Tetrahedron Letters 49 (2008) 4434–4436

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly efficient selective monohydrolysis of dialkyl malonates and their derivatives

Satomi Niwayama *, Hanjoung Cho, Chunlei Lin

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

ARTICLE INFO

Article history:
Received 21 April 2008
Revised 1 May 2008
Accepted 1 May 2008
Available online 7 May 2008

Keywords:
Desymmetrization
Hydrolysis
Half-ester
Monoalkyl malonate derivatives

ABSTRACT

The highly efficient selective monohydrolysis of symmetric diesters has been applied to monohydrolysis of several dialkyl malonates and their derivatives. The best conditions apply 0.8–1.2 equiv of aqueous KOH with a co-solvent, THF or acetonitrile, at 0 °C. The procedure is highly practical, yielding the corresponding half-esters in high yields in a straightforward manner, without inducing decarboxylation. It was found that the selectivity tends to become higher with increased hydrophobicity.

Half-esters are very important synthetic building blocks. In particular, half-esters of malonic acid and its derivatives have been applied to synthesis of a variety of significant compounds.[1] Half-esters are commonly prepared by monohydrolysis of symmetric diesters with the use of enzymes, reactions which provide no basis for prediction of the reactivity. Classical saponification tends to produce a dirty mixture of the starting diester, the diacid and the half-ester, even with the use of 1 equiv of a base.

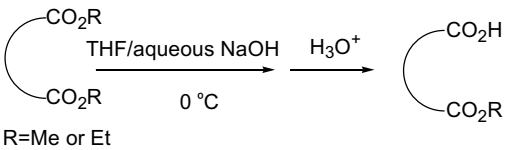
Half-esters of malonic acid and their derivatives are still difficult to obtain because of potential decarboxylation. A limited number of examples of selective monosaponification have been reported starting from diethyl malonate, dimethyl malonate,[2] or their derivatives.[3] However, most of these procedures require several steps, a large amount of the starting diesters, and a long time, and systematic studies have not been reported before. Some modified procedures have been reported that apply Meldrum's acid,[4] 4-nitro-3-oxobutyrate,[5] carboxylic acids,[6] or enzymes.[7] These methods produce rather modest yields of the corresponding half-esters, or isolated yields of the half-esters are not reported, and the enzymes reported are not commercially available.

However, by applying the selective monohydrolysis of symmetric diesters we reported before,[8] we have been able to obtain a series of half-esters of malonic acid derivatives in high yields in a straightforward manner. Herein we describe the synthesis of these half-esters of malonic acid and some derivatives by our modified procedure.

Earlier, we reported highly efficient selective monohydrolysis of symmetric diesters applying aqueous NaOH and THF media. This reaction enables monohydrolysis of a series of symmetric diesters in high yields (Scheme 1).[8]

The selectivity was 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 equiv 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 have been expanding the scope of this reaction to other diesters as well that do not necessarily adopt such ideal conformation. Here we applied this highly selective monohydrolysis reaction to selective monohydrolysis of diesters of malonic acid and their derivatives.

When we tried selective monohydrolysis of dimethyl malonate according to the conditions we reported before,[8] only 22% of the corresponding half-ester was obtained, perhaps due to the expected decarboxylation and overuse of the base, as well as lack of the ideal conformation of the starting diester. Therefore we reduced the equivalent of the base. We also switched the type of base to maximize the reaction conditions.



Scheme 1. Selective monohydrolysis of symmetric diesters.

* Corresponding author. Tel.: +1 806 742 3118; fax: +1 806 742 1289.
E-mail address: satomi.niwayama@ttu.edu (S. Niwayama).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.007

First the optimal amount of the base was examined for monohydrolysis of dimethyl malonate, **1**. We changed the amount of the base to 1.2, 1.0, or 0.8 equiv as well as the base itself and examined the yield of the half-ester. The procedures are similar to those we reported before.[9] The following table is a summary of the type of base, the equivalent, and the reaction times.

