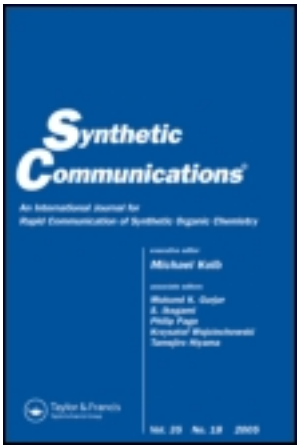

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An Efficient Synthesis of 4,5-Dihydro-3(2H)-pyridazinone Derivatives

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AN EFFICIENT SYNTHESIS OF 4,5-DIHYDRO-3(2H)-PYRIDAZINONE DERIVATIVES

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Abstract: Reaction of hydrazine with 5-(2-aryl-2-oxo-ethan-1-yl)-5-R Meldrum's acids **3** gives 4,6-disubstituted 4,5-dihydropyridazin-3(2H)-ones **4** at room temperature. The method is simple and the yield is good. The production of the starting material **3** also is discussed.

4,5-Dihydro-3(2H)-pyridazinones play an important role in the research of the pharmacologically valuable compounds. They have a wide variety of activities for example inhibition of platelet aggregation[1], reduction of blood pressure[2], positive inotropic activity[3] and others. These compounds are also important in the synthetic organic chemistry because they can be easily transformed to the unsaturated analogues, 3(2H)-pyridazinones[4,5].

4,5-Dihydro-3(2H)-pyridazinone derivatives can be obtained by the reaction of hydrazine with appropriately substitued 4-oxo-butanoic acids or its esters[6]. There

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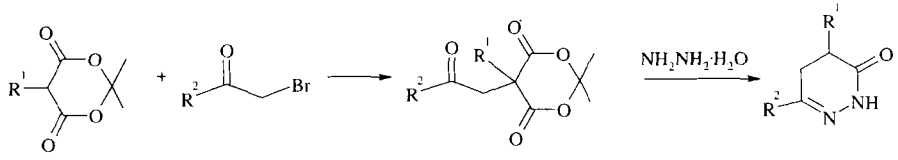
are numerous examples for the production of 6-substituted 4,5-dihydro-3(2H)--pyridazinones in the literature, such as an interesting one-pot method[7] but for 4,6--disubstituted 4,5-dihydro-3(2H)-pyridazinones there are not many. The reason can be found in the fact that one of the most important starting materials, 2,4--disubstituted 4-oxo-butanoic acids cannot be easily prepared.

Herein we offer efficient methods for the production of both starting materials **3** and the title compounds **4**.



1 **2** **3** **4**

The compounds **1** were obtained by the reaction of substituted malonic acids and acetone according to Meldrum's method[8] or more conveniently by a one-pot reaction[9] in wich 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, **1**, R^1=H) was reacted with aldehydes in the presence of triethylamine and formic acid. As it is known in the literature[10] Meldrum's acid and α-bromoketones **2** give 5-monosubstituted Meldrum's acid derivatives **3** (R^1=H) in the presence of acetic acid and sodium acetate in dimethylformamide. We tried to reproduce this reaction and found that twice substituted product **3** (R^1=R^2-CO-CH_2-) always formed, too independently of the reaction conditions. Authors[10] didn't carry out the reaction starting from 5-alkyl or 5-aryl Meldrum's acids **1**, but we succesfully performed 5-monosubtituted Meldrum's acids **1** with α-bromoketones **2**. The

reactions were complete within a day at room temperature and the products **3** could be easily isolated. It is worth mentioning that dimethyl (3,4--dimethoxyphenyl)methylmalonate was reacted with 4-chloro-α-bromoacetophenone in the same way but the conversion was only about 30%. Preparing nearly hundred compounds **3** we have found that the yield depends mainly on the structure of R^1 substituent, similarly to the production of dialkyl disubstituted malonates from monosubstituted malonates.

Table 1. Meldrum's acid derivatives **3** prepared

Product	R^1	R^2	Yield[a] (%)	Mp (°C)
3a	H	C_6H_5	47[b]	140-142[b]
3b	C_6H_5	C_6H_5	27	155-156
3c	3-$ClC_6H_4CH_2$	C_6H_5	66	206-208
3d	4-$ClC_6H_4CH_2$	C_6H_5	66	204-205
3e	3,4-$(OMe)_2C_6H_3CH_2$	C_6H_5	67	186-187
3f	3-$ClC_6H_4CH_2$	4-ClC_6H_4	67	186-188
3g	4-$ClC_6H_4CH_2$	4-ClC_6H_4	71	187-188
3h	3,4-$(OMe)_2C_6H_3CH_2$	4-ClC_6H_4	74	177-178
3i	2-thienylmethyl	4-ClC_6H_4	72	189-191

[a] Based on purified products.
[b] Lit[10]: 58% and 139-141° ; 11% of 5,5-disubstituted derivative was isolated by us, too.

