On the Reaction of Meldrum's Acid with *N*-Trimethylsilylanilines Substituted by Electron Withdrawing Groups

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The reaction of Meldrum's acid with silylated anilines substituted by an electron withdrawing group easily yields the corresponding *N*-phenyl malonamic acid, when the reaction is performed under high vacuum in dichlorobenzene.

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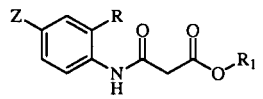
In conjunction with an ongoing program, we needed a convenient supply of *N*-phenyl malonamic acids derivatives **1** (Figure 1).

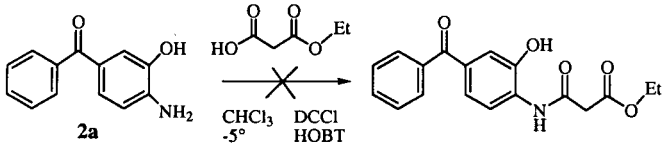


1 Z = electron withdrawing group

Figure 1

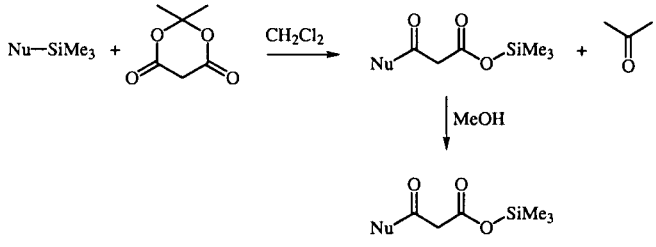
In a first approach towards these compounds, we tried to react monoethyl malonic acid [1] with 2-hydroxy-4-benzoylaniline **2a** in the presence of dicyclohexylcarbodiimide and hydroxybenzotriazole, but only the anilinium salt of ethyl malonic acid was obtained (Scheme 1).

Scheme 1



This result probably arises from the low nucleophily of 2-hydroxy-4-benzoyl aniline **2a.** Then we thought of condensating *N*-silyl amines with Meldrum's acid that we have already described [2], because this reaction succeeds with silylated derivatives (which have no nucleophilic properties [3]) of amines and alcohols, including hexamethyldisilazane and hexamethyldisiloxane (Scheme 2).

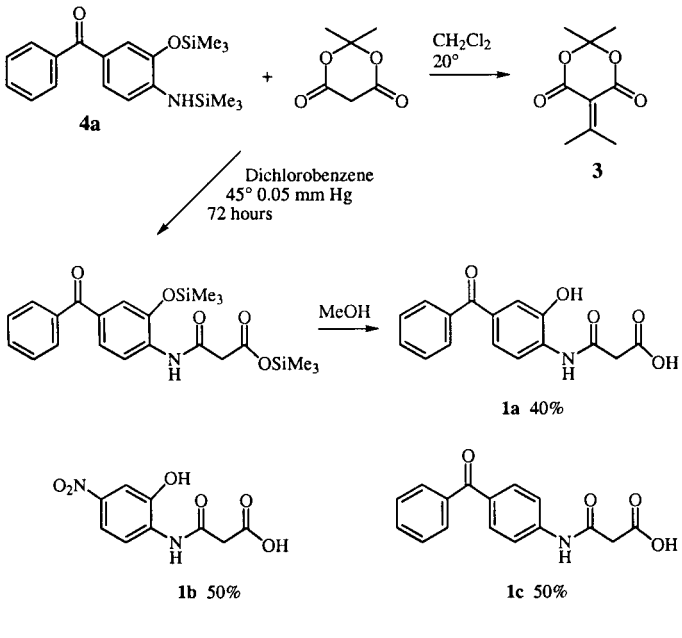
Scheme 2



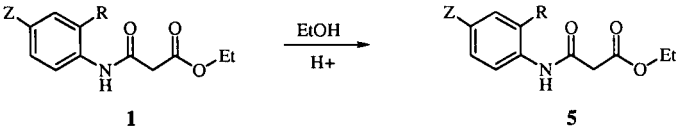
When this reaction was performed in the usual way [2] (dichloromethane, 20°) with disilylated compound **4a,** the condensation between the acetone produced and Meldrum's acid becomes the main reaction path, and only the tetramethyl product **3** was isolated. It was then found that heating at 45° for 3 days a dichlorobenzene solution of Meldrum's acid and *N*-silylamines **4a** while removing acetone under high vacuum, gives after hydrolysis a 40% yield of acid **1a.** In the same way, acids **1b** and **1c** were produced in 50% yield (Scheme 3). These reactions allowed to know that even a silylamine with very low nucleophilic properties reacted easier with Meldrum's acid that a trimethylsilylphenol, and that this procedure for the reaction between Meldrum's acid and an aromatic silylaniline substituted by an electron withdrawing group is quite general and allowed to obtain a modest yield of malonamic acids.

Esters **5** were then obtained by esterification of acids **1** (Scheme 4). The disilylated aminophenols **4a,b** were obtained by reacting amines **2a,b** with hexamethyldisilazane under reflux without catalyst. In the case of aniline **2c**, it is necessary to use trimethylchlorosilane as a catalyst (Scheme 5).

