Dimethyldioxirane Oxidation of Indole Derivatives. Formation of Novel Indole-2,3-epoxides and a Versatile Synthetic Route to Indolinones and Indolines

Xiaojun Zhang and Christopher S. Foote*

Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90024-1569

Received May 24, 1993

In the process of studying sensitized photooxygenation in the indole system,[1] we needed to know the stability of indole-2,3-epoxides. In an effort to make a previously unknown indole-2,3-epoxide, we found that the recently developed powerful oxidant dimethyldioxirane[2-4] (DMD) efficiently oxidizes a variety of *N*-acylindoles under very mild conditions to the corresponding indole-2,3-epoxide intermediates, among which four were quantitatively formed at −78 °C and were sufficiently persistent at 0 °C to be characterized by spectroscopic methods.

N-Acylindoles **1a–d** were transformed by DMD into the 2,3-epoxides **2** in acetone/CH_2Cl_2 at −78 °C in excellent yields (Scheme I). On warming to room temperature, the epoxides rearranged to indolin-2-ones **3** and -3-ones **5** and methyleneindolines **4**. The yields of products and conditions are shown in Table I. After completion of the experimental work, Adam et al. reported spectral evidence for enamine oxides stabilized by *N*-silylation. This group also studied *N*-acyl-2,3-dimethylindole and *N*-acyltetrahydrocarbazole and reported analogous final rearrangement products but not the intermediate epoxides.[5]

Epoxides **2a–d**[7] are much more stable than 2,3-dimethylbenzofuranepoxide[8-10] and could be stored overnight at 0 °C. However, rearrangement to **3**, **4**, and **5** at room temperature was fast enough that the epoxides could not be purified and were therefore characterized only by ^1H and ^{13}C NMR and IR spectra. ^{13}C chemical shifts (Table II) are extremely valuable for characterization because transformation from **1** to **2** is accompanied by a hybridization change at C-2 and C-3 from sp^2 to sp^3. The epoxide C-2 and C-3 ^{13}C resonances at 77.90–78.71 and 66.90–72.32 ppm are in a reasonable range for the doubly[11] and singly heteroatom-substituted benzylic carbon, respectively. The ^1H NMR spectra (Table III) also speak for the epoxide structure. For instance, **2c** showed two AB (J_{AB} = 22.17 Hz) signals at 2.42 and 1.80 ppm for the methylene protons, along with four aromatic protons and three methyls. The ^1H NMR of **2d** had four different methyls at 2.46, 1.96, 1.45, and 1.10 ppm, respectively, as expected considering the diasterotopicity of the isopropyl methyls.

Scheme I

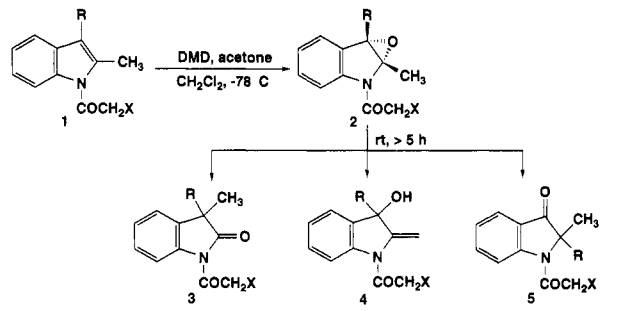


Table I. Oxidation of *N*-Acylindole Derivatives **1** by Dimethyldioxirane[a]

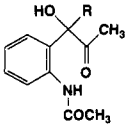
	substituents		time,	epoxide	rearrangement products, %[c]		
indole	X	R	h	**2**, %[b]	**3**	**4**	**5**
1a	H	CH_3	1.0	>97	92	8	0
1b	Cl	CH_3	2.0	>95	100	0	0
1c	H	Et	1.5	>98	78	22	0
1d	H	isopropyl	1.0	>98	36	54	10
1e	H	*tert*-butyl	1.0	*d*	0	70	30

[a] DMD was predried with 4-Å molecular sieves.[6] All reactions were carried out at −78 °C under argon. [b] Based on ^1H NMR at −20 °C. [c] Based on ^1H NMR integrations. [d] Not detected.

