Synthesis of Functionalized Furan Derivatives by Hydroxyalkylation of Methyl 2-Siloxycyclopropanecarboxylates

Christiane Brückner and Hans-Ulrich Reissig*

Institut für Organische Chemie der Universität, Am Hubland, D-8700 Würzburg, Federal Republic of Germany

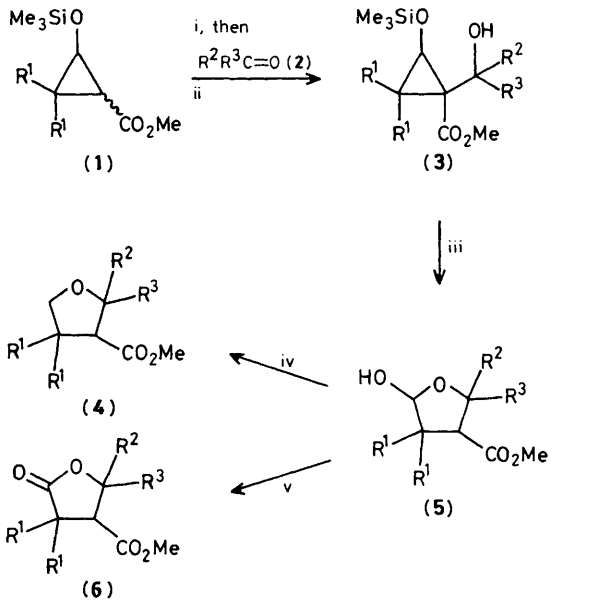
A variety of methyl tetrahydrofuran-3-carboxylates (**4**) or the 5-oxo analogues (**6**) are available in good overall yield by deprotonation of cyclopropanes (**1**), addition of carbonyl compounds, ring cleavage, and reductive or oxidative work-up, respectively.

We have recently demonstrated that deprotonation–alkylation[1] of easily accessible[2] methyl 2-siloxycyclopropanecarboxylates [*e.g.* (**1**) and (**7**)] markedly broadens the scope for preparation of a variety of synthetically valuable 4-oxoalkanoate derivatives.[3] Reactions of carbonyl compounds with ester enolates generated from (**1**) should lead to promising trifunctional products suitable for subsequent transformations. Paquette has recently reported the hydroxyalkylation of methyl cyclopropanecarboxylate,[4] and we now report our own results in this field.

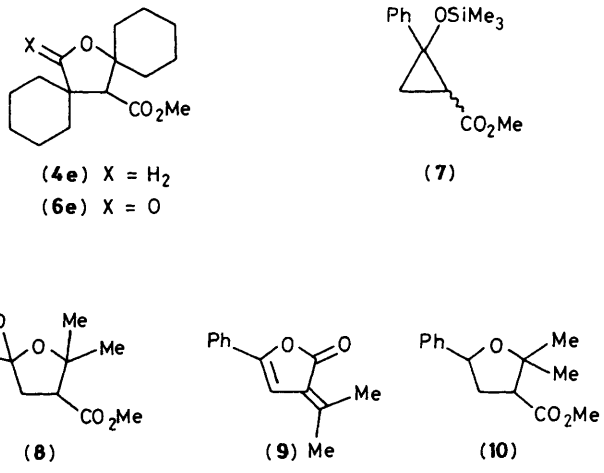
The enolates obtained from (**1**) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C smoothly add to aldehydes or ketones (**2**) (90 min; −78 °C) to give adducts (**3**). However, in only the minority of cases could the adducts (**3**) be isolated in reasonable yield [(**3a**): 64%; (**3e**): 51%] since these alcohols easily suffer ring opening and desilylation delivering (**5**). Deliberate and complete cyclopropane cleavage may be achieved by fluoride reagents ($NEt_3 \cdot 3HF$ or, preferably, NBu_4F, THF). It is of advantage to use the resulting γ-lactols (usually mixture of stereoisomers) as crude material transforming them by removal of the anomeric centre either into methyl tetrahydrofuran-3-carboxylates (**4**) ($HSiEt_3$; $BF_3 \cdot OEt_2$; CH_2Cl_2; 4 h; −78 to 20 °C), or into the 5-oxo analogues (**6**) [pyridinium chlorochromate (PCC); CH_2Cl_2; 3—5 days; 20 °C] (Scheme 1).

As shown in Table 1, aliphatic as well as aromatic aldehydes and ketones can be employed; even sluggish electrophiles like benzophenone can be added. Enolization of the carbonyl component obviously does not play a role and the total yields of (**4**) and (**6**) obtained over three steps are satisfactory. With aldehydes the end products are mixtures of *cis*- and *trans*-isomers as expected. The dispiro compounds (**4e**) and (**6e**) are depicted to demonstrate their genesis from cyclohexane carbaldehyde, glycine, and cyclohexanone.

