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$FeCl_3$-CATALYZED OXYGENATION OF 2-HALOCYCLOHEXANONES TO ADIPIC ACID DIESTERS

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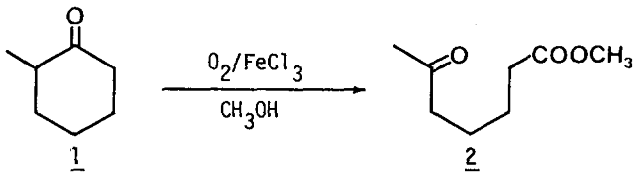
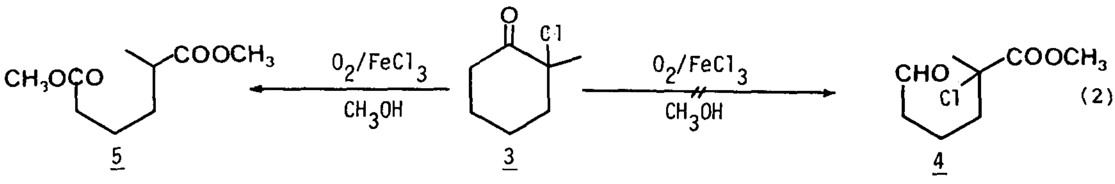
Summary: Ferric chloride-catalyzed aerobic oxygenation of 2-halocyclohexanones in methanol to yield adipic acid dimethyl esters.

Iron acts an important role in enzymatic oxygenations, where strong binding interactions between iron complexes and molecular oxygen (dioxygen) have been revealed by spectroscopic techniques.[1] Little is known, however, about the iron-catalyzed efficient oxygenations by dioxygen in non-enzymatic systems.[2]

We have recently reported that Fe(III) effectively catalyzes regiospecific epoxidation of terpene alcohol acetates[3] and oxidative ring-opening reaction of cycloalkanones[4] by dioxygen. In the course of our study on the iron-catalyzed oxygenations of cyclic ketones, we found the novel iron-catalyzed oxygenation of 2-halocyclohexanones yielding adipic acid diesters by molecular oxygen, in which iron seems to activate substrates and dioxygen simultaneously.



(1)



(2)

The oxygenation of 2-methylcyclohexanone (1) in the presence of $FeCl_3$ in methanol gives exclusively methyl 6-oxoheptanoate (2).[4] Similar oxygenation of 2-chloro-2-methylcyclohexanone (3) was expected to yield methyl 2-chloro-2-methyl-6-oxohexanoate (4) and/or its acetal. However, the treatment of a methanol solution of the ketone 3 (0.35 M) with $FeCl_3$ (20 - 30 mol%) at 60°C for 20 h under an oxygen atmosphere (1 atm) gave no 4 but 2-methyladipic acid (2-methylhexanedioic acid) dimethyl ester (5)[5] in a 73% yield (conv. 90%) as shown in the equation 2.

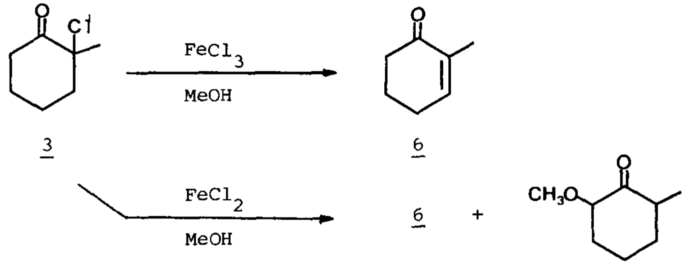
This result was perplexing in respect that the oxidative ring-opening of the cyclohexanone 3 was accompanied with a dehalogenation (formally reductive dehalogenation) at a different cite from the position of C-C bond cleavage. The normal features of the reactions of cyclohexanones with $FeCl_3$ are probably the oxidations such as α-chlorination[6] and/or dehydrogenation to yield cyclohexenones. The latter dehydrogenation likely comprises of the α-chlorination and successive dehydrochlorination (vide infra). Another mode of dehydrohalogenation of 2-chlorocyclohexanones is the Favorskii rearrangement, though it is hardly possible for 3 even under basic conditions.[7] Anyhow, participation of these reactions could not aptly account for the result shown in eq. 2.

Without dioxygen, $FeCl_3$ did not cause the oxidation but did dehydrochlorination of 3 to afford 2-methylcyclohexenone (6) in a 64% yield under the conditions similar to the case of eq. 2. The dehydrochlorination was effectively catalyzed by even less than 2 mol% of $FeCl_3$. These results showed that dioxygen is essentially required for the oxygenation of 3 into 5.

Ferrous salt, $FeCl_2$, showed no catalytic activity in the aerobic oxidation of 3 into 5, but catalyzed the dehydrohalogenation producing 6. Under an anaerobic condition, $FeCl_2$/ 3 / MeOH system gave an isomeric mixture of methoxymethylcyclohexanones including 7, which was scarcely obtained by the reaction of 3 with $FeCl_3$ under the anaerobic conditions.

