UNEXPECTED SYNTHESIS OF 4-R-PHENYLALLYLIDENE MELDRUM'S ACID DERIVATIVES

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Abstract: Six novel cinnamylidene Meldrum's acid derivatives **3** have been obtained from the reaction of benzaldehydes **1** and Meldrum's acid **2**, by heating under reflux in 2-ethoxyethanol and catalytic amounts of triethylamine. Analysis of the NMR-bidimensional experiments and X-ray diffraction of some derivatives **3** allowed us to determine unambiguously its structures.

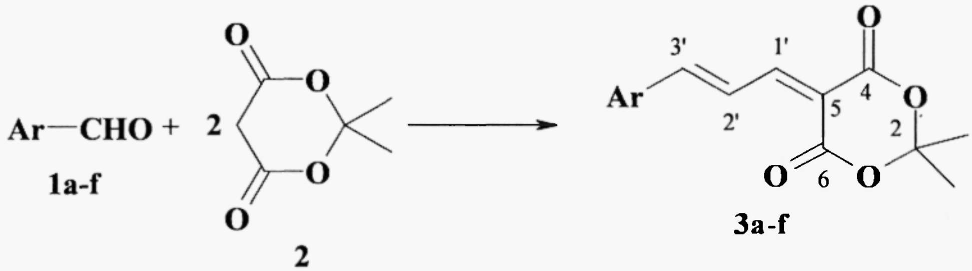
Introduction

From a synthetic viewpoint, Meldrum's acid and its derivatives are used most often in the preparation of arylidene-condensation products (i.e. compounds that have a strongly polarized double bond).[1] At the simplest level, Meldrum's acid can act as a methylene synthon from hydrolysis, loss of acetone molecule and exhaustive decarboxylation.[2]

The use of arylidene derivatives of Meldrum's acid in the synthesis of heterocyclic compounds has received little attention, although despite their relatively easy preparation and the mild reaction conditions required in their reactions made them quite valuable starting materials for synthetic purposes.[3] For example, it has been reported that the condensation of arylidene Meldrum's acid derivatives with heterocyclic monoamines and α,β-unsaturated carbonyl or β-dicarbonyl compounds affords coumarin[4] or pyridine[5] derivatives respectively.

Results and Discussion

As an attempt to prepare benzylidene derivatives of Meldrum's acid and use them in the reaction with heterocyclic amines, a mixture of equimolar amounts of benzaldehyde **1a** and Meldrum's acid **2** was heated at reflux in 5 mL of 2-ethoxyethanol and catalytic amounts of triethylamine. A new compound precipitated from the hot solution was fully characterized through spectroscopic and analytical methods as the 3-phenylpropylidene Meldrum's acid derivative **3a** in which apparently two molecules of **2** are involved in its formation (Scheme 1). The reaction was then optimized using a molar ratio 1:2 of **1a** and **2** increasing substantially the reaction yield. These results prompted us to explore other aldehydes (**1b-f**), showing a similar behavior and yielding their corresponding products **3b-f** in acceptable to good yields.



Ar = C_6H_5 (**a**), 4-$CH_3C_6H_4$ (**b**), 4-$CH_3OC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**), 4-$O_2NC_6H_4$ (**f**),

Scheme 1

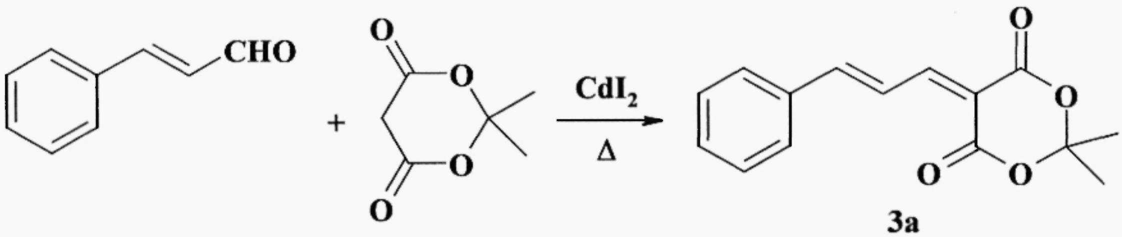
All compounds **3a-f** were extensively characterized by their ^1H, ^{13}C nmr and DEPT spectra (including 2D-techniques like COSY and HMBC), mass spectra, elemental analysis and X-ray diffraction.