The substitution pattern in the cyclopropane portion may also be flexible as illustrated by (**7**), in which position 3 is unsubstituted.[6] Deprotonation, addition of acetone, and subsequent treatment with MeOH–HCl delivers the acetal (**8**) (66%), whereas work-up under dehydrating conditions (*p*-$MeC_6H_4SO_3H$; C_6H_6; 5 h; 80 °C) affords the unsaturated compound (**9**) (46%).[6] The usual procedure and reduction ($HSiEt_3$, $BF_3 \cdot OEt_2$), on the other hand, provides (**10**) (44%; *cis* : *trans* = 1 : 1).



Scheme 1. *Reagents:* i, LDA; ii, NH_4Cl; iii, F^-; iv, Et_3SiH, $BF_3 \cdot Et_2O$; v, PCC.



Transformations of methyl 2-siloxycyclopropanecarboxylates *via* their enolates to different furan derivatives underline the particular synthetic potential for preparation of five-membered heterocycles[8] accessible by ring cleavage of this type of cyclopropane. Further stereoselective substitution reactions replacing the hydroxy function in γ-lactols like (**5**) by

† *E.g.* (**3a**): m.p. 78—79 °C; ^1H n.m.r. ($CDCl_3$): δ 3.66 (s, 3H, CO_2Me), 3.55 (s, 1H, 2-H), 1.62 (s, 1H, OH), and 1.40, 1.35, 1.32, and 1.03 (4s, 3H each, 4 Me); i.r. (CCl_4): 3610 (OH), 1735, and 1720 cm^{-1} (CO_2Me); (**5a**): m.p. 50—52 °C; ^1H n.m.r. (C_6H_6): δ 4.96 (s, 1H, 5-H), 3.70 (s, 3H, CO_2Me), 3.25 (s, 1H, 3-H), and 1.68, 1.50, 1.42, and 1.34 (4s, 3H each, 4 Me); i.r. (CCl_4): 3605, 3400 (OH), and 1745 cm^{-1} (CO_2Me); (**4a**): b.p. 100 °C at 0.02 Torr; ^1H n.m.r. ($CDCl_3$):δ 3.64 (s, 3H, CO_2Me), 3.53 (br. s, 2H, 5-H), 2.52 (s, 1H, 3-H), and 1.36, 1.30, 1.18, and 1.11 (4s, 3H each, 4 Me); i.r. (CCl_4): 1740 cm^{-1} (CO_2Me); (**6a**): b.p. 90 °C at 0.02 Torr; ^1H n.m.r. ($CDCl_3$): δ 3.70 (s, 3H, CO_2Me), 2.93 (s, 1H, 3-H), and 1.52, 1.50, 1.38, and 1.33 (4s, 3H each, 4 Me); i.r. (CCl_4): 1780 (C=O) and 1750 cm^{-1} (CO_2Me).

Table 1. Synthesis of compounds (4)—(6).[a]

	(1)	(2)		% Yield		
Entry	R^1_2	R^2	R^3	(5)	(4)	(6)
a	Me_2	Me	Me	48	43	67
b	Me_2	Ph	Ph	46	40 (88[b])	70 (80[b])[f]
c	Me_2	H	Me	—	61[c]	52[d]
d	Me_2	H	Ph	21	79[e]	57[e]
e	$-[CH_2]_5-$	$-[CH_2]_5-$		—	48	51
f	$-[CH_2]_5-$	H	Me	—	—	51[d]

[a] Non-optimized yields of isolated products after recrystallization or Kugelrohr distillation based on (1); all compounds provide characteristic spectra† and satisfactory elemental analyses. [b] Based on (5). [c] *cis* : *trans* 1:3. [d] *cis* : *trans* 1:1. [e] *cis* : *trans* 2:3. [f] Ref. 7.

C-nucleophiles should broaden the scope of this general approach and will be reported in due course.

This work was generously supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Universitätsbund Würzburg.

Received, 17th July 1985; Com. 1040

References

1 I. Reichelt and H.-U. Reissig, *Liebigs Ann. Chem.*, 1984, 531.
2 E. Kunkel, I. Reichelt, and H.-U. Reissig, *Liebigs Ann. Chem.*, 1984, 512.
3 E. Kunkel, I. Reichelt, and H.-U. Reissig, *Liebigs Ann. Chem.*, 1984, 802; I. Reichelt and H.-U. Reissig, *ibid.*, 1984, 820.
4 L. A. Paquette, C. Blankenship, and G. J. Wells, *J. Am. Chem. Soc.*, 1984, **106**, 6442.
5 This hydroxyalkylation method nicely complements Lewis acid-induced ring cleavage–addition to carbonyl compounds which so far has failed to proceed with 3,3-disubstituted methyl 2-siloxycyclopropanecarboxylates like (**1a**); H.-U. Reissig, *Tetrahedron Lett.*, 1981, **22**, 2981, and unpublished results.
6 L. Chassar, G. P. Chiusoli, and M. Foa, *Chim. Ind. (Milan)*, 1968, **50**, 518.
7 F. Bourelle-Warnier and B. Gastambide, *C. R. Acad. Sci., Ser. C.*, 1968, **266**, 1384.
8 C. Brückner and H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 588.