

Metallo-Aldehyde Enolates via Enal Hydrogenation: Catalytic Cross Aldolization with Glyoxal Partners As Applied to the Synthesis of 3,5-Disubstituted Pyridazines

Gwendolyn A. Marriner, Susan A. Garner, Hye-Young Jang, and Michael J. Krische*

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

mkrische@mail.utexas.edu

Received October 8, 2003

Abstract: Aldehyde enolates generated through rhodiumcatalyzed enal hydrogenation are subject to electrophilic trapping by exogenous glyoxal partners to afford β -hydroxy- γ -keto-aldehyde products, which upon exposure to hydrazine afford 3,5-disubstituted pyridazines in moderate yield in a two-step, one-pot sequence.

As part of a program in catalytic reaction development focused on the use of enones as latent enolates, rhodiumcatalyzed inter- and intramolecular reductive aldol coupling of enones to aldehydes and ketones under the conditions of hydrogenation was recently reported from our lab.^{1,2} Subsequently, related catalytic C-C bondforming hydrogenations involving the reductive coupling of dienes and divnes with α -keto aldehydes were developed.³ A unifying feature of these transformations relates to the heterolytic activation of elemental hydrogen by cationic rhodium catalysts, i.e., $H_2 + Rh^+X^- \rightarrow Rh-H +$ HX.^{4,5} Heterolytic activation of hydrogen promotes monohydride-based catalytic cycles, which attenuate simple hydrogenation pathways by disabling alkyl-hydrogen reductive elimination manifolds. Efficient aldolization under the mild conditions of hydrogenation (ambient temperature and pressure) suggests the feasibility of a hitherto elusive variant of the aldol reaction involving the use of metallo-aldehyde enolates. Aldolizations involving the use of alkali aldehyde enolates typically suffer from polyaldolization, product dehydration, and competitive Tishchenko-type processes.⁶ To date, catalytic al-

 (3) (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. Angew. Chem., Int. Ed. 2003, 42, 4074. (b) Huddleston, R. R.; Jang, H.-Y. Krische, M. J. J. Am. Chem. Soc. 2003, 125, 11488.

(4) For a review of the heterolytic activation of elemental hydrogen, see: Brothers, P. J. *Prog. Inorg. Chem.* **1981**, *28*, 1.
(5) Mild basic additives induce heterolytic activation of hydrogen

dolizations of this type have only been achieved indirectly through the use of preformed enol silanes and directly with iminium ion-enamine catalysis.⁷ Here, we report that aldehyde enolates generated via rhodium-catalyzed enal hydrogenation are subject to electrophilic trapping by exogenous glyoxal partners to afford β -hydroxy- γ -ketoaldehyde products, which upon exposure to hydrazine provide pyridazines in moderate yield in a two-step, onepot sequence.



To explore the applicability of catalytic hydrogenationaldolization methodology vis-à-vis aldehyde enolate generation, acrolein was hydrogenated in the presence of various aldehyde partners with Rh(COD)₂OTf as precatalyst. Whereas hydrogenation of acrolein in the presence of various electron-deficient aldehydes, for example, p-nitrobenzaldehyde and chlorodifluoroacetaldehyde monohydrate, was unproductive, condensation with phenyl glyoxal monohydrate affords the corresponding aldol product in 52% isolated yield as a 1:1 mixture of diastereomers. Suspecting that the modest yield of aldol product stems from the well-documented instability of the β -hydroxy aldehyde product,^{7a,8} a method for *in situ* trapping of the aldol was sought. Accordingly, it was found that upon complete consumption of phenyl glyoxal 1a, the addition of methanolic hydrazine to the reaction mixture results in rapid condensation to afford 3-methyl-5-phenylpyridazine 1b in 62% isolated yield. This protocol for tandem catalytic reductive aldol condensation-pyridazine formation proved general for the condensation of acrolein with aromatic and heteroaromatic glyoxals 1a-4a (Table 1, entries 1-4). As demonstrated by the conversion of crotonaldehyde to pyridazines **5b** and **6b**, β -substituted enals are also viable pronucleophiles (Table 1, entries 5 and 6).

A mechanism accounting for the formation of aldol products under hydrogenation conditions invokes heterolytic activation of elemental hydrogen to form a Rh(I)monohydride.^{3,4} Enal hydrometallation affords Rh(I)enolate **I**, which upon glyoxal addition provides the Rh(I) aldolate **II**. Oxidative addition of elemental hydrogen to

⁽¹⁾ Rhodium-catalyzed reductive aldol condensation employing hydrogen as the terminal reductant: (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 15156. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1143.

