Postprint of: Pawelska N., Ponikiewski Ł., Makowiec S., Boron difluoride complexes of carbamoyl Meldrum's acids, Journal of Fluorine Chemistry, Vol. 144 (2012), pp. 65-68, DOI: 10.1016/j.jfluchem.2012.07.004

Boron Difluoride Complexes of Carbamoyl Meldrum's Acids.

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Abstract:

5-[Hydroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones react with BF_3•Et_2O in mild conditions leading to the formation of boron difluoride complexes of carbamoyl Meldrum's acids. The X-ray structure has been obtained for one representative complex. The obtained new compounds are fairly stable at standard ambient conditions and easily isolable.

Key words: Meldrum's acid, Lewis acids, boron, complexes.

1. Introduction

Acyl derivatives of Meldrum acids have a broad scope of applications in organic synthesis [1]. Their use in organic synthesis is mainly due to the ability to create ketenes in the course of thermal decomposition [2], [3], [4]. These ketenes as strongly acylating agents can react with a wide range of nucleophiles and as a result form various useful compounds such as, for example: 3-substituted-β-lactams [5], [6] isooxazolols [7], pilicides [8], and derivatives of tetramic acid [9]. However, the formation of ketenes is not the only useful reaction of derivatives of Meldrum's acids. The addition of metaloorganic species or reduction of the conjugated double bond [10], [11], also may take place. The least explored area is action of the Meldrum's acid derivatives as the nucleophilic reagents, only in the case of thiocarbamoyl meldrum's acid the appropiate anion was used as nucleophilic agent [12] whereas in the case of the oxygene analog none example could be find.

2. Results and discussion

Recently we focused on the reactivity of carbamoyl ketenes generated from 5-[hydroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones 1. Ketenes formed during thermal decomposition of 1 can acylate amines [13], alcohols and thiols [14] leading to the formation of malonamide derivatives, but, more importantly, during our previous researches we observed that these ketenes can undergo cycloaddition to aldimines to form 3-carbamoyl-b-lactams in the modified Staudinger reaction. The initial success in the field of synthesis of β-lactams encouraged us to try to develop a method of synthesis 4-unsubstituted-3-carbamoyl-β-lactams. Preparation 4-unsubstituted-β-lactams in the typical or modified Staudinger reaction carries difficulties associated with unstability of monomeric formaldehyde aldimines or necessity to use surogates of formyl aldimines. In order to obtain 4-unsubstituted-β-lactams we performed several unsuccesful experiments with ketenes generated from 1 and surogates of formaldehyde aldimines described in literature, such as: dithiocarbamates [15], formaldehyde N,N-dialkylhydrazones [16], and glyoxal imines [17]. Eventually we ran a reaction of 1 eq of 1 in boiling toluene with 2 eq of N-methylene-tert-butylamine as a one of most stable formaldehyde aldimines. To ensure depolimerisation of imine we added 6 eq of boron trifluoride etherate as a well known agent for depolimerization

of hexahydro-1,3,5-triazines [18]. From the reaction mixture, beside a large amount of tar, we isolated a small amount of a new compound with the ^{1}H NMR spectra almost identical with that of the starting material except for the lack of acidic proton; on the other hand TLC chromatography also showed that the new compound is not as acidic as 5-[hydroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones. A similar experiment conducted with HCl or $SnCl_4$ instead of BF_3•Et_2O did not result in the formation of the new compound. Moreover, other experiments caried out between **1** and tripyrolidine in the presence of BF_3•Et_2O in boiling toluene also demonstrated the formation of the same new compound (entry 1, Table 1). These aforementioned experiments strongly indicate that **1** and BF_3•Et_2O are necessary for formation of the new compound. Structure elucidation with ^{1}H, ^{13}C and elemental analysis strongly suggested that the new formed compound might be a 5-[difluoroboroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **2a**. Which should be considered as a carbamoyl Meldrum's acid difluoroboric acid mixed anhydride.
Fortunately **2a** gave crystals suitable for X-ray crystallography. X-ray date has confirmed our previous suppositions, the acidic proton of the **2a** is replaced with BF_2 moiety which also coordinates to the adjacent carbonyl oxygen (Figure 1).

