Oxidation of Secondary Methyl Ethers to Ketones

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Supporting Information

ABSTRACT: We present a mild way of converting secondary methyl ethers into ketones using calcium hypochlorite in aqueous acetonitrile with acetic acid as activator. The reaction is compatible with various oxygen- and nitrogen-containing functional groups and afforded the corresponding ketones in up to 98% yield. The use of this methodology could expand the application of the methyl group as a useful protecting group.

INTRODUCTION

Well-established methodologies have been developed for the selective deprotection of aryl, allyl, and benzyl ethers, which are commonly used by organic chemists. In contrast, selective cleavage of aliphatic ethers is much less explored. These ethers, which in fact are often used as solvents, are extraordinarily unreactive toward a variety of reagents, including most well-known oxidants. Historically, the methyl group has been used as a protecting group for phenols and carboxylic acids, but rarely for aliphatic alcohols. For instance, the methyl group of an aryl methyl ether can be selectively removed by boron tribromide, sodium ethanethiolate in refluxing DMF, or lithium iodide in refluxing collidine, whereas aliphatic methyl ethers remain unaffected. Due to its inertness, it is difficult to selectively remove the methyl group from an aliphatic methyl ether while keeping other functional groups intact. Rigorous conditions are required to successfully cleave off the methyl group of methyl ethers, such as aqueous sulfuric, hydroiodic, hydrobromic, or hydrochloric acid. Other methods to transform methyl ethers into more reactive functional groups are based on oxidation. Olah et al. utilized uranium hexafluoride as the oxidant to transform secondary methyl ethers into the corresponding ketones. Other research groups observed the same result by using HOF, a manganese complex and m-CPBA as the stoichiometric oxidant, hydrogen peroxide over titanosilicates, and Bobbitt's salt. Mayhoub et al. also showed the selective oxidation of benzyl methyl ethers using NBS and UV light to afford aldehydes or esters. It may be clear that oxidation of ethers requires either the ether to be prone to oxidation (such as benzyl and allyl ethers) or expensive transition-metal catalysts. Herein, we describe an oxidation method to selectively transform secondary methyl ethers into ketones with the versatile and cheap oxidant calcium hypochlorite. We envisioned that multifunctionalized molecules would selectively form ketones from methyl or benzyl ethers leaving other functional groups unchanged. First, we looked for mild reaction conditions to oxidize ethers. We observed that THF (1) was oxidized to 2-butyrolactone (9) using both sodium and calcium hypochlorite (entries 1–2, Table 1). Calcium hypochlorite was the preferred oxidant, because it was easier to use stoichiometrically compared to the alkaline sodium hypochlorite solution. The oxidation of 2-methyl-tetrahydrofuran (2) was completely regioselective and overoxidation of primary alcohol 10 was not observed within 1 h (entry 3). Dioxane, 2-(chloromethyl)tetrahydro-2H-pyrane, and isosorbide were completely unaffected under these reaction conditions. Several benzyl ethers (3–7) were synthesized and submitted to the conditions used by Nwaukwa et al. for the oxidation of symmetrical ethers (6 equiv of oxidant, 9 equiv of acetic acid in a 1:3 mixture of acetonitrile/water). Benzylic ethers 3 and 4 (entries 4–5) were oxidized to ketones 11 and 12, respectively. The benzyl group of the ether was oxidized to chlorinated benzaldehydes and benzoic acids giving rise to an inseparable mixture. Primary alkyl benzyl ether 5 (entry 6) was partially oxidatively deprotected to give 13, but multiple unidentified side products were formed. Linear secondary alkyl benzyl ethers 6 and 7 (entries 7–9) were oxidized to the corresponding methyl ketones 14 and 15. Chlorination of the aromatic ring could be reduced (entry 9) by lowering the reaction temperature and by adding less oxidant portion wise.

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Then, we moved on to secondary methyl ether 8 for which similar conditions were used (entries 10–11) as for the oxidation of the aforementioned benzyl ethers. Reducing the amounts of oxidant (to 1.6 equiv) and acid (to 3.5 equiv) and lowering the reaction temperature to 0 °C (entries 12–13) eventually led to a clean reaction in which ketone 15 was obtained in 89% yield without the need for further purification.

