulfonyl peroxides are thus not useful reagents for electrophilic attachment of arenesulfonyloxy groups to simple olefins This

conversion, however, can be accomplished readily by the reaction of olefins with Koser's reagent [hydroxy(tosyloxy)iodobenzene][18-20] or its variants [21-23]

2 2 Enol Derivatives In order to make olefin addition by arenesulfonyl peroxides a useful reaction, the olefin must contain structural features that can stabilize the intermediate carbocation and reduce multiple pathways to product Enol ethers appeared to be excellent candidates since the electron rich double bond should react rapidly with the peroxide electrophile, and since the lone pairs on oxygen could stabilize the intermediate cation as an oxonium ion These predictions were tested by the reaction of 3,4-dihydro-2*H*-pyran (DHP) with **2b** in the presence of alcohols Generally high yields of 2-alkoxy-3-(((p-nitrobenzene)sulfonyl)oxy)-tetrahydropyrans, **5**, were obtained (Eqn 4) [24] These results suggest that resonance stabilization of the intermediate oxonium ion causes it to have a sufficiently long lifetime in solution to be captured nucleophilically by the alcohol solvent The stereochemistry of the addition products was found to depend on the steric bulk of the capturing alcohol, which is consistent with a lack of bridging in the intermediate oxonium ion



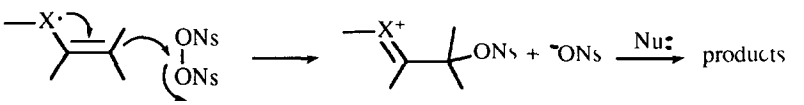
(4)

5

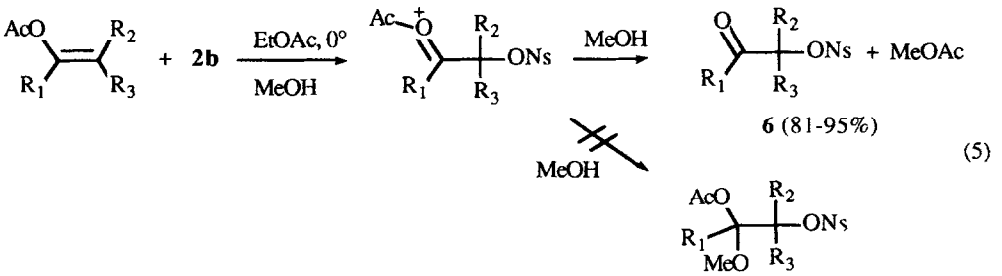
R=H, 85%, R=Me, 85%,
R=Et, 77%, R=CH_2CF_3, 15%
R=i-Pr, 80%, R=Ac, 91%
R=t-Bu, 91%

These results demonstrate that one way to achieve efficient oxidative attachment of the nosyloxy group to olefins is to stabilize the intermediate α-nosyloxy carbocation by lone pairs on substituents attached to the double bond, as depicted in Figure 3 This strategy was found to be successful for vinyl acetates,[25] trimethyl silyl enol ethers,[26] and enamines,[26] which all react smoothly with **2b** by electrophilic addition and ultimately yield α-nosyloxy ketones

Figure 3

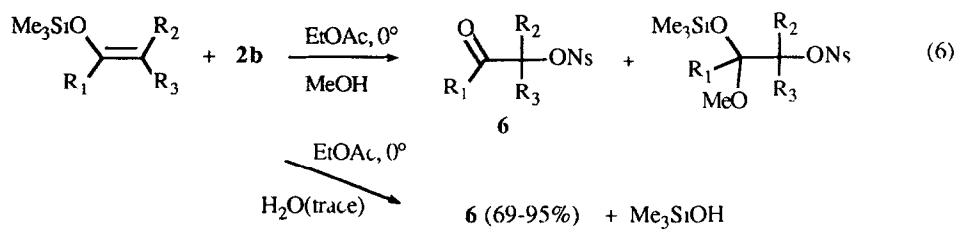


Vinyl acetates react with **2b** in ethyl acetate with methanol present to give high yields of 2-(((p-nitrobenzene)sulfonyl)oxy) ketones **6** (Eqn 5) [25] A variety of alkyl and aryl ketones gave uniformly good results with **2b** (and also **2e**) Interestingly, methanol attacks and removes the acetyl group in the oxonium ion intermediate, rather than undergoing addition to a ketal product



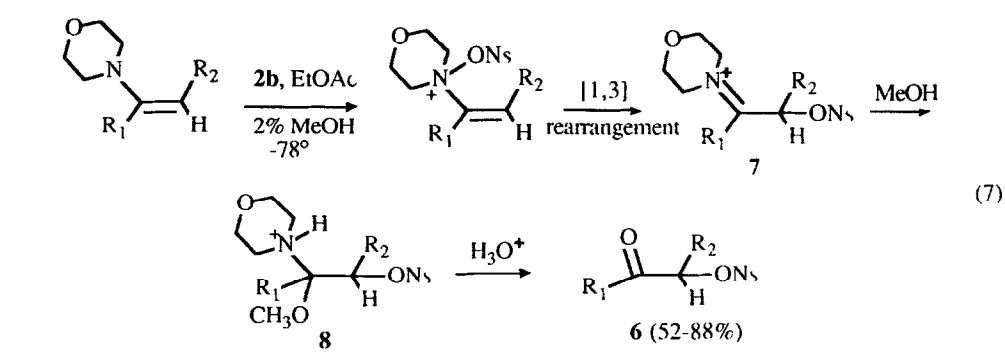
(5)

Silyl enol ethers also undergo analogous electrophilic addition/ desilylation (Eqn 6) [26] The use of methanol to scavenge the trimethylsilyl group gave both desilylation to **6** by attack on silicon, and addition to carbon to give an α-nosyloxy trimethylsilyloxy methoxy acetal These processes are competetive so that a mixture of products was obtained The two processes were made equivalent by the use of water as the capturing nucleophile and thus high yields of **6** could be obtained Regiospecifically prepared trimethylsilyl enol ethers gave regiospecific conversion to the α-nosyloxy ketone [27]



(6)

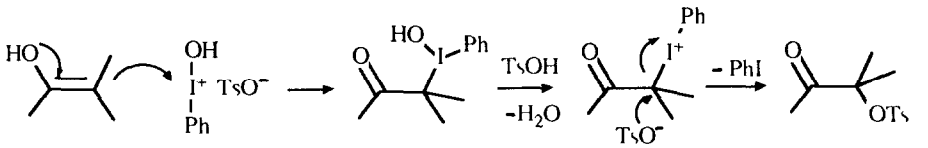
Enamines, which have a lone pair of electrons on a nitrogen substituent of the double bond, also react readily with **2b** Morpholine enamines of a series of ketones including cyclic and acyclic, aliphatic and aromatic ketones were treated with **2b** in ethyl acetate containing 2% methanol at -78°C and good yields (52-88%) of α-nosyloxy ketones **6** were obtained after workup (Eqn 7) [26] Based on the low temperature required and experience with the reaction of **2b** with amines (see below), electrophilic attack by **2b** probably occurs first on nitrogen, followed by a 1,3-rearrangement of the nosyloxy function to the α-position of iminium ion **7** The role of methanol is to convert the iminium ion to the more stable amino ether **8** prior to hydrolysis to product



(7)

