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FURTHER OBSERVATIONS ON THE LEWIS ACID-CATALYZED BENZYLIC HYDROPEROXIDE REARRANGEMENT: USE OF A BORON-TRIFLUORIDE/ HYDROGEN PEROXIDE PREFORMED, AGED REAGENT

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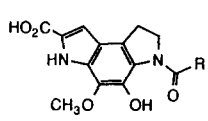
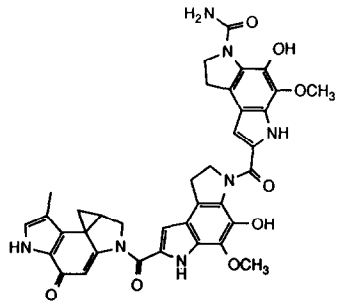
Abstract: *A preformed, aged reagent derived from boron trifluoride etherate and 90% hydrogen peroxide (2:1-4:1 complex) has been found to be a useful reagent for promoting the benzylic hydroperoxide rearrangement of readily oxidizable substrates bearing a free, basic amine. The use of this procedure for introduction of the C-4 phenol of the C-4/C-5 selectively-protected o-catechol unit found in PDE-I and PDE-II, naturally-occurring phosphodiesterase inhibitors constituting the central and right-hand segments of the antitumor-antibiotic CC-1065, is detailed.*

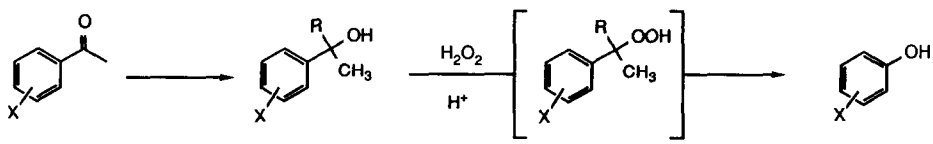
In recent studies requiring the preparation of phenol substrates including efforts directed at the total synthesis of PDE-I (1), PDE-II (2), and CC-1065 (3) we have encountered difficulty implementing successful Baeyer-Villiger oxidations of highly-substituted, electron-rich acetophenones possessing one or two substituents *ortho* to the aryl acetyl group.[2] Consequently, in conjunction with these efforts we have investigated the use of alternative, complementary procedures for phenol introduction and have detailed observations on the scope and preparative synthetic utility of the benzylic hydroperoxide rearrangement,[3] equation 1. Benzylic *secondary* and *tertiary* alcohol substrates derived from hindered, electron-rich acetophenones (or benzoates), which fail to participate effectively in the conventional peracid Baeyer-Villiger rearrangement, proved ideally suited for use in the benzylic hydroperoxide rearrangement and required unexpectedly mild conditions (10 mol% *p*-toluenesulfonic acid, 10-20 equiv H_2O_2, THF, 20-25°C, 6-24 h) for effecting the desired phenol introduction.



R = NH_2, PDE-I **1**
R = CH_3, PDE-II **2**



CC-1065 **3**



(1)

The presence of basic functionality in the benzylic alcohol substrate, *e.g.*, an unprotected free indoline nitrogen, was found to require the use of excess protic acid catalyst and under such conditions, substrate nitrogen protonation slowed the rate of desired benzylic hydroperoxide formation and rearrangement sufficiently to permit secondary processes to effectively compete. Boron trifluoride etherate ($BF_3{\cdot}Et_2O$) employed as the $BF_3{\cdot}Et_2O$/90% H_2O_2 (2:1 mol/mol complex)[4] proved to be a modestly effective Lewis acid catalyst for promoting the benzylic hydroperoxide rearrangement of such substrates.[3a] A basic amine functionality was found to withstand the strong oxidizing conditions required for hydroperoxide formation and rearrangement presumably as a consequence of Lewis acid coordination under the reaction conditions. Herein, we detail further observations and improvements on the Lewis acid-catalyzed benzylic hydroperoxide rearrangement and provide an excellent reagent (4:1 $BF_3{\cdot}Et_2O$/90% H_2O_2) suited for use with highly functionalized, readily oxidizable substrates.

