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OXIDATION OF ENAMINES TO α-HYDROXY KETONES AND α-AMINO KETONES USING N-SULFONYLOXAZIRIDINES

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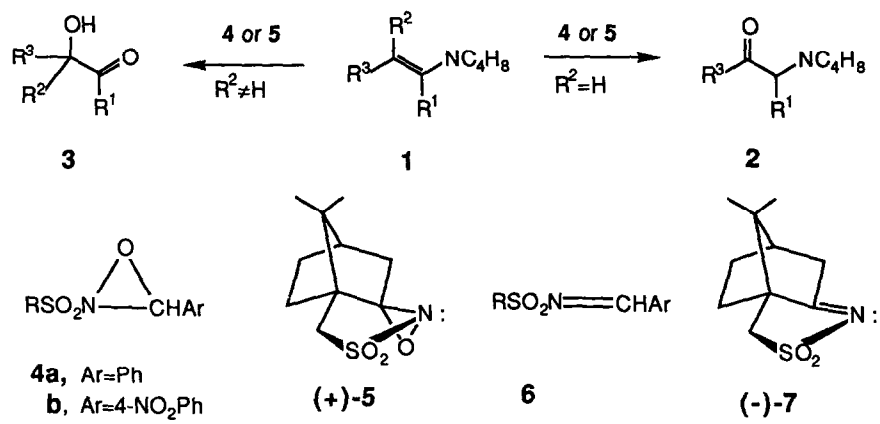
Summary: Tri-substituted enamines are oxidized to α-hydroxy ketones by N-sulfonyloxaziridines while di-substituted enamines are oxidized to α-amino ketones. A unified mechanism for the formation of both α-hydroxy ketones and α-amino ketones is proposed.

The α-hydroxy carbonyl array ($R_2C(OH)C(O)Z$) is a common feature of many biologically important molecules and a key intermediate in the synthesis of natural products.[1-3] In connection with our interest in the synthesis of this important structural unit we have examined the oxidation of enamines **1**, using N-sulfonyloxaziridines **4** and (+)-**5**, as a route to optically active α-hydroxy ketones.[1,4] Enamines are well known to be oxidized by various reagents (O_3,[5] peroxides,[6,7] thallium triacetate[8]) to α-hydroxy ketones in moderate to good yields. In this context we describe a novel and synthetically useful oxidation of tri-substituted enamines to α-hydroxy ketones **3** and of di-substituted enamines to α-amino ketones **2** (Scheme 1).

Scheme 1



Typically, 0.3 mmol of the enamines **1**, in 1 mL of solvent, were oxidized by addition of an equivalent amount of oxaziridines **4** or (+)-**5** in 1 mL of solvent. The enamines were prepared by standard methods using $TiCl_4$.[9] Products were isolated by removal of the solvent and extraction with n-pentane/ether to separate **2** and **3** from the more polar

sulfonimines **6** and (-)-**7**. In the case of the α-hydroxy ketones **3**, 5% HCl solution was added prior to removal of solvent and extraction into n-pentane/ether. Products were isolated by preparative TLC and identified by comparison of their spectral properties (^{1}H, ^{13}C NMR, MS, IR) with values recorded in the literature. Oxaziridine **4** was generally consumed within a few minutes on treatment with **1** as indicated by the disappearance of the oxaziridine CH proton at δ 5.6 ppm and the appearance of the CH sulfonimine proton in **6** at δ 9.0 ppm. However, the enamine of 2-methyl-1-tetralone was found to react with **4b** much faster than with **4a** (Table, entry 13). Oxidation using (+)-**5** proceeded considerably slower with more hindered enamines (compare entries 6 and 12 in Table). In the case of the pyrrolidine enamine of 2-methyl-1-tetralone there was no reaction even after 30 hr (entry 14). These results are summarized in the Table.

