Tandem Addition-Cycloaddition Reaction of Oximes with 2,3-Bis(phenylsulfonyl)-1,3-butadiene as a Method for 4-Piperidone Synthesis†

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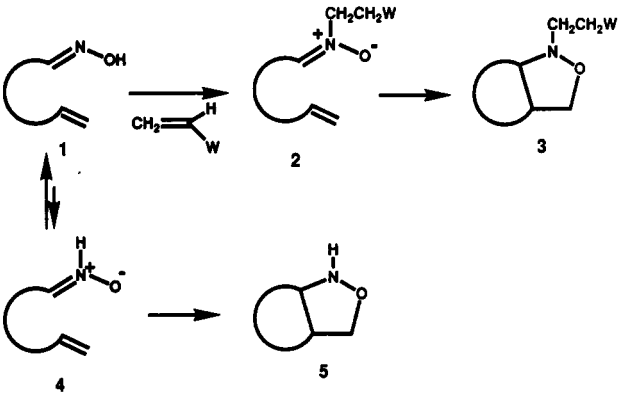
The reaction of oximes with 2,3-bis(phenylsulfonyl)-1,3-butadiene affords 7-oxa-1-azanorbornanes in high yield. The formation of the bicyclic isoxazolidine involves conjugate addition of the oxime onto the diene to give a transient nitrone that then undergoes a subsequent intramolecular dipolar cycloaddition reaction. The coupling of several oximes with divinyl sulfone was also studied, and related cycloadducts were obtained in excellent yield. The stereochemistry of the cycloaddition is best explained in terms of an exclusive reaction of the *Z* isomer of the nitrone via an easily attainable endo orientation of the reactive groups. Molecular mechanics calculations have been refined to accurately predict the regiochemistry of the intramolecular cycloaddition. Treatment of these 7-oxa-1-azanorbornanes with Raney nickel in methanol results in reductive nitrogen-oxygen bond cleavage to give substituted 4-piperidones. The bicyclic isoxazolidine derived from cyclohexanone oxime and bis(phenylsulfonyl)diene was converted to the azaspiro[5.5]undecane ring system, which is representative of the key ring skeleton of the perhydrohistrionicotoxin family of alkaloids.

Heterocyclic ring formation with simultaneous introduction of substituent groups in a stereocontrolled manner is of key interest to synthetic chemists. Because of the efficiency of the 1,3-dipolar cycloaddition reaction for the preparation of five-membered rings with control of stereochemistry, much effort has been devoted to studying the reaction of various 1,3-dipoles with π bonds.[1] In recent years, the 1,3-dipolar cycloaddition reaction of nitrones has emerged as a particularly powerful method for preparing highly functionalized nitrogen heterocycles.[2-13] Intramolecular nitrone cycloadditions have also been of considerable synthetic and mechanistic interest, especially since the resulting isoxazolidine ring can serve as a precursor to 1,3-amino alcohols.[14,15]

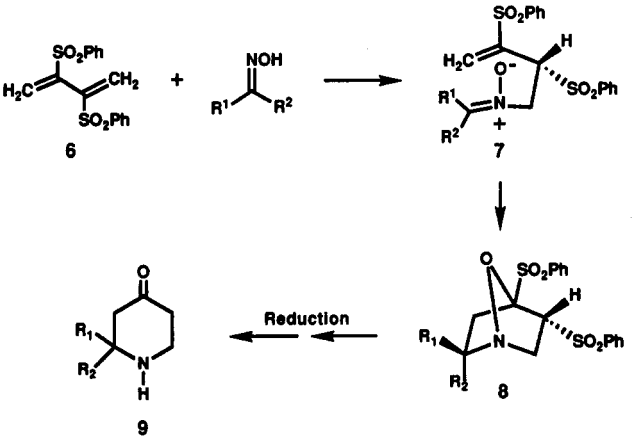
Condensation of carbonyl compounds with N-substituted hydroxylamines and oxidation of N,N-disubstituted hydroxylamines represent the most common methods for the synthesis of nitrones[16,17] (Scheme I). Recently, a number of groups have developed an alternative method for the synthesis of nitrones that involves the reaction of an oxime with an activated π bond.[18-24] The reaction generally requires the presence of a Michael acceptor olefin in order to produce the nitrone. Once formed, the nitrone has been observed to undergo both inter- and intramolecular dipolar cycloaddition. The reaction was first discovered by Ochiai and co-workers in 1967[18] and has been nicely exploited by both the Grigg[23] and Hassner[24] teams over the past several years. The intramolecular version of the oxime cyclization has been employed in a number of natural product syntheses.[25,26] A few examples are also known where the oxime undergoes an unassisted thermal cyclization, believed to involve a proton transfer from O to N to generate a 1,3-dipole (i.e., 4) as a reactive intermediate.[26-29]

As part of our ongoing interest in synthetic applications of nitrone cycloaddition chemistry,[30] we thought it worthwhile to examine a route to piperidones involving the addition of oximes to 2,3-bis(phenylsulfonyl)-1,3-butadiene (6) (Scheme II). We reasoned that the initially formed nitrone 7 would readily undergo cycloaddition to the neighboring π system to give the bicyclic isoxazolidine 8. Reductive cleavage of this system should eventually pro-

Scheme I



Scheme II



† Dedicated to Professor Rolf Huisgen on the occasion of his 70th birthday.

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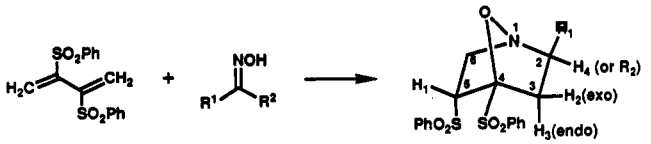
Table I. Cycloaddition Reactions of Aldehyde and Ketone Oximes with 2,3-Bis(phenylsulfonyl)-1,3-butadiene (6)



entry	R_1	R_2	% yield	mp, °C	conditions
8a	Ph	H	95	170–171	CH_3CN, 80 °C, 18 h
8b	p-BrC_6H_4	H	90	200–201	$PhCH_3$, 110 °C, 48 h
8c	CH_3	CH_3	95	152–153	CH_2Cl_2, 25 °C, 24 h
8d	CH_3	H	95	181–182	CH_2Cl_2, 25 °C, 18 h
8e	$-(CH_2)_4-$		67	164–165	CH_2Cl_2, 25 °C, 12 h
8f	$-(CH_2)_5-$		93	184–185	CH_2Cl_2, 25 °C, 24 h
8g	$-(CH_2)_6-$		91	156–157	CH_3CN, 80 °C, 18 h
8h	$(CH_2)_4OH$	H	85	oil	CH_2Cl_2, 25 °C, 18 h

duce piperidones of type 9. This paper outlines our successful achievement of this strategy.[31]

Results and Discussion

Conjugated dienes with electron-withdrawing substituents within the diene unit have attracted considerable attention during recent years.[32-35] Sulfur-substituted dienes, in particular, have been widely used in Diels–Alder reactions. The sulfur atom not only increases the reactivity of the diene but also adds control to the regioselectivity of the cycloaddition.[36] Recent work in our laboratory[37] as well as that of Bäckvall[38] has shown that the higher oxidized phenylsulfonyl dienes are versatile synthons that can be used for heterocyclic synthesis. The phenylsulfonyl group is an extremely useful functionality in organic synthesis since it can enhance chemical reactivity and then be easily removed to provide sulfur-free compounds.[39-41] In spite of its simplicity and its obvious potential as an activated diene, 2,3-bis(phenylsulfonyl)-1,3-butadiene (6) has not been extensively utilized for organic synthesis.[42] It seemed to us that the 2,3-activated diene 6 should be highly reactive toward nucleophilic addition because of its markedly lowered LUMO energy level compared to that of 1,3-butadiene.[43]

We have studied the reaction of aldehyde and ketone oximes with diene 6 in several solvents and at different temperatures and observed the formation of a single product (67–95%) in all the cases examined (see Table I). The structure of the cycloadduct 8 follows from its spectroscopic properties. The stereochemical assignment of the phenylsulfonyl group at C_5 as endo is based on the fact that the 5-exo hydrogen exhibits a long-range W-coupling (J = 2 Hz) with the exo C_3 proton. This exo hydrogen (i.e., H_2) is coupled by ca. 5 Hz with the hydrogen at C_2 (i.e., H_4), thereby fixing the geometry of the C_2 substituent (R_1) as exo.