All signals in the ^1H nmr spectra are consistent with the proposed structure for compounds **3**, where the most relevant feature is the presence of the proton signals of the fragment =CH(1')-CH(2')=CH(3')-Ar at δ 8.15-8.18, 8.25-8.42 and 7.35-7.43 ppm respectively, each one showing a doublet with J between 15.3 – 16.1 Hz. While the aromatic protons appear at δ = 7.08-8.31.

The ^{13}C nmr spectra shows a characteristic pattern for the fragment =CH(1')-CH(2')=CH(3')-Ar at δ 155.2-157.7, 121.7-127.3 and 149.9-155.0 ppm respectively. The other aliphatic and aromatic carbon atoms were also assigned.

All mass spectra are characterized by showing their molecular ions. This finding could reflects the relatively stability of these structures which is the base of their possible applications in organic synthesis.

Finally, we confirmed the proposed structure for compounds **3** by direct synthesis of the compound **3a** from the reaction of cinnamaldehyde and Meldrum's acid in the presence of CdI_2 (Scheme 2). This methodology has previously been successfully used by us for the synthesis of arylidene Meldrum's acid derivatives.[5b-d]



3a

Scheme 2

Furthermore, the crystalline structures for two of such compounds **3b** and **3d** have been recently reported by us,[6] confirming the proposed structures. Crystalline structures of two arylidenederivatives of Meldrum's acid were described in the work.[7]

In summary, we have synthesized and characterized six new 3-arylallylidene derivatives of Meldrum's acid in acceptable to good yields, starting with benzaldehydes under mild conditions. This finding open additional possibilities of potential applications of this kind of compounds, for example as □,□-unsaturated carboxylic systems in cyclocondensation reactions with heterocyclic monoamines.

EXPERIMENTAL

Melting points were determined in a Buchi Melting Point Apparatus and are uncorrected. The ^1H- and ^{13}C nmr spectra were run on a Bruker DPX 300 spectrometer operating at 300 MHz and 75 MHz respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. The mass spectra were scanned on a Hewlett Packard HP Engine-5989 spectrometer (equipped with a direct inlet probe) and operating at 70 eV. The elemental analysis has been obtained using a LECO CHNS-900 equipment.

General procedure for the preparartion of the 5-[3-(4-R-phenyl)allylidene]-2,2-dimethyl-[1,3]dioxane-4,6-diones 3a-f.

A solution of benzaldehyde **1a-f** (2.0 mmoles) and Meldrum's acid **2** (4.0 mmoles) in 2-ethoxyethanol (5 ml) and catalytic amounts of triethylamine was refluxed during 5-30 minutes (tlc control), after cooling the resulting precipitate was filtered, washed with ethanol, dryed and purified by column chromatography on silica-gel and chloroform as eluent.

5-[3-Phenylallylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3a

This compound was obtained according to general procedure as yellow crystals, mp 101 °C, yield 68 %. This compound also was obtained by the direct heating of mixture of cinnamaldehyde (2.0 mmoles) and Meldrum's acid **2** (2.0 mmoles) in presence of CdI_2 (mp 101 °C, yield 55 %) ^1H nmr (DMSO-d_6): $\delta = 1.77$ (s, 6H, $(CH_3)_2C$), 7.43-7.68 (m, 5H, C_6H_5), 7.43 (d, 1H, H-3'), 8.32 (dd, $J_{H1'-H2'} = 12.0$ Hz, $J_{H2'-H3'} = 14.9$ Hz, 1H, H-2'), 8.18 (d, 1H, H-1'). ^{13}C nmr (DMSO-d_6): $\delta = 27.0$ (CH_3), 104.5 (C-2), 111.6 (C-5), 123.9 (C-2'), 128.8 (C_o), 129.3 (C_m), 131.0 (C_p), 134.8 (C_i), 154.1 (C-3'), 156.9 (C-1'), 160.2 (C=O), 162.1 (C=O). The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 258 (M^+, 22), 201 (24), 200 (95), 172 (40), 155 (23), 144 (53), 132 (34), 131 (53), 128 (100), 127 (44), 116 (24), 115 (27), 102 (40), 77 (26), 51 (23), 43 (95), 39 (15).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.81; H, 5.56.