Optimal results were obtained when the methyl ether (1.0 equiv) was stirred for 20–24 h in a 1:1 mixture of acetonitrile/water (0.25 M) and acetic acid (3.5 equiv), while calcium hypochlorite (1.6 equiv) was added portion wise at 0 °C. To explore the scope and limitations of this oxidative demethylation various methyl ethers carrying other functional groups were synthesized from readily available starting materials (see Supporting Information). Oxidation reactions were conducted under the optimal reaction conditions, typically on a 1 mmol scale, unless otherwise stated (Table 2). If necessary, additional oxidant was added after 1 day. The reaction was tested in three series of compounds: acyclic compounds, cyclohexane derivatives, and functionalized piperidines. Benzoyl protected primary alcohol 16 (entry 1) gave the desired ketone 29 in excellent yield (98%). TBDMS-protected primary alcohol 17 (entry 2) was partially hydrolyzed to the hydroxy ketone 10, but still the corresponding ketone 30 was obtained in good yield (68%).

Remarkably, compound 31 (entry 3) was the only product (87%) from the oxidation reaction of poly ether 18, leaving the ether tail completely intact. The explanation for this regioselectivity was supported by failed attempts to oxidize dioxane and isosorbide under similar conditions. All those substrates have their heteroatoms in an ethylene glycol-like connectivity. We hypothesize that the inductive effect of one of the oxygen atoms lowers the nucleophilicity of the other oxygen. We observed similar unreactivity of the 1,3-dioxolane toward oxidation while forming ketone 37 (entry 9). Finally, we tried the reaction with the corresponding unprotected primary alcohol (4-methoxypentan-1-ol), although without success. Primary amine 19 (entry 4) protected as phthalimide afforded the corresponding amino ketone 32 in good yield (82%). The reaction of nitrile 20 (entry 5) was stopped after 27.5 h, purified, and product 33 was obtained in 43% yield, alongside 17% of 20. As expected, the reaction with a tertiary amine as substrate failed. The reaction of secondary amide 21 (entry 6) worked to a certain extent, but eventually we discovered that the amide functionality itself was prone to oxidation, leading to

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<td>20</td>
<td>1.5</td>
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<td>5</td>
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<td>12</td>
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<td>MeCN/H$_2$O (1:3)</td>
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<td>MeCN/H$_2$O (1:3)</td>
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<td>20</td>
<td>1.5</td>
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<td>MeCN/H$_2$O (1:3)</td>
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<td>C$_6$H$_5$Bn</td>
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<td>9.0</td>
<td>MeCN/H$_2$O (1:3)</td>
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<td>0</td>
<td>24</td>
<td>90</td>
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<td>3.0</td>
<td>12.0</td>
<td>MeCN/H$_2$O (1:3)</td>
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<td>20</td>
<td>3</td>
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<tr>
<td>11</td>
<td>C$_6$H$_5$Bn</td>
<td>15</td>
<td>2.0</td>
<td>9.0</td>
<td>MeCN/H$_2$O (1:3)</td>
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<td>20</td>
<td>20</td>
<td>90 (17)</td>
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<td>C$_6$H$_5$Bn</td>
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<td>20</td>
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<td>MeCN/H$_2$O (1:3)</td>
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<td>20</td>
<td>21.5</td>
<td>100 (89)</td>
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*Equivalents of oxidant; Ca(OCl)$_2$ contains two equivalents of oxidant. *Conversions are based on $^1$H NMR analysis. *Isolation of products was only achieved for entries 11–13. *NaOCl was used as oxidant in a pH 6 phosphate buffer.
several water-soluble unidentified side products (detected by NMR). Therefore, the crude mixture after aqueous extraction only contained methyl ether 21 and ketone 34. Due to negligible difference in polarity between these two compounds, we decided to isolate the ketone as the corresponding 2,4-dinitrophenyl hydrazone 34a (16%) using Brady’s reagent (2,4-dinitrophenyl-hydrazine). Benzyl methyl ether 22 (entry 7) heavily suffered from chlorination of the phenyl ring as a side reaction. Two successive rounds of silica gel column chromatography were insufficient to separate 35 from the complex mixture.

