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# The Selective Functionalization of Saturated Hydrocarbons.

# Part 43. Modified Gif Oxidation in Acetonitrile

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**Abstract.** The role of pyridine and of many substituted pyridines in Gif oxidation chemistry has been examined. In the presence of a suitable pyridine type base most of the solvent can be replaced by acetonitrile without diminishing the yield of oxidation products. The use of 4-*tert*-butylpyridine permits the isolation of cyclohexanone and cyclohexanol by simple distillation.


## Introduction

The selective functionalisation of saturated hydrocarbons under mild conditions is of both biochemical and industrial importance.[1-4] The oxidation of cyclohexane to cyclohexanone represents an important commercial reaction in the preparation of Nylon. The reaction requires conditions of elevated pressure and temperature using a cobalt catalyst[5]. While the yield for the formation of ketone is 4%, the conversion is 20%. Over the last decade we have developed Gif systems[6] capable of oxidizing saturated hydrocarbons predominately to the corresponding ketones. These reactions can be carried out at room temperature with relatively high conversion (up to 30%) and quantitative yield under mild and neutral conditions. However, the use of pyridine as a solvent in these systems makes the adaptation to an industrially useful process impractical. Schuchardt and his colleagues[7] have carried out an extensive investigation of the conversion of cyclohexane to cyclohexanone under Gif conditions. In many cases they have confirmed and improved upon our earlier results and have also commented on the need to replace the pyridine. In order to develop an industrially friendly system the oxidation should be performed in less toxic and cheaper solvents. Although

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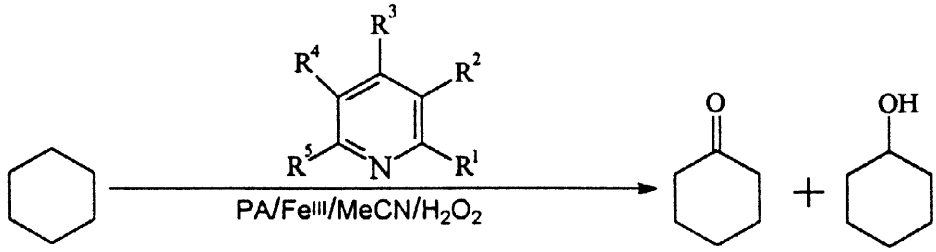
Gif reactions have been carried out in solvents other than pyridine but the yields were substantially lower[8-11]. Thus, pyridine still remained the solvent of choice[2]. Other investgations[12-17] have used a variety of solvents other than pyridine. In preliminary studies it was shown that the majority of the pyridine can be replaced by acetonitrile without affecting the oxidation[17-19]. However, it was clear that some pyridine was needed to act as a ligand to observe Gif chemistry[18]. This was indicated by the appropriate $^{13}C$ NMR experiments[17, 19]. Because the reaction can be carried out in acetonitrile with suitable addition of pyridine, we have investigated the effect that substituted pyridines and other bases have on the Gif system. This might lead to better basic ligands than pyridine itself. We now report the results of this study and the implications in optimizing the reaction conditions for Gif chemistry.




major minor

1: $R^1=R^2=R^3=R^4=R^5=H$
2: $R^1=CH_3$, $R^2=R^3=R^4=R^5=H$
3: $R^2=CH_3$, $R^1=R^3=R^4=R^5=H$
4: $R^3=CH_3$, $R^1=R^2=R^4=R^5=H$
5: $R^3=CH_2CH_3$, $R^1=R^2=R^4=R^5=H$
6: $R^1=R^3=CH_3$, $R^2=R^4=R^5=H$
7: $R^1=R^5=CH_3$, $R^2=R^3=R^4=H$
8: $R^1=R^3=R^5=CH_3$, $R^2=R^4=H$
9: $R^3=(CH_3)_3C$, $R^1=R^2=R^4=R^5=H$
10: $R^1=R^5=(CH_3)_3C$, $R^3=CH_3$, $R^2=R^4=H$
11: $R^3=(CH_3)_2N$, $R^1=R^2=R^4=R^5=H$
12: $R^3$=2'-Py, $R^1=R^2=R^4=R^5=H$
13. $R^1$=4'-Py, $R^2=R^3=R^4=R^5=H$
14. $R^2=Br$, $R^1=R^3=R^4=R^5=H$

