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Ferrocenylsubstituted α,β-unsaturated ketones in the synthesis of dihydropyrimidinethiones

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Abstract

The reaction has been studied of ferrocenylsubstituted α,β-unsaturated ketones with thiourea in alkaline ethanol leading to the corresponding dihydropyrimidinethiones. Products were isolated as yellow or orange crystals with yields of 65–95%. Structures were proved by high resolution ^{1}H NMR spectra. Ferrocenylsubstituted dihydropyrimidinethiones have been shown to convert quantitatively into the initial α,β-unsaturated ketones under heating with alkaline ethanol in the presence of water.

1. Introduction

The availability of chalkones with ferrocenyl substitute makes them virtually the only initial substances available for the synthesis of certain heterocyclic compounds, in particular ferrocenylsubstituted dihydropyrimidinethiones.

Although the ability of thiourea to react with α,β-unsaturated ketones is well known [1,2], there have been several reports in the literature which show that under the same conditions different authors obtained different derivatives [1,3]. The arguments advanced by the authors to support their conclusions seem to be convincing, but the yields of the substances desired are not, in general, high.

There have been some articles concerning the synthesis of ferrocenylsubstituted dihydropyrimidinethiones. Thus, Osman *et al.* [4] reported the synthesis of such derivatives from bisferrocenalcyclopentanone and bisferrocenalcyclohexanone, but the structures of

TABLE 1. Monocylic dihydropyrimidinethiones, their yields, melting points and element analysis data

Compound	R; R^1	Yield (%)	m.p. [a] (°C)	Element analysis found/calcd. (%)		
				C	H	N
IIIa	p-F–C_6H_4–; Fc [b]	95	100	60.72/61.23	4.49/4.38	7.00/7.14
IIIb	Fc; Ph	95	205	64.04/64.17	4.86/4.86	7.26/7.49
IIIc	Ph; Fc	80	96	64.43/64.17	4.38/4.86	7.17/7.49
IIId	p-I–C_6H_4–; Fc	87	[c]	48.02/48.02	3.60/3.43	5.46/5.60
IIIe	2-thienyl–; Fc	95	110	54.76/54.84	4.57/4.25	6.92/7.37
IIIf	Fc; p-Me_2N–C_6H_4–	80	222	63.37/63.30	5.67/5.57	9.83/10.07
IIIg	p-MeO–C_6H_4–; Fc	70	197	62.51/62.37	5.10/5.00	6.22/6.93
IIIh	p-Me–C_6H_4–; Fc	80	222	64.75/64.94	5.39/5.20	6.97/7.22
IIIi	$(CO)_3MnC_5H_4$–; Fc	95	207	53.16/52.82	3.32/3.43	5.72/5.60
IIIj	Fc; p-MeO–C_6H_4–	85	197	62.97/62.37	5.52/5.00	6.69/6.93

[a] Melting points are approximate, compounds melt in open capillary tubes with decay.

[b] Fc = $C_5H_5FeC_5H_4$.

[c] Compound decays before melting.

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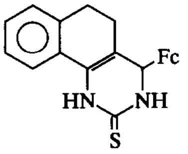
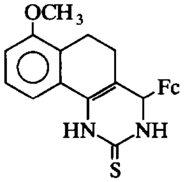
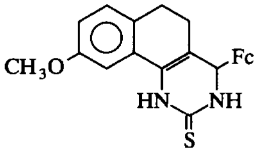
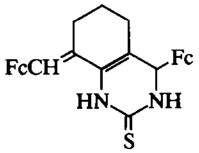
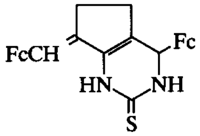
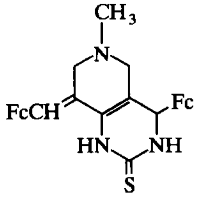
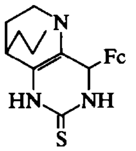
compounds obtained were assigned without sufficient proof. Toma and co-workers [5] succeeded in the synthesis of some monocyclic ferrocenylsubstituted dihydropyrimidinethiones but the products were obtained only in rather low yields by a process involving heating of initial substances in alkaline ethanol and sonication of the reaction mixture.

2. Results and discussion

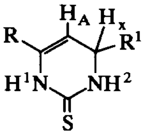
We have investigated the reaction of thiourea with linear (I) and cyclic (II) ferrocenylsubstituted α,β-unsaturated ketones and have shown that both **I** and **II** react with thiourea in alkaline ethanol and give corresponding dihydropyrimidinethiones **III** and **IV** as a

TABLE 2. Bi- and tricyclic dihydropyrimidinethiones, their yields, melting points and element analysis data

Compound	Structure	Yield (%)	M.P. [a] (°C)	Element analysis found/calcd. (%)		
				C	H	N
IVa		95	241	66.30/66.00	5.22/5.05	6.62/7.00
IVb		90	260	64.40/64.18	5.39/5.16	6.69/6.51
IVc		95	236	64.11/64.18	5.41/5.16	6.70/6.51
IVd		75	230	63.66/63.51	5.33/5.16	5.28/5.11
IVe		95	230	62.42/62.93	4.95/4.91	4.91/5.24
IVf		76	230	61.52/61.82	5.19/5.20	7.62/7.46
IVg		65	240	60.55/60.15	5.77/5.59	11.05/11.08

[a] Melting points are approximate; compounds melt in open capillary tubes with decomposition.

