Reaction of 11 with Pyrimidine 13. Preparation of 1-[(2,4-Diamino-5-nitropyrimidin-6-yl)amino]-2,2-dimethoxy-3-[(*p*-carboxyphenyl)amino]propane (16). A solution of 700 mg (4 mmol) of 6-chloro-2,4-diamino-5-nitropyrimidine in 200 mL of methanol was refluxed with 4 mmol of 11 for 4 h and evaporated to dryness, and the residue was triturated with 150 g of crushed ice, filtered and dried: yield 650 mg (80%); mp 262 °C; UV (0.1 N NaOH) λ_{max} 340, 280, 215 nm; NMR (TFA) δ 7.7, 6.7 (d, d, 4 H, aromatic), 4.0 (d, 2 H, methylene), 3.9 (br, 2 H, methylene), 3.3 (s, 6 H, dimethoxy). Anal. Calcd for $C_{16}H_{21}N_7O_6$: C, 47.17; H, 5.16; O, 23.59. Found: C, 46.99; H, 5.40; O, 23.30.

Conversion of 16 to 4-Amino-4-deoxypteroic Acid (3). A. Deprotection of 16. This reaction was carried out by dissolving 407 mg (1 mmol) of 16 in 10 mL of TFA and treating with 10 mL of 0.1 N HCl at 55 °C, as described for the deprotection of 14. After the addition of HCl was complete, the reaction mixture was evaporated to dryness and the residue was triturated with 50 g of crushed ice, filtered, and dried: yield 310 mg (86%); mp 212 °C dec; UV (0.1 N NaOH) λ_{max} 335, 270 nm.

B. Dithionite Reduction of 17. A solution of 271 mg (0.75 mmol) of 17 in 5 mL of DMF was kept in a water bath maintained at 55 °C. To this solution was added 1.5 g of solid purified sodium dithionite and the mixture was stirred. During a period of 15 min 5 mL of distilled water was added to this stirred suspension which was then diluted to 100 mL with crushed ice, whereupon the creamy white reduction product was separated. This was filtered, washed with water, and stirred with 75 mL of 0.05 N NaOH for 1.5 h (UV λ_{max} 285 nm with shoulder at 325 nm). Oxidation of this dihydro derivative to 3 was carried out by adding 2 mL of ethanol to this solution, followed by 1.0 mL of 5% $KMnO_4$ over 5 min. The oxidation was allowed to proceed for 15 min more and then the mixture was filtered. The bright yellow filtrate showed λ_{max} (0.1 N NaOH) 372 and 262 nm, indicating complete oxidation. Upon acidification of this solution to pH 4.5 with glacial HOAc, a bright orange precipitate of 3 was formed. The product was filtered, washed and dried: UV (0.1 N NaOH) λ_{max} 372 nm (ϵ 5210), 252 (21747); UV (0.1 N HCl) λ_{max} 336 nm (ϵ 8143), 298 (16443), 244 (12855); NMR (TFA) δ 8.5 (s, 1 H, pteridine), 7.85, 7.28 (d, d, 4 H, aromatic), 4.79 (2 H, methylene); yield 36.5% based on 17. Anal. Calcd for $C_{14}H_{13}N_7O_2$: C, 54.02; H, 4.18; N, 31.51; O, 10.29. Found: C, 53.95; H, 4.26; N, 31.45; O, 10.41.

Acknowledgment. This investigation was supported by grants from the National Institutes of Health (CA-27101, National Cancer Institute) and the American Cancer Society (CH-53C). We are indebted to Dr. Shiang-Yuan Chen for the preparation of 4 and Miss Loretta Holman for technical assistance.