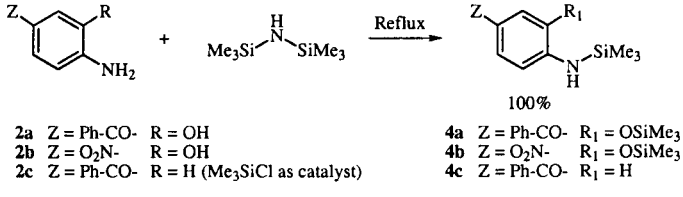
Scheme 3



Scheme 4

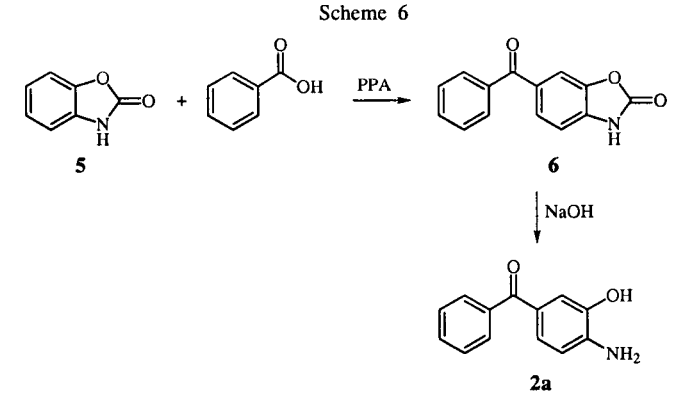


Scheme 5



Anilines **2b,c** are commercially available compounds; condensation of benzoic acid with benzoxazolinone **5** in polyphosphoric acid gives a 75% yield of 6-benzoylbenzoxazolone **6** [4], and sodium hydroxide hydrolysis of this compound yields 4-amino-3-hydroxybenzophenone **2a** in 70% yield. (Scheme 6).

Scheme 6



EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a 'Perkin-Elmer 700' spectrometer and the nmr spectra on a Varian 'Gemini 2000' or on a Bruker 'WP 80 SY', using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France). Melting points, ir spectra and elemental analyses were not determined for moisture sensitive compounds.

[*N*-(4-Benzoyl-2-hydroxy)phenylmalonamic Acid (**1a**).

A stirred mixture of compound **4a** (10.1 g, 0.028 mole) and Meldrum's acid (4.6 g, 0.028 mole) in dichlorobenzene (80 ml) was heated under vacuum (0.5 mm Hg) at 45°. After the disappearance of Meldrum's acid as checked by nmr (3 days), methanol (20 ml) was added. The precipitate of acid **1a** was recrystallized from methanol, mp 186°, yield 40%; ir (potassium bromide): ν cm^{-1} 3250 (OH, NH), 1740, 1690 (C=O); ^1H nmr (200 MHz, dimethyl-d_6 sulfoxide): δ ppm 3.54 (s, 2 H), 7.15 (s, 1 H), 7.27 (dd, J = 8.1; 1.5 Hz, 1 H), 7.50 (d, J = 7.4 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.76 (d, J = 7.4 Hz, 2 H), 8.21 (d, J = 8.1 Hz, 1 H), 9.89 (s, 1 H); ^{13}C nmr (50 MHz, dimethyl-d_6 sulfoxide): δ ppm 43.1, 116.4, 119.8, 122.7, 128.5, 129.8, 131.3, 132.3, 132.9, 138.3, 146.9, 165.3, 170.4, 195.5.

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68; O, 26.73. Found: C, 64.01; H, 4.43; N, 4.29; O, 26.98.

[*N*-(2-Hydroxy-4-nitro)phenyl]malonamic Acid (**1b**).

A stirred mixture of compound **4b** (3 g, 0.010 mole) and Meldrum's acid (3.9 g, 0.013 mole) in dichlorobenzene (80 ml) was heated under vacuum (0.5 mm Hg) at 45°. After 3 days the bistrimethylsilyl derivative of *N*-(4-nitro-2-hydroxy)phenylmalonamic acid was obtained; ^1H nmr (200 MHz, deuteriochloroform): δ ppm 0.35 (s, 9 H), 0.42 (s, 9 H), 3.53 (s, 2 H), 7.71 (d, J = 2.7 Hz, 1 H), 7.90 (dd, J = 9; 2.7 Hz, 1 H), 8.58 (d, J = 9 Hz, 1 H), 10.63 (s, 1 H). Methanol (10 ml) was added to this compound and the precipitate of acid **1b** was recristallized from methanol, yield 50%, mp 262°; ir (potassium bromide): ν cm^{-1} 3250, 3120 (OH), 1750, 1680 (C=O), 1640, 1610, 1450 (C=C); ^1H nmr (200 MHz, deuteriochloroform/dimethyl-d_6 sulfoxide): δ ppm 3.52 (s, 2 H), 7.75 (dd, J = 8.8, 2.4 Hz, 1 H), 7.80 (d, J = 2.4 Hz, 1 H), 8.37 (d, J = 8.8; Hz, 1 H), 9.98 (s, 1 H); ^{13}C nmr (50 MHz, deuteriochloroform/dimethyl-d_6 sulfoxide): δ ppm 43, 109.1, 115.3, 119.4, 133.4, 142.6, 146.9, 165.9, 169.6.

