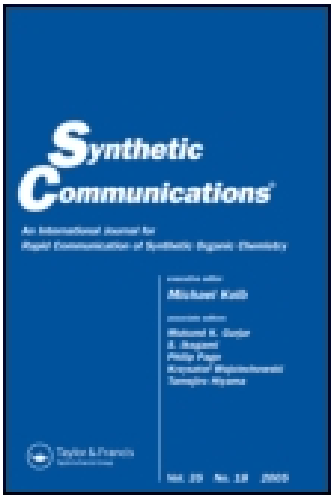

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 21 Aug 2006.

To cite this article: Zoltán Hell & László TŌke (1996) Efficient Method for Removal of a Carboxylic Acid Moiety from Sterically Crowded Cyclopropanedicarboxylic Acid Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:11, 2127-2133, DOI: 10.1080/00397919608003571

To link to this article: http://dx.doi.org/10.1080/00397919608003571

SYNTHETIC COMMUNICATIONS, 26(11), 2127-2133 (1996)

EFFICIENT METHOD FOR REMOVAL OF A CARBOXYLIC ACID MOIETY FROM STERICALLY CROWDED CYCLOPROPANEDICARBOXYLIC ACID DERIVATIVES

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Abstract: A versatile method was developed to the dealkoxycarbonylation of sterically crowded cyclopropanecarboxylic acid derivatives via a nonhydrolytic ester cleavage followed by a Barton-type decarboxylation.

In the course of the synthesis of valuable cyclopropane derivatives[1,2] the selective removal of one of the carboxylic acid unit from the sterically crowded cyclopropanedicarboxylic acid derivatives **1** and even from the parent compound **2** (Fig. 1) is frequently a delicate synthesis target to be solved.

The first step of these transformations, the hydrolysis itself gives rise difficulties. Base catalyzed aqueous hydrolysis of the ester groups[3] does not lead to

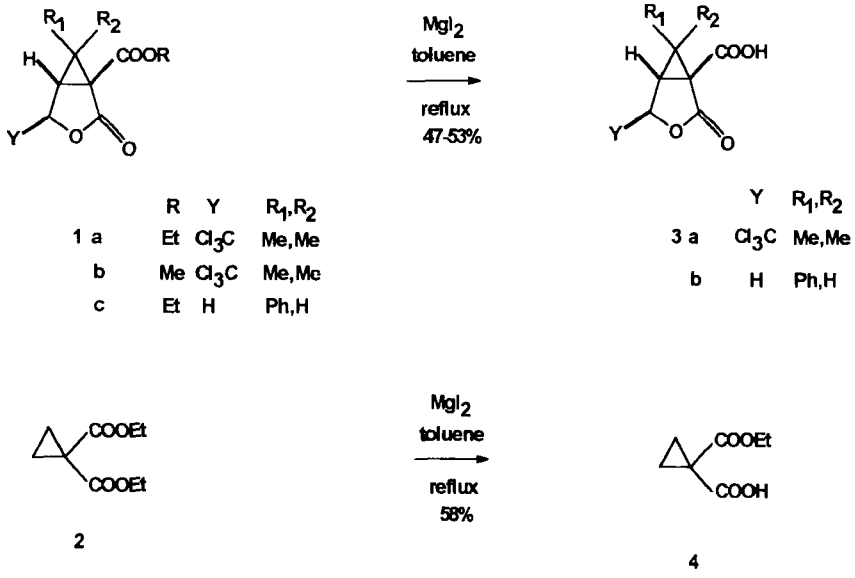
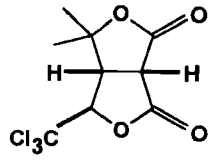


FIG. 1

acids; the ester group remains intact or in more vigorous conditions the ring in the electrophilic cyclopropanes gets opened up[4] resulting in the formation of undesired products.

A B_{Al}-type cleavage of the ester alkyl in **1a** by chloride ion in HMPTA has been described[2] in very modest yield (27%) but in our hands even this procedure proved to be useless.

