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Efficient synthesis of 4-hydroxycyclopentenones: dysprosium(III) triflate catalyzed Piancatelli rearrangement

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1. Introduction

The chemistry of 4-hydroxycyclopentenones was fueled in the 1980s by the synthesis of prostaglandins. Over the years this core structure has become a privileged building block that has been used to access a wide array of natural products and biologically active molecules (Fig. 1). Among the various methods available to access the 4-hydroxycyclopentenone core, the Piancatelli rearrangement discovered in 1976 remains one of the most direct. The cascade rearrangement transforms a furylcarbinol into a substituted 4-hydroxycyclopentenone in one-step. The reaction is believed to proceed through a series of cascading events that terminates with

Fig. 1. Representative applications of the Piancatelli rearrangement for the synthesis of 4-hydroxycyclopentenones.
a 4π electrocyclic ring closure of a pentadienyl cation (D), analogous to the Nazarov cyclization. Some of the current drawbacks with the Piancatelli rearrangement are the use of stoichiometric quantities of Brønsted or Lewis acid, the product is often isolated in low yield (40–55%), and the acid catalyzed reaction can result in the formation of polymeric material that may be difficult to remove, especially on scale. Moreover, the rearrangement often results in an inseparable mixture of 4-hydroxycyclopentenone isomers (2 and 9), which are typically processed through a second rearrangement step into the thermodynamically more stable isomer (9).

Despite these challenges, the Piancatelli rearrangement still remains a highly attractive method that is widely used in academia and industry. For example, Henschke and co-workers demonstrated the utility of the cascade rearrangement as an integral part in their strategy for the synthesis of a 4-hydroxycyclopentenone (12), a common intermediate from which several active pharmacological ingredients could be accessed.7 The reaction was conducted on multi kilogram scale with superstoichiometric quantities of ZnCl2 (16 equiv) and despite optimization the reaction resulted in a 1.0:1.1 mixture of cyclopentenone isomers that were converted to the thermodynamic isomer in 55% yield over two steps. Recently, Reiser and co-workers have demonstrated that the Piancatelli rearrangement can be accelerated at high temperature (240 °C) and pressure (1000 psi) using a microreactor.8 Under these conditions higher yields and shorter reaction times were observed. Clearly, progress is being made in further improving the Piancatelli rearrangement however Scheme 1, more research is still required to reduce the catalyst loading, increase the efficiency of the reaction and avoid the formation of cyclopentenone isomer mixtures.

Piancatelli rearrangement: Henschke and co-workers: ref. 7

\[
\text{ZnCl}_2 \rightarrow \begin{array}{c}
\text{i-Pr}_2\text{C} \text{OH} \\
\rightarrow \text{i-Pr}_2\text{C} \text{OH}
\end{array}
\]

Scheme 1. Recent examples of the Piancatelli rearrangement.

2. Results and discussion

In our efforts to develop new methods for the synthesis of substituted cyclopentenones, we recently demonstrated that dysprosium triflate (Dy(OTf)3) was an excellent catalyst for the aza- and oxa-Piancatelli rearrangements.9 These cascade rearrangements were shown to be compatible with aniline and alcohol nucleophiles using 5 mol % Dy(OTf)3 as the catalyst. Given the number of strategies used for the synthesis of biologically active molecules that rely on the Piancatelli rearrangement and the current limitations, we directed our efforts toward developing a catalytic cascade rearrangement using Dy(OTf)3. We envisioned that the milder catalytic conditions would be compatible with more functionalized substrates and would result in the exclusive formation of kinetic isomer 2, which could be transformed into the thermodynamic isomer 9 under known conditions if desired. It’s important to note that the initial inspiration for studying the catalytic activity of Dy(OTf)3 came from a pioneering report by Batey and co-workers in 2007.10 In this report they demonstrated the synthetic potential of rare earth Lewis acids, including Dy(OTf)3, in a related rearrangement of furfural.

Our initial optimization studies evolved from an observation made while investigating the oxa-Piancatelli rearrangement.9c,10d During these studies 4-hydroxycyclopentenone 16 was observed in 52% yield when 10 equiv of i-PrOH was added to 2-furylcarbinol 15 in the presence of 5 mol % Dy(OTf)3 and heated to 60 °C in acetonitrile (Scheme 2).