Anal. Calcd. for $C_9H_8N_2O_6$: C, 45.01; H, 3.36; N, 11.66; O, 39.97. Found: C, 45.39; H, 3.02; N, 11.35; O, 40.32.

4-Amino-2-hydroxybenzophenone (**2a**).

A stirred mixture of compound **6** (7.1 g, 0.03 mole) in sodium hydroxide solution (0.3 mole, 120 ml) was refluxed for 12 hours. After cooling, hydrochloric acid was added (*p*H 1), then a 10% aqueous sodium carbonate solution was added slowly (*p*H 8-9). The yellow solid obtained was washed with water giving 70% of product **2a**, mp 164° (ethanol); ir (potassium bromide): ν cm^{-1} 3445 (OH), 3320, 3150 (NH), 1635 (C=O); ^1H nmr (200 MHz, deuteriochloroform/dimethyl-d_6 sulfoxide): δ ppm 6.71 (d, J = 8.2 Hz, 1 H), 7.21 (dd, J = 8.2; 1.9 Hz, 2 H), 7.36-7.60 (m, 4 H), 7.70 (dd, J = 7.2; 1.5 Hz, 2 H).

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57; O, 15.01. Found: C, 73.51; H, 5.29; N, 6.30; O, 15.40.

N,O-Bistrimethylsilyl-2-amino-5-benzoylphenol (**4a**).

A stirred mixture of 2-amino-5-benzoylphenol [4], (6 g, 0.028 mole) and hexamethyldisilazane (11.4 g, 0.070 mole) was refluxed for five hours. After removing the excess of hexamethyldisilazane under vacuum, the product was obtained as an oil, in 100% nmr yield; ^{1}H nmr (60 MHz deuteriochloroform): δ ppm 0.31 (s, 18 H), 6.8-7.9 (m, 8 H).

N,O-Bistrimethylsilyl-2-amino-5-nitrophenol (**4b**).

This product was obtained in the same way as the silylamine **4a**, in a 100% nmr yield; ^{1}H nmr (200 MHz, deuteriochloroform): δ ppm 0.29 (s, 9 H), 0.31 (s, 9 H), 4.48 (s, 1 H), 6.67 (d, J = 9.3 Hz, 1 H), 7.58 (d, J = 2.6 Hz, 1 H), 7.79 (dd, J = 9.3; 2.6 Hz, 1 H).

N-Trimethylsilyl-4-aminobenzophenone (**4c**).

A stirred mixture of 4-aminobenzophenone (**2c**) (1.5 g, 0.008 mole), hexamethyldisilazane (3.1 g, 4 ml, 0.019 mole) and chlorotrimethylsilane (0.12 ml) was refluxed until the ammonia evolution ended. The hexamethyldisilazane excess was evaporated, giving a 100% nmr yield of silyl amine **4c**; ^{1}H nmr (60 MHz, deuteriochloroform): δ ppm 0.31 (s, 9 H), 4.5 (s, 1 H), 6.8-7.9 (m, 9 H).

Ethyl *N*-(4-Nitro-2-hydroxy)phenylmalonamate (**5b**).

A stirred mixture of acid **1b** (2 g, 0.008 mole) and para-toluenesulfonic acid (0.1 g) in a mixture of ethanol (20 ml) and toluene (40 ml), was refluxed in a Dean-Stark apparatus. After 12 hours, the cooled mixture was filtered and the solid was recristallized from methanol, giving a 56% yield of compound **5b**, mp 204°; ir potassium bromide): ν cm^{-1} 3080 (OH), 1730, 1650 (C=O), 1615, 1590, 1500 (C=C); ^{1}H nmr (200 MHz, deuteriochloroform/dimethyl-d_6 sulfoxide): δ ppm 1.34 (t, J = 7.2 Hz, 3 H), 3.56 (s, 2H), 4.27 (q, J = 7.2 Hz, 2 H), 7.75 (d, J = 9.1 H, 1 H), 7.81 (s, 1 H), 8.41 (d, J = 9.1 Hz, 1 H), 9.82 (s, 1H).

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44; O, 35.79. Found: C, 49.52; H, 4.55; N, 10.21; O, 35.42.

6-Benzoylbenzoxazolidone (**6**).

A stirred mixture of benzaxolinone **5** (13.5 g, 0.1 mole) and benzoic acid (14.7 g, 0.1 mole) in polyphosphoric acid (20 g) was heated at 120° for 5 hours. After cooling, the mixture was poured on ice then stirred for 40 minutes. The solid obtained was washed with water then with hexane. The yield of product **6**, identical to the described compound [4] was 75%, mp 165-167° (ethanol); ir (potassium bromide): ν cm^{-1} 3150 (NH), 1900, 1770, 1635 (C=O), 1620 (C=C); ^{1}H nmr (80 MHz, dimethyl-d_6 sulfoxide): δ ppm 12.10 (s, 1 H), 7.20-7.80 (m, 8 H).

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