ADDITION OF C- AND S-NUCLEOPHILES TO ACRYLOYLFERROCENE AND CINNAMOYLFERROCENE CATALYSED BY KF/Al_2O_3

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Michael addition of a series of C- and S-nucleophiles to acryloyl- and cinnamoylferrocene catalysed by KF/Al_2O_3 has been studied. In general, the reaction proceeded quantitatively and in shorter reaction time compared to the common procedure. The synthesis of acryloylferrocene has been improved.

Recently, much attention has been paid to organic reactions that take place on inorganic supports or with the use of catalysts immobilized on these supports[1-5]. In two cases[6,7], KF/Al_2O_3 has been applied as the catalyst for Michael addition. Jamawaki and coworkers[6] reported on the addition of nitromethane to chalcone and Clark[7] studied the addition of nitromethane to methyl vinyl ketone. Until now, however, Michael addition to ferrocenyl derivatives of α,β-unsaturated ketones has attracted little attention. Tirouflet[8] performed the addition of some C-nucleophiles to cinnamoylferrocene in boiling methanol, using sodium methoxide as the catalyst. However, the products were obtained in only low yields (5—30%). In our previous work[9] we described optimal conditions for the addition of some C-nucleophiles to cinnamoylferrocene, *p*-chlorocinnamoylferrocene and 1-phenyl-3-ferrocenyl-2-propanone.

In the present work we were interested in the Michael addition of various nucleophiles to acryloyl- and cinnamoylferrocene catalysed by KF/Al_2O_3. In order to ascertain the efficiency of this catalytic system, the above ferrocenyl derivatives were chosen because of their lower reactivity compared to benzene analogues, i.e. acryloylbenzene or chalcone, which results from the high electron-donating ability of the ferrocenyl group. It was found that the addition of ethyl α-cyanobutyrate to cinnamoylferrocene proceeds[10] at 25°C with the rate constant $k = 3{\cdot}1 \cdot 10^{-3}$ min^{-1} while that to chalcone with $k = 27{\cdot}9 \cdot 10^{-3}$ min^{-1}. The C- and S-nucleophiles used in this study are summarized in Tables I and II. Attempts at adding phenol and aniline have not been successful.

As seen from Table I, the addition of all the nucleophiles proceeds easily, giving products in high yields. Furthermore, the products are obtained pure by only one crystallization. The only exception is the lower reactivity of 2-mercaptobenzothiazole; the high yields of the products were obtained in this case only with one molar excess of the reagent and after substantially longer reaction times.

TABLE I

Elemental analysis of compounds of the type Fc—CO—CH_2—CH_2—X

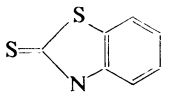
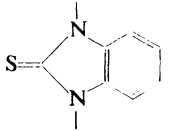
No	X	Formula	Mol. weight	Analysis % H calcld. found	% C calcld. found	% Fe calcld. found	% N calcld. found	Yield %	Reaction time Reaction temp.	M.p., °C Solvent for crystallization
1	S—C_6H_5	$C_{18}H_{18}FeS$	350·26	5·19 5·28	65·14 65·11	15·94 16·05	—	98	5 min 20°C	75—77 ether–petroleum ether
2	S—CH_2—$COOC_2H_5$	$C_{16}H_{20}FeO_2S$	360·25	5·55 5·64	56·67 56·76	15·50 15·90	—	96	5 min 20°C	48·5—50 petroleum ether
3	S—CH_2—COOH	$C_{14}H_{16}FeO_2S$	332·20	4·86 4·85	54·23 54·27	16·81 16·85	—	97	90 min 60°C	94—97 acetone–petroleum ether
4	—$CH(COOC_2H_5)_2$	$C_{19}H_{24}FeO_4$	400·25	6·05 6·17	60·01 60·22	13·95 13·95	—	96	30 min 20°C	49—52 ethanol–water
5	—$C(COOC_2H_5)_2$ | NHCHO	$C_{20}H_{25}FeO_5N$	443·28	5·70 5·62	56·89 56·63	12·60 12·36	3·16 3·10	98	30 min 20°C	99—100·5 acetone–petroleum ether
6		$C_{19}H_{17}FeNS_2$	407·33	4·20 4·22	58·82 58·80	13·67 13·65	3·43 3·38	96	240 min 60°C	153—156 dichloromethane–petroleum ether
7		$C_{31}H_{30}FeN_2S$		4·31 4·91	62·87 62·50	17·72 17·70	4·44 3·94	94	60 min 60°C	169—173 dichloromethane–petroleum ether
8	—S—CH_2CH_2OH	$C_{14}H_{17}FeOS$	318·21	5·69 5·80	56·43 57·49	17·49 17·17	—	97	5 min 20°C	dark red oil

