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Research Article

Synthesis and Characterization of Some Novel Ferrocenyl Derivatives of Pyrazole Analogues

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Abstract: Pyrazoles have been studied for over a century as an important class of heterocyclic compounds and continue to attract considerable interest due to the broad range of biological activities they possess. The incorporation of the essential structural features of pyrazoles with a ferrocene moiety could provide new derivatives with unexpected and/or enhanced biological activities since several ferrocene derivatives have already been shown to be active against a number of tumors. For this reason, we investigated the synthesis of ferrocenyl-substituted pyrazoles, such as sI-alkyl/aryl-5-ferrocenylpyrazoles, by employing the reaction between (2-formyl-1-chlorovinyl) ferrocene and hydrazine derivatives. Although this reaction is known, it was not studied in much detail and the low yields of ferrocenyl pyrazoles were obtained. Thus, reinvestigation of this reaction improved the yields of pyrazoles by optimizing the reaction conditions. (2-Formyl-1-chlorovinyl) ferrocene was first reacted with the excess amount (3 equivalents) of hydrazine derivative at 25^0C in dioxane under argon for 2 hours, and the resulting mixture was then heated at 100^0C for 6 hours in the same solvent. Under our optimized conditions, these reactions afforded 1-alkyl/aryl-5-ferrocenylpyrazole derivatives in moderate to good yields as a single or major product of the reaction.[1-2] In some cases, 1-alkyl/aryl-3-ferrocenylpyrazole derivatives resulted from these reactions as very minor products.
Keywords: Ferrocene, pyrazole, ferrocenyl pyrazole derivatives, 1-alkyl/aryl-5-ferrocenylpyrazoles, 1-alkyl/aryl-3-ferrocenylpytrazoles, hydrazines.

INTRODUCTION

The aim of this work is to synthesize some new ferrocenyl-substituted pyrazole derivatives since the incorporation of the essential structural features of pyrazoles with a ferrocene moiety could provide new derivatives with enhanced antitumor and biological activities. The goal of this work is to synthesize the ferrocenyl-substituted pyrazole derivatives since the incorporation of the essential structural features of pyrazoles with a ferrocene moiety could provide new derivatives with enhanced antitumor and biological activities. Although pyrazoles are among the most thoroughly studied compounds, we were surprised that there has been very limited study of the ferrocenyl-substituted pyrazoles. As part of general involvement in ferrocene containing potential pharmaceuticals, I investigated the synthesis of ferrocenyl pyrazoles. In particular, although there are numerous methods for the synthesis of pyrazoles, the reaction of (2-formyl-1-chlorovinyl) ferrocene with hydrazines can provide a rapid entry to ferrocenyl pyrazoles [3]. Reinvestigation of this reaction improved the yields of pyrazoles by optimizing the reaction conditions. (2-Formyl-1-chlorovinyl) ferrocene was first reacted with the excess amount (3 equivalents) of hydrazine derivative at 25^0C in dioxane under argon for 2 hours, and the resulting mixture was then heated at 100^0C for 6 hours in the same solvent. Under our optimized conditions, these reactions afforded 1-alkyl/aryl-5-ferrocenylpyrazole derivatives in moderate to good yields as a single or major product of the reaction [1-2]. In some cases, 1-alkyl/aryl-3-ferrocenylpyrazole derivatives resulted from these reactions as very minor products. In fact, the reaction of (2-formyl-1-chlorovinyl) ferrocene with hydrazine and phenyl hydrazine was carried out by Terent'ev and his co-workers for the first time but the low yield of products were obtained since these reactions were not investigated in much detail. We have restudied this reaction under a variety of condition and improved the yields of pyrazoles by optimizing reaction conditions. Moreover, we have examined this reaction with 7 hydrazine derivatives.

EXPERIMENTAL SECION

Synthesis of (2-formyl-1-chlorovinyl) ferrocene

In the first phase of this study, acetyl ferrocene was synthesized from ferrocene. Ferrocene behaves as an aromatic compound and easily undergoes Friedel-Crafts Acylation reaction to form acetyl ferrocene in 80% yield according to a known literature. The reaction was performed by using $AlCl_3$ under argon condition [4].

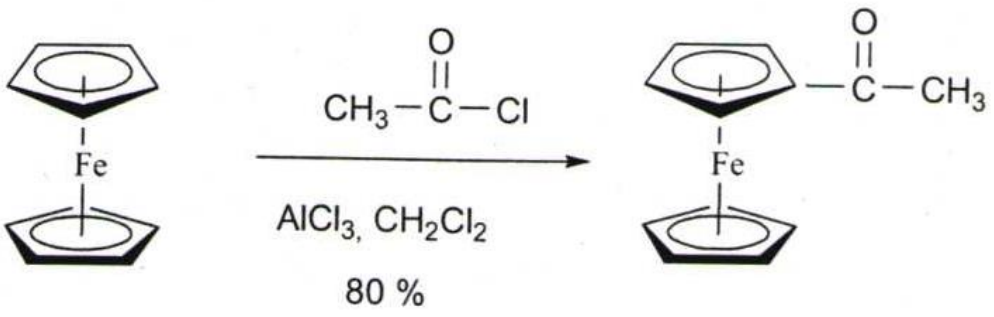

Fig. 1: Synthesis of acetyl ferrocene.