We also prepared compound **3c** by a method[11] for synthesis of 5,5-di(2-oxo-2--phenyl-ethan-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione among others. This reaction took place under solid-liquid phase-transfer conditions. No difference was observed between the yields therefore we preferred the former method[10] because it was simpler than the other[11].

The reaction of the compounds **3** and hydrazine resulted in the formation of 4,5-dihydro-3(2H)-pyridazinone derivatives **4**. The reaction took place at room temperature for a day, at 80° for 4 hours or at 100° for 2 hours. The reaction failed when the compounds **3** were reacted with substituted hydrazines, for example phenylhydrazine. At least two moles of hydrazine were needed, because acetone forming in the reaction by opening 1,3-dioxane-4,6-dione ring also reacts with hydrazine. With regard to weak solubility of acetone hydrazone in water and in most of the organic solvents it can be easily separated from the product **4**. Dimethylformamide and an alcohol can be the solvent. It is worth using 4 mol equivalents of hydrazine at room temperature but 2 mol equivalents of it is satisfactory boiling in ethanol.

The reaction involves a few steps. Our effort to separate intermediates failed. In the course of reactions a few changes of the phases could be seen in the most cases. Adding hydrazine to a solution of compound **3** a violent evolution of heat was observed. Probably the keto group reacts firstly with hydrazine then 1,3--dioxane-4,6-dione ring opens which is indicated by the appearance of acetone hydrazone as a heavy oil. The closure of pyridazinone ring was carried out simultaneously with the evolution of carbon dioxyde gas derived from the decarboxylation.

The yields of the crude products **4** usually exceeded 90%. The reaction, carrying out at room temperature, gave the crude products contained less than 5% of impurities in general and it could be used to further chemical performance without any purification. When the compound **3** had an acetoxy group in one of the phenyl rings desacetylation occured. A one-pot reaction was carried out for the synthesis

Table 2. 4,5-Dihydro-3(2H)-pyridazinones **4** prepared

Product	R^1	R^2	Yield[a] (%)	Mp (°C)
4a	H	C_6H_5	76[b]	150-151.5[b]
4b	C_6H_5	C_6H_5	91[c]	166-167[c]
4c	3-$ClC_6H_4CH_2$	C_6H_5	75	110-111
4d	4-$ClC_6H_4CH_2$	C_6H_5	81	139-140
4e	3,4-$(OMe)_2C_6H_3CH_2$	C_6H_5	73	119-121
4f	3-$ClC_6H_4CH_2$	4-ClC_6H_4	90	141-142
4g	4-$ClC_6H_4CH_2$	4-ClC_6H_4	82	180-181
4h	3,4-$(OMe)_2C_6H_3CH_2$	4-ClC_6H_4	84	154-155
4i	2-thienylmethyl	4-ClC_6H_4	85	179-180

[a] Based on purified products
[b] Lit[12] : 84% and 149-151°C
[c] Lit[13] : 69% and 163°C

of **4g** without preparing the intermediate **3g** starting from 5-(4-chloro-benzyl)--Meldrum's acid. The yield, based on 5-(4-chloro-benzyl)-Meldrum's acid was 41%, less than in the case when **4g** was synthetized in two steps (58%).

Nearly hundred compounds **4** were synthetized. Two of the four compounds studied showed good positive inotropic activity in the first tests.

EXPERIMENTAL PART

Melting points: Kofler instrument, uncorrected. IR: Perkin-Elmer 1605 FT-IR. NMR: Bruker WP-200SY.

5,5-Disubstituted 1,3-dioxane-4,6-dione 3; general procedure

Water free sodium acetate (8.61 g; 0.105 mol), acetic acid (10 ml) and α-bromo-methyl-ketone (0.105 mol) was added to a solution or suspension of 5-

-monosubstituted 1,3-dioxane-4,6-dione (**1**, 0.1 mol) in DMF (100 ml). The reaction mixture was stirred at room temperature for a day. It was poured on a mixture of ice-water (1000 g) and a saturated solution of Na_2CO_3 (100 ml). The solid was filtered out and washed with water. If the crude product separated as an oily and sticky material it was decantated and digested with cold water or/and a little volume of cold EtOH. The crude and wet product was crystallized from acetone.