**Scheme 1**

## Results and Discussion

The initial studies of the effect of pyridine and other bases was carried out using picolinic acid (PA) as ligand (Scheme 1). This has been shown to be one of the most efficient carboxylic acids for hydrocarbon oxidation[20]. The treatment of cyclohexane under these conditions in acetonitrile fails to give any oxidation. However, the addition of 10 mmol of pyridine to the mixture gave 0.8 mmol of oxidized products. With 24 mmol of pyridine the yield was increased to 1.4 mmol. This remained constant for higher concentrations of pyridine. The yields were approximately the same as when pyridine was used as the solvent (Fig 1).

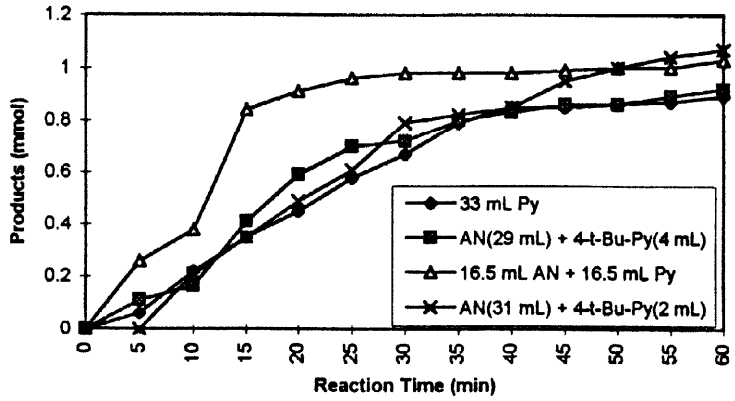



Fig 1. 4 mmol of picolinic acid, 1 mmol of $Fe^{III}$ chloride hexahydrate, 20 mmol of cyclohexane and 4 mmol of $H_2O_2$ in (a). 16.5mL of acetonitrile and 16.5 mL of pyridine ; (b). 31 mL of acetonitrile and 2 mL of 4-*tert*-butylpyridine; (c). 33 mL of pure pyridine or (d). 29 mL of acetonitrile and 4 mL of 4-*tert*-butylpyridine. The reactions were carried out at room temperature. The products were analyzed by GC, naphthalene was used as internal standard.

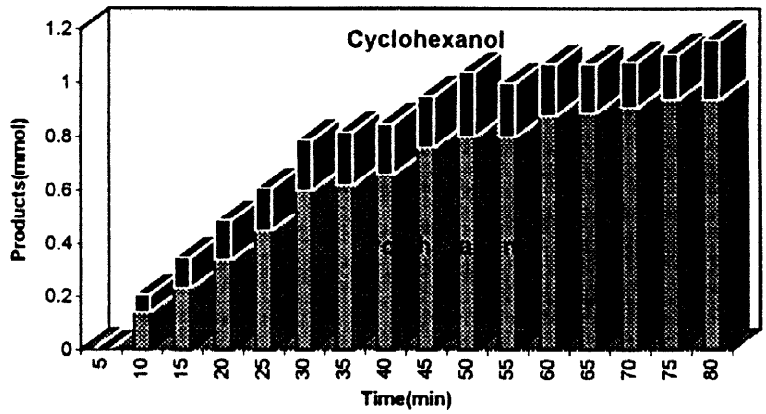
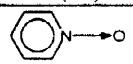
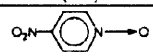
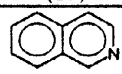



Fig 2. 4 mmol of picolinic acid, 1 mmol of $Fe^{III}$ chloride hexahydrate, 20 mmol of cyclohexane and 4mmol of $H_2O_2$ in 33 mL of a solution of acetonitrile (31 mL) and 4-*tert*-butylpyridine (2 mL). The reaction was carried out at room temperature. The products were analyzed by GC, naphthalene was used as internal standard.

