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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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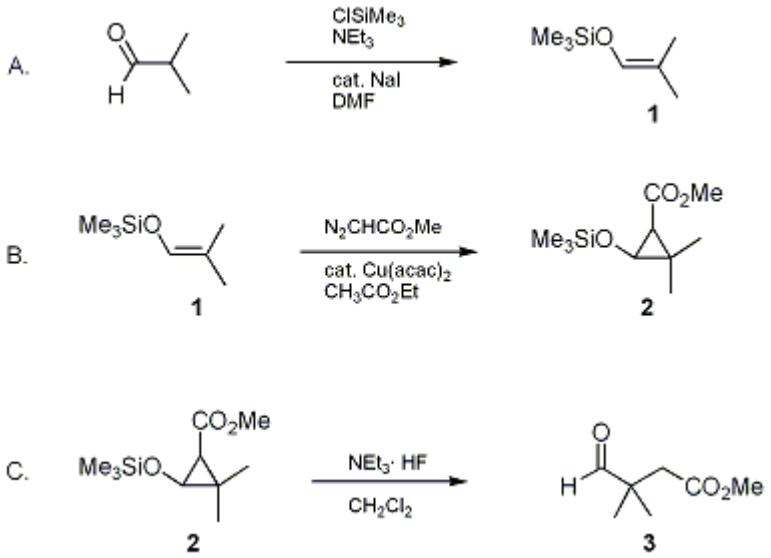
METHOXYCARBONYLMETHYLATION OF ALDEHYDES VIA SILOXYCYCLOPROPANES: METHYL 3,3-DIMETHYL-4-OXOBUTANOATE

[Butanoic acid, 3,3-dimethyl-4-oxo-, methyl ester]



Submitted by Hans-Ulrich Reissig[1], Ingrid Reichelt[2], and Thomas Kunz[2].
Checked by Lawrence Snyder and Albert I. Meyers.

1. Procedure

A. *2-Methyl-1-(trimethylsiloxy)propene* (**1**). A dry, 1-L, three-necked flask, equipped with an efficient mechanical stirrer, reflux condenser with nitrogen inlet, and a pressure-equalizing dropping funnel, is charged with 230 mL of dry dimethylformamide (Note 1), 7.5 g (50 mmol) of dry sodium iodide (Note 2), and 119 g (1.18 mol) of triethylamine (Note 3) under a nitrogen atmosphere. Chlorotrimethylsilane (Note 4), 64.3 g (0.592 mol) and 36.0 g (0.500 mol) of freshly distilled isobutyraldehyde are added sequentially to this stirred mixture via the dropping funnel at room temperature. Under vigorous stirring the resulting mixture is heated to 120°C (oil bath temperature) for 8 hr, then cooled to room temperature and poured into 400 mL of saturated aqueous sodium bicarbonate ($NaHCO_3$) solution. The mixture is extracted with three 200-mL portions of pentane, the combined organic phases are washed four times with 60 mL of ice-cold 2 N hydrochloric acid (Note 5) and finally with 100 mL of saturated $NaHCO_3$ solution, dried with magnesium sulfate ($MgSO_4$), filtered, and the pentane is removed at atmospheric pressure to provide crude product (80 g). This material is carefully distilled at atmospheric pressure through a column packed with glass beads (30 cm). Silyl enol ether **1** is the fraction boiling at 94–108°C; the yield is 48.8 g (67%, (Note 6)).

B. *Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate* (**2**). *CAUTION: This step should be performed behind a safety shield.* A 500-mL flask, equipped with a magnetic stirring bar and a reflux condenser that contains at its head a pressure-equalizing dropping funnel connected to a gas bubbler, is charged with 1.04 g (4.00 mmol) of copper(II) acetylacetonate [$Cu(acac)_2$] (Note 7) and 28.8 g (200 mmol) of silyl enol ether **1**. The suspension is heated to 90–100°C (oil bath temperature) and a solution of 24.0 g (240 mmol) of methyl diazoacetate (Note 8) dissolved in 250 mL of dry ethyl acetate (Note 9) is added dropwise within 3–4 hr (Note 10). After a short induction period, vigorous nitrogen evolution is observed and the suspension turns from blue to brownish-yellow. Addition of the diazo compound is regulated so that continuous liberation of nitrogen is observed at the gas bubbler. After the resulting black-brown suspension is cooled to room temperature, the solvent is removed on a rotary

