

Knoevenagel Condensation of Ferrocenecarbaldehyde with Some Methylene Active Reagents on Inorganic Supports

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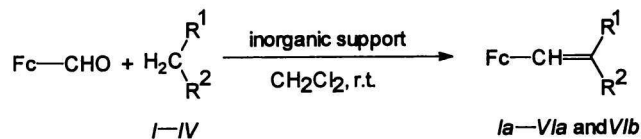
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Condensation of ferrocenecarbaldehyde with 1,3-indandione, malondinitrile, barbituric acid, thiohydantoin, 3-amino- and 3-ethylrhodanine on the inorganic supports has been studied. The conditions leading to a very good yield (> 80 %) have been found. The prepared solvatochromic effect on the UV VIS spectra of the products was observed, and their NLO properties are under study.

Inorganic supports have found a great application in organic synthesis due to the facts that many reactions can be carried out at very mild (r.t.) conditions either with a small amount of the solvent, or without any solvent [1–5] and with very simple products isolation. The most frequently used inorganic supports are Al_2O_3 , $\text{KF}/\text{Al}_2\text{O}_3$, SiO_2 or bentonite. Knoevenagel condensation of aldehydes and ketones with methyl cyanoacetate on Al_2O_3 was described some time ago [6]. Condensations of some *o*-benzyloxybenzaldehydes leading to benzofuran derivatives or condensation of phthalides with azines leading to isoquinoline derivatives on $\text{MX}/\text{Al}_2\text{O}_3$ were described [7]. The condensation of malondinitrile with some 1,1-dioxothio-4-pyranones on Al_2O_3 was also described [8]. No condensation using SiO_2 as the support was reported. The inorganic support was used very seldom [9, 10] at the reactions of ferrocenecarbaldehyde ($\text{Fc}-\text{CHO}$), in spite of the fact that there are many papers devoted to its condensation. The condensation of $\text{Fc}-\text{CHO}$ with *N*-methylrhodanine on $\text{KF}/\text{Al}_2\text{O}_3$ in microwave oven was recently described [11].

Condensation of ferrocenecarbaldehyde with the following methylene active compounds was studied: 1,3-indandione (*I*), malondinitrile (*II*), barbituric acid (*III*), thiohydantoin (*IV*), 3-ethylrhodanine (*V*), and 3-aminorhodanine (*VI*). Al_2O_3 , $\text{KF}/\text{Al}_2\text{O}_3$, $\text{KOH}/\text{Al}_2\text{O}_3$, SiO_2 , and KOH/SiO_2 were tested as inorganic supports (Scheme 1). Reactions have been carried out in the minimum amount of CH_2Cl_2 as the solvent. Just 0.5–1 cm^3 of the solvent was used for 0.5 mmol of the reactants, and 0.5 g of the inorganic support. The reaction products were purified by chromatography on SiO_2 column, and the yields of isolated products are given in Table 1.

From the results given in Table 1 it follows that









Scheme 1

the condensation with 1,3-indandione (*I*), with the exception of SiO_2 , was very fast and high yields of the product *Ia* were isolated. Small differences of the yields were caused just by the experimental error at the isolation. It should be pointed out that the classical condensation (ethanol/piperidine) resulted [10] in 43 % yields only. The reaction of malondinitrile (*II*) with ferrocenecarbaldehyde was even faster (2–4 min) and practically quantitative yields of the product *IIa* were isolated. Cooke *et al.* [10] described similar results, using Al_2O_3 without solvent at 65 °C.

Barbituric acid (*III*) and thiohydantoin (*IV*) behaved quite differently at the reaction with ferrocenecarbaldehyde. No reaction was observed when basic supports as $\text{KF}/\text{Al}_2\text{O}_3$, $\text{KOH}/\text{Al}_2\text{O}_3$ or KOH/SiO_2 were used. This could be expected as there is an acidic NH group in both *III* and *IV*, which was deprotonized by basic supports, and resulted in much less reactive intermediate. Reasonable yields of the products *IIIa* (95 % or 50 %) were achieved on neutral or slightly acidic support (Al_2O_3 or SiO_2). Condensation of thiohydantoin resulted in the formation of unseparable mixture of both *E* and *Z* isomers of *IVa* as could be proved by observing two singlets of the $-\text{CH}=\text{C}-$ group at $\delta = 6.41$ and 6.38. Condensation of barbituric acid with ferrocenecarbaldehyde was described in glacial acetic acid (95 °C), potassium acetate being the catalyst [13], and 80 % yield of the product was

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Table 1. Results of Knoevenagel Condensation of Ferrocenecarbaldehyde with Methylene Active Compounds