Besides linear substrates, cyclic substrates derived from cyclohexane were considered to be suitable for this reaction. The acetox group of methyl ether 23 (entry 8) was completely unreactive under the mild reaction conditions and ketone 36 was formed in 81% yield. As expected, a TMS-protected secondary alcohol (1-methoxy-4-[(trimethylsilyl)oxy]-cyclohexane) was hydrolyzed before any observable oxidation took place. The 1,3-dioxolane protecting group of compound 24 (entry 9) was not completely unreactive. The reaction was stopped after 20 h because of the formation of an additional product according to TLC. After purification, the monoprotected diketone 37 was isolated in 49% yield alongside 37% of the starting material. 4-Methoxycyclohexanone 25 (entry 10) reacted extremely slowly and after 5 days of stirring with additional oxidant, diketone 38 was isolated in only 20% yield, alongside 30% of the starting material. Then, we moved on to piperidine derivatives. Boc-protected 4-methoxypiperidine 26 (entry 11) was not unreactive under the acidic reaction conditions, giving rise to a number of unidentified side products. The corresponding 4-piperidone 39 was just isolated as a minor component (3% yield). Cbz-protection of compound 27 (entry 12) indeed made the carbamate functional group unreactive, but the aromatic ring was prone to chlorination. Within the crude mixture, product 40 was the predominant one, but isolation was not achieved. Sulfonamide 28 (entry 13) was cleanly converted into the corresponding ketone 41. However, the oxidation was extremely slow and after two successive rounds of oxidation (three and 6 days, respectively) the conversion was only 20%. Most of the material was recovered, but due to the negligible difference in polarity, attempts to isolate 41 were not successful, hence conversions are mentioned.

We propose a reaction sequence for the oxidative transformation of secondary methyl ethers into ketones (Figure 1).

Table 2. Scope of Methyl Ethers as Substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Methyl ether</th>
<th>Ketone</th>
<th>Yield [%]</th>
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<tr>
<td>1b</td>
<td>OMe</td>
<td>MeO</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>OTBDMS</td>
<td>OTBDMS</td>
<td>68</td>
</tr>
<tr>
<td>3b,c</td>
<td>NPhth</td>
<td>NPhth</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>NPhth</td>
<td>NPhth</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>CN</td>
<td>CN</td>
<td>43 (17)</td>
</tr>
<tr>
<td>6b</td>
<td>NMe</td>
<td>NMe</td>
<td>16f</td>
</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>OMe</td>
<td>50f</td>
</tr>
<tr>
<td>8</td>
<td>OAc</td>
<td>OAc</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>OAc</td>
<td>OAc</td>
<td>49 (37)</td>
</tr>
<tr>
<td>10f</td>
<td>OMe</td>
<td>OMe</td>
<td>20 (30)</td>
</tr>
<tr>
<td>11f</td>
<td>OMe</td>
<td>OMe</td>
<td>3</td>
</tr>
<tr>
<td>12f</td>
<td>OMe</td>
<td>OMe</td>
<td>50f</td>
</tr>
<tr>
<td>13b,c</td>
<td>NNs</td>
<td>NNs</td>
<td>20f (80)</td>
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*a*The recovered starting material [%] is given between brackets. b*Additional oxidant was added after 1 day and stirring was continued for another day. c*Reaction was performed on smaller scale (see Experimental Section). d*Isolated yield of the corresponding 2,4-dinitrophenyl hydrazone 34a. e*Conversion based on 1H NMR analysis of the crude mixture. f*Total reaction time exceeded 48 h (see Experimental Section).

The recovered starting material [%] is given between brackets.

Additional oxidant was added after 1 day and stirring was continued for another day.

Reaction was performed on smaller scale (see Experimental Section).

Isolated yield of the corresponding 2,4-dinitrophenyl hydrazone 34a.