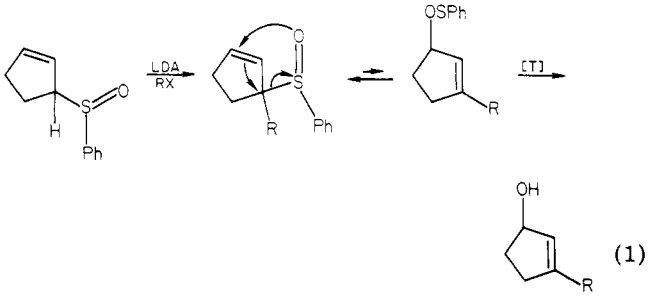
Registry No. 1, 119-24-4; 3, 36093-85-3; 4, 59081-60-6; 5, 574-02-7; 5 acid chloride, 77773-72-9; 5b, 77773-73-0; 6, 77773-74-1; 7, 77773-75-2; 8, 77773-76-3; 9, 77773-77-4; 10, 77773-78-5; 11, 77773-79-6; 12, 1007-99-4; 13, 6036-64-2; 14, 77773-80-9; 15, 62019-04-9; 16, 77773-81-0; 17, 77773-82-1; 18, 2134-76-1; 19, 77773-83-2; ethyl *p*-aminobenzoate, 94-09-7; bromoacetic acid, 79-08-3.

Communications

Synthesis of Allylic Sulfoxides from Alkenes by $EtAlCl_2$-Catalyzed Ene Reaction with *p*-Toluenesulfinyl Chloride

Summary: Ethylaluminum dichloride ($EtAlCl_2$) catalyzes the ene reaction of alkenes with arylsulfinyl chlorides to give allylic sulfoxides since $EtAlCl_2$ acts as a proton scavenger as well as a Lewis acid, reacting with the hydrogen chloride produced in the reation to give aluminum trichloride and ethane.

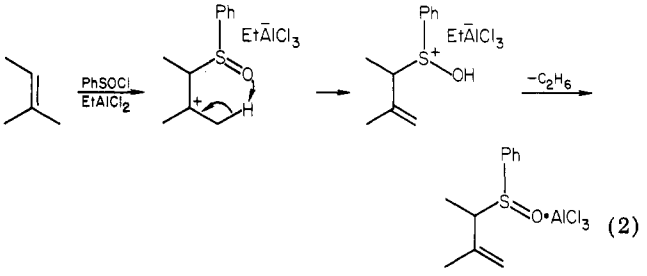
Sir: Allylic sulfoxides are versatile intermediates in organic synthesis, since they can be selectively alkylated in the α-position and converted to a rearranged allylic alcohol by trapping the allylic sulfenate, present in equilibrium with the sulfoxide, with a thiophile (eq 1).[2] These sulfoxides



(1)

have been synthesized by reaction of allylic alcohols with arylsulfenyl chlorides,[2] by oxidation of the sulfides formed from thiophenoxide and allylic halides,[2] and from carbonyl compounds via an aldol condensation or Wittig reaction to give a vinylic sulfoxide which can be isomerized to an allylic sulfoxide.[3] We report here a novel procedure which makes a wide variety of allylic sulfoxides available directly from an alkene.

Treatment of an alkene with 1 equiv of toluenesulfinyl chloride and 1 equiv of ethylaluminum dichloride ($EtAlCl_2$) in ether at 25 °C for 1–4 h gives an allylic sulfoxide via a formal ene reaction (see eq 2).[4] The reaction is quite versatile, proceeding in good yield with a wide variety of alkenes (see Table I).



(2)

The reaction sequence shown in eq 1 is analogous to the cyclization of unsaturated sulfinic acid derivatives obtained from penicillins to give the 3-methylenecepham sulfoxides developed by Kukolja (eq 3).[6,7] Due to the ease of six-membered-ring formation this cyclization can be carried out on the sulfinyl chloride (X = Cl) with a wide variety

(1) Fellow of the Alfred P. Sloan Foundation, 1979–1981.
(2) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147 and references cited therein.
(3) Hoffmann, R. W.; Goldmann, S.; Maak, N.; Gerlach, R.; Frickel, F.; Steinbach, G. *Chem. Ber.* **1980**, *113*, 819 and references cited therein.
(4) For a review of Lewis acid catalyzed ene reactions see: Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
(5) The instability of allylic and benzylic sulfoxides has been previously noted. See ref 2 and: Mizuno, H.; Matsuda, M.; Iino, M. *J. Org. Chem.* **1981**, *46*, 520 and references cited therein. Bond homolysis to give an allylic radical and sulfinyl radical occurs. Substitution in the α- and γ-positions stabilizes the allylic radical. Substitution in the α-position destabilizes the sulfoxide by steric hindrance.

