Study of the Kulinkovich Synthesis of 1-Methylcyclopropanol and Its Conversion into 1-Methylcyclopropyl 4-Nitrophenyl Carbonate

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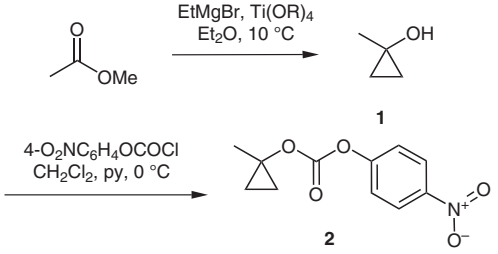
Received: 20.04.2013; Accepted after revision: 17.06.2013

Abstract: A detailed investigation of the preparation of 1-methylcyclopropanol via the Kulinkovich reaction is presented. Reaction and workup parameters were optimized to provide a reproducible procedure for the synthesis of multigram quantities of 1-methylcyclopropanol. Key improvements were the use of titanium tetra(2-ethyl)hexyloxide as catalyst, reduction in the volume of reaction solvent, addition of the methyl acetate starting material in portions, and azeotropic distillation to remove by-products. The preparation of the 4-nitrophenyl carbonate ester was likewise studied and optimized.

Key words: titanium, cyclopropanes, catalysis, carbene complexes, alcohols

The 1-methylcyclopropyl carbamate (MPoc) group has recently been introduced into medicinal chemistry as a versatile pharmacophore.[1] It is derived from 1-methylcyclopropanol (**1**), which is in turn prepared by the Kulinkovich cyclopropanation of an acetate ester.[2] We became interested in the chemistry of the MPoc group during the course of a recent medicinal chemistry program, and have recently reported its utility as a protecting group for amines.[3]

The key starting material for the synthesis of the MPoc group, 1-methylcyclopropanol (**1**), is prepared by the Kulinkovich reaction of an acetate ester with ethylmagnesium bromide in the presence of a titanium alkoxide (Scheme 1).[4] We found that the published preparations[5] of this compound suffer from a lack of experimental detail, poor yields, or an abundance of side products. Application of the Kulinkovich reaction to the preparation of **1** presents a number of significant technical challenges: the alcohol **1** is volatile (bp 104 °C/760 torr) and water miscible, has no UV chromophore, and cannot be detected on TLC. In addition, the crude **1** is accompanied by troublesome by-products: ethanol, propan-2-ol, toluene, butan-2-one, water, and 3-methylpentan-3-ol (see Supporting Information). Notably, **1** cannot be separated from water by simple distillation. Therefore the preparation of **1** is considerably more challenging than is the preparation of higher 1-alkylcyclopropanols because of the physical and chemical properties of this product.



Scheme 1 Synthesis of 1-methylcyclopropanol and 1-methylcyclopropyl 4-nitrophenyl carbonate

The original papers by Kulinkovich[2] do not indicate how these difficulties were overcome in the synthesis of 1-methylcyclopropanol. No other preparations of **1** by the Kulinkovich reaction have appeared in journal articles. Some procedures have been published in the patent literature. For example, a recent patent application[6] used a crude titanium tetra(cyclohexyloxide) catalyst, generated by alkoxide exchange between cyclohexanol and titanium tetra(methoxide), presumably to avoid the introduction of propan-2-ol. In this paper, we report our solutions to the challenges associated with the preparation of 1-methylcyclopropanol and present detailed, enabled syntheses of both **1** and its 4-nitrophenyl carbonate **2**.

Initially, we sought to (a) replace the titanium tetra(isopropoxide) catalyst, (b) reduce the volume of reaction solvent used, (c) reduce losses of **1** to the aqueous phase upon workup, (d) reduce the ethanol content of crude **1**, and (e) suppress 3-methylpentan-3-ol formation. Our findings were as follows:

a) In almost every published example of the Kulinkovich reaction, the catalyst used is titanium tetra(isopropoxide). This catalyst is a poor choice when applied to the preparation of **1**. The propan-2-ol that results from hydrolysis of titanium tetra(isopropoxide) upon workup co-distils with **1**. Likewise, the presence of propan-2-ol in **1** renders the chromatographic purification of **2** exceedingly difficult. Titanium tetra(2-ethylhexyloxide) was found to be a satisfactory catalyst. This titanium alkoxide is an inexpensive commercial product;[7] the by-product 2-ethylhexanol produced upon workup boils at 198 °C/760 Torr and was easily separated by distillation.

b) The Kulinkovich reaction could be carried out at three times the concentration originally reported without adverse effects. This substantially reduced the volume of diethyl ether and water that had to be removed from the crude reaction mixture.