evaporator (bath temperature below 35°C). The residue is treated with 50 g of alumina (Note 11) and 100 mL of pentane; the slurry is filtered and placed on a column that contains 200 g of alumina. Elution with pentane is accelerated by applying a slight pressure of nitrogen at the top of the column. Concentration of the colorless solution obtained (Note 12) provides crude **2** (55 g) that is distilled (bp 86–88°C, 12 mm) to give 35.0 g (81%, (Note 13)) of pure cyclopropane derivative **2** as a mixture of cis/trans isomers (Note 14).

C. *Methyl 3,3-dimethyl-4-oxobutanoate* (**3**). A 50-mL flask, connected to a gas bubbler and equipped with a magnetic stirring bar, is charged with 20 mL of dichloromethane (or tetrahydrofuran), 2.16 g (10.0 mmol) of siloxycyclopropane **2** and 3.64 g (30.0 mmol) of triethylamine hydrofluoride ($NEt_3 \cdot HF$) prepared in situ (Note 15). This mixture is stirred for 1 hr at room temperature (Note 16) and diluted with 20 mL of water. The aqueous phase is extracted with three 20-mL portions of dichloromethane. The combined organic phases are dried with magnesium sulfate, filtered, and concentrated on a rotary evaporator (bath temperature below 40°C). Crude product **3** is distilled with a Kugelrohr oven (oven temperature 105°C, 10 mm) to provide 1.26 g (87%) of pure **3** as a colorless liquid (Note 17).

2. Notes

1. Dimethylformamide (Aldrich Chemical Company, Inc.) was distilled from phosphorus pentoxide and stored over molecular sieves.
2. The procedure described is a slight variation of the published method.[3] We found addition of ca. 10% sodium iodide to be advantageous in terms of reaction times and yields. Sodium iodide was dried at 120°C/0.2 mm for 6 hr.
3. Triethylamine was distilled from calcium hydride (CaH_2) and stored over molecular sieves.
4. Chlorotrimethylsilane (obtained from Fluka Chemical Company or Janssen) was distilled from calcium hydride.
5. The washing process was performed until the aqueous phase was acidic to pH paper. The checkers found that gas pressure build-up was common, so the separatory funnel should be vented frequently during acidification.
6. The fraction boiling at 94–108°C was found to be ~99% pure by GLC and contained a trace of hexamethyldisiloxane. The impurity does not affect the outcome of the next step. The NMR spectrum was as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ: 0.14 (s, 9 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 5.98 (m, 1 H).
7. Copper(II) acetylacetonate, as supplied by Dynamit Nobel or by other commercial sources, was used.
8. Methyl diazoacetate was obtained according to a procedure for ethyl diazoacetate (Searle, N.E. *Org. Synth., Coll. Vol. IV* **1963**, 42). Although the experiments were usually performed with distilled methyl diazoacetate (bp 43°C at 25 mm, bath temperature below 60°C) without any problems, the cyclopropanation reaction described works equally well with undistilled diazo compound. If distilled diazo compound is desired, the submitters have stated that "a spatula of K_2CO_3 is added to the crude diazo ester to trap traces of acid and then distill behind a safety shield". The checkers did not evaluate this aspect of the procedure.
Crude methyl diazoacetate contains up to 20% of the solvent dichloromethane, which has to be taken into account when calculating the stoichiometry. The checkers had no problems in preparing, handling, and using undistilled methyl diazoacetate; however, it must be emphasized that this compound is a potential explosive and all operations should be performed behind an efficient safety shield.
9. Our first experiments were performed with benzene as solvent, which generally provides very good yields.[4] Use of the less hazardous solvent ethyl acetate gives inferior yields if the silyl enol ether contains triethylamine. Ethyl acetate was distilled from potassium carbonate.
10. If the solution of methyl diazoacetate is dropped through the condenser the diazo compound is further diluted by the refluxing solvent. This simple technique diminishes formation of dimethyl fumarate and dimethyl maleate as side products. For small scale experiments a motor driven syringe pump may replace the dropping funnel with good success.
11. Neutral aluminum oxide (activity III, Woelm) was used.
12. Siloxycyclopropane **2** is eluted very quickly. Final fractions contain dimethyl fumarate and maleate. If mixtures of **2** with these carbene dimers are obtained, the filtration through alumina has to be repeated.
13. Yields of 75–85% have been obtained in several experiments on this scale.