The preference for addition by water, generated in situ during the formation of oxocarbenium ion A (Fig. 1), in the presence of excess i-PrOH was surprising as in the aza-Piancatelli reaction water could be used as a co-solvent without observation of the 4-hydroxycyclopentenone product. Encouraged by the ability to use catalytic conditions and based on the importance of 4-hydroxycyclopentenones as intermediates in synthesis, we decided to explore the rearrangement with water in more detail. The results from these studies are described herein.

We elected to start by screening alcohol additives in the presence of water as a co-solvent (Table 1). In all cases examined the addition of an alcohol had a positive effect on the efficiency of the Piancatelli rearrangement. Even though the reaction benefited from the use of phenols, we decided to pursue the use of i-PrOH and t-BuOH. These alcohols are advantageous for synthesis due to their low cost and ease of purification. Further optimization revealed that 10 mol % Dy(OTf)3 in a solvent mixture of t-BuOH/H2O (5:1) at 80 °C gave the best results (entry 8). A side product originating from i-PrOH acting as a nucleophile was observed when a solvent system of i-PrOH/H2O (5:1) was used. We never observed any side product originating from the addition of t-BuOH probably due to its steric bulk preventing nucleophilic attack. In the absence of an alcohol additive the reaction was more sluggish and lower yielding (entry 10).

With the optimized reaction conditions in hand, we then investigated the substrate scope with furylcarbinols substituted with an aryl group at the 2-position (Scheme 3). Short reaction times and excellent yields were observed in all cases. Heteroaromatic groups, such as thiophene 23 were also well tolerated in the reaction. Importantly, the products were isolated exclusively as the trans-diestereomer, which is consistent with the proposed conrotatory 4π electrocyclization (Fig. 1).

After successfully demonstrating the generalizability of the Dy(OTf)3 catalyzed Piancatelli reaction with furylcarbinols bearing aromatic side-chains, we turned our attention to investigate the reaction with aliphatic side-chains. Disappointingly, the rearrangement with n-butylfurylcarbinol was exceedingly sluggish and extensive decomposition was observed. Because prostaglandin analogues

Scheme 2. Formation of 4-hydroxycyclopentenone via the oxa-Piancatelli rearrangement.
The use of 10 mol % Dy(OTf)3 gave the desired product in 60% yield, Lewis and Brønsted acid screen

Table 2

In an attempt to improve both reactivity and efficiency (Table 2), we sought to overcome this limitation by screening other Lewis and Brønsted acids commonly feature lengthy alkyl side-chains, we sought to overcome this limitation by screening other Lewis and Brønsted acids in an attempt to improve both reactivity and efficiency (Table 2). The use of 10 mol % Dy(OTf)3 gave the desired product in 60% yield, but 30 mol % resulted in decomposition. Switching to other sources of dysprosium, such as Dy(Cl)3 and Dy(OAc)3, proved unsuccessful (entries 3 and 4). The use of slightly more Lewis acidic Sc(OTf)3 (10 mol %) resulted in 53% yield, but decomposition was still extensively observed. Unfortunately, under the t-BuOH/H2O (5:1) solvent mixture stoichiometric ZnCl2 proved ineffective and catalytic trifluoroacetic acid resulted in only modest success (Table 2, entries 6–8). To our gratification, we found that utilizing a combination of Dy(OTf)3 (10 mol %) and TFA as co-catalysts (5 mol %) dramatically increased the yield and efficiency (entry 9). Yin and co-workers also observed that a combination of Lewis and Brønsted acid afforded optimal results for a related rearrangement.11 A small Brønsted acid screen: potassium dihydrogen phosphate, acetic acid, phosphoric acid, trifluoromethanesulfonic acid, and hydrochloric acid, at 5 mol % in combination with 10 mol % Dy(OTf)3 was performed, however, the combination of TFA with Dy(OTf)3 proved optimal. It is interesting to note that the efficiency of the Dy(Cl)3 and Dy(OAc)3 catalyzed reaction was also improved by the addition of 5 mol % TFA, albeit to a smaller extent (compare entries 3 and 4 to 10 and 11). Further studies are currently underway to fully elucidate the beneficial effect of the TFA additive. With optimized reaction conditions (entry 9) in hand for the rearrangement of a furylcarbinol substituted with an n-butyl side-chain, the scope was extended to include other aliphatic derivatives.

