Chirality Preservation in Pyrrolinone Iron Tetracarbonyl Complexes – a Route to Enantiopure 5-Substituted Pyrrolinones

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The enantiopure iron complex **4** reacts under the influence of $BF_3{\cdot}OEt_2$ with allylsilanes and enol acetates through a cationic intermediate in which the chirality of **4** is preserved, yielding enantiopure 5-substituted 3-pyrrolin-2-ones.

The use of transition metal π-complexes of unsaturated organic compounds is currently being explored extensively. Several transition metals receive attention, amongst which palladium,[1] nickel,[2] molybdenum[3] and iron[4] are particularly important. In view of our work in the field of chiral nitrogen heterocycles, we were interested in the use of transition metals for the stereocontrolled introduction of nucleophiles adjacent to nitrogen. The use of $Fe(CO)_4$-stabilized allylic cations as intermediates in substitution reactions of allylic acetates of α,β-unsaturated esters[5] prompted us to extend this methodology to enantiopure pyrrolinones.

We recently reported that the $Fe(CO)_4$ unit proved to have a sufficient stabilizing effect for the cation to be formed by BF_3-assisted removal of the isopropoxy group from *trans*-$Fe(CO)_4$ complex **1**,[6] which was impossible in the uncomplexed pyrrolinone. Furthermore, the chirality of the starting compound was preserved during the reaction with π-nucleophiles, yielding enantiomerically pure products. The corresponding *cis*-complex **2**, however, reacted much more slowly and suffered from epimerisation under the reaction conditions leading to products of low e.e. Thus, only one of the two possible enantiomers of the products was accessible in high enantiomeric purity.

Therefore, we decided to vary the *N*-substituent. It turned out that alkoxycarbonyl groups could not be used because of the instability of the resulting iron complexes owing to the insufficient electron-withdrawing properties of these *N*-substituents.[7] The strongly electron-withdrawing tosyl group, however, appeared to be a very useful substituent. Sulfonamide **3**† was prepared from 5-(*R*)-isopropoxy-4-(*S*)-trichloroacetoxy-2-pyrrolidinone[8] by reaction with 2.5 equiv. of lithium hexamethyldisilazide in the presence of 2.0 equiv. of toluene-*p*-sulfonic anhydride. The complexation with $Fe_2(CO)_9$ proceeded with high preference for the *cis*-configuration (*cis* : *trans* 85 : 15). This is probably a result of precoordination of the incoming $Fe(CO)_4$ moiety to the oxygen of the isopropoxy group.[9–11] The *cis*-η_2-$Fe(CO)_4$ complex **4** was easily purified by column chromatography followed by recrystallisation and appeared air stable in crystalline form (Scheme 1).‡

The complex showed the well-known[8,12] upfield shifts of the double bond protons in ^1H NMR (*ca.* 3 ppm in $CDCl_3$) and of C^3 and C^4 in ^{13}C NMR (*ca.* 85 ppm). The *cis*-configuration is reflected by the coupling constant J = 4.7 Hz between H^4 and H^5, clearly different from J < 0.5 Hz found for the *trans*-complexes. An X-ray single crystal structure determination unambiguously proved this assignment as well as the absolute configuration at C^5 (Fig. 1). It also revealed an elongation of the C^3–C^4 bond length from 1.32 Å in **3** to 1.40 Å, comparable to the bond lengths in the aryl ring.[12] This fact, like the upfield shifts of the NMR resonances, points to a significant increase in the electron density of the double bond as a result of complexation to iron.[13] One of the sulfonyl oxygens, the sulfur atom, the nitrogen atom and the ring carbonyl are essentially in one plane just like the imide moiety in the *N*-acetyl complex **1**, indicating electronic interaction between the sulfonyl group and the pyrrolinone ring.

In contrast with the *cis*-*N*-acetyl complex, the *cis*-*N*-tosyl complex **4** reacted with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 in 1 h at room temperature to give the *trans*-5-allyl complex **5** which, after treatment with 10 equiv. of trimethylamine *N*-oxide,[10] gave the enantiopure 5-allyl pyrrolinone **6**§ in 88% yield (Scheme 2). Again, sulfonamide **3** did not react under these conditions.