14. The cis/trans ratio is 25:75. The spectra are as follows: IR (CCl_4) cm^{-1}: 1728 (CO_2Me); ^1H NMR (270 MHz, $CDCl_3$) δ: 0.12 (s, 9 H, $SiCH_3$), 1.04, 1.15, 1.19, 1.30 (4 s, 6 H, 2-CH_3 of cis-**2** and trans-**2**), 1.35, 3.42 (2 d, J = 7, 0.25 H each, 1-H and 3-H of cis-**2**), 1.43, 3.60 (2 d, J = 3, 0.75 H each, 1-H and 3-H of trans-**2**), 3.63 (s, 3 H, CO_2CH_3). For ^{13}C NMR data, mass spectrum, and combustion analysis see reference [4].
15. The reagent was generated in situ by sequential addition of 1.63 mL of triethylamine trishydrofluoride (obtained from Riedel deHaen, Merck, or Aldrich Chemical Company, Inc.) and 2.80 mL of triethylamine to the solution of **2**. The procedure reported in reference [15] provides a reagent with an approximate stoichiometry of $NEt_3 \cdot 2HF$ that can also be used for the purpose described.[5]
16. A short period of gas evolution is observed. This is probably fluorotrimethylsilane (Me_3SiF).
17. This procedure can be performed without any problems on a larger scale (2.6 g, 90% yield was obtained by checkers). However, aldehyde **3** is of limited stability and should be stored with exclusion of oxygen at low temperature. It is advantageous to generate only the amount of **3** required for subsequent reactions and to use it immediately. The physical properties are as follows: IR (CCl_4) cm^{-1}: 1739, 1730 (CO_2Me, CO); ^1H NMR (270 MHz, $CDCl_3$) δ: 1.13 (s, 6 H, 3-CH_3), 2.52 (s, 2 H, CH_2), 3.63 (s, 3 H, CO_2CH_3), 9.53 (s, 1 H, CHO). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.59; H, 8.77.

Waste Disposal Information

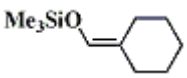
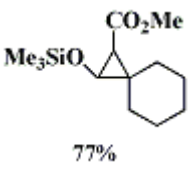
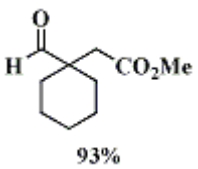
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

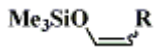
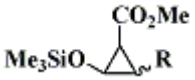
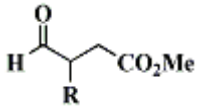
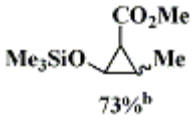
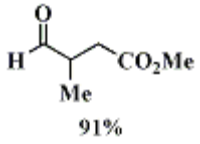
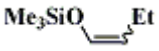
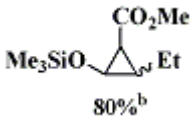
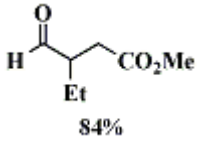
3. Discussion

This sequence illustrates a very general method for the synthesis of methyl γ-oxoalkanoates which are valuable intermediates in organic synthesis.[4,6] The scope of the cyclopropanation reaction is very broad; only functional groups interacting with the carbenoid generated from methyl diazoacetate are not compatible. Use of $Rh_2(OAc)_4$ instead of $Cu(acac)_2$ as catalyst did not afford better yields.[4] The cyclopropanation reaction has been performed with similar efficiency on scales from 4 mmol up to 500 mmol.