Since vinyl acetates, silyl enol ethers, and enamines are all derivatives of ketones, they are complementary substrates for the preparation of α-nosyloxy ketones from ketones (The use of **2e** gives comparable yields of α-(mTFBs) ketones [25]) α-Sulfonyloxy ketones can be prepared by several other routes In principle the condensation of 2-hydroxy ketones with sulfonyl chlorides could be used to introduce the sulfonyloxy group, however this route to α-sulfonyloxy ketones is much more problematic In many cases the α-sulfonyloxy ketone is unstable to the basic conditions required for its formation This problem can be circumvented by first preparing an α-sulfinyloxy ester, which is then oxidized to the sulfonyloxy ester [28-30] In contrast α-triflyloxy ketones can be prepared directly from α-hydroxy ketones by condensation with triflic anhydride [31,32] The high sulfonylating reactivity of triflic anhydride requires only non-nucleophilic, relatively weak bases as proton scavengers, thus the α-triflyloxy ketone is stable to the reaction conditions The required α-hydroxy ketones can be prepared from the carbonyl compound by a variety of oxidative methods [33]

Ketones can also be oxidatively converted to α-tosyloxy ketones[34] and α-mesyloxy ketones[35] with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent) and its mesyloxy analog, respectively An advantage of these reagents, over sulfonyl peroxides, is that they react directly with ketones with very small enol contents Another interesting feature of hypervalent iodine reagents is that although they deliver α-sulfonyloxy ketones, the attacking electrophile is electron deficient iodine The sulfonyloxy group is introduced by displacement in an intermediate iodonium ion (Eqn 8) [36]

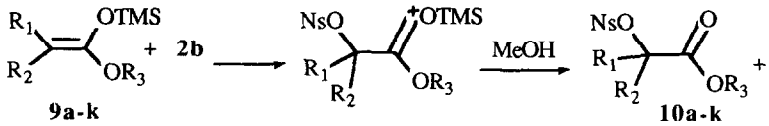


(8)

Regiospecificity in unsymmetric ketones can only be achieved by regiospecific preparation of silyl enol ethers and reaction with Koser's reagent, which yields isomerically pure α-tosyloxy ketones [37] The oxidative preparation of α-triflyloxy ketones can also be achieved from silyl enol ethers and a triflate analog of Koser's reagent generated *in situ* from iodosobenzene and trimethylsilyl triflate [38]

Reaction of ketene silyl acetal derivatives of esters with sulfonyl peroxides provides an analogous route to 2-sulfonyloxy esters Reaction of **2b** with a series of ketene silyl acetals **9a-k** gave 2-nosyloxy esters **10a-k** generally in high yields (Eqn 9) [39] The best procedure is to use 1 5 equivalents of sodium methoxide suspended in the reaction mixture, which serves to neutralize the arenesulfonic acid produced and thereby protects the rather acid- sensitive ketene silyl acetal At the same time it provides a source of methanol to accomplish desilylation Even very acid-labile compounds such as t-butyl ketene acetal **9c** gives a high yield of **10c** by this procedure, whereas only a very low yield was obtained in the presence of just methanol

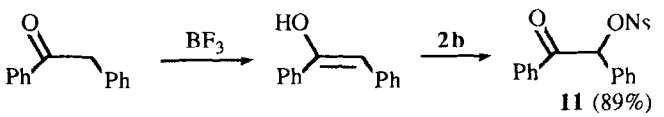
There are several alternate procedures for the preparation of α-sulfonyloxy esters The condensation of 2-hydroxy esters with sulfonyl chlorides to yield 2-sulfonyloxy esters works well Thus 2-mesyloxy, 2-tosyloxy, and 2-triflyloxy esters have all been prepared routinely in the literature by this route [28,31 40-42] While it has been reported that esters are unreactive towards Koser's reagent and its derivatives,[34] ketene silyl acetals of esters react readily with hypervalent iodine reagents to provide good yields of the 2-mesyloxy and 2-tosyloxy esters [37]



9a-k 10a-k (9)

	R_1	R_2	R_3	%		R_1	R_2	R_3	%
a	H	Me	Me	88	**g**	H	H	i-Pr	68
b	H	Me	Et	79	**h**	Me	Me	Me	67
c	H	Me	t-Bu	82	**i**	$-(CH_2)_4-$		Me	69
d	H	Et	Et	84	**j**	H	$-(CH_2)_3-$		73
e	H	Et	i-Bu	67	**k**	H	$-(CH_2)_2-$		61
f	H	C_6H_5	Me	79					

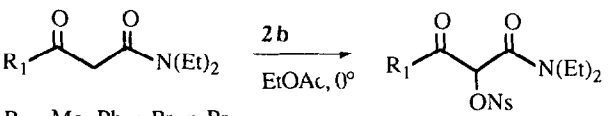
In terms of Figure 3, a hydroxyl group is the simplest oxygen containing functional group that can be attached to a double bond in order to stabilize a carbocation produced by electrophilic addition Thus if arenesulfonyl peroxides were to add to the enol form of carbonyl compounds, then the need to prepare stable enol derivatives of carbonyl compounds would be mitigated The validity of such an approach was confirmed when a mixture of deoxybenzoin and **2b** in dichloromethane was treated with boron trifluoride etherate and stirred at room temperature A good yield of α-nosyloxy ketone **11** was obtained (Eqn 10) [26] Under the same conditions a variety of other simple ketones failed to give products Evidently the equilibrium concentration of the enol is too low in simple ketones to react effectively with **2b**



11 (89%) (10)

For carbonyl compounds to undergo direct reaction with arenesulfonyl peroxides effectively, they must have high enol contents For example, β-keto esters and β-diketones contain a relatively high proportion of the enol tautomer at equilibrium that typically ranges from 5-95% depending on the structure and the solvent [43,44] A series of β-ketoesters **12a-i** and β-diketone **13** reacted smoothly with **2b** to give 2-nosyloxy-3-ketoesters **14a-i** and α-nosyloxy-β-diketone **15** in high yields (Table 1) [45] Where acid-sensitive functional groups are present, as in **12e**, suspension of one equivalent of anhydrous potassium carbonate in the reaction mixture to neutralize the sulfonic acid by-product gave improved results Diethyl malonate, which contains a low concentration of its enol tautomer,[43,44] failed to give product with **2b**

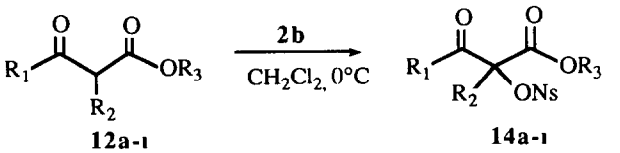
It is reasonable to assume that other ketones having substituents at the α-position which promote the formation of enols would also be appropriate substrates for direct reaction with arenesulfonyl peroxides Recently, β-keto amides have been found to react efficiently with **2b** to give the expected 2-nosyloxy products (Eqn 12) [46]



R_1= Me, Ph, i-Pr, n-Pr

16 (60-80%) (12)

Table I Yields of 2-((p-Nitrobenzenesulfonyl)oxy) 3-Ketoesters from the Reaction of β-Ketoesters and pNBSP



12a-i 14a-i (11)

Entry	Substrate	Prod	m p (°C)	Yield(%)[a]
1	**12a**, R_1=CH_3, R_2=H, R_3=CH_3	**14a**	86-88	62-65
2	**12b**, R_1=CH_3, R_2=H, R_3=Et	**14b**	84-86	56-57
3	**12c**, R_1=i-Pr, R_2=H, R_3=Et	**14c**	70-72	61-67
4	**12d**, R_1=CH_3, R_2=H, R_3=$CH_2CH_2OCH_3$	**14d**	67-69	51-67
5	**12e**, R_1=CH_3, R_2=H, R_3= t-Bu	**14e**	83-85	46-51
6	**12f**, R_1= C_6H_5, R_2=H, R_3=Et	**14f**	106-108	62-65
7	**12g**, R_1=4-$NO_2C_6H_5$, R_2=H, R_3=Et	**14g**	101-103	70-89
8	**12h**, R_1=CH_3, R_2=CH_3, R_3=Et	**14h**	55-58	43-57
9	**12i**, R_1, R_2 = $(CH_2)_3$, R_3= Et	**14i**	84-86	46-51
10	**13**, 2,4-pentanedione (R_1=CH_3, R_2=H, OR_3=CH_3)	**15**	83-85	67-72