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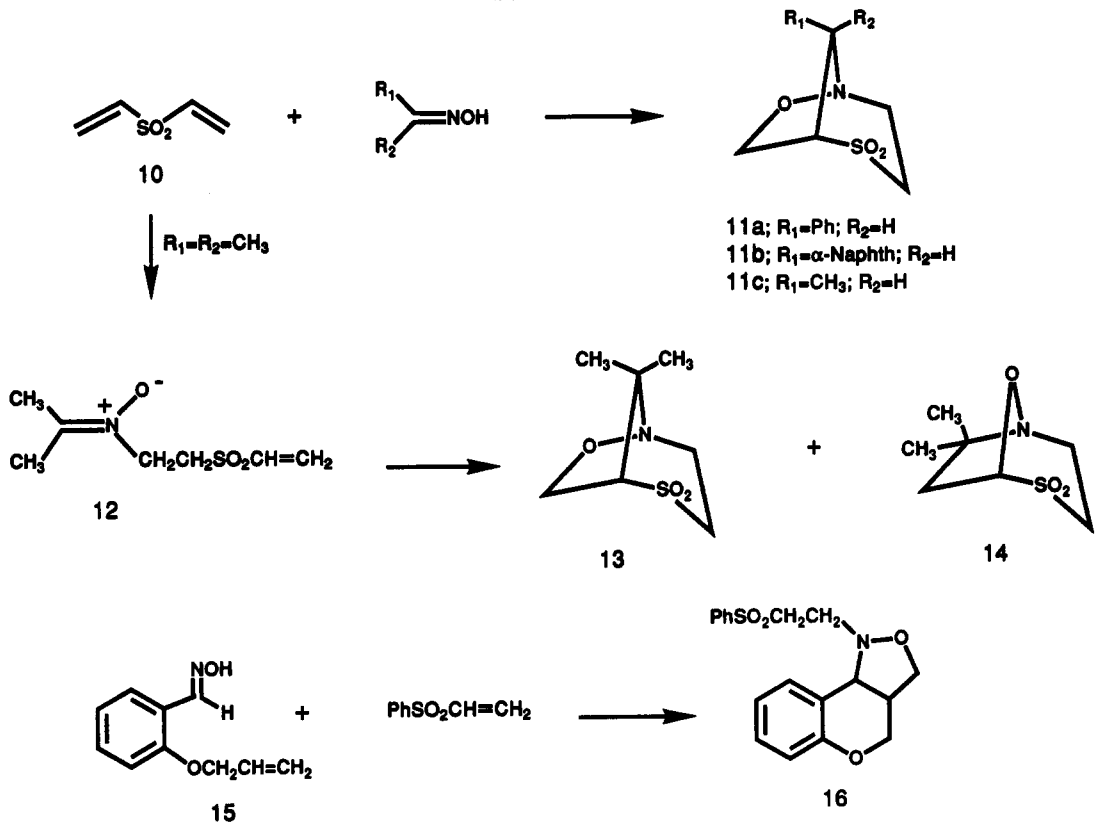
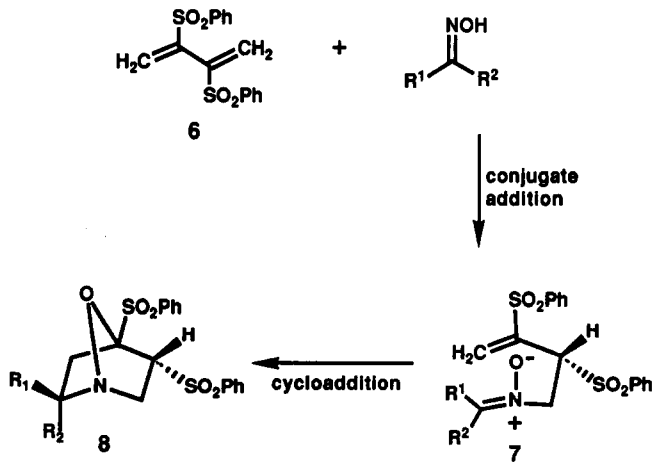
(43) MNDO Calculations (AM1) indicate a HOMO energy for diene 1 at −10.96 eV and a LUMO at −0.29 eV. QCPE No. 506 (AMPAC) was used for this determination.

Scheme III



The mechanism by which cycloadduct 8 is formed is of considerable interest. We believe that its formation involves conjugate addition of the oxime onto diene 6 to give a transient nitrone (i.e., 7), when then undergoes a subsequent intramolecular dipolar cycloaddition reaction. There is much precedent for this pathway in the literature; quite a number of examples have been reported dealing with oxime olefin cycloadditions.[18-29] Intramolecular cycloaddition of *N*-alkenyl-substituted nitrones has been previously shown to lead regioselectively to the 7-oxa-1-azanorbornane ring system, thereby providing good support for the proposed mechanism.[44-52]



Additional evidence for the proposed pathway was obtained by studying the reaction of several oximes with divinyl sulfone. The aldehydic oximes afforded cycloadduct 11 as the sole product in 90–95% yield (Scheme III). A significant loss of regioselectivity was observed, however, in the reaction of acetone oxime which produced a 3:2 mixture of cycloadducts 13 and 14 in near quantitative yield. A related reaction also occurred when oxime 15 was heated with phenyl vinyl sulfone in toluene at 110 °C for 12 h. In this case, a 90% yield of cycloadduct 16 was obtained. It should be pointed out that Grigg and co-workers have recently encountered analogous results with some related systems.[53]

The regiochemistry of the nitrone intramolecular dipolar cycloaddition reaction is complicated by a complex interplay of factors such as alkene polarity, ring strain, and other nonbonded interactions. In general, the intramolecular situation can be assessed as a competition between the bridged and fused modes of cycloaddition. Since LeBel first reported the facile intramolecular cycloaddition of unsaturated nitrones to form bicyclic isoxazolidines,[14] there has been considerable interest in this reaction.[2,3] Intramolecular *N*-alkenylnitrone cycloadditions generally proceed with high regio- and stereoselectivity. Up to four chiral centers can be predictably controlled. The complete stereoselective cycloaddition of nitrone 7 to the 7-oxa-1-azanorbornane system 8 is perfectly consistent with the

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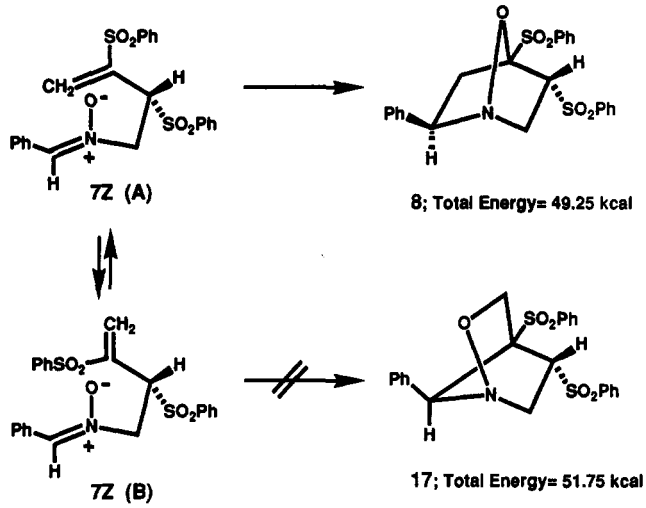
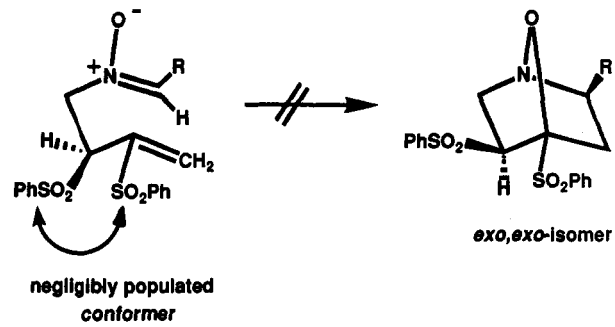
earlier regiochemical observations.[44-52] Examination of molecular models reveals the incompatibility of a two-carbon bridge linking the dipole and dipolarophile with an exo transition state because of severe angle strain. Accordingly, the stereochemistry of the cycloaddition is best explained in terms of an exclusive reaction of a *Z*-nitrone **7Z** via the easily attainable endo orientation of the reactive groups.

