An improved synthesis of 1-methylcyclopropanol using the Kulinkovich reaction

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**A R T I C L E   I N F O**

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**A B S T R A C T**

An improved process for the preparation of 1-methylcyclopropanol using the Kulinkovich reaction is described. The use of titanium tetramethoxide as catalyst resulted in minimal side product formation. The reaction, isolation and purification procedures were optimized so they can be easily implemented in multi-purpose equipment.

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1. Introduction

Cyclopropanols have spurred interest in the chemical community and the manipulation of this apparently simple-looking class of molecules is by no means a trivial task. The chemical synthesis and the reactivity of cyclopropanols have been reviewed by Kulinkovich in 2003.1 Since then, many research groups have contributed to the expansion of the portfolio of reactions involving cyclopropanols. A selection of recent examples is depicted in Scheme 1 and includes: – the use of cyclopropanol as an amphoteric metal homoenolate to generate enantiospecifically the corresponding cyclopropylamine, a motif found in numerous bioactive compounds2 ((1A in Scheme 1); – a rhodium catalyzed oxidative coupling between arenes and cyclopropanols to access β-aryl ketones3 ((1B) in Scheme 1); – fragmentation in the presence of fluorinated sodium sulfonates and aqueous tert-butyl hydroperoxide to afford the corresponding fluorinated ketones4 ((1C) in Scheme 1). Additionally, the very rich class of transition-metal-catalyzed C–C and C–X bond-forming transformations involving cyclopropanols has recently been reviewed by Orellana at York University.5 Cyclopropanols are very versatile intermediates and can react through a variety of modes allowing access to diverse classes of compounds.

The 1-methylcyclopropanol scaffold is also extensively used in modern medicinal chemistry programs on a wide variety of therapeutic areas. For example, it was used by Hyundai Pharm during the structure optimization of lead molecules used to prevent or treat metabolic diseases such as obesity, type 1 diabetes and type 2 diabetes.6 Forma Therapeutics recently disclosed efforts towards the lead optimization of bromodomain and extraterminal domain (BET) inhibitors for the treatment of cancer and inflammatory diseases containing this motif.7 While the final lead in these two studies does not contain the 1-methylcyclopropyl scaffold, it can be found in the final structure of complex new chemical entities. This is illustrated by the structure of a leucine-rich repeat kinase 2-inhibitor (LRRK2-inhibitor) recently discovered by Merck8 against Parkinson’s disease and by that of a human sphingomyelin synthase 2 inhibitor discovered by Takeda for the potential treatment of inflammatory responses and atherosclerosis (Fig. 1).9 In the former case, the authors explained that the 1-methylcyclopropyl introduction increased the LRRK2 IC50 by a 20-fold factor compared with the unsubstituted cyclopropanol. This effect was attributed to the enhanced hydrophobic interaction with Val1893 of LRRK2.

The various strategies employed in the medicinal chemistry programs to manipulate the 1-methylcyclopropanol scaffold mostly fall into two categories: Introduction of the 1-methylcyclopropoxy group (ether) via SAr or introduction of a 1-methylcyclopropylcarbamate moiety from the corresponding amine; The latter strategy usually requires pre-functionalization using standard techniques (Scheme 2).

Interestingly, the 1-methylcyclopropylcarbamates provide orthogonal protection to the more traditional Boc, Cbz, Alloc, and FMOC groups.10 During one of our development programs, 1-methylcyclopropanol was needed on a decagram scale using a process which would allow large scale implementation. While our
company has a rich history in making cyclopropyl and cyclobutyl derivatives, no cyclopropanol derivative had ever been the subject of active investigations.\(^{11}\) An initial literature survey showed that many methods exist to prepare the cyclopropanol scaffold, but in-depth analysis revealed that most of them lead to highly substituted cyclopropanols.\(^{7}\) Quite counterintuitively, the lack of chemical functionalities in 1-methylcyclopropanol drastically limits the number of enabling methods. The Kulinkovich reaction quickly appeared as the method of choice to access this small molecule. A specific literature search on 1-methylcyclopropanol was performed and Scheme 3 gathers the various known strategies to access this target.\(^{12a-c,13}\)