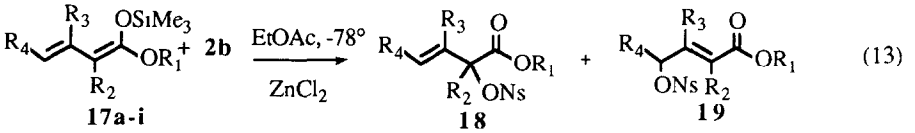
a Recrystallized yields of analytically pure products Ranges are results from several trials

Only oxidative methods can be used to access 2-sulfonyloxy-1,3-dicarbonyl compounds Hypervalent iodine reagents can also be used to oxidize β-diketones and β-keto esters to the corresponding 2-arenesulfonyloxy derivatives Koser's reagent produces 2-tosyloxy products,[34] and [hydroxy(mesyloxy)iodo]benzene gives 2-mesyloxy derivatives [35,47]

2 3 1-Silyloxy-1-Alkoxy Dienes The facile reaction of **2b** with enol derivatives also suggested that a study of conjugated enol derivatives would be useful Electrophilic addition to 1-trimethylsilyloxy-1-alkoxy dienes[48] using a variety of electrophiles has been reported to occur at both the α- and γ-positions, and the observed regiochemistry is dependent on the electrophile and the steric bulk of the substituents on the diene [49] Oxygen electrophiles are reported to give more α-attack, but only a few examples have been studied [50]

The regioselectivity of the addition of **2b** to 1-trimethylsilyloxy-1-alkoxy dienes **17** was found to depend of the substitution pattern in the diene (Table 2) [51] If there are no substituents other than hydrogen at C-2 and C-4 as in **17a,b,c,h,i**, then the major product is **18** from attack at the α-position (Entries 1-3,8,9) Substituents at C-3, **17c,h**, do not alter this preference (Entries 3,8) Substituents other than hydrogen at either C-2 or C-4, **17e,f,g** (Entries 5, 6, 7) or a bulky alkoxy group, **17d** (Entry 4) give only γ-product **19** It was observed that α-addition products **18** could be thermally rearranged to γ-isomers **19**, thus attack at the α-position is favored kinetically while the γ-product is thermodynamically more stable Since the individual regioisomers are separable chromatographically, pure samples can be prepared and carried on in subsequent reactions The ease of reaction and high yields bode well for electrophilic addition of **2b** to other electron rich diene systems

Table 2 Products from the Reaction of 1-Trimethylsilyloxy-1-Alkoxy-1,3-Dienes with **2b** in Ethyl Acetate at -78° in the Presence of Zinc Chloride



(13)

Entry	Substrate[a]	Yield(%)[b]	Ratio **18**	**19**
1	**17a**, R_1=Me	75	82	18
2	**17b**, R_1=Et	73 (100)	77	23
3	**17c**, R_1=Et, R_3=Me	78[c]	64	36
4	**17d**, R_1=t-Bu, R_3=Me	(100)	0	100
5	**17e**, R_1=Me, R_4=Me	68	0	100
6	**17f**, R_1=Me, R_4=Et	43	0	100
7	**17g**, R_1=Me, R_2=Me	71	0	100
8	**17h**, R_1=Et, R_3=Ph	80	100	0
9	**17i**, R_1=Me, OSi(*t*-Bu)Me_2	81	72	28

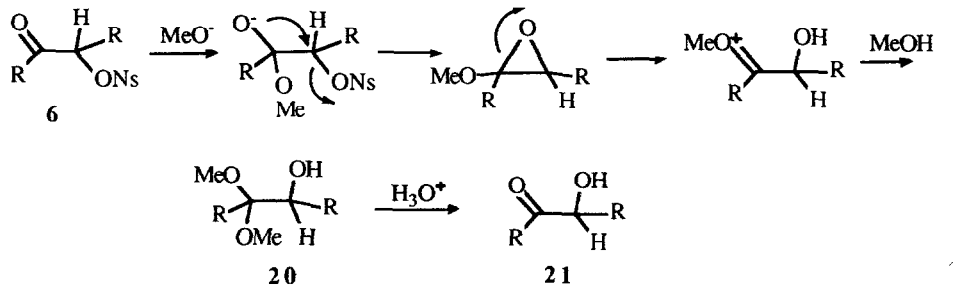
a Only substituents other than hydrogen are noted b Isolated yields of pure products Yields in parentheses are crude yields for reactions where the crude products were of high purity by pmr c Reaction carried out in the presence of $NaOCH_3$ (1 eq)

3 Reactions of α-Nosyloxy Carbonyl Compounds

3 1 α-Nosyloxy Ketones The use of **2b** as an equivalent of a p-$NO_2C_6H_4SO_2O^+$ electrophile allows the nosyloxy leaving group to be oxidatively attached to carbon in enol derivatives quite generally The structural features of α-nosyloxy ketones are similar to those of α-halo ketones in that both have leaving groups attached next to the ketone function It was therefore expected that the chemical behavior should be similar Several reports in the literature bolstered this expectation The use of α-mesyloxy and α-tosyloxy ketones as precursors for the production of α-keto carbocations by solvolysis was an early impetus for their preparation [52,53] Replacement of the α-sulfonyloxy group with nucleophiles was the subject of scattered reports,[31,54,55] and it was suggested that soft nucleophiles were superior for this purpose [54] The use of α-tosyloxy ketones as substrates for the Favorski rearrangement was also reported [56,57]

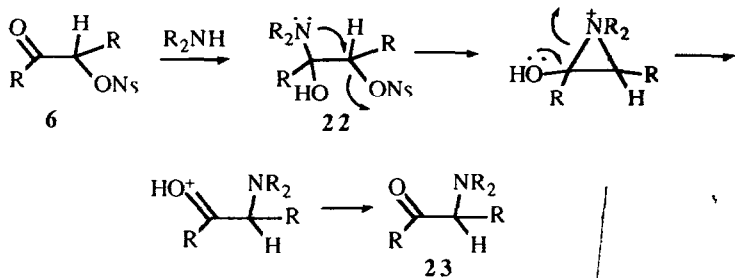
Systematic examination of the chemistry of α-sulfonyloxy ketones had not been undertaken however, mostly due to the difficulties in preparing them by condensation methods alluded to earlier On the other hand the success of oxidative attachment of α-nosylate groups by **2b** provides a convenient source of these compounds so that their chemistry could be examined in greater detail In contrast to α-halo ketones which can be attacked at six different positions by nucleophiles/bases,[58] only two distinct reaction processes have been identified for α-nosyloxy ketones in the presence of nucleophiles/ bases

One reaction process is nucleophilic addition to the carbonyl group followed by intramolecular delivery of a nucleophile to the 2-position When α-nosyloxy ketones are treated with potassium carbonate in methanol, hydroxy ketals **20** are isolated in high yields These products can be converted to α-hydroxy ketones **21** by acidic hydrolysis (Eqn 14) [59] While the the process depicted in Equation 14 is known to occur in α-halo ketones[58], it is often a minor pathway. A distinct feature of α-nosyloxy ketones is that the very good electron withdrawing power of the nosyloxy group in **6** activates the carbonyl group towards nucleophilic addition, making it the dominant pathway



(14)