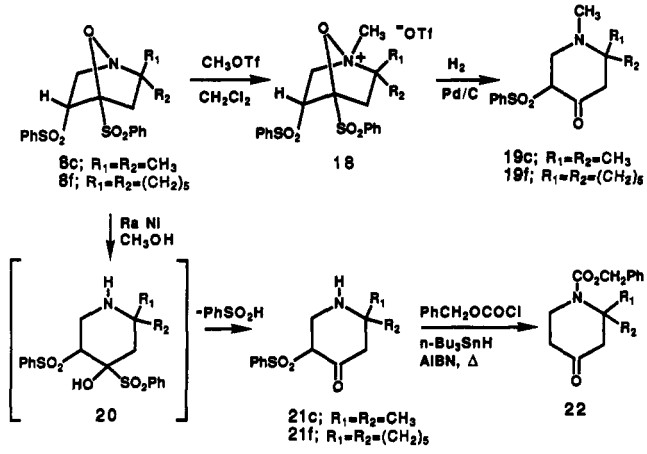


We have used molecular mechanics calculations to model energy differences in the diastereomeric transition states for the two possible cycloadducts (i.e., 8 vs 17). The stability of the diastereomeric cycloadducts was determined by calculation of their steric energies (i.e., the direct sum of the force field increments). These steric energies represent the thermally averaged energies relative to the same molecule but with all bond lengths, bond angles, and torsional angles set to their strainless values and the atoms having van der Waals and electrostatic interactions corresponding to infinite separation.[54] We assume that the relative energy differences of the two lowest energy conformations of the regioisomeric cycloadducts will parallel the energy differences in the transition state. This pair of compounds was subjected to energy minimization within the MODEL KS 2.93 program.[55] Global minima were found by making use of multiconformer generation in MODEL followed by Batch minimization using BAKMDL. The resulting lowest energy conformations were then submitted to MMX88 for the calculations of strain energies. Recently available parameters for transition-state oxygen permit MMX calculations on transition-state energies for the two possible orientations (A and B).[56] The calculations reveal that both ground- and transition-state energies are significantly lower (2.5 kcal/mol) for the formation of 8 than for 17 for which ring closure was not observed. Steric interaction between the two bulky diphenylsulfonyl groups



is undoubtedly responsible for the formation of a single diastereomer from the cycloaddition reaction. The MMX calculations also nicely explain the exclusive formation of cycloadduct 11 from the reaction of aldehyde oximes with divinyl sulfone and account for a mixture of isomers when acetone oxime was used. This difference in selectivity can be attributed to a 2.6-kcal energy difference between the two regioisomeric transition states for the aldehyde oximes but only a 0.6-kcal difference with acetone oxime. This subtle effect is not at all obvious on inspection of molecular models, but here MMX calculations serve well to predict regiochemistry in such intramolecular dipolar cycloadditions.

Since new methods of constructing the piperidone ring continue to be of interest in connection with alkaloid synthesis,[57,58] we thought it worthwhile to explore the reductive ring opening of these 7-oxa-1-azanorbornane derivatives. We found that the nitrogen–oxygen bond of the bicyclic isoxazolidines could be cleaved by two different methods. One procedure involves N-methylation of the isoxazolidine (**8c** or **8f**) with methyl triflate to give the expected quaternary ammonium salt **18** in quantitative yield. Subjection of the salt to catalytic hydrogenation



(Pd/C, 1 atm, CH_3OH) afforded *N*-methyl-5-(phenylsulfonyl)-4-piperidone (**19c** or **19f**) in 90–95% yield. An alternate procedure that also works extremely well (>95% yield) involves carrying out the reduction with Raney nickel in methanol at 60 °C for 20 min. The reaction proceeds via an intermediate 4-piperidinol **20**, which spontaneously eliminates benzenesulfinic acid to give the phenylsulfonyl substituted 4-piperidone **21**.

The further reduction of the phenylsulfonyl group present in piperidone **19** or **21** proved problematic. We

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(55) We thank Professor Kosta Steliou of the University of Montreal for providing a copy of the extensively rewritten STILL MODEL program and for providing a VMS version of the MMX PC modification of MM2.

(56) MMX is derived from MM2 (1977 Version QCPE) with the VESCF π subroutines from MMP1 (QCPE 318). Gilbert, K. E.; Gajewski, J. J. Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076. The relative energy differences of the transition states were estimated by calculating transition-state total energy. The program is parameterized for transition-state carbon (C$, C#, C*) as well as transition-state oxygen (O#). Transition-state bond orders of 0.3 were entered, which gave transition-state bond lengths and torsional angles very similar to those obtained from the more rigorous calculations. The observed results are fully consistent with the invariant formation of only one regioisomer from *N*-3-butenylnitrones.[49]

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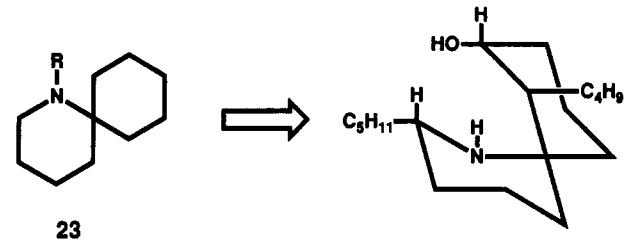
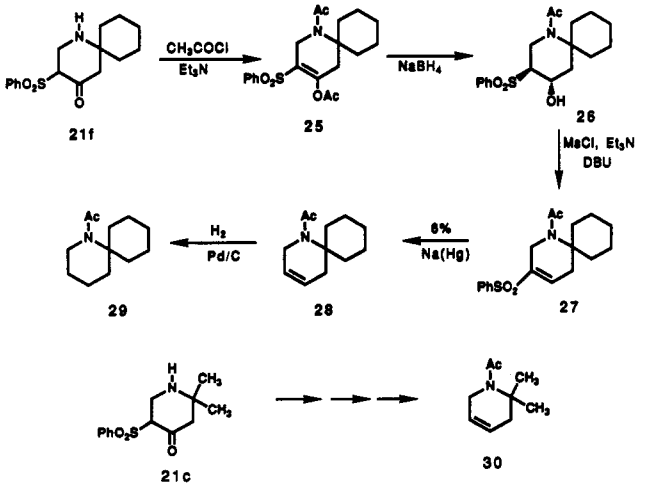
found that the conventional method[58] of Al(Hg) or Na(Hg) was ineffective for desulfonylation of this particular β-keto phenyl sulfone system. However, desulfonylation of **21c** as its carbobenzyloxy derivative could be carried out with excess tri-*n*-butylstannane and AIBN as described by Smith and co-workers.[59]