### Results

Upon examination, it was concluded that the chemistry deployed in the early papers was unsuitable for the efficient preparation of 1-methylcyclopropanol on large scale. The overall yields are not acceptable and the proposed routes rely on either toxic raw materials or convoluted strategies. The Kulinkovich method was deemed the most appropriate one but the process description proposed in an early paper by Kulinkovich was not devoid of practical issues (high dilution, use of diethyl ether, concentration to dryness, purification by column chromatography).\(^{13}\) Additionally, the physicochemical properties of the product (bp = 104 °C at atmospheric pressure, water miscibility, lack of UV chromophore, sensitivity to low and high pH) render its efficient preparation quite challenging. A research team from Pfizer Groton worked out some of these issues in a more recent paper while we were working on these problems (vide infra).\(^{14}\) The generally accepted mechanism for the Kulinkovich cyclopropanol formation has been depicted elsewhere\(^{14}\) and starts with the reaction between titanium tetraalkoxide and two equivalents of Grignard reagent. Careful examination of the proposed reaction pathway shows that the nature of the alkoxide grafted onto the titanium atom and that of the residue found in the starting acetate dictate the structure of the by-products obtained upon hydrolysis. We surmised that titanium (IV) methoxide and methyl acetate would be ideal reaction partners en route to a swift process. Indeed, if such a reaction was to work then methanol would be the only liquid by-product making the separation with the product easy. This approach is slightly different from that taken by the Pfizer team lead by Wright. Indeed, their strategy hinges on the use of a high molecular weight titanium alkoxide that would generate upon hydrolysis the corresponding high boiling alcohol. Their subsequent isolation protocol involves two distinct sequences: an initial distillation of the volatiles and the product (leaving the high boiling compounds in the pot) followed by a second fractional distillation. Table 1 details the key features of the original Kulinkovich approach, the procedure developed by Wright at Pfizer and this work. It shows that our modified procedure allows an easy access to 1-methylcyclopropanol in a robust fashion. The key features of the newly designed process include a change of solvent (MTBE vs Et\(_2\)O), a drastic reduction of solvent volume, a modification of the titanium catalyst and an overall simplification of product isolation and purification.

At the outset of the study, we identified that the principal factors to be optimized were the solvent and the reaction concentration. To this end, diethyl ether (class 1 solvent) had to be replaced with a more acceptable solvent. To simplify the envisioned liquid–liquid extractions, a water immiscible ethereal solvent was sought and MTBE (class 3 solvent, bp = 55 °C) emerged as a promising hit. It was also shown that 2-MeTHF could be successfully used in this reaction but in this case, isolation of 1-methylcyclopropanol (bp = 104 °C) by distillation was unsuccessful. This was attributed to the higher boiling point of 2-MeTHF (bp = 80 °C) as compared with that of MTBE. Solvents with higher boiling points such as TAME (tert-amyl methyl ether; bp = 86 °C) and CPME (Cyclopentyl methyl ether; bp = 106 °C) were not examined. Then, the amount of solvent used for the reaction was drastically reduced and it