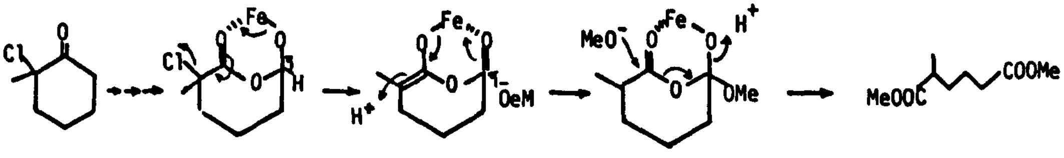
The mole ratio of $FeCl_3$ used also affected the reaction paths; the oxygenation of 3 yielding 5 competed with the formation of 6 when less than 10 mol% of $FeCl_3$ was used, while the yield of 5 was scarcely changed for the better by the use of more than 30 mol% $FeCl_3$. This fact suggests the participation of polyhalogenated ferric salt in the oxygenation of eq. 2.[8]

The mechanistic study described here results in conclusion as follows: the oxygenation of 3 into 5 competes with the dehydrochlorination affording 6. To surpass the latter reaction mode, the former reaction mode requires both dioxygen and polychlorinated ferric salt.[9] The ferric salt seems to activate dioxygen and the substrate 3 simultaneously.[10]



3 6 6 7

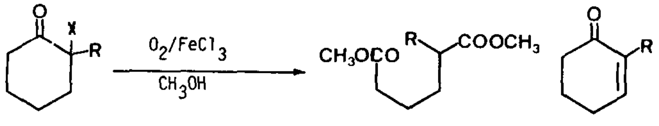
A plausible mechanism is shown in Scheme 1 in accord with the proposed mechanism of the oxygenation of 1 giving rise to oxoester 2.[4] Dehydrochlorination of the pseudoacid intermediate 8 might give enolate intermediate 9, which is successively suffered by nucleophilic attack of methanol to yield 5.



3 8 9 5

(Scheme 1)

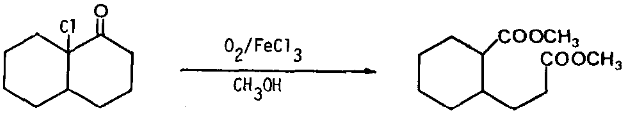
Other 2-halocyclohexanones than 3, such as 2-bromo-2-methyl- (10) and 2-chloro-2-ethylcyclohexanone (11), were similarly oxygenated into the corresponding adipates 5 and 12, respectively, though the cyclohexenones 6 and 13 were produced as byproducts. A bicyclic haloketone 14 was also oxygenated



10, 11 5, 12 6, 13

10 → 5 + 6: R=CH_3, X=Br

11 → 12 + 13: R=C_2H_5, X=Cl



14 15

to afford a diester 15 in a 42% yield.

Much investigation to elucidate the mechanistic aspects of this oxygenation and its synthetic application is now progress.

References and Notes

1. For example, see: a) Nozaki, M.; Nakazawa, T.; Fujisawa, H.; Kotani, S.; Kojima, Y.; Hayaishi, O. Adv. Chem. Ser., 1968, 77, 242. b) Fujisawa, H.; Uyeda, M.; Kojima, Y.; Nozaki, M.; Hayaishi, O. J. Biol. Chem., 1972, 247, 4414.
2. A combination of iron porphine complex with dioxygen has been reported to oxidize cyclohexene to yield a complex mixture: a) Belova, U. S.; Nikonova, L. A.; Raikman, L. M.; Borukaeva, M. R. Dokl. Akad. Nauk, USSR, 1972, 204, 455. b) Ohkatsu, Y.; Tsuruta, T. Bull. Chem. Soc., Jpn, 1978, 51, 188.
3. Ito, S.; Inoue, K.; Matsumoto, M. J. Amer. Chem. Soc., 1982, 104, 6450.
4. Ito, S.; Matsumoto, M. J. Org. Chem. Soc., 1983, 48, 1133.
5. Colorless oil (b.p. 60°C/ 0.25 torr). NMR ($CDCl_3$) δ 1.14 (d, J = 6.5 Hz, 3H), 1.33 - 1.78 (m, 4H), 2.14 - 2.52 (m, 3H), and 3.61 (s, 6H) ppm. IR (liquid film) 1734 cm^{-1}. Mass (m/z) 188 (M^+), 157 (37), 128 (64), 115 (42), 101 (22), 97 (50), and 88 (100).
6. Nakatani, Y.; Kakinuma, K.; Matsui, M. Tetrahedron Lett., 1967, 4085.
7. For a review, see: Kende, A. S. "Organic Reactions", John Wiley & Sons, New York, Vol. 11, pp 261 - 316, 1960.
8. Addition of lutidine to the reaction system (O_2/ $FeCl_3$/ MeOH) inhibited completely the oxygenation of 3. Inversely, addition of LiCl or HCl to the reaction mixture ($FeCl_3$: 2 mol%) raised a little selectivity of 5/ 6.
9. The reaction yielding 5 does not proceed through the cyclohexenone 6; in the present oxidation system, 6 was not converted into the diester 5.
10. The $FeCl_3$-catalyzed reaction of 3 was attempted with iodosobenzene instead of dioxygen as an oxidant to result in no oxidation. This fact suggested that an iron-oxenoid type intermediate did not participate as an active species in the reaction of eq. 2.

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