Table 1

Table 1: Optimization studies with alcohol additives

Table 2

Lewis and Brønsted acid screen

The optimization studies with alcohol additives

Scheme 3. Substrate scope with aromatic groups at the 2-position of the furylcarbinol.

Scheme 4. Substrate scope under the combination of Dy(OTf)3 and TFA catalysis.

Table 2: Lewis and Brønsted acid screen

Having determined that our Lewis/Brønsted acid catalyst system can be used to access a range of desirable cyclopentenones, we wanted to address a key part of the overall strategy for the synthesis of prostaglandin analogues, in controlling the formation of cyclopentenone isomers. Interestingly, using our catalytic Dy(OTf)3 conditions the more thermodynamically stable isomer was only observed for compounds 23 and 33 (5% and 6%, respectively). Presumably this is due to the activating group at the 5-position of the cyclopentenone, which helps facilitate the rearrangement. To promote the isomerization we chose to use conditions developed...
3. Conclusion

We have developed an efficient, catalytic method for the rearrangement of furylcarbinols to 4-hydroxycyclopentenones. Catalytic Dy(OTf)₃ was determined to be optimal for the rearrangement of furylcarbinols bearing aromatic substituents at the 2-position, while the combination of TFA and Dy(OTf)₃ was required for the more challenging substrates, such as those with aliphatic side-chains. This process is mild, operationally simple, and compatible with a variety of substituted furylcarbinols. In addition, the mild reaction conditions developed allow for both cyclopentenone isomers to be accessed in high yield using a controlled stepwise approach.

4. Experimental

4.1. Materials and general experimental details

Unless stated otherwise, reactions were conducted in air dried glassware under an atmosphere of air using reagent grade solvents. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F₂₅₄ pre-coated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 A, 230–240 mesh, Merck KGA).

¹H NMR spectra were recorded on Varian spectrometers (at 400, 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ¹H NMR spectra are reported as follows: chemical shift ( δ ppm), multiplicity, coupling constant (Hz), and integration. ¹³C NMR spectra were recorded on Varian spectrometers (125 or 150 MHz). Data for ¹³C NMR spectra are reported as follows: chemical shift ( δ ppm), multiplicity, and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum Two FT-IR spectrometer and are reported in terms of frequency of absorption ( cm⁻¹). Mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility on a (Waters Corp.) Micromass QTOF2 with an electrospray ionization source.

Furylcarbinol was prepared according to literature precedent by reacting furfural with the corresponding Grignard reagent.

4.2. General experimental procedure A: Scheme 3

Furylcarbinol was dissolved in a solution of r-BuOH/H₂O. To the reaction mixture at rt was added 10 mol % of Dy(OTf)₃. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 °C. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate, diluted with H₂O, and extracted with diethyl ether. The combined organic layers were dried over MgSO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography.

4.2.1. 4-Hydroxy-5-(2,4,6-trisopropylphenyl)cyclopent-2-en-1-one (16). According to general procedure A Dy(OTf)₃ (5 mg, 0.008 mmol, 0.1 equiv) was added to furan-2-yl(2,4,6-trisopropyl) methanol (25 mg, 0.08 mmol, 1 equiv) in 1.5 mL of r-BuOH and 0.3 mL H₂O. The resulting reaction mixture was heated to 80 °C for 2 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H₂O, and extracted with diethyl ether (3-7 mL). The combined organic layers were dried over MgSO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone 16 (21 mg, 84%) as a white solid. H NMR (400 MHz, CDCl₃) δ 7.54 (dd, J=5.8, 1.9 Hz, 1H), 7.26 (s, 1H), 7.03 (dd, J=1.8, 1Hz, 1H), 6.99 (d, J=1.9 Hz, 1H), 6.39 (dd, J=5.8, 1.3 Hz, 1H), 4.94 (dt, J=5.8, 1.8 Hz, 1H), 3.99 (d, J=3.1 Hz, 1H), 3.26–3.16 (m, 1H), 2.92–2.82 (m, 1H), 2.41 (d, J=5.9 Hz, 1H), 2.02–1.92 (m, 1H), 1.33 (d, J=6.6 Hz, 3H), 1.29–1.13 (m, 1H), 1.05 (d, J=6.5 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 205.1, 159.7, 148.7, 148.2, 147.5, 134.6, 128.3, 122.8, 121.3, 79.6, 57.4, 34.3, 30.9, 30.6, 25.2, 24.1, 21.4, 23.9, 23.5; IR (thin film, cm⁻¹) 3501, 2959, 1699, 1102, 765; HRMS (ESI) m/z 323.1973 (323.1987 calcd for C₂₀H₂₈NaO₂ [MNa]+).

