Pergamon

Tetrahedron Letters, Vol. 38, No. 40, pp. 7091-7094, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01656-0

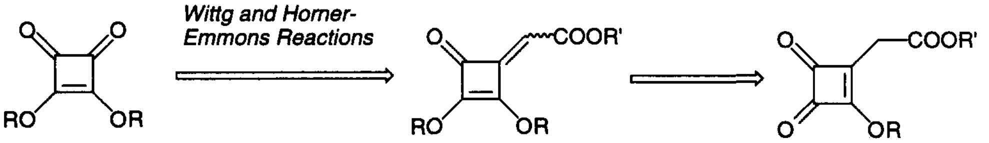
Olefination of Dialkyl Squarates by Wittig and Horner-Emmons Reactions. A Facile Synthesis of 3,4-Dioxo-1-cyclobutene-1-acetic Acid Esters.

Ken-ichi Hayashi, Tetsuro Shinada,* Kazuhiko Sakaguchi,
Manabu Horikawa,# and Yasufumi Ohfune*

Department of Material Science, Faculty of Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka 558, Japan
#Suntory Institute for Bioorganic Research, Wakayamadai, Shimamoto-cho, Mishima-gun, Osaka 618, Japan

Abstract: Olefination of dialkyl squarates **1-5** with several ylides **6** and phosphonates **7** gave the corresponding alkylidene products **8-12**. In the case of Horner-Emmons reactions, stereoselective formation of *Z*-alkylidene products was observed. An acid-catalyzed hydrolysis of **8-12** gave squarylacetic acid esters **13**. © 1997 Elsevier Science Ltd.

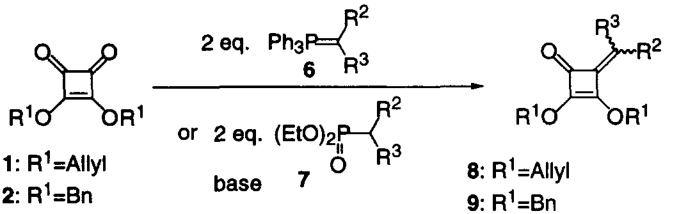
Squaric acid and its derivatives[1] have attracted considerable attention in view of their potential utility as advanced materials,[2] versatile C-4 synthons,[3] and an isoster of carboxylic acid.[4] In order to extend the utility of squaric acid, the carbon-carbon bond-forming reaction to squaric acid becomes an important subject in this area. One of the conventional methods for the carbon-carbon bond-forming reaction reported to date was an addition of a strong nucleophile such as organolithium or organomagnesium reagent.[5] However, this method was extremely limited due to its strong nucleophilicity which was incompatible with many unstable functional groups. Although several methods for carbon-carbon bond-forming reaction to squarates involving transition metal-catalyzed cross-coupling reactions[6] and an addition reaction of a silyl ketene acetal[7] to squaric acid derivatives have been reported, facile and practical methods are still sought. We expected that olefination reactions by Wittig and Horner-Emmons reactions would be an alternative. In this paper, we report a versatile method for olefination of dialkyl squarates and a subsequent conversion to the titled compound **13**.



Scheme 1

Since Wittig and Horner-Emmons olefinations to squarates have not been extensively examined,[8] we attempted these olefinations by the use of various kinds of ylides and phosphonates. As a result, we found that the use of ylides **6** and phosphonates **7** bearing an electron-withdrawing group gave the corresponding olefins **8-12** under mild reaction conditions.[9,10]

Results of the Wittig reactions are summarized in Table 1. Stable ylides **6a-e** derived from the acetates and acetonitrile smoothly reacted with the squarates **1-5** having both primary and secondary substituents on the alkoxy groups to give alkylidene products **8-12** with moderate stereoselectivities.



1: R^1=Allyl
2: R^1=Bn
3: R^1=*i*-Pr
4: R^1=3-Pentyl
5: R^1=2-Methyl-4-pentyl

8: R^1=Allyl
9: R^1=Bn
10: R^1=*i*-Pr
11: R^1=3-Pentyl
12: R^1=2-Methyl-4-pentyl

	R^2	R^3
a:	COOMe	H
b:	COOEt	H
c:	COO*t*-Bu	H
d:	COOEt	Me
e:	CN	H

Scheme 2

Table 1. Olefination with stable ylides **6a, c-e** [$Ph_3P=CR^2(R^3)$]