A more detailed study of the kinetics of a reaction, which was faster in 4-*tert*-butylpyridine/acetonitrile (2/31) than in other solvents, is shown in Fig 2. A number of substituted pyridines and tertiary bases were investigated and the results are tabulated in Table 1.

**Table 1. Effect of Bases on the Oxidation of Cyclohexane**

| Entry | BASE (X *mmol*) | Ketone (*mmol*) | Alcohol (*mmol*) | Oxygen (*mmol*) | Total (*mmol*) | Eff.* (%) |
|---|---|---|---|---|---|---|
| 1 | 1(10) | 0.49 | 0.30 | 0.20 | 0.99 | 49 |
| 2 | 2(10) | 0.30 | 0.22 | 0.23 | 0.75 | 37 |
| 3 | 3(10) | 0.75 | 0.33 | 0.51 | 1.59 | 79 |
| 4 | 3(15) | (0.95) | (0.28) | (0.57) | (1.80) | (90) |
| 5 | 4(10) | 0.63 | 0.23 | 0.42 | 1.28 | 64 |
| 6 | 5(10) | 0.71 | 0.29 | 0.45 | 1.45 | 72 |
| 7 | 6(10) | 0.59 | 0.30 | 0.40 | 1.29 | 64 |
| 8 | 7(10) | 0.35 | 0.30 | 0.23 | 0.88 | 44 |
| 9 | 8(10) | 0.35 | 0.28 | 0.25 | 0.88 | 44 |
| 10 | 9(10) | 0.72 | 0.28 | 0.21 | 1.21 | 60 |
| 11 | 9(15) | (0.97) | (0.22) | (0.21) | (1.40) | (70) |
| 12 | 10(10) | 0 | 0 | 0.11 | 0.11 | 5 |
| 13 | 11(11) | 0.45 | 0.19 | 0.23 | 0.87 | 43 |
| 14 | 12(5) | 0 | 0 | 0.20 | 0.20 | 10 |
| 15 | 13(5) | 0.15 | 0.09 | 0.10 | 0.34 | 17 |
| 16 | 14(10) | 0.09 | 0.07 | 0.25 | 0.39 | 19 |
| 17 |  (10) | 0 | 0 | 0.21 | 0.21 | 10 |
| 18 |  (10) | 0 | 0 | 0.20 | 0.20 | 10 |
| 19 |  (5) | 0.51 | 0.23 | 0.31 | 1.05 | 52 |
| 20 | (15) | 0.56 | 0.17 | 0.33 | 1.06 | 53 |
| 21 | (20) | 0.58 | 0.11 | 0.33 | 1.02 | 51 |
| 22 |  (5) | 0.40 | 0.29 | 0.16 | 0.85 | 42 |

4 mmol of picolinic acid, 1 mmol of $Fe^{III}$ chloride hexahydrate, 20 mmol of cyclohexane and 4mmol of $H_2O_2$ in 33 mL of a solution of acetonitrile (33 mL) and base (X mmol). The reactions were carried out at 0°C to room temperature overnight. The products were analyzed by GC, naphthalene was used as internal standard.

* Efficiency is based on $H_2O_2$ and includes oxygen formation.