At this stage of our studies, we came to recognize that 7-oxa-1-azanorbornane **8f** is a potential precursor to the 1-azaspiro[5.5]undecane system **23**. Owing to the unusual structure of the azaspiro[5.5]undecane ring system and their remarkable pharmacologic properties as neurotoxins, in conjunction with their low natural occurrence, much work over the last 10 years has been devoted to the study of the synthesis of these molecules. Most of the synthetic work has been directed toward perhydrohistrionicotoxin (**24**),[60] and only recently has the first and only total synthesis of histrionicotoxin itself been reported by Kishi.[61] One of the main problems in these studies is how to approach the azaspiro[5.5]undecane ring system with the appropriate functionalities in place. In order to ascertain whether the oxime cycloaddition approach could be effectively utilized for an eventual synthesis of perhydrohistrionicotoxin, we turned our attention to a more thorough examination of the reduction of piperidone **21f**. Unfortunately, the direct reduction of **21f** using standard desulfonylation conditions failed to give any characterizable material. Therefore, protection of the secondary amine was effected with use of triethylamine and acetyl chloride. It was impossible to prevent concomitant formation of the enol acetate, and consequently 2 equiv of each reagent was used to give **25**. Sodium borohydride reduction of the enol acetate gave the trans alcohol **26**, which was readily dehydrated by conversion to the corresponding mesylate followed by elimination with DBU. The resulting vinyl sulfone **27** was reduced by 6% sodium amalgam to give the unsaturated 1-aza spiro species **28**. This material was subjected to catalytic hydrogenation to afford 1-acetyl-1-azaspiro[5.5]undecane **29** in 61% overall yield from diene **6** and cyclohexanone oxime. A related set of reactions was also carried out with piperidone **21c**, producing *N*-acetyl-6,6-dimethyltetrahydropyridine (**30**) in high overall yield.



23 **24**



21f **25** **26** **27** **28** **29**

21c **30**

In conclusion, we have demonstrated that oximes react readily with 2,3-bis(phenylsulfonyl)-1,3-butadiene to give bicyclic isoxazolidines in excellent yield. The observed regio- and stereoselectivity are consistent with molecular mechanics calculations. The 7-oxa-1-azanorbornane cycloadducts were subjected to reductive cleavage of the nitrogen–oxygen bond to give substituted 4-piperidones in high yield. From cyclohexanone oxime, it was possible to prepare the 1-azaspiro[5.5]undecane framework found in the histrionicotoxin family of alkaloids. Further generalizations of these observations and their implications for the synthesis of various heterocyclic compounds are the object of ongoing investigations.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV.

General Procedure for the Bimolecular Cycloaddition Reactions of Oximes with 2,3-Bis(phenylsulfonyl)-1,3-butadiene (6). A solution containing 0.50 g (1.5 mmol) of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**6**)[42] and 1.5 mmol of the appropriate oxime in 25 mL of solvent was stirred for 24 h at the indicated temperature. The solvent was removed under reduced pressure, and the crude solid was recrystallized from 50% methylene chloride–ether to give pure material, whose structure was assigned on the basis of its spectral properties. On the basis of the above procedure, the following compounds were obtained:

2-*exo*-Phenyl-4,5-*endo*-bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane (8a) (acetonitrile, 80 °C): yield 95%; mp 170–171 °C; IR (KBr) 3070, 3020, 2960, 1975, 1910, 1830, 1785, 1595, 1500, 1450, 1320, 1200, 1160, 1090, and 1055 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.23 (ddd, 1 H, *J* = 12.8, 5.2, and 2.2 Hz), 3.70–3.85 (m, 3 H), 4.34 (dd, 1 H, *J* = 7.9 and 5.2 Hz), 4.53 (ddd, 1 H, *J* = 10.2, 4.6 and 2.2 Hz), 6.80 (d, 2 H, *J* = 7.5 Hz), 7.15 (m, 3 H), 7.55 (t, 2 H, *J* = 7.9 Hz), 7.65 (t, 2 H, *J* = 8.1 Hz), 7.75 (m, 2 H), 7.85 (d, 2 H, *J* = 8.1 Hz), and 8.00 (d, 2 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.4, 60.7, 66.5, 72.0, 102.8, 126.5, 127.6, 128.5, 128.6, 129.0, 129.5, 130.3, 134.4, 134.6, 134.8, 138.8, and 141.7. Anal. Calcd for $C_{23}H_{21}NO_5S_2$: C, 60.64; H, 4.65; N, 3.07. Found: C, 60.40; H, 4.72; N, 3.03.

2-*exo*-(4-Bromophenyl)-4,5-*endo*-bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane (8b) (toluene, 110 °C): yield 90%; mp 200–201 °C; IR (KBr) 3070, 2960, 1455, 1320, 1305, 1160, 1150, 750, 725, 695, 620, and 605 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 2.15 (ddd, 1 H, *J* = 15.8, 5.0, and 2.0 Hz), 3.68–3.87 (m, 3 H), 4.33 (dd, 1 H, *J* = 7.9 and 5.0 Hz), 4.52 (ddd, 1 H, *J* = 10.1, 4.7, and 2.0 Hz), 6.72 (d, 2 H, *J* = 8.4 Hz), 7.25 (d, 2 H, *J* = 8.4 Hz), 7.53–7.80 (m, 6 H), 7.86 (d, 2 H, *J* = 7.5 Hz), and 8.05 (d, 2 H, *J* = 7.2 Hz). Anal. Calcd for $C_{23}H_{20}NO_5S_2Br$: C, 51.69; H, 3.77; N, 2.62. Found: C, 51.57; H, 3.80; N, 2.58.

2,2-Dimethyl-4,5-*endo*-bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane (8c) (methylene chloride, 25 °C): yield 95%; mp 152–153 °C; IR (KBr) 3080, 2980, 1590, 1450, 1315, 1225, 1195, 1160, and 1090 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.90 (s, 3 H), 1.42 (s, 3 H), 1.94 (dd, 1 H, *J* = 12.6 and 2.1 Hz), 3.10 (d, 1 H, *J* = 12.6 Hz), 3.62 (dd, 1 H, *J* = 12.6 and 10.8 Hz), 3.95 (dd, 1 H, *J* = 12.6 and 5.1 Hz), 4.32 (ddd, 1 H, *J* = 10.8, 5.1 and 2.1 Hz), 7.52 (t, 2 H, *J* = 7.8 Hz), 7.63 (t, 2 H, *J* = 7.6 Hz), 7.70 (m, 2 H), 7.80 (d, 2 H, *J* = 7.8 Hz), and 7.98 (d, 2 H, *J* = 7.6 Hz). Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C, 56.00; H, 5.19; N, 3.44. Found: C, 55.92; H, 5.19; N, 3.42.

2-*exo*-Methyl-4,5-*endo*-bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane (8d) (methylene chloride, 25 °C): yield

(59) Smith, A. B., III; Hale, K. J. *Tetrahedron Lett.* **1989**, 1037. Smith, A. B., III; Hale, K. J.; McCauley, J. P. *Tetrahedron Lett.* **1989**, 5579.

(60) For some leading references, see: Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.

(61) Carey, S.; Aratani, M.; Kishi, Y. *Tetrahedron Lett.* **1985**, 5887.

95%; mp 181–182 °C; IR (KBr) 3105, 3080, 2990, 1590, 1450, 1315, 1220, 1160, 1100, 1080, 970, 770, 730, and 695 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.90 (d, 3 H, J = 6.1 Hz), 1.69 (dd, 1 H, J = 8.5 and 2.2 Hz), 3.36–3.49 (m, 2 H), 3.56 (dd, 1 H, J = 12.0 and 4.8 Hz), 3.71 (dd, 1 H, J = 12.0 and 10.5 Hz), 4.35 (ddd, 1 H, J = 10.5, 4.8, and 2.2 Hz), 7.54 (t, 2 H, J = 7.7 Hz), 7.63 (t, 2 H, J = 7.7 Hz), 7.71 (m, 2 H), 7.83 (d, 2 H, J = 7.7 Hz), and 7.98 (d, 2 H, J = 7.7 Hz). Anal. Calcd for $C_{18}H_{19}NO_5S_2$: C, 54.95; H, 4.87; N, 3.56. Found: C, 54.93; H, 4.92; N, 3.50.

