ORGANIC LETTERS

2011
Vol. 13, No. 16
4406–4409

Efficient Synthesis of Dissymmetric Malonic Acid *S,O*-Esters via Monoalcoholysis of Symmetric Dithiomalonates under Neutral Conditions

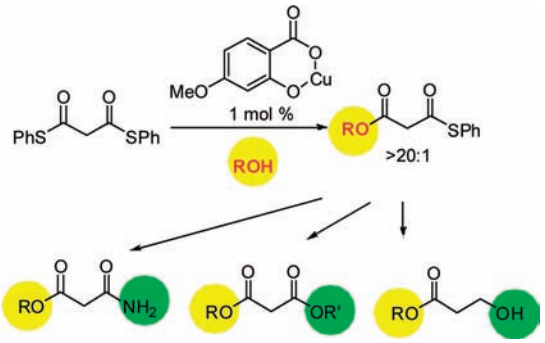
Kazumasa Matsuo[†] and Mitsuru Shindo*[,‡]

Interdisciplinary Graduate School of Engineering Sciences and Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga-koen, Kasuga 816-8580, Japan

shindo@cm.kyushu-u.ac.jp

Received June 28, 2011

ABSTRACT



A novel method for the highly selective synthesis of dissymmetric *S,O*-malonates starting from symmetric diphenyl dithiomalonates under neutral conditions is described. The key step is the thermal formation of an acylketene, the stability of which would contribute to the selectivity. The synthetic utility of the dissymmetric *S,O*-malonates is also shown.

Malonic acid and its derivatives are useful synthons for organic synthesis. Although symmetric malonic acid diesters can be derived from malonic acid via diesterification, dissymmetric malonates are not easily prepared from the symmetric malonates, because attempts at selective monoesterification of malonic acid usually produce a mixture of the starting malonic acid, the desired monoester, and the diester. To prepare the dissymmetric monoester selectively, enzymatic processes can be used but with the drawback of high substrate specificity.[1] Several chemical processes of dissymmetrization, for example, saponification[2] and nucleophilic ring-opening of Meldrum's acid, have also been used;[3] however, they are not always efficient due to facile decarboxylation and poor reproducibility. Recently, Niwayama reported a successful monohydrolysis of diesters including malonates **3** that gives the dissymmetric half esters **5** (Scheme 1).[4] Although the above methods have been used in organic synthesis, the development of a more efficient method for dissymmetrization of malonates that provides monoesters (e.g., **2**) with one *O*-ester and *one activated acyl group* would be very useful in synthon formation leading to functionalized malonates **4** from inexpensive symmetrical malonates.[5] We have been

[†] Interdisciplinary Graduate School of Engineering Sciences.
[‡] Institute for Materials Chemistry and Engineering.

(1) For a review, see: Gais, H.; Joachim; Theil, F. In *Enzyme Catalysis in Organic Synthesis*; Drauz, K., Waldman, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. II, p 335.

(2) Strube, R. E. *Org. Synth.* 1963, *Coll. Vol. 4*, 417–419.

(3) (a) Junek, H.; Ziegler, E.; Herzog, U.; Kroboth, H. *Synthesis* **1976**, 332–334. (b) Rigo, B.; Fasseur, D.; Cauliez, P.; Couturier, D. *Tetrahedron Lett.* **1989**, *30*, 3073–3076. The other synthetic methods for dissymmetric malonates, see:(c) Duthaler, R. *Helv. Chim. Acta* **1983**, *66*, 1475–1492. (d) Krapcho, A. P.; Jahngen, E. G. E., Jr.; Kashdan, D. S. *Tetrahedron Lett.* **1974**, *15*, 2721–2723.

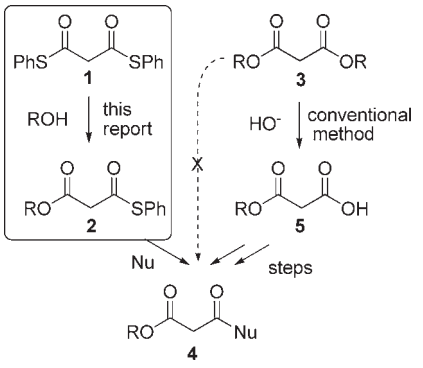
(4) Niwayama, S.; Cho, H.; Lin, C. *Tetrahedron Lett.* **2008**, *49*, 4434–4436.

(5) For recent examples for synthetic utility of dissymmetric malonates, see: (a) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M-h.; Jew, S-s.; Park, H-g. *J. Am. Chem. Soc.* **2011**, *133*, 4924–4929. (b) Mashiko, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 14990–14999. (c) Fortner, K.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 1032–1033.