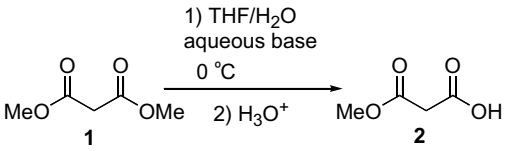
From these results, we found that the reactivity slightly increased with the use of KOH over NaOH with comparable selectivity, while LiOH slightly decreased the selectivity and reactivity. This tendency was expected from our previous studies comparing the selectivity of monohydrolysis of dimethyl glutarate with LiOH, NaOH, KOH, and CsOH.[10,11] In these reactions, the isolated yields of the half-ester and diester indicated that although a small amount of diacid (malonic acid) perhaps formed, it was not extracted during the work-up procedures, probably due to the small hydrophobic portion, indicating the practical aspect of this reaction. The product in this monohydrolysis reaction, monomethyl malonate, **2**, is among those most frequently applied to organic synthesis. This monohydrolysis appears to allow the highly practical synthesis of **2** with a reaction time of only about 1 h, which illustrates the synthetic utility of this monohydrolysis.

We next examined a wider range of dialkyl malonates and their derivatives using aqueous NaOH or KOH as a base. The results are summarized in Table 2. Most of these diesters are commercially available. Some diesters were prepared by the standard Fischer esterification.

Unlike classical monosaponification which tends to yield a complex yellowish reaction mixture, in all cases in our reactions, only pure half-esters, starting diesters, and in rare cases diacids, if extant, were isolated. Although in some cases in Table 2, based on the percentage of the yield of the half-ester and recovered diester, small amounts of the diacids appear to have formed, the diacids were not extracted when the reaction mixture was worked up. All the obtained half-esters had excellent purity, giving sharp elemental analysis data. No decarboxylated products were detected in any of the monohydrolysis reactions we tried. Overall, KOH tends to be more reactive and slightly more selective than NaOH, as was observed in the reaction above in Table 1. This tendency may be best illustrated in the monohydrolysis of diethyl phenylmalonate, **9** (entries 13 and 14), which showed enhanced reactivity and selectivity with the use of KOH, compared to the results we previously published with the use of NaOH for monohydrolysis of the same diester, **9**.[8]

Interestingly, an increase in the hydrophobicity of the molecule also seems to improve the selectivity. For example, the yields of the half-ester increase with ester groups that are more hydrophobic in comparison of the monohydrolysis of diesters **1**, **3**, and **4** (Table 1, and entries 1–4). The yields of half-esters become even higher when the additional methyl or phenyl group is introduced (entries 5–14). One of our hypotheses in this monohydrolysis reaction is that upon the monohydrolysis of the two identical ester groups, inter- and/or intramolecular hydrophobic attractive interactions within the remaining portion of the molecule may play an important role for this high selectivity, as such aggregates may be protected from further hydrolysis.[12] Therefore, this tendency may explain such potential hydrophobic interaction. The only exception is monohydrolysis of dipropyl phenylmalonate, **10** (entries 15 and 16), probably due to the extended period of the reaction time,

Table 1
Selective monohydrolysis of dimethyl malonate

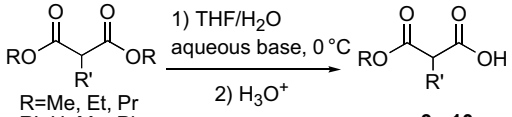


1 **2**

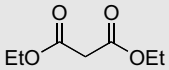
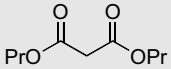
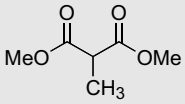
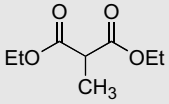
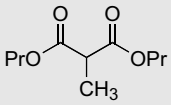
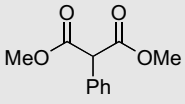
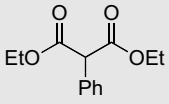
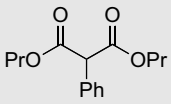
Entry	Base	Equivalent	Time	Half-ester **2**[a] (%)
1	LiOH	0.8	1 h	61 (13)
2	NaOH	0.8	0.5 h	62 (3)
3	KOH	0.8	1 h	84
4	LiOH	1.0	1 h	80 (10)
5	NaOH	1.0	1 h	82 (10)
6	KOH	1.0	1 h	83 (3)
7	LiOH	1.2	1 h	75 (10)
8	NaOH	1.2	1 h	83 (5)
9	KOH	1.2	1 h	74