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Fig. 1. Recently developed medicinally-relevant compounds bearing the 1-methylcyclopropanol moiety.
was shown that as little as 2.5 volumes (2.5 mL of solvent per gram of methyl acetate) gave satisfactory results. As explained above, the catalyst was changed from the most commonly used and cheap titanium (IV) isopropoxide or titanium (IV) ethylhexyloxide to titanium (IV) methoxide. The switch to titanium (IV) methoxide proved much beneficial and its lower molecular weight allowed for the use of less active substance (mass ratio). This innate feature compensates the extra-cost of using this unusual catalyst. The Grignard reagent was used as a 0.87 M solution in MTBE. Unfortunately, the somewhat low concentration of this reagent increases the final organic waste amounts. Next, the complex addition mode devised by the Wright group could be avoided in our process. Indeed, a simple extended addition (ca. 3 h) of the Grignard was necessary to control the reaction exotherm and the gas release. Most notably, the reaction was found to be dose-controlled, a much-desired feature on scale. The volume of the aqueous sulfuric acid solution used to quench the reaction was also reduced. Back extraction was shown to be needed to maximize the yield however, the volume of MTBE used for this operation (4 volumes) was not optimized. Two water washes were then applied to the organic layer to remove inorganic salts and traces of acid prior to distillation. The volume of water used (2 C2 C5 volumes) was not optimized and could probably be reduced. This extractive work-up provided us with a ready for distillation MTBE solution of 1-methylcyclopropanol. The extra-steps needed to ensure a smooth distillation described in the work of Wright were unnecessary in our case thus considerably reducing the labor associated with the product isolation. MTBE was removed under vacuum below 50 °C.

Table 1

<table>
<thead>
<tr>
<th>Item</th>
<th>Kulinkovich (1991)</th>
<th>Wright (2013)</th>
<th>This work</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting material amount</td>
<td>1.85 g</td>
<td>26.6 g</td>
<td>50 g</td>
</tr>
<tr>
<td>Solvent (class)</td>
<td>Et2O (class 1)</td>
<td>Et2O (class 1)</td>
<td>MTBE (class 3)</td>
</tr>
<tr>
<td>Total solvent volume for the reaction</td>
<td>43 vol</td>
<td>22.9 vol</td>
<td>2.5 vol</td>
</tr>
<tr>
<td>Catalyst</td>
<td>Ti(OiPr)4</td>
<td>Ti[OCH2CH(C2H5)(CH2)3CH3]4</td>
<td>Ti(OMe)4</td>
</tr>
<tr>
<td>m(catalyst)/m substrate</td>
<td>0.38</td>
<td>0.68</td>
<td>0.23</td>
</tr>
<tr>
<td>Grignard Addition mode</td>
<td>0.88 M/Et2O</td>
<td>Portionwise addition of Grignard then substrate (repeat until all reagents are added)</td>
<td>Regular addition of Grignard onto methyl acetate/solvent/catalyst mixture over 160 min</td>
</tr>
<tr>
<td>Quench solution</td>
<td>10% H2SO4</td>
<td>8% H2SO4</td>
<td>10% H2SO4</td>
</tr>
<tr>
<td>V (quench solution)</td>
<td>135 vol</td>
<td>27 vol</td>
<td>15 vol</td>
</tr>
<tr>
<td>Back extraction</td>
<td>2 × 27 vol of Et2O</td>
<td>1.9 vol of Et2O</td>
<td>4 vol of MTBE</td>
</tr>
<tr>
<td>Aqueous washes</td>
<td>Water 27 vol</td>
<td>Dry over Na2SO4, Concentration to dryness</td>
<td>Distillation of MTBE + volatile</td>
</tr>
<tr>
<td>Isolation</td>
<td>Dry over Na2SO4, Concentration to dryness</td>
<td>Dry over Na2SO4, add Bu4N (0.54 × m (substrate)) and mesitylene (0.37 × m (substrate))</td>
<td>Distillation at atmospheric pressure</td>
</tr>
<tr>
<td>Purification</td>
<td>Column chromatography</td>
<td>Fractional distillation</td>
<td>Fractional distillation</td>
</tr>
<tr>
<td>Yield</td>
<td>76%</td>
<td>59%</td>
<td>64%</td>
</tr>
<tr>
<td>Purity</td>
<td>NA</td>
<td>ca. 95% (1H NMR)</td>
<td>ca. 98% GC</td>
</tr>
<tr>
<td>V. aqueous waste/ kg product</td>
<td>220 L/kg</td>
<td>49 L/kg</td>
<td>40 L/kg</td>
</tr>
</tbody>
</table>

* According to ICHQ3C.
and the residue underwent a fractional distillation. The latter isolation procedure was not particularly optimized, and it would be worth evaluating the possibility of performing the distillation under atmospheric pressure. Four fractions were isolated and analyzed separately before being combined and reanalyzed. The targeted 1-methylcyclopropanol was isolated in 64% yield and 98.8% GC.