4.2.2. 4-Hydroxy-5-mesitylcyclopent-2-en-1-one (19). According to general procedure A Dy(OTf)₃ (7 mg, 0.0115 mmol, 0.1 equiv) was added to furan-2-yl(mesityl)methanol (25 mg, 0.15 mmol, 1 equiv) in 1.5 mL of r-BuOH and 0.3 mL H₂O. The resulting reaction mixture was heated to 80 °C for 2 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H₂O, and extracted with diethyl ether (3-7 mL). The combined organic layers were dried over MgSO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone 19 (20 mg, 80%) as a yellow oil. H NMR (400 MHz, CDCl₃) δ 7.56 (dd, J=5.9, 2.0 Hz, 1H), 6.79 (d, 2H), 6.32 (m, 1H), 5.07–5.04 (m, 1H), 3.89 (d, J=3.1 Hz, 1H), 2.39 (s, 3H), 2.26 (s, 4H), 1.90 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 205.4, 160.3, 138.4, 137.0, 136.1, 134.3, 130.1, 129.2, 78.2, 58.3, 21.2, 20.8, 20.3; IR (thin film, cm⁻¹) 3419, 3062, 2963, 2921, 1701, 852; HRMS (ESI) m/z 239.1055 (239.1055 calcd for C₉H₁₆NaO₂ [MNa]+).

4.2.3. 4-Hydroxy-5-(2-(thiophen-2-yl)cyclopent-2-en-1-one (22). According to general procedure A Dy(OTf)₃ (8.7 mg, 0.014 mmol, 0.1 equiv) was added to furan-2-yl(thiophen)methanol (25 mg, 0.14 mmol, 1 equiv) in 1.5 mL of r-BuOH and 0.3 mL H₂O. The resulting reaction mixture was heated to 80 °C for 6.5 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H₂O, and extracted with diethyl ether (3-7 mL). The combined organic layers were dried over MgSO₄, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone 22 (21 mg, 84%) as brown oil. Spectral data for 22 were consistent with those previously reported.

4.2.4. 4-Hydroxy-5-(thiophen-2-yl)cyclopent-2-en-1-one (23). According to general procedure A Dy(OTf)₃ (8.5 mg, 0.014 mmol, 0.1 equiv) was added to furan-2-yl(thiophen)methanol (25 mg, 0.14 mmol, 1 equiv) in 1.5 mL of r-BuOH and 0.3 mL H₂O. The resulting reaction mixture was heated to 80 °C for 1 h. The reaction was then quenched with 1.5 mL of saturated aqueous
sodium bicarbonate, diluted with 3 mL H2O, and extracted with diethyl ether (3 × 7 mL). The combined organic layers were dried over MgSO4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentene 23 (18 mg, 72%) as an orange oil. 1H NMR (600 MHz, CDCl3) 0.758 (dd, J = 5.9, 2.1 Hz, 1H), 7.25 (dd, J = 5.2, 1.3 Hz, 1H), 7.03–7.00 (m, 1H), 7.00–6.97 (m, 1H), 6.31 (dd, J = 5.9, 1.5 Hz, 1H), 5.09–5.03 (m, 1H), 3.74 (d, J = 3.0 Hz, 1H), 2.63 (d, J = 6.1 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 203.1, 161.3, 137.7, 133.8, 127.3, 126.1, 125.0, 79.0, 57.1; IR (thin film, cm−1) 3397, 3106, 2889, 1696, 1027, 967; HRMS (ESI) m/z 203.0130 (203.0143 calcd for C7H8NaO2S1[MNa]+).