Subsequently, (2-formyl-1-chlorovinyl) ferrocene has been prepared from acetyl ferrocene in 93% yield according to known literature. Treatment of acetyl ferrocene with phosphorus oxychloride in dimethyl formamide (DMF) leads to a mixture of (2-formyl-1-chlorovinyl)ferrocene and (1-chlorovinyl)ferrocene with the different product ratio depending on the stoichiometry. However, the formation of (1-chlorovinyl)ferrocene can be effectively suppressed by employing an excess of phosphorus oxychloride. Using DMF as solvent leads to satisfactory results only for small-scale preperations. However, modification of the stoichiometry and experimental conditions led to the above described procedure which is useful for large-scale preperations. Use of conditions employing a comparatively small excess of DMF and phosphorus oxychloride resulting in a heterogeneous reaction mixture, as well as use of solid sodium acetate trihydrate surmount the problems of scale up and enable the removal of organic impurities. The purity and yield of (2-formyl-1-chlorovinyl)ferrocene are substantially improved using the present procedure, and this intermediate is obtained in pure form without need of chromatography [5].

Synthesis of Acetylferrocene

In a dry flask, ferrocene (2 g, 0, 0108 mol) was added and it was dissolved with stirring in dry dichloromethane (15 ml) under argon. To the resultant dark orange/red solution acetyl chloride (1,03 ml, 0, 0118 mol) was added and then flask was immersed in an ice water bath at 0-5 ^{o}C. Anhydrous aluminium chloride (1, 44g, 0, 0108 mol) was added in 10 portions (2min. between each addition). the reaction mixture darkened. It was stirred for 2 h allowing the ice-water warm to room temperature. Solution was recooled and hydrolized with water by slow addition of 4 x 0, 5 ml of cold water. Then, 3 ml of cold water was added more rapidly. The mixture was transferred to a separating funnel and extracted with dichloromethane then organic extracts were combined and washed with 5% sodium hydroxide solution. Red/orange solution was dried over magnesium sulfate for 10 min, then filtered off. Solvent was removed on a rotary evaporator to give a red/orange solid. This solid was purified by flash chromatography on silica gel using hexane as the eluent[6]. The red/orange fraction (R_f = 0.1in 9:1 hexane/ethyl acetate) was collected to give acetyl ferrocene (1, 96 g, 80%).

^{1}H-NMR ($CDCl_3$): δ 4.60 (s, 2H), 4.32 (s,5H), 2.17 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 79.2 (C), 72.3 (CH), 69.8 (CH), 69.5 (CH), 27.3 (CH_3). The spectral data is in agreement with those reported previously for this compound.

Synthesis of (2-Formyl-1-Chlorovinyl) Ferrocene

To a two necked flask, acetylferrocene (2 g, 8.8 mmol) was placed and addition funnel was connected. N,N-dimethyl formamide (DMF) (2.17 ml, 28.2 mmol) was added on it. The system was flushed with argon, cooled to 0^{o}C by means of an ice bath, and the brown reaction mixture was stirred for several minutes. Separately, in a flask joined with argon, DMF (2.17 ml, 28.2 mmol) was added and cooled to 0^{o}C with good stirring phosphorus oxychloride (2.21 ml, 24 mmol) was added. The resulting viscous, red complex was transferred to the dropping funnel and added to the magnetically stirred mixture of acetylferrocene and DMF dropwise over 30 min. Complete addition was assured by washing the addition funnel and walls of the flask with small amount of DMF. The mixture was stirred at 0^{o}C for 2 hr during which time the colour of the reaction mixture changed from dark brown to olive and ultimately to deep blue. Prior to neutralization, 20 ml portion of diethyl ether was added and viscous mixture was stirred vigorously for several minutes. At 0^{o}C, (10.18 g, 74.6mmol) sodium acetate trihydrate was cautiously added to the reaction mixture in one portion followed by addition of 2 ml water with vigorous stirring. The ice bath was removed whereupon the organic layer undergoes a striking colour change from blue to ruby red indicating the formation of the formyl derivative [7]. After 1 hr, an additional 2 ml of diethyl ether was added and stirring was continued for 3 hr at room temperature to ensure complete quenching. The reaction mixture was transferred to a separator funnel with ether and water and mixed thoroughly, and the organic phase was separated. The aqueous phase was extracted several times with ether. The combined organic phases were carefully washed with 20 ml of saturated aqueous sodium bicarbonate solution. The

organic phase was dried over magnesium sulfate, filtered and concentrated using a rotary evaporator [8]. The resulting (2-formyl-1-chlorovinyl)ferrocene was obtained as an only product (2.25 g, 93%).

