

Gif Chemistry for Oxidation of Activated Methylenes to Ketones

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







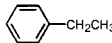
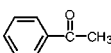










Keywords : Gif oxidations, GoAgg^V, Activated methylenes, Ketones.

Gif reaction^{1,2} attempts to imitate the principle of oxidation catalyzed by cytochrome P450 (P450).^{3,4} Hydrocarbons can be thus oxidized by O₂, KO₂, H₂O₂ or *t*-BuOOH with Fe(II) or Fe(III) being the catalyst. Recently, Gif reagents⁵ have been represented by Fe(III)/*t*-BuOOH assisted by the presence of 2-picolinic acid to enhance rate of catalytic oxygenation (GoAgg^V).^{5,6} Acetonitrile and pyridine (CH₃CN/C₅H₅N)^{7,8} were employed as the solvent for the Gif oxidations. However, the identity of the active oxidant has been in serious dispute whether it involves radical nature or nonradical pathway.⁸⁻¹⁴ The oxidation of cycloalkane^{10,13} using *tert*-butyl hydroperoxides under GoAgg^V conditions may involve *t*-BuO•/*t*-BuOO• system for the formation of cycloalkanol and cycloalkanone. We'd like to herein report the oxidation of benzylic and allylic C-H bonds which are much weaker than secondary C-H. Reduction of the bond strength may divert different reaction mechanism other than the radical pathway. Normal GoAgg^V employed C₅H₅N/CH₃COOH as solvent. However, present GoAgg^V condition involves C₅H₅N/CH₃CN.

FeCl₃·6H₂O (0.2 mmol) and 2-picolinic acid (0.5 mmol) were dissolved in C₅H₅N (1 mL)/CH₃CN (5 mL), stirred for 30 min and the substrate (10 mmol) was slowly added. 30% aqueous *t*-BuOOH (30 mmol) was then added dropwise with syringe pump for 30 min and the reaction went on for the appropriate period. Sodium oxalate (3.73 mmol) was added to eliminate Fe(III) ion. The filtrate was evaporated to dryness that was dissolved in small amount CH₂Cl₂ (1-2 mL) for the Silicagel column chromatography.

The outcome of oxidation of various hydrocarbons are shown in Table 1. The ketonization in entries 1-4 proceeds smoothly and show excellent yield for relatively short duration. In a previous study,⁶ yield of 9,10-anthraquinone marked 50% which is far below 80% (entry 1). 9-Fluorenone also show quite improvement of yield from 55%⁵ to 82% (entry 2). The oxidation of xanthene to xanthone⁶ took 20 h to give 82% yield. The same reaction indicates 3 h in our hand with similar isolated yield (entry 4). Ethylbenzene¹⁵ was oxidized to acetophenone by Gif^{IV} with yield of 9.4% (compare 84% of entry 5). Benzophenone was produced⁵ in 43% yield that becomes 92% with entry 6. Cyclohexene is oxidized to 2-cyclohexene-1-one with yield of 84% (entry 7). However, only 5% of yield of the same ketone was obtained in the foregoing study.⁵ The less activated and

Table 1. Oxidation of Hydrocarbons by GoAgg^V

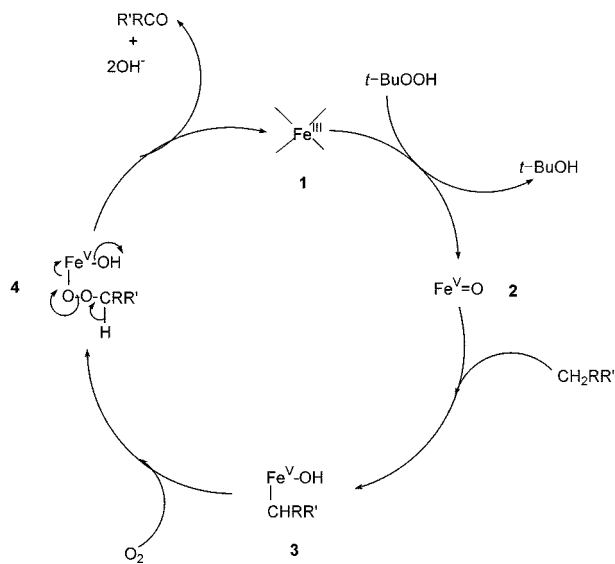
$\text{>C(H)-H} \xrightarrow[\text{r.t.}]{\text{GoAgg}^{\text{V}}} \text{>C=O}$					
GoAgg ^V :	Fe ^{III}	PA	<i>t</i> -BuOOH	substrate	C ₅ H ₅ N / CH ₃ CN
	0.2 mmol	0.5 mmol	30 mmol	10 mmol	1 mL / 10 mL
Entry	Substrate	Time (h)	Product ^a	% Yield ^b	
1		3		80 (100)	
2		6		82 (100)	
3		3		(100)	
4		3		82 (92)	
5		10		84	
6		24		(92)	
7		24		84 (93)	
8		24		75 (92)	
9		24		(88)	
10		10		66	

^aProducts are identified by NMR (Varian Gemini 2000), GC-MS (QP-5050A, Shimadzu), and GC (Varian 3300). ^bYield is measured by isolation and GC. The figure in parenthesis is of the GC yield employing naphthalene as an internal standard.

therefore stronger C-H bonds seem to require longer period to give good yields (entries 5-10).

Benzylic (allylic) C-H bonds are 7-10 Kcal/mol¹⁶ weaker than secondary C-H of cycloalkane. The reaction time varies from 3h-24h in Table 1. If the radical process involving *t*-BuO•/*t*-BuOO• were to intervene, the reaction could occur more rapidly. Two molecules of 2-picolinic acid are coordinated¹ to ferric ion to give a iron-porphyrin like structured **1**. **1** is oxidized with *t*-BuOOH with formation of iron-oxo complex **2**. Hydrocarbons with rather low C-H bond strength may add to **2** to give **3**. Molecular oxygen from air

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**Scheme 1**

is inserted into **3** for the formation of **4**. **4** collapses to yield ketone and **1** (Scheme 1).

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