TABLE II

^{1}H NMR spectrum of compounds of the type Fc—CO—CH_2—CH_2—X

No	C_5H_5	H_α	H_β	$COCH_2$	CH_2—X	Others
1	4·13 (5 H; s)	4·71 (2 H, m)	4·45 (2 H; m)	3·16 (4 H; m)	3·16 (4 H; m)	7·31 (5 H; m) (SC_6H_5)
2	4·30 (7 H; m)	4·85 (2 H; m)	4·58 (2 H; m)	3·01 (4 H; m)	3·01 (4 H; m)	1·28 (CH_3—CH_2—O; 3 H; t) 4·30 (CH_3CH_2—O; 7 H; m) 3·28 (CH_2—S; 2 H; s)
3	4·20 (5 H; s)	4·75 (2 H; m)	4·48 (2 H; m)	2·99 (4 H; m)	2·99 (4 H; m)	3·25 (CH_2—S; 2 H; s)
4	4·20 (9 H; m)	4·78 (2 H; m)	4·50 (2 H; m)	2·83 (2 H; t)	2·30 (2 H; m)	1·27 (CH_3—CH_2—O; 6 H; t) 4·20 (CH_3—CH_2—O; 9 H; m) 3·53 ($HC(COOC_2H_5)$; 1 H; t)
5	4·20 (9 H; m)	4·76 (2 H; m)	4·48 (2 H; m)	2·74 (4 H; m)	2·74 (4 H; m)	1·27 (CH_3—CH_2—O; 6 H; t) 4·20 (CH_3—CH_2—O; 9 H; m) 7·14 (NH; 1 H; s) 8·30 (CHO; 1 H; s)
6	4·17 (5 H; s)	4·80 (4 H; m)	4·52 (2 H; m)	3·30 (2 H; t)	4·80 (4 H; m)	7·40 (C_6H_4; 4 H; m)
7	4·10 (10 H; s)	4·76 (8 H; m)	4·54 (4 H; m)	3·38 (4 H; m)	4·76 (8 H; m)	7·35 (C_6H_4; 4 H; m)
8	4·20 (7 H; m)	4·80 (2 H; m)	4·50 (2 H; m)	2·70 (4 H; m)	2·70 (4 H; m)	4·20 (CH_2—O; 7 H; m) 3·79 (CH_2—S; 2 H; t) 2·95 (OH; 1 H; t)

Results in Table III demonstrate the lower reactivity of cinnamoylferrocene, which led in most cases to prolongation of reaction times and in the case of thioglycolic acid, ethyl malonate and ethyl acetoacetate also to the use of one molar excess of the reagent. Even under such conditions, the addition of 2-mercaptobenzothiazole did not take place.

From the viewpoint of comparison of our results with those reported earlier[9], the addition of ethyl malonate and of ethyl acetoacetate is of interest. Under generally used conditions[9], the addition of ethyl malonate – using the reaction components in 1 : 1·5 mol ratio – yields the mono- and bis-adduct in 1 : 1 mol ratio. The selectivity of the reaction can be increased only by using ethyl malonate in four-molar excess. (The reaction is effected in dry ether in the presence of sodium methoxide as the catalyst.) The addition catalysed by KF/Al_2O_3 gives the mono-adduct selectively and in much shorter reaction time (4 h *vs* 2 days). The addition of ethyl acetoacetate to cinnamoylferrocene is accompanied[9] by consecutive aldolization or Claisen–Schmidt condensation to give cyclohexanone derivatives. With KF/Al_2O_3 catalyst, the only product is that of the intramolecular Claisen–Schmidt reaction, *i.e.* 3-ferrocenyl-6-ethoxycarbonyl-2-cyclohexanone, which was obtained in 66% yield. The structure of this product was confirmed by ^{1}H NMR spectrum: 1·03 ($\mathbf{CH_3}$—CH_2—O, t, 3 H); 2·95 (CH_2, d, 2 H); 3·75 (CH—Ph, m, 1 H); 4·15 (C_5H_5 + + CH_3—$\mathbf{CH_2}$—O + CH—COOR, m, 8 H); 4·52 (C_5H_4, b.s., 4 H); 6·35 (=CH—, s, 1 H), and 7·35 (C_6H_5, m, 5 H). The most characteristic of this structure is a broad multiplet of hydrogens of the cyclopentadienyl ring. If the product of the 1 : 1 addition of ethyl acetoacetate were formed, the spectrum would have shown well separated chemical shifts of H^α and H^β atoms. In the case of the simple aldolization product, the chemical shift of hydrogens of both cyclopentadienyl rings would have occurred as one sharp singlet. The aldol structure is excluded also by the absence of OH vibrations in the IR spectrum of the product.