4.2.5. 4-Hydroxy-5-(naphthenal-2-yl)cyclopent-2-en-1-one (24). According to general procedure A Dy(OTf)3 (6.8 mg, 0.012 mmol, 0.1 equiv) was added to furan-2-yl(naphthalen-2-yl)methanol (25 mg, 0.12 mmol, 1 equiv) in 1.5 mL of t-BuOH and 0.3 mL H2O. The resulting reaction mixture was heated to 80 °C for 5 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H2O, and extracted with diethyl ether (3 × 7 mL). The combined organic layers were dried over MgSO4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentene 24 (22 mg, 86%) as yellow oil. 1H NMR (600 MHz, CDCl3) δ 7.81 (d, J = 4.9 Hz, 1H), 7.66–7.61 (m, 1H), 7.60 (dd, J = 5.8, 2.1 Hz, 1H), 7.48 (qd, J = 7.0, 3.4 Hz, 2H), 7.14 (dd, J = 8.4, 1.8 Hz, 1H), 6.33 (dd, J = 5.8, 1.4 Hz, 1H), 5.01 (s, 1H), 3.57 (d, J = 2.8 Hz, 1H), 2.66 (d, J = 5.7 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 205.5, 162.0, 134.6, 134.2, 133.6, 132.7, 129.0, 127.8, 126.5, 126.2, 125.8, 79.0, 62.4; IR (thin film, cm−1) 3397, 3054, 2902, 1697, 1035, 745; HRMS (ESI) m/z 247.0724 (247.0735 calcd for C15H12NaO2 [MNa]+).

4.2.6. 4-Hydroxy-5-(6-vinylbenzo[d]1,3]dioxol)methanol (25 mg, 0.12 mmol, 1 equiv) was added to furan-2-yl(6-vinylbenzo[d]1,3]dioxol)methanol (25 mg, 0.12 mmol, 1 equiv) in 1.5 mL of t-BuOH and 0.3 mL H2O. The resulting reaction mixture was heated to 80 °C for 3 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H2O, and extracted with diethyl ether (3 × 7 mL). The combined organic layers were dried over MgSO4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentene 25 (16 mg, 64%) as a brown oil. 1H NMR (400 MHz, CDCl3) δ 7.59 (dd, J = 5.8, 2.2 Hz, 1H), 7.00 (s, 1H), 6.73 (dd, J = 17.1, 10.9 Hz, 1H), 6.39 (s, 1H), 6.37 (dd, J = 5.87, 1.39 Hz, 1H), 5.94 (dd, J = 6.84, 1.5 Hz, 2H), 5.54 (dd, J = 17.4, 1.3 Hz, 1H), 5.24 (dd, J = 10.9, 1.2 Hz, 1H), 4.99–4.86 (m, 1H), 3.69 (d, J = 2.9 Hz, 1H), 2.43 (d, J = 5.9 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 205.6, 161.4, 147.9, 147.5, 134.8, 134.1, 132.1, 128.2, 116.2, 108.6, 101.4, 79.4, 59.6; IR (thin film, cm−1) 3406, 3084, 2902, 1698, 1483, 1036, 733; HRMS (ESI) m/z 267.0615 (267.0633 calcd for C14H12NaO4 [MNa]+).

4.3. General experimental procedure B: Scheme 4

Furylcarbinol was dissolved in a solution of t-BuOH/H2O. To the reaction mixture at rt were added 10 mol % of Dy(OTf)3 and 5 mol % TFA. The reaction mixture was immediately fitted with a reflux condenser and placed in an oil bath pre-heated to 80 °C. The reaction was monitored by TLC. Upon completion, the reaction was then quenched with saturated aqueous sodium bicarbonate, diluted with H2O, and extracted with diethyl ether. The combined organic layers were dried over MgSO4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography.
0.013 mmol, 0.1 equiv) was added to 5-methylfuran-2-yl(phenyl)methanol (25 mg, 0.132 mmol, 1 equiv) in 1.5 mL of t-BuOH and 0.3 mL H2O. The resulting reaction mixture was treated with trifluoroacetic acid (0.6 μL, 0.007 mmol, 0.05 equiv) and heated to 80 °C for 15.5 h. The reaction was then quenched with 1.5 mL of saturated aqueous sodium bicarbonate, diluted with 3 mL H2O, and extracted with diethyl ether (3×7 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopentenone 35 (25 mg, 100%) as an oil. Spectral data for 35 matched literature precedent.16

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References and notes