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Synthesis of Substituted Chromanones: An Organocatalytic Aldol/oxa-Michael Reaction

Jeffrey D. Butler, Wayne E. Conrad, Michael W. Lodewyk, James C. Fettinger, Dean J. Tantillo, and Mark J. Kurth*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616

mjkurth@ucdavis.edu

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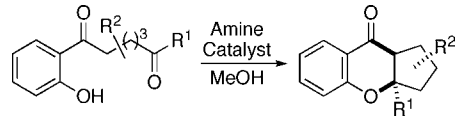
ABSTRACT



A diastereoselective organocatalytic aldol/oxa-Michael reaction has been developed to efficiently deliver medicinally relevant 2,3-ring-substituted chromanones. Development of this synthetic strategy revealed an unexpected kinetic anti-Saytzeff elimination; an origin for the observed selectivity is suggested on the basis of the results of quantum chemical calculations. This unusual kinetic selectivity necessitated an isomerization protocol that in turn led to the discovery of an intriguing Pd-mediated isomerization/intramolecular Friedel−Crafts-type alkylation.

Chromanones are medicinally pertinent heterocycles,[1] and the chroman parent system has been identified in natural products such as sappanone B[2] and robustadial[3] in addition to being a bioisostere for the hydantoin moiety.[4] With this biological relevance, chromanone synthesis has received considerable attention by our group[5] and others.[6] Asymmetric preparations of chromanones have also been reported.[7] A less explored aspect of the chemistry of this heterocycle is the development of syntheses that impart α- and/or *β*-substitution or, more specifically, fused-ring chromanones (coumarin derivatives and tetrahydro-xanthones). These structures are found in the cores of pseudobruceol-I[8] and diversonol[9] (Figure 1). Although the laboratories of Toste,[10] Tietze,[11] and Akiba[12] have made advances in this area, our goal is the development of an organocatalyzed aldol/oxa-Michael reaction that delivers fused-ring chromanones (**I**) from precursors of type **II** (Figure 1). Herein, we report a short synthetic strategy for the diastereoselective preparation of cyclopentane-fused chromanones using organocatalysis. As this synthetic strategy developed, we encountered an unexpected anti-Saytzeff[13] alkene formation that fortuitously led to the discovery of a unique catalytic Pd-mediated isomerization/intramolecular Friedel−Crafts-type alkylation.

(1) Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 247–256.
(2) Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713–2716.
(3) Majewski, M.; Irvine, N. M.; Bantle, G. W. *J. Org. Chem.* **1994**, *59*, 6697–6702.
(4) Lipinski, C. A.; Aldinger, C. E.; Beyer, T. A.; Bordner, J.; Bussolotti, D. F.; Inskeep, P. B.; Siegel, T. W. *J. Med. Chem.* **1992**, *35*, 2169–2177.
(5) Carpenter, R. D.; DeBerdt, P. B.; Holden, J. B.; Milinkevich, K. A.; Min, T.; Willenbring, D.; Fettinger, J. C.; Tantillo, D. J.; Kurth, M. J. *J. Comb. Chem.* **2008**, *10*, 225–229.
(6) (a) Chandrasekhar, S.; Vijeender, K.; Reddy, K. V. *Tetrahedron Lett.* **2005**, *46*, 6991–6993. (b) Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 12596–12597.
(7) (a) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899–1902. (b) McKervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1992**, 823–824. (c) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831. (d) Carpenter, R. D.; Fettinger, J. C.; Lam, K. S.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6407–6410.
(8) Rashid, M. R.; Armstrong, J. A.; Gray, A. I.; Waterman, P. G. *Phytochemistry* **1992**, *31*, 3583–3588.
(9) Turner, W. B. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1365–1368.
(10) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168–17169.
(11) Tietze, L. F.; Spiegl, D. A.; Stecker, F.; Major, J.; Raith, C.; Brobe, C. *Chem.—Eur. J.* **2008**, *14*, 8956–8963.
(12) Lee, Y.-G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K. *J. Org. Chem.* **1991**, *56*, 2058–2066.
(13) (a) Saytzeff, A. M. *Justus Liebigs Ann. Chem.* **1875**, *179*, 296. (b) Braida, B.; Prana, V.; Hiberty, P. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5724–5728.

