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Practical Large Scale Synthesis of Half-Esters of Malonic Acid[1)]

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A practical large-scale synthesis of monomethyl malonate and monoethyl malonate, which are among the most commonly applied half-esters in organic synthesis, is described, applying the highly efficient selective monohydrolysis of symmetric diesters we reported before. The optimal conditions with regard to the type of base, equivalent, co-solvents, and the reaction time have been examined for large-scale reactions. Monomethyl malonate and monoethyl malonate were obtained in high yields with near 100% purity within only half a day. The conditions of this selective monohydrolysis reaction are environmentally benign and straightforward, as it requires only water, a small proportion of a volatile co-solvent, and inexpensive reagents, and produces no hazardous by-products, and therefore the synthetic utility of this reaction in process chemistry is expected.

Key words selective monohydrolysis; half-ester; green chemistry; monoalkyl malonate

Half-esters of malonic acid such as monomethyl malonate and monoethyl malonate are very important building blocks. They have been frequently applied to synthesis of a variety of significant pharmaceuticals and natural products.[2—13)] However, their commercial availability is still limited and quite expensive, and they are more commonly available as the corresponding potassium salts. In particular, monomethyl malonate became commercially available only last year, but is expensive, or the purities are typically less than 99%, such as 96%. Therefore, development of a more efficient synthetic method for monoalkyl malonates on a large scale is essential.

One method for preparation of half-esters is monosaponification of symmetric diesters, but successful distinction of the two identical ester groups remains challenging. In fact, monosaponification typically produces a dirty mixture of the starting diester, the corresponding half-ester, and the diacid, even with the use of one equivalent of a base. In particular, the synthesis of half-esters of malonic acid is still difficult especially on a large scale, because of potential decarboxylation. Only a limited number of examples of monosaponification of dimethyl or diethyl malonate have been reported,[14—16)] but they require a long time and more than one step. Some modified methods are reported applying Meldrum's acid,[17,18)] but Meldrum's acid is costly and not suitable for large-scale production of monoalkyl malononate. The enzymatic monohydrolysis of dialkyl malonates reported utilizes an enzyme not commercially available.[19)] Other methods by carbalkoxylation of malonic acid are also reported, but the yields are rather modest.[20)]

Herein we describe a large-scale synthesis of monomethyl malonate and monoethyl malonate applying the selective monohydrolysis of symmetric diesters we reported before. Earlier, we reported a selective monohydrolysis that enables a series of symmetric diesters with the use of an aqueous NaOH or KOH and a co-solvent such as tetrahydrofuran (THF) or CH_3CN at 0 °C (Chart 1).[21)] This reaction is practical, mild, and environmentally benign, and has been of interest in process chemistry, exhibiting the potential of scaling up.

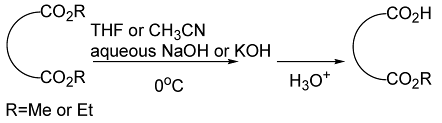

Chart 1

The selectivity of this reaction was initially found to be particularly high for cyclic 1,2-diesters with the two ester groups in close proximity, even with the use of almost 2 equivalents (or greater) of the base, producing the corresponding half-esters in near-quantitative yields. We reasoned that electrostatic attractive interaction between the two closely located carbonyl groups may play a role in this high selectivity. We recently modified the conditions of this reaction and applied them to monohydrolysis of a series of dialkyl malonates and their derivatives on the scale of 1.2 mmol.[22)] They show that the yields are around 80% to near quantitative. Here we examined the possibility of scaling up this reaction, focusing on monomethyl malonate and monoethyl malonate, which are among the synthetic building blocks most commonly applied to organic synthesis.

In scaling up the reaction, we first examined the reaction parameters, such as the co-solvent, types of base, the equivalent of the base, and the reaction time. From previous studies, we knew that relatively polar aprotic solvents, such as THF, acetonitrile, and dimethyl sulfoxide (DMSO), help improve the selectivity and accelerate the reaction time.[23)] Among the bases that are commonly applied to organic synthesis, we had found that KOH tends to be more reactive and selective than NaOH, but LiOH is less reactive and less selective for this selective monohydrolysis reaction.[24)] Therefore we first optimized these reaction parameters using THF and acetonitrile, which are volatile upon work-up and therefore more suitable than DMSO, as co-solvents, and KOH and NaOH as the base.