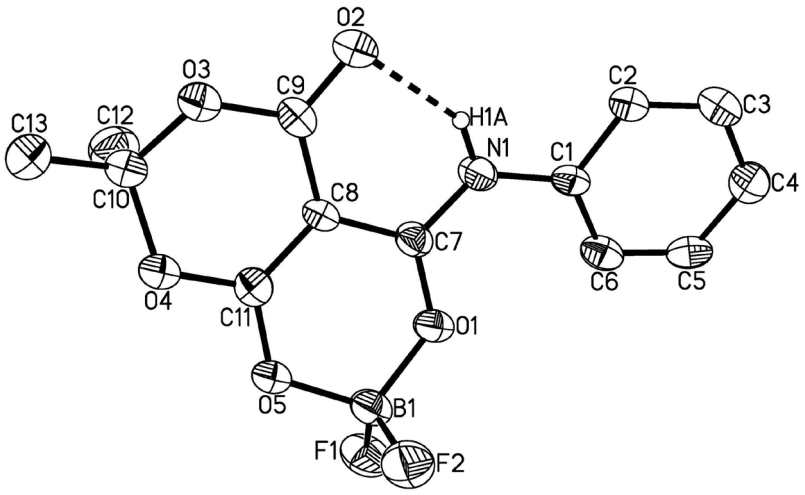
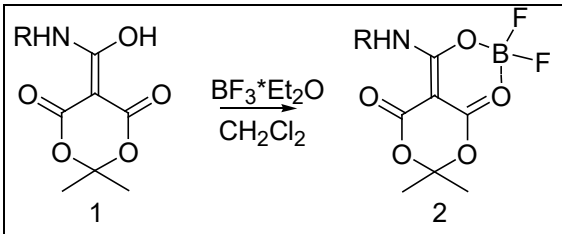


Figure 1 X-ray crystal structure representation of the complex **2a** [22]

To the best of our knowledge such a derivative of Meldrum's acids was not described up to now in chemical literature.
At this point we decided to check whether it is possible to increase the yield of **2** and whether the observed process is a general phenomenon or limited only to this model of reactants. At the beginning we decreased the temperature of the process as the observed reaction shouldn't require as a high temperature as decomposition of Meldrum's acid derivative to keten. We also anticipate that in boiling toluene part of the initially formed **2** may subsequently decompose to an keten. Therefore, we performed two experiments in boiling dichloromethane using **1a** and **1b** as starting materials and leaving all other parameters of the reaction unchanged. After the disappearance of the starting material, which takes 3.5 h from the reaction mixtures, we isolated anhydrides **2a** and **2b** with high yield (entries 2 and 6, Table 1). We also ran the reaction of **1a** with 6 eq of BF_3•Et_2O in boiling DCE; however, as in the case of toluene we observed the formation of a large amount of byproducts.
In subsequent studies we carried out a two series of reactions: first where **1a-f** were heated in boiling DCM only in the presence of 6 eq of BF_3*Et_2O (entries 3, 7, 9, 11, 13 and 15, Table 1) and the second series where **1a-f** were heated in boiling DCM with 6 eq of BF_3*Et_2O in the presence of 2 eq of triethyl amine (entries 8, 10, 12, 14 and 16, Table 1). In the case of the

reactions carried out in the presence of tertiary amine yields of the **2** were even two to four fold higher that in the reaction without base. This fact clearly demonstrates that formation of anionic form of the carbamoyl Meldrum's acid strongly facilitates ligand substitution on the boron atom. Additionally we run the reaction of 1a with in the strongly acidic solution of HBF4 in diethyl ether but in this case we observed formation only a small amount of **2a**. (entries 4 and 5, Table 1).

Table 1 Synthesis of boron difluoride complexes of carbamoyl Meldrum's acids



Entry	**1**,**2**	R	Time (h)	Yield (%)
1[a]	a	Ph	4	27
2[b]	a	Ph	5	62
3	a	Ph	3	60
4[c]	a	Ph	4	15
5[d]	a	Ph	3.5	15
6[b]	b	3-ClC_6H_4	5	71
7	b	3-ClC_6H_4	3.5	45
8[e]	b	3-ClC_6H_4	4.5	66
9	c	Et	3	43
10[e]	c	Et	3	56
11	d	Cyclo-hexyl	2.5	36
12[e]	d	Cyclo-hexyl	2.5	79
13	e	Naphtyl	5	48
14[e]	e	Naphtyl	5	63
15	f	4-$NO_2C_6H_4$	4	14
16[e]	f	4-$NO_2C_6H_4$	4.5	55

[a] 0.33 eq of tripyrolidine was used, and toluene as a solvent, [b] 2 eq of N-methylene-tert-butylamine was used, [c] 3 eq of HBF_4•Et_2O was used, [d] 6 eq of HBF_4•Et_2O was used, [e] 2 eq of triethylamine was used

The last aspect we decided to test was the problem if other acyl derivative of Meldrum's acid are also able to react in such a way and form chelates with boron trifluoride. We ran two reactions of 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones with 6 eq of BF_3•Et_2O, first was performed in boiling DCM and the second at room temperature.
In both cases the reactions was led to the disappearing of the starting material what took respectively 5 and 24 h, and in both cases we isolated only acetophenone as the main product. We already observed that decomposition to keten catalyzed by acid is faster for usual acyl Meldrum's acids than in the case of carbamoyl derivatives; however it is surprising that even at room temperature this reaction path is overwhelming.
From the other hand, selective ability of carbamoyl Meldrum's acids for formation of difluoroboron complexes might be explained taking into account the presence of nitrogen atom with the lone electron pair at the end of the conjugated system which is capable for stabilizing such a complex.