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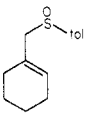
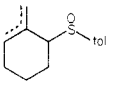
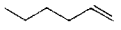
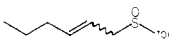
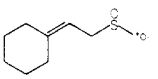
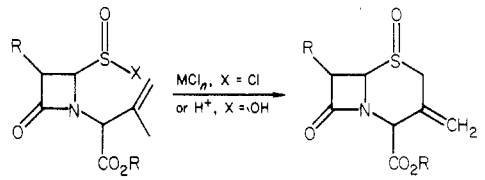
Table I. Allylic Sulfoxides from the $EtAlCl_2$-Catalyzed Ene Reaction of Alkenes with *p*-Toluenesulfinyl Chloride[a]

alkene	adduct	% yield
		63
		73
		69[b,c]
		77[b,d]
		77[b]
		76[b,e]
		60[f,g]
		35[f]

[a] A typical procedure is given in the text. The reaction, which could be monitored by observing the separation of the sulfoxide–$AlCl_3$ complex as a dark oil, was slower (3–5 h) for mono- and 1,2-disubstituted alkenes. [b] Sulfoxides that are α,α- or α,γ-disubstituted are unstable at 25 °C and decomposed slowly, presumably via a radical pathway, to give *p*-tolyl toluenethiosulfonate among other products.[5] The crude products were 80% pure but due to decomposition could not be further purified by chromatography. [c] A 52:48 mixture of trisubstituted–disubstituted double bond was formed. [d] A 9:1 mixture of endocyclic–exocyclic double bond was formed. [e] Crystallization by dissolution in hexane and cooling to −20 °C allowed the isolation of pure sulfoxide (mp 60–61 °C), which NMR indicated to be predominantly a single diastereomer. [f] With terminal alkenes ca. 20% ethyl *p*-tolyl sulfoxide was formed. [g] A 70:30 mixture of *E* and *Z* isomers was isolated.



(3)

of Lewis acids or on the free sulfinic acid (X = OH) with Brønsted acids. On the other hand, the choice of conditions is critical in the intermolecular reactions described here (eq 2). $EtAlCl_2$ acts as an acid scavenger as well as a Lewis acid, reacting with the HCl produced by the reaction to give ethane and $AlCl_3$.[8] Use of ether as solvent serves to moderate the reaction by complexing competitively with the Lewis acid. Use of normal Lewis acids such as $AlCl_3$ or $ZnCl_2$ is unsuccessful due to side reactions caused by HCl.[9]

These reactions probably proceed through an intermediate as shown in eq 2. β-Pinene, which undergoes concerted ene reactions with facility,[10] gives a complex mixture of products, presumably via rearrangement of the intermediate cation. Mono- and 1,2-disubstituted double bonds are less reactive since a secondary rather than a tertiary carbenium ion is formed. The formation of the intermediate may be reversible, since vinylcyclohexane, in which a hindered tertiary hydrogen must be transferred, gives a much lower yield of sulfoxide than 1-hexene. Styrene derivatives which have no allylic hydrogens give β-chloro sulfoxides on treatment with arylsulfinyl chlorides and zinc chloride in ether.[11]