[a] Isolated yield of the half-ester. The recovered diester is shown in the parentheses (%).

Table 2
Selective monohydrolysis dialkyl malonate derivatives



R=Me, Et, Pr
R'=H, Me, Ph
3-10 **3a-10a**

Entry	Diester	Base	Equivalent	Time	Half-ester[a] (%)
1		KOH	0.8	1 h	90
2	**3**	NaOH	1.0	1 h	86 (3)
3		KOH	0.8	1 h	91 (8)
4	**4**	NaOH	1.0	0.5 h	92 (8)
5		KOH	1.2	1.5 h	94 (2)
6	**5**	NaOH	1.2	1.5 h	93 (6)
7		KOH	1.2	1.5 h	96 (2)
8	**6**	NaOH	1.2	1.5 h	96 (4)
9		KOH	1.2	1.75 h	97 (3)
10	**7**	NaOH	1.2	1.75 h	98 (2)
11		KOH	1.2	1 h	95 (5)
12	**8**	NaOH	1.2	1 h	95 (5)
13		KOH	1.2	5 h	94 (4)
14	**9**	NaOH	1.2	5 h	86 (13)
15[b]		KOH	0.8	33 h	77 (22)
16[b]	**10**	NaOH	0.8	33 h	68 (32)

[a] Isolated yield of the half-ester. The recovered diester is shown in the parentheses (%).
[b] Acetonitrile was used instead of THF as a co-solvent.

which also sometimes allowed isolation of a visible amount of the corresponding diacid. Here the use of another slightly polar aprotic solvent that is slightly miscible with water, acetonitrile, instead of THF as a co-solvent helped accelerate the reaction time to some extent, increasing the yield of the half-ester by about 10%. Earlier we studied the influence of the co-solvent in this monohydrolysis and found that a slightly polar aprotic solvent with a small degree of miscibility with water appears to be an effective co-solvent.[13] It may also be possible that introduction of several bulky groups prohibited adoption of a preferable conformation for this selectivity.

In summary, we have found highly practical conditions with aqueous KOH or NaOH with THF or acetonitrile as a co-solvent at 0 °C to selectively monohydrolyze a series of dialkyl malonates and their derivatives. The yields here are among the highest reported. All the half-esters prepared here showed excellent purity[14] and are quite stable over a long period of time. We also found that the selectivity generally increases as the hydrophobicity of the starting diesters increases.

Acknowledgment

This work is supported by the National Science Foundation-CAREER (CHE-0443265).

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for half-esters, **2**, **3a**, **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, and **10a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.007.

