Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Efficient General Synthesis of Squarate Esters

Hiu Liu [a], Craig S. Tomooka [a] & Harold W. Moore [a]
[a] Department of Chemistry, University of California, Irvine, CA, 92717

Version of record first published: 22 Aug 2006.

To cite this article: Hiu Liu, Craig S. Tomooka & Harold W. Moore (1997): An Efficient General Synthesis of Squarate Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:12, 2177-2180

To link to this article: http://dx.doi.org/10.1080/00397919708006826

SYNTHETIC COMMUNICATIONS, 27(12), 2177-2180 (1997)

AN EFFICIENT GENERAL SYNTHESIS OF SQUARATE ESTERS

Hiu Liu, Craig S. Tomooka, and Harold W. Moore*
Department of Chemistry
University of California, Irvine, CA 92717

Abstract: An efficient and general method for the synthesis of alkyl squarates is presented. This involves the reactions of squaric acid with the desired alcohol in the presence of an orthoformate. This was applicable for the synthesis of dimethyl-, diethyl-, diisopropyl, di-*n*-butyl and di-*t*-butyl squarates in yields ranging from 77-97%. It is a convenient and safe method that can be accomplished on a multigram scale.

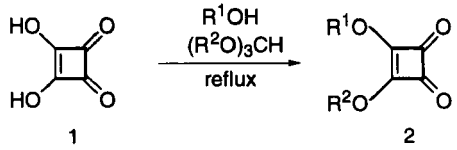
Reported here is a general procedure for the synthesis of dialkyl squarates, **2**, starting from squaric acid (**1**).[1] This brief report outlines the most efficient available route to squaric acid esters, a class of compounds that has been shown to be versatile starting materials for the regiospecific synthesis of a large variety of highly substituted organic compounds.[2] Other methods employed for the synthesis of these esters are limited in scope and often involve expensive or hazardous reagents.[3-5] For example, diisopropyl squarate (**2c**) can be easily prepared by a procedure involving the azeotropic removal of water from a refluxing benzene solution of squaric acid and isopropanol. However, this method is not useful for the synthesis of dimethyl squarate (**2a**). The dimethyl ester can be prepared from **2c** by transesterification or by procedures involving methylation (CH_3I) of the disilver salt of squaric acid or treatment of the acid

*To whom correspondence should be addressed.

itself with diazomethane. The transesterification route is useful but inefficient in that several steps are required; the silver salt method is expensive and it, as well as the diazomethane methylation, are inherently unsuited for large scale preparation.

The method presented here provides a convenient, safe and inexpensive route for the preparation of dialkyl squarates and is suitable for large scale syntheses. It involves refluxing an alcoholic solution of squaric acid (**1**) in the presence of an orthoformate. The corresponding esters **2a-e** are thus obtained on a multigram (1-20 g) scale in yields ranging from 77-97%.

Figure 1. Synthesis of Dialkylsquarates



1 2

	R^1	R^2	Yield
a	CH_3	CH_3	89
b	C_2H_5	C_2H_5	91
c	$(CH_3)_2CH$	$(CH_3)_2CH$	81
d	*n*-C_4H_9	*n*-C_4H_9	97
e	$(CH_3)_3C$	$(CH_3)_3C$	77
f	$(CH_3)_3C$	CH_3	21

For all examples outlined here, except for **2e**, the orthoformate employed corresponded to that of the incorporated alcohol. In the case of **2e**, trimethyl orthoformate was substituted since the *t*-butyl analog is not readily available. As a result, methanol is produced during the reaction and this competes with *t*-butanol in the ester-forming step. The result is the formation of both **2e** and **2f** in 77% and 21% yield, respectively.

Experimental Section[6]

All reagents were of commercial quality, reagent grade, and were used without further purification.

3,4-Dimethoxy-3-cyclobutene-1,2-dione (2a). A 500 mL round-bottomed flask was charged with squaric acid (20.53 g, 180.0 mmol),

methanol (180 mL), and trimethyl orthoformate (40.0 mL, 365 mmol). The reaction flask was equipped with a drying tube containing drierite and a condenser. The mixture was refluxed for 4 h and then 50 mL of the solvent was removed by short path distillation over the next 2 h. The remaining solution was allowed to reflux for an additional 18 h. The crude product was then concentrated under reduced pressure and the resulting pale yellow solid was dissolved in methylene chloride (40 mL) and subjected to flash chromatography through a short column of silica gel (hexanes/ethyl acetate 2:1). The solvent was removed under reduced pressure to afford dimethyl squarate (22.75 g, 89%) as a white solid, mp 55-56 °C; lit.[3] mp 56-58 °C.

