Communications

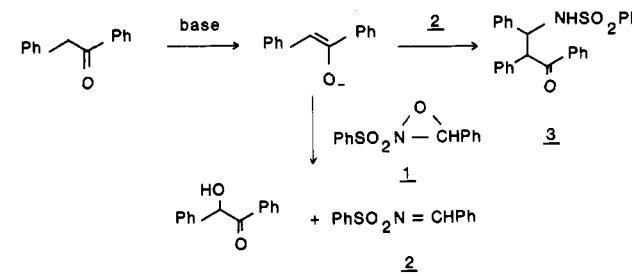
Synthesis of α-Hydroxy Carbonyl Compounds (Acyloins): Direct Oxidation of Enolates Using 2-Sulfonyloxaziridines

Summary: Direct oxidation of ketone and ester enolates, using 2-sulfonyloxaziridine 1, affords α-hydroxy carbonyl compounds (acyloins) in high yield with excellent stereoselectivity.

Sir: α-Hydroxy carbonyl compounds, acyloins, are key structural subunits of natural products and valuable synthetic intermediates. As a consequence of their importance many methods have been devised for their preparation.[1] A disadvantage of these procedures, however, is that they nearly all involve multistep transformation of a carbonyl group. The most practical and simplest route to α-hydroxy carbonyl compounds is direct enolate oxidation which has been explored in detail with only two reagents, molecular oxygen (O_2)[2] and Vedejs' reagent, molybdenum peroxide–pyridine–hexamethylphosphoramide (MoOPH).[3] Enolate oxidations using these reagents are sensitive to carbonyl structure, and byproducts are frequently formed. For example, with O_2 oxidative α-carbon cleavage may occur as well as α-dicarbonyl formation. While enolate oxidation using MoOPH is more general, oxidation of 1,3-dicarbonyl enolates fails and overoxidation to α-dicarbonyl compounds (RC(O)C(O)R) does occur.[3] Furthermore, the stereoselectivity exhibited by these reagents is often poor, affording mixtures of stereoisomers.[4]

Previous results from these laboratories have demonstrated the important synthetic utility of 2-sulfonyloxaziridine 1, a new class of aprotic and neutral oxidizing reagents, in oxidation reactions.[5] In addition to the epoxidation of alkenes[5a] and heteroatom (S, Se, N)[5b,c] oxidation these reagents also oxidize lithium and Grignard reagents to alcohols and phenols.[6] Since the mechanism of anion oxidation by 1 is thought to involve a nucleophilic S_N2-type attack of RM on the electrophilic oxaziridine oxygen atom, it suggested their application in the direct oxidation of enolates. The aprotic nature of 2-sulfonyloxaziridine 1 means that it will not be destroyed by the enolate prior to oxidation. An added advantage in using 1 in these oxidations is that it is easily prepared and stable, requiring no special conditions for storage.[7]

Scheme I



We report that enolate oxidations using 2-(phenylsulfonyl)-3-phenyloxaziridine (1)[7] affords α-hydroxy carbonyl compounds in higher yields and with better stereoselectivity than either MoOPH or O_2.

A typical procedure is illustrated by the oxidation of deoxybenzoin enolate to benzoin (Scheme I). In a 50-mL flask, equipped with rubber septum and magnetic stirring bar and purged with argon, is placed 5 mL of dry THF and 1.5 equiv (typically 0.25–0.30 mmol) of the appropriate base. After being cooled to −78 °C, 1.0 equiv of deoxybenzoin is added, and the solution is allowed to stir at this temperature for 15–30 min followed by addition of 1.5 equiv of 2-sulfonyloxaziridine 1, in 5 mL of THF via syringe. After being stirred for 20 min, the reaction is quenched at −78 °C with 1–2 mL of saturated NH_4Cl solution, solvent is reduced, and the residue extracted into 15–20 mL of ether. Products were analyzed by GLC by comparison with authentic materials.[3] The α-hydroxy carbonyl compounds were easily separated from the sulfonimine 2[8] by preparative TLC (silica gel G), developing with 1:1 methylene chloride–hexane. These results are summarized in Table I.

Noteworthy is the fact that in none of the enolate oxidations using 1 were α-dicarbonyl compounds detected (GLC). Overoxidation was an important side reaction in MoOPH oxidation of the enolates of deoxybenzoin and valerophenone (Table I, compare entries 1 and 9 with 5 and 10).[3] Compound 3,[9] the adduct of sulfonimine 2 and deoxybenzoin enolate, was observed, albeit in low yield, when *t*-BuOK/HMPA was used to generate the enolate (Table I, entry 4). In a separate experiment it was determined that the rate of addition of deoxybenzoin enolate to 2 is very slow at −78 °C and only becomes important at room temperature.[9] Enolate sulfonimine addition

(1) (a) For leading references to the synthesis of α-hydroxy carbonyl compounds, see: Krepski, L. R.; Heilmann, S. T.; Rasmussen, J. K. *Tetrahedron Lett.* **1983**, *24*, 4075. Adamczyk, M.; Dolence, E. K.; Watt, D. S.; Reibenspies, J. H.; Anderson, O. P. *J. Org. Chem.* **1984**, *49*, 1378. (b) For leading references on the synthesis of chiral α-hydroxy esters, see: Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531.