We first tested monohydrolysis of a 0.12-mol scale of dimethylmalonate. Since on the large scale, a far greater amount of solvent and a far larger reaction vessel are required, the concentration on this larger scale is 200 times greater than that we reported earlier.[22)] We also attempted the same concentration for monohydrolysis of diethyl malonate, but it resulted in reduced yields. The potential reason may be that the corresponding mono carboxylate had somewhat reduced solubility in the reaction media, possibly due to the increased hydrophobicity. Therefore we applied 50 times

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more concentrated conditions than those we had reported earlier[22] for 0.8 mol of diethyl malonate.

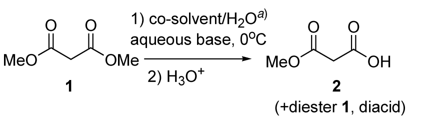
The results are summarized in Table 1 for monohydrolysis of dimethyl malonate, and Table 2 for that of diethyl malonate. The formed half-esters are obtained by distillation under reduced pressure instead of column chromatography. The reactions were monitored by TLC and stopped when the consumption or near-consumption of the starting diesters was observed.

A small amount of diacid (malonic acid) was extracted upon work-up unlike smaller scale reactions, but a larger portion of the formed diacid remained in the aqueous layer, and the extracted diacid conveniently remained after the distillation.

From Table 1, it is apparent that 0.8 equivalent of the base is not enough to maximize the yield. In fact, 0.8 equivalent of NaOH was found insufficient for monohydrolysis of diethyl malonate (entry 1, Table 2). Therefore in Table 2, we applied only 1.0 and 1.2 equivalents of NaOH and KOH for the remaining trials of monohydrolysis of diethyl malonate (entries 2—10).

From these results, it appears that for monohydrolysis of dimethylmalonate, either aqueous base (NaOH or KOH) showed comparable reactivity and selectivity when one equivalent of the base with either THF or acetonitrile was used, although the optimal conditions were found when 1.0 equivalent of aqueous KOH and acetonitrile was used. On the other hand, for monohydrolysis of diethylmalonate, the optimal conditions were more clearly found when 1.0 equivalent of aqueous KOH and acetonitrile was used. This observation makes an interesting contrast with the smaller scale synthesis of the same half-esters, which did not exhibit critical differences by the choice of co-solvents or base or its equivalent. The efficacy of the co-solvent also became more apparent in these large-scale reactions, as it appeared to increase the solubility of the diesters or monocarboxylate and also more efficiently dispersed them in the reaction mixture, which was expected from our previous studies.[23]

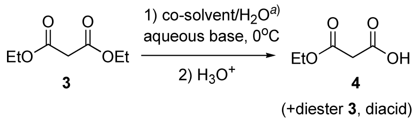
Table 1



Entry	Base	Eq.	Co-solvent	Time	Half-ester (%)[b]	Diacid (%)
1	NaOH	0.8	THF	1 h	67.1 (24.5)	0
2	NaOH	1.0	THF	1 h	81.9 (7.0)	2.7
3	NaOH	1.2	THF	1 h	67.4 (1.7)	8.3
4	NaOH	0.8	CH_3CN	1 h	69.0 (23.9)	0
5	NaOH	1.0	CH_3CN	1 h	82.1 (6.6)	4.4
6	NaOH	1.2	CH_3CN	1 h	71.3 (0)	15.8
7	KOH	0.8	THF	1 h	75.0 (20.9)	1.5
8	KOH	1.0	THF	1 h	83.1 (3.4)	4.3
9	KOH	1.2	THF	1 h	72.4 (0)	17.2
10	KOH	0.8	CH_3CN	1 h	75.7 (16.3)	1.9
11	KOH	1.0	CH_3CN	1 h	84.5 (0)	4.3
12	KOH	1.2	CH_3CN	1 h	69.1 (0)	17.1
13	KOH	1.0	None	2 h	79.6 (1.9)	4.4
14	KOH	1.2	None	1.5 h	76.0 (0)	9.8

a) The ratio between co-solvent and H_2O is 1 : 10. *b*) Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

