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VANADIUM-CATALYZED ACHMATOWICZ AND AZA-ACHMATOWICZ REARRANGEMENT REACTIONS

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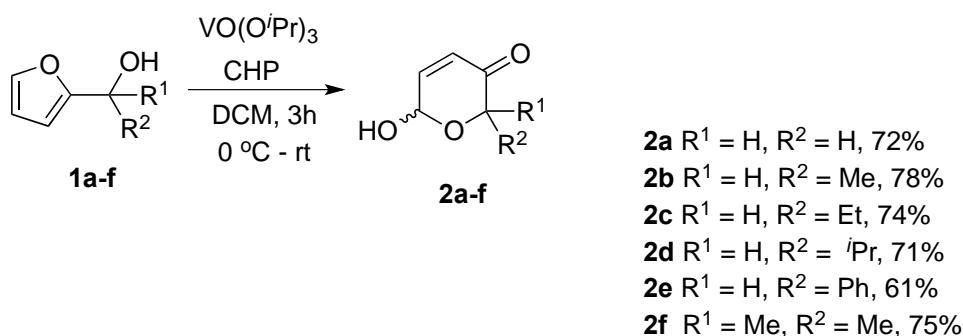
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Abstract – A novel and efficient synthesis of substituted pyranones and pyridinones is developed using cumene hydroperoxide as oxidant by vanadium-catalyzed Achmatowicz rearrangement and aza-Achmatowicz rearrangement reactions. It offers a sustainable and environmentally benign approach to access multisubstituted pyranones or pyridinones derivatives.

Furan is an important heterocyclic structure and has numerous applications in organic synthesis, materials science and medicinal chemistry.¹ Recently, the increased consumption of fossil fuel resources make the biobased furanics emerging as the sustainable feedstock solutions to the energy crisis.² Furfurals could be generated from about 300,000 tonnes of agricultural raw materials each year.³ Hence the furan transformations have attracted increasing attention due to their renewable, sustainable and environmentally benign. The Achmatowicz rearrangement of furans appears a powerful tool for the preparation of substituted pyranones or pyridinones from furfuryl alcohols or α -furanamines.⁴ However, traditional reagents such as *m*-chloroperoxybenzoic acid (*m*-CPBA), methanolic bromine and *N*-bromosuccinimide (NBS) used for this transformation suffer from significant disadvantages including stoichiometric waste, poisonous byproducts and difficult isolation.⁴ Other environmentally friendly oxidants such as hydrogen peroxide,⁵ urea hydrogen peroxide (UHP)⁶ and oxone⁷ have been utilized. Visible-light or enzyme-catalyzed Achmatowicz rearrangements are also developed recently.⁸ However, when water is used as solvent or medium in this transformation, many Achmatowicz rearrangement products are water soluble which result in the challenges in the separation. Compared to stoichiometric oxidizing reagents, transition metal-catalyzed Achmatowicz rearrangement is an ideal and alternative choice. Pyranones could be obtained by VO(acac)₂/*tert*-butyl hydroperoxide (TBHP) catalytic system.⁹ However, the other combinations of metals and oxidants are urgent to be screened. The transition

metal-catalyzed aza-Achmatowicz is still undeveloped. During our previous study in the *de novo* synthesis of carbohydrates,¹⁰ we found a novel method to achieve Achmatowicz rearrangement in a more atom-economic and efficient manner. Herein we reported a vanadium-catalyzed Achmatowicz and aza-Achmatowicz rearrangement reactions using cumene hydroperoxide (CHP) as oxidant to access various substituted pyranones and pyridinones.

