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Journal of Organometallic Chemistry 681 (2003) 225–227
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

The unusual stereochemical behaviour of ferrocenecarboxaldehyde in reaction with chiral alkylammonium hypophosphite

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Received 13 March 2003; accepted 5 June 2003

Abstract

The reaction of aldehydes with chiral α-methylbenzylammonium hypophosphite, which, in majority of cases led exclusively to one diastereoisomer, turned out to be much less stereoselective in case of ferrocenecarboxaldehyde. Attempts have been undertaken to explain it.

Keywords: Ferrocenecarboxaldehyde; Stereoselectivity; Azomethine bond; Addition

In 1995, Hamilton et al. [1] found out that the reaction of an aldehyde with (*R*)-α-methylbenzylammonium hypophosphite led exclusively to *RS*-isomers of *N*-(*R*)-α-methylbenzylaminophosphonous acids. They studied several aliphatic and aromatic aldehydes and, as we extended studies on some heteroaromatic aldehydes [2] finding out the same, it was postulated that the reaction of any aldehyde with chiral alkylammonium hypophosphites led exclusively to the one diastereoisomer, so it is stereoselective to 100%. Now, I wish to report that it is not a general rule, as I have found that ferrocenecarboxaldehyde behaved in another way.

Our studies on ferrocene-derived organophosphorus compounds [3,4] brought us to consider a chiral aminophosphonous acid bearing ferrocene moiety. In order to obtain it, we applied the reaction of ferrocenecarboxaldehyde (**1**) with (*R*)-α-methylbenzylammonium hypophosphite (**2**) (Section 1.2). Achieved results were very surprising, however, because the expected *RS*-isomer was not the exclusive product of the reaction. Instead, we obtained a mixture of both diastereoisomers of (ferrocene)-*N*-(*R*)-α-methylbenzylaminomethanephosphonous acid (**3**) in 1:4 ratio, which clearly means that the reaction, which was expected to be totally stereoselective, in fact is not.

This fact encouraged me to make attempts to find the answer, why the reaction, which led exclusively to the *RS* product in majority of cases, turned out to be much less selective, when applied to ferrocenecarboxaldehyde. In order to do this, it is first necessary to discuss the mechanism of the reaction depicted in Scheme 1 and, subsequently, the mechanism of its stereochemistry.

There are two possible mechanisms of this reaction, the first postulates formation of Schiff base, followed by the addition of hypophosphorous acid (Scheme 2, path A) and the second takes into account the nucleophilic addition of hypophosphorous acid to an aldehyde and subsequent substitution of a hydroxyl group with the alkylamino one (Scheme 2, path B).

According to March [5], in the case of the Strecker synthesis, which is rather similar to the discussed one, both pathways of the mechanism are equally possible. Therefore, one could postulate that it is the same in the case of the discussed reaction.

Nevertheless, I am persuaded that the discussed reaction follows the mechanism according to the path A and there are two arguments for it:

1) The stereoselectivity of the reaction. In the case of the mechanism according to the path B, the addition of hypophosphorous acid should be controlled by the chiral amine and, in my opinion, (*R*)-α-methylbenzylamine is too simple to have any influence on the attack.

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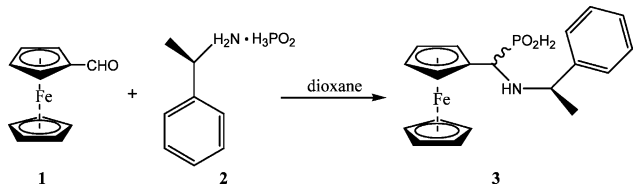
doi:10.1016/S0022-328X(03)00620-X



Scheme 1.

2) The stereoselectivity was exactly the same, when the Schiff base **4** (Scheme 3) was synthesised first, isolated and then reacted with hypophosphorous acid (Section 1.3).

If we consider the mechanism according to path A to be operating, it is possible to discuss the reasons for the stereoselectivity. The key step is the control of the hypophosphorous acid attack to the azomethine bond of intermediate Schiff bases, so the conformation of the latter is very important.

The AM1 semiempirical geometry optimisation helped to evaluate their most convenient conformations and Schiff bases turned out to be easily accessible from the pro-*S* side according to the Cram–Felkin–Ahn model [6], which was applied to the azomethine bond by Yamamoto et al. [7] (Scheme 4). Apparently, the ferrocene moiety should follow the same rules, when sterical aspects are considered. Accordingly, I would suggest that the iron central ion must create some interactions with hypophosphorous acid, which change the stereochemistry. This might be possible as shown in Scheme 4.

The above approach considers the kinetic control of the reaction, but there is also the possibility that the reaction is thermodynamically controlled. In such case, the difference in the total energies between the *RS* and *RR* isomers of the ferrocene-derived acid should be much lower than analogous differences of other compounds, i.e. (ferrocene)-*N*-(*R*)-α-methylbenzylamino-(*S*)-methane-phosphonous acid is less stable in comparison with other studied *N*-(*R*)-α-methylbenzylamino-(*S*)-methane-phosphonous acids. This problem is now under careful study, but results are so far ambiguous. Very recently, Cristau et al. [8] reported synthesis of some α-aminophosphonous acid with a chiral *N*-diphenylhydroxyethyl group, which is not stereoselective to 100%.

Generally, there is a lot of hypotheses around this topic and I do realise that it requires detailed study. Following the old maxim: "everything is wrong unless it is otherwise proven", I wished simply to report the proven fact that ferrocenecarboxaldehyde behaves differently from other non-metallocene aldehydes in the reaction with (*R*)-α-methylbenzylammonium hypophosphite.