Representative results of a study of the (Lewis) acid-catalyzed benzylic hydroperoxide rearrangements of *secondary* and *tertiary* alcohol substrates derived from 7-acetylindoline[3a] are detailed in Table I. Treatment of the *tertiary* alcohol **5** with a 2:1 mixture of $BF_3{\cdot}Et_2O$/90% H_2O_2 (5 equiv H_2O_2) in CH_2Cl_2 at room temperature followed by exhaustive acetylation (Ac_2O, K_2CO_3, 100°C) of the crude 7-hydroxyindoline **6** provided **8** in moderate yield (57%). Subjection of *secondary* alcohol **4** to identical reaction conditions was less successful and provided **8** in 19% yield. Decreasing the amount of H_2O_2 from 5 equiv to 1.5 equiv while maintaining the concentration of Lewis acid (by increasing the ratio of $BF_3{\cdot}Et_2O$/90% H_2O_2 from 2:1 to 4:1 in the preformed reagent) markedly improved the conversion of **5** to 7-hydroxyindoline. Subsequent, selective *N*-acetylation (1.2 equiv Ac_2O, NaOAc, THF, 20°C) of crude **6** afforded **7** in excellent overall yield (83%). In comparison, subjection of *tertiary* alcohol **5** to more vigorous, but standard, hydroperoxide rearrangement conditions (55% H_2SO_4, 3 equiv H_2O_2)[5] followed by acetylation (Ac_2O, K_2CO_3, 100°C) afforded **8** in 44% optimized yield.

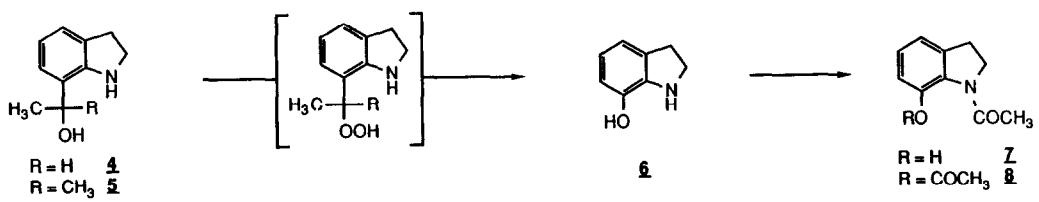


Table I. Lewis Acid-Catalyzed Benzylic Hydroperoxide Rearrangement of *Secondary* and *Tertiary* Alcohols 4, 5.

substrate	rearrangement conditions	acylation conditions[a]	product	yield
4	5 equiv H_2O_2, 10 equiv $BF_3{\cdot}Et_2O$ CH_2Cl_2, 22°C, 18-22 h	A	8	19%
5	5 equiv H_2O_2,10 equiv $BF_3{\cdot}Et_2O$ CH_2Cl_2, 22°C, 18-22 h	A	8	57%
5	55% H_2SO_4, 3 equiv H_2O_2[b] CH_2Cl_2, 23°C, 10 min	A	8	44%
5	1.5 equiv H_2O_2, 6 equiv $BF_3{\cdot}Et_2O$ CH_2Cl_2, 19-20°C, 36 h	B	7	83%

[a]A = neat Ac_2O, K_2CO_3, 100°C, 6 h; B = 1.2 equiv Ac_2O, NaOAc, THF, 20°C. [b]See reference 5.