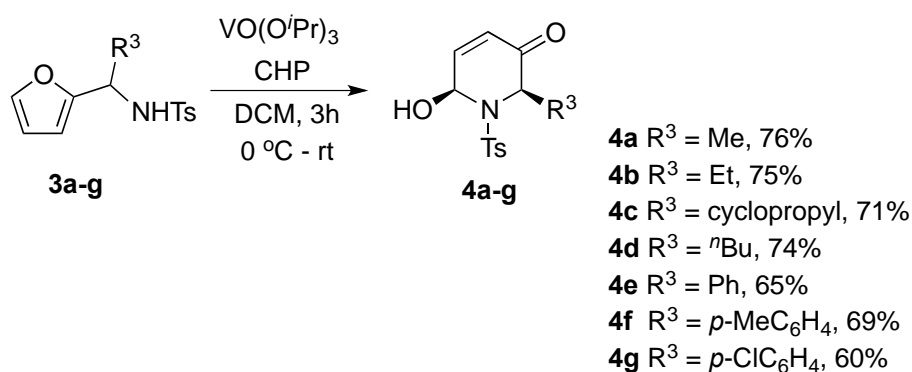
We first optimized the reaction conditions by screening the combinations of oxidants (TBHP vs CHP) and catalysts ($\text{VO}(\text{acac})_2$ vs $\text{VO}(\text{O}^i\text{Pr})_3$). For the substrate **1b** in Scheme 1, the $\text{VO}(\text{O}^i\text{Pr})_3/\text{CHP}$ catalytic system could give 78% yield of **2b**. But only 61% yield of **2b** was obtained using the $\text{VO}(\text{acac})_2/\text{TBHP}$ combination, which was the similar result to the literature reported in the Achmatowicz rearrangement.^{9a} For the substrate **3a** in Scheme 2, the $\text{VO}(\text{O}^i\text{Pr})_3/\text{CHP}$ catalytic system provided higher yield of **4a** (76%) than the $\text{VO}(\text{acac})_2/\text{TBHP}$ combination (64%) in the aza-Achmatowicz rearrangement reactions. With the optimized conditions in hand, we explored the substrate scope of vanadium-catalyzed Achmatowicz rearrangement (Scheme 1). Treatment of furfuryl alcohols (**1a-f**) with $\text{VO}(\text{O}^i\text{Pr})_3$ and CHP in DCM from 0 °C to ambient temperature gave corresponding substituted pyranones (**2a-f**) in good yields. Furfuryl alcohol (**1a**) was first selected as substrate for the examination. 6-Hydroxy-2*H*-pyran-3(6*H*)-one (**2a**) was acquired in 72% isolated yield. If the methyl substituted substrate (**1b**) was employed instead of **1a**, the yield of **2b** increased to 78%. We were pleased to find the ethyl and isopropyl substituted substrates (**1c**, **1d**) could also be tolerated in this reaction. But the yield for the phenyl substituted substrate (**2e**) dramatically decreased to 61%. The reaction also occurred for the substrate with dimethyl groups substituted in C2 position (**1f**) in 75% yield.



Scheme 1. Vanadium-catalyzed Archmatowicz rearrangement

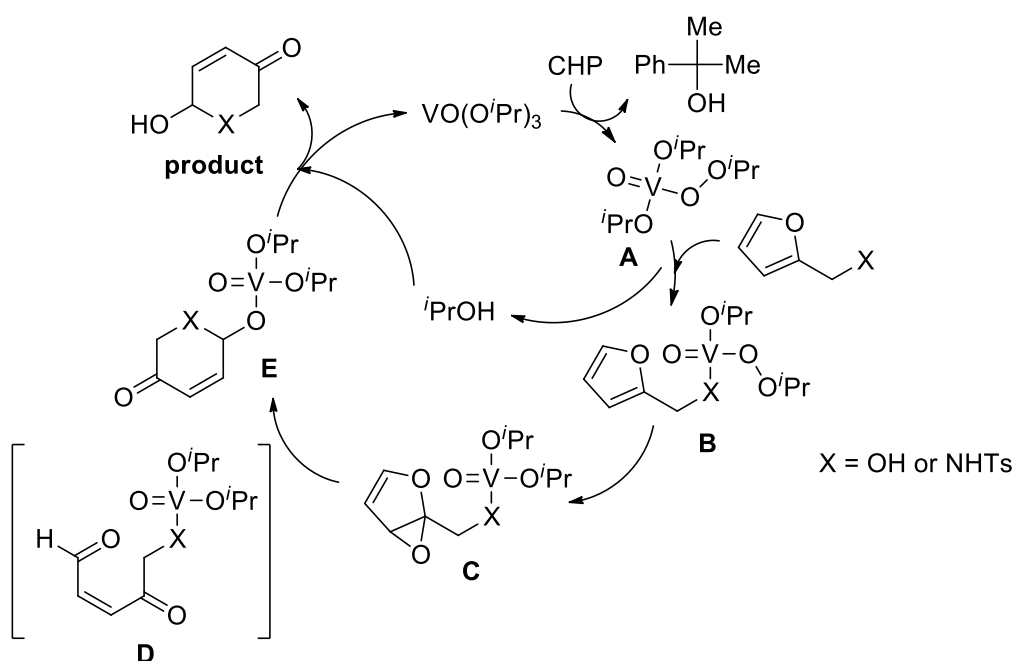
Subsequently, the substrate scope of vanadium-catalyzed aza-Achmatowicz rearrangement was investigated in the similar reaction condition of the Achmatowicz rearrangement (Scheme 2). *N*-(1-(Furan-2-yl)ethyl)-4-methylbenzenesulfonamide (**3a**) was first applied to generate *cis*-6-hydroxy-2-methyl-1-tosyl-1,6-dihydropyridin-3(2*H*)-one (**4a**) in 76% yield. The *cis*-isomer was based on NMR spectroscopic analysis (1D-NOE). The exclusive *cis*-geometry was controlled by the