Other *N*-sulfonylpyrrolinones and their iron complexes were also synthesized. The electron-withdrawing pentafluorophenyl group resulted in an unstable *cis*-complex **8a** which was isolated in poor yield only. The 2-naphthyl substituted iron complex **8b**

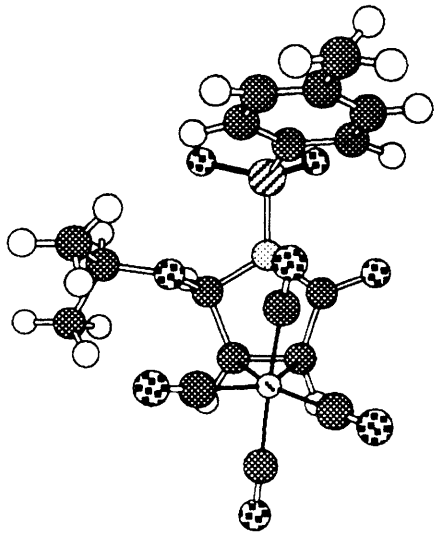
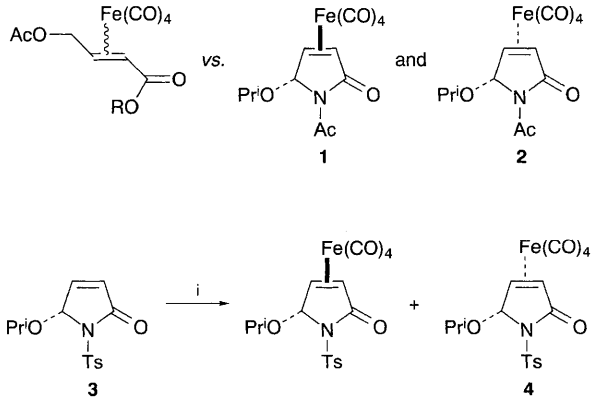
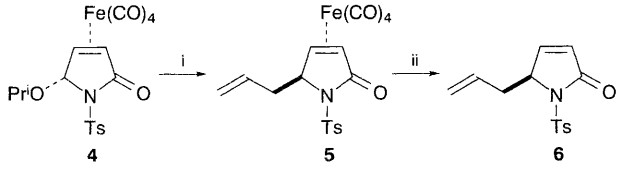


Fig. 1 Chem 3D™ view of the crystal structure of **4**



Scheme 1 *Reagents and conditions*: i, $Fe_2(CO)_9$ (2.0 equiv.), diethyl ether, room temp., 70%



Scheme 2 *Reagents and conditions*: i, allyltrimethylsilane (3.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), CH_2Cl_2, room temp.; ii, $Me_3NO{\cdot}2H_2O$ (10 equiv.), room temp., 88%

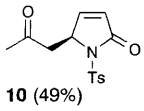
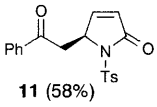
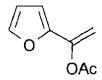
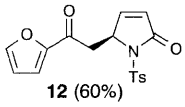
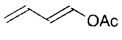
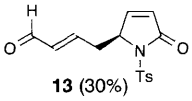
(*cis*:*trans* 84:16) was isolated as a solid in 64% yield. In the reaction with allyltrimethylsilane, the pentafluorophenyl substituted complex **8a** gave a complex reaction mixture. Reaction of **8b** yielded the allyl substituted pyrrolinone **9b** in 67% yield. Both reactions were slower than those of **4**.

Complex **4** failed to react with silyl enol ethers under the conditions of the allylsilane coupling. However, enol acetates gave fair to good yields of substituted pyrrolinones (Table 1).

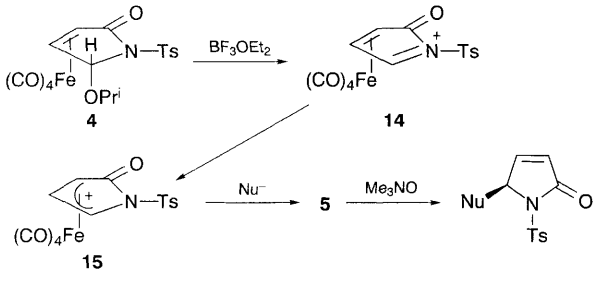
The $BF_3{\cdot}OEt_2$-induced nucleophilic substitution reactions can be rationalized by the following mechanism (Scheme 3). Firstly the *N*-acyl-*N*-tosyliminium ion **14** is formed because the iron group is in the *cis*-orientation and therefore cannot assist the departure of the isopropoxide.[14] Cation **14** is likely to rearrange quickly to the η^3-allyl iron cation **15**. The attack of the nucleophile occurs stereoselectively *trans* to the $Fe(CO)_4$ group.

The different behaviour (rate difference and stereoselectivity) of the *cis*-*N*-acetyl complex **2** and the *cis*-*N*-tosyl complex **4** in the nucleophilic substitution reactions might be explained by assuming that the electron-withdrawing effect of the sulfonyl group is somewhat weaker than that of the acetyl group. This would make the *N*-acyl-*N*-tosyliminium ion **14** more stable than the *N*-acetyl analogue, and consequently, reaction of **4** with the Lewis acid faster than the same reaction of **2**.

