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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

Keywords

enone epoxidation; iodosylbenzene; enones

Iodosylbenzene (PhIO) is widely used as an oxygen source.¹ It is made by treatment of $\text{PhI}(\text{OAc})_2$ with sodium hydroxide.² Iodosylbenzene is a polymeric substance with the characteristic [T] shape common for $\text{I}^{(\text{III})}$ 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.

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 CH_3NO_2) 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 $\text{I}^{(\text{III})}$ 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

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). CDCl_3 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 **611** 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 **1015** 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 **1217** in a respectable 75% yield (entry 8). The Meldrums acid derivative **1318** undergoes epoxidation very rapidly (<2 h) to afford the epoxide **1419** 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 PKa 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.

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 CDCl₃ (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): δ = 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).

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17. Compound **12**: ^1H NMR (400 MHz, CDCl_3): δ = 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). ^{13}C NMR (400 MHz, CDCl_3): δ = 16.7, 22.6, 35.8, 51.6, 63.1, 114.1, 196.8.
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19. Tsuno T, Sugiyama K, Ago H. Heterocycles. 1994; 38:2631. (b) Compound **14**: IR (CH_2Cl_2): 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, CDCl_3): δ = 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). ^{13}C NMR (400 MHz, CDCl_3): δ = 12.8, 27.8, 28.2, 55.6, 64.7, 105.9, 161.9, 163.7. ES-MS: found $[\text{M} + \text{Na}]^+$ 209.0420.

Figure 1.

Scheme 1.

Scheme 2.

Scheme 3.

Table 1

Epoxidation of Electron Deficient Enones^a

Entry	Enone	Cond.	Approx. PK _a of conj. acid	Product	Yield (%)
1		1.1 equiv	18	None	0
2		1.1 equiv	16.4	None	0
3		1.1 equiv	16.4	None	0
4		1.1 equiv	14.2	None	0
5		1.1 equiv	14.2		90

Entry	Enone	Cond.	Approx. PK _a of conj. acid	Product	Yield (%)
6 ^b		1.1 equiv	13.3		45
7		1.1 equiv	12.5		91
8 ^c		4.1 equiv	10.2		75
9		1.1 equiv	7.3		>95

Entry	Enone	PhIO	CHCl ₃	Cond.	Approx. PK _a of conj. acid	Product	Yield (%)
10				1.1 equiv	13.3		92

^a Conditions: 0.1 M in CDCl₃, 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.