A_{1,3}-strain from the tosyl group forcing the 2,6-substituents to adopt a pseudoaxial orientation.¹¹ A sulfonamide protecting group provided the necessary stability.¹² Besides the methyl group, other alkyl group such as ethyl, cyclopropyl and *n*-butyl group substituted substrates could also give the corresponding pyridinones (**4b-4d**) in similar yields. Unfortunately, when aryl group was introduced to C6 position of the substrates, the yields significantly dropped (**4e-4g**). The substrate with electron-donating group worked better than the one with electron-withdrawing group. The electron effect was observed for the products **4e-4g**.



Scheme 2. Vanadium-catalyzed aza-Archmatowicz rearrangement

On the basis of the above results, the mechanism for the Achmatowicz rearrangement and aza-Achmatowicz rearrangement is proposed in Scheme 3. The precatalyst species, VO(O^{*i*}Pr)₃, is initially oxidized to the peroxide intermediate **A** by CHP.⁹



Scheme 3. The proposed mechanism for the vanadium-catalyzed Archmatowicz rearrangement

Binding between the intermediate **A** and furfuryl alcohol or α -furanamine would generate intermediate **B**. An intramolecular oxidation undergoes to form the epoxide intermediate **C**. The rearrangement of intermediate **C** gives the dicarbonyl intermediate **D**. Then a vanadium-promoted ring closure occurs to provide intermediate **E**. The substituted pyranones or pyridinones could be afforded after the alcoholysis of intermediate **E**.

In conclusion, we have developed a novel and efficient method to access the substituted pyranones and pyridinones using CHP as oxidant by vanadium-catalyzed Achmatowicz rearrangement and aza-Achmatowicz rearrangement reactions. It offers a sustainable and environmentally benign approach to prepare multisubstituted pyranones or pyridinones derivatives, which could be further used in the synthesis of carbohydrates or alkaloids. Efforts to further expand the substrate scope and the investigation of the mechanism are underway in our laboratories.

EXPERIMENTAL

Thin layer chromatography was performed using precoated silica gel plates and visualized with UV light at 254 nm. Flash column chromatography was performed with silica gel (40–60 μm). ^1H and ^{13}C nuclear magnetic resonance spectra (NMR) were obtained on a Bruker Avance II 400 MHz or Bruker Avance III 500 MHz recorded in ppm (δ) downfield of TMS ($\delta=0$) in CDCl_3 unless noted otherwise. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad (br) with coupling constants (J) in hertz (Hz). High resolution mass spectra (HRMS) were performed by Agilent apparatus on an Electron Spray Injection (ESI) mass spectrometer. Melting points were determined by XP-4 melting point apparatus.

Starting Materials. The furfuryl alcohols and α -furanamines were prepared by the appropriate literature reported.⁶⁻¹⁰ All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of 6-Hydroxy-2H-pyran-3(6H)-one (2a): To a stirred solution of **1a** (0.4 mmol, 1 equiv, 39 mg) in DCM (4 mL, 0.1 M), was added $\text{VO}(\text{O}^i\text{Pr})_3$ (0.02 mmol, 0.05 equiv, 4.8 mg) and CHP (0.48 mmol, 1.2 equiv, 91.2 mg, 80% concentration) at 0 °C. Then the mixture was stirred for 3 h at ambient temperature. The mixture was quenched by saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (4 mL). The organic materials were extracted with DCM (3 \times 4 mL). The combined extracts were washed with brine (8 mL) and dried over anhydrous Na_2SO_4 . Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel to give **2a** (32.8 mg, 72%). White solid. Mp 60–62 °C. ^1H -NMR (500 MHz, CDCl_3): δ 6.96 (dd, $J = 10.0, 3.0$ Hz, 1H), 6.18 (d, $J = 10.0$ Hz, 1H), 5.65 (dd, $J = 5.0, 3.0$ Hz, 1H), 4.58 (d, $J = 15.0$ Hz, 1H), 4.14 (d, $J = 15.0$ Hz, 1H), 3.20–3.17 (m, 1H). The spectra are identical to the literature data.^{9b}