The application of this methodology for the C-4 phenol introduction employed in the total syntheses of PDE-I and PDE-II[2a] is detailed in Table II. Subjection of the *secondary* alcohol 9 to the initially defined conditions for the Lewis acid-catalyzed benzylic hydroperoxide rearrangement (5 equiv H_2O_2, 10 equiv $BF_3{\cdot}Et_2O$, CH_2Cl_2, 23°C, 1 h) followed by selective *N*-acetylation of the readily oxidized, free indoline phenol **11** (Ac_2O, NaOAc, THF, 23°C) provided PDE-II methyl ester (**13**), consistent with expectations albeit in low yield. Exposure of the more reactive *tertiary* alcohol **10** to the identical reaction conditions (30 min) led to the rapid consumption of **10** without detection of **11**. Conducting this reaction with a reduction of the number of equivalents of oxidant and Lewis acid catalyst (2.5 equiv H_2O_2, 5 equiv $BF_3{\cdot}Et_2O$, 23°C, 10 min) afforded **13** in low yield (27%) after acetylation. Further optimization of the Lewis acid-catalyzed hydroperoxide rearrangement by continuing to reduce the number of equivalents of H_2O_2 while maintaining the concentration of Lewis acid (1.5 equiv H_2O_2, 6 equiv $BF_3{\cdot}Et_2O$, 23°C) improved the conversion of **10** to **11**.[6] Acylation of the crude, unstable indoline **11** with trimethylsilylisocyanate or acetic anhydride afforded good overall yields of PDE-I and PDE-II methyl esters, **12** and **13**, respectively. Moreover, aging the preformed reagent prepared by the addition of 90% H_2O_2 (1 equiv) to neat $BF_3{\cdot}Et_2O$ (4 equiv) at 0°C for 30-45 min prior to use in the Lewis acid-catalyzed benzylic hydroperoxide rearrangement of **10** resulted in a significant improvement in the quality and conversion (% yield) of the reaction.

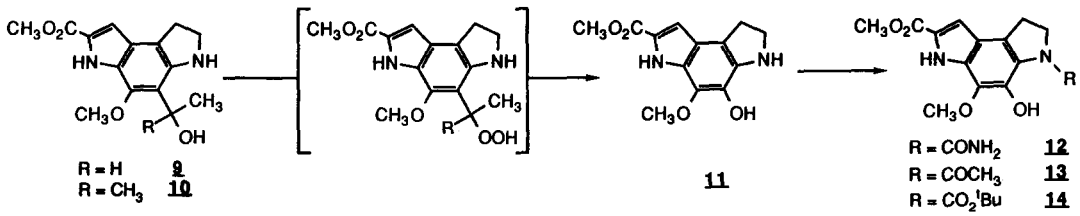


Table II. Lewis Acid-Catalyzed Benzylic Hydroperoxide Rearrangement of *Secondary* and *Tertiary* Alcohols 9, 10.

substrate	equiv H_2O_2[a]	equiv $BF_3{\cdot}Et_2O$[a]	time[b]	acylation[c]	product	yield
9	5.0	10.0	1 h	B	13	< 10%
10	5.0	10.0	30 min	B	13	0%
10	2.5	5.0	10 min	B	13	27%
10	1.5	6.0	7 min	B	13	62%[d]
10	2.5	7.5	7 min	C	14	35%
10	1.5	6.0	5 min	C	14	46%
10	1.5	6.0	5 min	A	12	41%
10	1.5	6.0	7 min	A	12	64%[d]
10	1.4	5.6	8 min	A	12	81%[d]

[a]Preformed reagent was prepared by addition of 90% H_2O_2 to $BF_3{\cdot}Et_2O$ at 0°C immediately prior to use: see reference 4. [b]All reactions were conducted at 21-23°C in CH_2Cl_2. [c]A = trimethylsilylisocyanate; B = acetic anhydride; C = di-*tert*-butyldicarbonate. [d]The preformed $BF_3{\cdot}Et_2O/H_2O_2$ reagent was stirred at 30-45 min at 0°C prior to use.

Activated, electron-rich benzylic alcohols bearing a free amine have been found to readily participate in a Lewis acid-catalyzed benzylic hydroperoxide rearrangement employing a preformed 4:1 $BF_3{\cdot}Et_2O$/90% H_2O_2 reagent. Moreover, in instances when the rearrangement proceeds rapidly (< 1 h) and the phenol product derived from such electron-rich benzylic alcohols is subject to further, rapid oxidation reactions, the use of the preformed, aged reagent (4:1 $BF_3{\cdot}Et_2O$/90%

H_2O_2, 0°, 30-45 min) improves the conversion to phenol product. The application of the Lewis acid-catalyzed benzylic hydroperoxide rearrangement to the preparation of PDE-I and PDE-II methyl esters (**12** and **13**, respectively)[2a] is illustrative.

***N*-Acetyl 7-hydroxyindoline (7).** A 4:1 mixture of $BF_3{\cdot}Et_2O$/90% H_2O_2 was prepared by the addition of 90% H_2O_2 (50 *u*L, *ca.* 36 *M*, 1.8 mmol) to $BF_3{\cdot}Et_2O$ (0.88 mL, 1.02 g, 7.2 mmol) at 0°C under argon. The reagent was stirred 30 min (0°C) prior to use.