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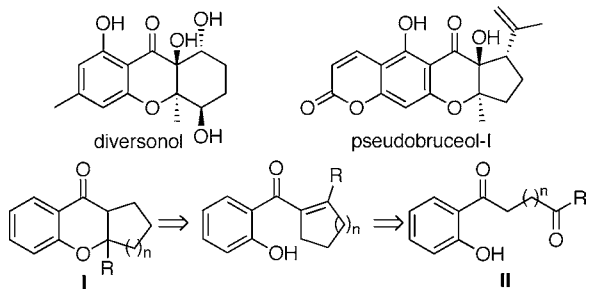

Figure 1. Fused chromanone containing natural products and description of a linear synthetic approach.

Our synthetic efforts began with the lithiation of 2-bromophenol and subsequent addition of 2-methylcyclohexanone (Figure 2). After an acid-promoted (aq HCl) dehydration of the resulting benzyl alcohol, we were surprised to find a predominance of the anti-Saytzeff product in a 1:1.3 ratio (entry 1, **1a**:**1b**, Figure 2) as determined by relative ^{1}H NMR integration. This alkene mixture was not found in the reported cyclopentene-substituted case.[14] Lowering the temperature of the dehydration step from 0 °C to −40 or −78 °C gave a ∼1:3.1 (entry 2, **1a**:**1b**) or 1:5.0 ratio (entry 3, **1a**:**1b**), respectively. These results showed no dependence on the acid employed as H_2SO_4 and H_3PO_4 gave comparable ratios. Methyl substitution in the 3-, 4-, or 5-position had little effect on the mixture (entries 4−6). However, a sterically larger *i*-Pr substituent at the 2-position generated a 1:19 ratio of alkenes (entry 7). In addition, similar alkene mixtures were found when 2-bromoanisole was used instead of 2-bromophenol (entry 8).

To better understand these unusual results, we utilized DFT calculations (B3LYP/6-31+G(d,p), see Supporting Information for details) to examine the energies and structures of the possible alkene products (**1a**/**1b**) as well as the presumed common benzylic cation precursor. The results of these calculations indicate that alkene **1a** is indeed the thermodynamically favored product, lying approximately 2.3 kcal/mol lower in energy than alkene **1b** (see Supporting Information).

Shown in Figure 3 are five conformers (two chair conformations and three twist-boat conformations) of the benzylic cation that we were able to locate, along with their computed relative energies. The results show that the three lowest energy conformers (**cat1.1**, **cat1.3**, and **cat1.4**) have the R^1 methyl substituent in alignment with the empty p-orbital of the carbocation, rather than the tertiary hydrogen atom that would lead to the thermodynamic product upon deprotonation. In fact, the two conformers (**cat1.2** and **cat1.5**) that have this hydrogen atom aligned with the empty p-orbital of the carbocation lie more than 3 kcal/mol higher in energy than the lowest energy conformer. We postulate that these energy differences are likely manifested to some extent in the barriers for deprotonation, consistent with alkene **1b** being the kinetically favored product for this reaction.

(14) Wang, Q.; Chen, C. *Org. Lett.* **2008**, *10*, 1223–1226.

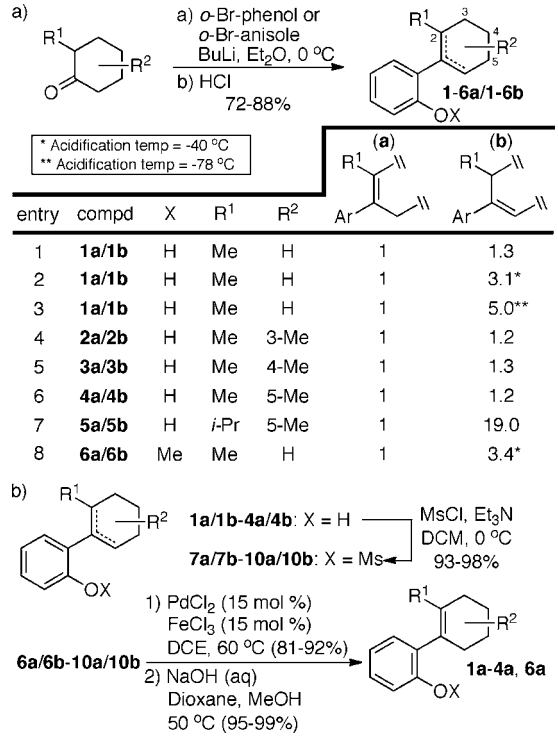

Figure 2. General synthetic method: (a) regioselectivity and (b) isomerization of cyclohexenylphenol derivatives.