10.1021/ol201744u
Published on Web 07/26/2011

focusing our group on thioesters,[6] which are not only more reactive than *O*-esters but also more stable and more easily handled than regular active acylating reagents such as acid halides and anhydrides. Indeed, thioesters act as a critical, acylating functionality in biological systems. Based on these facts, we considered *S,O*-esters **2** with one *S*-ester and one *O*-ester as very valuable synthons.[7] Herein, we report the highly efficient dissymmetrization of symmetric malonic acid dithioesters affording *S,O*-malonic acid esters via catalytic and/or noncatalytic selective monoalcoholysis through acylketenes as the key intermediate.

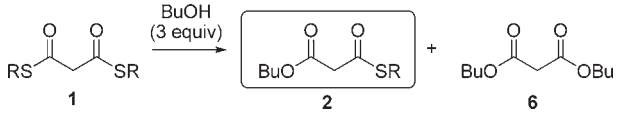
Scheme 1



We first attempted the alcoholysis of malonic acid diphenyl dithioester (**1a**) by mixing butanol in toluene, CH_2Cl_2, and ether, but no reaction occurred (Table 1, entries 1−3). However, when the mixture was placed in THF at 60 °C, a trace amount of the dissymmetric *S,O*-malonate **2a** could be detected (entry 4). Encouraged by this result, we examined more polar solvents in the alcoholysis of the dithiomalonate **1a** with butanol. Accordingly, the monoalcoholysis proceeded very smoothly in acetonitrile to afford **2a** almost quantitatively within 2 h, and only a trace amount of dibutyl malonate was detected, based on ^{1}H NMR analysis (entry 5). In the more polar solvents of DMF and DMSO, the reactions were further accelerated, but the yield was slightly diminished (entries 6−7) and a small amount of dibutyl malonate was generated. The dialkyl dithiomalonate (**1b**) did not react with butanol in acetonitrile (entry 8), but in DMF the desired product **2b** was obtained at higher temperature along with a small amount of **6** (entries 9−10). Consequently, we decided to examine the dissymmetrization of **1a** with various alcohols in acetonitrile at 60 °C.

Based on these results, we examined the monoalcoholysis of diphenyl dithiomalonates with various alcohols as shown in Table 2. Primary, secondary, and even sterically hindered tertiary alcohols, which however required a longer reaction time, reacted with **1a** to afford the *S,O*-dissymmetric malonates **2** with high selectively in good to excellent yields (entries 1−6). Unsaturated alcohols, such as allyl alcohol and propargyl alcohol, however, did not react at all under the standard conditions (entries 7−8).

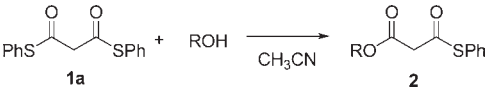
Table 1. Monoalcoholysis of Dithiomalonates under Neutral Conditions



entry	R	solvent[a]	temp/ °C[b]	time/ h	conversion/%	yield/% (**2**:**6**)
1	Ph (**1a**)	toluene	60	3.5	0	0
2	Ph (**1a**)	CH_2Cl_2	40	3.5	0	0
3	Ph (**1a**)	ether	34	3.5	0	0
4	Ph (**1a**)	THF	60	3.5	0	trace
5	Ph (**1a**)	CH_3CN	60	2	99	96 (**2a**) (>20:1)
6	Ph (**1a**)	DMF	60	1.2	>99	83 (**2a**) (>20:1)
7	Ph (**1a**)	DMSO	60	0.3	>99	83 (**2a**) (11:1)
8	Et (**1b**)	CH_3CN	60	1	0	0
9	Et (**1b**)	DMF	80	2	95	84 (**2b**) (12:1)
10	$C_{12}H_{25}$ (**1c**)	DMF	105	0.5	95	74 (**2c**) (3.5:1)

[a] 0.1 M. [b] Internal temperature.

Table 2. Monoalcoholysis of Dithiomalonates with Alcohols



entry	ROH (equiv)	time/ h	conversion/%	yield/%[a]
1	*t*-BuCH_2OH (3)	7	98	93 (**2d**)
2	dodecanediol (3)	6	98	89 (**2e**)
3	*s*-BuOH (3)	24	93	92 (**2f**)
4	*i*-PrOH (3)	24	97	93 (**2g**)
5	menthol (3)	5	>99	92 (**2h**)
6	*t*-BuOH (3)	24	75	70 (**2i**)
7	propargyl alcohol (3)	24	0	0
8	allyl alcohol (3)	24	0	0

[a] *O,O*-Malonates were generated in less than 5% yield.