Conversion based on 1H NMR analysis of the crude mixture.

Total reaction time exceeded 48 h (see Experimental Section).

First, protonation of hypochlorite anion by acetic acid is required to generate hypochlorous acid, which is the active species. The chlorinating species hypochlorous acid is in equilibrium with acetyl hypochlorite and molecular chlorine, which are other chlorinating species.

Figure 1. Proposed reaction sequence for the oxidation of methyl ethers to ketones.
Then, chlorination occurs at the nucleophilic ether oxygen of I to form oxonium ion II. Subsequent selective HCl elimination via an E2 mechanism at the most substituted carbon forms the most stable oxocarbenium intermediate III. The stabilized cation III is trapped by a water molecule and the formed hemiacetal IV collapses to form the corresponding ketone V upon release of one molecule of methanol. The regioselectivity is supported by the observation that during the oxidation of secondary methyl ethers, the corresponding secondary alcohol was never detected with TLC analysis. In contrast, this secondary alcohol was always detected as an intermediate in the oxidation of secondary benzyl ethers.

**CONCLUSIONS**

A novel and versatile method to transform secondary methyl ethers into ketones has been developed. From our perspective, the secondary methyl ether can now be considered as a masked ketone, and hence, this reaction should find use in organic synthesis where it might reduce the number of protection and oxidation steps. The reaction is rather slow, but highly regioselective. The scope and limitations have been determined and we can safely state that a variety of oxygen- and nitrogen-containing functional groups are tolerated. Under the mild acidic reaction conditions used, in particular some acid labile groups are tolerated. However, nonactivated aromatic systems were chlorinated, making this reaction not suitable for aromatic compounds of this particular kind.

**EXPERIMENTAL SECTION**

**General Information.** Reagents were obtained from commercial suppliers and were used without purification. Reactions were followed using thin-layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254). Detection was performed with UV light and/or by charring at 150 °C after dipping in a solution of Brady’s reagent (2,4-dinitrophenylhydrazine) or a solution of KMnO4. Column chromatography was performed manually using Acros silica gel, 0.035 mm thick gel column chromatography (pentane/dichloromethane, 4:1) furnished 8 (2.60 g, 97%) as a transparent yellow oil.1H NMR (400 MHz, CDCl3) δ 3.33 (s, 3 H), 3.33–3.32 (m, 1 H), 1.59–1.46 (m, 1 H), 1.43–1.20 (m, 15 H), 1.12 (d, J = 6.1 Hz, 3 H), 0.92–0.85 (m, 3 H); 13C NMR (101 MHz, CDCl3) δ 76.9, 55.9, 36.3, 31.9, 29.8, 29.7, 29.6, 29.3, 25.5, 22.7, 19.0, 14.1. **Undecan-2-one (15).** According to the general procedure, substrate 8 (186 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. The reaction mixture was stirred for 21.5 h before it was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The product was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL); then dried over magnesium sulfate and concentrated. Silica gel column chromatography (pentane/dichloromethane, 4:1) furnished 8 (2.60 g, 97%) as a transparent yellow oil.1H NMR (400 MHz, CDCl3) δ 3.33 (s, 3 H), 3.33–3.32 (m, 1 H), 1.59–1.46 (m, 1 H), 1.43–1.20 (m, 15 H), 1.12 (d, J = 6.1 Hz, 3 H), 0.92–0.85 (m, 3 H); 13C NMR (101 MHz, CDCl3) δ 76.9, 55.9, 36.3, 31.9, 29.8, 29.7, 29.6, 29.3, 25.5, 22.7, 19.0, 14.1.
Sodium hydride (660 mg, 16.5 mmol, 1.2 equiv) was added to the residue, followed by 1 N HCl to make the solution acidic. The product was extracted with diethyl ether (3 × 20 mL). The combined etheral extracts were washed with water (10 mL) and brine (10 mL); then it was dried over magnesium sulfate and the solvent was evaporated in vacuo to a yellow liquid.