5-[3-(4-Methylphenyl)allylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3b

This compound was obtained according to general procedure as orange crystals, mp 128 °C, yield 65 %. ^1H nmr (DMSO-d_6): δ = 1.76 (s, 6H, $(CH_3)_2C$), 2.41 (s, 3H, CH_3), 7.57 (d, 2H, H_o), 7.24 (dd, 2H, H_m), 7.40 (d, 1H, H-3'), 8.28 (dd, $J_{H1'-H2'}$ = 12.0 Hz, $J_{H2'-H3'}$ = 14.8 Hz, 1H, H-2'), 8.17 (d, 1H, H-1'). ^{13}C nmr (DMSO-d_6): δ = 21.1 (CH_3), 27.0 ($4-CH_3C_6H_4$), 104.4 (C-2), 110.8 (C-5), 123.0 (C-2'), 129.0 (C_o), 129.9 (C_m), 142.2 (C_p), 132.2 (C_i), 154.5 (C-3'), 157.2 (C-1'), 160.3 (C=O), 162.2 (C=O). The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 272 (M^+, 32), 215 (23), 214 (88), 1186 (27), 158 (46), 155 (46), 142 (67), 141 (100), 131 (62), 129 (20), 127 (19), 116 (15), 115 (81), 65 (11), 63 (14), 43 (82), 39 (16).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.49; H, 5.87.

5-[3-(4-Methoxyphenyl)allylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3c

This compound was obtained according to general procedure as orange crystals, mp 147 °C, yield 52 %. ^1H nmr (DMSO-d_6): δ = 1.76 (s, 6H, $(CH_3)_2C$), 3.87 (s, 3H, CH_3O), 7.64 (d, 2H, H_o), 6.95 (dd, 2H, H_m), 7.39 (d, 1H, H-3'), 8.25 (dd, $J_{H1'-H2'}$ = 11.9 Hz, $J_{H2'-H3'}$ = 14.9 Hz, 1H, H-2'), 8.16 (d, 1H, H-1'). ^{13}C NMR (DMSO-d_6): δ = 26.9 (CH_3), 55.5 (OCH_3), 104.3 (C-2), 109.5 (C-5), 121.7 (C-2'), 131.2 (C_o), 114.9 (C_m), 156.5 (C_p), 127.2 (C_i), 155.5 (C-3'), 157.7 (C-1'), 160.4 (C=O), 162.4 (C=O). The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 288 (M^+, 34), 231 (14), 230 (51), 185 (15), 174 (17), 162 (19), 159 (13), 158 (76), 143 (18), 131 (14), 128 (20), 116 (11), 115 (100), 89 (17)m 63 (15), 43 (58), 39 (10).

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.65; H, 5.51.

5-[3-(4-Chlorophenyl)allylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3d

