Acylation of Meldrum´s acid with arylacetic acid imidazolides as a convenient method for the synthesis of 4-aryl-3-oxobutanoates

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C-Acylation of Meldrum´s acid by (het)arylacetic acids in ethanol in the presence of 1,1'-carbonyldiimidazole leads to ethyl 4-(het)aryl-3-oxobutanoates in high yields.

Key words: β-keto esters, Meldrum´s acid, imidazolides, arylacetic acids.

β-Keto esters are widely used for the preparation of various heterocyclic systems, particularly coumarins,[1,2] dihydropyridines,[3] pyrazolones,[4] quinolines,[5,6] dihydropyrimidines,[7,8] *etc*. Furthermore, they are starting compounds in the synthesis of β-amino acid derivatives,[9,10] cyclohexenones[11,12] and other practically useful compounds.

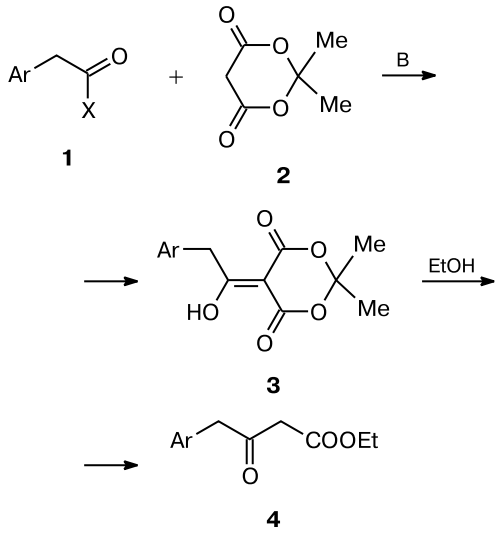
Among numerous approaches to the preparation of β-keto esters,[13] those based on acylation of monoethyl malonate[14] and Meldrum's acid are the most convenient and efficient.[15,16] The latter allows one to prepare keto esters with different ester groups and amides of appropriate β-keto acids[17] without recourse to organometallic reagents (the Grignard reagents, *n*-butyllithium) and low temperatures, which stimulated us to investigate this reaction in more detail to prepare 4-aryl-3-oxobutanoates, the members of an important class of 1,3-dicarbonyl compounds.

The classical method for the preparation of keto esters by this way involves the acylation of Meldrum's acid with the acid chloride—pyridine system[15,18] followed by the reaction of the acylation product **3** with a primary alcohol (Scheme 1).

However, in our experiments with arylacetyl chlorides, keto esters **4a,b** were obtained in 30—40% yields, and the main products according to ^{1}H NMR were the corresponding arylacetates. In the case of 2,5-dimethylthiophen-3-ylacetic acid, under these conditions its esterification takes place mainly (Table 1, method A). The best results were obtained by replacing pyridine by *N,N*-dimethylaminopyridine (DMAP),[19,20] but in this case, too, attempts to exclude completely the formation of by-products failed (see Table 1, method B).

The arylacetic acid—dicyclohexylcarbodiimide (DCC) system[21] as the acylation agent led to moderate yields of keto esters. Furthermore, we observed the formation of large amount of by-products (see Table 1, method C).

Scheme 1



B is base

The results obtained provide evidence that acylation of Meldrum's acid with arylacetic acid derivatives considerably differs from similar reactions of aliphatic and aro-

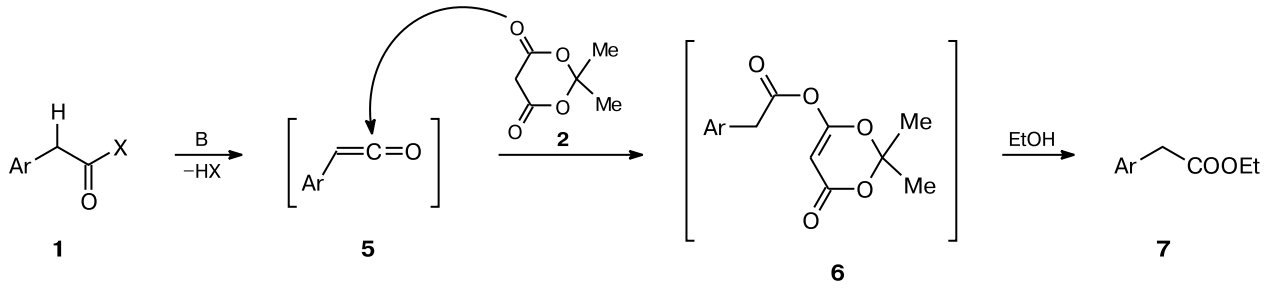
Table 1. The yields of keto esters **4** under differrent conditions*