Oxidation of di-substituted enamines **1** (R^2=H) with **4** or (+)-**5** gave α-amino ketones **2**. The expected α-hydroxy ketones **3** could not be detected by GLC. When the oxidation of **1** (R^2=H) was carried out with optically active (+)-(camphorylsulfonyl)oxaziridine (**5**) chirality transfer was extremely low affording racemic **2** (entries 2, 6 and 7). Changes in the reaction parameters, solvent, temperature and time all failed to alter the product distribution or the optical activity of the products.

Alternatively, oxidation of tri-substituted enamines **1** (R^2≠H) with **4** or (+)-**5** gave only the expected α-hydroxy ketones **3**. The corresponding α-amino ketones **2** were not detected. Although NMR analysis of the reaction mixture revealed that the oxaziridines were completely consumed within a few minutes, a considerable amount of the reaction product could not be accounted for, particularly when the solvent was chloroform (entries 8 and 10). Longer reaction times resulted in reduced yields. We observed, as did Hoffman[7] in his studies of enamine oxidations to α–hydroxy ketones using (p-nitrophenyl)sulfonyl peroxide, that addition of 2% methanol as co-solvent resulted in improved yields (entries 9 and 11).

A plausible mechanism for the oxidation of **1** to **2** and **3** (Scheme) involves the initial attack of the oxaziridine at the enamine double bond to give α-amino epoxide **8**. This is analogous to the oxidation of silyl enol ethers by **4** to α-siloxy epoxides **8** (C_4H_8N=OTMS).[10] Indeed, α-amino epoxides have been invoked as intermediates in the oxidation of enamines[11] and in the rearrangement of α-halo ketones and amines to α-amino ketones.[12,13] Furthermore, the synthesis of an α-amino epoxide has been reported.[12] However, our attempts to detect **8** by NMR have been unsuccessful. Alternatively, zwitterion **9**, formed directly or via rearrangement of **8**, should give on hydrolysis **3**.[14] When R^2 is H the enol amine intermediate **10** would afford **2**. Not only could **10** explain why only di-substituted enamines **1** (R^2=H) give **2**, but this would also be consistent with the lack of chirality transfer observed using N-sulfonyloxaziridine (+)-**5**. Addition of a nucleophile, such as methanol, will trap **8** or **9** minimizing side reactions and increasing the yields of the products.[7] However, addition of methanol did not alter the outcome for oxidation of **1**, R^2=H (entries 4 and 5), most likely reflecting the greater rate of rearrangement to **10**.

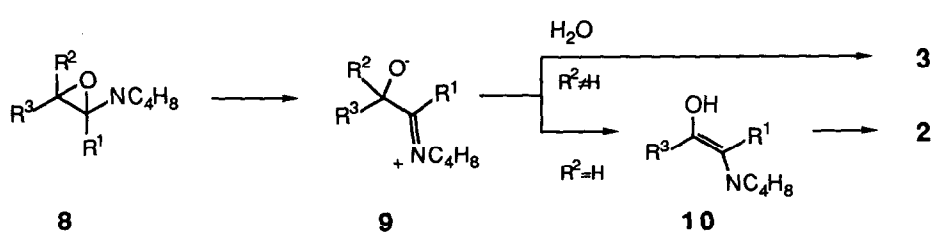
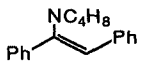
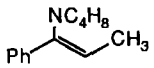
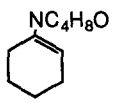
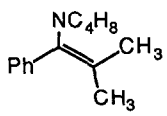
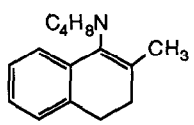
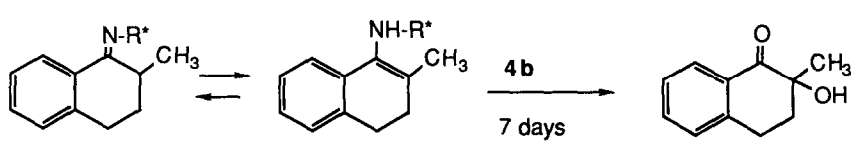