References and notes

1. For example, (a) Bulychev, A.; Bellettini, J. R.; O'Brien, M.; Crocker, P. J.; Samama, J.-P.; Miller, M. J.; Mobashery, S. *Tetrahedron* **2000**, *56*, 5719–5728; (b) Bihovsky, R.; Pendrak, I. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1541–1542; (c) Horikawa, M.; Shirahama, H. *Synlett* **1996**, 95–96; (d) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396–10399; (e) Kim, H.-J.; Lindsey, J. *J. Org. Chem.* **2005**, *70*, 5475–5486; (f) Knoelker, H.-J.; Wolpert, M. *Tetrahedron Lett.* **1997**, *38*, 533–536; (g) Marcaccini, S.; Pepino, R.; Pozo, M. C.; Basurto, S.; Garcia-Valverde, M.; Torroba, T. *Tetrahedron Lett.* **2004**, *45*, 3999–4001; (h) List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Job, A.; Rios Torres, R. *Tetrahedron* **2006**, *62*, 476–482; (i) Balasubramanian, T.; Lindsey, J. S. *Tetrahedron* **1999**, *55*, 6771–6784; (j) Hudson, R. D. A.; Osborne, S. A.; Stephenson, G. R. *Synlett* **1996**, 845–846; (k) Ashton, M. J.; Hills, S. J.; Newton, C. G.; Taylor, J. B.; Tondu, S. C. D. *Heterocycles* **1989**, *28*, 1014–1035; (l) Williams, D. R.; Kammler, D. C.; Goundry, R. F. *Heterocycles* **2006**, *67*, 555–559.
2. (a) Strube, R.E. Organic Synthesis; Wiley: New York, NY, 1963; Collect. Vol. 4, pp 417–419.; (b) Grakauskas, V.; Guest, A. M. *J. Org. Chem.* **1978**, *43*, 3485–3488; (c) Hutchinson, C. R.; Nakane, M.; Gollman, H.; Knutson, P.L. Organic Synthesis; Wiley: New York, NY, 1990; Collect. Vol. 7, pp 323–326.
3. For example, (a) Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897–5905; (b) Vecchi, A.; Melone, G. J. *J. Org. Chem.* **1959**, *24*, 109–110; (c) Westermann, J.; Schneider, M.; Platzek, J.; Petrov, O. *Org. Process Res. Dev.* **2007**, *11*, 200–205; (d) de Meijere, A.; Ernst, K.; Zuck, B.; Brandl, M.; Kozhushkow, S. I.; Tamm, M.; Yufit, D. S.; Howard, J. A. K.; Labahn, T. *Eur. J. Org. Chem.* **1999**, *11*, 3105–3115; (e) De Kimpe, N.; Boeykens, M.; Tehrani, K. A. *J. Org. Chem.* **1994**, *59*, 8215–8219; (f) Robertson, A.; Sandrock, W. F. *J. Chem. Soc.* **1933**, 1617–1618; (g) Eaton, P. E.; Nordari, N.; Tsanaktsidis, J.; Upadhyaya, S. P. *Synthesis* **1995**, 501–502.
4. (a) Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 3073–3076; (b) Junek, H.; Ziegler, E.; Herzog, U.; Kroboth, H. *Synthesis* **1976**, 332–334.
5. Duthaler, R. *Helv. Chim. Acta* **1983**, *66*, 1475–1492.
6. Ozaki, E.; Uragaki, T.; Sakashita, K.; Sakimae, A. *Chem. Lett.* **1995**, 539–540.
7. Krapcho, A. P.; Jahngen, E. G. E., Jr.; Kashdan, D. S. *Tetrahedron Lett.* **1974**, *15*, 2721–2723.
8. Niwayama, S. *J. Org. Chem.* **2000**, *65*, 5834–5836.
9. *Typical procedures are as follows*: Dimethyl malonate, **1**, (159 mg, 1.20 mmol) was dissolved in 2 mL of THF, and 20 mL of water was added. The reaction mixture was cooled to 0 °C in an ice-water bath. To this mixture was added the indicated equivalent of a 0.25 M aqueous NaOH, KOH, or LiOH solution dropwise with stirring. The reaction mixture was stirred for 30 min to one hour, acidified with 1 M HCl at 0 °C to make the pH about 2, saturated with NaCl, immediately extracted with ethyl acetate (X4), and dried over Na_2SO_4. This extract was concentrated in vacuo and purified by silica gel column chromatography with hexane–ethyl acetate (3:1) and then ethyl acetate as typical eluents to afford monomethyl malonate.
10. Niwayama, S.; Rimkus, A. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 498–500.
11. We are finding a similar tendency in selective monohydrolysis of other symmetric or non-symmetric diesters. These results will be published in due course.
12. We are investigating further mechanistic studies to detect potential intermediates by physicochemical techniques.