The epoxides rearranged on standing at room temperature to products **3**, **4**, and **5**, which were easily separated by preparative thin-layer chromatography and characterized by ^1H and ^{13}C NMR, DEPT, ^1H-^{13}C HETCOR (in some cases), FT-IR, and exact mass measurement.[12] Indolin-3-one **5** and -2-one **3** can be distinguished because the former shows a benzylic carbonyl near 200 ppm in the ^{13}C NMR and a carbonyl absorption at 1710 cm^{-1} in the IR, but the latter shows a β-lactam carbonyl near 180 ppm in the ^{13}C NMR and absorbs at 1750 cm^{-1} in the IR.[13]

The ratios of **3**, **4**, and **5**[14] formed from the various compounds are best understood in terms of ring opening via a carbocation intermediate. With a methyl or ethyl at C-3, the cation develops exclusively or predominantly at the benzylic position because of the conjugation with the aromatic ring and stabilization[15] by the alkyl group, leading to the pinacol-rearranged indolin-2-ones **3a–c** as the major products. On the other hand, with an isopropyl or a *tert*-butyl group at C-3, the cation develops mainly at C-2, stabilized by the nitrogen heteroatom, giving mainly indolin-3-ones **5d,e** and elimination products **4d,e**. This suggestion was substantiated by the results of the oxidation of isomers **6** and **7** by DMD (Scheme II). Reaction of **6** afforded the isolable indolin-2-ones **8** and **9** in a ratio of 11:1 in almost quantitative yield. On the contrary, DMD oxidation of **7** produced indolin-3-ones **10** and **11** in a ratio of 10:1, again in almost quantitative yield. Thus, methyl substitution at C-3 resulted in indolin-2-one with high regioselectivity, whereas 2-substitution afforded the indolin-3-one. Hydroxyindolinones **9** and **11** probably result from further oxidation of **8** and **10** by DMD.[16] Hydroxylation of carbonyl compounds with dimethyldioxirane has been described recently.[17,18]

(1) Zhang, X.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1993**, *58*, 47–51.
(2) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205–211.
(3) Oishi, S.; Nelson, S. D. *J. Org. Chem.* **1992**, *57*, 2744–2747.
(4) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187–1201.
(5) Adam, W.; Ahrweiler, M.; Paulini, K.; Reissig, H.-U.; Voerckel, V. *Chem. Ber.* **1992**, *125*, 2719–2721.
(6) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.
(7) The *N*-acylindole-2,3-epoxides are white crystalline solids at 0 °C. They react with H_2O very rapidly: for example, reaction of **2c** and **2d** with H_2O in $CDCl_3$ at 0 °C afforded the hydrolyzed ortho-disubstituted benzenes **20** and **21**.



20: R = CH_2CH_3
21: R = *iso*-propyl

(8) Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha, M. C.; Wild, D. *Angew. Chem.* **1991**, *103*, 187–189.
(9) Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha-Möller, C. R.; Wild, D. *J. Am. Chem. Soc.* **1991**, *113*, 8005–8011.
(10) Adam, W.; Bialas, J.; Hadjiarapoglou, L.; Sauter, M. *Chem. Ber.* **1992**, *125*, 231–234.
(11) Crandall, J. K.; Batal, D. J.; Sebesta, D. P.; Lin, F. *J. Org. Chem.* **1991**, *56*, 1153–1166.
(12) See supplementary material for the details of the spectroscopic data.
(13) Kawada, M.; Kawano, Y.; Sugihara, H.; Takei, S.; Imada, I. *Chem. Pharm. Bull.* **1981**, *29*, 1900–1911.
(14) All *N*-acylindolin-3-ones **5** show very broad signals for the 7-H and C_2-R protons at room temperature, indicating dynamic rotation around the amide C–N bond.
(15) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1985; pp 64–66.
(16) A referee suggested that hydroxylation of **8** to **9** could also be viewed as benzylic (rather than α-keto) oxidation.
(17) Guertin, K. R.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 715–718.
(18) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369–2372.

0002-7863/93/1515-8867$04.00/0

Table II. ^{13}C NMR Spectral Data of *N*-Acylindole-2,3-epoxides **2** (δ, ppm relative to TMS)[a]

	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	CO	CH_2X	C2-CH_3	C3-R
2a	78.05	66.90	128.21	129.71	123.73	123.18	116.76	144.37	170.80	26.15	16.67	12.31
2b	78.08	67.28	129.80	130.14	124.17	123.98	117.07	143.62	166.27	44.20	16.51	12.48
2c	77.90	70.46	127.92	129.79	124.24	123.10	116.97	144.62	170.74	26.56	16.79	20.27, 10.05
2d	78.71	72.32	127.03	129.52	125.47	122.82	116.92	145.00	170.79	26.56	16.58	28.65, 18.54, 18.33

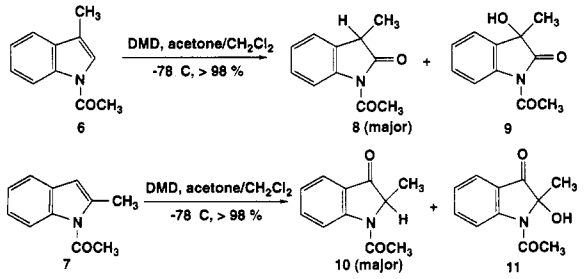
[a] –20 °C, Bruker AM 360 at 90 MHz. Carbon multiplicities were determined by DEPT experiments.