A typical experimental procedure is given below. $EtAlCl_2$ (1.7 mL of a 1.57 M solution in heptane, 2.8 mmol, 1.4 equiv)[12] was added to a solution of 2-methyl-2-butene (2 mmol) and *p*-toluenesulfinyl chloride (2 mmol)[13] in 5 mL of ether under nitrogen at 0 °C. The solution was allowed to warm to 25 °C and stirred for a total of 2 h. The sulfoxide–$AlCl_3$ complex oiled out of solution as it was formed. The reaction was quenched by addition of water. The workup was accomplished by extraction with three portions of ether which were combined and washed with 10% NaOH solution and brine, dried ($MgSO_4$), and evaporated to give crude product which was ca. 80% pure. Chromatography on silica (1:1 hexane–EtOAc) gave 304 mg (73%) of pure adduct as a mixture of diastereomers.[14]

This procedure allows the facile synthesis in high yield of a wide variety of allylic sulfoxides from simple starting materials. Allylic sulfones and sulfides which are equally valuable synthons are also readily accessible via oxidation or reduction of the sulfoxide.[15]

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. GM-23159).

Registry No. 1-(*p*-Toluenesulfinyl)cyclohexene, 77944-37-7; 2-methyl-3-(*p*-toluenesulfinyl)-1-butene, 37616-10-7; 2-ethyl-3-(*p*-toluenesulfinyl)-1-butene, 77944-38-8; 3-methyl-4-(*p*-toluenesulfinyl)-2-pentene, 42104-28-9; 2-(*p*-toluenesulfinyl)methylenecyclohexane, 77944-39-9; 1-methyl-6-(*p*-toluenesulfinyl)cyclohexene, 77944-40-2; 2,3-dimethyl-3-(*p*-toluenesulfinyl)-1-butene, 77944-41-3; 3-(*p*-toluenesulfinyl)cyclopentene, 77944-42-4; (*E*)-1-(*p*-toluenesulfinyl)-2-hexene, 77944-43-5; (*Z*)-1-(*p*-toluenesulfinyl)-2-hexene, 77944-44-6; (*p*-toluenesulfinylethylene)cyclohexane, 77944-45-7; *p*-toluenesulfinylchlorine, 10439-23-3; methylenecyclohexane, 1192-37-6; 2-methyl-2-butene, 513-35-9; 3-methyl-2-pentene, 922-61-2.

(6) Kukolja, S.; Lammert, S. R.; Gleissner, M. R. B.; Ellis, A. I. *J. Am. Chem. Soc.* **1976**, *98*, 5040.

(7) Use of the S=O double bond as an enophile is well-known: Rogič, M. M.; Masilamani, D. *J. Am. Chem. Soc.* **1977**, *99*, 5219. Peterson, P. E.; Brockington, R.; Dunham, M. *Ibid.* **1975**, *97*, 3517. Bordwell, F. G.; Suter, C. M.; Webber, A. J. *Ibid.* **1945**, *67*, 827.

(8) For a discussion of the use of alkylaluminum halides as Lewis acids see: Snider, B. B. *Tetrahedron*, **1981**, *37*, in press.

(9) With methylenecyclohexane, use of $AlCl_3$ gives a mixture of the expected ene adduct and those obtained from 1-methylcyclohexene, while $ZnCl_2$ gives a mixture of the expected ene adduct and 1-chloro-1-methylcyclohexane. With cyclopentene, $ZnCl_2$ gives a complex mixture containing traces of ene adduct. Use of Me_2AlCl in ether or CH_2Cl_2 leads to complex mixtures of products.

(10) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556.

(11) Schoberl, A.; Wagner, A. In "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Georg Thieme Verlag: Stuttgart, 1955; Vol. IX, p 217. Glaros, G.; Sullivan, S. *Synth. Commun.* **1976**, *6*, 495.

(12) Purchased from Texas Alkyls, Inc., as a 25% solution in heptane.

(13) Kurzer, F. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 937.

(14) All compounds were characterized by NMR and IR spectroscopy and were chromatographically pure. All new compounds, except entries 3–5 of Table I which were unstable, gave satisfactory elemental analyses.