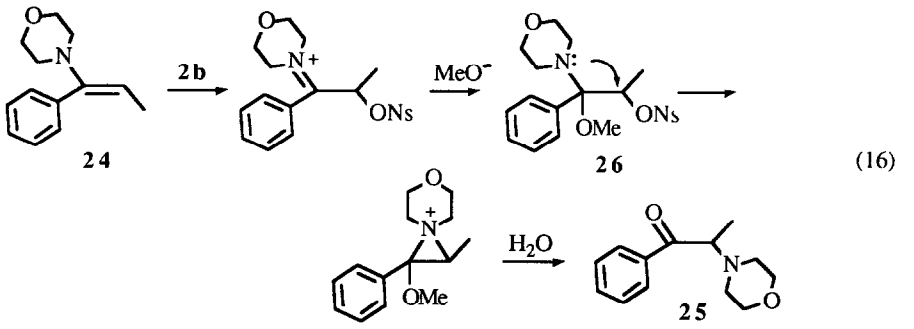
Amine nucleophiles also add to the carbonyl group of **6**, however, in the tetrahedral intermediate **22**, either the hydroxy group or the amino group could function as the intramolecular nucleophile As expected, the nitrogen displaces nosylate at the two position preferentially to produce α-amino ketones **23** in high yields (Eqn 15) [59]



(15)

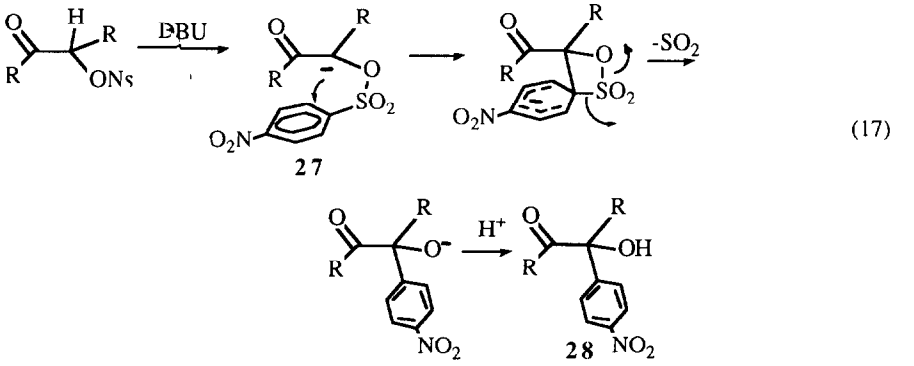
While the products from reaction of methoxide with α-nosyloxy ketones rule out a direct displacement of nosylate (no α-methoxy ketones are detected in the products), amino ketone **23** could result from a simple displacement of the nosylate by the amine Support for the pathway shown in Equation 15 was obtained from additions of **2b** to enamines Reaction of morpholine enamine **24** with **2b** followed by addition of sodium methoxide led to amino ketone **25** Methoxide addition to the iminium ion produced by addition of **2b** yields a tetrahedral intermediate **26**, analogous to **22**, which proceeds to product by intramolecular displacement of nosylate (Eqn 16) [59]

The α-nosyloxy group orchestrates nucleophilic addition to the carbonyl group as a major reaction pathway of α-nosyloxy ketones This preference is very useful as a selective way to incorporate nucleophiles at the α-position of ketones



(16)

A second major effect of an α-nosyloxy group is to increase the acidity of the α-proton (probably by abc 1-2 pK_a units) Reaction with non-nucleophilic bases gives α-proton removal In the case of α-nosyloxy ketone the nosyloxy enolate **27** undergoes rapid ipso substitution to deliver nitrophenyl alcohols **28,** which are presumably formed by sulfur dioxide extrusion from a four-membered ring Meisenheimer intermediate (Eqn 17) [59]



(17)

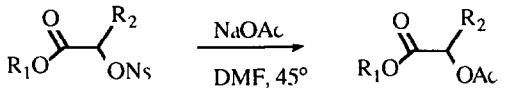
The two processes by which α-nosyloxy ketones react in the presence of nucleophiles/bases, namely carbonyl addition by nucleophiles and enolate formation with non-nucleophilic bases, are also observed for α-triflyloxy ketones In the presence of sodium methoxide, α-triflyloxy ketones give α-hydroxy ketals as in Equation 14, [52,60] and the enolate formed in the presence of non-nucleophilic bases undergoes reductive elimination to diketones (ipso substitution is not possible in triflates) [32,61] In this respect α-nosyloxy ketones an α-triflyloxy ketones exhibit comparable chemical behavior towards nucleophiles and bases- nucleophiles add to the carbonyl carbon and bases remove the α-proton

In contrast α-mesyloxy ketones and α-tosyloxy ketones do not react by carbonyl addition- rearrangement with nucleophiles[60] nor do they give the α-sulfonyloxy enolate and reductive elimination to dicarbonyl compounds [61] Instead, most reports of these compounds describe only direct displacement of the sulfonyloxy group by nucleophiles, particularly soft nucleophiles such as thiols, sulfides, and phosphines [54,62] More work is certainly needed to confirm these differences and understand them, but at present there seems to be a distinct

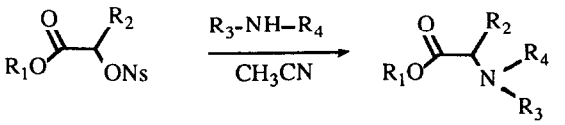
difference in behavior between α-triflyloxy and α-nosyloxy ketones on the one hand, and α-tosyloxy and α-mesyloxy ketones on the other If these differences were understood, it might be possible to install a particular α-sulfonyloxy group in order to select one reaction pathway over another, and thus select the type of product which is produced Such choices are not possible in α-halo ketones

3 2 2-Nosyloxy Esters If the reactions of α-nosyloxy ketones with nucleophiles could be extrapolated to α-nosyloxy esters, then the ester function could also be used to deliver nucleophiles cleanly to the α-position In fact it has been shown that a variety of nucleophiles displace the nosylate group of 2-nosyloxy esters, **10**, effectively to give α-substituted esters At present a direct nucleophilic displacement mechanism of substitution explains the results satisfactorily Except for some very recent findings, evidence for the carbonyl addition-rearrangement mechanism has not been forthcoming

For example, treatment of 2-nosyloxy esters with sodium ethoxide in ethanol gives only α-proton removal and ipso substitution analogous to those in Equation 17 Less basic nucleophiles, however, readily displace nosylate giving a variety of 2-substituted esters Sodium acetate in DMF gives α-acetoxy esters **29** in good yields (Eqn 18) [63] Amines and amine derivatives give α-amino esters (Eqn 19) [63,64] The use of O-benzyl hydroxylamine and t-butyl carbazate gives N-hydroxy and N-amino amino acid esters **32** and **33**, respectively, thus providing an efficient route to these unusual amino acids directly from esters in three steps [64]

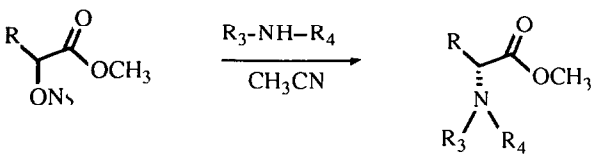


29 (65-75%) (18)



31 (R_3,R_4= H, alkyl) >90%
32 (R_3=H, R_4=OBn) 70-80%
33 (R_3=H, R_4=NHBoc) 60-80% (19)

Only racemic products can be produced by this method Enantiomerically pure 2-nosyloxy esters were prepared from enantiomerically pure 2-hydroxy esters by condensation with p-nitrobenzenesulfonyl chloride Reaction with amines gives high yields of N-substituted amino esters of completely inverted configuration, but reaction with hydroxylamine or hydrazide nucleophiles gives ee's ≈ 70-85% (Eqn 20) [64] The lower