While these mixtures may likely be avoided by employing modern palladium coupling methods, we viewed this as an opportunity to confirm our computational results and set out to develop an isomerization method. Attempts to isomerize **1b** → **1a** under acidic conditions (TsOH, EtOH, reflux) resulted in dihydrobenzofuran formation where the nucleophic phenol intercepts the cationic intermediate upon anti-Markovnikov protonation.[15]

In contrast, anisole **6b** slowly isomerizes to the desired tetrasubstituted alkene **6a** (TsOH, EtOH, reflux, 14 d) without heterocyclization. However, compatible methods to demethylate the *o*-methoxy group proved unreliable and difficult to scale-up in our hands. Encouraged by the recent report by Wang et al. of a mild *ortho*-enhanced isomerization,[16] we employed their conditions (cat. $PdCl_2$, $FeCl_3$, DCE 60 °C) and found that **6a**/**b** is efficiently isomerized to only **6a** in 4 h (Figure 2). However, isomerization attempts on the phenol mixture **1a**/**1b** resulted in formation of the aforementioned oxy-cyclized product. To circumvent this, the mixture of phenolic alkenes **1a**/**1b**−**4a**/**4b** were mesyl-protected and to our delight, nicely participated in the $PdCl_2$ isomerization reactions to give **7a**−**10a**. The mesyl group was subsequently removed by hydrolysis yielding the desired phenolic cyclic styrenes **1a**−**4a** (Figure 2).

As delineated in Figure 4, **1a**−**4a** were subjected to ozonolysis conditions to yield linear diketo phenols **11**−**14**.

(15) Lévy, J.; Sigaut, F. *Tetrahedron Lett.* **1983**, *24*, 4987–4988, See product characterization in Supporting Information.

(16) Fan, J.; Wan, C.; Wang, Q.; Gao, L.; Zheng, X.; Wang, Z. *Org. Biomol. Chem.* **2009**, *7*, 3168–3172.

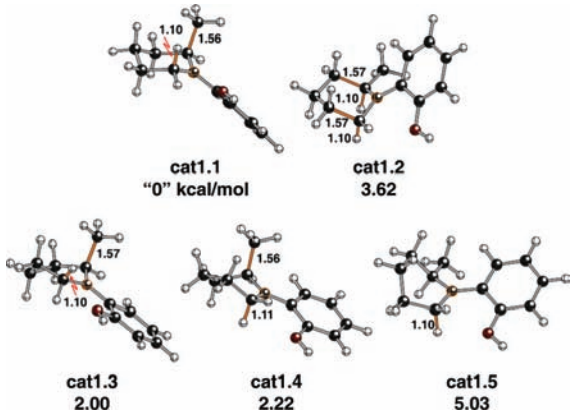

Figure 3. Computed structures and energies (B3LYP/6-31+G(d,p)) for the cationic precursor to **1a**/**1b**. The benzylic cation center and σ-bonds aligned with the empty p-orbital are highlighted in orange. Distances are shown in Å, and energies are in kcal/mol.

Gratifyingly, treatment of **11** with pyrrolidine at 50 °C in MeOH delivered the fused chromanone **15** as a single diastereomer in 87% yield and in an efficient 61% overall yield. To explore the impact of cyclopentane ring substitution on diastereoselectivity, racemic methyl-substituted diketo phenols **12**−**14** were exposed to the chromanone-forming conditions (pyrrolidine, MeOH, 50 °C) to give methyl-substituted chromanones **16**−**18a/18b**. As outlined in Figure 4, methyl substitution at the 3-position gave good diastereoselectivity (a 9:1 ratio of **16a**:**16b**). Methyl substitution at either the 4- (**17a**/**17b**) or 5-position (**18a**/**18b**) shows reduced selectivity; 2.3:1 and 5:1, respectively. To further assess the diastereoselectivity and scope of this strategy, we wanted to explore chiral diones **19** and **20**. Treatment of the protected alkene mixture **5a**/**5b** from (+)-menthone with the isomerization reagents and subsequent hydrolysis, yields only **21** (Figure 5), whose structure was confirmed by X-ray crystallography. This result represents a unique isomerization/Friedel−Crafts-type alkylation.