^{1}H-NMR ($CDCl_3$): δ 10.06 (d, 1H, *J*=7.1 Hz), 6.38 (d, 1H, *J*=7.1 Hz), 4.73 (t, 2H, *J*=1.68 Hz), 4.22 (s, 5H). The spectral data is in agreement with those reported previously for this compound.

Reaction of (2-formyl-1-chlorovinyl)ferrocene with phenyl hydrazine hydrochloride salt

General Procedure 1 was followed by using (2-formyl-1-chlorovinyl)ferrocene (300 mg, 1.089 mmol), phenyl hydrazine hydrochloride salt (472.4 mg, 327 mmol). After chromatographic purification, a purple fraction (R_f =0.43 in 9:1 hexane/ethyl acetate) was collected to give 1-phenyl-3-ferrocenylpyrazole (18 mg, 15%) and an orange fraction (R_f =0.21 in 9:1 hexane/ethyl acetate) was collected to give 1-phenyl-5-ferrocenylpyrazole (49 mg, 41%).

^{1}H-NMR ($CDCl_3$): δ 7.84 (d, 1H, *J* =2.4 Hz), 7.71 (d, 2H, *J*=7.8 Hz), 7.44 (t, 2H, *J*=7.8 Hz), 7.25 (t, 1H, *J*=7.8 Hz), 6.48 (d, 1H, *J*=2.4 Hz), 4.76 (s, 2H), 4.29 (s, 2H), 4.07 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 152.5 (C), 140.3 (C), 129.4 (CH), 127.4 (CH), 126.0 (CH), 119.0 (CH), 105.6 (CH), 78.4 (C), 69.6 (CH), 68.7 (CH), 66.9 (CH); IR (neat): 3742 (s), 3669 (w), 3030 (vw), 2959 (vs), 2865 (s), 1719 (vs), 1681 (b), 1506 (s), 1257 (vs), 1129 (w), 1043 (m), 868 (w), 820 (m); MS (EI): 328 (M^+), 326, 263, 246, 206, 178, 149, 121, 91, 77, 56; HRMS (EI): Calc. For $C_{19}H_{16}{}^{56}FeN_2$: 328.0663. Found: 328.0665.

^{1}H-NMR ($CDCl_3$): δ 7.62 (s, 1H), 7.40 (m, 5H), 6.50 (s, 1H), 4.17 (s, 2H), 4.14 (s, 2H), 4.05 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 141.5 (c), 140.4 (C), 140.0 (CH), 128.8 (CH), 128.0 (CH), 126.1 (CH), 106.8 (CH), 75.1 (C), 69.9 (CH), 68.8 (CH),68.6 (CH); IR (neat): 3744 (w), 3098 (m), 3048 (s), 1737 (vw), 1665 (s), 1597 (s), 1498 (vs), 1402 (s), 1312 (vw), 1259 (vs), 1145 (s), 923 (s), 822 (vs); MS (EI): 328 (M^+), 326, 263, 235, 207, 170, 153, 121, 77, 56; HRMS (EI): Calc. For $C_{19}H_{16}{}^{56}FeN_2$: 328.0663. Found: 328.0661.

Reaction of (2-formyl-1-chlorovinyl)ferrocene with benzyl hydrazine dihydrochloride salt

General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene (100 mg, 0.363 mmol), benzyl hydrazine dihydrochloride salt (212.44 mg, 1.089 mmol). After chromatographic purification, the orange colored fraction (R_f =0.17 in 9:1 hexane/ethyl acetate) was collected to give 1-benzyl-5-ferrocenylpyrazole (68 mg, 55%).

^{1}H-NMR ($CDCl_3$): δ 7.44 (s, 1H), 7.23 (t, 2H, *J*=7.28 Hz), 7.15 (t, 1H, *J*=7.28 Hz), 6.96 (d, 2H, *J*=7.28 Hz), 6.35 (s, 1H, 5.42 (s, 2H), 4.29 (s, 2H), 4.17 (s, 2H), 4.00 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 141.7 (C), 139.1 (C), 137.7 (CH), 128.6 (CH), 127.3 (CH), 126.3 (CH), 106.0 (CH), 74.9 (C), 70.0 (CH), 68.8 (CH), 68.4 (CH), 53.3 (CH_2); IR(neat): 3096 (w), 2954 (s), 2930 (s), 2858 (w), 1721 (vs), 1673 (b), 1405 (s), 1281 (vs), 1130 (s), 1076 (s), 928 (s), 822 (s); MS (EI): 342 (M^+), 277, 252, 223, 185, 157, 121, 91, 65, 56; HRMS (EI): Calc. For $C_{20}H_{18}{}^{56}FeN_2$: 342.0819. Found: 342.0817.