4,5-*endo*-Bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-1′-cyclopentane (8e) (methylene chloride, 25 °C): yield 67%; mp 164–165 °C; IR ($CHCl_3$) 3090, 2980, 2945, 2895, 1600, 1455, 1310, 1160, 1095, 1050, 1035, 990, 835, and 695 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.04 (m, 1 H), 1.42–1.81 (m, 6 H), 2.05 (dd, 1 H, J = 12.7 and 1.9 Hz), 2.13 (m, 1 H), 3.21 (d, 1 H, J = 12.7 Hz), 3.66 (dd, 1 H, J = 12.4 and 10.5 Hz), 3.84 (dd, 1 H, J = 12.4 and 5.3 Hz), 4.28 (ddd, 1 H, J = 10.5, 5.3, and 1.9 Hz), 7.57 (t, 2 H, J = 7.7 Hz), 7.63 (t, 2 H, J = 7.7 Hz), 7.70 (m, 2 H), 7.78 (d, 2 H, J = 7.7 Hz), and 7.97 (d, 2 H, J = 7.7 Hz). Anal. Calcd for $C_{21}H_{23}NO_5S_2$: C, 58.18; H, 5.35; N, 3.23. Found: C, 58.11; H, 5.39; N, 3.23.

4,5-*endo*-Bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-1′-cyclohexane (8f) (methylene chloride, 25 °C): yield 93%; mp 184–185 °C; IR (KBr) 3080, 2935, 2850, 1585, 1445, 1325, 1310, 1290, 1160, 1150, 1085, 1055, 765, 755, 735, 725, 690, and 620 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.00–1.75 (m, 9 H), 1.93 (dd, 1 H, J = 12.6 and 1.8 Hz), 2.05 (m, 1 H), 2.98 (d, 1 H, J = 12.6 Hz), 3.63 (dd, 1 H, J = 12.6 and 10.6 Hz), 4.00 (dd, 1 H, J = 12.6 and 5.0 Hz), 4.30 (ddd, 1 H, J = 10.6, 5.0, and 1.8 Hz), 7.52 (t, 2 H, J = 7.7 Hz), 7.63 (t, 2 H, J = 7.7 Hz), 7.70 (m, 2 H), 7.77 (d, 2 H, J = 7.7 Hz), and 7.98 (d, 2 H, J = 7.7 Hz). Anal. Calcd for $C_{22}H_{25}NO_5S_2$: C, 59.04; H, 5.63; N, 3.13. Found: C, 58.97; H, 5.67; N, 3.10.

4,5-*endo*-Bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane-2-spiro-1′-cycloheptane (8g) (acetonitrile, 80 °C): yield 91%; mp 156–157 °C; IR ($CHCl_3$) 3080, 2930, 2865, 1450, 1320, 1310, 1165, 1085, 690, and 615 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 0.97 (m, 1 H), 1.15–1.42 (m, 5 H), 1.48–1.80 (m, 5 H), 1.88 (dd, 1 H, J = 12.7 Hz and 1.8 Hz), 2.36 (m, 1 H), 3.10 (d, 1 H, J = 12.7 Hz), 3.65 (dd, 1 H, J = 12.6 and 11.3 Hz), 3.97 (dd, 1 H, J = 12.6 and 5.1 Hz), 4.32 (ddd, 1 H, J = 11.3, 5.1, and 1.8 Hz), 7.49 (t, 2 H, J = 7.7 Hz), 7.62 (t, 2 H, J = 7.7 Hz), 7.69 (m, 2 H), 7.76 (d, 2 H, J = 7.7 Hz), and 7.98 (d, 2 H, J = 7.7 Hz). Anal. Calcd for $C_{23}H_{27}NO_5S_2$: C, 59.85; H, 5.90; N, 3.03. Found: C, 59.95; H, 5.93; N, 3.00.

2-*exo*-(4-Hydroxybutyl)-4,5-*endo*-bis(phenylsulfonyl)-7-oxa-1-azabicyclo[2.2.1]heptane (8h) (methylene chloride, 25 °C): yield 85%; IR (neat) 3500, 3080, 2955, 2880, 1460, 1315, 1160, 1095, 735, and 705 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.20–1.40 (m, 3 H), 1.50 (m, 2 H), 1.65 (m, 2 H), 1.75 (ddd, 1 H, J = 12.0, 4.3, and 2.2 Hz), 3.28 (m, 1 H), 3.35 (dd, 1 H, J = 12.0 and 7.4 Hz), 3.50–3.58 (m, 3 H), 3.69 (dd, 1 H, J = 12.0 and 10.5 Hz), 7.53 (t, 2 H, J = 7.7 Hz), 7.62 (t, 2 H, J = 7.7 Hz), 7.73 (m, 2 H), 7.82 (d, 2 H, J = 7.7 Hz), and 7.96 (d, 2 H, J = 7.7 Hz). Anal. Calcd for $C_{20}H_{23}NO_6S_2$: C, 54.90; H, 5.30; N, 3.20. Found: C, 54.85; H, 5.26; N, 3.09.

8-Phenyl-5,5-dioxo-1-aza-2-oxa-5-thiabicyclo[3.2.1]octane (11a). A solution containing 0.25 g of divinyl sulfone and 0.26 g of benzaldoxime in 20 mL of benzene was heated at reflux for 4 days. The solvent was removed under reduced pressure, and the crude solid was recrystallized from 50% methylene chloride–ether to give 0.43 g (84% yield) of a white solid, mp 161–162 °C, whose structure was assigned as cycloadduct **11a** on the basis of its spectral properties: IR (KBr) 3020, 2960, 2900, 1505, 1460, 1310, 1240, 1180, 1140, 1090, 975, 850, 825, 760, 730, and 705 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.08 (m, 1 H), 3.40 (m, 2 H), 3.70–3.92 (m, 3 H), 4.48 (d, 1 H, J = 9.4 Hz), 5.15 (s, 1 H), and 7.20–7.45 (m, 5 H). Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.24; H, 5.52; N, 5.82.

8-(1-Naphthyl)-5,5-dioxo-1-aza-2-oxa-5-thiabicyclo[3.2.1]octane (11b). A solution containing 0.25 g of divinyl sulfone and 0.36 g of 1-naphthaldoxime in 10 mL of benzene was heated at 95 °C in a sealed tube for 4 days. The solvent was removed under reduced pressure, and the crude material was chromatographed on a silica gel column using a 70% hexane–ethyl acetate mixture as the eluent. The major fraction contained 0.52 g (85% yield) of a white solid, mp 128–129 °C, whose structure was assigned as cycloadduct **11b** on the basis of its spectral properties: IR ($CHCl_3$) 3030, 2980, 1515, 1330, 1305, 1140, and 985 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.17 (m, 1 H), 3.45–3.55 (m, 2 H), 3.85 (m, 2 H), 3.91 (m, 1 H), 4.50 (d, 1 H, J = 9.4 Hz), 5.75 (s, 1 H), 7.30–7.60 (m, 3 H), and 7.65–7.90 (m, 4 H). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.22; N, 4.84. Found: C, 62.33; H, 5.25; N, 4.82.

8-Methyl-5,5-dioxo-1-aza-2-oxa-5-thiabicyclo[3.2.1]octane (11c). A solution containing 0.25 g of divinyl sulfone and 0.12 g of acetaldoxime in 25 mL of methylene chloride was heated for 14 h at reflux. The solvent was removed under reduced pressure, and the crude material was chromatographed on a silica gel column with a 90% chloroform–methanol mixture as the eluent. The major fraction contained 0.33 g (89% yield) of a white solid, mp 103–104 °C, whose structure was assigned as cycloadduct **11c** on the basis of its spectral properties: IR (KBr) 3000, 2970, 1450, 1385, 1310, 1130, 955, and 745 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.1.10 (d, 3 H, J = 6.7 Hz), 2.89 (m, 1 H), 3.17 (m, 2 H), 3.50 (m, 2 H), 3.95 (q, 1 H, J = 6.7 Hz), 4.08 (dd, 1 H, J = 9.9 and 5.9 Hz), and 4.35 (d, 1 H, J = 9.9 Hz); HRMS for $C_6H_{11}NO_3S$; calcd 177.0460, found 177.0453. Anal. Calcd for $C_6H_{11}NO_3S$: C, 40.67; H, 6.26; N, 7.90. Found: C, 40.53; H, 6.38; N, 8.02.