31 (R_3,R_4= H, alkyl) ee >95%
32 (R_3=H, R_4=OBn) ee 70-85%
33 (R_3=H, R_4=NHBoc) ee 70-80% (20)

nucleophilicity of hydroxylamines and hydrazides requires a higher reaction temperature, at which either the starting nosylate or the substituted product is partially racemized Optically active 2-triflyloxy esters, prepared by a similar sequence, are much more reactive towards nucleophiles and provide a better match in reactivity with hydroxylamine and hydrazide nucleophiles They are converted to N-hydroxy and N-amino amino esters in high yields and high optical purities [64,65]

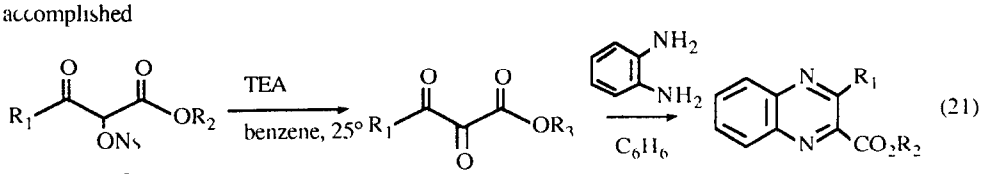
As is again evident, 2-nosyloxy and 2-triflyloxy esters exhibit similar chemical properties, notwithstanding the significantly greater reactivity of the triflates, which have been reported to react quite cleanly with a variety of nucleophiles [31,41,42,66,67] Rates of displacement are much higher for triflyloxy esters than for nosyloxy esters,[64] which parallels leaving group abilities, but both leaving groups can be used effectively for substitutions at the 2-positions of esters It has been reported that α-mesyloxy esters and α-tosyloxy esters are unsuitable substrates for such displacements,[41,42] once again illustrating the dichotomy between triflates-nosylates and tosylates-mesylates attached next to carbonyl groups

The synthetic advantage of sulfonyl peroxides in this regard is that they allow oxidative attachment of a nosylate group to the α-position of ketones and esters and thus provide access to subsequent transformations that are selective and versatile The triflate analog of Koser's reagent, which could be used for attaching the triflate group oxidatively, is an important synthetic complement which needs to be developed further

3 3 3-Keto-2-Nosyloxy Esters 2-Nosyloxy-3-ketoesters **14** represent a hybrid between α-nosyloxy ketones and 2-nosyloxy esters The high, differentiated functional group density in these compounds makes them intriguing synthetic intermediates for the preparation of other 1,2,3-trifunctionalized compounds in a selective fashion Indications are that such is the case

Treatment of **14** with triethylamine gives rapid reductive elimination of p-nitrobenzenesulfinate and formation of tricarbonyl compounds **34** (Eqn 21) [68] The tricarbonyl products could not be isolated in high yields due to their known instability towards isolation,[69] but they were trapped as their quinoxaline derivatives in high yields Chloro nosylate **36** underwent double elimination to vinyl tricarbonyl **37,** which was converted *in situ* to pyrrole **38** with benzylamine (Eqn 22) This route to tricarbonyl compounds is also observed for 2-nosyloxy-β-diketones[68] and 2-nosyloxy-3-ketoamides,[46] and is a simple and attractive alternative method for their preparation The interest in, and use of, tricarbonyl compounds has risen dramatically recently due to their occurrence in the powerful immunosuppressant FK-506 and related antibiotics,[70] and their importance as synthetic intermediates, demonstrated by Wasserman [71]

Replacement of the nosylate in 2-nosyloxy-3-ketoesters by nucleophiles is limited by the fact that the 2-proton is quite acidic and is removed if the nucleophile is at all basic As a result substitution for nosylate has not been accomplished

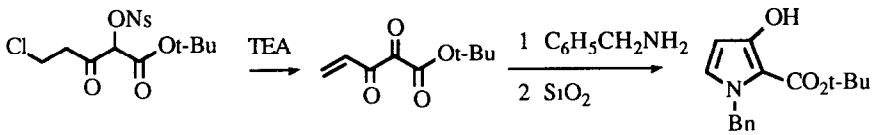


(21)

14a R_1=CH_3, R_2=Me
14b R_1=CH_3, R_2=Et
14c R_1=$CH(CH_3)_2$, R_2= Et
14f R_1= Ph, R_2=Et

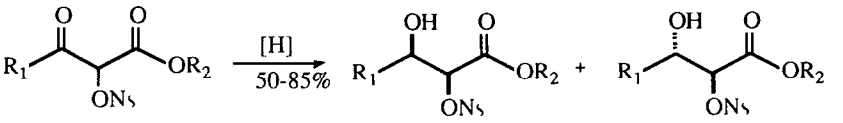
34a-c,f

35a - 94%
35b - 74%
35c - 84%
35f - 92%



36 37 38 (68%) (22)

The ketone function of 2-nosyloxy-3-ketoesters can be reduced to the alcohol group in good yields by several reagents (Eqn 23) [63] Two diastereomeric 3-hydroxy-2-nosyloxy esters **39**-*syn* and **39**-*anti* can be produced Preliminary results suggest that two factors control the diastereoselection of the reduction, which ranges from fair to excellent The first is the size of R_1 and the second is the identity of the metal ion of the reductant

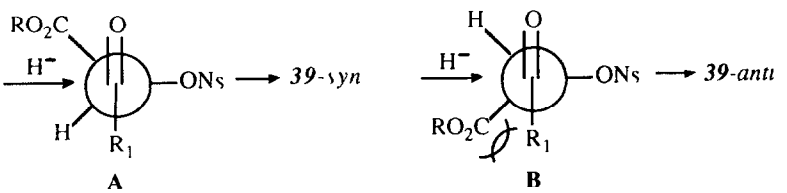


14 **39**-*syn* **39**-*anti* (23)

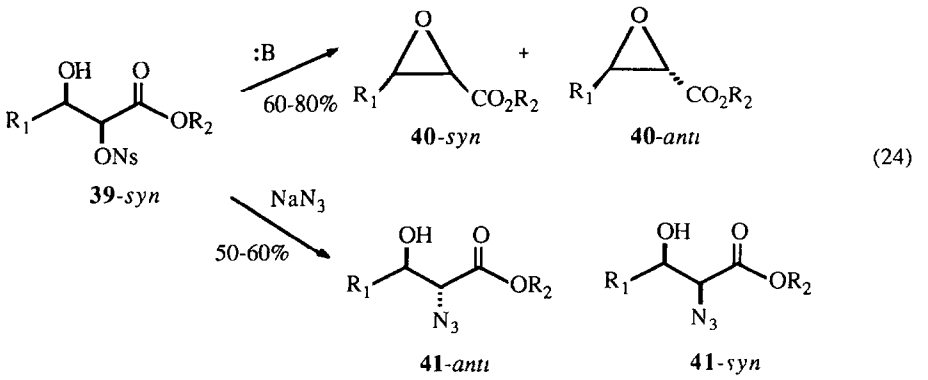
Substrate		$NaBH_4$ (*syn anti*)	L-Selectride (*syn-anti*)
R_1	R_2		
Me	Me	24 76	57 43
Ph	Et	100 0	100 0
i-Pr	Et	93 7	100 0
i-Pr	t-Bu	100 0	100 0

