A one-pot reaction of Meldrum's acid with ethyl orthoformate and hydrazines

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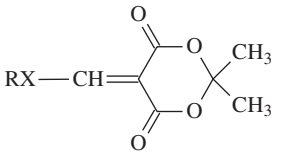
Meldrum's acid has been converted into its corresponding nitrogenous derivatives under a parallel condition by successive treatment with triethyl orthoformate and hydrazines in one-pot reaction.

Keywords: Meldrum's acid, hydrazines, triethyl orthoformate, one-pot reaction

In recent years, 5-substituted Meldrum's acids **1** have been reported as key building blocks in the construction of heterocyclic combinatorial libraries[1-3] and as important reagents which have been widely used in many fields[1-10] with many advantages over their corresponding acyclic malonic esters.[1] The nitrogenous derivatives of Meldrum's acid are useful as intermediates for preparing 5-membered and 6-membered heterocycles.[5,7,11]



1, R = alkyl, aralkyl; X = O, NH, S

In the special case where X is a hydrazo group (NHNH), 5-(hydrazinomethylene)Meldrum's acids **2** (**1**, X = NHNH) might also be of use as building blocks in the construction of heterocyclic combinatorial libraries. Using **2** as starting material, some heterocyclic compounds which may be of potential pharmaceutical activity should be obtained by known procedures, such as Fischer indolisation. Although the synthesis of 5-substituted Meldrum's acids **1** (X = nitrogen) has been described by many chemists,[8,11-13] the direct synthesis of 5-(hydrazinomethylene)Meldrum's acids **2** from Meldrum's acid has not been reported yet. As a potential precursor of Fischer indoles, in fact, 5-(hydrazinomethylene) Meldrum's acids **2** were easily prepared by successive treatment of Meldrum's acid with triethyl orthoformate and hydrazines in a one-pot procedure in good yields (see Scheme 1 and the Table 1). However, an alternative procedure for the one-pot reaction which differed feeding sequence afforded only moderate yields.

Table 1 shows that we could obtain the products in high yields and that the method is a practical and convenient route for the preparation of a variety of 5-(hydrazinomethylene) Meldrum's acids **2**. Further studies on the application of these products will be reported in due course.

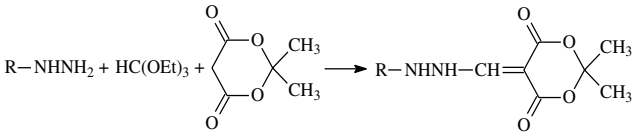
Experimental

Melting points are uncorrected. ^{1}H NMR spectra were determined on a Varian instrument using TMS as an internal standard and $CDCl_3$ or DMSO-d_6 as a solvent. IR spectra were recorded on a Perkin-Elmer 683 instrument. Mass spectra were obtained on an AEI MS-902 instrument. Elemental analyses were performed on a Carlo-Erba 1106 analytical instrument.

General procedure for synthesis of **2**.

2a is used as an example and is also for **2b** and **2e–h** but 17ml of solvent and triethyl formate (3 mmol) for **2c** and **2d**.

2a: Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (3 mmol) and triethyl orthoformate (20 ml) were heated under reflux for 2 h, followed by addition of phenylhydrazine (3 mmol). The mixture was stirred under reflux for 1 h to complete the reaction



Scheme 1

Table 1 Reaction conditions and results for the formation of 5-(hydrazinomethylene)Meldrum's acids **2**[a]

	R	Solvent	Time/min	Yield/%
2a	C_6H_5-	[b]	60	92
2b	4-ClC_6H_4-	[b]	150	81
2c	2,4-$Cl_2C_6H_3$-	Acetonitrile	120	85
2d	2,4-$(NO_2)_2C_6H_3$-	Benzene	240	86
2e	3-$CH_3C_6H_4$-	[b]	150	75
2f	2-$CH_3CH_2C_6H_4$-	[b]	60	90
2g	4-$NH_2SO_2C_6H_4$-	[b]	150	80
2h	CH_3CO-	[b]	30	89

[a]Prepared according to Scheme 1 (see also Experimental); [b]excess triethyl orthoformate.

(The reaction process was monitored by thin layer chromatography). The precipitated crystals were collected, washed with water and methanol and dried to give a colourless product **2a**, yield 92%. The product can be further purified by recrystallisation (using acetonitrile as a solvent) to give pure product **2a**.

Other products were synthesised by a similar method. The appropriate solvents and reaction times are listed in Table 1 and all the products were duly characterised by ^{1}H NMR, MS, IR and elemental analysis as follows. The melting points for **2a**, **2b** and **2c** differs from those in the literature and have been checked.

2a: M.p. 190–191 °C (lit.[12] 202–204 °C); IR (KBr, cm^{-1}) 3230, 3200, 1710, 1667, 1630, 1498, 1445, 1284, 1202, 820, 752; ^{1}H NMR ($CDCl_3$) δ 1.74(6H, s), 7.35–7.55(5H, m), 8.12(1H, d, *J*=10 Hz), 8.46(1H, s), 11.82(1H, d, *J*=10 Hz); MS (*m/z*, %) 263(3.42), 262(0.74, M$^+$), 205(100), 204(55.97), 161(95.44), 160(34.75), 149(42.85), 105(17.20); Anal. calcd. for $C_{13}H_{14}N_2O_4$ C 59.5% H 5.4% N 10.7%, Found C 60.0% H 5.3% N 10.5%.