Silyl enol ethers derived from aldehydes (see Table, entries 1–5) or ketones (entries 6–9) can be used. If unsymmetrical ketones are used as starting material, the regiochemistry established at the silyl enol ether stage is cleanly transferred to the siloxycyclopropanes and eventually to the methyl γ-oxoalkanoates (entries 7–9). For some chiral silyl enol ethers, high stereoselectivities can be attained in the [2+1]-cycloaddition. Because of the very mild conditions for the ring opening step, using the only weakly acidic fluoride reagent, the stereoselectivity is transmitted to the γ-oxoalkanoate without accompanying epimerization (entry 9).[5,7] This mild, ring-opening procedure that uses $NEt_3 \cdot HF$ is essential for preparation of the β-formyl esters as described in the procedure and for entries 1–5 in the Table. For simple ketone-derived products ring cleavage can also be effected with 2 N hydrochloric acid.[5]

TABLE
SYNTHESIS OF SILOXYCYCLOPROPANES AND γ-OXOALKANOATES

Entry	Silyl Enol Ether	Siloxycyclopropane[a] (% yield)	γ-Oxoalkanoate (% yield)
1		 77%	 93%
		77%	93%

			
2		 73%[b]	 91%
		73%	91%
3		 80%[b]	 84%
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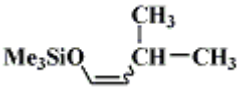
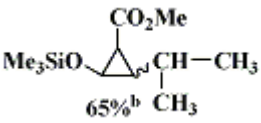
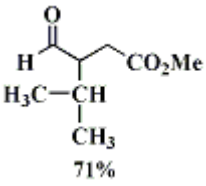
4		 65%[b]	 71%
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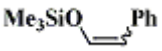
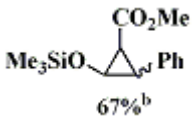
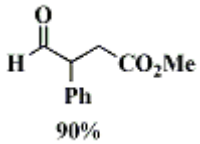
5		 67%[b]	 90%
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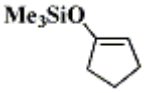
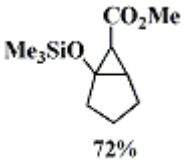
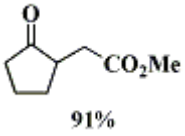
6		 72%	 91%
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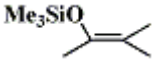
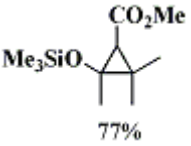
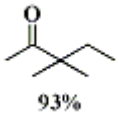
7		 77%	 93%
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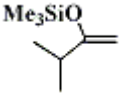
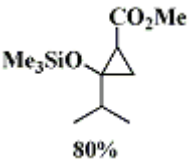
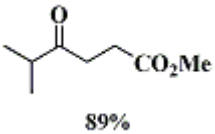
8		 80%	 89%
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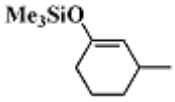
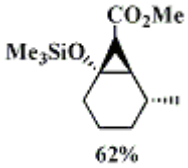
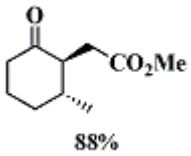
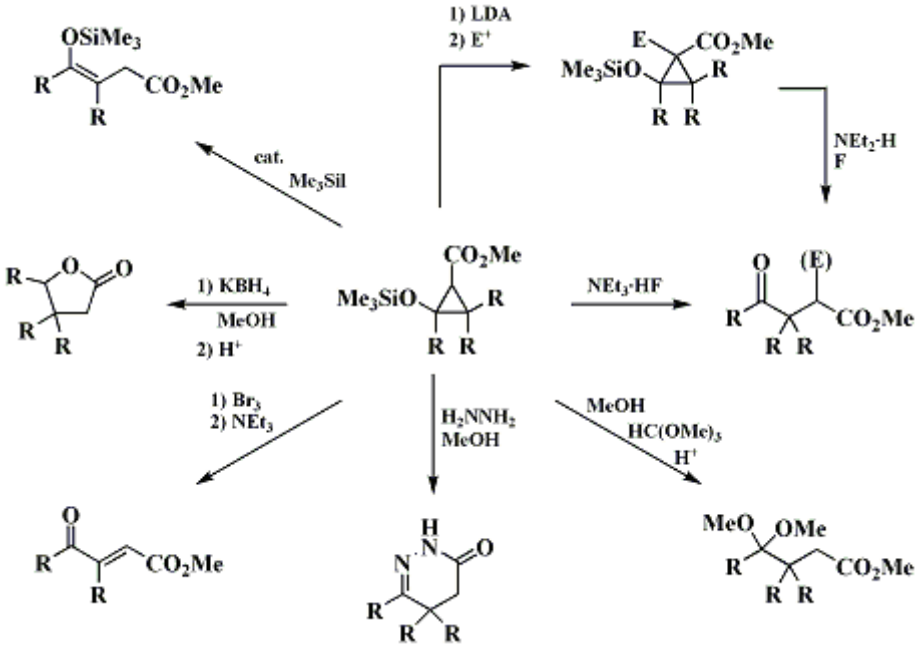
9				
		62%	88%	