Table 1 Reactions of **4** with enol acetates[a]

Entry	Enol acetate	Product (yield)[b]	$[\alpha]^{20}_D$
1		 **10** (49%)	Not determined[c]
2		 **11** (58%)	102 (*c* 0.78, $CHCl_3$)
3		 **12** (60%)	174 (*c* 0.36, $CHCl_3$)
4		 **13** (30%)	143 (*c* 0.22, $CHCl_3$)

[a] *Reagents and conditions*: enol acetate (3.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), CH_2Cl_2, room temp., then MNO (10 equiv.), room temp., 15 min. [b] After column chromatography. Yields are not optimized. [c] **10** could not be separated from byproducts.



Scheme 3 Proposed mechanism for the alkylation of **4**

We thank K. Goubitz and J. Fraanje of the Department of Crystallography of this University for the determination of the crystal structure. This investigation was supported by the Netherlands' Foundation for Chemical Research (SON) with financial aid from the Netherlands' Organization for the Advancement of Pure Research (NWO).

Received, 16th December 1994; Com. 4/07684B

Footnotes

† *Selected data* for (*R*)-**3**: mp 152–153 °C; $[\alpha]^{20}_D$ −38 (*c* 0.41, $CHCl_3$); IR ν/cm^{-1} ($CHCl_3$): 1730, 1355, 1165; ^{1}H NMR ($CDCl_3$; *J*/Hz): δ 1.26 and 1.29 (each d, 3 H, *J* 5.8), 2.43 (s, 3 H), 4.26 (spt, 1 H), 6.03 (d, 1 H, *J* 5.4, H^5), 6.04 (d, 1 H, *J* 2.5, H^3), 6.97 (dd, 1H, *J* 1.7, 6.2, H^4), 7.32 (d, 2 H, *J* 8.1), 7.98 (d, 2 H, *J* 8.4); ^{13}C NMR ($CDCl_3$): δ 21.6, 23.0, 73.0, 88.7, 126.5 (C^3), 128.0, 129.5, 136.2, 144.8, 147.9 (C^4), 166.8.

‡ *Selected data* for (*R*)-**4**: $[\alpha]^{20}_D$ −140 (*c* 2.0, $CHCl_3$); IR ν/cm^{-1} ($CHCl_3$): 2100, 2030, 2000, 1720, 1350, 1165; ^{1}H NMR ($CDCl_3$; *J*/Hz): δ 1.31 and 1.35 (each d, 3 H, *J* 6.1), 2.36 (s, 3 H), 3.73 (d, 1 H, *J* 5.8, H^3), 4.02 (dd, 1 H, *J* 5.7, 4.8, H^4), 4.38 (spt, 1 H, *J* 6.1), 5.92 (d, 1 H, *J* 4.7, H^5), 7.22 (d, 2 H, *J* 8.4), 7.86 (d, 2 H, *J* 8.4); ^{13}C NMR ($CDCl_3$): δ 22.5, 23.0, 44.6 (C^3), 57.9, (C^4), 73.3, 88.4, 128.2, 129.0, 136.3, 144.5, 174.4, 206.0.

§ *Selected data* for (*S*)-**6**: $[\alpha]^{20}_D$ 227 (*c* 0.22, $CHCl_3$); IR ν/cm^{-1} ($CHCl_3$): 1728, 1362, 1170; ^{1}H NMR ($CDCl_3$; *J*/Hz): δ 2.41 (s, 3 H), 2.56 (dt, 1 H, *J* 8.0), 2.98 (m, 1 H), 4.86 (m, 1 H), 5.10 (dd, 1 H, *J* 1.3, 17.0), 5.11 (d, 1 H, *J* 10.9), 5.57 (ddd, 1 H, *J* 7.5, 11.1, 16.2), 6.00 (dd, 1 H, *J* 6.1, 1.6), 7.16 (dd, 1 H, *J* 2.0, 6.1), 7.31 (d, 2 H, *J* 8.2), 7.95 (d, 2 H, *J* 8.3); ^{13}C NMR ($CDCl_3$): δ 21.6, 63.7, 120.0, 125.9, 128.1, 129.6, 130.8, 144.9, 136.1, 151.4, 168.8. The e.e. was determined as >97% by ^{1}H NMR using the chiral shift reagent Eu(hfc)$_3$. The absolute configuration was proven by an X-ray crystal structure determination, details of which will be published elsewhere.

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