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The mixture was stirred at 20 °C for 20.5 h and subsequently diluted with ethyl acetate (50 mL); washed with 1 M HCl (2 × 20 mL), saturated aqueous sodium bicarbonate (2 × 20 mL), and brine (20 mL); and then dried over magnesium sulfate and the solvent was removed in vacuo to afford ester 23 (240 mg, 77%, mixture of cis and trans) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 4.82 (t, J = 7.1, 3.5 Hz, 4.78–4.70 (m, 5 H), 3.34 (s, 0.9 H), 3.33 (s, 2.1 H), 3.29 (tt, J = 6.6, 3.3 Hz, 0.7 H), 3.25–3.18 (m, 0.3 H), 2.04 (s, 2.1 H), 2.03 (s, 0.9 H), 2.02–1.93 (m, 1.2 H), 1.86–1.70 (m, 2.8 H), 1.70–1.56 (m, 2.8 H), 1.46–1.37 (m, 1.2 H); 13C NMR (101 MHz, CDCl3) δ 170.7, 170.6, 77.3, 75.8, 71.8, 70.6, 55.9, 55.6, 28.3, 28.3, 27.1, 27.1, 21.4, 21.4.

8-Methoxy-1,4-dioxaspiro[4.5]decane (24).25,26 Magnesium sulfate (361 mg, 3.0 mmol, 2.5 equiv) and a catalytic amount of p-toluene sulfonic acid (26 mg, 0.15 mmol, 10 mol%) in toluene (3 × 5 mL) was added to a solution of ketone (240 mg, 1.0 mmol, 1.0 equiv) in dichloromethane (3 mL). The resulting mixture was refluxed for 4 h. The reaction was cooled to 20 °C and quenched with saturated aqueous sodium bicarbonate (10 mL). The product was extracted with ethyl acetate (3 × 5 mL) and the combined ethereal extracts were successively washed with brine (10 mL), dried over sodium sulfate, and the solvent was removed in vacuo to obtain ketol ine (5 mL). The resulting orange mixture was stirred for 3.5 h at 20 °C while the color changed from orange to brown. Upon completion of the reaction, the mixture was filtered through Celite, concentrated, and purified with silica gel column chromatography (ethyl acetate/heptane 1:2) to afford ketone (241 mg, 85%) as a colorless transparent oil. 

A solution of alcohol (367 mg, 3.0 mmol, 1.0 equiv) in THF (10 mL) was added at 0 °C and stirring was continued for another 20 h before the reaction was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The combined organic extracts were washed with brine (25 mL) and dried over magnesium sulfate and the solvent was removed in vacuo to obtain an orange oil. The crude mixture was dissolved in dichloromethane (20 mL) and successively washed with 0.1 M HCl (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (20 mL); then dried over magnesium sulfate and the solvent was removed in vacuo to give sultonamide (28) (238 mg, 72%) as a pale orange solid. 1H NMR (400 MHz, CDCl3) δ 8.41–8.35 (m, 2 H), 7.97–7.92 (m, 2 H), 3.44 (tt, J = 6.3, 3.2 Hz, 1 H), 3.25 (s, 3 H), 3.00–3.06 (m, 4 H), 1.93–1.83 (m, 2 H), 1.83–1.72 (m, 2 H); 13C NMR (101 MHz, CDCl3) δ 176.8, 170.7, 118.7, 124.3, 73.2, 55.8, 42.7, 29.5. MS (EI+) calcd for (C12H16N2O5S)1+ 268.052, found 268.079; HRMS (FD +) calcd for (C12H16N2O5S)1+ 268.078, found 268.078.

4-Oxopentyl Benzate (29).5 According to the general procedure, compound (222 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added. After stirring for 26 h, additional calcium hypochlorite (44 mg, 0.2 mmol, 0.4 equiv) was added at 0 °C and stirring was continued for another 20 h before the reaction was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and the residue was removed in vacuo to afford ketone (290 mg, 98%) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 6.92–6.81 (m, 2 H), 7.40–7.35 (m, 1 H), 7.16–7.12 (m, 1 H), 3.75–3.68 (m, 2 H), 3.63–3.58 (m, 2 H), 2.51 (t, J = 6.4 Hz, 2 H), 2.47 (s, 3 H), 1.88 (s, 3 H), 1.78 (s, 3 H), 1.64 (s, 3 H), 1.53–1.40 (m, 2 H), 0.90 (s, 9 H), 0.04 (s, 3 H), 13C NMR (101 MHz, CDCl3) δ 170.7, 166.5, 133.0, 130.2, 129.5, 128.4, 66.1, 64.0, 30.0, 23.9.