A solution of **5**[3a] (102.4 mg, 0.578 mmol) in dry CH_2Cl_2 (5.0 mL) at 19°C was treated with the above 4:1 $BF_3{\cdot}Et_2O$/90% H_2O_2 reagent (0.46 mL, *ca.* 0.87 mmol H_2O_2, 1.5 equiv) and the resulting reaction mixture was stirred 35 h (19-20°C). The excess H_2O_2 was reduced by the addition of saturated aqueous Na_2SO_3 (3 mL). The reaction mixture was diluted with water (10 mL) and was extracted with EtOAc (4 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford crude 7-hydroxyindoline (**6**) as an unstable, brown crystalline solid. A solution of the crude **6** in THF (2.0 mL) at 19°C under nitrogen was treated sequentially with anhydrous NaOAc (50 mg, 0.61 mmol) and Ac_2O (66 *u*l, 71.5 mg, 0.7 mmol) and the resulting reaction mixture was stirred for 12 h (19-20°C). Removal of the NaOAc by filtration, and concentration of the reaction mixture *in vacuo* afforded crude *N*-acetyl 7-hydroxyindoline (**7**). Flash chromatography (1 x 15 cm SiO_2, 50% ether-hexane) afforded pure **7** (84.8 mg, 102.4 mg theor., 83%) as a white, crystalline solid: mp 111.5-112°C (ether, white needles); ^1H NMR ($CDCl_3$, 200 MHz, ppm) 7.02 (apparent t, 1H, J = 8 Hz, C5-H), 6.80 (d, 1H, J = 8 Hz, C4-H), 6.68 (d, 1H, J = 7 Hz, C6-H), 4.05 (t, 2H, J = 8 Hz, NCH_2CH_2), 3.15 (t, 2H, J = 8 Hz, NCH_2CH_2), 2.31 (s, 3H, $NCOCH_3$); IR (KBr) ν_{max} 3433, 2969, 2574, 1634, 1603, 1572, 1505, 1476, 1448, 1405, 1266, 1124, 1037, 907, 894, 785, 722, 597, 540 cm^{-1}; EIMS, *m/e* (relative intensity) 177 (M^+, 37), 135(base), 116(6), 77(9), 43(38); CIMS (isobutane), *m/e* 178 (M^+ + H, base).

Anal. Calcd. for $C_{10}H_{11}NO$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.46; H, 6.32; N, 7.92.

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References and Notes

1. (a) National Institutes of Health Research Career Development Award recipient, 1983-1988 (CA 00898/01134). Alfred P. Sloan Research Fellow, 1985-1989. (b) National Institutes of Health predoctoral trainee, 1984-1985 (GM 07775). David Ross Fellow, Purdue University, 1986-1987.

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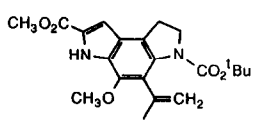
6. On occasions when *tertiary* alcohol **10** did not completely react under the hydroperoxide rearrangement conditions, olefin *i* could be isolated from the reaction mixture after acylation with di-*tert*-butyldicarbonate. This product appears to be derived from unreacted starting material, produced during or subsequent to acylation of the crude hydroperoxide rearrangement reaction mixture. Compound *i* is characterized: ^1H NMR ($CDCl_3$, 200 MHz, ppm) 8.9 (br s, 1H, NH), 7.06 (d, 1H, J = 2 Hz, C8-H), 5.17 (br s, 1H, C=CH), 5.02 (br s, 1H, C=CH), 4.16 (t, 2H, J = 8 Hz, NCH_2CH_2), 3.96 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.12 (t, 2H, J = 8 Hz, NCH_2CH_2), 2.26 (s, 3H, $C{=}C{-}CH_3$), 1.48 (s, 9H, CMe_3); EIMS, *m/e* (relative intensity) 386 (M^+, 8), 330(31), 298(3), 286(9), 254(38), 149(9), 57(base); CIMS (isobutane), *m/e* 387 (M^+ + H, 36), 331(base).



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