Table 2



Entry	Base	Eq.	Co-solvent	Time	Half-ester (%)[b]	Diacid (%)
1	NaOH	0.8	THF	1 h	46.9 (27.4)	7.0
2	NaOH	1.0	THF	1 h	55.4 (13.0)	14.3
3	NaOH	1.2	THF	1 h	60.9 (1.9)	16.4
4	NaOH	1.2	THF	0.5 h	74.1 (0.2)	10.0
5	NaOH	1.0	CH_3CN	1 h	76.0 (6.6)	4.1
6	NaOH	1.2	CH_3CN	0.5 h	67.0 (4.4)	12.4
7	KOH	1.0	THF	1 h	75.0 (4.4)	4.6
8	KOH	1.2	THF	0.5 h	76.9 (0.7)	8.3
9	KOH	1.0	CH_3CN	1 h	81.0 (1.4)	1.4
10	KOH	1.2	CH_3CN	0.5 h	63.4 (1.9)	17.5
11	KOH	1.0	None	4 h	42.2 (16.4)	29.8
12	KOH	1.2	None	6 h	35.6 (6.9)	36.6

a) The ratio between co-solvent and H_2O is 1 : 10. *b*) Isolated yield of the half-ester. The recovered diester is shown in parentheses (%).

Therefore using these optimal reaction conditions, we tried a large-scale monohydrolysis of dimethyl malonate and diethyl malonate. The scales for these reactions are 1.2 mol (158.30 g) and 0.8 mol (128.66 g), respectively. Since the reaction temperature is an important factor,[25] the reactions were carried out in a cold room maintained at 0—4 °C. After the reaction mixture was worked up, the half-ester was collected by distillation. The yields were 81% for monomethyl malonate and 82% for monoethyl malonate by these procedures. The boiling point of the diester and the corresponding half-ester are quite different in both cases, and the small amount of diacid (malonic acid) remained entire after the distillation. Therefore, the separation of the diester, half-ester, and diacid are straightforward, and comparable to column chromatography on a smaller scale, the separation by distillation on these larger scales was found to be an efficient way to isolate pure monomethyl or monoethyl malonate.

This procedure can produce monomethyl malonate and monoethyl malonate in high yields by one step within a reaction time of only about one hour even on this large scale. This reaction time is substantially shorter than the reported selective monosaponification,[14,15] which typically requires two steps. The total amount of time required for the entire procedure is only half a day, as opposed to the previously reported large-scale selective monosaponification,[14,15] which takes more than one day. The elemental analysis of the produced monomethyl and monoethyl malonates are close to the theoretical components within 0.4% error, indicating that these half-esters have a purity of nearly 100%. The entire procedure requires only water and a small proportion of acetonitrile, and produces no hazardous by-products, demonstrating the greenness of this reaction.[26]

Recently, water-mediated reactions have become important as environmentally friendly reactions. To our knowledge, this selective monohydrolysis is among the first examples of water-mediated reactions that are applied to desymmetrization. We are currently investigating the reaction mechanisms for the high selectivity by various physicochemical techniques, and the results will be reported in due course.

In summary, we have examined conditions for a large scale synthesis of monomethyl malonate and monoethyl malonate, applying the selective monohydrolysis of symmetric diesters we reported previously. Since this reaction is extremely green and practical, with mild and safe conditions, and requires only inexpensive reagents, its synthetic utility, particularly in process chemistry, is expected.

Experimental

The ^{1}H-NMR at 300 MHz and ^{13}C-NMR at 75 MHz spectra were measured as solutions in CDCl$_3$ using tetramethylsilane (TMS) as an internal standard. The IR spectra were recorded on an FT-IR instrument. The 5 M KOH was titrated with 20 ml of 0.5 M oxalic acid.

Synthesis of Monomethyl Malonate, 2 In a 1 l-sized one-necked flask, equipped with a magnetic stirrer, was placed 158.30 g (1.2 mol) of dimethyl malonate, **1**, and 10 ml of acetonitrile was added to dissolve this dimethyl malonate, **1**. After the solution was stirred for one minute, the reaction mixture was cooled to 0 °C with an ice-water bath in a cold room maintained at 0—4 °C. To this mixture, 100 ml of water was added and the mixture was stirred for 30 min. To this reaction mixture was added 240 ml of 5 M aqueous KOH (1.2 mol) solution dropwise with continuous stirring for a period of 15 min with an addition funnel. When this addition was completed, the reaction mixture was stirred for one additional hour while covered with a stopper and immersed in the ice-water bath in the cold room maintained at 0—4 °C. The reaction was monitored by TLC using a staining solution prepared with bromocresol green (40 mg) dissolved in ethanol (100 ml, 200 proof).