Two transition state models of the Felkin-Anh type can be drawn for **14** (Fig 4) [72] Conformation **A** is of lower energy than **B** due to decreased steric interactions between the ester group and R_1 Furthermore structure **A** can have a metal ion chelated to the ester and ketone carbonyl groups When R_1 is small (methyl or n-alkyl) and sodium borohydride is the reductant, there is no significant chelation, **A** and **B** are similar in energy, and a mixture of **39**-*syn* and **39**-*anti* is produced in a ratio of ≈ 2 1 favoring **39**-*anti* When R_1 is larger (phenyl or isopropyl), **B** is much higher in energy and **39**-*syn* is produced as the major product (de ≈ 90%) The use of L-Selectride as the reductant further stablilizes **A** by chelation and more *syn* isomer is produced For instance when small R_1 groups are present, the product ratio changes from 1 2 *syn anti* ($NaBH_4$) to 1 4 1 (L-Selectride) For large R_1 groups, steric and chelation effects reinforce each other to the extent that **39**-*syn* is the only isomer detected

Figure 4



3 4 3-Hydroxy-2-Nosyloxy Esters More work is needed to refine the model and to obtain better stereocontrol of the reduction of 2-nosyloxy-3-ketoesters since the hydroxy nosylate products are interesting intermediates in their own right For example they can be converted to epoxy esters **40**-*syn* and **40**-*anti* in good yields (Eqn 24) [63] Starting with **39**-*syn*, isomer **40**-*syn*, the product with stereochemistry expected from direct closure of **39**-*syn* is favored by 3 1 (≈ 25% isomerization) The nosylate group of **39**-*syn* can be replaced by azide to yield hydroxy azides **41**-*anti* and **41**-*syn* as a 3 1 mixture (Eqn 24) [63] Again about 25% isomerization is found While both processes are stereoselective (de≈ 50%), the point at which isomerization occurs is not yet known, but it must be determined if stereospecificity is to be achieved



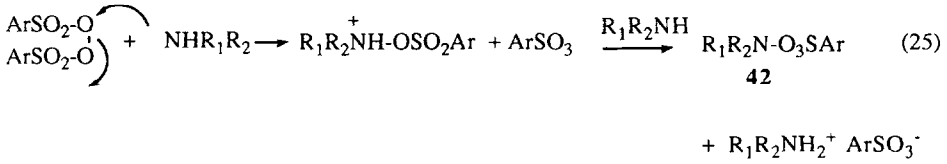
(24)

These results show that 3-keto-2-nosyloxy esters are exciting intermediates for the synthesis of 1,2,3-trifunctional molecules, since chemistry at both the 2- and 3-positions can, within some limits, be carried out independently and selectively These limits require further definition, but a multitude of other products are potentially accessible from these intermediates

4 Oxidation of Amines with Arenesulfonyl Peroxides

Sulfonyl peroxides oxidize electron donor functions other than π-systems For example, in the analysis of sulfonyl peroxides by iodometric titration, a key step is the oxidation of iodide to iodine, which presumably occurs by the nucleophilic attack of iodide on the peroxide bond [73] In another study the oxidation of triphenylphosphine to triphenylphosphine oxide by **2c** was shown to result from nucleophilic attack by the phosphine on the peroxide oxygens [74]

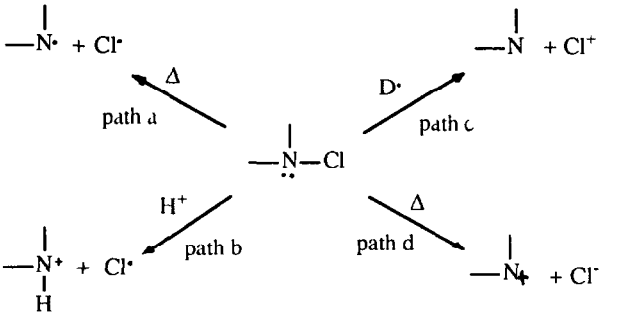
The corresponding reaction between amines and arenesulfonyl peroxides is of great interest, since it would provide a direct synthesis of N-(arenesulfonyl)oxy amines **42** (Eqn 25) These compounds, because of the excellent leaving ability of the arenesulfonate group, could undergo ionization of the N-O bond and yield an electron deficient nitrogen intermediate (nitrenium ion), which is of great synthetic and mechanistic interest [75]



(25)

Approaches to nitrenium ions have largely relied on N-chloramines as substrates because of their ease of preparation [75] Unfortunately chloramines characteristically exhibit many mechanistic variations in their chemical reactions As illustrated in Figure 5, four different modes of N-Cl bond cleavage have been identified, two free radical and two ionic pathways [76] Of these four, only **path d** gives a nitrenium ion Furthermore the pathway actually followed is very sensitive to the reaction conditions It is not surprising that mechanistic interpretation of solvolysis results on the basis of chloramine precursors has engendered many lively discussions in the literature [77]

Figure 5



One way to favor the production of electron deficient nitrogen is to increase the leaving ability of the group attached to nitrogen and thus lowering the activation barrier to **path d** and favoring it at the expense of other modes of reaction Several groups reported attempts to put tosyloxy leaving groups on the nitrogen of alkyl amines by condensation of the corresponding hydroxylamine with tosyl chloride (Eqn 26) [78-82] This corresponds to the "normal" method of attaching sulfonyloxy groups to substrates (Fig 2, path a) by sulfonylation of a hydroxyl group In some cases the N-tosyloxy compounds were isolated and used as aminating agents,[79-83] but in most cases the compounds are unstable, and only products of decomposition are obtained N-Aryl hydroxamic acids have been converted to their mesylate[85] and sulfate[86] derivatives, which are much more stable and were used as solvolysis substrates N-Aryl hydroxylamines also form stable N-sulfate derivatives,[87] which were also used as solvolysis substrates

$$R_2\text{—}\underset{\displaystyle R_1}{\overset{\displaystyle |}{N}}\text{—OH} \xrightarrow[\text{Base}]{\text{TsCl}} R_2\text{—}\underset{\displaystyle R_1}{\overset{\displaystyle |}{N}}\text{—OTs} \qquad (26)$$

Since N-unsubstituted sulfonyloxy amines are well known,[88] it is clear that placing one or more alkyl substituents on the nitrogen of N-sulfonyloxy amines decreases their stability markedly As a result little systematic study of the chemistry of these compounds was possible, and their use as progenitors of nitrenium ions was limited until recently

We envisioned that sulfonyl peroxides might provide a new route to N-arenesulfonyloxy amines by the chemistry shown in Equation 25 This route has some advantages over condensation strategies previously employed since amines, and not hydroxylamines, are the required precursors, base is not required in the reaction, and the best arenesulfonyloxy leaving groups, particularly nosylate, could be attached to nitrogen

It was found, in fact, that arenesulfonyl peroxides **2b** and **2e** react readily with amines at low temperatures to give N-nosyloxy amines and N-(trifluoromethyl)benzenesulfonyloxy amines **42**, respectively (Eqn 27) [89] The amine peroxide adducts **42** are rather unstable materials whose rate of decomposition depends on the R-group attached to nitrogen Adduct **42a** is relatively stable and can be stored for months at -20°C and handled at room temperature for short periods without noticeable decomposition On the other hand **42c** begins to degrade after several hours at -20°C In solution, all of these adducts undergo decomposition with $t_{1/2}$ = 1-20 h and are especially sensitive to base This behavior explains why condensation methods for the synthesis of N-sulfonyloxy amines often fails to deliver products, since bases are required to catalyze the condensation

$$2\ R{-}NH_2 \xrightarrow[\text{EtOAc, -78°}]{(ArSO_2O)_2} \underset{\mathbf{42}}{R{-}\overset{H}{\underset{|}{N}}{-}OSO_2Ar} + RNH_3^+\ ArSO_3^- \qquad (27)$$