Reaction of Acetone Oxime with Divinyl Sulfone. A solution containing 500 mg of acetone oxime and 810 mg of divinyl sulfone in 50 mL of methylene chloride was heated at reflux for 24 h. The solvent was removed under reduced pressure to leave behind a white solid that consisted of a 3:2 mixture of cycloadducts **13** and **14**. Recrystallization of the mixture from 50% methylene chloride–ether gave 1.24 g (85%) of **13** and **14**. These materials could not be separated by fractional recrystallization. Careful flash chromatography on silica, however, using a 50% hexane–ethyl acetate as the eluent provided a pure sample of the major isomer as a white crystalline solid, mp 155–156 °C. This material was assigned as 8,8-dimethyl-5,5-dioxo-1-aza-2-oxa-5-thiabicyclo[3.2.1]octane (**13**) on the basis of is spectral properties: IR ($CHCl_3$) 2990, 2950, 1445, 1405, 1315, 1295, 1160, 1135, 1125, 1015, and 830 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3 H), 1.67 (s, 3 H), 3.00 (dq, 1 H, J = 14.3 and 2.9 Hz), 3.35 (m, 2 H), 3.54 (m, 2 H), 4.28 (dd, 1 H, J = 9.9 and 5.9 Hz), and 4.57 (d, 1 H, J = 9.9 Hz). Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 43.87; H, 6.88; N, 7.27.

The minor isomer was assigned as 2,2-dimethyl-5,5-dioxo-1-aza-8-oxa-5-thiabicyclo[3.2.1]octane (**14**) on the basis of its NMR spectrum: NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3 H), 1.42 (s, 3 H), 2.54 (dd, 1 H, J = 14.5 and 2.2 Hz), 2.68 (dd, 1 H, J = 12.8 and 5.6 Hz), 3.48 (dd, 1 H, J = 15.5 and 5.6 Hz), 4.01 (ddd, 1 H, J = 15.5, 12.8, and 4.8 Hz), and 4.95 (dd, 1 H, J = 8.8 and 2.2 Hz). Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 43.71; H, 6.59; N, 7.08.

***N*-[2-(Phenylsulfonyl)ethyl]benzopyrano[4,3-*c*]isoxazolidine (16).** To a stirred solution containing 5.0 g of 2-(allyloxy)benzaldehyde and 1.23 g of sodium hydroxide in 100 mL of 30% aqueous acetonitrile was added 2.36 g of hydroxylamine hydrochloride. The reaction was stirred at 25 °C for 2 h, after which the solvent was removed under reduced pressure. The reaction mixture was extracted with methylene chloride, and the combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 4.10 g (75% yield) of a clear oil whose structure was assigned as 2-(allyloxy)benzaldehyde oxime (**15**) on the basis of its spectral properties: IR (neat) 3300 (Br), 3080, 2940, 1605, 1495, 1445, 1250, 1115, 965, and 760 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 4.60 (d, 2 H, J = 5.0 Hz), 5.30 (dd, 1 H, J = 6.0 and 2.0 Hz), 5.40 (dd, 1 H, J = 13.0 and 2.0 Hz), 6.05 (m, 1 H), 6.90 (t, 2 H, J = 9.0 Hz), 7.30 (dt, 1 H, J = 7.0 and 1.5 Hz), 7.75 (dd, 1 H, J = 7.0 and 1.5 Hz), 8.65 (s, 1 H), and 9.60 (s, 1 H).

A solution containing 0.50 g of the above oxime and 0.48 g of phenyl vinyl sulfone in 20 mL of toluene was heated at reflux for 12 h. The solvent was removed under reduced pressure, and the crude material was recrystallized from 50% methylene chloride–ether to give 0.88 g (91% yield) of white needles, mp 103–104 °C, whose structure was assigned as *N*-[2-(phenylsulfonyl)-ethyl]benzopyrano[4,3-*c*]isoxazolidine (**16**) on the basis of its spectral properties: IR ($CHCl_3$) 3080, 2985, 2975, 2890, 1615, 1590, 1500, 1455, 1310, 1255, 1230, 1150, 1095, and 915 cm^{-1}; NMR

($CDCl_3$, 300 MHz) δ 2.93 (m, 1 H), 3.17 (m, 1 H), 3.44–3.58 (m, 4 H), 3.66 (d, 1 H, J = 6.5 Hz), 3.84 (dd, 1 H, J = 1.05 and 8.8 Hz), 4.03 (dd, 1 H, J = 11.0 and 4.5 Hz), 4.07 (t, 1 H, J = 8.1 Hz), 6.88 (d, 1 H, J = 8.2 Hz), 6.94 (t, 1 H, J = 7.5 Hz), 7.14 (d, 1 H, J = 7.5 Hz), 7.23 (m, 1 H), 7.49 (t, 2 H, J = 7.6 Hz), 7.62 (t, 1 H, J = 7.3 Hz), and 7.82 (d, 2 H, J = 7.6 Hz); HRMS for $C_{18}H_{19}NO_4S$, calcd 345.1035, found 345.1045. Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.41; H, 5.38; N, 4.02.

***N*-Methyl-5-(phenylsulfonyl)-4-piperidones 19.** A solution containing 0.61 mmol of the appropriate bicyclic isoxazolidine **8c** (or **8f**) in 10 mL of methylene chloride was stirred at 0 °C under a nitrogen atmosphere while 0.61 mmol of methyl triflate was added via syringe. The reaction mixture was allowed to warm to 25 °C and was then stirred for an additional 6 h. The white solid that precipitated was collected by vacuum filtration and used without further purification. A solution containing the methyl triflate salt (**18**) and 50 mg of 10% palladium on carbon in 25 mL of dry methanol was stirred at 25 °C under a hydrogen atmosphere (1 atm) for 18 h. The solution was filtered over Celite and concentrated under reduced pressure. The crude residue was chromatographed on a silica gel plate with use of a 95% methylene chloride–methanol mixture as the eluent. The major fraction contained the pure *N*-methyl-5-(phenylsulfonyl)-4-piperidone (**19**) as a clear oil. In the above fashion, the following compounds were obtained:

1,2,2-Trimethyl-5-(phenylsulfonyl)-4-piperidone (19c): 91% yield; IR (neat) 3080, 2990, 2850, 2815, 1720, 1470, 1450, 1370, 1310, 1150, 1085, 915, and 740 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.01 (s, 3 H), 1.02 (s, 3 H), 2.32 (d, 1 H, J = 13.9 Hz), 2.34 (s, 3 H), 2.59 (d, 1 H, J = 13.9 Hz), 3.23 (dd, 1 H, J = 13.2 and 6.0 Hz), 3.47 (dd, 1 H, J = 13.2 and 6.5 Hz), 3.95 (dd, 1 H, J = 6.5 and 6.0 Hz), 7.53 (t, 2 H, J = 7.4 Hz), 7.65 (t, 1 H, J = 7.4 Hz), and 7.90 (d, 2 H, J = 7.4 Hz); HRMS for $C_{14}H_{19}NO_3S$, calcd 281.1086, found 281.1084.

1-Methyl-3-(phenylsulfonyl)-1-azaspiro[5.5]undecan-4-one (19f): 95% yield; IR (neat) 3080, 2945, 2870, 1715, 1615, 1560, 1450, 1300, 1160, 1090, 1045, 920, 735, and 695 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.20–1.50 (m, 6 H), 1.55–1.70 (m, 4 H), 2.35 (s, 2 H), 2.50 (s, 3 H), 3.52 (dd, 1 H, J = 14.1 and 6.4 Hz), 3.73 (dd, 1 H, J = 14.1 and 8.2 Hz), 3.84 (dd, 1 H, J = 8.2 and 6.4 Hz), 7.52 (t, 2 H, J = 7.4 Hz), 7.63 (t, 1 H, J = 7.4 Hz), and 7.94 (d, 2 H, J = 7.4 Hz); HRMS for $C_{17}H_{23}NO_3S$, calcd 321.1398, found 321.1397.