The reaction mixture was acidified with 150 ml of 12 M aqueous HCl solution in the ice-water bath, saturated with NaCl, and extracted with five 500 ml portions of ethyl acetate with a 1 l separatory funnel. The extract was washed with 500 ml of a saturated aqueous NaCl solution. The ethyl acetate extract was dried over approximately 100 g of anhydrous sodium sulfate. After the drying agent was removed by gravity filtration, the ethyl acetate solution was concentrated by a rotary evaporator and distilled under a reduced pressure at 2.5 mmHg. The fraction showing a boiling point of 91—92 °C was collected to yield monomethyl malonate, **2**, as a colorless oil. The yield of monomethyl malonate, **2**, was 114.77 g (81%).[27] ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 3.47 (2H, s), 3.78 (3H, s), 10.88 (1H, br s). ^{13}C-NMR (75 MHz, CDCl$_3$) δ: 40.52 (t), 52.51 (q), 167.09 (s), 171.33 (s). IR (neat) cm^{-1}: 1724, 1741, 2960—3185. *Anal.* Calcd for C$_4$H$_6$O$_4$: C, 40.68; H, 5.12. Found: C, 40.29; H, 5.27.

Synthesis of Monoethyl Malonate, 4 In a 1 l-sized one-necked flask, equipped with a magnetic stirrer, was placed 128.66 g (0.8 mol) of diethyl malonate, **3**, and 30 ml of acetonitrile was added to dissolve this diethyl malonate, **3**. After the solution was stirred for 1 min, the reaction mixture was cooled to 0 °C with an ice-water bath in a cold room maintained at 0—4 °C. To this mixture, 300 ml of water was added and the mixture was stirred for 30 min. To this reaction mixture was added 160 ml of 5 M aqueous KOH (0.8 mol) solution dropwise with continuous stirring for a period of 15 min with an addition funnel. When this addition was completed, the reaction mixture was stirred for one additional hour while covered with a stopper and immersed in the ice-water bath in the cold room maintained at 0—4 °C. The reaction was monitored by TLC using a staining solution prepared with bromocresol green (40 mg) dissolved in ethanol (100 ml, 200 proof).

The reaction mixture was acidified with 120 ml of 12 M aqueous HCl solution in the ice-water bath, saturated with NaCl, and extracted with five 500 ml portions of ethyl acetate with a 1 l separatory funnel. The extract was washed with 500 ml of a saturated aqueous NaCl solution. The ethyl acetate extract was dried over approximately 100 g of anhydrous sodium sulfate. After the drying agent was removed by gravity filtration, the ethyl acetate solution was concentrated by a rotary evaporator and distilled under a reduced pressure at 2.5 mmHg. The fraction showing a boiling point of 79—81 °C was collected to yield monoethyl malonate, **4**, as a colorless oil. The yield of monoethyl malonate, **4**, was 87.073 g (82%).[28] ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.30 (3H, t, J=7.2 Hz), 3.44 (2H, s), 4.24 (2H, q, J=7.2 Hz), 10.21 (1H, br s). ^{13}C-NMR (75 MHz, CDCl$_3$) δ: 13.78 (q), 40.88 (t), 61.80 (t), 166.64 (s), 171.76 (s). IR (neat) cm^{-1}: 1722, 1741, 2914—3182. *Anal.* Calcd for C$_5$H$_8$O$_4$: C, 45.46; H, 6.10. Found: C, 45.76; H, 6.20.

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References and Notes

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26) Under comparable conditions on a 0.12 mol-scale with a reaction time of 1 h, we have also obtained the half-esters of dimethyl methyl malonate and diethyl methyl malonate in 90% and 83% yields, respectively.
27) Under the same pressure, 6.55 g (4%) of dimethyl malonate was collected at 45 °C, and 1.31 g (1%) of malonic acid remained after the distillation.
28) Under the same pressure, 5.60 g (4%) of diethyl malonate was collected at 43 °C, and 4.79 g (6%) of malonic acid remained after the distillation.