3,4-Diethoxy-3-cyclobutene-1,2-dione (2b). A 250 mL round-bottomed flask was charged with squaric acid (6.84 g, 60.0 mmol), ethanol (60 mL), and triethyl orthoformate (25.0 mL, 150 mmol). The mixture was refluxed for 4 h and then 30 mL of the solution was removed by short path distillation over the next 0.5 h. The resulting solution was allowed to reflux for the next 19.5 h. The crude product was then concentrated under reduced pressure and the resulting orange oil was subjected to flash chromatography through a short column of silica gel (hexanes/ethyl acetate 2:1). The solvent was removed under reduced pressure to afford diethyl squarate (9.32 g, 91%) as a yellow oil.[3,4]

3,4-Diisopropoxy-3-cyclobutene-1,2-dione (2c). In a manner analogous to the above, squaric acid (1.14 g, 10.0 mmol), isopropanol (20 mL), and triisopropyl orthoformate (6.68 mL, 30.0 mmol) afforded di-isopropyl squarate (1.61 g, 81%) as a white solid, mp 43-44 °C; lit[4,5] mp 43-44 °C.

3,4-Di-n-butyl-3-cyclobutene-1,2-dione (2d). In a manner analogous to the above, squaric acid (1.14 g, 10.0 mmol), *n*-butanol (20 mL), and of tri-*n*-butyl orthoformate (10.6 mL, 40.0 mmol) afforded di-*n*-butyl squarate (2.19 g, 97%) as a yellow oil.[4]

3,4-Di-t-butyl-3-cyclobutene-1,2-dione (2e) and 3-*t*-Butyl-4-methyl-3-cyclobutene-1,2-dione (2f). A 500 mL round-bottomed flask was charged with squaric acid (6.84 g, 60.0 mmol), and *t*-butanol (240 mL). The mixture was refluxed for 1 h, during which time trimethyl orthoformate (66 mL, 600 mmol) was added and the resulting distillate (150 mL) was collected simultaneously *via* short path distillation. The crude product was then concentrated under reduced pressure. The resulting white solid was dissolved in ethyl acetate (20 mL) and subjected to flash

chromatography on a column of silica gel (hexanes/ethyl acetate 9:1-0:1) to afford di-*t*-butyl squarate (**2e**) (10.48 g 77%, mp 103-104 °C, lit[4] mp 104-105 °C), and *t*-butylmethyl squarate (**2f**) (mp 89-90 °C, 2.36 g, 21%): IR 1720, 1592, 1463, 1384, 1374, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.32 (s, 3H), 1.51 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 189.5, 188.5, 185.7, 184.6, 87.4, 60.8, 28,6; LRMS (EI) *m/e* 184 (M, 76), 169 (10), 129 (100); HRMS calcd for $C_9H_{12}O_4$ 184.0736, found 184.0737.

Acknowledgment: The authors thank the National Institutes of Health (GM-36312) for financial support and SmithKline Beecham Pharmaceuticals for a generous gift of squaric acid.

References and Notes

1. For leading reviews on the synthesis of squaric acid and derivatives see: a) Schmidt, A. H.; Ried, W. *Synthesis*, **1978**, 1; b) Schmidt, A. H.; Ried, W. *Synthesis*, **1978**, 869.
2. Moore, H. W.; Yerxa, B. R *Adv. in Strain in Org. Chem.*, **1995**, Vol 4, pp 81-161.
3. Cohen, S.; Cohen, S. G. *J. Am. Chem. Soc.* **1966**, 88, 1533.
4. Dehmlow, E. V.; Schell, H. G. *Chem. Ber.* **1980**, *113*, 1.
5. Liebeskind, L. S.; Fengl, R. W., Wirtz, K. R., Shawe, T. T. *J. Org. Chem.*, **1988**, 53, 2482.
6. *Caution!* One should be very careful when preparing dialkylsquarates since many members are know to be powerful skin irritants and sensitizes.

(Received in the USA 24 January 1997)