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acetate/heptane 1:3) separately gave starting material 34a (76 mg, 48%), 1-(4-chlorophenyl)ethan-1-one and 1-(3-chlorophenyl)ethan-1-one. The ratio of 35-side products was roughly 1:1. Attempts to separate the product by silica gel column chromatography (pentane → dichloromethane) failed.

4-Oxacyclohexyl Acetate (36). According to the general procedure, compound 22 (136 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL) water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. The reaction mixture was stirred for 47 h before the reaction was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The products were extracted with dichloromethane (3 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography (ethyl acetate/heptane 1:3) yielded ketone 32 (190 mg, 82%) as a white solid. 1H NMR (400 MHz, CDCl3) δ 7.87–7.82 (m, 2H), 7.75–7.69 (m, 2H), 3.71 (t, J = 6.7 Hz, 2H), 2.50 (t, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.96 (p, J = 7.0 Hz, 2H), 13C NMR (101 MHz, CDCl3) δ 207.4, 168.5, 134.0, 132.1, 123.2, 40.6, 37.2, 29.9, 22.7. 5-Oxohexanenitrile (33). According to the general procedure, nitrile 20 (127 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. The reaction mixture was stirred for 27.5 h before it was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The product was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography (ethyl acetate/heptane 1:3) gave ketone 33 (48 mg, 43%) as an off-white liquid. 1H NMR (400 MHz, CDCl3) δ 2.65 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 7.0 Hz, 2H), 2.19 (s, 3H), 1.92 (p, J = 6.9 Hz, 2H). 4-(2,4-Dinitrophenyl)hydrazinylidene-1-(piperidin-1-yl)-pentan-1-one (34). According to the general procedure, compound 21 (199 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. Stirring was continued for 46 h, while additional calcium hypochlorite (44 mg, 0.2 mmol, 0.4 equiv) was added after 24 h. Finally, the reaction was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The product was extracted with dichloromethane (5 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated to give a transparent yellow oil (116 mg) that contained both starting material 21 and ketone 34. Separation of these two compounds by means of silica gel column chromatography was no achieved so another separation method was used. Treatment of the crude mixture with Brady’s reagent (2,4-dinitrophenyl hydrazine in ethanol and sulfuric acid) transformed the ketone into the corresponding 2,4-dinitrophenyl hydrazone whereas the methyl ether remained intact. The solution was poured into diethyl ether (75 mL). The layers were separated and the ethereal extract was washed with water (25 mL) and concentrated to give a red precipitate. The red precipitate was redissolved in diethyl ether (10 mL) and successively washed with 0.1 M HCl (3 × 10 mL), dried over magnesium sulfate, and concentrated. The residue was purified with silica gel column chromatography (ethyl acetate/heptane 1:2/1) to give 219 mg (59 mg, 16%, 8:1 mixture of E and Z, ratio based on the 1H NMR signals between 12 and 11 ppm) as an orange solid. E-isomer: 1H NMR (400 MHz, CDCl3) δ 11.06 (s, 1H), 9.13 (d, J = 2.5 Hz, 1H), 8.27 (dd, J = 9.6, 2.6, 0.7 Hz, 1H), 7.89 (d, J = 9.6 Hz, 1H), 3.61–3.53 (m, 2H), 3.53–3.47 (m, 2H), 2.81 (t, J = 6.4 Hz, 2H), 2.72 (t, J = 6.4 Hz, 2H), 2.13 (s, 3H), 1.74–1.60 (m, 4H), 1.60–1.50 (m, 2H), 13C NMR (400 MHz, CDCl3) δ 169.7, 157.4, 145.2, 137.6, 129.8, 129.0, 123.6, 116.2, 46.5, 42.9, 33.8, 28.8, 26.6, 25.6, 24.6, 16.9. Z-isomer: Signals could not be identified due to overlap with the signals of the E-isomer. HRMS (ESI+) for (C16H15N3O4 + Na)+ 386.1440, found 386.1437.