Similarly, the hindered ester groups in **1** do not change in acidic conditions[3]. On the other hand, in concentrated acids (H_3PO_4 or H_2SO_4) a rearrangement occurs[5] and with the involvement of the cyclopropane ring and the carboxylic acid moiety compounds with five membered lactone rings are formed, e.g. from **1a** the dilactone **5** (Fig. 2) was prepared[6].



5

FIG. 2

Introduction of a *t*-butyl ester group during the synthesis of the cyclopropane derivative **1d** (Y = Cl_3C, R = t-Bu, R_1, R_2 = Me) by using ethyl-*t*-butyl-malonate would give a solution to the hydrolysis problem as the *t*-butyl group can easily be removed with trifluoroacetic acid treatment[1] but this series of reactions could be applied in special cases only as the preparation of these esters is very tedious.

The yield of the decarboxylation of the free acids **3** or **4** is also rather poor because at higher temperature these compounds also tend to rearrange except those cases where a free radical type fission of the carboxyl group is forced out to occur as described in this paper.

Our method gives an acceptable solution both for obtaining the free acids from **1** and their decarboxylation to the lactones **6** (Fig. 3). To check the applicability of our method we prepared the known cyclopropane derivative **4** and examined its decarboxylation, too.

For the cleavage of the ester group in **1** and **2** the anhydrous magnesium iodide[7], freshly prepared from iodine and magnesium turnings in ether[8] proved to be superior. The free acids were formed in clean form and in satisfactory yield by treating **1** or **2** with one mole of MgI_2 in toluene at reflux temperature for 8 hours.

For the decarboxylation the Barton esters[9] were prepared from the acids **3** and **4** either in the reaction of the appropriate acid chloride with 1-hydroxy-

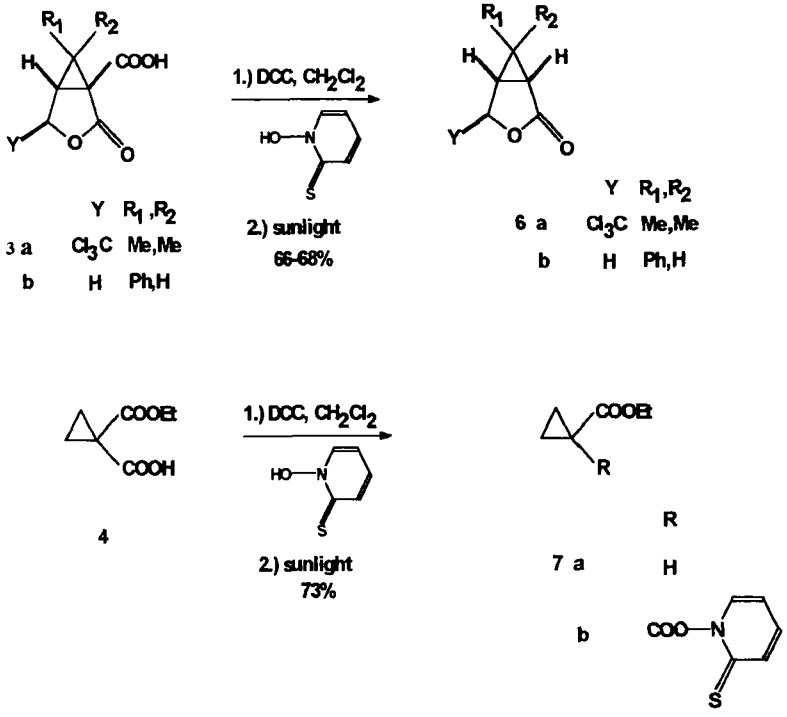


FIG. 3

pyridine-2-thione sodium salt or by coupling the thione with the acid in the presence of DCC. The latter gave better yield in a simplier reaction. These esters can be prepared from the solution in clean form[10] or they were decomposed quickly at room temperature in the same reaction mixture on exposure of the sunlight giving the desired monocarboxylic acid derivatives **6** or **7** in good yields.

Experimental

IR spectra were measured on Perkin-Elmer Model 1600, NMR spectra were obtained on Bruker AW 80 (80 MHz) with TMS as internal standard. Coupling

constants given in Hz. Melting points are taken on Gallenkamp melting point apparatus and are uncorrected. All new compounds gave satisfactory elemental nalysis: C ± 0.32, H ± 0.15, N ± 0.24

The starting lactones **1** and the diester **2** were prepared by the method described in refs. 11 and 12, respectively.