[a]Cis/trans isomers in all examples. [b]Mixture of all four diastereomers. [c]Trans compound >95% (racemic mixture).

The methyl γ-oxoalkanoates shown are not available by alternative methods with similar efficiency and flexibility. Although the reaction of enamines with alkyl α-bromoacetates proceeds well in some cases, yields are only moderate in many examples.[8] A further drawback is that the methods for enamine generation lack the high degree of selectivity and mildness that is characteristic of the preparation of silyl enol ethers. Related alkylations of lithium enolates often afford low yields or polyalkylated products, and are in general very inefficient when aldehydes are utilized as the starting materials.[9]

An alternative method to prepare β-formyl esters uses different building blocks to assemble the 1,4-dicarbonyl system and is complementary in many cases.[10] Base-catalyzed addition of nitromethane to α,β-unsaturated esters, followed by a variation of the Nef reaction, provides γ-dialkoxy-substituted esters. The scope of this sequence has not yet been explored. Another approach involves cuprate additions to norephedrine-derived 2-alkenyloxazolidines; this process allows small-scale synthesis of several β-formyl esters in optically active form (ee up to 95%).[11]

A major advantage of the sequence presented here is that the aldehyde group is protected at the siloxycyclopropane stage, which allows convenient storage of this stable intermediate. Of equal importance is the valuable carbanion chemistry that can be carried out α to the ester function. Efficient substitution can be achieved by deprotonation with LDA and subsequent reaction with electrophiles.[12,13,6] This process makes several α-substituted β-formyl esters available. Other ring opening variants of siloxycyclopropanes—mostly as one-pot-procedures—are contained in Scheme I. They underscore the high versatility of these intermediates for the synthesis of valuable compounds.[6] Chiral formyl esters (see Table, entries 2–5) are of special interest as starting materials for chelate-controlled synthesis of disubstituted γ-lactones.[14]



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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

copper(II) acetylacetonate

dimethyl fumarate and maleate

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ethyl acetate (141-78-6)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

nitrogen (7727-37-9)

sodium iodide (7681-82-5)

Pentane (109-66-0)

Nitromethane (75-52-5)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

aluminum oxide (1344-28-1)

ethyl diazoacetate (623-73-4)

isobutyraldehyde (78-84-2)

Tetrahydrofuran (109-99-9)

dimethylformamide (68-12-2)

triethylamine (121-44-8)

calcium hydride (7789-78-8)

Dimethyl fumarate (624-49-7)

CHLOROTRIMETHYLSILANE (75-77-4)

siloxycyclopropane

hexamethyldisiloxane (107-46-0)

fluorotrimethylsilane (420-56-4)

phosphorus pentoxide (1314-56-3)

dimethyl maleate (624-48-6)

Methyl 3,3-dimethyl-4-oxobutanoate,
Butanoic acid, 3,3-dimethyl-4-oxo-, methyl ester (52398-45-5)

2-Methyl-1-(trimethylsiloxy)propene (6651-34-9)

Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate (77903-45-8)

methyl diazoacetate

triethylamine hydrofluoride

triethylamine trishydrofluoride (73602-61-6)