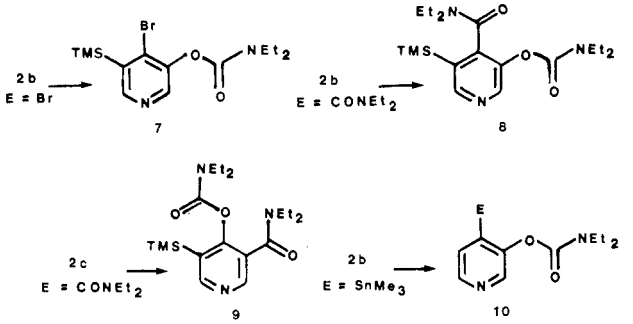
2-pyridone[8a] and 4-methyl-3-hydroxypyridine,[8b] respectively. The regiospecific formation of monobromo- and monoiodopyridones and hydroxypyridines underscores the advantage and complimentarity of this methodology vis-à-vis the electrophilic halogenation approach.[9]

By analogy to the *O*-aryl carbamates,[3] the metalated pyridyl carbamates **1b**, **1c**, and **2c** underwent the anionic Fries rearrangement (−78 °C → room temperature/8 h) to give the isonicotinamide **3** and nicotinamides **4a** and **4b**, respectively (see Table I). In view of the well-known facile reductive conversion of hydroxypyridines to the corresponding pyridines via their chloro derivatives,[10] **2a–c** and **3**, **4** systems are, in principle, prototype precursors to diversified pyridines. As an illustrated of such a sequence, the substituted 4-pyridone **4**, E = Me, prepared by anionic Fries rearrangement of **2c**, E = Me (2.1 equiv *sec*-BuLi/TMEDA/THF/−78 °C → room temperature/8 h), was transformed into the 4-chloropyridine **5** ($POCl_3$/reflux/10 min) and hydrogenolyzed (H_2/Pd–$BaSO_4$/EtOH/16 h)[10] to afford the 5-methylnicotinamide **6** in 40% unoptimized yield.



As initial tests of further directed metalation possibilities on the derived *O*-pyridyl carbamates, metalation and Me_3SiCl quench sequences were carried out on **2b**, E = Br,[11] **2b**, E = $CONEt_2$, and **2c**, E = $CONEt_2$. The isolated products, **7** (65%), **8** (66%), and **9** (68%), respectively, indicate that metalation occurs at the 5-position irrespective of the directing group.[12,13] The propensity of pyridine tin derivatives to undergo electrophile-induced ipso destannylation,[14] invited iodination and acylation experiments on **2b**, E = $SnMe_3$. In the event, treatment with I_2 ($CHCl_3$/room temperature/4 h) and MeCOCl (PhH/reflux/40 h) afforded the ipso-substituted products **10a** (90%) and **10b** (57%), respectively, thus offering an additional connecting link between the directed metalation tactic and electrophilic substitution chemistry.

The directed ortho metalation chemistry of *O*-pyridyl carbamates **1a–c** described herein provides efficient and short avenues to new diversely functionalized pyridines which should be useful in heterocyclic and natural product synthesis.[15,16]

Registry No. **1a**, 98976-68-2; **1b**, 51581-40-9; **1c**, 98976-69-3; **2a** (E = D), 98976-70-6; **2a** (E = Me), 98976-71-7; **2a** (E = $CONEt_2$), 98976-72-8; **2a** (E = Me_3Si), 98976-73-9; **2a** (E = Br), 98976-74-0; **2a** (E = I), 98976-75-1; **2b** (E = D), 98976-76-2; **2b** (E = Me), 98976-77-3; **2b** (E = $CONEt_2$), 98976-78-4; **2b** (E = Me_3Si), 98976-79-5; **2b** (E = Me_3Sn), 98976-80-8; **2b** (E = Br), 98976-81-9; **2c** (E = D), 98976-82-0; **2c** (E = Me), 98976-83-1; **2c** (E = $CONEt_2$), 98976-84-2; **2c** (E = Me_3Si), 98976-85-3; **3**, 98976-87-5; **4a**, 98976-88-6; **4b**, 98976-89-7; **5**, 98990-26-2; **6**, 98976-90-0; **7**, 98976-91-1; **8**, 98976-92-2; **9**, 98976-93-3; **10a**, 98976-94-4; **10b**, 98990-27-3; 3-bromo-2-pyridone, 98976-86-4; 4-methyl-3-hydroxypyridine, 1121-19-3.