4	Ar	A	B	C	D
a	Phenyl	41	66	17	78
b	1-Naphtyl	28	72	40	83
c	2-Dimethylthiophen-3-yl	3**	60	41	81

* Conditions of acylation of Meldrum's acid: A, $ArCH_2COCl$, Py; B, $ArCH_2COCl$, DMAP; C, $ArCH_2COOH$, DCC; D, $ArCH_2COOH$, *N,N´*-carbonyldiimidazole (CDI).
** Ethyl 2,5-dimethylthiophen-3-ylacetate was the major product (75%).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 134—136, January, 2011.

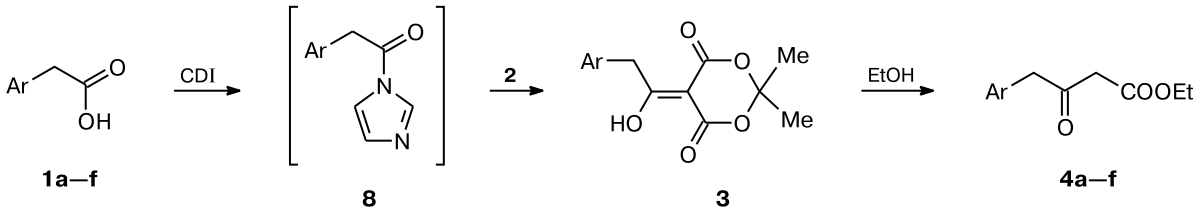
Scheme 2



1 **5** **6** **7**

B is base

Scheme 3



1a—f **8** **3** **4a—f**

Ar = Ph (**a**), 1-naphtyl (**b**), 2,5-dimethylthiophen-3-yl (**c**), 3-$MeOC_6H_4$ (**d**), 4-$MeOC_6H_4$ (**e**), 2-methyl-1-benzothiophen-3-yl (**f**)

matic carboxylic acids. Apparently, under these reaction conditions they can convert to ketenes **5,** due to the presence of active methylene group.[22] Ketenes acylate Meldrum's acid at the oxygen atom, which results in arylacetates **7** (Scheme 2).

We assumed that the use of milder acylation agents, particularly imidazolides **8**,[23] which could be produced *in situ* by reaction of carboxylic acids with *N*,*N*´-carbonyldiimidazole (CDI), will promote C-acylation of Meldrum´s acid. In this case, in the course of reaction, imidazole, the soft base, is released (Scheme 3).

In fact, when carrying out the acylation in the presence of CDI, the yields of keto esters **4a—c** increased to 78—83% (see Table 1, method D). In this case, in the second step of the process one can use 96% alcohol in place of anhydrous ethanol. By similar method, we obtained keto esters **4d—f** in 60—78% yields.

Thus, we developed a convenient method for the preparation of 4-aryl-3-oxobutanoates based on the acylation reaction of Meldrum's acid by the arylacetic acid—CDI system, which is characterized by high yields and selectivity.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer. Mass spectra were acquired using the Kratos instrument (direct inlet probe, ionizing energy 70 eV). High resolution mass spectra were recorded on a Bruker maXis spectrometer. Melting points were measured on a Boetius hot stage and are uncorrected. The course of the reaction was monitored by TLC on silica gel 60 F_{254} Merck. Column chromatography was carried out on silica gel 0.060—0.200 Merck. Arylacetic acid **1c** was obtained by Wilgerodt—Kindler's reaction from 3-acetyl-2,5-dimethylthiophene,[24] and acid **1f** was prepared by reduction of ethyl 2-(2-methylbenzothiophen-3-yl)-2-oxoacetate with triethylsilane.[25]