1. Experimental

1.1. N-Ferrocenylidene-(R)-α-methylbenzylamine (4)

To a solution of ferrocenecarboxaldehyde (**1**) (1.07 g, 5 mmol) in methanol (30 ml), an amine (0.61 g, 5 mmol) was added. The mixture was then stirred for 20 h at room temperature, then the mixture was evaporated, the solid residue dissolved in benzene and precipitated with hexane to give a pure product in 90% (1.43 g) as reddish-brown crystals, m.p.: 48–50 °C, literature [4] 48–50 °C.

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 8.21 (s, CH=N, 1H); 7.37–7.25 (m, ArH, 5H); 4.73 (m, CH_{fer}, 1H); 4.65 (m, CH_{fer}, 1H); 4.43 (quart, $J = 6.8$ Hz, CHPh, 1H); 4.36 (m, CH_{fer}, 2H); 4.12 (s, C_5H_5, 5H); 1.58 (d, $J = 6.8$ Hz, CH_3, 3H).

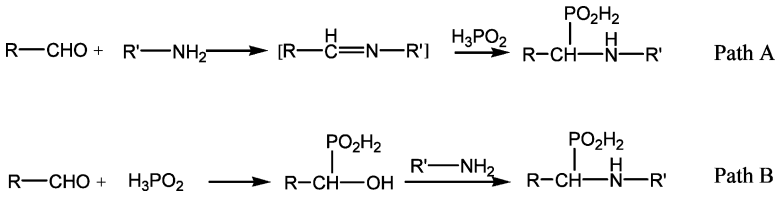
Elemental analysis: Anal. Found: C, 71.86; H, 6.15; N, 4.53. Calc. for ($C_{19}H_{19}FeN$): C, 71.94; H, 6.04; N, 4.42%.

1.2. Method A

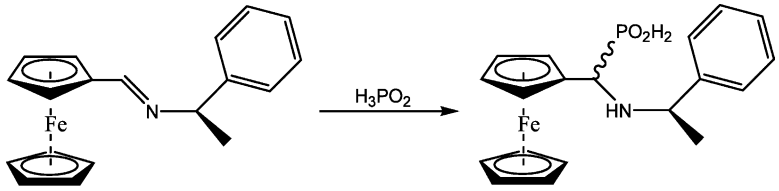
Ferrocenecarboxaldehyde (**1**) (1.07 g, 5 mmol) and (*R*)-α-methylbenzylammonium hypophosphite (0.94 g, 5 mmol) were stirred in acetonitrile (30 ml) for 7 days at room temperature. After this time, the precipitate was collected by filtration and washed several times with cold water to remove impurities to obtain *N*-(*R*)-α-methylbenzylamino(ferrocenyl)methanephosphonous acid in 60% yield (1.15 g), m.p.: 215–217 °C.

1.3. Method B

The Schiff base **4** (1.59 g, 5 mmol) was dissolved in acetonitrile (30 ml) and hypophosphorous acid (0.33 g, 5 mmol) was added and the solution was stirred for 5 days at room temperature. After this time, the precipitate was



Scheme 2.



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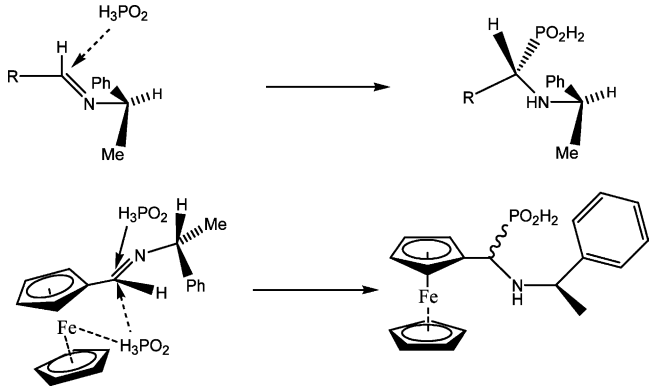
Scheme 3.



Scheme 4.

collected by filtration and washed several times with cold water to remove impurities to obtain *N*-(*R*)-α-methylbenzylamino(ferrocenyl)methanephosphonous acid in 65% yield (1.24 g), m.p.: 215–217 °C.

^{1}H-NMR ($NaOD/D_2O$, 200 MHz, δ ppm): 7.23 (m, CH_{fur}, 1H); 6.47 (m, CH_{fur}, 2H); 6.67 (dd, $^{1}J_{PH} = 521.6$ Hz and $^{3}J_{HH} = 1.6$ Hz, HP, 1H); 6.58 (dd, $^{1}J_{PH} = 514.9$ Hz and $^{3}J_{HH} = 1.6$ Hz, HP, 1H); 4.19 and 4.13 (2quart, $J = 6.7$ Hz); 4.00 and 3.92 (m, CH_{fer}, 4H); 3.78 (s, CH_{fer}, 5H); 3.23 and 3.13 (dd, $^{2}J_{PH} = 9.8$ Hz and $^{3}J_{HH} = 1.6$ Hz, 1H, CHP); 1.32 and 1.16 (2d, $J = 6.7$ Hz, 3H, CH_3). ^{31}P-NMR ($NaOD/D_2O$, 81 MHz, δ ppm): 28.52 and 26.04.

Elemental analysis: Anal. Found: C, 59.17; H, 5.86; N, 3.59. Calc. for ($C_{19}H_{22}FeNO_2P$): C, 59.55; H, 5.79; N, 3.66%.

Acknowledgements

Financial support of the Polish State Committee for Scientific Research (KBN) is kindly acknowledged.

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