(8) (a) mp 175–179 °C, lit. mp 181–187 °C, see ref 1, p 844. (b) mp 114–115 °C, lit. mp 117–119 °C, see ref 1, p 981.

(9) Monohalogenation of these systems is difficult to achieve, see: Katritzky, A. R.; Khan, G. R.; Leahy, D. E.; DeRosa, M. *J. Org. Chem.* **1984**, *49*, 4784 and ref 1, p 800.

(10) See, for example: Stevens, J. R.; Beutel, R. H.; Chamberlain, E. *J. Am. Chem. Soc.* **1942**, *64*, 1093.

(11) Metalation was carried out according to the conditions (LDA/THF/−78 °C) described for 3-bromopyridine by Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.

(12) The reluctance to even partial 2-metalation in **1b**, **2b** (E = Br, $CONEt_2$, Me_3Si), and **2c** (E = $CONEt_2$) is somewhat surprising in view of the recent result on metalation (*n*-BuLi/*t*-BuOK/THF/−105 °C) of pyridine which show kinetic acidity ratios of 6:1:6 for the (2 + 6):(3 + 5):4 positions: Verbeek, J.; George, A. V. E.; de Jong, R. L. P.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 257.

(13) In the *O*-aryl carbamate series, inter- and intramolecular competition experiments have shown that the $OCONEt_2$ is a somewhat more powerful directed ortho metalation group than the $CONEt_2$: Miah, M. A. J.; Snieckus, V., unpublished results.

(14) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull. Jpn.* **1982**, *30*, 1731. Yamamoto, Y.; Yanagi, A. *Heterocycles* **1982**, *19*, 168.

(15) All new compounds show analytical and spectral (IR, ^1H NMR, MS) data in full agreement with the assigned structures.

(16) We are grateful to NSERC Canada and Merck Frosst Canada for financial support of our programs. M.A.J.M. is indebted to the University of Waterloo for a scholarship and Rajashahi University, Bangladesh, for a study leave. We thank Reilly Tar and Chemical Co. for providing generous samples of pyridine derivatives.

M. A. J. Miah, V. Snieckus*
The Guelph Waterloo Centre for Graduate Work in Chemistry
University of Waterloo, Waterloo
Ontario, Canada N2L 3G1
Received July 16, 1985

Concerted 1,2-Carbonyl Migrations in Organic Synthesis. A Practical Synthesis of Spiro Cyclic 1,3-Diketones

Summary: A general method for the synthesis of α,β-unsaturated cyclic enones is described that involves the α-thioalkylation of cyclic silyl enol ethers in tandem with a low-temperature metaperiodate oxidative dehydrosulfenylation of a β-keto sulfoxide. The facile Lewis acid catalyzed acyl migration of a series of α,β-epoxy ketones affords a practical synthesis of cyclic spiro 1,3-diketones.