The study showed that pyridines with groups α to the nitrogen gave lower yields of oxidation products. This is in accordance with the theory with the base acting as a ligand which should not hinder the

coordination to the iron. This was clearly indicated in the example of 2,6-di-*tert*-butyl-4-methylpyridine (Entry 12) which fails to give any oxidation. However, alkyl substituents in the 3 and 4 positions do not inhibit the oxidation and even enhance it. 3-Methyl and 4-methylpyridine (Entries 3, 4 and 5) gave better yields of products than for the same amount of pyridine (Entry 1) while 4-*tert*-butylpyridine (Entries 10 and 11) was found to be the best of the pyridines giving 1.2 mmol of product. As expected the use of N-oxides failed to give any oxidation (Entries 17 and 18). Quinoline and isoquinoline gave reasonable results (Entries 19-22). These experiments confirm that an appropriate heterocyclic base must be present in the reaction mixture. The best ligands were the 3-methyl and 4-*tert*-butylpyridine. 4-*tert*-Butylpyridine was chosen as the base to conduct further study due to the fact that its low volatility allows the products to be isolated by distillation. Simple tertiary amines like triethylamine and N-*tert*-butyltetramethylguanidine gave minimal oxidation.

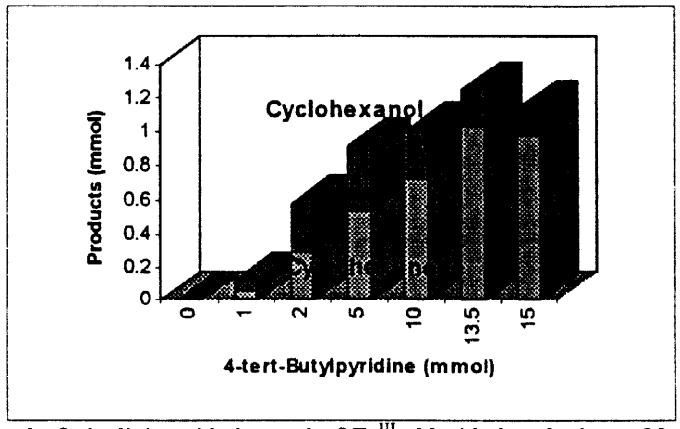



Fig 3. 4 mmol of picolinic acid, 1 mmol of $Fe^{III}$ chloride hexahydrate, 20 mmol of cyclohexane and 4 mmol of $H_2O_2$ in acetonitrile and 4-*tert*-butylpyridine to make a total of 33 mL. The reactions were carried out at 0°C to room temperature overnight. The products were analyzed by GC, naphthalene was used as internal standard.

When the amount of 4-*tert*-butylpyridine was increased the ratio of ketone to alcohol was also increased. (Fig 3). The optimum amount of 4-*tert*-butylpyridine was also concluded to be 13.5 mmol which corresponds to 2 mL in 31 mL of acetonitrile. The number of turnovers of the catalyst was not affected by the amount of 4-*tert*-butylpyridine added to the reaction (Fig 4). However, a significant observation was that the turnover numbers were greater in the acetonitrile systems than when pyridine was used as the only solvent (Fig 5).

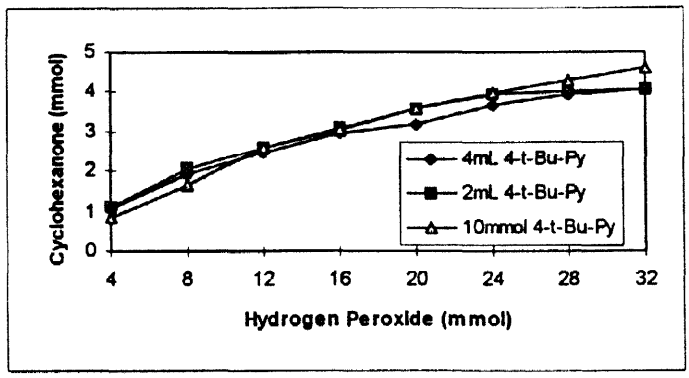



Fig 4. 4 mmol of picolinic acid, 1 mmol of $Fe^{(III)}$ chloride hexahydrate, 20 mmol of cyclohexane and 4 mmol of $H_2O_2$ in acetonitrile and 4-*tert*-butylpyridine to make a total of 33 mL. The reactions were carried out at room temperature. The products were analyzed by GC, naphthalene was used as internal standard.

