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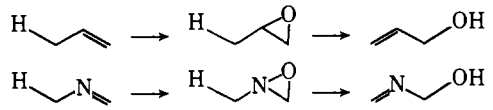
## The Oxidative Deamination of Amines to Ketones via Oxaziridines

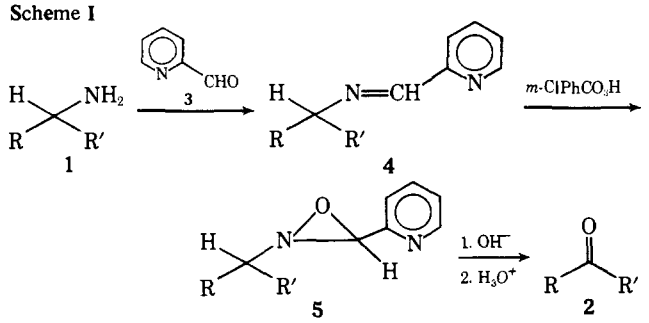
*Sir:*

The transposition of a carbon–nitrogen double bond plays a pivotal role in the enzymatic oxidative deamination of $\alpha$-amino acids to pyruvic acids mediated by pyridoxal pyrophosphate.[1] In developing synthetic methodology for the oxidative deamination of amines **1** to ketones **2**,[2] we have sought to mimic this biochemical process.[3] The conversion of olefins to allylic alcohols via epoxides proceeds with concomitant carbon–carbon double bond transposition[4] and suggests that oxaziridines could be utilized to effect carbon–nitrogen double bond transposition.



We now wish to report an oxidative deamination procedure which incorporates this approach (Scheme I).

Scheme I

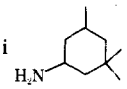
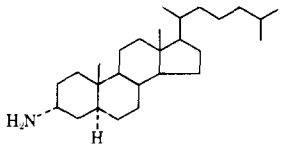
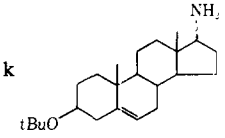


The condensation of 2-pyridinecarboxaldehyde[5] (**3**) (1.0 equiv) with amines **1** in THF (5 ml/mmol of **1** at 25° for 2 hr) over 5A molecular sieves furnished imines **4** in high yield (Table I). The selection of **3** bearing no $\alpha$ hydrogens circumvented any problems in the regioselectivity of oxaziridine ring opening later in the sequence. The *m*-chloroperoxybenzoic acid oxidation[6] (1 equiv/$CH_2Cl_2$/0° for 0.5 hr) of imines **4** provided a mixture of *E* and *Z* isomers[7] of oxaziridines[8] **5** in good yield[9] (Table I). The formation of nitrones or pyridine *N*-oxides was not problematical.

The base-catalyzed ring opening of oxaziridines was reported to liberate ammonia in high yield[10] but to afford carbonyl compounds in low yield.[11] The desired ring opening of an oxaziridine **5** would regenerate 2-pyridinecarboxaldehyde (**3**) as well as liberate a ketone **2** according to the postulated mechanism shown below. To allow for the efficient conversion of oxaziridines **5** to ketones **2** required the suppression of two competing reactions: the rearrangement of **5** to amide **6**[12] and the Aldol condensation of the ketone **2** and 2-pyridinecarboxaldehyde (**3**).

We have found that the ring opening of **5** to ketones **2** proceeds smoothly using potassium hydroxide in an aqueous acetone solution containing methanol or *N,N*-dimethylformamide as a cosolvent[13] (Table I). The dramatic influence of other bases on the course of the reaction is summarized in Table II. In marked contrast to the effective use of dialkylamides and alkoxides in the ring opening of epoxides,[4] only hydroxide ion proved suitable in the ring opening of oxaziridines **5** to ketones **2**.[14] Finally, acetone[15] served to trap the regenerated **3** as the enone **7**. The pyridine ring in **7** allowed for the facile removal of this contaminant (and any unreacted **3**) in an acidification step.