Sir: The methodology for the elaboration of quaternary carbon centers has become increasingly sophisticated.[1] When the molecular architecture includes a spiro carbon center, the synthetic challenge is particularly demanding.[2] A systematic study demonstrating the synthetic utility of 1,2-acyl migrations in α,β-epoxy ketones has not appeared, although there have been sporadic reports on this Lewis acid catalyzed rearrangement.[3] Acyl migration has yet to be established as an effective transformation in organic synthesis since the unusual migratory aptitude of the carbonyl group has not been generally recognized. Mechanistic studies have established that 1,2-carbonyl

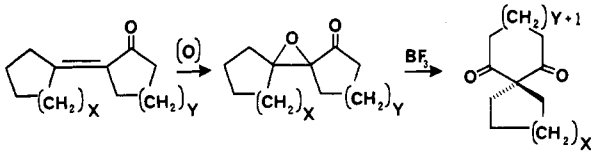
(1) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(2) (a) Krapcho, A. P. *Synthesis* **1976**, 425. (b) Trost, B. M.; Adams, B. R. *J. Am. Chem. Soc.* **1983**, *105*, 4849 and references therein.

(3) (a) Williams, J. R.; Sarkisian, G. M.; Quigley, J.; Hasiuk, A; VanderVernen, R. *J. Org. Chem.* **1974**, *39*, 1028. (b) Hawkins, E.; Large, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2169. (c) Hartman, B. C.; Richborn, B. *J. Org. Chem.* **1972**, *37*, 943. (d) Watanabe, H.; Katsuhara, J.; Yamamoto, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1328. (e) Hart, H. *Acc. Chem. Res.* **1971**, 337. (f) Nojima, M.; Hinove, K.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 827. (g) Reusch, W.; Anderson, D. F.; Johnson, C. K. *J. Am. Chem. Soc.* **1968**, *90*, 4988. (h) House, H. O.; Ryerson, G. D. *J. Am. Chem. Soc.* **1961**, *83*, 979 and references therein. (i) Shapiro, E. L.; Steinberg, M.; Gould, D.; Gentles, M. J.; Herzog, H. L.; Gilmore, M.; Charney, W.; Hershberg, E. B.; Mandell, L. *J. Am. Chem. Soc.* **1959**, *81*, 6483. (j) Collins, D. J. *J. Chem. Soc.* **1959**, 3919.

0022-3263/85/1950-5438$01.50/0

Table I. Lewis Acid Catalyzed Acyl Migration of the α,β-Epoxy Ketones



X	Y	cat., equiv	time	temp	isolated yield of 1,3-dione,[a] %	
1	1	0.01	5 min	25	86 (99)	2
1	1	1.0	2 h	−78	(98)	2
2	1	0.1	1 min	25	71 (99)	3
2	1	1.0	5 min	−23	71 (98)	3
3	1	0.1	1 min	25	91 (99)	4
4	1	0.1	1 min	25	83 (99)	5
1	3	0.5	5 min	25	62 (90)	6
2	3	0.5	1 min	35	73 (91)	7

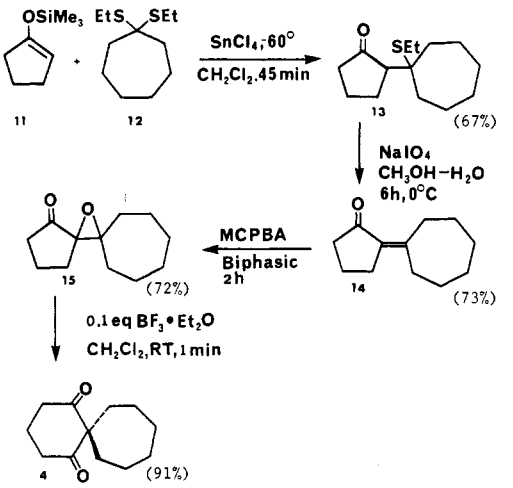
[a] The number in parentheses is the GLC yield.

migration to an adjacent developing positive center is a concerted process involving neighboring group participation (NGP) by the carbonyl carbon.[4] We now report a method for the synthesis of 1,3-diketo spiranes that introduces the quaternary center with a concerted 1,2-carbonyl migration proceeding with inversion of configuration at the migration terminus.