A comparison of quinoline, isoquinoline, pyridine and 4-*tert*-butylpyridine is also made in Fig 5. The superiority of a limited amount of pyridine or 4-*tert*-butylpyridine was clearly demonstrated.

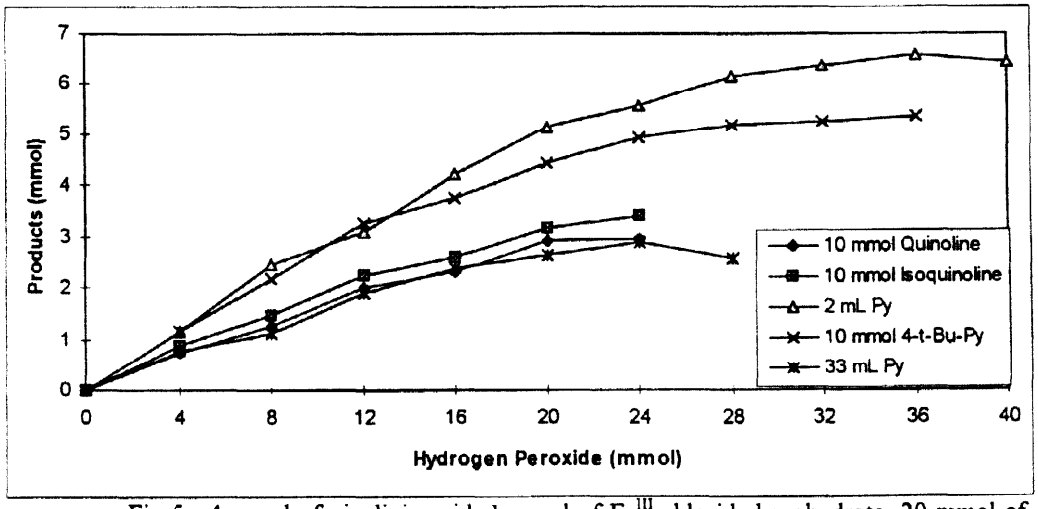



Fig 5. 4 mmol of picolinic acid, 1 mmol of $Fe^{III}$ chloride hexahydrate, 20 mmol of cyclohexane and 4-40 mmol of $H_2O_2$ in 33mL of acetonitrile and base or in 33 mL of pyridine. The reactions were carried out at room temperature. The products were analyzed by GC, naphthalene was used as internal standard.

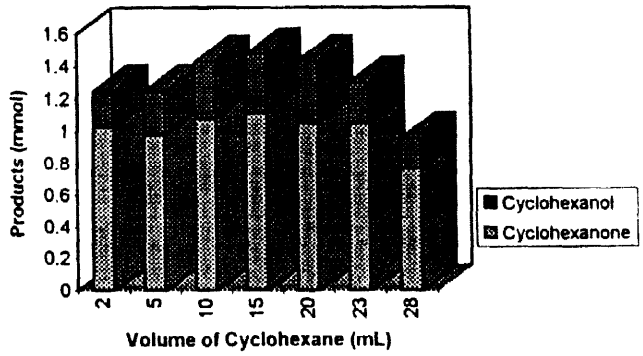
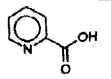
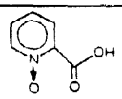
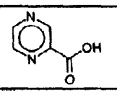
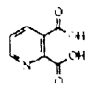
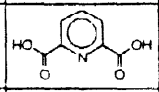
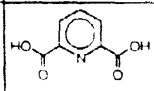
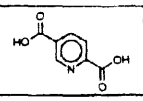
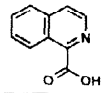



Fig 6. 4 mmol of picolinic acid, 1mmol of $Fe^{III}$ chloride hexahydrate, 2 mL of 4-*tert*-butylpyridine and 4 mmol of $H_2O_2$ in 33 mL of the mixture of acetonitrile and cyclohexane. The reactions were carried out at 0°C to room temperature overnight. The products were analyzed by GC, naphthalene was used as internal standard.

