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Stereoselective alkylation of [2-(diphenylphosphino)ferrocenyl]acetonitrile

Martin Lamač, Petr Štěpnička *

Department of Inorganic Chemistry, Faculty of Science, Charles University, Hlavova 2030, 12840 Prague, Czech Republic

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Abstract

Deprotonation of racemic [2-(diphenylphosphino)ferrocenyl]acetonitrile (**1**) with $NaN(SiMe_3)_2$ in THF followed by reaction with electrophiles MeI and Ph_2PCl affords the substituted nitriles, 2-[2-(diphenylphosphino)ferrocenyl]propionitrile (**2a**) and 2-(diphenylphosphino)-[2-(diphenylphosphino)ferrocenyl]acetonitrile (**2b**), respectively. Whereas the former reaction yields a 15:1 mixture of isomers differing in configuration at the alkylated α-carbon from which the major diastereoisomer can be isolated by simple recrystallization, the latter gives **2b** as a single diastereoisomer. The dominating product of the methylation reaction was characterized by X-ray diffraction analysis as $(S,R_p/R,S_p)$-**2a**, which is in accordance with the possible access of the electrophile towards deprotonated **1**.

Keywords: Ferrocene; Nitriles; Alkylation; Chiral donors; Structure elucidation

In recent years, there has been much effort devoted to the preparation of new chiral ferrocene ligands for catalytic applications. Their synthesis has been accomplished mostly via metallation/functionalization approach from precursors bearing chiral substitents that are 'equipped' with functional groups capable of promoting ortho-metallation. An inverse method based on deprotonation of achiral ferrocenes with chiral bases has been utilized less frequently [1,2].

It is well established in organic chemistry that strongly electron-withdrawing groups activate C–H bonds in adjacent positions towards the action of bases. Anions resulting from deprotonation of polar substrates are valuable synthetic intermediates that bring polar group(s) capable of further reactions into the molecules of products. In ferrocene chemistry, selective α-deprotonation of ferrocenylacetonitrile followed by alkylation (with RX) to give doubly substituted nitriles $FcCR_2CN$ has been reported as early as in 1973 (Fc = ferrocenyl) [3]. (Ferrocenylmethyl)phenylsulfone $FcCH_2SO_2Ph$ [4] and phosphine chalcogenides $FcCH_2P(E)Ph_2$ (E = O and S) [5] were shown to behave similarly. To the best of our knowledge, these reactions were not studied further nor found utilization in the synthesis of other ferrocene derivatives. This contribution deals with diastereoselective alkylation of planarly chiral, but racemic [2-(diphenylphosphino)ferrocenyl]acetonitrile (**1**), to give substituted (phosphinoferrocenyl)nitriles **2**, that combine central and planar chirality.

We have found that selective deprotonation of nitrile **1** [6] can be accomplished easily by treatment with $NaN(SiMe_3)_2$ in THF at low temperature. Addition of iodomethane [7] or chloro-diphenylphosphine [8] to the deprotonated nitrile then furnished good yields of the respective alkylation products **2a** and **2b** (Scheme 1), substituted in α-position to the nitrile group.

Notably, the reactions proceeded with a high stereoselectivity: whereas the crude methylation product was shown by NMR spectroscopy to be a 15:1 mixture of diastereoisomers, the phosphanylated nitrile **2b** was obtained in diastereoisomerically pure form. Pure major isomer of **2a** was subsequently isolated by recrystallization of the mixture of diastereoisomers from aqueous acetic acid and

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* Corresponding author. Fax: +420 221 951 253.
E-mail address: stepnic@natur.cuni.cz (P. Štěpnička).

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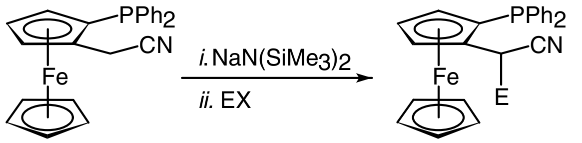

1

2a (E = Me; EX= MeI)
2b (E = PPh$_2$, EX = Ph$_2$PCl)

Scheme 1.

structurally characterized (see below). Both alkylation products **2a** [9] and **2b** [10] gave correct HR MS analyses and their formulation is in accordance with spectral data (IR and NMR).