Preparation of keto esters 4 (general procedure). ***A.*** To a suspension of acid **1** (12 mmol) in dry CH_2Cl_2 (20 mL), thionyl chloride (2.0 mL, 27 mmol) and two drops of DMF were added. The mixture was refluxed for 3 h and concentrated *in vacuo*. The resulting acid chloride was dissolved in dry CH_2Cl_2 (20 mL) and added to a cooled to 0 °C suspension of Meldrum's acid (2.0 g, 14 mmol) and pyridine (2.0 mL, 14 mmol) in dry CH_2Cl_2 (20 mL). After keeping for 20 min at this temperature, the mixture was allowed to warm to room temperature and kept for 16 h. Then the reaction mixture was poured into 5% HCl (70 mL) and extracted with CH_2Cl_2 (3×20 mL). The extract was washed with 5% HCl (50 mL) and with water (50 mL) and concentrated *in vacuo*. To the residue, ethanol (10 mL) was added and the resulting mixture was refluxed for 2 h. The obtained solution was concentrated and 5% $NaHCO_3$ (70 mL) was added to the residue. The obtained mixture was extracted with ethyl acetate (3×20 mL). The extract was washed with water, filtered through thin layer of silica gel (2 cm) and concentrated *in vacuo*.

B. To a suspension of acid **1** (12 mmol) in dry CH_2Cl_2 (20 mL), thionyl chloride (2.0 mL, 27 mmol) and two drops of DMF were added. The mixture was refluxed for 3 h and concentrated *in vacuo*. The resulting acid chloride was dissolved in dry CH_2Cl_2 (20 mL) and added to a suspension of Meldrum´s acid

(2.0 g, 14 mmol) and DMAP (3.2 g, 26 mmol) in dry CH_2Cl_2 (20 mL) cooled to 0 °C. After keeping for 20 min at this temperature, the mixture was allowed to warm to room temperature and kept for 16 h. The reaction mixture was worked up analogously to method ***A***.

C. To a suspension of acid **1** (12 mmol) in dry CH_2Cl_2 (20 mL), DCC (3.0 g, 14 mmol), DMAP (0.17 g, 1.4 mmol) and Meldrum's acid (1.9 g, 13 mmol) were added. The resulting mixture was kept for 16 h at room temperature. The precipitate of dicyclohexylurea was filtered off, the mother liquor was concentrated *in vacuo*. Ethanol (10 mL) was added to the residue and the mixture was refluxed for 2 h. The resulting solution was poured onto ice (200 g), extracted with ethyl acetate (3×20 mL), the extract was concentrated *in vacuo*. The product **4** was isolated by column chromatography on silica gel eluting with light petroleum—ethyl acetate (8:1).

D. To a suspension of acid **1** (12 mmol) in dry CH_2Cl_2 (20 mL), CDI (2.1 g, 13 mmol) was added. After stirring for 0.5 h, Meldrum's acid (1.86 g, 13 mmol) was added and stirred for additional 12 h. The reaction mixture was worked up analogously to method ***A***.

Ethyl 4-phenyl-3-oxobutanoate (4a). Yellowish liquid.[16,26] ^{1}H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.0 Hz); 3.45 (s, 2 H, CH_2); 3.84 (s, 2 H, CH_2); 4.18 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.0 Hz); 7.19—7.39 (m, 5 H, H^{arom}). Mass spectrum (EI, 70 eV), m/z (I_{rel} (%)): 206 $[M]^+$ (52), 161 $[M - EtO]^+$ (29), 118 $[M - CH_3COOEt]^+$ (50), 91 $[PhCH_2]^+$ (100).

Ethyl 4-(1-naphtyl)-3-oxobutanoate (4b). Yellowish liquid.[16] ^{1}H NMR ($CDCl_3$), δ: 1.24 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.0 Hz); 3.42 (s, 2 H, CH_2); 4.15 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.0 Hz); 4.28 (s, 2 H, CH_2); 7.40 (d, 1 H, H^{arom}, J = 6.6 Hz); 7.45 (d, 1 H, H^{arom}, J = 8.1 Hz); 7.48—7.57 (m, 2 H, H^{arom}); 7.83 (d, 1 H, H^{arom}, J = 7.7 Hz); 7.86—7.93 (m, 2 H, H^{arom}). Mass spectrum (EI, 70 eV), m/z (I_{rel} (%)): 256 $[M]^+$ (83), 210 $[M - EtOH]^+$ (25), 206 (34), 168 $[M - CH_3COOEt]^+$ (64), 141 $[C_{10}H_7CH_2]^+$ (100).