(2) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578. Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731.

(3) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(4) See, for example: Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. Herold, P.; Mohr, P.; Tamm, C. *Helv. Chem. Acta* **1983**, *66*, 744. Boeckman, R. K., Jr.; Cheon, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 4112. Krohn, K.; Sarstedt, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 875.

(5) For leading references on the oxygen-transfer reactions of 2-sulfonyloxaziridines, see: (a) Alkenes: Davis, F. A.; Abdul-Malik, N. F.; Awad, S. B.; Harakal, M. E. *Tetrahedron Lett.* **1981**, *22*, 917. Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123. (b) Sulfides/disulfides: Davis, F. A.; Jenkins, R. H., Jr.; Yocklovich, S. G. *Tetrahedron Lett.* **1978**, 5171. Davis, F. A.; McCauley, J. P., Jr.; Harakal, M. E. *J. Org. Chem.* **1984**, *49*, 1467. (c) Selenides: Davis, F. A.; Stringer, O. D.; Billmers, J. M. *Tetrahedron Lett.* **1983**, *24*, 1213.

(6) Davis, F. A.; Mancinelli, P. A.; Balasubraminian, K.; Nadir, U. K. *J. Am. Chem. Soc.* **1979**, *101*, 1044.

(7) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1744.

(8) Sulfonimine 2 is hydrolyzed on silica gel to benzenesulfonamide and benzaldehyde. In cases where this hydrolysis complicates the chromatographic workup the following alternative procedure can be applied: The reaction (0.24-mmol scale) was quenched at −78 °C with 200 μL of H_2O and warmed to 0 °C and 200 μL of triethylamine added. After 5 min 10 mL of 5% HCl was added and the reaction mixture stirred for 15 min. Normal extractive workup affords the hydroxylated product which is isolated by chromatography.

(9) Compound 3 was prepared in 85% yield by addition of the potassium enolate of deoxybenzoin in THF to sulfonimine 2 at 25 °C.[10]

(10) Physical properties are found in the supplementary material section.

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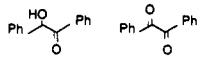
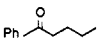
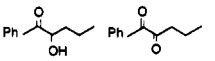
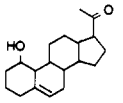
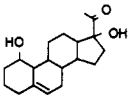
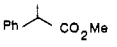
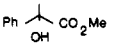
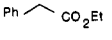
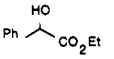
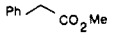
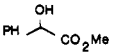
Table I. Oxidation of Enolates Using 2-(Phenylsulfonyl)-3-phenyloxaziridine (1) in THF at −78 °C

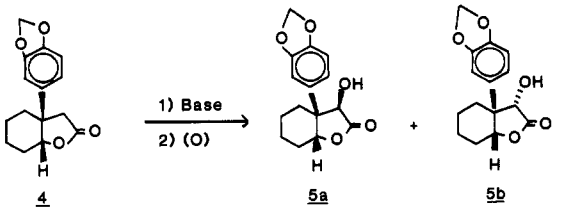
entry	ketone/ester	conditions (carbonyl/base/1)[a]	products % GLC yield[b] (% isolated yield)[c]
			
1		MoOPH/LDA[d]	(34) (25)
2		LDA (1:1:1)	15
3		LDA (1:1:2)	32
4		*t*-BuOK/HMPA/25 °C (1:1:1)	71 3 (12)
5		KHMDS (1:1:1.5)	81 (75)
			
6		MoOPH/LDA[d]	(70)
7		LHMDS (1:1.5:1.5)	(23)
8		KHMDS (1:1.5:1.5)	(85)
			
9		MoOPH/LDA[d]	(60) (13)
10		KHMDS (1:1.5:1.5)	90 (75)
			
11		*t*-BuOK (1:1:1)	(53)
12		KHMDS (1:1.5:1.5)	(78)
			
13		LHMDS (1:1:2)	74
14		KHMDS (1:1.5:1.5)	68
			
15		MoOPH/LDA[d]	58
16		LHMDS (1:1:1)	15
17		LHMDS (1:1:2)	40
18		LHMDS/HMPA (1:1:2)	17
19		KHMDS (1:1.5:1.5)	83
20		KHMDS/HMPA (1:1.5:1.5)	60
21		*sec*-BuLi (1:1:1)	45
			
22		KHMDS (1:1:1)	50
23		KHMDS (1:1.5:1.5)	95 (87)

[a] Molar ratio of ketone or ester:base:oxaziridine. [b] GLC yields using a 6 ft × 1/8 in., 3% OV-17 on Anakorm Q (90/100 mesh) column. The analyses were determined by comparison of peak areas with standard solutions of the reaction products. [c] Isolated yields. [d] See ref 3.

products were not detected when potassium hexamethyldisilazine (KHMDS)[11] was used as the base and the oxidation was carried out at −78 °C (entry 5).