SYNTHESIS 2013, 45, 2481–2484
Advanced online publication: 26.07.2013
DOI: 10.1055/s-0033-1338504; Art ID: SS-2013-M0303-OP

c) Losses to the aqueous phase upon workup were reduced by the use of the minimum volume of aqueous sulfuric acid required to hydrolyze and dissolve the magnesium and titanium salts present. This afforded a nearly saturated solution of magnesium salts, which was separated with little loss of **1** to the aqueous phase. Subsequent washing with water was minimized to prevent significant losses of **1**. This could be illustrated by washing a C_6D_6 solution of **1** (containing mesitylene as an internal standard) with D_2O and subsequent examination of the C_6D_6 solution and the D_2O wash by ^1H NMR analysis.

d) Ethanol was largely eliminated by the choice of methyl acetate as the starting acetate ester. A small amount of ethanol remained, the source of which remained unknown but could have been present in the ether solvent or have resulted from oxidation of the Grignard reagent. 2-Ethylhexyl acetate was also used successfully as the starting acetate ester but methyl acetate was more convenient.

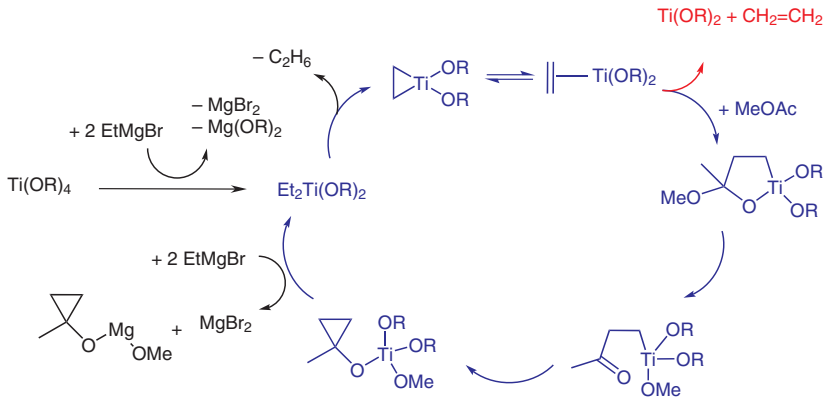
e) We reasoned that formation of the Grignard addition product 3-methylpentan-3-ol could be suppressed by keeping the concentration of the acetate ester close to that of the titanium catalyst, instead of following the customary procedure of placing all of the acetate ester in the reaction vessel at the outset. However, we recognized that the ester concentration should not become too low during the reaction, because the titanacycle intermediate in the catalytic cycle of the Kulinkovich reaction is unstable and can suffer irreversible disproportionation to $Ti(OR)_2$ and ethylene (Scheme 2, red) if it does not react with an ester (Scheme 2, blue).[8] In that event, the catalytic cycle will terminate and conventional Grignard addition to the ester would become the only reaction pathway available. Addition of the acetate ester in portions provided a convenient solution to minimizing the formation of 3-methylpentan-3-ol while maintaining a competent catalytic cycle.