General procedures:

a.) Cleavage of the esters

To a mixture of 0.15 g (6.25 mmol) of magnesium turnings in 20 cm^3 dry ether 1.28 g (5 mmol) of iodine was added portionwise under nitrogen atmosphere. When the colour of the iodine disappeared, the ether was evaporated, the residue was dissolved in 20 cm^3 toluene and 5 mmol of the compound **1** or **2** was added to the solution. After 8 h reflux the mixture was diluted with 40 cm^3 10% aq. $NaHCO_3$-solution, the layers was separated, the aqueous layer was acidified with conc. HCl and extracted with methylene dichloride. The organic solution was dried over magnesium sulphate and the solvent was evaporated yielding the free acid.

6,6-Dimethyl-4-trichloromethyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-carboxylic acid, **3a**;

yield: 47% from **1a** , 53% from **1b**, mp.: 145.9-147.7 °C, IR(KBr): 3305, 1790, 1695 cm^{-1}, NMR(CDCl3): 1.45 d, J=6Hz, 2.97s, 4.65 s, 7.86 s

6-Phenyl-3-oxa-bicyclo[3,1,0]hexane-2-one-1-carboxylic acid, **3b**; yield: 51%, oil, IR(neat): 3500, 1786, 1731 cm^{-1}, NMR($CDCl_3$): 2.25 s, 3.86 m, 4.23 m, 7.21 m, 10.22 s

Cyclopropane-1,1-dicarboxylic acid monoethyl ester, **4**; yield: 58%, oil, IR(neat): 1733, 1673 cm^{-1}, NMR($CDCl_3$): 1.24 t, J=2.4Hz, 1.3 d, J=3.2Hz, 4.2 q, 8.3 s

b.) Decarboxylation

10 mmol of the appropriate acid was dissolved in 30 cm^3 chloroform and 3.48 g (10 mmol) of dicyclohexyl-carbodiimide and 1.27 g (10 mmol) of 1-hydroxy-pyridine-2-thione was added to the solution. The mixture was stirred for 6 h at room temperature then the solid residue was filtered, the filtrate was evaporated and the residue was purified by column chromatography (Merck Kieselgel 60 to 200 mesh, eluent: hexane: acetone 4:1).

6,6-Dimethyl-4-trichloromethyl-3-oxa-bicyclo[3,1,0]hexane-2-one, **6a**; yield: 68%, mp.:126-127.6 °C, IR(KBr): 1790 cm^{-1}, NMR(CDCl3): 1.65 d, J=2.4Hz, 2.9 dd, J_1=2.2Hz, J_2=2Hz, 4.9 s

6-Phenyl-3-oxa-bicyclo[3,1,0]hexane-2-one, **6b**; yield: 66%, IR(neat): 1785 cm^{-1}, NMR($CDCl_3$): 2.21 s, 3,45 s, 3,76 m, 7,24 m

Cyclopropanecarboxylic acid ethyl ester, **7a**[10]; yield: 73%, oil, IR(neat): 1731 cm^{-1}, NMR($CDCl_3$): 1.24 m, 4.23 q

Acknowledgement

The authors wish to thank the OTKA-Committee for the financial support (F-4299).

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[6] mp.: 128-129 °C, IR(KBr): 1800 cm^{-1} , NMR($CDCl_3$): 1.6 s, 3.33, 3.52 dd, J_1 = 9 Hz, J_2 = 1.5 Hz, 4.04, 4.2 ss, 5.02 d, J = 1.5 Hz

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[10] When the reaction time was 1 h, the thiohydroxamate **7b** could be separated chromatographically, IR(neat): 1731, 1673 cm^{-1}, NMR (CDCl3) 1.24 m, 4.18 q, J=2.4 Hz, 7.57 d, J=1.6 Hz, 8.4 d, J=1.6 Hz References for getting **7a** from **4** are missing in the literature.

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(Received in the UK 16th October 1995)