Table 2. Effect of Ligands on the Oxidation of Cyclohexane

| Entry | Ligand | $H_2O$ (*mL*) | Base (*mmol*) | Ketone (*mmol*) | Alcohol (*mmol*) | Oxygen (*mmol*) | Total (*mmol*) | Eff.* (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  | 0 | 10 | 0.72 | 0.28 | 0.21 | 1.21 | 61 |
| | | 0 | 25 | 1.03 | 0.22 | 0.22 | 1.47 | 74 |
| 2 |  | 0 | 10 | 0.56 | 0 | 0.90 | 1.46 | 73 |
| 3 | | 0 | 25 | 1.00 | 0.22 | 0.59 | 1.81 | 90 |
| 4 |  | 0 | 10 | 0.68 | 0.22 | 0.53 | 1.43 | 71 |
| 5 |  | 0 | 10 | 0.34 | 0.18 | 0.33 | 0.85 | 42 |
| 6 | | 0 | 15 | 0.95 | 0.28 | 0.57 | 1.80 | 90 |
| 7 |  | 0 | 10 | 0 | 0.17 | 0 | 0.17 | 8 |
| 8 |  | 2 | 10 | 0.32 | 0.28 | 0 | 0.60 | 30 |
| 9 | | 10 | 10 | 0.90 | 0.14 | 0 | 1.04 | 52 |
| 10 | | 15 | 10 | 0.14 | 0.06 | 0 | 0.20 | 10 |
| 11 |  | 0 | 10 | 0.62 | 0.34 | 0.58 | 1.54 | 77 |
| 12 | | 7 | 10 | 0.92 | 0.09 | 0 | 1.01 | 50 |
| 13 |  | 0 | 10 | 0.56 | 0.22 | 0.25 | 1.03 | 51 |

4 mmol of ligand, 1 mmol of $Fe^{III}$ chloride hexahydrate, 20 mmol of cyclohexane and 4 mmol of $H_2O_2$, 4-*tert*-butylpyridine as base in 33 mL of the solution of acetonitrile and $H_2O$. The reactions were carried out at 0°C to room temperature overnight. The products were analyzed by GC, naphthalene was used as internal standard.

* Efficiency is based on $H_2O_2$ and includes oxygen formation.

Varying the amount of cyclohexane in the reaction mixture (31 mL of acetonitrile and 2 mL of 4-*tert*-butylpyridine) resulted in heterogeneous reaction mixtures when the hydrocarbon exceeded 50 mmol. Nevertheless, the amount of oxidation did not change greatly (Fig 6).

In previous work we have reported on the effect of various heterocyclic carboxylate ligands[21, 22]. We have also investigated the effectiveness of these ligands on Gif chemistry in the presence of 4-*t*-butylpyridine. These results of this study are listed in Table 2. Although most ligands gave approximately 1 mmol of oxidation products. Picolinic acid N-oxide (Entry 3) and pyridine-2,3-dicarboxylic acid (Entry 6) gave results which were even better than picolinic acid.

**Table 3. Effect of Solvents on Gif Oxidation**

| Entry | Solvent (X mL) | 4-*t*-Bu-Pyridine (Y mL) | Ketone (mmol) | Alcohol (mmol) | $O_2$ (mmol) | Total (mmol) | Eff.* (%) |
|---|---|---|---|---|---|---|---|
| 1 | Acetone (31) | 2 | 0.12 | 0.10 | 0.31 | 0.53 | 26.5 |
| 2 | Acetone (33) | 0 | - | - | 0.32 | 0.32 | 16.0 |
| 3 | $CH_3CN$ (31) | 2 | 0.97 | 0.16 | 0.21 | 1.34 | 67.0 |
| 4 | $CH_3CN$ (33) | 0 | - | - | 0.07 | 0.07 | 3.5 |
| 5 | *t*-BuOH (31) | 2 | 0.28 | 0.11 | 0.08 | 0.83 | 41.5 |
| 6 | *t*-BuOH (33) | 0 | 0.05 | 0.07 | 0.58 | 0.70 | 35.0 |
| 7 | AcOEt (31) | 2 | 0.08 | 0.08 | 0.98 | 1.14 | 57.0 |
| 8 | AcOEt (31) | 0 | - | 0.02 | 0.95 | 0.97 | 48.5 |
| 9 | AcOH (31) | 2 | 0.42 | 0.28 | 0.29 | 0.99 | 49.5 |
| 10 | AcOH (33) | 0 | 0.23 | 0.21 | 0.12 | 0.56 | 28.0 |
| 11 | Pyridine (33) | 0 | 0.99 | - | 0.16 | 1.15 | 57.5 |