For purposes of comparison, we made an attempt at the addition of thioglycolic acid to cinnamoylferrocene catalysed by both sodium methoxide and KF/Al_2O_3 in acetonitrile, using room temperature and 60°C. We have found that at room temperature sodium methoxide is a somewhat more efficient catalyst, although the reaction gave the product only in low yields (13–17%). On the other hand, at 60°C KF/Al_2O_3 is the better catalyst (63% yield *vs* 30% obtained with sodium methoxide). The additional advantage of KF/Al_2O_3 is that the same yields are obtained also when the not dried acetonitrile is used as the solvent.

The results discussed above demonstrate that KF/Al_2O_3 is the excellent catalyst for Michael addition. The products are obtained in high yields and in short reaction times, the reaction proceeds in most cases with the higher selectivity and the work up of the reaction mixture and the isolation of products is in general very simple.

TABLE III

Elemental analysis of compounds of the type Fc—CO—CH_2—CHX—Ph

No	X	Formula	Mol. weight	Analysis: % H calcld. found	Analysis: % C calcld. found	Analysis: % Fe calcld. found	Yield %	Reaction time Reaction temp.	M.p., °C Solvent for crystallization
9	—S—C_6H_5	$C_{24}H_{22}FeS$	426·36	5·20 5·26	70·27 70·01	13·07 12·78	97	5 min 20°C	124·5—126 benzene–ether
10	—S—$CH_2COOC_2H_5$	$C_{22}H_{24}FeO_2S$	436·35	5·54 5·59	63·17 62·89	12·77 12·58	96	5 min 20°C	97—99 ether
11	—S—CH_2COOH	$C_{20}H_{20}FeO_2S$	408·29	4·94 4·94	61·63 61·50	13·65 13·40	67	240 min 60°C	140—142 acetone–petroleum ether
12	—$CH(COOC_2H_5)_2$	$C_{25}H_{28}FeO_4$	476·35	5·93 6·01	65·42 65·18	11·70 11·89	89	240 min 60°C	114—116 ether–acetone
13	—$C(COOC_2H_5)_2$ | NHCHO	$C_{26}H_{29}FeO_5N$[a]	519·38	5·64 5·71	62·44 62·73	10·76 10·54	32	240 min 60°C	130—131·5 acetone–petroleum ether
14	—$CHCOOC_2H_5$ | $COCH_3$	$C_{25}H_{24}FeO_3$	428·32	5·65 5·63	70·10 70·06	13·04 13·05	66	240 min 60°C	135—138[b] ethanol–water

[a] Calculated 2·70% N, found 2·41% N; [b] ref.[9] records 143°C.

EXPERIMENTAL

Compounds Used and Procedure

Starting compounds, *i.e.* cinnamoylferrocene and 3-chloropropionylferrocene were prepared by reported procedures[9,11,12]. The catalyst, KF/Al_2O_3, was obtained as reported[6]. Acetonitrile, used as the solvent, was not dried or further purified. Melting points of the compounds were determined on a Kofler hot plate and were not corrected. ^1H NMR spectra were measured on Tesla BS 487 instrument working at 80 MHz, using solutions of the compounds in C^2HCl_3 (99% of ^2H isotope). Tetramethylsilane was used as internal reference.

Synthesis of Acryloylferrocene

A mixture of 0·28 g (1 mmol) of 3-chloropropionylferrocene, 0·5 g of KF/Al_2O_3 and 10 ml of acetonitrile was placed in a 100 ml flask. The mixture was stirred at room temperature for 2 h and then at 60°C for another 2 h. The reaction course was followed by TLC. After filtration of the catalyst followed by its washing with acetonitrile (2 × 5 ml), the acetonitrile solutions were combined and the solvent was evaporated, giving 0·23 g (97%) of acryloylferrocene, m.p. 71—74°C. Ref.[10] gives 71—72°C.

Michael Addition to Acryloylferrocene

The reactions were carried out analogously to the synthesis of acryloylferrocene. When the reaction did not proceed quantitatively (as indicated by TLC), an additional amount of the reagents (1·1 mmol) was added to the reaction mixture after 2 h (designated by[b] in Table III). After completion of the reaction and usual work up, the solvent was evaporated and the residue was chromatographed on SiO_2 or Al_2O_3. The results are presented in Table III and ^1H NMR spectra of the compounds obtained are given in Table IV.