Ethyl 4-(2,5-dimethylthiophen-3-yl)-3-oxobutanoate (4c). Yellow oil. ^{1}H NMR ($CDCl_3$), δ: 1.27 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.0 Hz); 2.29 (s, 3 H, CH_3); 2.38 (s, 3 H, CH_3); 3.41 (s, 2 H, CH_2); 3.65 (s, 2 H, CH_2); 4.18 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.0 Hz); 6.46 (s, 1 H, H^{thioph}). Mass spectrum (EI, 70 eV), m/z (I_{rel} (%)): 240 $[M]^+$ (47), 152 $[M - CH_3COOEt]^+$ (54), 125 $[M - COCH_2COOEt]^+$ (100). Found: m/z 263.0696 $[M + Na]^+$. $C_{12}H_{16}NaO_3S$. Calculated: M + Na = 263.0712.

Ethyl 4-(3-methoxyphenyl)-3-oxobutanoate (4d). Yield 64%, Yellow oil.[27] ^{1}H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, $CH_2C\underline{H}_3$ J = 7.0 Hz); 3.44 (s, 2 H, CH_2); 3.78 (s, 5 H, CH_3 + CH_2); 4.16 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.0 Hz); 6.71—6.86 (m, 3 H, H^{arom}); 7.24 (t, 1 H, H^{arom}, J = 8.1 Hz). Mass spectrum (EI, 70 eV), m/z (I_{rel} (%)): 236 $[M]^+$ (62), 190 $[M - EtOH]^+$ (30), 148 $[M - CH_3COOEt]^+$ (74), 121 $[M - COCH_2COOEt]^+$ (100).

Ethyl 4-(4-methoxyphenyl)-3-oxobutanoate (4e). Yield 60%, yellow oil.[16,26] ^{1}H NMR ($CDCl_3$), δ: 1.24 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.0 Hz); 3.42 (s, 2 H, CH_2); 3.74 (s, 2 H, CH_2); 3.76 (s, 3 H, CH_3); 4.15 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.0 Hz); 6.85 (d, 2 H, H^{arom}, J = 8.4 Hz); 7.11 (d, 2 H, H^{arom}, J = 8.4 Hz). Mass spectrum (EI, 70 eV), m/z (I_{rel} (%)): 236 $[M]^+$ (68), 190 $[M - EtOH]^+$ (40), 148 $[M - CH_3COOEt]^+$ (64), 121 $[M - COCH_2COOEt]^+$ (100).

Ethyl 4-(4-methyl-1-benzothiophen-3-yl)-3-oxobutanoate (4f). Yield 78%, yellow oil. ^{1}H NMR ($CDCl_3$), δ: 1.24 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.0 Hz); 2.54 (s, 3 H, CH_3); 3.40 (s, 2 H, CH_2); 3.99 (s, 2 H, CH_2); 4.14 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.0 Hz); 7.25—7.40 (m, 2 H, H^{arom}); 7.57 (d, 1 H, H^{arom}, J = 7.7 Hz); 7.77 (d, 1 H, H^{arom}, J = 7.7 Hz). Mass spectrum (EI, 70 eV), m/z (I_{rel} (%)): 276 $[M]^+$ (42), 188 $[M - CH_3COOEt]^+$ (24), 161 $[M - COCH_2COOEt]^+$ (100). Found: m/z 299.0712 $[M + Na]^+$. $C_{15}H_{16}NaO_3S$. Calculated: M + Na = 299.0712.

This work was financially supported by the Council on Grants at the President of the Russian Federation (State Support Program for Young scientists and Leading Scientific Schools, Grant MK-269.2009.3).

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Received May 31, 2010;
in revised form September21, 2010