We were surprised to find that, while the formation of 3-methylpentan-3-ol could be largely eliminated, butan-2-one continued to be present in varying amounts. Initially, we believed that butan-2-one was formed by the acylation of methyl acetate by the ethyl Grignard reagent. However, we observed that certain samples of crude **1** contained more butan-2-one following distillation than prior to distillation. This led us to speculate that **1** might rearrange to butan-2-one upon exposure to acid and heat. This could happen during distillation of crude **1** if traces of acid were carried forward with the crude **1** into the distillation. Drying the ethereal extract of **1** over anhydrous K_2CO_3 reduced the formation of butan-2-one upon distillation, but a more effective solution was to add 20 mol% of tributylamine to **1** prior to distillation. In this way, any protic (H_2SO_4) or Lewis [Ti(IV), Mg(II)] acids in the crude **1** were neutralized. Fortunately, **1** did not appear to be decomposed to butan-2-one by exposure to cold dilute H_2SO_4 during the reaction workup.

Remarkably, we found that **1** also decomposed to butan-2-one upon exposure to strong base. A ^1H NMR study in THF-d_8 of the effectiveness of various drying agents showed that **1** was completely decomposed to butan-2-one over KOH within one hour at 20 °C.[9] This is in sharp contrast to the known stability of other tertiary alcohols towards base. The diethyl ether solution of crude **1** could be dried reasonably well with $MgSO_4$; however, water was always present in the crude **1**.

Removal of the reaction solvent was initially problematic. Attempts to remove diethyl ether by rotary evaporation at atmospheric pressure were accompanied by significant co-distillation of **1**, as shown by examination of the distillate. Rotary evaporation of diethyl ether at reduced pressure, even at 0 °C, was still attended by losses of **1**. Comparison of published data of vapor pressure versus temperature for diethyl ether and *tert*-butyl alcohol (the latter used as a model for **1**) suggested that the greatest separation would be attained by distillation at atmospheric pressure. Therefore, the diethyl ether was distilled at atmospheric pressure through a Vigreux column until the bulk of the diethyl ether had been removed, after which the residue was transferred to a smaller flask for the final distillation of **1**.

Purification of **1** by distillation proved to be essential to be able to obtain consistent yields of **1** and the carbonate **2**. Hexane was used to transfer the crude **1** to a smaller flask for distillation; this facilitated both a quantitative transfer of **1** and the removal of ethanol, propan-2-ol, and butan-2-one, all of which form azeotropes with hexane. Mesity-



Scheme 2 Catalytic cycle of the Kulinkovich reaction

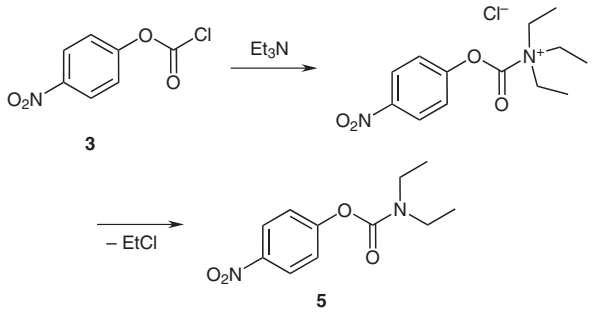
lene was added as a 'chaser': a liquid of higher boiling point that will displace the desired product from the interior surface of the distillation glassware and thus minimize hold-up losses during distillation. Lastly, tributylamine was added to suppress isomerization of **1** to butan-2-one.

Pleasingly, distillation through a vacuum jacketed Vigreux column at atmospheric pressure afforded an effective separation of **1** from the other components. Material distilling at temperatures up to 98 °C contained little product. The desired **1** distilled between 100 and 106 °C; the distillate was typically 95 mole percent desired **1** as judged by ^{1}H NMR analysis, with the remaining 5% consisting primarily of mesitylene and butan-2-one. Most importantly, the hexane azeotrope efficiently removed residual ethanol and propan-2-ol. This procedure was scaled up to a 360 mmol scale to provide **1** in 65% yield.

The preparation of **2** from **1** and 4-nitrophenyl chloroformate (**3**) also presented problems. Initial conditions[1] involved the addition of pyridine or triethylamine to a THF solution of **3** followed by the addition of **1**. Yields were variable, usually between 35 and 60%, which was unacceptable in view of the effort invested in the preparation of **1**. The **2** produced required chromatographic purification, with a large weight ratio of silica gel to **2** to remove side products.