PA (4 mmol), $FeCl_3 \cdot 6H_2O$ (1 mmol), Cyclohexane (20 mmol), Solvent (X mL) 4-*tert*-Butylpyridine (Y mL), $H_2O_2$ (4 mmol). The reactions were carried out at 0°C to room temperature overnight. The products were analyzed by GC, naphthalene was used as internal standard.

* Efficiency is based on $H_2O_2$ and includes oxygen formation.

We have also examined (Table 3) the effect of other solvents on Gif chemistry with and without the addition of the appropriate amount of 4-*tert*-butylpyridine. Acetone gave little oxidation of cyclohexane.

Acetonitrile, without 4-*tert*-butylpyridine afforded no oxidation. *tert*-Butanol and ethyl acetate gave little oxidation. Acetic acid with pyridine base was, as expected, more efficient. Pyridine alone gave, as usual, an impeccable formation of pure ketone with only little oxygen formation.

**Table 4. Effect of the Amount of Catalyst on Gif Oxidation**

| Entry | PA (X mmol) | $FeCl_3 \cdot 6H_2O$ (Y mmol) | $O_2$ (mmol) | Ketone (mmol) | Alcohol (mmol) | Ketone / Alcohol | Total (mmol) | Eff.* (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.4 | 0.1 | 0.20 | 0.92 | 0.21 | 4.38 | 1.33 | 66.5 |
| 2 | 0.8 | 0.2 | 0.36 | 0.97 | 0.25 | 3.88 | 1.58 | 79.0 |
| 3 | 1.2 | 0.3 | 0.45 | 1.12 | 0.24 | 4.67 | 1.81 | 90.5 |
| 4 | 1.6 | 0.4 | 0.45 | 1.15 | 0.23 | 5.00 | 1.83 | 91.5 |
| 5 | 2.0 | 0.5 | 0.56 | 1.00 | 0.30 | 3.31 | 1.86 | 93.0 |
| 6 | 4 | 1.0 | 0.50 | 1.03 | 0.22 | 4.68 | 1.75 | 87.5 |
| 7 | 8 | 2.0 | 0.58 | 0.90 | 0.32 | 2.81 | 1.80 | 90.0 |

PA (X mmol), $FeCl_3 \bullet 6H_2O$ (Y mmol), Cyclohexane (20 mmol), Acetonitrile (31 mL) 4-*tert*-Butylpyridine (2 mL), $H_2O_2$ (4 mmol). The reactions were carried out at 0°C to room temperature overnight. The products were analyzed by GC, naphthalene was used as internal standard.

* Based on $H_2O_2$ including oxygen formation.

We have also examined the effect of the amount of catalyst on the formation of ketone, alcohol and oxygen (Table 4) using acetonitrile. It is clear that over the twentyfold range of 0.1 to 2.0 the iron catalyst affords essentially the same amount of oxidation. Thus the concentration of the iron catalyst is not the product determining factor in the reaction. This is simply the amount of $H_2O_2$ added. Of course we always ran blank reactions without iron. No oxidation products were formed.

## Conclusion

In conclusion we have demonstrated that pyridine can be largely substituted by acetonitrile as the solvent for Gif chemistry with the use of a small amount 4-*t*-butylpyridine as the heterocyclic base. This system gives rise to increased efficiency and a greater number of turnovers. A further advantage in the use of 4-*t*-butylpyridine is that it allows easy purification of the oxidation products by simple distillation. Our work is complementary to the recent studies of Stavropoulos *et al.* in the complexes involved in Gif Chemistry[23].