Reaction of (2-formyl-1-chlorovinyl)ferrocene with 2-hydroxy ethyl hydrazine dihydrochloride salt

General Procedure was followed by using (2-formyl-1-chlorovinyl)ferrocene (100 mg, 0.363 mmol), 2-hydroxy ethyl hydrazine dihydrochloride salt (162.25 mg, 1.089 mmol). After chromatographic purification, the bright yellow coloured fraction (R_f = 0.107 in 1:1 hexane/ethyl acetate) was collected to give 1-(2-hydroxy ethyl)-3-ferrocenylpyrazole (3 mg, 3%) and yellow/orange colored fraction (R_f = 0.054 in 1:1 hexane/ethyl acetate) was collected to give 1-(2-hydroxy ethyl)-5-ferrocenylpyrazole (36.7 mg, 34%).

^{1}H-NMR ($CDCl_3$): δ 7.46 (d, 1H, *J*=1.8 Hz), 6.30 (d, 1H, *J*=1.8 Hz), 4.49 (s, 2H), 4.36 (t, 2H, *J*=4.5 Hz), 4.33 (s, 2H), 4.18 (s, 5H), 4.02 (t, 2H, *J*=4.5 Hz); ^{13}C-NMR ($CDCl_3$): δ 141.4 (C), 138.7 (CH), 106.0 (CH), 74.9 (C), 69.6 (CH), 68.9 (CH), 68.8 (CH), 61.8 (CH_2), 51.0 (CH_2); IR (neat): 3049 (w), 2925 (vs), 2863 (s), 1724 (s), 1623 (b), 1458 (w), 1285 (s), 1142 (w), 1071 (w), 1034 (vw), 824 (s); MS (EI): 296 (M^+), 294, 265, 252, 231, 200, 187, 146, 121, 103; HRMS (EI): Calc. For $C_{15}H_{16}{}^{56}FeN_2O$. Found: 296.0610.

^{1}H-NMR ($CDCl_3$): δ 7.31 (s, 1H), 6.22 (s, 1H), 4.76 (s, 2H), 4.35 (s, 2H), 4.21 (t, 2H, J= 4.3 Hz), 4.12 (s, 5H), 3.97 (t, 2H, J= 4.3 Hz); ^{13}C-NMR ($CDCl_3$): δ 151.3 (C), 130.8(CH), 103.0 (CH), 78.3 (C), 69.4 (CH), 68.3 (CH), 66.6 (CH), 62.1 (CH_2), 53.5 (CH_2); IR (neat): 3051 (s), 2926 (s), 2858 (s), 1727 (s), 1461 (vw), 1376 (w), 1261 (vs), 1243 (b), 1070 (vw), 821 (vw); MS (EI): 296 (M^+), 294, 278, 264, 231, 213, 199, 173, 148, 121, 103, 81; HRMS (EI): Calc. For $C_{15}H_{16}{}^{56}FeN_2O$: 296.0612. Found: 296.0614.

Reaction of (2-formyl-1-chlorovinyl)ferrocene with 4-hydroxybenzhydrazide

General Procedure was followed by using (2-formyl-1-chlorovinyl) ferrocene (100 mg, 0.363 mmol), 4-hydroxybenzhydrazide (165.68 mg, 1.089 mmol). After chromatographic purification, the orange colored fraction (R_f = 0.283 in 4:1 hexane/ethyl acetate) was collected to give (58 mg, 43%). Also, 1-*H*-5-ferrocenyl pyrazole was collected (46 mg, 50%).

^{1}H-NMR ($CDCl_3$): δ 8.33 (s, 1H), 8.21 (d, 2H, *J* = 7.95 Hz), 6.89 (d, 2H, *J* = 7.95Hz), 6.51 (s, 1H), 5.87 (s, OH), 4.81 (s, 2H), 4.40 (s, 2H), 4.14 (s, 5H); ^{13}C-NMR ($CDCl_3$): δ 165.1 (C), 160.3 (C), 156.6 (C), 134.5 (CH), 131.5 (CH), 123.6 (C), 115.3 (CH), 107.9 (CH), 78.2 (C), 71.2 (CH), 71.1 (CH), 68.6 (CH); IR (neat): 3946 (m), 3690 (vw), 3058 (vs), 2981 (s), 2676

(w), 2295 (s), 1418 (vs), 1266 (vs), 1150 (vw), 896 (s), 705 (s); MS (EI): 372 (M^+), 370, 307, 252, 224, 187, 158, 141, 121, 93, 84; HRMS (EI): Calc. For $C_{20}H_{16}{}^{56}FeN_2O_2$: 372.0561. Found: 372.0563.

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