At this point raises the remark that the obtained difluoroboron complexes of carbamoyl Meldrum's can be considered as far analogies to difluoroboron complexes of 1,4-dihydro-4-oxoquinoline-3-carboxylic acid [19].

3. Conclusion

A new reaction of 5-[hydroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **1** with BF_3•Et_2O in the presence of tertiary amine is reported. We obtain carbamoyl Meldrum's acid difluoroboric acid mixed anhydrides in mild conditions with high yield. The new product **2** is easily isolable and stable at room temperature.

4. Experimental

4.1 General experimental procedures.

Reagents were purchased from Sigma-Aldrich. Toluene were distilled from potassium under argon. Dichloromethane and 1,2-dichloroethane was distilled from K_2CO_3 Analytical TLC was performed on aluminum sheets of silica gel UV-254 Merck. Flash chromatography was performed using 40-63 microns of Zeochem silica gel and with aluminium oxide neutral Grade I POCH. The 1H, 13C were recorded on Varian Gemini 200 and Varian Unity Plus 500, chemical shifts (δ) in ppm rel. to internal Me4Si; coupling constants J in Hz. Elemental analysis were performed on Vario El Cube CHNS Elementar. High-resolution (HRMS) was recorded on MicroMas Quattro LCT mass spectrometer. Melting points were determined with Warsztat Elektromechaniczny W-wa apparatus and are not corrected. Commercially unavailable reagents were prepared using literature procedures as follows: 5-[hydroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1a** [20], 5-{[hydroxy(3-chlorophenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1b** [6], 5-[Hydroxy(ethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1c** [6], 5-[Hydroxy(cyclohexylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione **1d** [6], N-methylene-tert-butylamine [21].

*4.2 Syntheses of carbamoylo Meldrums's acids **1e-f***

5-[Hydroxy(1-naphthylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1e**). Following the typical literature procedure [6, 20] for 1a-b using Meldrum's acid (0.72 g, 5 mmol) anhyd. DMF (5 ml) Et_3N (1.4 ml, 10 mmol); naphtylisocyanate (0.845 g, 5 mmol,) yield 1.345 g (86%); Mp 119-120 °C. ^{1}H NMR (200 MHz, CDCl3): δ = 1.82 (s, 6 H), 7.48-7.62 (m, 3 H), 7.63-8.00 (m, 4 H), 11.60 (brs, 1 H), 13.62 (brs, 1 H). ^{13}C NMR (50 MHz, CDCl3): δ = 26.9, 74.3, 105.7, 121.7, 122.2, 125.8, 127.2, 127.7, 128.2, 128.7, 129.2, 130.4, 134.6, 165.1, 168.4, 171.2. HRMS (ESI-): m/z [M - H] calcd for $C_{13}H_{11}N_2O_7$: 307.0566; found: 307.0563.

5-[Hydroxy(4-nitrophenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**1f**). Following the typical literature procedure [6, 20] for 1a-b using Meldrum's acid (0.72 g, 5 mmol) anhyd. DMF (5 ml) Et_3N (1.4 ml, 10 mmol); p-nitro-phenylisocyanate (0.820 g, 5 mmol,) yield 1.243 g (80%); crystallized from CH_2Cl_2, mp 210-215 °C dec. ^{1}H NMR (500 MHz, CDCl3): δ = 1.78 (s, 6 H), 7.67 (d, J = 9.1 Hz, 2 H), 8.27 (d, J = 9.1 Hz, 2 H), 11.45 (brs, 1 H), 16.50 (brs, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.5, 74.9, 106.2, 121.8, 125.3, 141.1, 145.2, 164.3, 170.0, 171.6. HRMS (ESI-): *m/z* [M - H] calcd for $C_{17}H_{14}NO_5$: 312.0872; found: 312.0877.

*4.3 Syntheses of 5-[Difluoroboroxy(aryl/alkylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-diones **2a-f***

4.3.1 General procedure

To a solution of **1** (1 mmol) in anhd. CH_2Cl_2 15 ml, 6 mmol BF_3*Et_2O was added, triethyl amine or N-methylene-*tert*-butylamine (2 mmol) was added if specified in Table 1. The resulting mixture was stirred and heated to reflux for the time specified in Table 1. After disappearance of starting material, reaction mixture was washed with sat. aq $NaHCO_3$ (5 ml) and if amine was added with 2 M aq HCl (5 ml). The organic solution was dried with $MgSO_4$, filtered and solvents was removed under reduced pressure, and the residue was purified as follow

5-[Difluoroboroxy(phenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2a**) Purification by flash column chromatography on silica gel (EtOAc-toluene, 1:7); mp 139-142 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.88 (s, 12 H), 7.28-7.54 (m, 10 H), 10.99 (s, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4, 74.9, 109.6, 123.1, 128.2, 130.0, 134.0, 162.1, 164.4, 172.1. Anal. Calcd for $C_{13}H_{12}BF_2NO_5$: C, 50.20; H, 3.89; N, 4.50; Found: C, 49.89; H, 3.95; N, 4.59.