Reductive Cleavage of the Bicyclic Isoxazolidine Ring System Using Raney Nickel. A solution containing 1.0 g of 2,2-dimethyl-4,5-*endo*-bis(phenylsulfonyl)-7-oxa-1-azabicyclo-[2.2.1]heptane (**8c**) and 100 mg of freshly washed Raney nickel in 35 mL of methanol was heated at 60 °C for 20 min at reflux. Standard workup afforded 0.65 g (99% yield) of a yellow oil whose structure was assigned as 2,2-dimethyl-5-(phenylsulfonyl)-4-piperidone (**21c**) on the basis of its spectral properties: IR (neat) 3340, 3070, 2975, 2930, 1715, 1620, 1450, 1310, 1150, 1085, 730, and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 3 H), 1.35 (s, 3 H), 2.15 (bs, 1 H), 2.42 (d, 1 H, J = 13.8 Hz), 2.78 (d, 1 H, J = 13.8 Hz), 3.40 (dd, 1 H, J = 15.5 and 5.0 Hz), 3.61 (dd, 1 H, J = 5.0 and 1.3 Hz), 3.92 (dd, 1 H, J = 15.5 and 1.3 Hz), 7.55 (t, 2 H, J = 7.6 Hz), 7.67 (m, 1 H), and 7.83 (d, 2 H, J = 7.6 Hz); HRMS for $C_{13}H_{17}NO_35$, calcd 267.0929, found 267.0918.

To a solution containing 200 mg of **21c** in 5 mL of tetrahydrofuran at 0 °C was added 5 mL of a 2.0 N solution of potassium hydroxide. To the resulting mixture were rapidly added 0.08 mL (0.12 g) of benzyl chloroformate and 2.5 mL of a 4.0 N potassium hydroxide solution simultaneously via a syringe over 5 min. The solution was stirred for 10 min and acidified to pH 2 with concentrated hydrochloric acid. Standard workup gave 60 mg (20%) of a white solid: mp 120–121 °C; IR ($CHCl_3$) 3080, 3040, 1740, 1720, 1460, 1270, 1090, 750, and 730 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 3 H), 1.20 (s, 3 H), 2.35 (d, 1 H, J = 13.6 Hz), 3.00 (d, 1 H, J = 13.6 Hz), 3.95 (dd, 1 H, J = 10.6 and 5.9 Hz), 4.20 (dd, 1 H, J = 14.5 and 10.6 Hz), 4.65 (dd, 1 H, J = 14.5 and 5.9 Hz), 5.10 (s, 2 H), 7.3–7.8 (m, 10 H). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.76; H, 5.64; N, 3.21.

A stirred solution containing 60 mg of the above carbamate and 0.16 mL of tri-*n*-butyltin hydride in 10 mL of dry toluene was heated at reflux. To this mixture was added 0.05 g of AIBN. The solution was heated at reflux for 10 min and was then cooled and concentrated under reduced pressure. The residue was chromatographed on a silica gel plate to give 0.035 g of a pale yellow oil whose structure was assigned as *N*-carbobenzoxy-2,2-dimethyl-4-piperidone (**22**) on the basis of its spectral properties: IR (neat) 3020, 3000, 2950, 1740, 1710, 1690, 1580, 1560, 1420, 1360, 1340, 1310, 1270, 1250, 1230, 1210, 1160, 1100, 1050, 1020, 790, 760, and 710 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 6 H), 2.55 (t, 2 H, J = 6.0 Hz), 2.60 (s, 2 H), 3.95 (t, 2 H, J = 6.0 Hz), 5.10 (s, 2 H), and 7.35 (m, 5 H). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.78; H, 7.09; N, 5.29.

3-(Phenylsulfonyl)-1-azaspiro[5.5]undecan-4-one (**21f**) was prepared in 98% yield by the same procedure as was used for **21c**. The structure of piperidone **21f** was assigned on the basis of its spectral properties: IR (neat) 3350, 3080, 2945, 2870, 1710, 1610, 1445, 1310, 1150, 1085, 765, 715, 690, and 630 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.10–1.75 (m, 10 H), 1.98 (bs, 1 H), 2.45 (d, 1 H, J = 13.6 Hz), 2.67 (d, 1 H, J = 13.6 Hz), 3.32 (dd, 1 H, J = 15.5 and 5.0 Hz), 3.61 (dd, 1 H, J = 5.0 and 1.0 Hz), 3.86 (dd, 1 H, J = 15.5 and 1.0 Hz), 7.52 (t, 2 H, J = 7.6 Hz), 7.66 (t, 1 H, J = 7.6 Hz) and 7.83 (d, 2 H, J = 7.6 Hz); HRMS for $C_{16}H_{21}NO_3S$, calcd 307.1242, found 307.1237.

1-Acetyl-1-azaspiro[5.5]undecane (29). To a solution containing 1.00 g of 3-(phenylsulfonyl)-1-azaspiro[5.5]undecan-4-one (**21f**) in 35 mL of methylene chloride at 0 °C was added 0.72 g of triethylamine. After the mixture was stirred for 5 min, 0.56 g of acetyl chloride was added over a period of several minutes. The reaction was allowed to warm to 25 °C and was stirred for an additional 2 h. Standard workup gave 1.15 g (90% yield) of a white crystalline solid, mp 169–170 °C, whose structure was assigned as 4-acetoxy-1-acetyl-3-(phenylsulfonyl)-1-azaspiro-[5.5]undec-3-ene (**25**) on the basis of its spectral properties: IR ($CHCl_3$) 2950, 2870, 1780, 1650, 1445, 1395, 1325, 1180, 1150, 1090, 1010, 690, and 645 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.22–1.60 (m, 8 H), 1.89 (s, 3 H), 2.21 (s, 3 H), 2.44 (s, 2 H), 2.60 (m, 2 H), 4.14 (s, 2 H), 7.55 (t, 2 H, J = 7.5 Hz), 7.66 (t, 1 H, J = 7.5 Hz), and 7.89 (d, 2 H, J = 7.5 Hz). Anal. Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.23; H, 6.29; N, 3.63.

To a solution containing 0.70 g of **25** in 50 mL of 1:1 tetrahydrofuran–methanol at 0 °C was added 0.37 g of sodium borohydride. The solution was allowed to warm to 25 °C and was stirred for an additional 10 h. The mixture was quenched with 50 mL of ethyl acetate, and the solvent was removed under reduced pressure. Standard workup gave 0.58 g (82% yield) of a white crystalline solid, mp 150–151 °C, whose structure was assigned as 1-acetyl-4-hydroxy-3-(phenylsulfonyl)-1-azaspiro[5.5]-undecane (**26**) on the basis of its spectral properties: IR ($CHCl_3$) 3570, 2940, 2875, 1650, 1445, 1405, 1305, 1150, 1085, 1020, 840, 810, and 695 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.30–1.60 (m, 8 H), 1.72 (dd, 1 H, J = 13.9 and 10.2 Hz), 2.00 (s, 3 H), 2.21 (dd, 1 H, J = 13.9 and 4.8 Hz), 2.68 (m, 2 H), 3.00 (d, 1 H, J = 2.7 Hz), 3.17 (m, 1 H), 3.57 (dd, 1 H, J = 14.5 and 5.6 Hz), 3.63 (dd, 1 H, J = 14.5 and 6.6 Hz), 4.52 (m, 1 H), 7.62 (t, 2 H, J = 7.4 Hz), 7.73 (t, 1 H, J = 7.4 Hz), and 7.93 (d, 2 H, J = 7.4 Hz). Anal. Calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.46; H, 7.02; N, 3.83.