Entry	Substrate	Ylide	Solvent	Temp.	Time (h)	Product	Yield (%)	*E* / *Z* [a]
1	**1**	**6a**	CH_2Cl_2	rt	120	**8a**	82	2:1
2	**1**	**6c**	CH_2Cl_2	rt	48	**8c**	49	2:1
3	**2**	**6a**	CH_2Cl_2	rt	120	**9a**	85	3:1
4	**2**	**6c**	CH_2Cl_2	rt	48	**9c**	64	2:1
5	**3**	**6a**	CH_2Cl_2	rt	48	**10a**	93	2:1
6	**3**	**6c**	CH_2Cl_2	rt	48	**10c**	88	1:1
7	**4**	**6a**	CH_2Cl_2	reflux	20	**11a**	97	2:1
8	**5**	**6a**	CH_2Cl_2	reflux	42	**12a**	96	2:1
9	**3**	**6d**	benzene	reflux	48	**10d**	95	1:1.3
10	**3**	**6e**	THF	reflux	11	**10e**	63	2:1

[a] The ratios of the stereoisomers were determined by ^{1}H-NMR.[11] Stereostructures of *E*- and *Z*-**10a,d** were characterized by NOE experiments.[11] Stereostructures of *E*- and *Z*-**8a, 8c, 9a, 9c, 10c, 11a, 12a**, and **10e** were determined by the comparison of the chemical shift values of the olefinic protons with those of *E*- and *Z*-**10a**.

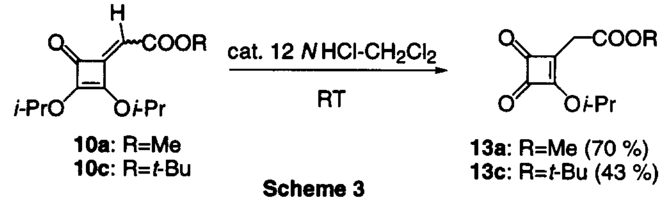
Horner-Emmons reactions also proceeded in the same manner as in the case of the Wittig reactions, except entry 1 (Table 2). Diisopropyl squarates **3** reacted with phosphonates **7b-e** to afford alkylidene products **10b-e**. Noteworthy was that the reactions proceeded in a stereoselective manner to give the *Z*-isomers as the major products (entries 2-6).[11] When phosphonate **7b** was employed for the olefination with diallyl squarates **1**, a small amount of the desired product was obtained (entry 1). This would be attributed to the 1,4-addition of the phosphonate. In fact, allyl alcohol was detected from the reaction mixture. Therefore, sterically bulky *t*-butyl ester **7c** was employed to diminish the undesired 1,4-addition. As expected, treatment of **1** and **2** with **7c** gave olefins **8c** and **9c** in good yields, respectively (entries 2 and 3).

Table 2. Olefination with phosphonates **7b-e** [$(EtO)_2P(O)CHR^2(R^3)$]

Entry	Substrate	Phosphonate	Base	Solvent	Temp.	Time	Product	Yield (%)	*E* / *Z*[a]
1	**2**	**7b**	NaH	THF	-20 °C	1 h	**9b**	<10	1:2
2	**2**	**7c**	NaH	THF	-20 °C	1 h	**9c**	68	1:14
3	**1**	**7c**	NaH	THF	-20 °C	30 min	**8c**	70	1:>19
4	**3**	**7b**	NaH	THF	-20 °C	3 h	**10b**	86	1:12
5	**3**	**7c**	NaH	THF	-20 °C	1 h	**10c**	91	1:19
6	**3**	**7d**	NaH	THF	rt	30 min	**10d**	86	1:>19
7	**3**	**7e**	*n*-BuLi	THF	rt	30 min	**10e**	71	1:1

[a] The ratios of the products were determined by ^{1}H-NMR.

We found that the alkylidene products can be converted into squarylacetic acid esters **13a,c**.[7a,12] Treatment of alkylidene product **10a,c** with 12 *N* hydrochloric acid provided **13a,c**, respectively (Scheme 3).[13]



10a: R=Me
10c: R=*t*-Bu

13a: R=Me (70 %)
13c: R=*t*-Bu (43 %)

Scheme 3

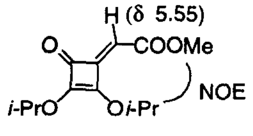
In summary, we have succeeded in an efficient synthesis of the squarylacetic acid esters **13** by the Wittig and Horner-Emmons reactions of dialkyl squarates followed by acid treatment. Since **13a,c** possessing an active methylene group are equivalent to a malonic ester, these squarates would be a useful building block for the synthesis of advanced materials and biologically active compounds.

Acknowledgments: This work was financially supported by a Grant-in-Aid (No. 09878122) from the Ministry of Education, Science and Culture, Japan, and New Energy and Industrial Technology Development Organization (NEDO), Ministry of International Trade and Industry, Japan.