The structure of the major diastereoisomer, (*S*,*R*$_p$/*R*,*S*$_p$)-**2a**, as determined by single-crystal X-ray diffraction [11] (Fig. 1) clearly shows that the attack of the electrophile occurs preferably from the *exo* side with respect to the ferrocene unit. The molecular geometry of (*S*,*R*$_p$/*R*,*S*$_p$)-**2a** is very much similar to that of the parent nitrile **1** [6]. The most notable, albeit only a slight difference can be found in the C(1)–C(11)–C(13) angle being more acute than in **1** (by ca. 4°), which corresponds with a larger steric demands of the methyl group. However, the data indicate that no torsional deformation occurs at the C(1)–C(2) bond; cf. the torsion angle [C(11)–C(1)–C(2)–P] of 0.5(3)°, which is even lower than in solid **1**. The cyano(ethyl) side arm is rotated with respect to ferrocene unit so that the angles subtended by the C(11)–C(12) and C(11)–C(13) bond vectors and the Cp(1) plane are, respectively, 68.6(2)° and 29.7(2)°. Ferrocene cyclopentadienyl (Cp) planes are almost perfectly parallel and equally distant from the iron atom: relative difference of the Fe–Cg(1,2) bond lengths is lower than 1% (see Fig. 1).

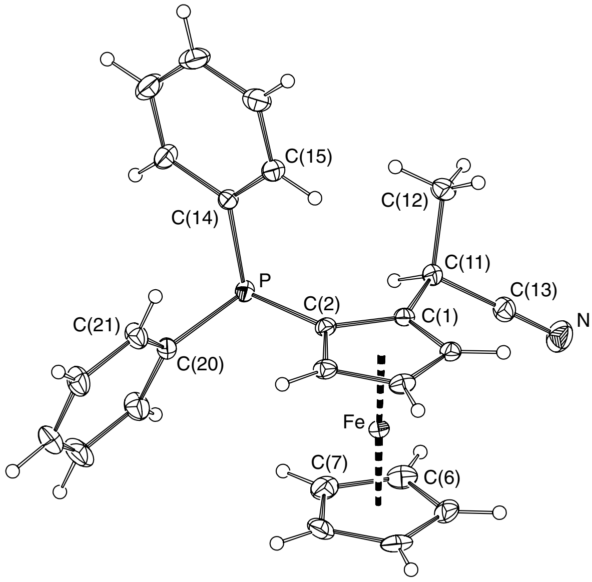

Fig. 1. View of the molecular structure of the major isomer of **2a** (the (*S*,*R*$_p$)-isomer is shown). Displacement parameters enclose 30% probability level. Selected geometric parameters [in Å and °]: P–C(2) 1.813(2), P–C(14) 1.843(2), P–C(20) 1.832(2), C(1)–C(11) 1.514(3), C(11)–C(12) 1.539(4), C(11)–C(13) 1.475(3), C(13)–N 1.135(3) and C(2)–P–C(14) 101.0(1), C(2)–P–C(20) 101.8(1), C(14)–P–C(20) 101.0(1), C(1)–C(11)–C(12) 112.1(2), C(1)–C(11)–C(13) 109.6(2), C(12)–C(11)–C(13) 110.5(2), C(11)–C(13)–N 179.3(3); metallocene geometry: Fe–Cg(1) 1.638(1), Fe–Cg(2) 1.654(1), ∠Cp(1), Cp(2) 0.9(2). Definitions of the ring planes: Cp(1) = C(1–5), Cp(2)=C(6–10); Cg(1,2) are the respective ring centroids.

The course of the deprotonation reaction seems to be controlled largely by steric properties of the (phosphino)ferrocenyl moiety, which provides geometric bias to the diastereotopic hydrogens in the parent nitrile, and by steric relation between the formed cyano[2-(diphenylphosphino)ferrocenyl]methanide salt and the electrophile (cf. different selectivity observed in the reactions yielding **2a** and **2b**). On the other hand, the base seems to play a less important role. For instance, substituting NaN(SiMe$_3$)$_2$ for LiN(*i*Pr)$_2$ (prepared freshly from butyl lithium and diisopropylamine) in the preparation of **2a** did not alter the product yield nor the diastereoisomer ratio.

The presented results show that deprotonation/alkylation of ferrocenylacetonitrile **1** proceeds with very good stereoselectivity, yielding α-substituted nitriles **2**. Extension of this approach towards other, possibly homochiral (cyanomethyl)ferrocenes, as well as further synthetic modification of **2**-type products may open an alternative routes to a variety of new chiral ferrocene donors (a single isomer from optically pure precursors), e.g., to novel ferrocene phosphinocarboxylic ligands [12].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.inoche.2005.12.003.