Table: Oxidation of Enamines using N-Sulfonyloxaziridines 4 and (+)-5 at 25 °C.

entry	Enamine R^1, R^2, R^3	Oxaziridine	Solvent[a]	time (hr)	Products % (Isolated Yield) [GLC yield][b]
1		**4a**	$CDCl_3$	0.5	**2** (55)[c]
2		(+)-**5**	$CDCl_3$	0.5	**2** (53)
3		**4a**	$CDCl_3$	0.5	**2** (54)[d]
4		**4a**	$CDCl_3$/MeOH	0.5	**2** (56)
5		**4a**	THF/MeOH[e]	1.0	**2** (52)
6		(+)-**5**	$CDCl_3$	0.5	**2** (55)
7		(+)-**5**	$CDCl_3$	30.0	**2** (66)[f]
8		**4a**	$CDCl_3$	0.08	**3** [60][g]
9		**4a**	$CDCl_3$/MeOH	0.08	**3** (69) [81]
10		**4a**	THF	0.25	**3** [81]
11		**4a**	THF/MeOH	0.25	**3** (79) [92]
12		(+)-**5**	THF/MeOH	30.0	**3** [65]
13		**4b**	THF/MeOH	0.5	**3** (75) [85][h]
14		(+)-**5**	THF/MeOH	30.0	No Reaction

a) As noted 2% by volume of methanol was used a cosolvent. b) GLC analysis using a 6 ft. x 1/8 " 3% OV-17 on 80/100 Supelcoport column. The analyses were determined by comparison of peak areas on standard solutions of the reaction products. c) Sasaki, T.; Kanematsu, K.; Minamoto, K.; Fujimura, H., *Chem. Ph. Bull.*, **1964**, 191. d) Klemmenser, P.; Schroll, G.; Lawesson, S. O., *Ark. Kemi*, **1967**, 405. e) Diluted to 15 mL with THF and carried out at 0 °C . f) See ref. 7b. g) See Ref. 10. h) See Ref. 4b.

To date our attempts to prepare optically active enamines of 2-methyl-1-tetralone with several optically active secondary amines have been unsuccessful. However, chiral imines in tautomeric equilibrium with their tri-substituted enamines, have been reported to undergo alkylation with high stereoselectivities.[16] Indeed, treatment of (+)-**11**[17] with **4b** gave, after 7 days, a 46% isolated yield of optically active (-)-2-hydroxy-2-methyltetralone in 16% ee.[18]



(+)-**11** (-)-**12**

In summary, methodology for the preparation of tetra-substituted α-hydroxy ketones **3** by oxidation of tri-substituted enamines with N-sulfonyloxaziridines is described and is potentially useful in the synthesis of optically active α-hydroxy ketones.[1] Di-substituted enamines are oxidized by these reagents to α-amino ketones **2** in good yields.

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References and Notes

1. For leading references see: Davis, F.A.; Ulatowski, T. G.; Haque, M. S., *J. Org. Chem.*, **1987**, *52*, 5288.

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14. In the oxidation of enamines with arylsulfonyl peroxides Hoffman suggests that oxidation takes place first on the enamine nitrogen atom followed by a 1,3-rearrangement to give an iminium ion similar to **9**.[7a] Since (+)-**5** does not oxidize tertiary amines this argues against oxidation at the enamine nitrogen atom by N-sulfonyloxaziridines.[15]

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17. Imine **11** was prepared in 50% yield from (-)(S)-1-phenylethyl amine by azeotropic removal of water using TsOH: bp 169-72 °C (0.25 mm); $[\alpha]_D$ +69.01 (c = 7.29 $CHCl_3$). NMR indicates an imine:enamine ratio of 85:15.

18. Determined using the $Eu(hfc)_3$ chiral shift reagent.

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