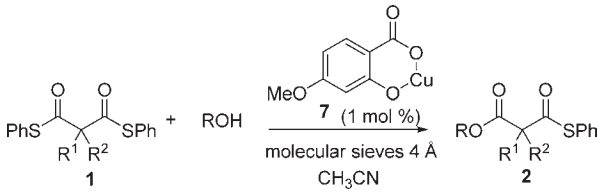
In order to increase the reactivity, the copper catalyst **7**, developed for activation of thioesters in the one-pot transesterification−Wittig lactonization,[6] was employed in the presence of 4 Å molecular sieves (17 mg per 1 mmol of the substrates), and it resulted in a considerable acceleration as shown in Table 3. Monoalcoholysis with BuOH and *t*-BuOH was complete within 1 h, and the less reactive allyl and propargyl alcohols afforded the dissymmetric *S,O*-esters in excellent yield with acceptable selectivity (Table 3, entries 1−4). Although the alcoholysis was retarded by the introduction of the α-alkyl-substitution on the dithiomalonates, the catalyst could accelerate the reaction sufficiently to afford the desired products in good yield (entries

(6) Matsuo, K.; Shindo, M. *Org. Lett.* **2010**, *12*, 5346–5349.

(7) (a) Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967–2970. (b) Vedejs, E.; Nader, B. *J. Org. Chem.* **1982**, *47*, 3193–3195. (c) Imamoto, T.; Kodera, M.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2303–2304.

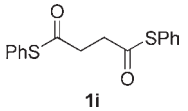
5−8). The α-fluoromalonate (**1g**) exhibited much lower reactivity, even though its steric hindrance is supposed to be negligible (entry 9). Neither α,α-dimethylmalonate (**1h**) nor diphenyl dithiosuccinate (**1i**) reacted with butanol even in the presence of the catalyst (entries 10−11).

Table 3. Cu-Catalyzed Monoalcoholysis of Dithiomalonates with Alcohols



entry	R^1, R^2	ROH (equiv)	time/ h	conversion/%	yield/ %	ratio[a]
1	H, H (**1a**)	BuOH	0.6	99	91 (**2a**)	20:1
2	H, H (**1a**)	*t*-BuOH (1.2)	1	96	82 (**2i**)	>20:1
3	H, H (**1a**)	allyl alcohol (1.2)	2.5	98	82 (**2j**)	14:1
4	H, H (**1a**)	propargyl alcohol (1.2)	4	93	71 (**2k**)	>20:1
5	Me, H (**1d**)	BuOH (3)	5	97	88 (**2l**)	17:1
6	Me, H (**1d**)	*t*-BuOH (3)	24	>99	80 (**2m**)	14:1
7	Et, H (**1e**)	BuOH (3)	5	74	72 (**2n**)	>20:1
8	*i*-Pr, H (**1f**)	BuOH (3)	48	76	74 (**2o**)	>20:1
9	F, H (**1g**)	BuOH (3)	48	67	55 (**2p**)	8:1
10	Me, Me (**1h**)	BuOH (3)	48	0	0	
11	**1i**	BuOH (3)	48	0	0	

[a] The ratio of **2** vs dialcoholysis.

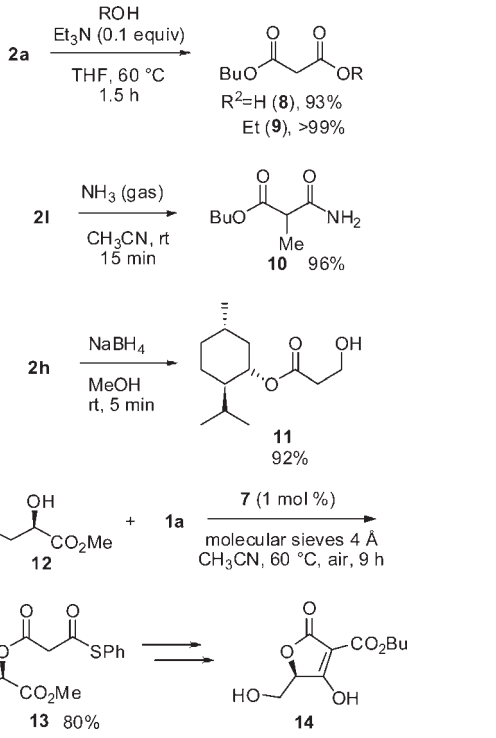


1i

In order to show synthetic utility, the *S*,*O*-dissymmetric malonates were converted into other synthons as depicted in Scheme 2. Hydrolysis, alcoholysis, and aminolysis of the half-thioesters (**2a**, **2l**) provided the corresponding dissymmetric products (**8**, **9**, **10**) in good yields. The reduction of **2h** with $NaBH_4$ provided the *β*-hydroxyester **11** in excellent yield. The α-hydroxyl ester **12** was subjected to the alcoholysis to furnish the corresponding ester **13**, which led to the bioactive tetronic acid (**14**).[8]

(8) Sodeoka, M.; Sampe, R.; Kojima, S.; Baba, Y.; Usui, T.; Ueda, K.; Osada, H. *J. Med. Chem.* **2001**, *44*, 3216–3222.