(15) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. Block, E. "Reactions of Organosulfur Compounds"; Academic Press: New York, 1978.

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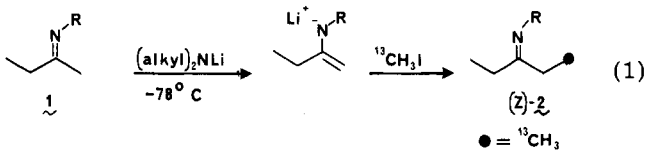
Regioselectivity in Deprotonation of Imines Derived from 3-Pentanone

Summary: Regioselectivity in deprotonation of (*Z*)-*tert*-butyl, (*Z*)-cyclohexyl, (*Z*)-benzyl, and (*Z*)-phenyl ketimines of 3-pentanone has been shown to be generally low and variable. Deprotonation of $^{13}CH_3$-labeled *Z* ketimines with either lithium diisopropylamide or lithium diethylamide in THF and methylation at −78 °C was used to determine regiochemistry. Syn/anti deprotonation ratios varied from 74/26 to 22/78 with different ketimines and different bases.

Sir: Metalated imines and related species have become synthetically important alternatives to simple ketone enolates.[1-3] However, in spite of numerous synthetic applications of these reagents, there is a surprising lack of information about the stereoselectivity and regioselectivity of their formation in deprotonation reactions. In light of our recent studies on regioselectivity in deprotonation of ketone dimethylhydrazones,[4-6] we have undertaken a study to determine the extent of regioselectivity, if any, in deprotonation of a series of 3-pentanimines. Our results discussed below clearly show that the 1-azaallyllithium reagents are kinetically formed with low regioselectivity and that what regioselectivity is seen is a function both of the *N*-alkyl group of the alkyl ketimine and of the structure of the hindered lithium dialkylamide base used in the deprotonation.[7]

We have prepared $^{13}CH_3$-labeled ketimines with defined C=N stereochemistry for use in our regiochemistry studies using the procedure of eq 1. Deprotonation of ketimines



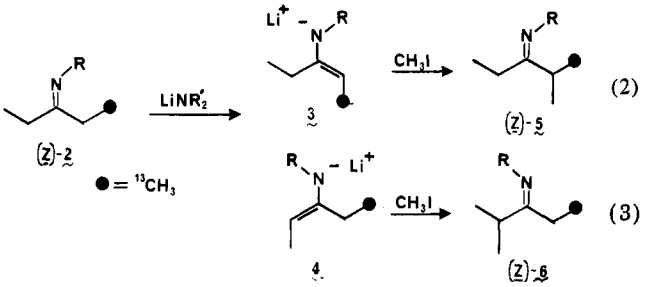
(1)

of 2-butanone (1) at −78 °C gave the (*Z*)-azaallyllithium species (R syn to the charged carbon, vide infra). Subsequent methylation with 30% ^{13}C-enriched methyl iodide gave (*Z*)-**2** as the only labeled species detectable by ^{13}C NMR. When (*Z*)-**2** was allowed to stand at 25 °C, isomerization to a mixture of (*E*)- and (*Z*)-**2** occurred. In each case, the signal from the labeled methyl group of (*Z*)-**2** was downfield from that of the labeled methyl group of (*E*)-**2** (Table I). The regiochemistry of deprotonation of the ketimines (*Z*)-**2** was then followed by alkylating the intermediate azaallyllithium reagents with methyl iodide and examining the methylation products by ^{13}C NMR spectroscopy. The method (eq 2 and 3) is analogous to that

Table I. ^{13}C-Labeled Methyl Chemical Shifts[a]