A general synthetic procedure affording spiro 1,3-diketones by this reaction requires a simple route to the epoxy ketone precursors. Although epoxides such as **1** can be readily prepared from a cyclic enone resulting from a simple aldol condensation of cyclopentanone, a general synthetic method has not been developed for epoxides derived from unsymmetrically substituted cyclic enones.[5] The lewis acid catalyzed α-thioalkylation of silyl enol ethers initially reported by Reetz[6] provides a highly efficient method for formation of the carbon–carbon bond adjoining the two cyclic fragments (Scheme I). Trost's[7] dehydrosulfenylation sequence involving oxidation of the β-thiol group with IO_4^- afforded the enone with surprising facility. Stereospecific syn elimination[8] of ethylsulfenic acid from the intermediate β-keto sulfoxide readily occurs *at temperatures as low as 0 °C*. In contrast, α-keto alkyl sulfoxide thermolysis involving intramolecular abstraction of a less acidic β-hydrogen typically requires temperatures as high as 110–130 °C.[9]

In a typical reaction sequence, 15.7 g (0.1 mol) of 1-(trimethylsiloxy)cyclopentene (**11**) and 20.4 g (0.1 mol) of 1,1-bis(ethylthio)heptane (**12**) were treated with 1.1 equiv of $SnCl_4$ (−60 °C) to yield 16.5 g (67%) of 2-[1-(ethylthio)-1-cycloheptyl]cyclopentanone (**13**). Treatment of **13** with 1.1 equiv of $NaIO_4$ in methanol–water (9:1) at 0 °C for 6 h afforded 6.5 g (73%) of 2-cycloheptylidenecyclopentanone (**14**).[11] A biphasic epoxidation of 3.56 g of **14** using MCPBA afforded 2.8 g (72%) of 2-cycloheptylidenecyclopentanone oxide **15**. The remaining enones in Table I can be prepared in similar fashion. The overall yields were not optimized and reflect material loss upon isolation.

Scheme I



Rearrangement of α,β-epoxy ketone **15** was achieved by adding 0.1 equiv of $BF_3{\cdot}Et_2O$ to a solution of 1.94 g (10 mmol) of **15** in 50 mL of CH_2Cl_2. After 1 min at 25 °C the reaction mixture was washed with $NaHCO_3$ and NaCl (aqueous) and dried ($MgSO_4$). The solution was concentrated and chromatographed (5:1 hexane–ethylacetate) to afford 1.76 g (91%) of spiro[5.6]dodecane-2,6-dione (**4**): mp 70–71 °C.; ^{13}C NMR 209.9 (C=O), 69.4 ppm (spiro carbon); IR 1722, 1692 cm^{-1}; MS (70 eV) calcd $C_{12}H_{18}O_2$ 194.1307, found 194.1309.[12]

When the oxirane functionality is endo or contained within the ring of an α,β-epoxy ketone, carbonyl migration results in ring contraction.[4g] However, when the epoxide is exo to the ring bearing the carbonyl functionality, as in **1**, treatment with a Lewis acid results in a cycloexpansion–spiroannulation (eq 1). The carbon p orbital of the

(4) (a) Domagala, J. M.; Bach, R. D.; Wemple, J. *J. Am. Chem. Soc.* **1976**, *98*, 1975. (b) Domagala, J. M.; Bach, R. D. *Ibid.* **1978**, *100* 1605. (c) Domagala, J. M.; Bach, R. D. *Ibid.* **1979**, *101*, 3118. (d) Bach, R. D.; Domagala, J. M. *J. Org. Chem.* **1984**, *49*, 4181. (e) Bach, R. D.; Domagala, J. M. *J. Chem. Soc., Chem. Commun.* **1984**, 1472. (f) Bach, R. D., Domagala, J. M. *Tetrahedron Lett.* **1976**, 4025. (g) Bach, R. D., Klix, R. C. *Tetrahedron Lett.* **1985**, 985.

(5) Sands, R. D. *Org. Prep. Proced. Int.* **1974**, *6*, 153.

(6) Reetz, M. T.; Giannis, A. *Synth. Commun.* **1981**, *11*, 315.