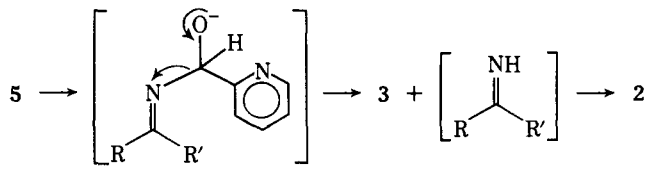
Table I. The Oxidative Deamination of Amines ($RR'CHNH_2$) **1** to Ketones ($RR'C{=}O$) **2**

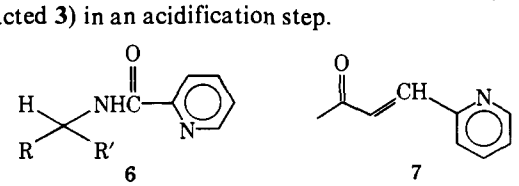
| | R | R' | % isolated yields: Imine **4** | Oxaziridine **5** | Cosolvent (Time, hr) | Ketone **2** |
|---|---|---|---|---|---|---|
| a | $n$-$C_5H_{11}$ | $n$-$C_5H_{11}$ | 91 | 88 | DMF (18) | 73 |
| b | $n$-$C_6H_{13}$ | $n$-$C_6H_{13}$ | 97 | 86 | DMF (21) | 73 |
| c | $-CH_2(CH_2)_4CH_2-$ | | 89 | 82 | MeOH (1.5) | 64[b] |
| d | $-CH_2(CH_2)_5CH_2-$ | | 92 | 77 | DMF (6.5) | 44 |
| e | $-CH_2(CH_2)_9CH_2-$ | | 92 | 80 | DMF (14) | 66 |
| f | $-C_2H_5$ | $-CH_2CH_2Ph$ | 92 | 78 | MeOH (2.5) | 74 |
| g | H | Ph | 93 | ... | MeOH (1) | 64[a] |
| h | $CH_3$ | Ph | 94 | ... | MeOH (0.25) | 42[a] |
| i |  | | 93 | 90 | MeOH (3) | 47[b] |
| j |  | | 99 | 89 | DMF (23) | 77 |
| k |  | | 100 | ... | DMF (16) | 44[a,c] |

[a] Oxaziridine too labile to isolate by thick layer chromatography. [b] Isolated as the 2,4-dinitrophenylhydrazone derivative. [c] Oxaziridine generated at −78° by inverse addition of *m*-$ClPhCO_3H$ to imine.

Table II. Base-Catalyzed Ring Opening of Oxaziridine **5b**

| Base (equiv) | Conditions | % isolated yields: Ketone **2b** | Amide **6b** |
|---|---|---|---|
| KOH(10) | $H_2O$–DMF–acetone | 73 | ... |
| KOH(10) | $H_2O$–MeOH–acetone | 64 | 3 |
| NaOMe(1.5) | THF | 22 | 12 |
| KO-*t*-Bu(1.5) | THF | 20 | 3 |
| Li-N(*i*-Pr)$_2$(1.5) | THF | | 56 |
| $Cu(OAc)_2$(1.0) | $H_2O$–MeOH | | 68 |





In several cases, we have found that our oxidative deamination sequence is superior to literature procedures. For example, application of our procedure to **1j** provided **2j** in 66% yield (without isolation of the intermediate imine or oxaziridine) but application of the mesitylglyoxal procedure[3c] af-

forded **2j** in only 33% yield. Moreover, the hydrogen peroxide–sodium tungstate oxidation[16] of amines to oximes failed completely for **1j**. We feel that the ease of operation, availability of reagents, and acceptable yields will make our oxidative deamination sequence a synthetically useful process. The experimental procedures will follow in the microfilm edition; see paragraph at end of paper regarding supplementary material.

**Acknowledgment.** The financial support of the Research Corporation, the Cancer Advisory Committee of the American Cancer Society at the University of Colorado, and Sigma Xi, The Scientific Research Society of North America, is gratefully acknowledged. We also wish to thank Searle, Inc. for a generous gift of steroid precursors.

**Supplementary Material Available.** A detailed experimental section tabulating spectral data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring code number JACS-75-6900.

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(9) The use of benzene, chloroform, and nitromethane furnished **5** in similar yield but with variation in the *E/Z* isomer ratio.
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(11) The only precedent for this reaction in which the conditions and yields are clearly defined involves the base-catalyzed ring opening of 2-(1-phenethyl)-3-isopropyloxazirane to afford 8% of isobutylidene acetophenone, the Aldol condensation product of acetophenone with "regenerated" isobutyraldehyde (ref 10).
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(13) In a typical ring opening experiment, 1 mmol of **5** was treated with 1 ml of 10 *M* KOH in $H_2O$, 20 mmol of acetone, and sufficient cosolvent (MeOH or DMF) to obtain 5 ml of total volume.
(14) Our failure to exclude completely the formation of the amide **6** in the ring opening of **5** led us to synthesize phenyl 2-pyridyl ketone and 2-pyridyl *tert*-butyl ketone. Not unexpectedly, the condensation of these ketones with amines **1** proceeded in low yield even under forcing conditions.
(15) In the absence of acetone, the yields of ketones were reduced by a factor of three.
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## Nucleophilic Catalysis of the Aromatization of an Arene Oxide. The Reaction of Trimethylamine with 4-Carbo-*tert*-butoxybenzene Oxide