5-[Difluoroboroxy(3-chlorophenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2b**) Purification by flash column chromatography on neutral aluminium oxide (EtOAc-toluene, 1:5); mp 136-139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.87 (s, 12 H), 7.26-7.37 (m, 6 H), 7.40 (s, 2 H), 11.02 (brs, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5, 75.0, 109.9, 121.3, 123.3, 128.3, 131.0, 135.0, 135.7, 162.0, 164.8, 171.8. Anal. Calcd for $C_{13}H_{11}BClF_2NO_5$: C, 45.19; H, 3.21; N, 4.05; Found: C, 45.18; H, 3.26; N, 4.04.

5-[Difluoroboroxy(ethylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2c**) Purification by flash column chromatography on neutral aluminium oxide (EtOAc-toluene, 1:5); mp 145-147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.3 Hz, 6 H), 1.81 (s, 12 H), 3.55-3.61 (m, 4 H), 9.13 (brs, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.6, 26.4, 36.7, 74.8, 109.2, 161.9, 165.9, 171.0. Anal. Calcd for $C_9H_{12}BF_2NO_5$: C, 41.10; H, 4.60; N, 5.33; Found: C, 39.67; H, 5.26; N, 5.73.

5-[Difluoroboroxy(cyclohexylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2d**) Purification by flash column chromatography on neutral aluminium oxide (EtOAc-toluene, 1:5); mp 137-140 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34-1.42 (m, 12 H), 1.62-1.75 (m, 4 H), 1.81 (s, 12 H), 1.96-2,01 (m, 4 H), 3.91-4.09 (m, 2 H), 9.12 (brs, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.7, 25.5, 26.4, 32.7, 51.0, 74.3, 109.2, 161.9, 164.5, 171.0. Anal. Calcd for $C_{13}H_{18}BF_2NO_5$: C, 49.24; H, 5.72; N, 4.42; Found: C, 49.37; H, 5.84; N, 4.66.

5-[Difluoroboroxy(naphtylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2e**) Purification by flash column chromatography on neutral aluminium oxide (EtOAc-toluene, 1:5); mp 248-251 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.90 (s, 12 H), 7.49-7.60 (m, 6 H), 7.63-7.95 (m, 6 H), 11.43 (brs, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5, 75.3, 109.8, 121.0, 122.9, 125.9, 127.2, 127.4, 128.2, 128.9, 129.1, 129.4, 134.4, 162.5, 165.5, 171.9. Anal. Calcd for $C_{17}H_{14}BF_2NO_5$: C, 56.54; H, 3.91; N, 3.88; Found: C, 56.55; H, 3.96; N, 3.92.

5-[Difluoroboroxy(4-nitrophenylamino)methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**2f**) Purification by flash column chromatography on neutral aluminium oxide (EtOAc-toluene, 1:7); mp 154-156 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.89 (s, 12 H), 7.69-7.74 (d, *J* = 9.1 Hz,

4 H), 8.30-8.35 (d, J = 9.1 Hz, 4 H), 11.32 (brs, 2 H). ^{13}C NMR (50 MHz, acetone-d_6): δ 26.1, 76.3, 111.1, 125.3, 126.1, 141.0, 147.4, 162.2, 166.8, 173.0. Anal. Calcd for $C_{13}H_{11}BF_2N_2O_7$: C, 43.85; H, 3.11; N, 7.87; Found: C, 44.15; H, 3.07; N, 8.16.

Acknowledgment

Scientific work financed from funds for science in 2010-2011 as a research project N N204 088338.

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[22] X-ray crystal data for **2a**: $C_{13}H_{12}BF_2NO_5$, M = 311.05, monoclinic, space group $P2_1/c$, a = 15.5284(2), b = 5.547(8), c = 16.278(3) Å, β = 99.190(15)°, V = 1362.6(3) Å^3, T = 298(2) K, Z = 4, μ(Mo-Kα) = 0.132 mm^{-1}, Dc = 1.516 g cm^{-3}, 4714 reflections measured, 2645 unique (R_{int} = 0.0695), 880 observed [$I > 2\sigma(I)$]. The final R_1 and $wR_2(F^2)$ were 0.0588 [$I > 2\sigma(I)$] and 0.1197, respectively. Further details of the X-ray structure can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC 870688)