Chemoselective Epoxidation of Electron Deficient Enones with Iodosylbenzene

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Abstract: The epoxidation of electron deficient olefins is demonstrated with PhIO and an assortment of enones.

Key words: enone epoxidation, iodosylbenzene, enones





source.¹ It is made by treatment of PhI(OAc)₂ with sodium hydroxide.² Iodosylbenzene is a polymeric substance with the characteristic [T] shape common for I^(III) compounds (Figure 1).³ While resembling most hypervalent compounds in regard to thermal instability,⁴ the polymeric and insoluble nature of iodosylbenzene decreases its reactivity as an oxidant.



Figure 1

During a recent synthesis of epoxysorbicillinol,⁵ we found that the most electron deficient enone contained within 15 undergoes chemoselective and diastereoselective epoxidation with PhIO (0.1 M in CH₃NO₂) to afford 16 in a 92% yield (Table 1, entry 10). Presumably, the oxygen atom of PhIO serves as a nucleophile in this transformation. This reactivity, commonly observed with ROO⁻ systems, has rarely been observed with I(III) reagents.6 Although predicted by theoretical calculations,⁷ careful scrutiny of the literature reveals only one example, where unmodified iodosylbenzene has been reported to effect an epoxidation of an electron deficient olefin (Scheme 1).⁸





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In the same report, the conversion of ketenes to polyesters is proposed to proceed through a similar process by epoxidation of a ketene intermediate (Scheme 2).9 This suggests that PhIO might epoxidize other electron deficient alkenes.

To determine the scope of this reaction, a series of enones were examined in combination with iodosylbenzene (Table 1, entries 1-10). CDCl₃ was used as the solvent, which thereby enabled the reactions to be followed by ¹H NMR. The bromo-enone 1⁹ and PhIO prove unreactive under these conditions (entry 1). Similarly, the diesters 2-4 are recovered unchanged along with PhIO (entry 2-4). It is interesting to note, however, that the cyclohexenone 5,¹⁰ which is presumed to form a similarly stabilized anion, undergoes reaction with iodosylbenzene to furnish the epoxide 6^{11} in 90% yield (entry 5). The cyclohexenone 7, which proves difficult to handle and store because of its propensity towards enolization,¹² affords the corresponding epoxide 8 in a 45% yield along with the trione 17 (entry 6).¹³ The α -sulfonated cyclohexenone 9¹⁴ affords the epoxide 10^{15} in a 91% yield (entry 7). To our surprise, the nitrile cyclohexenone derivative 11,¹⁶ appears to lead to the decomposition of iodosylbenzene. However, addition of 4.1 equivalents of PhIO produces the epoxide 12^{17} in a respectable 75% yield (entry 8). The Meldrums acid derivative 13¹⁸ undergoes epoxidation very rapidly (<2 h) to afford the epoxide 14^{19} in >95% yield (entry 9).

On the basis of this series of compounds, we speculate that a correlation exists between reactivity of substrates with PhIO and the stability of the anticipated anionic intermediate. Highly electron deficient enones, where the resulting anion should be fairly stable with the PK_a of conjugate acid <14.2, appear to smoothly undergo this epoxidation procedure. The only substrate that does not fit this reasoning is compound 4. However, we presume compound 4 is less reactive than compound 5 because of extended conjugation with the phenyl ring system.

Table 1 Epoxidation of Electron Deficient Enones^a



Entry	Enone	Cond.	Approx. PK _a of conj. acid	Product	Yield (%)
1	Br	1.1 equiv	18	None	0
2		1.1 equiv	16.4	None	0
3		1.1 equiv	16.4	None	0
4	3 Me	1.1 equiv	14.2	None	0
5	4 O OEt	1.1 equiv	14.2	O OEt	90
6 ^b	5 0 0	1.1 equiv	13.3	6 \$	45
7	7 SO ₂ Ph	1.1 equiv	12.5	8 SO ₂ Ph	91
8°	9 CN	4.1 equiv	10.2		75
9		1.1 equiv	7.3		>95
10	13	1.1 equiv	13.3	14	92
	15) 16	

^a *Conditions*: 0.1 M in $CDCl_3$, 1.1 equiv of PhIO added in one portion at r.t. In most cases, complete reaction required from 2–18 h. ^b In addition to the epoxides **6**, the known β -diketone **17** is also formed in small amounts.^{14 c} More than 1.1 equiv is required for complete epoxidation.

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General Procedure: Compounds 2, 3 were purchased from Aldrich and used without purification. All other starting compounds 1, 4, 5, 7, 9, 11, 13, and 15 were prepared according to known literature procedures. Epoxides 6, 10 and 16 are known compounds. Key spectroscopic data for 8, 12 and 14 are provided. The starting material (0.1 mmol) was dissolved in $CDCl_3$ (1 mL) and placed in a sealable NMR tube. PhIO was added and the reaction vessel was intermittently vortex stirred. After 12 h, 1 equiv of DMF was added as a standard and a ¹H NMR spectrum was obtained. The yields of epoxides were based on comparison with the standard. However, compounds 6, 8, 10, 12, and 14 were also isolated by chromatography in comparable yields in larger scale reactions conducted in chloroform. Volatility makes isolation of the epoxides 6 and 8 problematic and their isolated yields are lower.

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- (13) Compound 8: ¹H NMR (400 MHz, CDCl₃): $\delta = 3.60$ (m, 1 H), 2.59 (m, 1 H), 2.35 (m, 1 H), 2.26 (s, 3 H), 2.16 (m, 1 H), 1.86 (m, 1 H), 1.76 (m, 1 H). We believe that byproduct **17** arises upon bifurcation of the mechanism as shown below (Scheme 3).



Scheme 3

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- (17) Compound **12**: ¹H NMR (400 MHz, CDCl₃): $\delta = 1.73-1.79$ (m, 1 H), 1.88–1.97 (m, 1 H), 2.05–2.14 (m, 1 H), 2.19–2.27 (m, 1 H), 2.34–2.40 (m, 1 H), 2.61–2.68 (m, 1 H), 4.04–4.06 (m, 1 H). ¹³C NMR (400 MHz, CDCl₃): $\delta = 16.7$, 22.6, 35.8, 51.6, 63.1, 114.1, 196.8.
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- (19) (a) Tsuno, T.; Sugiyama, K.; Ago, H. *Heterocycles* **1994**, *38*, 2631. (b) Compound **14**: IR (CH₂Cl₂): 3061, 3007, 2935, 1797, 1769, 1408, 1382, 1334, 1275, 1265, 1257, 1223, 1200, 1169, 1128, 1109, 1043, 1022, 985, 916, 908 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.60$ (d, 1 H, J = 5.3 Hz), 1.84 (s, 3 H) 1.85 (s, 3 H), 3.76 (q, 1 H, J = 5.3 Hz). ¹³C NMR (400 MHz, CDCl₃): $\delta = 12.8$, 27.8, 28.2, 55.6, 64.7, 105.9, 161.9, 163.7. ES-MS: found [M + Na]⁺ 209.0420.