⁽²⁾ Rhodium-catalyzed reductive aldol condensation employing silane as the terminal reductant: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Matsuda, I.; Takahashi, K.; Sata, S. *Tetrahedron Lett.* **1990**, *31*, 5331. (c) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528.

⁽⁵⁾ Mild basic additives induce heterolytic activation of hydrogen via deprotonation of cationic rhodium dihydride intermediates: (a) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2134. (b) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 2143. (c) Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 4450.

^{(6) (}a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds. Pergamon Press: New York, 1991; Vol. 2, p 133. (b) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858.

^{(7) (}a) Denmark, S.; Ghosh, S. K. Angew. Chem., Int. Ed. 2001, 40, 4759. (b) Northrup, A. B.; MacMillan, D. W. C. J. Am. Chem. Soc. 2002, 124, 6798. (c) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. Angew. Chem., Int. Ed. 2003, 42, 2785.

⁽⁸⁾ β -Hydroxy aldehydes predominately exist as dimers: Rychnovsky, S. D.; Salitzky, D. J. *J. Org. Chem.* **1992**, *57*, 2336 and references therein.

 TABLE 1. Tandem Catalytic Reductive Aldol

 Condensation to Pyridazines



^a Procedure: To a flame-dried 50-mL round-bottomed flask under an atmosphere of Ar (g) charged with Rh(COD)₂OTf (4.7 mg, 0.01 mmol, 1 mol %) and Ph₃P (6.3 mg, 0.024 mmol, 2.4 mol %) was added DCE (10 mL, 0.1 M). The resulting solution was stirred for 5 min at which point KOAc (98.2 mg, 1 mmol, 100 mol %), glyoxal monohydrate (1 mmol, 100 mol %), and then the enal (5 mmol, 500 mol %) were added. The system was flushed with hydrogen and stirred under 1 atm of H₂ at ambient temperature until complete consumption of the glyoxal was observed, at which point hydrazine (314 μ L, 10 mmol, 1000 mol %) was added as a methanolic solution (10 mL, 1 M) and the reaction mixture was allowed to stir for 45 min. Evaporation of the reaction mixture onto silica gel and purification by silica gel chromatography provides pyridazines 1b-6b. ^b The glyoxal was not used as the crystalline monohydrate, but was purified via Kügelrohr distillation prior to use and was added to the reaction mixture along with an equimolar quantity of water. ^c For this singular example, a 3 mol % loading of Rh(COD)2OTf and a 7.2 mol % loading of Ph3P were used. d Reactions performed with crotonaldehyde were conducted in THF (0.05 M) at 40 °C with a 5 mol % loading of Rh(COD)₂OTf and a 12 mol % loading of Ph₃P.

the Rh(I) aldolate **II** gives the Rh(III) dihydride **III**, which upon oxygen-hydrogen reductive elimination provides the aldol product with concomitant regeneration of the starting Rh(I) monohydride (Scheme 1).

To corroborate the proposed mechanism, the catalytic reductive aldol condensation of acrolein with phenyl glyoxal monohydrate was performed under 1 atm of elemental deuterium. Exposure of the aldol product to excess hydrazine in situ results in the formation of the pyridazine *deuterio*-**1b**, which incorporates precisely one

SCHEME 1. Proposed Catalytic Cycle for the Reductive Aldol Condensation of Enals with Glyoxal Partners



deuterium atom in a manner consistent with the proposed mechanism.



In summary, catalytic enal hydrogenation represents a viable method for the reductive generation of metalloaldehyde enolates, as demonstrated by catalytic cross aldol condensation with aromatic and heteroaromatic glyoxal partners. Future studies will be devoted to the development of related catalytic C–C bond-forming hydrogenations.

Experimental Section

5-Methyl-3-phenylpyridazine (1b). The title compound was prepared in accordance with the procedure described in Table 1. The title compound was obtained in 62% yield as a yellow solid, identical in all respects with previously reported material.⁹

5-Methyl-3-naphthalen-2-ylpyridazine (2b). The title compound was prepared in accordance with the procedure described in Table 1. The title compound was obtained in 59% yield as a yellow solid. Mp 137–140 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.96 (d, J = 1.7 Hz, 1H), 8.50 (d, J = 1.0 Hz, 1H), 8.19 (dd, J = 8.7, 1.9 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.92 (m, 1H), 7.86 (m, 1H), 7.72 (m, 1H), 7.51 (m, 2H), 2.38 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 158.5, 151.5, 137.8, 133.9, 133.6, 133.2, 128.6, 128.6, 127.6, 126.9, 126.4, 124.2, 124.2, 18.4. FTIR (film) 1636 cm⁻¹. HRMS calcd for C₁₅H₁₃N₂ (M + 1) 221.1079, found 221.1083.