Table III. ^1H NMR Spectral Data of *N*-Acylindole-2,3-epoxides **2** (δ, ppm relative to TMS)[a]

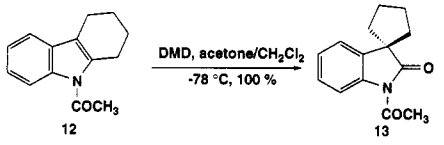
	aromatic protons	$COCH_2X$	C2-CH_3	C3-R
2a	7.91 (d), 7.45 (d), 7.33 (dd), 7.10 (dd)	2.51 (s, 3 H)	2.01 (s)	1.78 (s, 3 H)
2b	7.92 (d), 7.49 (d), 7.36 (dd), 7.16 (dd)	4.49 (s, 2 H)	2.06 (s)	1.80 (s, 3 H)
2c	7.92 (d), 7.46 (d), 7.32 (dd), 7.09 (dd)	2.49 (s, 3 H)	2.01 (s)	2.42 (m, AB, 1 H), 1.80 (m, AB, 1 H), 1.11 (t, 3 H)
2d	7.94 (d), 7.66 (d), 7.30 (dd), 7.06 (dd)	2.46 (s, 3 H)	1.96 (s)	1.95 (m, 1 H), 1.45 (d, 3 H), 1.10 (d, 3 H)

[a] –20 °C on Bruker AM 360 or AM 500 spectrometer.

Scheme II

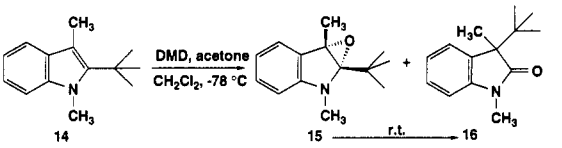


The synthetic merit of this new procedure for preparation of indolinones can be clearly seen in the case of *N*-acyltetrahydrocarbazole **12**, which is quantitatively converted into spiroindolinone **13**. No intermediate epoxide could be detected in this case, even at –78 °C. This result is in agreement with Adam's report.[5]

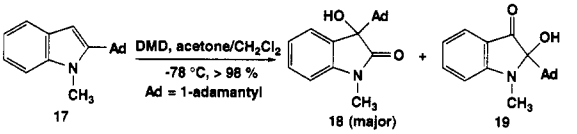


Two *N*-methyl-substituted indoles were also studied. Oxidation of 1,3-dimethyl-2-*tert*-butylindole (**14**) at –78 °C with DMD produced a mixture of indole-2,3-epoxide **15** and indolin-2-one **16**[19] in a ratio of 1:1.5 at complete conversion of **14**, as shown by low-temperature ^1H NMR spectroscopy. Epoxide **15** rearranged rapidly at room temperature to **16** in high yield and purity.

Oxidation of 2-(1-adamantyl)-1-methylindole (**17**)with 2.5 equiv of DMD resulted in rapid and quantitative formation of **18**



and **19** in a ratio of 10:1. Both products were isolated and fully characterized.



In summary, dimethyldioxirane oxidation of *N*-acylindoles gives the previously unknown moderately stable 2,3-epoxides in many cases. Rearrangement of the epoxides constitutes a convenient and versatile synthetic route to indolinones and indolines. Substitution at C-3 exerts a high degree of regio- and chemoselectivity for the production of indolinones or indolines. The novel structure and reactivity of the *N*-acylindole-2,3-epoxides also suggest a variety of chemistry to be explored in the future.[20]

Acknowledgment. This work was supported by NIH GM20080.

Supplementary Material Available: Representative experimental procedure and physical data for all new compounds; ^1H NMR, ^{13}C NMR, DEPT, and HETCOR spectra (40 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of this journal and can be ordered from ACS. Ordering information is given on any current masthead page.

(19) Saito, I.; Matsugo, S.; Matsuura, T. *J. Am. Chem. Soc.* **1979**, *101*, 4757–4759.

(20) Note Added in Proof: Several *N*-acyl indole epoxides have just been prepared by a similar route: Adam, W.; Ahrwesler, M.; Sauter, M.; Schmiedeskamp, B. *Tetrahedron Lett.* **1993**, *33*, 5247–5250.