5-Phenyl-5-(2-oxo-2-phenyl-ethan-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione 3b

IR (KBr) $\nu_{CO}(cm^{-1})$: 1776, 1740, 1684. ^1H NMR ($CDCl_3$/TMS), δ(ppm): 1.36 (s, 3H), 1.94 (s, 3H), 4.14 (s, 2H), 7.3-8.0 (m, 10H). Anal. calcd. for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 71.14; H, 5.40.

5-(3-chloro-benzyl)-5-(2-oxo-2-phenyl-ethan-1-yl)-2,2-dimethyl-1,3-dioxane--4,6-dione 3c

IR: 1754, 1720, 1680. ^1H NMR ($CDCl_3$): 0.85 (s, 3H), 2.00 (s, 3H), 3.30 (s, 2H), 4.05 (s, 2H); 7.0-8.1 (m, 9H). Anal. calcd. for $C_{21}H_{19}ClO_5$: C, 65.20; H, 4.95; Cl, 9.17. Found: C, 65.31; H, 4.94; Cl, 9.21.

5-(4-chloro-benzyl)-5-(2-oxo-2-phenyl-ethan-1-yl)-2,2-dimethyl-1,3-dioxane--4,6-dione 3d

IR: 1762, 1732, 1681. ^1H NMR ($CDCl_3$): 0.86 (s, 3H), 2.01 (s, 3H), 3.30 (s, 2H),

4.05 (s, 2H); 7.0-8.1 (m, 9H). Anal. calcd. for $C_{21}H_{19}ClO_5$: see **3c**. Found: C, 65.46; H, 4.86; Cl, 9.33.

5-(3,4-Dimethoxy-benzyl)-5-(2-oxo-2-phenyl-ethan-1-yl)-2,2-dimethyl-1,3--dioxane-4,6-dione 3e

IR: 1759, 1719, 1676. ^{1}H NMR ($CDCl_3$): 0.86 (s, 3H), 2.00 (s, 3H), 3.27 (s, 2H), 3.87 (s, 6H), 4.03 (s, 2H); 6.4-8.1 (m, 8H). Anal. calcd. for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.91; H, 5.95.

5-(3-chloro-benzyl)-5-(2-oxo-2-(4-chloro-phenyl)-ethan-1-yl)-2,2-dimethyl--1,3-dioxane-4,6-dione 3f

IR: 1757, 1725, 1686. ^{1}H NMR ($CDCl_3$): 0.86 (s, 3H), 2.00 (s, 3H), 3.27 (s, 2H), 4.00 (s, 2H); 7.0-8.0 (m, 8H). Anal. calcd. for $C_{21}H_{18}Cl_2O_5$: C, 59.87; H, 4.31; Cl, 16.83. Found: C, 59.90; H, 4.18; Cl, 16.94.

5-(4-chloro-benzyl)-5-(2-oxo-2-(4-chloro-phenyl)-ethan-1-yl)-2,2-dimethyl--1,3-dioxane-4,6-dione 3g

IR: 1757, 1719, 1672. ^{1}H NMR ($CDCl_3$): 0.83 (s, 3H), 1.98 (s, 3H), 3.26 (s, 2H), 3.99 (s, 2H); 7.0-8.0 (m, 8H). Anal. calcd. for $C_{21}H_{18}Cl_2O_5$: see **3f**. Found: C, 60.03; H, 4.21; Cl, 16.98.

5-(3,4-Dimethoxy-benzyl)-5-(2-oxo-2-(4-chloro-phenyl)-ethan-1-yl)-2,2--dimethyl-1,3-dioxane-4,6-dione 3h

IR: 1756, 1727, 1677. ^{1}H NMR ($CDCl_3$): 0.83 (s, 3H), 1.97 (s, 3H), 3.25 (s, 2H), 3.85 (s, 6H), 3.98 (s, 2H); 6.5-8.0 (m, 7H). Anal. calcd. for $C_{23}H_{23}ClO_7$: C, 61.82; H, 5.19; Cl, 7.93. Found: C, 62.12; H, 5.22; Cl, 8.03.