Study of the transformation of **1** to **2** was made more challenging by the facts that **1** could not be observed by traditional techniques (TLC, GCMS, LCMS), and the chloroformate **3** was decomposed under these conditions. Therefore, the progress of the reaction mixture could not be monitored by these methods. One reaction by-product was quickly identified as bis(4-nitrophenyl)carbonate (**4**). This substance was notable because of its relatively low solubility in most solvents. The formation of **4** would likely indicate the presence of water in the reaction mixture, presumably water that co-distilled with **1**. In fact, the formation of **4** could be minimized by changing the reaction solvent to dichloromethane and predrying of the solution of **1** in dichloromethane with sodium sulfate.

Study of the conversion of **1** into **2** by ^{1}H NMR proved to be very informative. It was established that the methyl and cyclopropyl resonances of **1** and **2** could be easily distinguished by ^{1}H NMR, as could the aryl protons of **1**, **3**, and **4**. Reaction of **1** with **3** in CD_2Cl_2 in the presence of 1 equivalent of pyridine at 20 °C to afford **2** was complete in less than 30 minutes. Aging of the reaction mixture resulted in no change in the ^{1}H NMR spectrum, indicating that **2** was stable to these reaction conditions. A D_2O–DCl wash of the mixture removed pyridine hydrochloride and afforded a CD_2Cl_2 solution of **2** containing 20 mol% of **4**. The reaction of **1** with **3** in CD_2Cl_2 in the presence of 1 equivalent of triethylamine at 20 °C to afford **2** was likewise complete in less than 30 minutes. In contrast to the reaction in the presence of pyridine, a D_2O–DCl wash of the mixture removed triethylamine hydrochloride but ethyl resonances were still plainly evident in the CD_2Cl_2 solution. These resonances were determined to be due to the presence of chloroethane and **5**, which was subsequently identified by comparison with an authentic sample. The formation of **5** likely occurred via the pathway shown in Scheme 3. The ^{1}H NMR experiments also showed that the order of addition of reagents was important. Treatment of **1** with **3** in CD_2Cl_2 in the absence of an amine base showed that **1** was completely decomposed to butan-2-one within 90 minutes.



Scheme 3 Proposed mechanism for the formation of **5**

By comparison, a ^{1}H NMR study of the reaction of 3-methylpentan-3-ol with **3** showed that this alcohol underwent mixed carbonate formation much more slowly than **1**. Thus the formation of the 4-nitrophenylcarbonate of 3-methylpentan-3-ol, if present in **1**, could be suppressed by appropriate control of reaction time. In addition, the 4-nitrophenylcarbonate of 3-methylpentan-3-ol was a liquid that could therefore be removed by crystallization of **2**.

All evaporations were carried out on a rotary evaporator at ca. 30 Torr. Commercial reagents were used as received without additional purification. Solvents were commercial anhydrous grades and were used without further drying. Melting points are uncorrected. Infrared spectra were recorded as neat films on a Nicolet Avatar 360 FT-IR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-III 400 MHz spectrometer. Mass spectral data were recorded on an Agilent Technologies 6890N gas chromatograph fitted with an Agilent Technologies 5975 inert mass selective detector using electron impact ionization (EI).

1-Methylcyclopropanol (1)

A 2000 mL 4-necked flask was equipped with a mechanical stirrer, inert gas inlet, thermometer, and two pressure-equalizing addition funnels. The flask was flushed with N_2 and charged with anhyd Et_2O (490 mL) followed by titanium tetra(2-ethylhexyloxide) (18.2 mL, 30 mmol). One addition funnel was charged with a solution prepared from MeOAc (28.6 mL, 360 mmol) diluted to 120 mL with Et_2O. The second addition funnel was charged with 3 M EtMgBr (200 mL) in Et_2O (the use of EtMgCl produces substantially more 3-methylpentan-3-ol). The reaction flask was cooled in an ice water bath to keep the internal temperature at 10 °C or below. MeOAc solution in Et_2O (40 mL) was added to the flask. The Grignard reagent was then added dropwise from the addition funnel at a rate of about 2 drops every second, and no faster than 2 mL per min. After the first 40 mL of Grignard reagent had been added, another 20 mL portion of MeOAc solution in Et_2O was added. After the second 40 mL of Grignard reagent had been added, another 20 mL portion of MeOAc solution in Et_2O was added. After the third 40 mL of Grignard reagent had been added, another 20 mL portion of MeOAc solution in Et_2O was added. After the fourth 40 mL of Grignard re-