Acetophenone (35). According to the general procedure, compound 22 (136 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. The reaction was stirred for 26 h before it was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The products were extracted with dichloromethane (3 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. The solution was coolied to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. The reaction mixture was stirred for 47 h before it was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The product was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography (pentane → methanol) gave ketone 35 (126 mg, 81%) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 5.17 (p, J = 4.9 Hz, 1H), 2.61–2.49 (m, 2H), 2.42–2.32 (m, 2H), 2.11 (s, 3H), 2.13–2.03 (m, 4H), 13C NMR (101 MHz, CDCl3) δ 209.8, 170.4, 68.6, 37.3, 30.4, 21.3. 1,4-Dioxaspiro[4.5]decane-8-one (37). According to the general procedure, ketal 24 (172 mg, 1.0 mmol, 1.0 equiv, mixture of cis and trans) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. The reaction mixture was stirred for 47 h before it was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The product was extracted with dichloromethane (3 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography (pentane → methanol) gave ketone 37 (59 mg, 37%, 8:1 mixture of E and Z) as an orange solid. The combined compound, cyclohexane-1,4-dione (trace amounts), was detected in the crude mixture, but not isolated. 1H NMR (400 MHz, CDCl3) δ 4.03 (s, 4H), 2.55–2.48 (m, 4H), 2.06–1.97 (m, 4H), 13C NMR (101 MHz, CDCl3) δ 210.4, 107.1, 64.7, 38.2, 33.9.
Cyclohexane-1,4-dione (38). According to the general procedure, compound 25 (128 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 0.8 equiv) was added portion wise over 3 h. Stirring was continued for 116 h, while additional calcium hypochlorite (308 mg, 1.4 mmol, 1.4 equiv) was added in portions after 19, 27, and 51 h. Finally, the reaction was quenched with aqueous sodium thiosulfate (10% in water, 5 mL). The product was extracted with dichloromethane (5 × 10 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over magnesium sulfate, and concentrated. Purification by silica gel column chromatography (ethyl acetate/heptane 1:1) separately gave starting material 25 (38 mg, 30%) and diketone 38 (22 mg, 20%) as a yellow solid. 1H NMR (400 MHz, CDCl3) δ 2.72 (s, 8 H)

tert-Butyl 4-oxopiperidine-1-carboxylate (39). According to the general procedure, compound 26 (215 mg, 1.0 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL), water (2 mL), and acetic acid (0.2 mL, 3.5 equiv). The solution was cooled to 0 °C and calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. Stirring was continued for 119 h, while additional calcium hypochlorite (176 mg, 0.8 mmol, 1.6 equiv) was added portion wise over 3 h. Stirring was continued for 72 h, while additional calcium hypochlorite (242 mg, 1.1 mmol, 4.4 equiv) was added after 22 h (0.2 equiv), 2 days (1.0 equiv), and 3 days (1.0 equiv). Apparently, the reaction did not proceed any further than 20% conversion. Eventually, the reaction was quenched with aqueous sodium thiosulfate (10% in water, 2.5 mL). The products were extracted with dichloromethane (3 × 5 mL), the combined organic extracts were subsequently washed with saturated aqueous sodium bicarbonate (5 mL) and brine (5 mL), dried over magnesium sulfate, and the solvent was removed in vacuo to afford a white-orange solid (139 mg). Attempts to separate product 41 via silica gel column chromatography failed. Analytical data could be acquired from the crude 1H NMR spectrum. 1H NMR (400 MHz, CDCl3) δ 8.43–8.39 (m, 2 H), 8.02–7.99 (m, 2 H), 3.48 (t, J = 6.3 Hz, 4 H), 2.39 (t, J = 6.3 Hz, 4 H).