5-(2-Thienyl-methyl)-5-(2-oxo-2-(4-chloro-phenyl)-ethan-1-yl)-2,2--dimethyl-1,3-dioxane-4,6-dione 3i

IR: 1758, 1718, 1682. ^{1}H NMR ($CDCl_3$): 0.98 (s, 3H), 2.01 (s, 3H), 3.56 (s, 2H), 4.00 (s, 2H); 6.8-8.0 (m, 7H). Anal. calcd. for $C_{19}H_{17}ClO_5S$: C, 58.09; H, 4.36; Cl, 9.02; S, 8.16. Found: C, 58.12; H, 4.41; Cl, 9.00; S, 8.30.

4,5-Dihydropyridazin-3(2H)ones 4, general procedure

Hydrazine hydrate (9.7 ml; 0.2 mol) was added to a cooled solution or suspension of Meldrum's acid derivative (**3**, 0.05 mol) in DMF (50-100 ml) at 20-30° for 10 minutes. The reaction mixture was stirred at room temperature for 7 hours then it was allowed to stand for 17 hours. The mixture was poured onto a mixture of ice and water (400 g) in such a way that the oily acetone hydrazone wasn't added to it. Hydrochloric acid (17%) was added to the suspension until pH 4-5. The solid was filtered out, washed with water then it was dried. The crude product was crystallized from methanol, ethanol or from a mixture of ethanol and DMF.

4-(3-Chloro-benzyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one 4c

IR : 1675. ^{1}H NMR($CDCl_3$): 2.5-3.0 (m, 4H); 3.32 (m, 1H); 7.0-7.7 (m, 9H); 8.89 (s, 1H). Anal. Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 68.50; H, 5.06; Cl, 11.89; N, 9.40.

4-(4-Chloro-benzyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one 4d

IR : 1664. ^{1}H NMR($CDCl_3$): 2.5-3.0 (m, 4H); 3.30 (m, 1H); 7.0-7.7 (m, 9H); 8.77 (s, 1H). Anal. Calcd. for $C_{17}H_{15}ClN_2O$: see **4c**. Found: C, 68.16; H, 4.97; Cl, 11.87; N, 9.34.

4-(3,4-Dimethoxy-benzyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one 4e

IR : 1670. ^{1}H NMR($CDCl_3$): 2.5-3.0 (m, 4H); 3.23 (m, 1H); 3.71 (s, 3H); 3.86 (s, 3H); 6.5-7.8 (m, 8H); 8.68 (s, 1H). Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.22; N, 8.63. Found: C, 70.09; H, 6.19; N, 8.51.

4-(3-Chloro-benzyl)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-3(2H)-one 4f

IR : 1670. ^{1}H NMR($CDCl_3$): 2.5-3.0 (m, 4H); 3.32 (m, 1H); 7.0-7.7 (m, 8H); 8.82 (s, 1H). Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O$: C, 61.28; H, 4.23; Cl, 21.28; N, 8.41. Found: C, 61.39; H, 4.06; Cl, 20.73; N, 8.46.

4-(4-Chloro-benzyl)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-3(2H)-one 4g

IR : 1679. ^{1}H NMR(DMSO): 2.5-3.2 (m, 5H); 7.1-7.8 (m, 8H); 11.07 (s, 1H). Anal. Calcd. for $C_{17}H_{14}Cl_2N_2O$: see **4f**. Found: C, 61.19; H, 4.20; Cl, 21.15; N, 8.56.

4-(3,4-Dimethoxy-benzyl)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-3(2H)--one 4h

IR : 1672. ^{1}H NMR($CDCl_3$): 2.5-2.9 (m, 4H); 3.22 (m, 1H); 3.28 (s, 3H); 3.38 (s, 3H); 6.6-7.7 (m, 7H); 8.87 (s, 1H). Anal. Calcd. for $C_{19}H_{19}ClN_2O_3$: C, 63.60; H, 5.34; Cl, 9.88; N, 7.81. Found: C, 63.79; H, 5.22; Cl, 9.91; N, 7.79.

4-(2-Thienyl-methyl)-6-(4-chloro-phenyl)-4,5-dihydropyridazin-3(2H)-one 4i

IR : 1675. ^{1}H NMR(DMSO): 2.6-3.3 (m, 5H); 6.8-7.8 (m, 7H); 11.09 (s, 1H). Anal. Calcd. for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; Cl, 11.63; N, 9.19; S, 10.52. Found: C, 58.98; H, 4.17; Cl, 11.65; N, 9.28; S, 10.80.

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