6-Hydroxy-2-methyl-2H-pyran-3(6H)-one (2b): Colorless oil. ^1H -NMR (500 MHz, CDCl_3): major

isomer δ 6.90 (dd, $J = 10.0, 3.0$ Hz, 1H), 6.10 (d, $J = 10.0$ Hz, 1H), 5.68 (d, $J = 5.0$ Hz, 1H), 4.72 (q, $J = 5.2$ Hz, 1H), 4.14 (d, $J = 5.0$ Hz, 1H), 1.39 (d, $J = 5.2$ Hz, 3H). The spectra are identical to the literature data.¹³

2-Ethyl-6-hydroxy-2H-pyran-3(6H)-one (2c): Colorless oil. ¹H-NMR (500 MHz, CDCl₃): major isomer δ 6.90 (dd, $J = 10.0, 3.0$ Hz, 1H), 6.10 (d, $J = 10.0$ Hz, 1H), 5.67 (d, $J = 5.0$ Hz, 1H), 4.52-4.49 (m, 1H), 1.94-1.79 (m, 2H), 0.98 (t, $J = 7.5$ Hz, 3H). The spectra are identical to the literature data.¹³

6-Hydroxy-2-isopropyl-2H-pyran-3(6H)-one (2d): Yellow oil. ¹H-NMR (500 MHz, CDCl₃): major isomer δ 6.90 (dd, $J = 10.0, 3.0$ Hz, 1H), 6.12-6.06 (m, 1H), 5.66 (d, $J = 5.0$ Hz, 1H), 4.41-4.38 (m, 1H), 2.45-2.37 (m, 2H), 1.04-1.01 (m, 3H), 0.87 (d, $J = 7.0$ Hz, 3H). The spectra are identical to the literature data.⁷

6-Hydroxy-2-phenyl-2H-pyran-3(6H)-one (2e): Yellow oil. ¹H-NMR (500 MHz, CDCl₃): major isomer δ 7.36-7.30 (m, 5H), 6.91-6.88 (m, 1H), 6.20-6.14 (m, 1H), 5.62 (d, $J = 3.0$ Hz, 1H), 5.56 (s, 1H). The spectra are identical to the literature data.⁷

6-Hydroxy-2,2-dimethyl-2H-pyran-3(6H)-one (2f): Yellow oil. ¹H-NMR (500 MHz, CDCl₃): δ 6.79 (dd, $J = 10.0, 3.0$ Hz, 1H), 6.10 (dd, $J = 10.0, 3.0$ Hz, 1H), 5.78 (d, $J = 3.0$ Hz, 1H), 1.49 (s, 3H), 1.38 (s, 3H). The spectra are identical to the literature data.⁷

Typical Procedure for the Preparation of *cis*-6-Hydroxy-2-methyl-1-tosyl-1,6-dihydropyridin-3(2H)-one (4a): To a stirred solution of **3a** (0.2 mmol, 1 equiv, 53 mg) in DCM (2 mL, 0.1 M), was added VO(O^{*i*}Pr)₃ (0.01 mmol, 0.05 equiv, 2.4 mg) and CHP (0.24 mmol, 1.2 equiv, 45.6 mg, 80%) at 0 °C. Then the mixture was stirred for 3 h at ambient temperature. The mixture was quenched by saturated aqueous Na₂S₂O₃ (2 mL). The organic materials were extracted with DCM (3×2 mL). The combined extracts were washed with brine (8 mL) and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel to give **4a** (42.7 mg, 76%). White solid. Mp 113-115 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.65 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 6.89 (dd, $J = 8.0, 4.0$ Hz, 1H), 5.99 (d, $J = 8.0$ Hz, 1H), 5.94 (dd, $J = 8.0, 4.0$ Hz, 1H), 4.39 (q, $J = 8.0$ Hz, 1H), 2.41 (s, 3H), 1.62 (d, $J = 8.0$ Hz, 3H). The spectra are identical to the literature data.^{11b}

***cis*-2-Ethyl-6-hydroxy-1-tosyl-1,6-dihydropyridin-3(2H)-one (4b):** White solid. Mp 95-97 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.60 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 6.78 (dd, $J = 8.0, 4.0$ Hz, 1H), 5.92 (d, $J = 8.0$ Hz, 1H), 5.87-5.85 (m, 1H), 4.23 (t, $J = 8.0$ Hz, 1H), 3.78 (s, 1H), 2.40 (s, 3H), 2.03-1.89 (m, 2H), 1.08 (t, $J = 8.0$ Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ 194.6, 144.2, 142.8, 136.6, 130.1, 126.6, 126.6, 73.6, 62.7, 28.9, 21.5, 10.6. HRMS (ESI) Calcd for C₁₄H₁₇NO₄S [M+Na]⁺: 318.0771. Found: 318.0776.