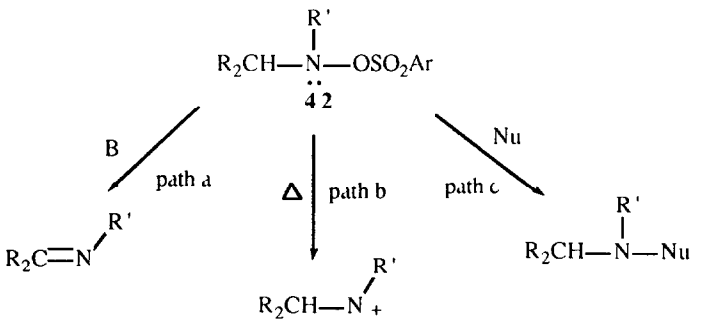
Ar= p-$NO_2C_6H_4$ Ar= 3-$CF_3C_6H_4$
a R=CH_3 (96%) **d** R= t=Bu (90%)
b R= t-Bu (87%) **e** R= $C_6H_5CH_2$ (83%)
c R= 3-$ClC_6H_4CH_2$ (63%)

5 Reactions of N-Alkyl-N-Arenesulfonyloxy Amines

Because sulfonyl peroxides are very effective for the oxidative attachment of arenesulfonyloxy leaving groups to amines, the chemistry of N-sulfonyloxy amines could be studied in detail The instability of these compounds poses some problems in their isolation In many cases they were prepared, characterized spectroscopically, and allowed to react without isolation This protocol is not only much easier experimentally, it also avoids decomposition which can occur *during* isolation

Three major processes might be expected to occur from ionic reactions of **42** As shown in Figure 6, base promoted elimination (path a), ionization to a nitrenium ion (path b), and nucleophilic displacement on nitrogen (path c) all have analogy in the reactions of carbon atoms substituted with leaving groups Studies of N-sulfonyloxy amines **42** indicate that both elimination (path a) and ionization (path b) occur readily under appropriate conditions

Figure 6



5 1 Elimination Treatment of N-sulfonyloxy amines, which contain α-hydrogens, with bases gives smooth elimination to an imine (path a) [90,91] Only mild amine bases are required Elimination followed by hydrolysis results in overall oxidative deamination (Eqn 28) The yields of oxidative deamination obtained are comparable and often superior to those of other methods [92] The results show, however, that a major stumbling block in oxidative deamination by *any* method is the inherent instability of the first-formed imine product prior to hydrolysis

$$R_1R_2CH{-}NHR_3 \xrightarrow{\mathbf{2b}} R_1R_2CH{-}\underset{R_3}{N}{-}ONs \xrightarrow{:B} R_1R_2C{=}NR_3 \xrightarrow{H_3O^+} R_1R_2C{=}O + R_3NH_2 \qquad (28)$$

The oxidation-elimination sequence can also be applied effectively to amine derivatives such as hydrazines which yield azo-compounds [93] A variety of mono and disubstituted hydrazines and hydrazides gave 60-85% yields of compounds derived from the azo product

Base-promoted eliminations in N-arenesulfonyloxy amines are similar to base-promoted, olefin forming eliminations in all-carbon systems in that they are concerted, E2-type reactions [90] A detailed picture of the transition state for imine-forming eliminations has been drawn which shows that while concerted, the transition state is very E1-like[94-97] with significant electron deficiency developed on the nitrogen atom

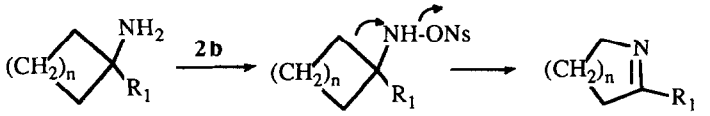
5 2 Ionization-Rearrangement In the absence of base, or in substrates where no α-hydrogens are available for elimination, N-arenesulfonyloxy amines **42** undergo ionization coupled with skeletal rearrangement (Fig 6, path b) This process was first observed in trityl amines,[98] but was soon found to be a general reaction of **42** in the absence of base (Eqn 29) [99,100] Skeletal rearrangement is concerted with loss of leaving group Thus free nitrenium ions are not reaction intermediates [77] Of synthetic importance is the fact that a new carbon nitrogen bond is formed by a rearrangement process that utilizes an amine as the starting material Other well known cationic, carbon-to-nitrogen rearrangements, such as the Beckmann rearrangement and the Schmidt rearrangement, also give new carbon-nitrogen bonds, but they require carbonyl compounds as starting materials [101]

$$R_2\overset{R_1}{\underset{R_3}{C}}{-}NH_2 \xrightarrow{(ArSO_2O)_2} R_2\overset{R_1}{\underset{R_3}{C}}{-}NH\text{-}OSO_2Ar \;(\mathbf{42}) \longrightarrow \begin{cases} R_2\overset{R_1}{C}{=}N{-}R_3 \\ R_3\overset{R_1}{C}{=}N{-}R_2 \\ R_3\overset{R_2}{C}{=}N{-}R_1 \end{cases} \qquad (29)$$

When dissimilar groups are attached to the migration origin, several isomeric imine products can be obtained Three factors are important in determining the product mixture a the inherent migratory aptitudes of the groups on the α-carbon, b electronic effects at the migration origin, and c stereoelectronic effects resulting from the requirement that the migrating group be antiperiplanar to the leaving group [101] Understanding these factors

allowed control of the reaction outcome by selection of appropriate rearrangement precursors so that only a single product is obtained

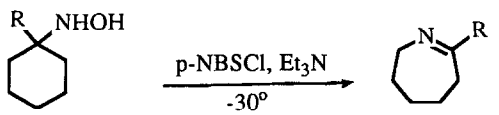
The rearrangement is particularly suited to cyclic amines which undergo insertion of nitrogen into the ring to yield ring-expanded imines A method was developed for the synthesis of azacyclic products from suitable cyclic amine substrates (Eqn 30) [102] A variety of ring sizes can be produced by this process



(30)

n= 2,3,4

The ability to produce and then study N-arenesulfonyloxy amines has provided a great deal of insight into the stability and properties of this little known group of compounds Once their reactions had been surveyed, it was clear why earlier attempts to prepare them by condensation methods had failed It was also clear under what circumstances condensation methods could be effective for the generation and rearrangement of N-arenesulfonyloxy amines Thus the reaction of tertiary, cyclic hydroxylamines with p-nitrobenzenesulfonyl chloride gave good yields of ring expanded products (Eqn 31) [102]

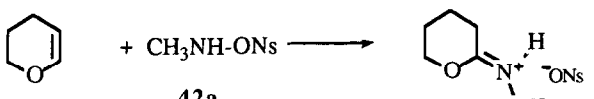


(31)

R = -$CH_2C_6H_5$ (85%)
R = -C_4H_9 (53%)

5 3 Addition to Oxonium Ions Despite numerous attempts, the displacement of the arenesulfonate group by nucleophiles in **42** (Fig 6, path c) has not been achieved [103] It is unlikely that N-sulfonyloxy amines with substituents other than hydrogen on the nitrogen atom can be developed as electrophilic aminating agents Nevertheless, some new synthetic uses of N-sulfonyloxy amines were found in the effort to accomplish nucleophilic substitution on nitrogen

Due to the sensitivity of N-arenesulfonyloxy amines to bases, which promote elimination, only non-basic nucleophiles were considered Enol ethers were likely candidates since they are good, non-basic electron donors Reaction of dihydropyran (DHP) with methylamine nosylate **42a** gave imidate salt **43** in quantitative yield by pmr (Eqn 32) [104] While **43** was difficult to hydrolyze cleanly, a mixture of hydrolysis products could be isolated in >69% yield

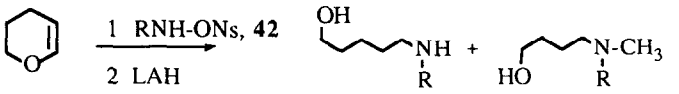


43

(32)