Reagent	Inorganic support yield/%(time)				
	Al ₂ O ₃	KF/Al ₂ O ₃	KOH/Al ₂ O ₃	SiO ₂	KOH/SiO ₂
I 	85 (10 min)	75 (20 min)	70 (60 min)	72 (20 min)	93 (20 min)
II 	98 (2 min)	92 (2 min)	90 (2 min)	98 (24 min)	93 (3 min)
III 	92 (48 h)	0	0	95 (48 h)	0
IV 	20 (90 h ^a)	0	0	10 (90 h)	0
V 	83 (20 h)	80 (10 h)	71 (24 h)	41 (84 h)	57 (40 h)
VI 	50 (5 h ^b)	70 (24 h ^b)	50 (48 h ^b)	5 (48 h ^b)	80 (24 h ^b)

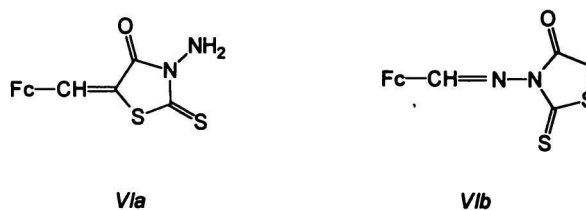
a) 50 % of the product was isolated when DMSO was used instead of CH₂Cl₂.

b) The yields of the isomers mixture are given.

isolated. Condensation product of thiohydantoin with ferrocenecarbaldehyde was described [9] as the result of condensation of 3-acetylhydantoin with Fc—CHO on Al₂O₃ (72 h, 95 %).

Condensation of 3-ethylrhodanine (V) with ferrocenecarbaldehyde was going on rather slowly (reaction times 10—40 h), but reasonable yields of well characterized product *Va* were isolated. 3-Aminorhodanine (VI) behaved quite differently. The condensation was slow and the worst results were achieved on SiO₂. TLC revealed the presence of two products which were difficult to separate. There was evidence that one of the isomers was converting to the second one even at chromatography on SiO₂ column. The first isomer — condensation product on the methylene active group *VIa* was isolated by repetition of flash chromatography on SiO₂ using isohexane—ethyl acetate ($\varphi_r = 5:1$) as the eluent. The second isomer — condensation product on the —NH₂ group *VIb* was prepared on Al₂O₃ by prolonging the reaction time to 30 h (Formula 1).

Isomers *VIa* and *VIb* were distinguished by the H/D exchange of —NH₂ protons by D₂O. The great



Formula 1

solvatochromic effect in the UV VIS spectra of the product was observed, which means that the products can have NLO properties, as described for some 1-ferrocenyl-2-arylethylenes [14]. The NLO properties of the products are therefore under investigation.

From the above-mentioned results it follows that all condensations of ferrocenecarbaldehyde with methylene active compounds on inorganic supports were going well. There was no impressive effect of the quality of inorganic support observed, and therefore the cheapest Al₂O₃ can be recommended for all similar reactions.

EXPERIMENTAL

All reagents were used as purchased from Aldrich, melting points were measured on a Kofler instrument. ^1H NMR spectra were measured on a Tesla 587 80 MHz instrument as the solution in $^2\text{HCCl}_3$ if not indicated otherwise, tetramethylsilane was used as the internal standard.

Preparation of the Supports

KF/ Al_2O_3 was prepared by dissolving 20 g of KF in 100 cm^3 of H_2O , and pouring this solution onto 20 g of Al_2O_3 . Water was evaporated on rotatory vacuum evaporator, and the residue was dried at 100°C and 2 kPa for 6 h. KOH/ Al_2O_3 was prepared in the same manner, just dissolving 5 g of KOH in 50 cm^3 of H_2O , and 20 g Al_2O_3 was added. KOH/ SiO_2 was prepared similarly by dissolving 5 g of KOH in 100 cm^3 of H_2O , and 20 g of SiO_2 was added.

All inorganic supports were activated in microwave oven (2 min, high power) just before the reaction.

Knoevenagel Condensation of Ferrocenecarbaldehyde with Methylene Active Compounds

Reagent with an active methylene group (0.5 mmol) was dissolved in $0.5\text{--}1\text{ cm}^3$ of dry dichloromethane, and 0.5 mmol of ferrocenecarbaldehyde was then added to this solution. Inorganic support (0.5 g) was then added in one portion and the reaction mixture was left to stand at room temperature. The course of the reaction was checked by TLC. When the reaction was over, the mixture which was a thick suspension, was transferred on SiO_2 ($100\text{--}160\ \mu\text{m}$) column, and the product was separated by chromatography using isohexane—ethyl acetate mixture ($\varphi_{\text{r}} = 5:1\text{--}3:1$) as the eluent.

2-Ferrocenylmethylene-1,3-indandione *Ia*: blue crystals, m.p. = $167\text{--}170^\circ\text{C}$, Ref. [10] gives m.p. = $167\text{--}168^\circ\text{C}$. For $\text{C}_{20}\text{H}_{14}\text{FeO}_2$ ($M_{\text{r}} = 342.18$) w_{i} (calc.): 70.20 % C, 4.21 % H, 16.32 % Fe; w_{i} (found): 69.05 % C, 4.21 % H, 16.39 % Fe. ^1H NMR spectrum, δ : 4.22 (s, 5H, C_5H_5), 4.84 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\beta}$), 5.43 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\alpha}$), 7.87 (m, 5H, $\text{C}_6\text{H}_4\text{—CH=}$).