This compound was obtained according to general procedure as orange crystals, mp 182 °C, yield 70 %. ^1H nmr (DMSO-d_6): δ = 1.77 (s, 6H, $(CH_3)_2C$), 7.40 (d, 2H, H_o), 7.60 (dd, 2H, H_m), 7.36 (d, 1H, H-3'), 8.29 (dd, $J_{H1'-H2'}$ = 12.0 Hz, $J_{H2'-H3'}$ = 15.1 Hz, 1H, H-2'), 8.15 (d, 1H, H-1'). ^{13}C NMR (DMSO-d_6): δ = 27.0 (CH_3), 104.9 (C-2), 112.1 (C-5), 124.4 (C-2'), 129.4 (C_o), 130.4 (C_m), 136.0 (C_p), 133.7 (C_i), 152.2 (C-3'), 156.4 (C-1'), 160.1 (C=O), 162.0 (C=O). The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 294/292 (M^+, 10/26), 236 (31), 235 (22), 206 (30), 189 (18), 178 (35), 166 (17), 164 (26), 162 (69), 161 (15), 155 (16), 131 (67), 127 (78), 126 (37), 115 (19), 101 (17), 77 (25), 75 (24), 51 (13), 43 (100), 39 (10).

Anal. Calcd. for $C_{15}H_{13}ClO_4$: C, 61.55; H, 4.48. Found: C, 61.62; H, 4.44.

5-[3-(4-Bromophenyl)allylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3e

This compound was obtained according to general procedure as orange crystals, mp 182 °C, yield 74 %. ^{1}H nmr (DMSO-d$_6$): δ = 1.77 (s, 6H, (CH$_3$)$_2$C), 7.52 (d, 2H, H$_o$), 7.58 (dd, 2H, H$_m$), 7.35 (d, 1H, H-3'), 8.30 (dd, $J_{H1'-H2'}$ = 12.0 Hz, $J_{H2'-H3'}$ = 15.2 Hz, 1H, H-2'), 8.15 (d, 1H, H-1'). ^{13}C NMR (DMSO-d$_6$): δ = 27.0 (CH$_3$), 104.6 (C-2), 112.2 (C-5), 124.5 (C-2'), 130.6 (C$_o$), 132.3 (C$_m$), 125.0 (C$_p$), 134.0 (C$_i$), 152.3 (C-3'), 156.4 (C-1'), 160.1 (C=O), 162.0 (C=O). The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 338/336 (M$^+$, 12/13), 336 (13), 281 (11), 280 (44), 279 (12), 278 (39), 252 (15), 250 (14), 224 (14), 222 (13), 208 (16), 206 (16), 155 (16), 131 (52), 127 (81), 126 (35), 115 (19), 101 (20), 77 (27), 75 (20), 51 (16), 50 (14), 43 (100), 39 (10).

Anal. Calcd. for $C_{15}H_{13}BrO_4$: C, 53.43; H, 3.89. Found: C, 53.50; H, 3.86.

5-[3-(4-Nitrophenyl)allylidene]-2,2-dimethyl-[1,3]dioxane-4,6-dione 3f

This compound was obtained according to general procedure as orange crystals, mp 196 °C, yield 77 %. ^{1}H nmr (DMSO-d$_6$): δ = 1.79 (s, 6H, (CH$_3$)$_2$C), 7.82 (d, 2H, H$_o$), 8.29 (dd, 2H, H$_m$), 7.43 (d, 1H, H-3'), 8.42 (dd, $J_{H1'-H2'}$ = 11.9 Hz, $J_{H2'-H3'}$ = 15.5 Hz, 1H, H-2'), 8.17 (d, 1H, H-1'). ^{13}C NMR (DMSO-d$_6$): δ = 27.1 (CH$_3$), 104.9 (C-2), 114.1 (C-5), 127.3 (C-2'), 124.3 (C$_o$), 129.6 (C$_m$), 140.9 (C$_p$), 148.3 (C$_i$), 149.9 (C-3'), 155.2 (C-1'), 160.0 (C=O), 161.8 (C=O). The mass spectrum shows the following peaks: ms: (70 eV) m/z (%) = 303 (M$^+$, 10), 246 (28), 245 (100), 217 (32), 189 (43), 161 (14), 160 (58), 154 (25), 131 (15), 130 (18), 127 (47), 126 (35), 115 (29), 101 (71), 77 (32), 75 (20), 63 (14), 59 (14), 51 (18), 43 (92), 39 (10).

Anal. Calcd. for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.35; H, 4.23; N, 4.54.

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