agent had been added, the last 20 mL portion of MeOAc solution in Et_2O was added, followed by the last 40 mL of Grignard reagent. The mixture was stirred for an additional 15 min following the completion of the addition of Grignard reagent. It was then poured into a mixture of ice (660 g) and concd H_2SO_4 (60 mL), with rapid stirring to dissolve all solids. The phases were separated, and the aqueous phase was extracted again with Et_2O (50 mL), then the combined Et_2O extracts were washed with 10% aq Na_2CO_3 (15 mL), brine (15 mL), and dried over $MgSO_4$ (30 g) for 1 h with stirring. The Et_2O solution was then filtered. Bu_3N (14.3 mL, 60 mmol) and mesitylene (10 mL) were added. Most of the Et_2O was removed by distillation at atmospheric pressure using a 2.5 cm × 30 cm vacuum jacketed Vigreux column. The remaining liquid was transferred to a smaller distillation flask using two 10 mL portions of hexane to facilitate the transfer. Distillation at atmospheric pressure was continued through a 2 cm × 20 cm vacuum jacketed Vigreux column. The liquid distilling at 98–105 °C was collected to provide 15.35 g (70%) of **1** as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.42–0.48 (m, 2 H), 0.74–0.80 (m, 2 H), 1.45 (s, 3 H), 1.86 (br s, 1 H). The ^{1}H NMR also showed the presence of mesitylene (3 mol%) and butan-2-one (2 mol%).

^{13}C NMR (100 MHz, C_6D_6): δ = 14.98, 25.44, 52.42.

Anal. Calcd for C_4H_8O: C, 66.63; H, 11.18. Found: C, 66.82; H, 11.01.

H_2O content (by coulometric titration): 1.04%.

1-Methylcyclopropyl 4-Nitrophenyl Carbonate (2)

4-Nitrophenyl chloroformate (**3**; 3.84 g, 19 mmol) was dissolved in CH_2Cl_2 (40 mL) and cooled to <5 °C. To this was added a cold solution of **1** (1.30 g, 17 mmol) in CH_2Cl_2 (10 mL), previously dried with Na_2SO_4. A solution of pyridine (1.7 mL, 21 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring over 10 min with continued cooling. The mixture was stirred for an additional 90 min, then quenched with 0.1 M H_2SO_4 (50 mL). The CH_2Cl_2 layer was washed with H_2O (25 mL), aq $NaHCO_3$ (25 mL), brine (25 mL), and dried ($MgSO_4$). After filtration, the CH_2Cl_2 layer was diluted with twice its volume of hexane. A white precipitate of bis(4-nitrophenyl) carbonate formed gradually. This was filtered and discarded. The filtrate was concentrated to dryness to afford 3.99 g of a colorless semisolid. This was digested with hexane (50 mL) under reflux, filtered while hot, and the precipitate was washed with boiling hexane (2 × 10 mL). The filtrate was concentrated to give 3.42 g of a white solid, which was recrystallized from hexane (5 mL) to afford 3.21 g (79%) of analytically pure **2**; mp 46–48 °C.

IR (film): 1770, 1524, 1349 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72–0.82 (m, 2 H), 1.02–1.15 (m, 2 H), 1.66 (s, 3 H), 7.38 (d, J = 9.4 Hz, 2 H), 8.27 (d, J = 9.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.85, 20.48, 60.64, 121.67, 125.19, 145.24, 151.89, 155.41.

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.52; H, 4.52; N, 5.94.

Acknowledgment

The authors thank Dr. Vincent Mascitti for valuable discussion of the decomposition pathways of **1**.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are the experimental procedure and ^{1}H NMR spectra of the NMR study of the conversion of **1** into **2** mediated by pyridine and triethylamine and notes on the origin of by-products in the Kulinkovich reaction.

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