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[7] Preparation of 2-[2-(diphenylphosphino)ferrocenyl]propionitrile (**2a**). To a stirred solution of nitrile **1** [6] (197 mg, 0.48 mmol) in dry THF (15 mL) cooled to −78 °C (dry ice/ethanol bath), $NaN(SiMe_3)_2$ (0.6 mL of 1.0 M solution in THF, 0.58 mmol; Aldrich) was added dropwise. The colour of the reaction solution turned from orange to dark red. The mixture was stirred at −78 °C for 15 min and then treated with methyl iodide (355 mg, 2.5 mmol), while the colour changed to brown–yellow. The reaction mixture was stirred for another 30 min at −78 °C and then at room temperature for 1 h and then quenched by adding saturated aqueous NH_4Cl solution (10 mL). The organic phase was separated, washed with saturated aqueous NaCl, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was immediately purified by column chromatography (silica gel, diethyl ether) to give **2a** as an orange oil, that solidified at 4 °C. Yield: 125 mg (62%). NMR analysis revealed the product to be a mixture of two diastereoisomers in a molar ratio of 15:1. Recrystallization from aqueous acetic acid afforded pure major diastereoisomer as an orange crystalline solid.

[8] Preparation of 2-(diphenylphosphino)-[2-(diphenylphosphino)ferrocenyl]acetonitrile (**2b**). Similar to the previous procedure, nitrile **1** [6] (205 mg, 0.50 mmol in dry THF (15 mL)) was deprotonated with $NaN(SiMe_3)_2$ (0.8 mL, 1.0 M in THF, 0.80 mmol) at −78 °C for 30 min and then treated with neat chlorodiphenylphosphine (0.2 mL, 1.1 mmol; freshly distilled). The reaction was completed by stirring for 15 min at −78 °C and then at room temperature for 90 min and then terminated by addition of saturated aqueous NaCl solution (10 mL). The organic phase was separated, washed twice with saturated aqueous NaCl, dried over $MgSO_4$, and pre-adsorbed onto silica gel by co-evaporation. The solid material was transferred onto the top of a chromatographic column (silica gel, hexane-ether 10:1) and eluted with the same solvent mixture. A subsequent evaporation yielded diphosphine **2b** as a single diastereoisomer. Yield: 200 mg (67%), viscous orange oil.

[9] Analytical data for **2a**. *Mixture of isomers:* IR (Nujol): ν/cm^{-1} 2239 w $\nu(C\equiv N)$, 1584 w, 1434 s, 1305 w, 1246 w, 1166 w, 1097 m, 1066 w, 1038 w, 999 w, 844 w, 819 s, 745 s, 697 s, 553 w, 502 m, 486 m, 455 m. *Major diastereoisomer:* M.p. 159–161 °C. ^1H NMR ($CDCl_3$): δ 1.13 (d, $^3J_{HH} = 7.2$ Hz, 3H, CHMe), 3.87 (m, 1H, C_5H_3), 4.11 (s, 5H, C_5H_5), 4.13 (qd, $^3J_{HH} = 7.2$ Hz, $^4J_{PH} = 5.0$ Hz, 1H, C*H*Me), 4.38 (apparent t, $J \approx 2.6$ Hz, 1H, C_5H_3), 4.65 (m, 1H, C_5H_3), 7.12–7.58 (m, 10H, P Ph_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 22.47 (CH_3), 26.26 (d, $^3J_{PC} = 14$ Hz, $CHCH_3$), 69.23 (d, $J_{PC} = 4$ Hz, *C*H C_5H_3), 69.91 (*C*H C_5H_3), 70.34 (C_5H_5), 71.57 (d, $J_{PC} = 5$ Hz, *C*H C_5H_3), 74.90 (d, $^1J_{PC} = 9$ Hz, *C*–P C_5H_3), 90.81 (d, $^2J_{PC} = 27$ Hz, *C*–CH C_5H_3), 122.07 ($C\equiv N$), 128.21 (CH_m PPh_2), 128.27 (d, $^3J_{PC} = 2$ Hz, CH_m PPh_2), 128.29, 129.40 (2 × CH_p PPh_2); 132.42, 134.87 (2 × d, $^2J_{PC} = 21$ Hz, CH_o PPh_2); 136.49, 139.26 (2 × d, $^1J_{PC} = 8$ Hz, C_{ipso} PPh_2). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ−25.9 (s). EI MS (direct inlet): m/z (relative abundance) 423 (100), 384 (7), 302 (4), 276 (9), 239 (9), 217 (7), 199 (8), 183 (17), 149 (16), 147 (30), 121 (17), 105 (14), 75 (56), 56 (15). HR MS calcd. for $C_{25}H_{22}{}^{56}FeNP$: 423.0839, found 423.0835. *Minor diastereoisomer:* $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −24.6 (s).