To a solution containing 350 mg of **26** in 10 mL of methylene chloride at 0 °C was added 0.69 mL of triethylamine. To this solution was added 0.23 mL of methanesulfonyl chloride over a 10-min interval. The reaction was stirred at 0 °C for 30 min, after which time 0.82 mL of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) was added. The solution was allowed to warm to 25 °C and was stirred for an additional 14 h. Standard workup gave 320 mg (97% yield) of a yellow oil whose structure was assigned as 1-acetyl-3-(phenylsulfonyl)-1-azaspiro[5.5]undec-3-ene (**27**) on the basis of its spectral properties: IR (neat) 3070, 2935, 2860, 1735, 1660, 1450, 1400, 1310, 1225, 1150, 1090, 915, 725, 690, and 650 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15–1.55 (m, 8 H), 1.67 (s, 3 H), 2.35 (s, 2 H), 2.52 (m, 2 H), 3.93 (s, 2 H), 7.00 (s, 1 H), 7.53 (t, 2 H, J = 7.6 Hz), 7.62 (t, 1 H, J = 7.6 Hz), and 7.85 (d, 2 H, J = 7.6 Hz); HRMS $C_{18}H_{23}NSO_3$, calcd 333.1398, found 333.1398.

To a solution containing 250 mg of vinyl sulfone **27** in 50 mL of a 30% tetrahydrofuran–methanol mixture was added 2.14 g of sodium phosphate dibasic at 25 °C. The solution was vigorously stirred while 2.88 g of freshly prepared 6% sodium amalgam was added all at once. The mixture was stirred at 25 °C under a

nitrogen atmosphere for 12 h and was then filtered over a pad of Celite. Standard workup afforded 135 mg (93% yield) of a yellow oil whose structure was assigned as **28** on the basis of its spectral properties: IR (neat) 2930, 2860, 1650, 1435, 1400, 1375, 1225, 1150, 1055, 830, 735, and 655 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15–1.60 (m, 8 H), 2.08 (s, 3 H), 2.15 (m, 2 H), 2.66 (m, 2 H), 3.82 (m, 2 H), 5.65 (m, 1 H), and 5.73 (m, 1 H); HRMS for $C_{12}H_{19}NO$, calcd 193.1467, found 193.1466.

To a solution containing 44 mg of **28** in 5 mL of methanol was added 10 mg of 10% palladium on activated carbon. The resulting suspension was subjected to hydrogenation on the Parr shaker at 50 psi of hydrogen for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give 0.44 mg (100% yield) of a yellow oil, whose structure was assigned as 1-acetyl-1-azaspiro[5.5]undecane (**29**) on the basis of its spectral properties: IR ($CHCl_3$) 2940, 2875, 1640, 1445, 1415, 1140, 915, and 795 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.15–1.75 (m, 14 H), 2.08 (s, 3 H), 2.82 (m, 2 H) and 3.33 (m, 2 H); HRMS for $C_{12}H_{21}NO$, calcd 195.1623, found 195.1630.

1-Acetyl-6,6-dimethyl-1,2,5,6-tetrahydropyridine (30). To a solution containing 0.83 g of **21c** in 20 mL of methylene chloride at 0 °C was added 0.69 g of triethylamine. After the mixture was stirred for 5 min, 0.54 g of acetyl chloride was added over a period of several minutes. The reaction was allowed to warm to 25 °C and was stirred for an additional 2 h. Standard workup gave 0.78 g (72% yield) of a yellow oil whose structure was assigned as 4-acetoxy-1-acetyl-6,6-dimethyl-3-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine on the basis of its spectral properties: IR (neat) 3080, 3020, 2975, 2935, 1780, 1730, 1660, 1585, 1410, 1310, 1195, 1150, 1020, 800, 765, 750, and 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 6 H), 2.00 (s, 3 H), 2.20 (s, 3 H), 2.50 (s, 2 H), 4.25 (s, 2 H), 7.65 (m, 3 H), and 8.00 (m, 2 H).

To a solution containing 1.38 g of the above compound in 50 mL of 1:1 tetrahydrofuran–methanol at 0 °C was added 0.74 g of sodium borohydride. The reaction was allowed to warm to 25 °C and was stirred for an additional 10 h. Standard workup gave 0.62 g (54% yield) of a white solid, mp 151–152 °C, whose structure was assigned as 1-acetyl-2,2-dimethyl-4-hydroxy-5-(phenylsulfonyl)piperidine on the basis of it spectral properties: IR ($CHCl_3$) 3540, 3075, 2980, 2935, 1655, 1450, 1400, 1310, 1170, 1150, 1085, 1060, 980, 795, 690, and 635 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 3 H), 1.48 (s, 3 H), 1.52 (dd, 1 H, J = 14.7 and 3.0 Hz), 1.84 (dd, 1 H, J = 14.7 and 5.0 Hz), 1.95 (s, 3 H), 3.18 (td, 1 H, J = 7.6 and 2.7 Hz), 3.50 (s, 1 H), 3.76 (d, 2 H, J = 7.6 Hz), 4.39 (m, 1 H), 7.56 (t, 2 H, J = 7.5 Hz), 7.67 (t, 1 H, J = 7.5 Hz), and 7.90 (d, 2 H, J = 7.5 Hz).

To a solution containing 70 mg of the above alcohol in 4 mL of methylene chloride at 0 °C was added 0.156 mL of triethylamine. To this solution was added dropwise 0.052 mL of methanesulfonyl chloride over a 10-min interval. The reaction was stirred at 0 °C for 30 min, after which time 0.185 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The reaction mixture was allowed to warm to 25 °C and was stirred for an additional 14 h. Standard workup gave 65 mg (98% yield) of a yellow oil whose structure was assigned as 1-acetyl-6,6-dimethyl-3-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine on the basis of its spectral properties: IR (neat) 3075, 2980, 2940, 1650, 1450, 1405, 1310, 1155, 1090, 920, 765, 730, 695, and 645 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 6 H), 1.82 (s, 3 H), 2.37 (d, 2 H, J = 4.7 Hz), 3.96 (s, 2 H), 7.14 (t, 1 H, J = 4.7 Hz), 7.53 (t, 2 H, J = 7.5 Hz), 7.64 (t, 1 H, J = 7.5 Hz), and 7.85 (d, 2 H, J = 7.5 Hz).

To a solution containing 90 mg of the above vinyl sulfone in 30 mL of a 30% tetrahydrofuran–methanol mixture was added 960 mg of sodium phosphate dibasic at 25 °C. The solution was vigorously stirred while 1.31 g of freshly prepared 6% sodium amalgam was added all at once. Standard workup gave 43 mg (91% yield) of a clear oil whose structure was assigned as 1-acetyl-6,6-dimethyl-1,2,5,6-tetrahydropyridine (**30**) on the basis of its spectral properties: IR ($CHCl_3$) 2980, 2855, 1645, 1385, and 1025 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 6 H), 2.07 (s, 3 H), 2.12 (m, 2 H), 3.84 (m, 2 H), 5.81 (m, 1 H), and 5.89 (m, 1 H); HRMS for $C_9H_{15}NO$, calcd 153.1154, found 153.1158. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.41; H, 9.80; N, 8.78.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra (75 MHz) for all compounds with high-resolution mass spectra (9 pages). Ordering information is given on any current masthead page.

Selenium Nucleophiles for the Preparation of Antiviral Nucleosides

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The reactivity of nucleophilic selenium species toward nucleoside derivatives has been examined. A number of new 2′-deoxyribose nucleosides have been synthesized using this methodology. The cis elimination of the selenoxide obtained from the oxidation of the corresponding phenylselenide has been shown to be an efficient method for the preparation of the 2′,3′-unsaturated antiviral nucleoside 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)thymine (D4T).

Introduction

Acquired immunodeficiency syndrome (AIDS) is a consequence of infection by the human immunodeficiency virus (HIV).[1] Several 2′,3′-dideoxynucleosides have been shown to be effective in the treatment of cells infected with HIV, and one compound, 3′-azido-3′-deoxythymidine (AZT, 1), has been approved by the Food and Drug Administration (FDA) for the treatment of individuals with AIDS.[2] These compounds, as their 5′-triphosphates, are

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