***cis*-2-Cyclopropyl-6-hydroxy-1-tosyl-1,6-dihydropyridin-3(2H)-one (4c):** White solid. Mp 126-128 °C. ¹H-NMR (400 MHz, CDCl₃): δ 7.51 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 6.74 (dd, $J = 8.0, 4.0$

Hz, 1H), 5.92 (d, $J = 8.0$ Hz, 1H), 5.71 (d, $J = 4.0$ Hz, 1H), 3.52 (d, $J = 8.0$ Hz, 1H), 2.31 (s, 3H), 1.65-1.60 (m, 1H), 1.38-1.34 (m, 2H), 0.67-0.65 (m, 1H), 0.56-0.49 (m, 1H). ^{13}C -NMR (100 MHz, CDCl_3): δ 193.1, 144.2, 142.8, 136.7, 130.1, 127.1, 126.6, 73.6, 65.2, 21.5, 17.0, 5.1, 4.9. HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_4\text{S}$ $[\text{M}+\text{Na}]^+$: 330.0771. Found: 330.0778.

***cis*-2-Butyl-6-hydroxy-1-tosyl-1,6-dihydropyridin-3(2H)-one (4d)**: Colorless oil. ^1H -NMR (400 MHz, CDCl_3): δ 7.58 (d, $J = 8.0$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 6.75 (dd, $J = 12.0, 4.0$ Hz, 1H), 5.89 (d, $J = 8.0$ Hz, 1H), 5.82-5.80 (m, 1H), 4.28 (t, $J = 8.0$ Hz, 1H), 3.48 (d, $J = 4.0$ Hz, 1H), 2.38 (s, 3H), 1.99-1.95 (m, 1H), 1.85-1.76 (m, 1H), 1.51-1.40 (m, 2H), 1.38-1.30 (m, 2H), 0.88 (t, $J = 4.0$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl_3): δ 194.8, 144.2, 142.7, 136.5, 130.1, 126.6, 126.6, 73.7, 61.3, 35.3, 27.9, 22.2, 21.5, 13.9. HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{S}$ $[\text{M}+\text{Na}]^+$: 346.1084. Found: 346.1089.

***cis*-6-Hydroxy-2-phenyl-1-tosyl-1,6-dihydropyridin-3(2H)-one (4e)**: Yellow solid. Mp 123-124 °C. ^1H -NMR (400 MHz, CDCl_3): δ 7.64 (d, $J = 8.0$ Hz, 2H), 7.56-7.54 (m, 2H), 7.34-7.24 (m, 5H), 6.87 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.12 (d, $J = 8.0$ Hz, 1H), 6.00-5.96 (m, 1H), 5.47 (s, 1H), 3.47 (d, $J = 4.0$ Hz, 1H), 2.40 (s, 3H). The spectra are identical to the literature data.³

***cis*-6-Hydroxy-2-(*p*-tolyl)-1-tosyl-1,6-dihydropyridin-3(2H)-one (4f)**: Yellow solid. Mp 151-152 °C. ^1H -NMR (400 MHz, CDCl_3): δ 7.65 (d, $J = 8.0$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.85 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.10 (d, $J = 8.0$ Hz, 1H), 5.95 (d, $J = 4.0$ Hz, 1H), 5.43 (s, 1H), 2.40 (s, 3H), 2.31 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3): δ 191.3, 144.4, 143.6, 138.1, 136.3, 133.8, 130.1, 129.3, 127.6, 127.4, 126.9, 73.5, 63.8, 21.5, 21.1. HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{19}\text{NO}_4\text{S}$ $[\text{M}+\text{Na}]^+$: 380.0927. Found: 380.0933.

***cis*-2-(4-Chlorophenyl)-6-hydroxy-1-tosyl-1,6-dihydropyridin-3(2H)-one (4g)**: Yellow solid. Mp 166-167 °C. ^1H -NMR (400 MHz, CDCl_3): δ 7.65 (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 7.29-7.27 (m, 4H), 6.89 (dd, $J = 8.0, 4.0$ Hz, 1H), 6.12 (d, $J = 10.4$ Hz, 1H), 6.00 (d, $J = 4.0$ Hz, 1H), 5.42 (s, 1H), 2.42 (s, 3H). ^{13}C -NMR (100 MHz, CDCl_3): δ 191.2, 144.5, 143.6, 136.7, 136.4, 130.3, 129.1, 128.8, 127.6, 127.4, 126.9, 73.5, 64.0, 21.5. HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{16}\text{ClNO}_4\text{S}$ $[\text{M}+\text{Na}]^+$: 400.0381. Found: 400.0387.

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