Significantly, in nearly every example, formation of enolates using KHMDS rather than the lithium bases results in a dramatic increase in the yields of α-hydroxy carbonyl compounds (Table I, entries 5, 8, 10, 12, 19, 22, and 23). Lithium diisopropylamide (LDA), the base most frequently used to generate enolates, gives low yields of benzoin (15–20%). Isopropylamine, formed in generating the enolate, may compete with the enolates for 1. This conjecture is supported by the fact that increased yields of products are observed with a 1:2 ratio of base to oxaziridine (compare entries 2 and 3) or when *sec*-butyllithium is used as the base (entry 21).

The stereoselectivity of enolate oxidations using MoOPH or O_2 is generally low, giving mixtures of α-hydroxy carbonyl epimers.[4] The superior stereoselectivity exhibited by 2-sulfonyloxaziridine 1 compared to MoOPH or O_2 is illustrated by oxidation of the enolate of lactone 4.[12] The



4 5a 5b

enolate of lactone 4, formed with LDA, on treatment with MoOPH afforded, in low conversion (15%, unoptimized), a 3:1 mixture (by NMR) of hydroxy lactones **5a** and **5b**.[15]

(11) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

(12) Lactone 4 was prepared by cycloaddition of dichloroketene to 1-[(3,4-methylenedioxy)phenyl]cyclohexene[13] followed by Baeyer–Villager oxidation (30% H_2O_2/NaOH).[10] Details of the synthesis of 4 will appear elsewhere.[13]

Treatment of the lithio enolate of 4 (from 4 and 1.5 equiv of LHMDS as described above) with 1 at −78 °C resulted in a single hydroxy lactone, **5a** in 62% yield. When KHMDS is used to generate the enolate the isolated yield of **5a** increased to 91%. The major hydroxy lactone product, **5a**, is presumed to have the cis stereochemistry based on the fact that chiral 2-sulfonyloxaziridines[16] and MoOPH[17] attack the face of the enolate from the sterically least hindered direction.[18,20]

The chiral synthesis of (+)-kjellmanianone (44% yield, 38% ee), using optically active 2-sulfonyloxaziridines, has previously demonstrated the application of these reagents in the oxidation of enolates of 1,3-dicarbonyl compounds.[19] However, attempts to oxidize the 1,3-dicarbonyl enolates of dibenzoylmethane and ethyl benzoylacetate have been unsuccessful to date.

In summary, direct enolate oxidation (Scheme I) using 2-sulfonyloxaziridine **1** results in better yields of α-hydroxy carbonyl compounds than does O_2 or MoOPH. The fact that **1** is easily prepared, stable, and aprotic makes this oxidant the reagent of choice for direct enolate oxidation, particularly when high stereoselectivity is desired.

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Registry No. **1**, 63160-13-4; **2**, 13909-34-7; **3**, 90867-72-4; **4**, 90867-73-5; **5a**, 90867-74-6; **5b**, 90886-01-4; $PhCH_2COPh$, 451-40-1; $PhCO(CH_2)_3CH_3$, 1009-14-9; $PhCH(Me)CO_2Me$, 31508-44-8; $PhCH_2CO_2Et$, 101-97-3; $PhCH_2CO_2Me$, 101-41-7; $PhCOCH(OH)CH_2CH_2CH_3$, 20907-23-7; $PhCOCOCH_2CH_2CH_3$, 20895-66-3; $PhC(Me)(OH)CO_2Me$, 20731-95-7; $PhCH(OH)CO_2Et$, 774-40-3; $PhCH(OH)CO_2Me$, 771-90-4; PhCH(OH)COPh, 119-53-9; PhCOCOPh, 134-81-6; 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, 76-22-2; 1-hydroxy-18,19-dinorpregn-5-en-20-one, 90867-75-7; dichloroketene, 4591-28-0; 1-[(3,4-methylenedioxy)phenyl]cyclohexene, 90867-76-8; 1,7,7-trimethyl-3-hydroxybicyclo[2.2.1]heptan-2-one, 21488-68-6; 1,17-dihydroxy-18,19-dinorpregn-5-en-20-one, 90867-77-9.