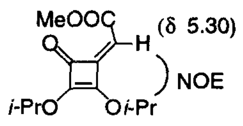
REFERENCES AND NOTES

1. For reviews: (a) Schmidt, A. H. *Synthesis* **1980**, 961-994. (b) Synder, J. P. *Nonbenzenoid Aromatics*; West, R.; Niu, J.; Academic Press: New York and London, 1969; p.311-345.
2. (a) Law, K. Y. *Chem. Rev.* **1993**, *93*, 449-486.
3. (a) Paquette, L. A.; Kuo, L. H.; Doyon, J. *J. Am. Chem. Soc.* **1997**, *118*, 3038-3047. (b) Yamamoto, Y.; Noda, M.; Ohno, M.; Eguchi, S. *J. Org. Chem.* **1997**, *62*, 1292-1298. (c) Sun, L; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *117*, 12473-12474. (d) Tomoka, C. S.; Liu, H.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 6009-6012. (e) Moore, H. W.; Yerxa, B. R. *ChemTracts* **1992**, *5*, 273-313.

4. (a) Chan, P. C. M.; Roon, R. J.; Koerner, J. F.; Taylor, N. J.; Honek, J. F. *J. Med. Chem.* **1995**, *38*, 4433-4438. (b) Campbell, E. F.; Park, A. K.; Kinney, W. A.; Fengl, R. W.; Liebeskind, L. S. *J. Org. Chem.* **1995**, *60*, 1470-1472. (c) Kim, C. U.; Misco, P. F. *Tetrahedron Lett.* **1992**, *33*, 3961-3962. (d) Ueda, Y.; Crast, L. B.; Mikkilineni, Jr., A. B.; Partyka, R. A. *Tetrahedron Lett.* **1991**, *32*, 3767-3770.
5. (a) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482-2488. (b) Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477-2482. (c) Kraus, J. L. *Tetrahedron Lett.* **1985**, *26*, 1867-1870. (d) Dehmlow, E. V.; Schell, H.G. *Chem. Ber.* **1980**, *113*, 1-8.
6. (a) Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3389-3904. (b) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 9868-9869. (c) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048-9055. (d) Liebeskind, L. S.; Wang, J. *Tetrahedron* **1993**, *49*, 5461-5470. (e) Edwards, J. P.; Krysan, D. J.; Liebeskind, L. S. *J. Org. Chem.* **1993**, *58*, 3942-3952. (f) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550-3556. (g) Liebeskind, L. S.; Yu, M. S.; Fengl, R. W. *J. Org. Chem.* **1993**, *58*, 3543-3549. (h) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293-4296.
7. (a) Yamamoto, Y.; Nunokawa, K.; Okamoto, K.; Ohno, M.; Eguchi, S. *Synthesis* **1995**, 571-576. (b) Yamamoto, Y.; Ohno, M.; Eguchi, S. *Chem. Lett.* **1995**, 525-526. (c) Ohno, M.; Yamamoto, Y.; Eguchi, S. *Tetrahedron* **1994**, *50*, 7783-7798. (d) Ohno, M.; Yamamoto, Y.; Eguchi, S. *Tetrahedron Lett.* **1993**, *34*, 4807-4810. (e) Ohno, M.; Yamamoto, Y.; Shirasaki, Y.; Eguchi, S. *J. Chem. Soc. Perkin Trans I* **1993**, 263-271. (f) Ohno, M.; Yamamoto, Y.; Eguchi, S. *J. Chem. Soc. Perkin Trans I* **1991**, 2272-2273.
8. Very recently, olefination of a dialkyl squarate by Tebbe reagent was reported. In this paper, difficulty in using the Wittig olefination was noted: Petasis, N. A.; Hu, Y.; Fu, D. *Tetrahedron Lett.* **1995**, *36*, 6001-6004.
9. Several attempts using unstable ylides, such as propylidene and benzylidene ylides, afforded the alkylidene products in moderate yields. The products were found to be unstable under the isolation processes and easily decomposed when stored under the ambient conditions.
10. Olefinations with the stabilized ylides required more than two equivalents of ylides or phosphonates for completion of the reactions.
11. Selected ^{1}H-NMR and NOESY data of *E*- and *Z*-**10a**.



E-**10a**



Z-**10a**

12. Bellus, D. *J. Am. Chem. Soc.* **1978**, *100*, 8027-8028.
13. Squarylacetic acid ester **13a** was obtained in a multi-gram scale by the present method.

(*Received in Japan* 18 *July* 1997; *revised* 4 *August* 1997; *accepted* 8 *August* 1997)