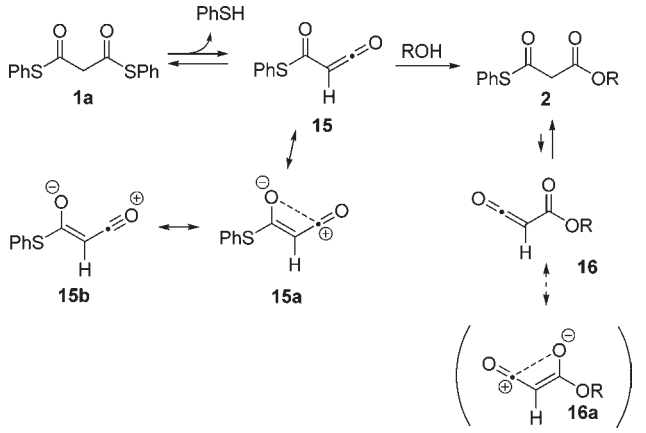
Scheme 2



The thermal transesterification of ethyl acetoacetate has been known to proceed through an acetylketene intermediate, supported by kinetic studies, which reveal that the first-order reaction rate constants are independent of the concentration of alcohol.[9,10] Judging from the inertness of α,α-dimethylmalonate (**1h**) and dithiosuccinate (**1i**), the acylketenes might also be a key intermediate in the alcoholysis of dithiomalonates. In order to confirm this hypothesis, kinetic studies on the reaction of **1a** (1.0 M) with butanol at 1.2, 3.0, and 5.0 M were examined under reflux conditions (82 °C) in acetonitrile. The first-order reaction rate constants (*k*) were 0.082, 0.091, 0.073 s^{-1}, respectively, which indicate that the rate constants are independent of the concentration of butanol. From these results, the key intermediates in this alcoholysis would be the thiocarboxyketenes **15** (Scheme 3), and the rate-determining step would be the formation of **15**. According to Tidwell in his discussion of acetylketenes,[11] the considerable stability of **15** would be attributed to resonance structures (**15a** and **15b**) and to a favorable intramolecular electrostatic interaction in **15a**. The solvent effect, polar solvents giving much better results, could be explained by the stabilization of the acylketenes as the zwitterionic species **15a** and **15b**.[11] The thiocarboxyketene **15** would be much more stable than the oxocarbonylketene **16**, because *O*-esters are less

(9) Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401–1404.
(10) Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186–2193.
(11) (a) Gong, L.; McAllister, M. A.; Tidwell, T. T. *J. Am. Chem. Soc.* **1991**, *113*, 6021–6028. (b) McAllister, M. A.; Tidwell, T. T. *J. Org. Chem.* **1994**, *59*, 4506–4515.

Scheme 3



easily enolized than thioesters and hence the zwitterionic stabilization as shown in **16a** would not be expected. The high selectivity of the monoalcoholysis could be attributed to the different thermal stabilities of the acylketenes. The copper catalyst would accelerate the formation of the thiocarboxyketene **15** by activation of the C−S bond. In the case of the less reactive alcohols and maybe less reactive malonates, the rate-determining step would be shifted to acylation (**15**→**2**), since the reaction rates are dependent on the alcohol. The copper catalyst might also activate the alcohols as well as increase the concentration of the ketene **15**. In the case of the α-substituted dithiomalonates, the rate-determining step would also be the acylation, since it is known that nucleophilic addition to ketenes is affected by the steric hindrance of α-substituents.[12]

In conclusion, we have developed a novel method for a highly selective synthesis of dissymmetric *S,O*-malonates starting from diphenyl dithiomalonates. It is noteworthy that the reaction can be carried out under neutral, mild conditions. The key step of this process is the thermal formation of the acylketene intermediates, the stability of which could contribute to the selectivity. The synthetic utility of the *S,O*-malonates was shown by several transformations.

Acknowledgment. This research was partially supported by a Grant-in-Aid for Scientific Research (B) (19390007) and an Inovative Areas "Organic Synthesis based on Reaction Integration" (22106534) from the MEXT and the Program for Promotion of Basic and Applied Research for Innovations in Bio-oriented Industry (BRAIN). One of the authors (K.M.) also acknowledges the support of the JSPS.

Supporting Information Available. Experimental procedures and characterization data for key compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Tidwell, T. T. *KETENES*, 2nd ed.; John Wiley & Sons: NJ, 2006; p 244.