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SYNTHESIS AND STUDY OF ANTI INFLAMMATORY ACTIVITY OF SOME NOVEL FERROCENYL DERIVATIVES OF PYRAZOLE ANALOGUES

S. SAMBATH KUMAR[*]

[*]Research Scholar, Singhania University, Pacheri Bari Jhun Jhunu-333515,(Raj.) INDIA

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.

Keywords Ferrocene, pyrazole, ferrocenyl pyrazole derivatives, 1-alkyl/aryl-5-ferrocenylpyrazoles, 1-alkyl/aryl-3-ferrocenylpytrazoles, hydrazines, Anti-inflammatory activity.

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 our general involvement in ferrocene containing potential pharmaceuticals, I was 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. 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

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.

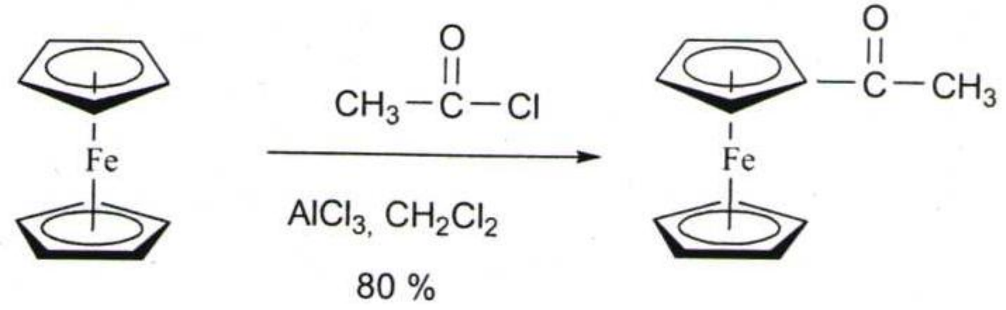

Figure-1 : Synthesis of acetyl ferrocene.

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.[1] 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.[2]

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 °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.[3] 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-dimethylformamide (DMF) (2.17 ml, 28.2 mmol) was added on it. The system was flushed with argon, cooled to 0°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°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°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°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. 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.[4] The organic phase was dried over magnesium sulfate, filtered and concentrated using a rotary evaporator. 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[5] (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.

MATERIALS AND METHODS

Screening of Anti-Inflammatory Activity

Carrageenan induced paw oedema

The activity was evaluated by using carrageenan induced hind paw oedema method reported by Winter (1962). The Wistar albino rats of either sex were divided into eight groups comprising six animals in each group (n=6). Male or female albino rats with body weight of 150-180 gm were selected for the study. The animals were starved overnight and deprived of water only during the experiment. Inflammation of the hind paw was induced by injecting 0.1ml of the 1% w/v carrageenan (Sigma Chemicals Co., USA) in normal saline into the sub-planter surface of the right hind paw.[6] The negative control group was treated with tween-80 (2% w/v) solution at a dose of 10 ml/kg body weight. The positive control group was treated with Ibuprofen (10 mg/kg body weight). The remaining six groups received the newly synthesised compounds at dosage of 250, 500, 750 mg/kg body weight. All of the treatments were given one hour before the carrageenan injection. The measurement of paw volume was accomplished immediately by displacement technique using the Plethysmometer before the carrageenan injection and at 1, 2, 3 hrs after the carrageenan injection. Oedema was expressed as theincrement in paw volume due to carrageenan administration.[7-9]

Mean increase in the paw volume was measured and percentage inhibition was calculated by using following formula:

$$\% \text{ Inhibition} = (1-dt/dc)100$$

Where, dt = Difference in paw volume in drug treated group.

dc = Diference in paw volume in control animals.

Groups	**Dose (mg/kg bodyweight)**	**Mean Increase in Paw Volume (ml)**			**Percentage Inhibition of Paw Oedema**		
		1 hr.	2 hr.	3 hr.	1 hr.	2 hr.	3 hr.
Group I	---	0.38±0.060	0.70±0.120	1.00±0.025	---	---	---
Group II	10	0.18±0.024**	0.22±0.024**	0.31±0.023**	52.63	68.57	69.00
Group III	250	0.38±0.017	0.46±0.023	0.67±0.016	00.00	34.29	33.00
Group IV	500	0.33±0.013*	0.45±0.019*	0.65±0.026**	13.16	35.71	35.00
Group V	750	0.21±0.010**	0.31±0.016**	0.51±0.018**	44.74	55.71	49.00
Group VI	250	0.30±0.041	0.42±0.039**	0.63±0.022**	21.05	40.00	37.00
Group VII	500	0.29±0.014	0.41±0.017**	0.61±0.024**	23.68	41.43	39.00
Group VIII	750	0.17±0.007**	0.28±0.013**	0.47±0.016**	55.26	60.00	53.00

*$P<0.05$, **$P<0.01$ as compared to control, as per one way analysis of variance (ANOVA) fallowed by Dunnett's multiple comparison test. Value are presented as mean ± SEM, n= 6 animal in each group

Table-1 : Evaluation of anti-inflammatory activity of newly synthesised compounds in carrageenan induced rat hind paw oedema

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