(7) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887; *Ibid.* **1973**, *95*, 6840.

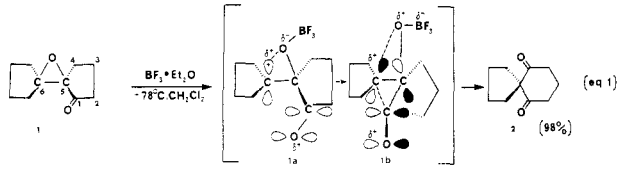
(8) Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810.

(9) Temperatures for elimination of α-phenyl sulfoxides are around 50 °C.[7] Elimination of benzenesulfenic acid from β-keto phenyl sulfoxides have been reported[10] but reaction periods of up to 48 h were used in refluxing CCl_4–$CHCl_3$ (80 °C). Our data suggest that such harsh reaction conditions were probably not necessary.

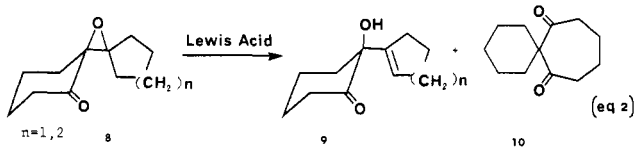
(10) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, 993; **1979**, 995; **1979**, 2179.

(11) The oxidative dehydrosulfenylation affording the corresponding 2-cyclohexylidene enones required reaction times of 12 and 3 h, respectively, at 0 °C. At room temperature ethanesulfenic acid elimination is typically complete in less than 1 h. We suggest that elimination of the corresponding phenyl sulfoxides should be even faster.

(12) All new compounds gave satisfactory elemental analyses. The low temperature carbonyl migrations were quenched at −78 °C by the introduction by cannula of CH_3OH saturated with $NaHCO_3$.



carbonyl π-bond is ideally poised to overlap with the developing empty carbon p orbital at C_6 early on the reaction coordinate as depicted in **1a**. Rotation about the C_4–C_5 bond allows the π_{CO} bond to become parallel to the C_5–C_6 bond axis.[4f] As the 1,2-migration proceeds the partially empty p orbital on oxygen, resulting from reverse polarization of the carbonyl π-bond, is able to mix with the Walsh orbitals of the developing cyclopropyloxenium ion[4d-f] and effectively disperse the positive charge arising from C–O bond cleavage (**1b**). Essentially quantitative acyl migration was observed at −78 °C in about 2 h; at room temperature the rearrangement is complete in less than 1 min. In general, one can anticipate facile acyl migration when a transition state resembling **1b** can be attained without undue bond angle deformation or steric interactions. However molecular models suggest that attempted ring expansion of a cyclohexanone derivative such as **8** will move the carbonyl carbon away from the migration terminus unless the internal bond angles of the ring are compressed. Consequently, the transition state cannot be effectively stabilized by nonclassical stabilization as in **1b** and an E_1 elimination occurs affording allylic alcohol **9** as the major product with both BF_3•Et_2O and $Mg(ClO_4)_2$ (eq 2). Carbonyl migration in **8** (n = 1) has been noted with



$SbCl_5$ in SO_2 solvent[3b,3f] but the formation of a chlorohydrin intermediate[4d] preceding carbonyl migration remains a distinct possibility. We observe the formation of a fluorohydrin intermediate that precedes carbonyl migration in the formation of **6** and **7**.

In summary, the overall reaction sequence in Scheme I provides a practical route to a variety of 1,3-diketospiranes and clearly demonstrates the synthetic utility of rearrangements involving carbonyl migration. In all cases (Table I), acyl migration with attendant *ring expansion proceeded with no detectable competing alkyl migration.* The geometric requirements for formation of a uniquely stabilized transition state resembling **1b** provides a qualitative rationale for both rate differences and the different product distribution observed upon treatment of α,β-epoxyketones with Lewis acids.[4d] The unusually mild reaction conditions required for introducing the spiro center should provide a convergent synthesis of more highly functionalized natural products comprising β-vetivone and related compounds.