R	chemical shift (*Z*)-2	(*E*)-2	3	4	(*Z*)-5	(*E*)-5	(*Z*)-6	(*E*)-6
tert-butyl	10.8	10.1	13.4[b]		18.8	20.5	10.6[c]	10.9[c]
c-C_6H_{11}	11.5	10.3	13.8[b]		19.2	19.6	9.8	11.3
phenyl	12.2	11.9	*d*	*d*	19.0	19.6	9.4	10.8
benzyl	10.0	9.5	13.9	12.9	18.5	19.5	9.5	10.0

[a] Chemical shifts in δ units: the β-carbon signal of THF is defined as δ 25.0. [b] The signals for the two anions were not resolved. [c] The equilibrium ratio of (*Z*)-**6** and (*E*)-**6** measured by ^{13}C NMR was 25:75. [d] Not measured.



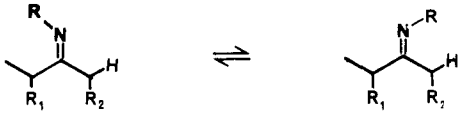
(2) (3)

used in our earlier ketone dimethylhydrazone studies.[6] Table II lists the regioselectivity we observed in several deprotonation reactions using either lithium diethylamide (LDEA) or lithium diisopropylamide (LDA) as a base.

As can be seen from the data in Table II, there were significant differences in regioselectivity for deprotonation of different ketimines. The *tert*-butyl and phenyl ketimines both seemed to favor anti deprotonation while the benzyl ketimine favored syn deprotonation. Only modest regioselectivity was observed in either case. Regioselectivity in deprotonation of the cyclohexyl ketimine with LDEA was essentially zero. Minor differences in deprotonation regioselectivity for ketimines were seen when LDEA was substituted for LDA in the deprotonation step.[7]

The low regioselectivity we observed in these deprotonations did not result from prior isomerization of the ketimine (*Z*)-**2**. When the deprotonation of (*Z*)-**2** was monitored by ^{13}C NMR spectroscopy, no (*E*)-**2** could be detected except in the deprotonation of (*Z*)-**2** (R = *tert*-butyl) with LDA wherein we observed ca. 15% isomerization of (*Z*)-**2** to (*E*)-**2** when the deprotonation reaction was ca. 75% complete.

Our results from the methylation experiments confirmed the previous reports that the azaallyllithium reagents formed in deprotonation of ketimines are syn.[8] We typically observed that alkylation of the intermediate heteroallyllithium reagents **3** and **4** with methyl iodide produced the thermodynamically less stable imines (*Z*)-**5** and (*Z*)-**6**. Subsequent thermal isomerization produced the *E* imine products (eq 4). *tert*-Butyl ketimines, which have the


(4)

(*Z*)-**5**, R_1=$^{13}CH_3$, R_2=CH_3 (*E*)-**5**, R_1=$^{13}CH_3$, R_2=CH_3

(*Z*)-**6**, R_1=CH_3, R_2=$^{13}CH_3$ (*E*)-**6**, R_1=CH_3, R_2=$^{13}CH_3$

(1) Wender, P. A.; Schaus, J. M. *J. Org. Chem.* **1978**, *43*, 782–784.
(2) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178–2180. Wittig, G.; Reiff, H. *Angew. Chem., Int. Ed., Engl.* **1968**, *7*, 7–14.
(3) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032–3039.
(4) Bergbreiter, D. E.; Newcomb, M. *Tetrahedron Lett.* **1979**, 4145–4148.
(5) Jung, M. E.; Shaw, T. J.; Fraser, R. R.; Banville, J.; Taymaz, K. *Tetrahedron Lett.* **1979**, 4149–4152.
(6) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.* **1980**, *45*, 4666–4669.
(7) Lithium dialkylamide base identity can also affect stereoselectivity and regioselectivity of ketone enolate formation. Cf.: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081. Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934–946.
(8) Regardless of the regioselectvity in the deprotonation step, *syn*-azaallyllithium reagents are thermodynamically favored. Cf.: Houk, K. N.; Stozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chauqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426–1429 and references therein.

0022-3263/81/1946-3157$01.25/0