[10] Analytical data for **2b.** ^1H NMR ($CDCl_3$): δ 3.91 (m, 1H, C_5H_3), 3.98 (C_5H_5), 4.05 (m, 1H, C_5H_3), 4.26 (apparent t, $J \approx 2.6$ Hz, 1H, C_5H_3), 4.89 (dd, $^2J_{PH} = {}^4J_{PH} = 5.3$ Hz, 1H, C*H*PPh_2), 7.24–7.67 (m, 10H, PPh_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 31.19 (dd, $^1J_{PC} = 36$ Hz, $^3J_{PC} = 15$ Hz, *C*HPPh_2), 70.01 (*C*H C_5H_3), 70.35 (C_5H_5), 71.00 (*C*HC_5H_3), 72.00 (d, $^2J_{PC} = 4$ Hz, *C*H C_5H_3), 74.94 (dd, $^1J_{PC} = 10$ Hz, *C*–P C_5H_3), 86.84 (dd, $^2J_{PC} = 28$ Hz, $^3J_{PC} = 17$ Hz, *C*–CH C_5H_3), 118.56 (d, $^2J_{PC} = 2$ Hz, $C\equiv N$), 127.79, 128.75 (2 × CH_P PPh_2); 127.83, 128.18 (2 × d, $^3J_{PC} = 6$ Hz, CH_m PPh_2), 128.27, 128.57 (2 × d, $^3J_{PC} = 5$ Hz, CH_m PPh_2); 129.40, 130.56 (2 × CH_P PPh_2); 131.56 (d, $^2J_{PC} = 18$ Hz, CH_o PPh_2), 132.61 (dd, $^2J_{PC} = 17$ Hz, $J_{PC} = 2$ Hz, CH_o PPh_2), 132.66 (d, $^1J_{PC} = 21$ Hz, C_{ipso} PPh_2), 135.18 (d, $^2J_{PC} = 20$ Hz, CH_o PPh_2), 135.40 (d, $^2J_{PC} = 21$ Hz, CH_o PPh_2), 135.43 (d, $^1J_{PC} = 18$ Hz, C_{ipso} PPh_2), 137.58, 139.62 (2 × d, $^1J_{PC} = 6$ Hz, C_{ipso} PPh_2). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −26.1 (d, $^4J_{PP} = 20$ Hz, $C_5H_3PPh_2$), 2.0 (d, $^4J_{PP} = 20$ Hz, $CHPPh_2$). IR (DRIFTS, KBr): ν/cm^{-1} 2227 w $\nu(C\equiv N)$, 1585 w, 1570 w, 1477 m, 1433 s, 1244 w, 1165 w, 1128 w, 1107 w, 1092 m, 1026 w, 999 w, 827 m, 816 m, 748 s, 739 s, 698 vs, 515 s, 503 m, 480 m, 451 w. MS (direct inlet): m/z (relative abundance) 593 (52), 516 (2), 425 (7), 409 (100), 370 (4), 306 (11), 285 (8), 261 (47), 199 (16), 186 (53), 183 (82), 152 (15), 121 (17), 108 (98), 71 (31), 57 (62), 43 (59). HR MS calcd. for $C_{36}H_{29}{}^{56}FeNP_2$: 593.1125, found 593.1102.

[11] Diffraction data were measured on a Nonius KappaCCD diffractometer at 150(2) K. The structure was solved by direct methods (SIR97 [11a]) and refined by full-matrix least squares on F^2 (SHELXL97 [11b]). The non-hydrogen atoms were refined with anisotropic displacement parameters; all hydrogen atoms were included in calculated positions (riding model). Crystal data and refinement parameters: triclinic, space group $P\bar{1}$ (no. 2), $a = 10.1434(2)$ Å, $b = 10.3163(2)$ Å, $c = 11.9958(3)$ Å; $\alpha = 109.317(2)°$, $\beta = 109.802(1)°$, $\gamma = 102.574(2)°$; $V = 1034.83(4)$ Å^3, $Z = 2$, $D_{calc} = 1.358$ g cm^{-3}, μ(Mo Kα) = 0.816 mm^{-1}, 19040 total ($2\theta \leqslant 55°$), 4759 independent ($R_{int} = 3.2\%$) and 4111 observed [$I_o > 2$ (I_o)] diffractions. Final refinement parameters: $R = 4.16\%$ (observed data); $R = 5.10\%$, $wR = 11.24\%$ (observed data); $\Delta\rho$ +2.23, −0.42 e Å^{-3} (The positive residual electron density is due to the phosphorus lone pair; attempted refinement of this electron density maximum as a helium atom (2 electrons) lead to a decrease of the R value by 1%. Thus, the second largest positive difference electron density peak (+0.37 e Å^{-3}) should be regarded as true positive residual electron density). Geometric calculations were performed with Platon program [11c]. CCDC Deposition No.: 288346. References: (a) A. Altomare, M.C. Burla, M. Camalli, G.L. Cascarano, C. Giacovazzo, A. Guagliardi, A.G.G. Moliterni, G. Polidori, R. Spagna, J. Appl. Crystallogr. 32 (1999) 115; (b) G.M. Sheldrick, SHELXL97. Program for the Refinement of Crystal Structures, University of Goettingen, Germany, 1997;
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