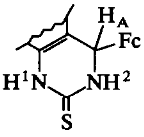
TABLE 3. NMR ^{1}H spectrum data of monocyclic dihydropyrimidinethiones δ(ppm), J (Hz)



Compound	H_A, H_X	H^1, H^2	R	R^1
IIIa [a]	H_A 5.21 $J_{AH^1} = 4.0$	7.33	p-F–C_6H_4–	Fc– 4.23 (5H)
	H_X 4.99 $J_{AH^2} = 2.0$	8.18	7.43 (2H)	4.15–4.25 (4H)
	$J_{AX} = 4.0$ $J_{XH^2} = 2.0$		7.09 (2H)	
IIIb [a]	H_A 5.12 H_X 5.02	6.93	Fc– 4.22 (5H)	Ph– 7.30–7.45 (5H)
		7.47	4.37 (2H); 4.28 (2H)	
IIIe [b]	H_A 5.63 $J_{A1} = 2.4$	8.03	2-thienyl–	Fc– 4.27 (5H)
	H_X 5.00 $J_{A2} = 1.6$	8.78	7.12 (1H); 7.50 (1H)	4.29 (1H); 4.24 (1H)
	$J_{AX} = 4.8$ $J_{X2} = 2.4$		7.57 (1H)	4.20 (1H)
IIIg [c]	H_A 5.54 $J_{A1} = 4.2$	11.15	p-MeO–C_6H_4–	Fc– 4.34 (5H)
	H_X 5.20 $J_{A2} = 1.6$	9.87	3.71 (3H); 7.73 (2H)	4.43 (1H); 4.39 (1H)
	$J_{AX} = 4.4$ $J_{X2} = 2.4$		7.07 (2H)	4.19 (2H)
IIIi [a]	H_A 5.27 $J_{A1} = 4.0$	7.73	$(CO)_3MnC_5H_4$–	Fc– 4.23 (5H)
	H_X 5.20 $J_{A2} = 2.0$	7.22	5.07 (1H); 5.05 (1H)	4.17–4.23 (4H)
	$J_{AX} = 4.0$ $J_{X2} = 1.6$		4.80 (1H); 4.77 (1H)	
IIIj [c]	H_A 5.37 H_X 5.31	10.57	Fc– 4.26 (5H)	p-MeO–C_6H_4– 3.66 (3H)
		9.31	4.81 (2H); 4.32 (2H)	7.51 (2H); 6.98 (2H)

[a] In $CDCl_3$. [b] In acetone-d_6. [c] In pyridine-d_5.

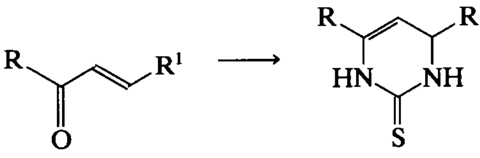
TABLE 4. NMR ^{1}H spectral data of bi- and tricyclic dihydropyrimidinethiones δ (ppm), J (Hz)



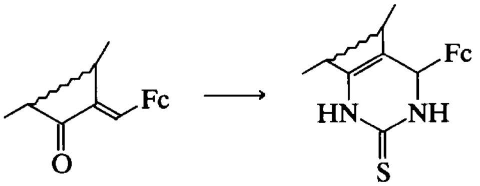
Compound	H_A	H^1, H^2	Fc	remaining molecule signals
IVb [a]	4.37	10.78	4.43 (5H)	3.71 (3H); 2.96 (1H)
	$J_{A2} = 1.6$	9.32	4.10–4.40 (4H)	2.73 (1H); 2.25 (2H)
				7.60–6.92 (3H)
IVc [a]	4.89	11.02	4.43 (5H)	3.59 (3H)
	$J_{A2} = 2.8$	9.30	4.44 (1H)	2.60–2.70 (2H)
			4.37 (1H)	2.23–2.31 (2H)
			4.21 (1H)	7.68–6.68 (3H)
			4.17 (1H)	
IVd [a]	4.74	10.27	4.43 (5H)	2.01 (1H); 2.78 (1H)
		9.19	4.10 (5H)	2.39 (1H); 2.25 (1H)
			4.10–4.45 (8H)	2.02 (1H); 1.61 (1H)
IVe [b]	4.93	7.61	4.20 (5H)	5.88 (1H)
		6.85	4.00 (5H)	2.15–2.80 (4H)
			3.95–4.50 (8H)	
IVf [b]	4.85	10.57	4.44 (5H)	2.37 (3H)
		9.22	4.11 (5H)	3.75; 3.39 (2H) $J = 12.8$
			4.10–4.45 (8H)	3.08; 3.20 (2H) $J = 15.2$
				7.13 (1H)
IVg [a]	4.73	8.54	4.29 (5H)	1.30–3.00 (9H)
	$J_{A2} = 1.9$	6.88	4.10–4.25 (4H)	
	$J_{A1} = 0.4$			

[a] In pyridine-d_5. [b] In $CDCl_3$.

single product with high yields.



I III



II IV

The substances obtained are listed in Tables 1 and 2.

The structures **III** and **IV** have been proved by high resolution NMR spectrum data (Tables 3 and 4). The place of the ferrocenyl substitute in heterocycle is confirmed definitely by the chemical shift values of the α- and β-protons of the substituted cyclopentadienyl ring [6]. All the spin-spin couplings were verified by double homonuclear resonance experiments.

We have also shown the reaction of chalkones with thiourea to be reversible. All the dihydropyrimidinethiones we have obtained are converted into the initial chalkones quantitatively after brief heating in alkaline ethanol with some drops of water. Perhaps that is why the authors of previous publications obtained pyrimidinethiones in only low yields [5].

3. Experimental section

The synthesis of **III** and **IV** was carried out by reflux of an ethanolic solution of corresponding α,β-unsaturated ketones with an excess of thiourea in the presence of sodium ethoxide. The completion of the reaction was checked by TLC. Substances were isolated and purified by crystallisation as yellow or orange crystals (in this connection, see ref. 4).

NMR spectra were recorded on a VXR-400 spectrometer with TMS as internal standard.

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