2b: M.p. 181–183 °C(lit.[12] 218–220 °C); IR (KBr, cm^{-1}) 3281, 3233, 1724, 1666, 1638, 1493, 1451, 1275, 1205, 1014, 924, 795, 659; ^{1}H NMR ($CDCl_3$) δ 1.74(6H, s), 6.47(1H, br), 6.76–6.80(2H, m), 7.26–7.29(2H, m), 8.38–8.41(1H, dd, *J*=1 Hz, *J*=12 Hz), 10.35(1H, d, *J*=12 Hz); MS (*m/z*, %) 298(0.33), 297(0.90), 296(0.44, M$^+$), 238(51.83), 194(45.51), 139(20.02), 111(22.07); Anal. calcd. for $C_{13}H_{13}ClN_2O_4$ C 52.6% H 4.4% N 9.4%, Found C 53.2% H 4.4% N 9.3%.

2c: M.p. 190–192 °C (lit.[12] 214–216 °C); IR (KBr, cm^{-1}) 3330, 3163, 1724, 1686, 1618, 1441, 1301, 1289, 1207, 934, 816; ^{1}H NMR ($CDCl_3$) δ 1.75 (6H, s), 7.36–7.37(3H, m), 7.50–7.51(1H, m), 8.61(1H, d, *J*=14 Hz), 11.64(1H, d, *J*=14 Hz); MS (*m/z*, %) 317(12.32), 315(18.64), 260(25.54), 259(27.85), 258(40.95), 257(37.08), 178(46.14), 150(10.66); Anal. calcd. for $C_{13}H_{12}Cl_2N_2O_4$ C 47.15% H 3.65% N 8.5%, Found C 47.5% H 3.7% N 8.6%.

2d: M.p. 190–192 °C; IR (KBr, cm^{-1}) 3327, 3270, 1728, 1687, 1619, 1452, 1344, 1271, 1148, 793, 740; ^{1}H NMR (DMSO-d_6) δ 1.68(6H, s), 2.50–2.51(2H, m), 7.28(1H, d, *J*=9 Hz), 8.24(1H, s), 8.39–8.42(1H, dd, *J*=9 Hz, *J*=3 Hz), 8.87(1H, d, *J*=3 Hz), 10.93(H, s); MS (*m/z*, %) 351(2.43, M-1), 291(6.56), 239(99.26), 180(41.15), 163(55.82); Anal. calcd. for $C_{13}H_{12}N_4O_8$ C 44.3% H 3.4% N 15.9%, Found C 44.5% H 3.5% N 16.0%.

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2e: M.p. 108–110 °C; IR (KBr, cm^{-1}) 3250, 3168, 1730, 1674, 1629, 1596, 1437, 1273, 1202, 1011, 824, 735; ^{1}H NMR ($CDCl_3$) δ 1.759(3H, s), 1.765(3H, s), 7.04–7.10(4H, m), 7.30–7.31(1H, m), 8.64(1H, d, *J*=14 Hz), 11.20(1H, d, *J*=14 Hz); MS (*m/z*, %) 277(0.60, M+1), 261(21.67), 203(92.29), 158(62.34), 144(80.59), 130(100), 91(49.61); Anal. calcd. for $C_{14}H_{16}N_2O_4$ C 60.9% H 5.8% N 10.1%, Found C 61.2% H 5.95% N 10.1%.

2f: M.p. 184–187 °C; IR (KBr, cm^{-1}) 3272, 3189, 1710, 1674, 1635, 1604, 1439, 1276, 1196, 1128, 922, 809, 735; ^{1}H NMR ($CDCl_3$) δ 1.27(3H, t, *J*=8 Hz), 1.71(6H, s), 2.58(2H, q, *J*=8 Hz), 6.61(1H,s), 6.79–7.20(4H, m), 8.41(1H, d, *J*=12 Hz), 10.34(1H, d, *J*=12 Hz); MS (*m/z*, %) 275(0.70), 232(76.98), 188(9.62), 146(21.68), 119(100); Anal. calcd. for $C_{15}H_{18}N_2O_4$ C 62.1% H 6.25% N 9.65%, Found C 61.9% H 6.2% N 9.6%.

2g: M.p. 186–188 °C; IR (KBr, cm^{-1}) 3335, 3269, 3226, 1723, 1664, 1600, 1449, 1320, 1287, 1157, 923, 795, 731, 541; ^{1}H NMR (DMSO-d_6) δ 1.66(6H, s), 6.83–6.86(2H, m), 7.15(2H, s), 7.66–7.69(2H, m), 8.08(1H, d, *J*=13 Hz), 9.32(1H, s), 11.04(1H, d, *J*=13 Hz); MS (*m/z*, %) 293(100), 156(53.01), 184(18.39); Anal. calcd. for $C_{13}H_{15}N_3O_6S$ C 45.7% H 4.4% N 12.3%, Found C 46.0% H 4.4% N 12.2%.

2h: M.p. 178–180 °C; IR (KBr, cm^{-1}) 3243, 3162, 1728, 1671, 1630, 1557, 1442, 1284, 1202, 1011, 914, 800, 731, 550; ^{1}H NMR ($CDCl_3$) δ 1.63(6H, s), 1.92(3H, s), 8.01(1H, s), 11.05(2H, br); MS (*m/z*, %) 229(0.10), 228(0.22), 171(3.27), 170(2.29), 126(6.40), 84(27.92); Anal. calcd. for $C_9H_{12}N_2O_5$ C 47.4% H 5.3% N 12.3%, Found C 47.4% H 5.35% N 12.3%.

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