Ferrocenylmethylenemalondinitrile *IIa*: deep violet crystals, m.p. = $96\text{--}97^\circ\text{C}$, Ref. [15] gives m.p. = $100\text{--}101^\circ\text{C}$. For $\text{C}_{14}\text{H}_{10}\text{FeN}_2$ ($M_{\text{r}} = 262.09$) w_{i} (calc.): 62.20 % C, 3.85 % H, 10.69 % N; w_{i} (found): 63.66 % C, 3.82 % H, 10.81 % N. ^1H NMR spectrum, δ : 4.32 (s, 5H, C_5H_5), 4.81 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\beta}$), 5.10 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\alpha}$), 7.71 (s, 1H, —CH=).

5-Ferrocenylmethylenobarbituric acid *IIIa*: deep violet crystals, m.p. $> 360^\circ\text{C}$, decomp. (see also [12]). For $\text{C}_{15}\text{H}_{12}\text{FeO}_3\text{N}_2$ ($M_{\text{r}} = 324.12$) w_{i} (calc.): 55.55 % C, 3.73 % H, 8.64 % N; w_{i} (found): 55.50 % C, 3.63 % H, 8.22 % N. ^1H NMR spectrum (DMSO- d_6), δ : 4.29 (s, 5H, C_5H_5), 4.93 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\beta}$), 5.36 (t, 2H,

$\text{C}_{\text{p}},\text{H}_{\alpha}$), 8.18 (s, 1H, —CH=), 10.58 (bs, 2H, N—H) (exchangeable with D_2O).

5-Ferrocenylmethylenethiohydantoin *IVa*: red crystals, m.p. = $182\text{--}184^\circ\text{C}$. For $\text{C}_{14}\text{H}_{12}\text{FeON}_2\text{S}$ ($M_{\text{r}} = 312.17$) w_{i} (calc.): 53.86 % C, 3.87 % H, 9.01 % N; w_{i} (found): 53.41 % C, 4.06 % H, 8.81 % N. ^1H NMR spectrum (DMSO- d_6), δ : 4.19 (s, 5H, C_5H_5), 4.53 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\beta}$), 4.99 (t, 2H, $\text{C}_{\text{p}},\text{H}_{\alpha}$), 5.00 (t, 1H, $\text{C}_{\text{p}},\text{H}_{\alpha}$), 6.38 (s, 1H, —CH=), 6.41 (s, 1H, —CH=) (mixture of *E* and *Z* isomers), 11.87 (bs, 2H, N—H) (exchangeable with D_2O).

3-Ethyl-5-ferrocenylmethylenerrhodanine *Va*: deep red crystals, m.p. = $188\text{--}190^\circ\text{C}$. For $\text{C}_{16}\text{H}_{15}\text{FeONS}_2$ ($M_{\text{r}} = 357.29$) w_{i} (calc.): 53.79 % C, 4.23 % H, 3.92 % N; w_{i} (found): 53.65 % C, 4.19 % H, 3.78 % N. ^1H NMR spectrum, δ : 1.28 (t, 3H, CH_3), 4.14 (q, 2H, CH_2), 4.20 (s, 5H, C_5H_5), 4.59 (s, 4H, C_5H_4), 7.63 (s, 1H, —CH=).

3-Amino-5-ferrocenylmethylenerrhodanine *VIa*: deep red crystals, m.p. $> 200^\circ\text{C}$, decomp. For $\text{C}_{13}\text{H}_{12}\text{FeON}_2\text{S}_2$ ($M_{\text{r}} = 344.24$) w_{i} (calc.): 48.85 % C, 3.81 % H, 8.17 % N; w_{i} (found): 48.22 % C, 3.83 % H, 7.83 % N. ^1H NMR spectrum, δ : 4.23 (s, 5H, C_5H_5), 4.65 (t, 4H, C_5H_4), 5.32 (s, 2H, NH_2) (exchangeable with D_2O), 7.75 (s, 1H, —CH=).

3-Ferrocenylmethyleniminorhodanine *VIb*: violet crystals isolated in 83 % yield after prolongation of the reaction time on Al_2O_3 to 30 h, m.p. $> 200^\circ\text{C}$. For $\text{C}_{13}\text{H}_{12}\text{FeON}_2\text{S}_2$ ($M_{\text{r}} = 344.24$) w_{i} (calc.): 48.85 % C, 3.81 % H, 8.17 % N; w_{i} (found): 47.78 % C, 3.42 % H, 7.85 % N. ^1H NMR spectrum, δ : 1.26 (s, 2H, CH_2), 4.23 (s, 5H, C_5H_5), 4.65 (t, 4H, C_5H_4), 7.75 (s, 1H, —CH=).

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