4-Methoxypentan-1-ol (43). Compound 17 (2.32 g, 10 mmol, 1.0 equiv) was dissolved in THF (20 mL) and triethylamine trihydrochloride (1.63 mL, 10 mmol, 1.0 equiv) was added. The mixture was stirred for 27.5 h at 20 °C before it was concentrated at the rotary evaporator. The residue was purified with silica gel column chromatography (ethyl acetate/heptane 1:1) to afford 43 (1.063 g, 90%) as a yellow liquid. 1H NMR (400 MHz, CDCl3) δ 3.64 (t, J = 6.0 Hz, 2 H), 3.41–3.32 (m, 1 H), 3.34 (s, 3 H), 2.09 (bs, 1 H), 1.74–1.54 (m, 4 H), 1.16 (d, J = 6.1 Hz, 3 H). 13C NMR (101 MHz, CDCl3) δ 76.8, 76.0, 70.2, 56.0, 37.4, 32.2, 25.3, 18.9.

4-Methoxy-1-(4-methylbenzyl)piperidine (44). Methanesulfonyl chloride (0.5 mL, 6.4 mmol, 1.3 equiv) and triethylamine (1.0 mL, 7.2 mmol, 1.4 equiv) were successively added at 0 °C to a solution of alcohol 43 (591 mg, 5.0 mmol, 1.0 equiv) in dichloromethane (50 mL). The reaction mixture was stirred for 1 h and then allowed to warm to 20 °C. The mixture was poured into water (50 mL) and the product was extracted with dichloromethane (50 mL). The combined organic extracts were dried over magnesium sulfate and the solvent was removed in vacuo to afford sulfonate 44 (987 mg, 99%) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 4.31–4.20 (m, 2 H), 3.38–3.30 (m, 1 H), 3.51 (s, 3 H), 3.01 (s, 3 H), 1.94–1.74 (m, 2 H), 1.61–1.53 (m, 2 H), 1.15 (d, J = 6.1 Hz, 3 H). 13C NMR (101 MHz, CDCl3) δ 76.0, 70.2, 56.0, 37.4, 32.2, 25.3, 18.9.

4-Methoxy-1-(4-chlorobenzyl)piperidine (45). Sodium hydride (1.0 g, 25 mmol, 1.0 equiv, 60% dispersion in mineral oil) was added at 0 °C to a solution of cyclohexene-1,4-diol (47, 2.9 g, 25 mmol, 1.0 equiv, mixture of cis and trans) in THF (50 mL). The mixture was stirred for 30 min and then methyl iodide (1.9 mL, 30 mmol, 1.2 equiv) was added. NMR analysis showed an actual conversion of only 10% after stirring for 18 h. Therefore, extra sodium hydride (0.5 g, 12.5 mmol, 0.5 equiv, 60% dispersion in mineral oil) and methyl iodide (1.55 mL, 25 mmol, 1.0 equiv) were added. Stirring was continued for 60 h and the reaction was quenched by the careful addition of water (40 mL). The product was extracted with ethyl acetate (3 × 50 mL), and the combined organic extracts were washed with aqueous sodium thiosulfate (10%, 50 mL) and brine (50 mL), dried over magnesium sulfate, and concentrated. Purification with silica gel column chromatography (ethyl acetate/heptane 1:1) separately gave 1,4-dimethoxy-1-cyclohexane (375 mg, 10%), mixture of cis and trans (580 mg, 18%, mixture of cis and trans) as a clear transparent liquid. 1H NMR (400 MHz, CDCl3) δ 3.74 (p, J = 5.8 Hz, 3 H), 3.71–3.64 (m, 0.3 H), 3.34 (s, 0.9 H), 3.32 (s, 2.1 H), 3.28 (t(t, J = 6.1, 3.1 Hz, 0.7 H), 3.21–3.15 (m, 0.3 H), 2.07–1.94 (m, 1.2 H), 1.89–1.78 (m, 1.4 H), 1.69–1.62 (m, 2.8 H), 1.59–1.50 (m, 1.4 H), 1.36–1.28 (m, 1.2 H).
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