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Robert D. Bach,* Russell C. Klix

Department of Chemistry
Wayne State University
Detroit, Michigan 48202

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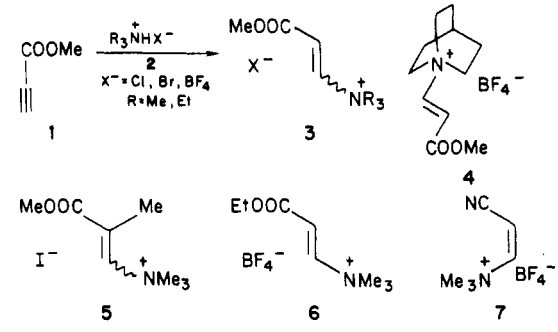
Alkenyltrialkylammonium Salts as Dienophiles in Diels–Alder Reactions: Preparation, Cycloadditions, and Further Reactions. β-(Dimethylamino)acrylonitrile Equivalent in Cycloadditions[1]

Summary: Diels–Alder cycloadditions of a new class of dienophiles, alkenylammonium salts, can be carried out in acetonitrile, giving the desired cycloadducts in excellent yield.

Sir: Although the Diels–Alder reaction is one of the most powerful constructive methods available to synthetic chemists today, there is still a need for further improvements and innovations. One particular drawback is the inability to use dienophiles containing dialkylamino substituents in cycloadditions, a process with significant potential for alkaloid synthesis.[2] We now report a method for accomplishing this transformation which involves the first cycloadditions of alkenylammonium salts, a potentially quite useful class of electron-deficient olefins.

Treatment of methyl propiolate (**1**) with trialkylammonium halides **2** produces (90%) mainly the *trans*-carbomethoxyvinyl trialkylammonium salts **3** (t:c = 90:10).[3]



Exchange of halide for BF_4^- via ion exchange chromatography gives the corresponding BF_4^- salts, which can be prepared more easily (89%) by adding the corresponding BF_4^- salts to **1** (t:c = 55:45, separable by fractional crystallization).[4] The quinuclidinium salt **4** was prepared by addition of the free base quinuclidine to **1** to give the betaine (80%) followed by carboxylate salt methylation with dimethyl sulfate (95%) and ion exchange. The salt **5** was prepared by a method developed for cyclic derivatives, namely, thiophenylation of methyl β-(dimethylamino)-α-methylpropionate (LDA, PhSSPh, 80%) followed by selective N-methylation (excess MeI, 100%), oxidation (MCPBA, 95%) and thermal elimination (80 °C, PhH, 84%).[5] Finally the trans ethyl acrylate derivative **6** and the cis acrylonitrile derivative **7** were prepared analogously from ethyl propiolate and propiolonitrile, respectively. In the case of **7**, the cis isomer preferentially crystallizes from solution.

Seldom have salts been used as dienophiles in cycloadditions.[6] We hoped that the electron-withdrawing

(1) Presented at the 5th International Conference on Organic Synthesis, Freiburg, Germany, Aug 1984.

(2) Although enamines can be used in reverse-electron demand Diels–Alder reactions, the corresponding β-(dialkylamino)acrylates, -acrylonitriles, etc., cannot.

(3) (a) Herkes, F. E.; Simmons, H. E. *J. Org. Chem.* **1973**, *38*, 2845. (b) McCulloch, A. W.; McInnes, A. G. *Can. J. Chem.* **1974**, *52*, 3569.

(4) All new compounds possessed spectroscopic data (high field NMR, IR, FAB MS, and/or elemental analysis) in full accord with their assigned structure.

(5) This reaction was carried out by Dr. G. S. Arora and gives a 4:1 mixture of **5** (one isomer, stereochemistry unknown) and methyl α-(trimethylammoniummethyl)acrylate.

0022-3263/85/1950-5440$01.50/0