The Kulinkovich reaction of methyl acetate and ethyl magnesium bromide in the presence of titanium (IV) methoxide generates several low-level impurities as detected by GC and a typical in-process control by GC shows approximately 2% of residual methyl acetate, 2% of methanol, 1% of methyl ethyl ketone, 3% of ethanol and 86% of 1-methylcyclopropanol. The missing 6% are displayed over more than 20 small peaks (see GC chromatograms in the supporting information). It should be mentioned here that the analytical sample was prepared by quenching 1 mL of the reaction mixture onto 1 mL of 10% sulfuric acid in water; The organic layer was then sampled for GC injection. The GC chromatograms may not perfectly reflect the composition of the reaction mixture. Methyl ethyl ketone might stem from either the direct addition of ethyl magnesium bromide to methyl acetate or from the opening of 1-methylcyclopropanol under basic conditions. Ethanol might come from either oxidation of ethyl magnesium bromide or from the catalyst itself (The latter was purchased from Sigma Aldrich and is 95% pure only). Small amount of titanium (IV) ethoxide could contaminate this catalyst but this has not been verified. Finally, methyl acetate may also contain a small amount of ethyl acetate which would in turn generate ethanol under the reaction conditions. Performing a reaction using extra-pure methyl acetate and titanium (IV) methoxide might give more precise information regarding the actual impurity profile of the Kulinkovich reaction.

Our industrial experience tends to show that finding the right conditions for a robust product isolation is often more complicated than finding the right reaction conditions. An unoptimized 1-methylcyclopropanol process developed here can be performed in an abbreviated time using multi-purpose equipment. The high sensitivity of 1-methylcyclopropanol towards base and acid observed by the Pfizer team was also confirmed during our study, hence the need to wash the organic layer with water until pH 7 is reached prior to distillation. This ensures that no acid traces remain in the organic layer prior to distillation. As thermal stability issues often hamper isolation by distillation, samples of the organic layer obtained after the azeotropic washes were heated to reflux (ca. 55 °C) for extended periods and no thermal degradation was observed during those stress tests.

To the best of our knowledge, this process is the only example of a Kulinkovich cyclopropanol preparation using titanium (IV) methoxide as such. Several patent applications from Pfizer could be found in the literature where titanium (IV) methoxide was used as a precursor for the preparation of a heavier catalyst via ligand exchange en route to the preparation of GPR119 modulators. Cyclohexanol was used for instance to generate titanium (IV) cyclohexyloxide and the latter was used in lieu of titanium (IV) (2-ethyl)hexyloxide for the preparation of 1-methylcyclopropanol using a similar process as the one described above albeit with lower yield. In sharp contrast with the work described by Kulinkovich and by Wright at Pfizer, little to no Grignard addition to the acetate was observed during our study. One could hypothesize that the methoxide ligands around the titanium atom do not generate excessive steric hindrance thus allowing the Grignard to react in a productive fashion. The table below shows metrics associated with our newly devised process and with the process described by Wright (Table 2). The process mass intensity (PMI) was estimated for both processes and were shown to be equivalent. The rather high value of PMI of our process can be attributed mostly to the volume of the Grignard reagent. The latter being quite dilute (0.87 M), the volumes needed are rapidly growing and impact the PMI. However, the number of operations in our process is significantly lower reflecting higher processability and cost savings.

