Cyclization of *O*-Pentafluorobenzoyloxime Having (diene)Fe(CO)$_3$ Moiety

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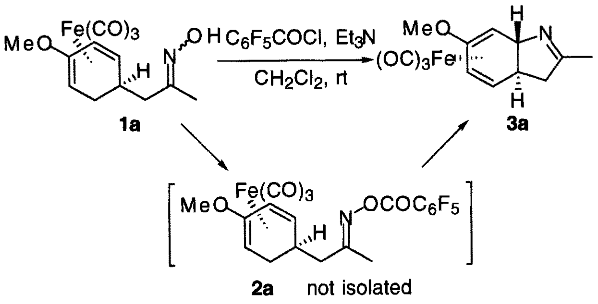
O-Pentafluorobenzoyloxime having (cyclohexadiene)Fe(CO)$_3$ moiety cyclizes to give *trans*-fused dihydroindole derivative. This C-N bond formation proceeds by radical chain mechanism initiated by molecular oxygen. Thus formed *trans*-fused dihydroindoles easily isomerize to the *cis*-fused isomers on acidic silica gel.

Previous reports from our laboratory demonstrate the utilization of oxime derivatives for the C-N bond formation such as nucleophilic substitution on sp^2 nitrogen atom,[1] electron transfer reaction,[2,3] and Heck-type reaction.[4] In this paper, we would like to report a novel cyclization of *O*-pentafluorobenzoyloxime having (diene)Fe(CO)$_3$ moiety.

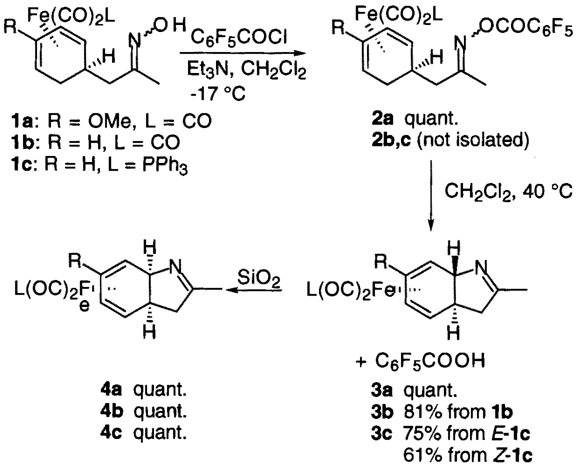
During our study on intramolecular Heck-type carbon-nitrogen bond formation reaction, we attempted to prepare *O*-pentafluorobenzoyloxime **2a**, having (diene)Fe(CO)$_3$ moiety. Treatment of oxime **1a** with C_6F_5COCl-Et_3N afforded **2a**, which was unexpectedly unstable and easily cyclized to give *trans*-fused dihydroindole derivative **3a**[5] (Eq. 1).



(1)

It was found, however, that the *O*-pentafluorobenzoyloxime **2a** could be isolated when the reaction was performed at -17 °C with careful chromatographic isolation at temperature below 0 °C. A *syn/anti* mixture of **2a** was cyclized to **3a** quantitatively in CH_2Cl_2 under air at 40 °C within 30 min.[6] It is noteworthy that $C_6F_5CO_2H$ was also isolated quantitatively. The *trans*-fused derivative **3a** was obtained by flash column chromatography on Merck Silica gel 60N. By using acidic media such as Wakogel B-5F, the *trans* derivative **3a** was easily isomerized to the *cis* derivative **4a**[5].

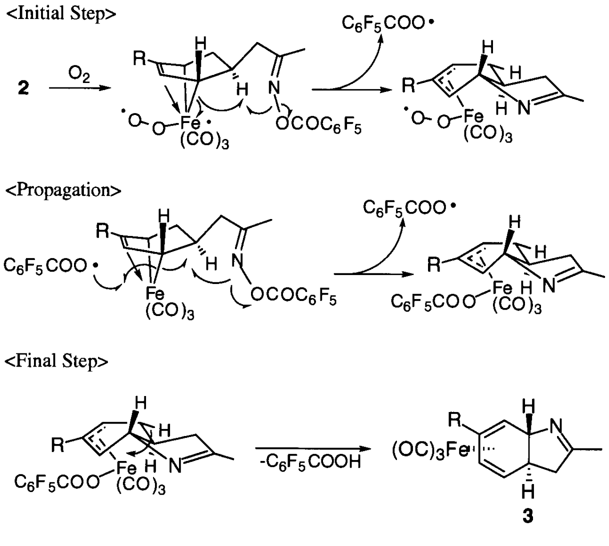
The *O*-pentafluorobenzoyloximes **2b** (R=H, L=CO) and **2c** (R=H, L=PPh_3) were prepared from the corresponding oximes **1b** and **1c** and were found to be less stable than the complex **2a** and the cyclization gradually proceeded during the isolation. **3b** was synthesized directly from **1b** without isolation of **2b** in 81% yield.[7] Since the *syn* and *anti* oximes of the PPh_3 complex **1c** were able to be separated, the reactivity of these isomers was compared. From both isomers the cyclization proceeded smoothly and the same cyclized product **3c** was obtained from *E*-**1c** and *Z*-**1c** in 75% and 61% yield, respectively (Scheme 1).



Scheme 1. Iron complex mediated cyclization.

In order to observe the reaction rate of the cyclization of **2a** was prepared a carefully degassed sealed NMR sample of **2a** in CD_2Cl_2 solution. No cyclized product **3a** was detected when the sample was heated at 40 °C for 4 h, whereas after introduction of air into the sealed sample the reaction started suddenly at 40 °C. The reaction is very fast ($k = 9.6 \times 10^{-3}$ s^{-1}, $t_{1/2} = 4.0$ min) and is the first order in [**2a**] over the last half of the reaction. In addition, the cyclization did not occur when a CH_2Cl_2 solution of **2a** was heated in the presence of 20 mol% of galvinoxyl for 4 h under air.