*Sir:*

The reactivity of arene oxides in solution is characterized by their facile isomerization to phenols (NIH-shift)[1] via specific acid and spontaneous pathways[2] as well as general acid catalysis.[3,4] The aromatization of substituted benzene oxides by either specific acid catalysis or spontaneous rearrangement exhibits a $\rho^+$ of ca. $-7$[5] and gives the corresponding phenolic products consistent with epoxide opening to the most stable carbonium ion.[6]

Benzene oxides are also subject to competing nucleophilic attack and are particularly susceptible to soft nucleophiles as evidenced by reports that benzene oxide itself reacts readily with azide and mercaptide anions, while is unreactive toward the hard nucleophiles $NH_3$ and $^-NH_2$.[7] To date, the competition between nucleophilic reactivity and spontaneous aromatization rates of arene oxides provides the most distinguishing feature between non-K-region oxides and the biologically important K-region oxides.[8] While trimethylamine is unreactive towards benzene oxide,[9] we have discovered via kinetic and isolation techniques the formation and subsequent aromatization of a 1,6-nucleophilic addition adduct of trimethylamine and 4-carbo-*tert*-butylbenzene oxide (**1**),[10] thus providing the first case of *nucleophilic catalysis* in the aromatization of an arene oxide.

The aromatization of (**1**) in water between pH 0 and 10 in the absence of buffer exhibited excellent *pseudo*-first-order kinetics ($k_{obsd}$). The pH-dependence of log $k_{obsd}$ (Figure 1) follows the rate law of eq 1

$$k_{obsd} = k_H a_H + k_0 \quad (1)$$

where $a_H$ is the hydrogen ion activity determined at the glass electrode, $k_H = 0.185\ M^{-1}\ sec^{-1}$, and $k_0 = 1.55 \times 10^{-5}\ sec^{-1}$. The products were identified spectrophotometrically as a mixture of 94% *tert*-butyl *m*-hydroxybenzoate (**2**) and 6% *tert*-butyl *p*-hydroxybenzoate (**3**) by employing extinction coefficients and $pK_a$'s of independently prepared samples of **2** ($pK_a = 9.15$ measured at 325 nm) and **3** ($pK_a = 8.42$ measured at 295 nm). The ratio of the two isomeric benzoates was constant over the pH-range studied. In contrast to previous studies on non-K-region oxides, a base catalyzed reaction predominated at high pH with the biphasic formation (280 nm) of a complex product mixture containing some *tert*-butyl *trans*-2,3-dihydroxy-2,3-dihydrobenzoate[12] between pH 10 and 14 (Figure 1).

The reaction of **1** with excess trimethylamine (TMA; 0.032–0.5 *M*; $pK_a$ 9.95) at 30° ($\mu = 1.0$, KCl) and constant pH (9.02–10.82) was found to be biphasic. Both the appearance (eq 2) and disappearance (eq 3) of intermediate (280 nm) were pseudo first order to greater than three half-lives.

$$k_{obsd_1} = k_1[TMA]_T \frac{K_a}{(K_a + a_H)} \quad (2)$$

$$k_{obsd_2} = k_2[TMA]_T \frac{K_a}{(K_a + a_H)} + \frac{k_3 K_w}{a_H} \quad (3)$$

The sole product of the reaction was identified spectrophotometrically as **2**. For the initial phase of reaction, plots of $k_{obsd_1}$ vs. total TMA concentration ($[TMA]_T = [TMA] + [TMAH^+]$) at varying pH are linear giving coincident intercepts on the $k_{obsd}$ axis near $k_0$ at $[TMA]_T = 0$. The slopes of these plots when plotted vs. $K_a/(K_a + a_H)$ were found to be linear of slope $k_1$ (Figure 2). For the second phase of the reaction, plots of $k_{obsd_2}$ vs. $[TMA]_T$ at varying pH's were linear with pH-dependent intercepts on the $k_{obsd}$