Comparative Experiments Concerning the Addition of Thioglycolic Acid to Cinnamoylferrocene

Catalysis by KF/Al_2O_3 *at room temperature.* A 100 ml round-bottom flask was charged with 0·32 g (1 mmol) of cinnamoylferrocene dissolved in 10 ml of acetonitrile, 0·1 g (1·1 mmol) of thioglycolic acid and 0·5 g of KF/Al_2O_3. The reaction mixture was stirred at room temperature for 2 h. Then, 0·1 g (1·1 mmol) of thioglycolic acid was added and the stirring was continued for another 2 h. The catalyst was filtered off and washed with acetonitrile. The solvent was evaporated in vacuo, the residue was dissolved in dichloromethane and the product was extracted with 10% $NaHCO_3$. After evaporation of dichloromethane, 0·25 g (80%) of the starting cinnamoylferrocene was obtained. The sodium hydrogen carbonate solution was acidified with 10% HCl and the product was extracted with dichloromethane. After solvent evaporation, 0·05 g (12·5%) of the adduct was obtained; m.p. 140—142°C.

Catalysis by KF/Al_2O_3 *at* 60°C. The reaction was carried out using the same weight amounts of the reactants as in the previous case, except that the reaction temperature was 60°C. The reaction afforded 0·1 g (38%) of cinnamoylferrocene and 0·24 g (60%) of the adduct.

Catalysis by CH_3ONa *at room temperature.* A 100 ml round-bottom flask was charged with the sodium methoxide obtained from 0·08 g (3·4 mmol) of Na and 0·13 ml of methanol. Then, 0·32 g (1 mmol) of cinnamoylferrocene and 0·1 g (1·1 mmol) of thioglycolic acid were added. The reaction mixture was stirred at room temperature for 2 h, then 0·1 g (1·1 mmol) of thioglycolic acid was added, and the stirring was continued for another 2 h. The solvent was evaporated and

TABLE IV

^{1}H NMR spectra of compounds of the type Fc—CO—CH_2CHX—Ph

No	C_5H_5	H_α	H_β	CO—CH_2	CH—X	C_6H_5	Others
9	3·96 (5 H; s)	4·68 (2 H; m)	4·43 (2 H; m)	3·30 (2 H; d)	5·00 (1 H; t)	7·25 (10 H; m)	
10	4·03 (7 H; m)	4·75 (3 H; m)	4·48 (2 H; m)	3·25 (2 H; d)	4·75 (3 H; m)	7·30 (5 H; m)	4·03 (7 H; m; O**C**H_2—CH_3) 3·05 (2 H; s; S—**C**H_2) 1·22 (**C**H_3—CH_2; 3 H, t)
11	3·97 (5 H; s)	4·70 (3 H; m)	4·43 (2 H; m)	3·28 (2 H; d)	4·70 (3 H; m)	7·25 (5 H; m)	2·96 (S—**C**H_2; 2 H; s)
12	3·95 (10 H; m)	4·70 (3 H; m)	4·42 (2 H; m)	3·20 (2 H; d)	4·70 (3 H; m)	7·30 (5 H; m)	1·10 (**C**H_3—CH_2—O; 6 H; t) 3·95 (CH_3—**C**H_2—O; 10 H; m) 3·95 (HC—($COOC_2H_5$)$_2$; 10 H, m)
13	4·08 (9 H; m)	4·68 (3 H; m)	4·48 (2 H; m)	3·29 (2 H; d)	4·68 (3 H; m)	7·30 (5 H; m)	1·27 (**C**H_3—CH_2—O; 6 H; t) 4·08 (CH_3—**C**H_2—O; 9 H; m) 7·14 (NH; 1 H; s) 8·27 (CHO; 1 H; s)

the product was extracted with 10% $NaHCO_3$. The evaporation of the dichloromethane solution yielded 0·23 g (75%) of the starting cinnamoylferrocene. The sodium hydrogen carbonate solution was acidified with 10% HCl and the product was extracted with dichloromethane. Solvent evaporation afforded 0·07 g (17·5%) of the addition product.

Catalysis by CH_3ONa *at* 60°C. The reaction was performed as described above, except that the reaction temperature was 60°C. A total of 0·2 g (65%) of cinnamoylferrocene and 0·12 g (30%) of the addition product were obtained.

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