Supplementary Material Available: ^1H NMR, IR, and physical data for adduct **3**, lactone **4**, and hydroxy lactones **5a,b** (1 page). Ordering information is given on any current masthead page.

(13) Prepared by addition of 1-lithio-3,4-(methylenedioxy)benzene to cyclohexanone followed by acid-catalyzed dehydration according to procedures previously described. See: Jeffs, P. W.; Cortese, N. A.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3881.

(14) Finn, J.; Jeffs, P., manuscript in preparation.

(15) Hydroxy lactones **5a,b** were isolated by preparative TLC (silica gel), eluting with petroleum ether/ether (1:1).[10]

(16) Chiral 2-sulfonyloxaziridines epoxidize alkenes and oxidized sulfides to sulfoxides, approaching in the least hindered direction. See ref 5a,b.

(17) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586.

(18) Inspection of Dreiding molecular models indicate that **5a** would be sterically favored.

(19) Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, *22*, 4385.

(20) **Note Added in Proof:** The structure of the major hydroxy lactone was confirmed as **5a** by X-ray crystallography.

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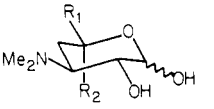
Synthesis of 5-*epi*-Desosamine via a Stereoselective Intramolecular *N*-Sulfinyl Diels–Alder Cycloaddition

Summary: 5-*epi*-Desosamine (**2**) has been synthesized in six steps from diene alcohol **3** through a key intramolecular *N*-sulfinyl dienophile Diels–Alder process which establishes the relative stereochemistry of the three chiral centers of the amino sugar.

Sir: We recently reported a diastereoselective method for synthesis of unsaturated vicinal amino alcohols from 3,6-dihydrothiazine 1-oxides, which are readily prepared by Diels–Alder reactions of *N*-sulfinyl dienophiles.[1,2] It seemed to us that this methodology should be applicable to construction of amino sugars of various types provided one could employ intramolecular [4 + 2] cycloadditions to control both regiochemistry and stereochemistry. Although we reported the first to examples of intramolecular *N*-sulfinyl Diels–Alder reactions in our initial paper,[1] nothing is currently known about the stereochemistry of the process. Thus, as a means of probing salient stereochemical features of this sort of cycloaddition, a synthetic sequence was explored which was directed at the common amino sugar desosamine **1**[3] and/or its unnatural C-5 epimer **2**.



1, R_1 = Me; R_2 = H
2, R_1 = H; R_2 = Me

The starting (*E,E*)-diene alcohol **3** required for this route was prepared by the method of Corey and Kang.[4] The dianion generated from triphenylmethylphosphonium bromide (2 equiv of *sec*-butyllithium, ether, −78 °C, 2 h) was treated with propylene oxide, followed by crotonaldehyde, affording **3** in 57% yield as one geometric isomer. This alcohol was converted to carbamate **4** with sodium cyanate/trifluoroacetic acid (PhH, room temperature, sealed tube, 80%).[5] When **4** was treated with thionyl chloride/pyridine (PhMe, 0 °C to room temperature) a single Diels–Alder adduct **6** was formed (80%). The structure and stereochemistry of this dihydrothiazine oxide was determined by single-crystal X-ray analysis.

Our rationale for the stereoselectivity in this cycloaddition is shown in Scheme I. This explanation is completely consistent with that offered for two intramolecular imino Diels–Alder reactions[6] and an "all carbon" cycloaddition[7] which stereoselectively produced 6/6 fused ring systems containing a chiral center in the connecting chain. The *N*-sulfinyl carbamate derived from **4** can potentially react as the *E* or *Z* isomer. Although *N*-sulfinylaniline[8]

(1) Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499. Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *Ibid.*, in press.

(2) For reviews of this cycloaddition, see: Kresze, G.; Wucherpfennig, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 49. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(3) Previous syntheses of **1**: Richardson, A. *J. Chem. Soc.* **1964**, 5364. Baer, H. H.; Chiu, C.-W. *Can. J. Chem.* **1974**, *52*, 122.

(4) Corey, E. J.; Kang, J. *J. Am. Chem. Soc.* **1982**, *104*, 4724.

(5) Loev, B.; Kormendy, M. R. *J. Org. Chem.* **1963**, *28*, 3421.

(6) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

(7) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.

(8) Janelli, L.; Lamanna, U.; Lumbroso, H. *Bull. Soc. Chim. Fr.* **1966**, *3626*. Dederer, B.; Gieren, A. *Naturwissenschaften* **1979**, *66*, 470. Meij, R.; Oskam, A.; Stufkens, D. J. *J. Mol. Struct.* **1979**, *51*, 37.

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