The reaction was shown to be general for a series of N-substituted N-nosyloxy amines Reduction of the crude product gave two amino alcohol products **44** and **45** (Eqn 33) [104] The reaction scenario which best

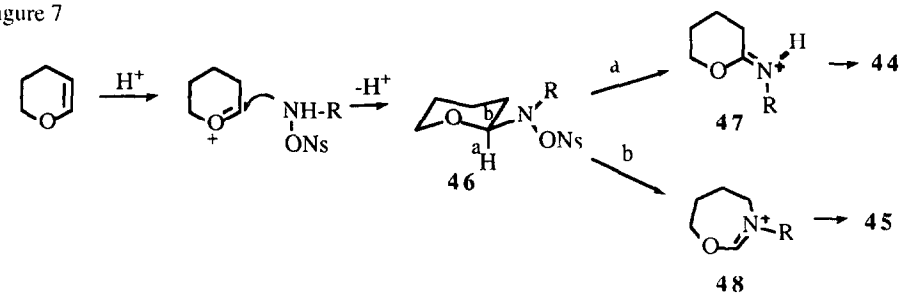
accounts for these products is one in which the N-sulfonyloxy amine adds as a nucleophile to an oxonium ion formed from by protonation of DHP to produce a new N-sulfonoxy amine derivative **46** (Fig 7) Intermediate **46** undergoes ionization-rearrangement either by hydride migration (path a) to imidate **47** and thus **44**, or by ring expansion (path b) to **48** and thus **45** Normally ring expansion (alkyl migration) would not compete with hydride migration because of the difference in migratory aptitudes of these two groups Stabilization of the migration origin by the oxygen substituent is sufficient to mask this difference to a large extent Another effect of oxygen stabilization of the migration origin is that no hydride migration from the R-group is observed



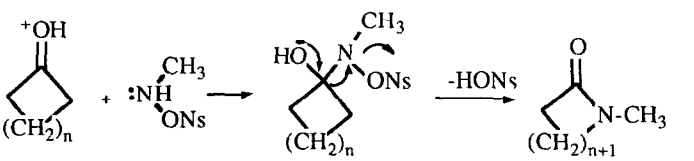
(33)

42a R=Me	**44a** 29%	**45a** 3%
b R=Et	**44b** 32%	**45b** 13%
c R=n-Pr	**44c** 35%	**45c** 12%
d R=n-Bu	**44d** 36%	**45d** 12%

Figure 7

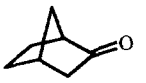


A most important feature is that N-sulfonoxy amines function effectively as nucleophiles towards oxonium ions to produce new N-sulfonyloxy amine rearrangement substrates Oxonium ions produced by other methods should behave similarly The simplest oxonium ions are those formed by protonation of carbonyl compounds (aldehydes and ketones) It was found accordingly that treatment of a series of cyclic ketones with N-nosyloxy methylamine, **42a**, gave ring expanded N-methyl lactams **49** in good to excellent yields (60-95%) by rearrangement of the carbinolamine intermediate **50** (Eqn 34) [105] A variety of ring sizes were used (n=1,2,3) with good success, and fair regioselectivity was observed when substituents were present at the 2-position of the



(34)

Table 3 The Reaction of Cyclic Ketones with N-(p-Nitrobenzenesulfonyloxy) Methylamine, **42a**, in Chloroform at 25°C

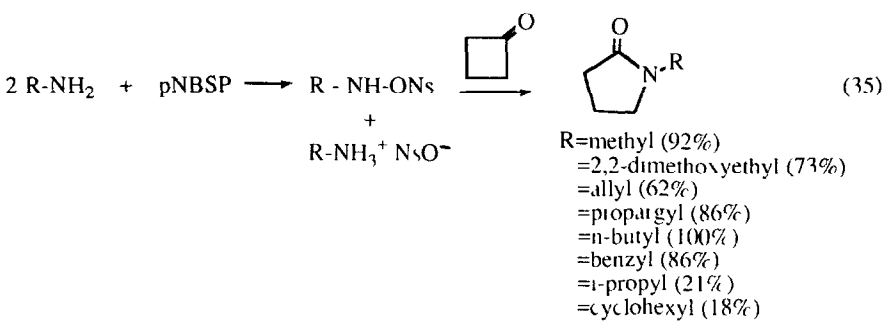
Entry	Ketone	Product	Yield(%)
1	Cyclobutanone	N-methylpyrrolidinone	96
2	2-Methylcyclopentanone	N,6-dimethylpiperidinone	82
3	Cyclohexanone	N-methylcaprolactam	73
4	2-Methylcyclohexanone	N,7-dimethylcaprolactam N,3-dimethylcaprolactam	84 (4 1)
5	3-Methylcyclohexanone	N,6-dimethylcaprolactam N,4-dimethylcaprolactam	62 (1 1)
6	4-t-Butylcyclohexanone	5-t-butyl-N-methylcaprolactam	68
7			100 (3 2)
8	Cycloheptanone	N-methylazacyclooctanone	12

starting ketone (Table 3) In general the more substituted carbon migrated with a 4 1 or greater preference (Entries 2,4), similar to the migratory preference of secondary over primary carbons in open chain systems [100]

Steric features that slow the formation of the tetrahedral intermediate **50** (or reduce its equilibrium concentration) decrease the yield significantly (Entry 8) as competitive decomposition of the N-sulfonyloxy amine takes over On the other hand ring strain both speeds the addition and drives the rearrangement significantly (Entries 1,7)

This transformation of ketones to lactams is reminiscent of the β-lactam synthesis of Wasserman without the need for stable carbinolamine intermediates,[106] and analogous to Barton's procedure without the need for the preparation of nitrone intermediates [107] It is a simple, one step transformation

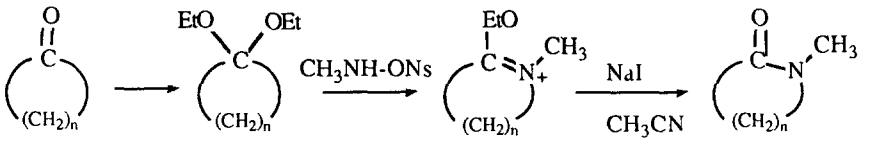
The instability of N-nosyloxy amines with N-alkyl substituents different than methyl requires high reactivity in the ketone so that addition-rearrangement is faster than decomposition of the N-nosyloxy amine Cyclobutanone is well suited for this purpose and reacts with N-nosyloxy amines generated *in situ* from amines



(35)

and pNBSP High yields of N-substituted pyrrolidinones are obtained (Eqn 35) [105] Branched chain amines, however, add too slowly for good results

Ketals can also serve as a source of oxonium ions which cannot revert to the ketone readily Thus they add **42a** effectively, even for large ring sizes Rearrangement proceeds well to give imidate salts which are dealkylated to N-methyl lactams A one pot procedure was developed to convert cyclic ketones to N-methyl lactams in good yields using this sequence (Eqn 36) [108]



(36)

n=4, 76%
n=5, 90%
n=6, 48%
n=7, 58%
n=11, 63%

6 Summary

The oxidative attachment of sulfonoxy leaving groups to the α-carbon of enol derivatives and to the nitrogen of amines through the use of arenesulfonyl peroxides has made available several classes of compounds heretofore difficult to prepare and thus little known The good leaving ability of the nosyloxy group, most commonly employed, enforces ionic modes of reaction in these compounds and permits the formation of new bonds to the substrate by several nucleophilic processes including both displacements and rearrangements As a result of this two electron oxidative process, namely electrophilic attachment of the arenesulfonate followed by its loss as an anion, we have developed new synthetic approaches to several classes of compounds Many other transformations can be envisioned for these materials, but these remain to be placed into practice

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