## Acknowledgments

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**References**


1. Olah, G.A., Monlar. A., "Hydrocarbon Chemistry" Wiley, New York, Chichester, **1995**.
2. Barton, D. H. R.; Martell, A. E.; Sawyer, D. T., Eds., "The Activation of Dioxygen and Homogenous Catalytic Oxidation" Plenum, New York, **1993**.
3. Shilov, A. E., "Activation of Saturated Hydrocarbons by Transition Metal Complexes" Reidel, Dordrecht, **1984**.
4. Hill, C. L., Ed., "Activation and Functionalization of Alkanes" Wiley, New York, Chichester, **1989**.
5. Ingold, K. U., *Aldrichimica Acta* **1989**, *22*, 69.
6. Barton, D. H. R. and Doller, D., *Acc. Chem. Res.* **1992**, *25*, 504.
7. Schuchardt, U., Carvalho, W.A. and Spinace, E.V., *Synlett* **1993**, 713 and references there cited.
8. Barton, D. H. R.; Boivin, J.; Motherwell, W. B.; Ozbalik, N.; Schwartzentruber, K. M., *New J. Chem.* **1986**, *10*, 387.
9. Barton, D. H. R.; Doller, D.; Geletii, Yu. V., *Mendeleev Commun.* **1991**, 115.
10. Barton, D. H. R.; Beviere S. D.; Chavasiri, W.; Csuhai, E.; Doller, D.; Liu, W. G.; Reibenspies, J. H., *New J. Chem.* **1992**, *16*, 1019.
11. Sheu, C.; Sobkowiak, A.;Zhang, L.; Ozbalik, N.; Barton, D. H. R.; Sawyer, D. T., *J. Am. Chem. Soc.* **1989**, *111*, 8303; Tung, H.-C.; Kang, C.; Sawyer, D. T., *Ibid.* **1992**, *114*, 3445.
12. Khenkin, A. M.; Stepanova, M. L., *Mendeleev Commun.* **1992**, 57.
13. Kotani, E.; Kobayashi, S.; Ishii, Y.; Tobinaga, S., *Chem. Pharm. Bull.* **1985**, *33*, 4671.
14. Sugimoto, H. and Sawyer, D. T., *J. Am. Chem. Soc.* **1984**, *106*, 4283.
15. Sugimoto, H. and Sawyer, D. T., *J. Am. Chem. Soc.* **1985**, *107*, 5712.
16. Sugimoto, H. and Sawyer, D. T., *J. Org. Chem.* **1985**, *50*, 1784.
17. Sugimoto, H.; Spencer, L.; Sawyer, D. T., *Proc. Natl. Acad. U. S. A.* **1987**, *84*, 1731
18. Sheu, C.; Richert, S. A.; Cofre, P.; Ross, B., Jr.; Sobkowiak, A.; Sawyer, D. T.; Kanofsky, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 1936.
19. Barton, D. H. R.; Hu, B.; Li, T.; MacKinnon, J., *Tetrahedron Lett.* **1996**, *37*, 8329
20. About-Jaudet, E.; Barton, D. H. R.; Csuhai, E.;.Ozbalik, N., *Tetrahedron Lett.* **1990**, *31*, 1657.
21. Barton, D. H. R.; Hu, B.; Taylor, D. K.; Rojas Wahl, R. U., *Tetrahedron Lett.* **1996**, *37*, 1133.
22. Barton, D. H. R.; Hu, B.; Taylor, D. K.; Rojas Wahl, R. U., *J.Chem. Soc., Perkin Trans. 2* **1996**, 1031.
23. Singh, B.; Long, J. R.; Fabrizi de Biani, F.; Gatteschi, D.; Stavropoulos, P., *J. Am. Chem. Soc.* **1997**, *119*, 7030.