Judging from the above phenomena, this cyclization proceeds by radical chain mechanism (Scheme 2). Molecular oxygen plays a role as an initiator to generate a radical species.[8]



Scheme 2. Reaction mechanism.

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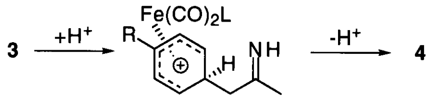
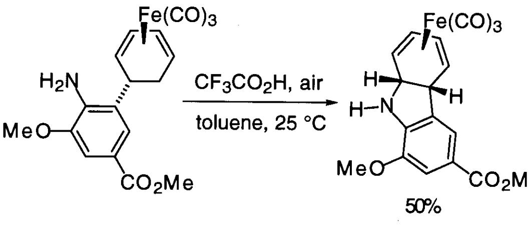
Once pentafluorobenzoyloxy radical ($C_6F_5COO\cdot$) is generated, it attacks the Fe center of **1**. From thus generated 19 electron intermediate, homolytic cleavage of carbon-iron bond and successive formation of carbon-nitrogen bond occurs, regenerating $C_6F_5COO\cdot$. Finally, elimination of C_6F_5COOH affords the cyclized product **3**. The cyclization might proceed from the same side of $Fe(CO)_3$ moiety simultaneously with the C-Fe bond cleavage, producing the *trans*-fused dihydroindole **3** selectively. Benzoyl peroxide (BPO) or AIBN could also be used as an initiator of this reaction, though the reaction was not clean and the yield of **3** was relatively low.

The isomerization from the *trans*-fused complex **3** to the *cis*-fused complex **4** might proceed *via* cationic η^5-(cyclohexadienyl)$Fe(CO)_3$ intermediate (Scheme 3) generated by the heterolytic scission of carbon-nitrogen bond.[9] Because η^5-(cyclohexadienyl)$Fe(CO)_3$ complex has a planer structure, nitrogen atom attacks the cyclohexadienyl ligand from the *anti* site of the $Fe(CO)_3$ moiety, giving the *cis*-fused complex **4**.



Scheme 3. Isomerization of *trans* **3** to *cis* **4**.

A similar cyclization involving a (diene)$Fe(CO)_3$ is observed in a Knölker's carbazole synthesis (Eq. 2).[10] In Knölker's reaction, active species may be a protonated nitrogen-centered radical generated by air-oxidation, which attacks the diene moiety of the iron complex from *anti* side of $Fe(CO)_3$ to afford the *cis*-fused dihydrocarbazole derivative. The same reaction also occurs in acidic media by the oxidation with metallic oxidant such as MnO_2.[9,11] Thus, Knölker's reaction requires strong acid and gives *cis*-fused products. In our reaction, carbon-nitrogen bond formation proceeds at the same side of $Fe(CO)_3$ moiety, giving *trans*-fused dihydroindoles, which can be isomerized to the *cis*-fused compounds.



(2)

As described above, cyclization of *O*-pentafluorobenzoyloxime having (diene)$Fe(CO)_3$ moiety proceeds by radical chain mechanism. This cyclization is initiated by molecular oxygen and $C_6F_5COO\cdot$ works as a chain carrier. By this cyclization both *trans*- and *cis*-fused dihydroindoles, which are useful intermediates for alkaloid synthesis, can be constructed stereoselectively.

References and Notes

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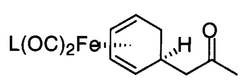
5 **3a**: Mp. 141 °C (from CH_2Cl_2/Pentane); IR (KBr) 2056, 1981, 1959, 1628, 1493, 1358, 1227, 985 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ= 2.23 (3H, s), 2.35 (1H, d, J = 18.0 Hz), 2.68 (1H, dd, J = 6.3 and 3.9 Hz), 2.68 (1H, dd, J = 18.0 and 10.0 Hz), 2.94 (1H, br), 3.65 (3H, s), 3.80 (1H, s), 4.79 (1H, br), 5.18 (1H, d, J = 6.3 Hz); ^{13}CNMR ($CDCl_3$) δ= 19.1, 39.3, 46.9, 51.0, 51.9, 55.5, 68.2, 74.8, 140.8, 181.1, 208.0.
4a: Mp. 105-106 °C (from CH_2Cl_2/Pentane); IR (KBr) 2040, 2033, 1979, 1643, 1483, 1419, 1255 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ= 1.83 (3H, s), 2.03 (1H, dd, J = 18.0 and 3.6 Hz), 2.43 (1H, dd, J = 18.0 and 10.0 Hz), 2.65-2.70 (2H, m), 3.60 (3H, s), 3.67 (1H, dd, J = 4.1 and 2.1 Hz), 4.48 (1H, br), 5.08 (1H, dd, J = 6.8 and 2.1 Hz); ^{13}CNMR ($CDCl_3$) δ= 19.7, 39.9, 47.5, 52.6, 54.6, 55.3, 67.3, 78.8, 139.9, 171.3, 208.0. Found: C, 51.40; H, 4.49; N, 4.70%. Anal. Calcd for $C_{13}H_{13}FeNO_4$: C, 51.52; H, 4.32; N, 4.62%.

6 Heating is not necessarily required. The cyclization sometimes occurs even at 0 °C. Under the described conditions, the reaction is quite reproducible.

7 The ketones **5b**,**c** were yielded as by-products.



5b,c

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