13. Niwayama, S.; Wang, H.; Hiraga, Y.; Clayton, J. C. *Tetrahedron Lett.* **2007**, *48*, 8757–8760.
14. The structures of all the half-esters reported here were determined by ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis. The spectral data are as follows:
    Monomethyl malonate (**2**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.39 (2H, s), 3.70 (3H, s), 11.19 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 40.50, 52.50, 167.03, 171.46; IR (neat, cm^{-1}) 1741, 1746, 2960–3185. Anal. Calcd for $C_4H_6O_4$: C, 40.68; H, 5.12. Found: C, 40.51; H, 5.34.
    Monoethyl malonate (**3a**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.25 (3H, t, J = 7.2), 3.39 (2H, s), 4.19 (2H, q, J = 7.2), 10.67 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.84, 40.90, 61.85, 166.69, 171.77; IR (neat, cm^{-1}) 1736, 1741, 2914-3182. Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.83; H, 6.30.
    Monopropyl malonate (**4a**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.93 (3H, t, J = 7.7), 1.66 (2H, m), 3.42 (2H, s), 4.11 (2H, q, J = 7.2), 10.14 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.13, 21.69, 40.89, 67.42, 166.81, 171.75; IR (neat, cm^{-1}) 1723, 1740, 2883–3181. Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.43; H, 7.14.
    Monomethyl methylmalonate (**5a**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43 (3H, d, J = 7.2), 3.48 (1H, q, J = 7.2), 3.74 (3H, s), 9.42 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.08, 45.48, 52.39, 170.16, 175.38; IR (neat, cm^{-1}) 1721, 1739, 2956–3202. Anal. Calcd for $C_5H_8O_4$: C, 45.46; H, 6.10. Found: C, 45.65; H, 5.94.
    Monoethyl methylmalonate (**6a**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.22 (3H, t, J = 7.2), 1.40 (3H, d, J = 7.5), 3.44 (1H, q, J = 7.2), 4.19 (2H, q, J = 7.2), 11.21 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.44, 13.90, 45.93, 61.69, 169.83, 176.00; IR(neat, cm^{-1}) 1722, 1735, 2946–3200. Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.68; H, 6.75.
    Monopropyl methylmalonate (**7a**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.92 (3H, t, J = 7.5), 1.43 (3H, d, J = 7.2), 1.65 (2H, m), 3.47 (1H, q, J = 7.2), 4.10 (2H, q, J = 7.2), 10.62 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.17, 13.51, 21.77, 45.94, 67.24, 169.93, 175.96; IR (neat, cm^{-1}) 1717, 1739, 2883–2971. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.74; H, 7.49.
    Monomethyl phenylmalonate (**8a**):
    White solid; mp 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.75 (3H, s), 4.65 (2H, s), 7.35 (5H, m), 8.99 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 53.06, 57.33, 128.55, 128.77, 129.15, 131.96, 168.59, 173.24; IR (neat, cm^{-1}) 1717, 1740, 2956–3212. Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.92; H, 5.40.
    Monoethyl phenylmalonate (**9a**):
    White solid; mp 74 °C (lit. 76–77 °C);[3a] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.25 (3H, t, J = 7.2), 4.21 (2H, q, J = 7.2), 4.63 (1H, s), 7.37 (5H, m), 10.16 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 13.81, 57.51, 62.10, 128.39, 128.62, 129.13, 132.01, 167.95, 173.84; IR (neat, cm^{-1}) 1717, 1737, 2941–3190. Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.30; H, 5.80.
    Monopropyl phenylmalonate (**10a**):
    Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.87 (3H, t, J = 7.5), 1.64 (2H, m, J = 7.2), 4.12 (2H, m), 4.64 (1H, s), 7.35 (5H, m), 10.02 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 10.16, 21.74, 57.47, 67.72, 128.48, 128.73, 129.12, 132.21, 168.41, 173.07; IR (neat, cm^{-1}) 1717, 1736, 2881–3067. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.17; H, 6.61.