5-Methyl-3-thiophen-2-ylpyrizadine (3b). The title compound was prepared in accordance with the procedure described in Table 1. The title compound was obtained in 31% yield as an orange solid. Mp 118–120 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.87 (d, J = 1.4 Hz, 1H), 7.65 (dd, J = 3.8, 1.0 Hz, 1H), 7.57 (d, J = 1.0 Hz, 1H), 7.47 (dd, J = 5.0, 0.9 Hz, 1H), 7.14 (dd, J = 5.1, 3.8 Hz, 1H), 2.38 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 154.4, 151.4, 140.6, 137.8, 129.0, 128.0, 126.0, 122.4, 18.4. FTIR (film) 3039 (w), 1596 (m), 1448 (w) cm⁻¹. HRMS calcd for C₉H₉N₂S (M + 1) 177.0486, found 177.0489.

5-Methyl-3-(1-methyl-1*H***-pyrrol-2-yl)pyridazine (4b).** The title compound was prepared in accordance with the procedure described in Table 1. The title compound was obtained in 30% yield as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ 8.81 (d,

⁽⁹⁾ South, M. S.; Jakuboski, T. L.; Westmeyer, M. D.; Dukesherer, D. R. *J. Org. Chem.* **1996**, *61*, 8921.

 $J = 2.1 \text{ Hz}, 1\text{H}), 7.48 \text{ (q}, J = 0.91 \text{ Hz}, 1\text{H}), 6.80 \text{ (m}, 1\text{H}), 6.64 \text{ (m}, 1\text{H}), 6.22 \text{ (dd}, J = 2.4, 1.4 \text{ Hz}, 1\text{H}), 4.09 \text{ (s}, 3\text{H}), 2.35 \text{ (s}, 3\text{H}). ^{13}\text{C} \text{ NMR} \text{ (CDCl}_3, 100 \text{ MHz}) \delta 154.1, 150.0, 137.2, 128.9, 127.8, 124.4, 112.0, 108.0, 37.8, 18.3. FTIR (film) 2957,1601 cm^{-1}. \text{HRMS calcd for } C_{10}\text{H}_{12}\text{N}_3 \text{ (M} + 1) 174.1031, found 174.1032.}$

5-Ethyl-3-phenylpyridazine (5b). The title compound was prepared in accordance with the procedure described in Table 1. The title compound was obtained in 47% yield as a yellow solid, identical in all respects with previously reported material.⁹

5-Ethyl-3-naphthalen-2-yl-pyridazine (6b). The title compound was prepared in accordance with the procedure described in Table 1. The title compound was obtained in 50% yield as a yellow solid. Mp 102–104 °C. ¹H NMR (CDCl₃, 400 MHz) δ 9.03 (s, 1H), 8.53 (s, 1H), 8.22 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.96 (m, 2H), 7.88 (d, *J* = 5.1 Hz, 1H), 7.78 (s, 1H), 7.53 (m, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.35 (t, *J* = 7.7 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 158.8, 150.8, 143.4, 133.9, 133.7, 133.2, 128.7, 128.6, 127.6, 126.9, 126.8, 126.4, 124.2, 122.9, 25.8, 13.7. FTIR (film) 2970 (w), 1642 (m) cm⁻¹. HRMS calcd for C₁₆H₁₅N₂ (M + 1) 235.1235, found 235.1227.

5-*d*₁**-Methyl-3-phenylpyridazine** (*deuterio***-1b**). The title compound was prepared in accordance with the procedure described in Table 1, substituting deuterium for hydrogen gas.

Mp 87–88 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.97 (d, J= 2.0 Hz, 1H), 8.04 (dd, J= 8.0, 1.5 Hz, 2H), 7.63 (m, 1H), 7.48 (m, 3H), 2.38 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 151.6, 136.4, 129.8, 128.9, 127.1 124.2, 18.3 (m). FTIR (film) 3039 (w), 1595 (m). HRMS calcd for C₁₁H₁₀DN₂ (M + 1) 172.0985, found 172.0980.

Acknowledgment. We thank the Robert A. Welch Foundation (F-1466), the NSF-CAREER program (CHE0090441), the Herman Frasch Foundation (535-HF02), the NIH (RO1 GM65129-01), donors of the Petroleum Research Fund, administered by the American Chemical Society (34974-G1), the Research Corporation Cottrell Scholar Award (CS0927), the Alfred P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, and Eli Lily for partial support of this research.

Supporting Information Available: Tabulated spectral data (¹H NMR, ¹³C NMR, HRMS, IR) and scanned images of ¹H and ¹³C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org. JO030310A