### 3. Conclusion

The process provides access to 1-methylcyclopropanol in a simple fashion and involves only standard unit operations. In theory, the MTBE waste stream (contaminated with methanol) could be washed with water and distilled to sufficiently high purity to allow recycling therefore reducing the environmental impact of the process. The modus operandi described in the experimental procedure below would require only minimum improvement before its implementation to large scale could be done. A thorough process safety study including Rc1 and DSC would have to be performed prior to scale-up. Further improvement could involve the use of a more concentrated formulation of ethyl magnesium bromide.

### 4. Experimental procedure

A 4-L four-neck round bottom flask equipped with an addition funnel and a mechanical stirrer was charged with methyl acetate (50.0 g, 675 mmol, 1.0 equiv.), MTBE (125 mL, 2.5 vol) and titanium (IV) methoxide (11.6 g, 67.5 mmol, 0.1 equiv.) at 20–25 °C. To this white suspension was added 0.87 M EtMgBr in MTBE (1700 mL, 2.2 equiv.) in approximately 160 min (gaseous stream evolves in a controlled fashion during the addition) at 20–25 °C. The ensuing grey suspension was stirred for a further 30 min before a sample was analyzed by GC (sample preparation: 1 mL reaction mixture added to 1 mL 10% aq. sulfuric acid; injection of the organic layer). A second 4-L four-neck round bottom flask was charged with 10% aqueous sulfuric acid (850 mL, 17 vol) and the temperature was adjusted to 0–5 °C. The reaction mixture was transferred through a thick cannula at such a rate that the

<table>
<thead>
<tr>
<th>Time</th>
<th>P (mbar)</th>
<th>T_{max} (°C)</th>
<th>T_{top of column} (°C)</th>
<th>Mass (g)</th>
<th>IPC (GC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 → 1 h 34</td>
<td>210–230</td>
<td>20.0</td>
<td>23.5</td>
<td>5.2</td>
<td>CD4314-1-F1</td>
</tr>
<tr>
<td>1 h 34 → 1 h 42</td>
<td>54</td>
<td>41.7</td>
<td>36.6</td>
<td>4.7</td>
<td>CD4314-1-F2</td>
</tr>
<tr>
<td>1 h 42 → 1 h 47</td>
<td>58</td>
<td>38.9</td>
<td>33.4</td>
<td>2.0</td>
<td>CD4314-1-F3</td>
</tr>
<tr>
<td>1 h 47 → 2 h 25</td>
<td>59–56</td>
<td>39.8–37.5</td>
<td>34–35.5</td>
<td>19.2</td>
<td>CD4314-1-F4</td>
</tr>
</tbody>
</table>
temperature into the second reactor did not exceed 20 °C (pH aq. layer is 1). The mixture was then stirred for 15 min at 20–25 °C and the layers were separated. The aqueous layer (bottom layer) was extracted back with MTBE (200 mL, 4.0 vol) and the organic layers were combined and washed twice with water (2 × 5.0 vol; the pH of the last aqueous layer reached 7). The organic layer was introduced into a 2-L three-neck round bottom flask equipped with a short path distillation apparatus. The solvent was distilled under vacuum at max. 50 °C and the residue (103 g) was introduced in a 250 mL four-neck round bottom flask equipped with a 20 cm Vigreux column. Fractional distillation was carried out and data regarding this isolation step is given in the table below (Table 3).

Four fractions (F1, F2, F3 and F4; see chromatograms in supporting information) were combined to yield 31.1 g of 1-methylcyclopropanol (64% total yield, 98.8% GC; see chromatograms and IR spectra in the supporting information). It is worth mentioning that the vacuum/distillation trap contained 47 g of a mixture composed mostly of MTBE and some product (amount not measured). The distillation residue was a yellow liquid (m = 8.5 g) and still contained some product (amount not measured). The 1-methylcyclopropanol sample was analyzed by GC and IR before being sent to our customer who approved its quality.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bmc.2017.12.029.

References