To access the desired diones **19** and **20**, an alternate synthesis was required. The Baeyer−Villiger oxidation products of (+)- and (−)-menthone (**22** and **23**, Figure 4), synthesized via literature protocol,[17] were treated with the Li-exchanged product of 2-bromophenol and BuLi. Subsequent oxidation afforded diones **19** and **20**, which were exposed to the chromanone forming conditions yielding only **24** and enantiomer **25**, respectively.

Next, we probed the role(s) of the organocatalyst in our newly developed aldol/oxa-Michael reaction. As depicted in Figure 6, we only observed products (chromanone and uncyclized enone) formed by chemoselective enamine formation, *exo-trig* cyclization, and dehydration.[18] It is noteworthy that no reaction is observed (**11** → **15**) if catalytic Et_3N is used in place of pyrrolidine, evidence of an enamine-

(17) For oxidation of menthol, see: Sanborn, L. T. *Org. Synth.* **1929**, *9*, 52. For Baeyer−Villiger of menthone, see: (a) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Chem. Lett.* **2004**, *33*, 248–249. (b) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, *4*, 462–464.

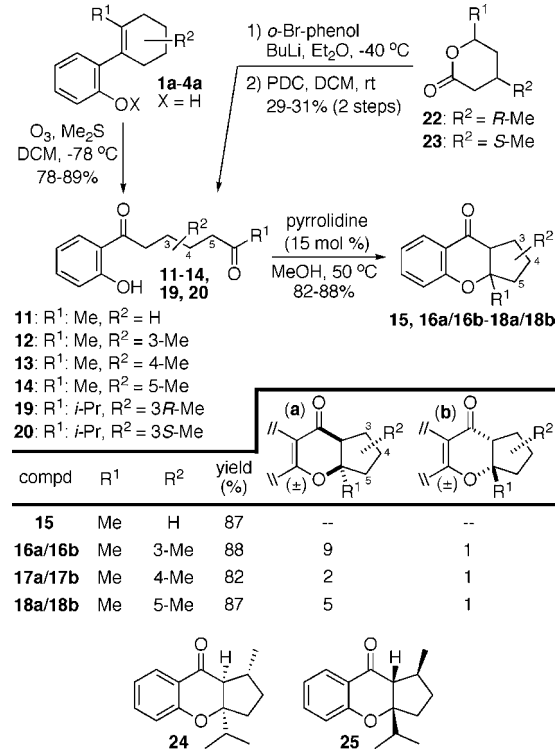

Figure 4. General synthetic method for tetrahydrocyclopenta-[*b*]chromanones.

mediated process. Upon cyclization/dehydration, the forward pathway could diverge. Possibilities include conjugate addition to the iminium followed by hydrolysis or, alternatively, hydrolysis of the iminium and Michael addition to the enone. Although both give the same end product, catalyst involvement in each is distinctly different. That said, understanding the role(s) of the catalyst and reaction pathway(s) is vital.

Conveniently, the 9:1 diastereomeric mixture of **16a**:**16b** is separable by standard flash chromatography and allowed us the opportunity to probe reaction reversibility and gain insight as to the role(s) of the pyrrolidine catalyst in this tandem reaction. Several informative experiments were conducted; these conditions and results are summarized in Figure 7.

In the absence of catalyst, (Expt. A, Figure 7) **16a** showed no reaction. However, upon addition of catalyst (Expts. B and C), both **16a** and **16b** returned to the thermodynamic 9:1 ratio of **16a**:**16b**. If catalytic Et_3N is added to **16a** without catalyst (Expt. D), a 9:1 ratio is again formed. For Expts.

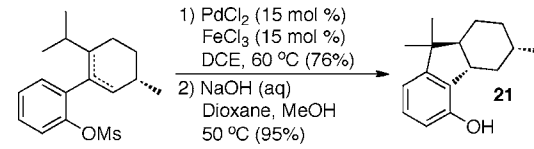

Figure 5. Synthesis of hexahydrofluorenol derivative.

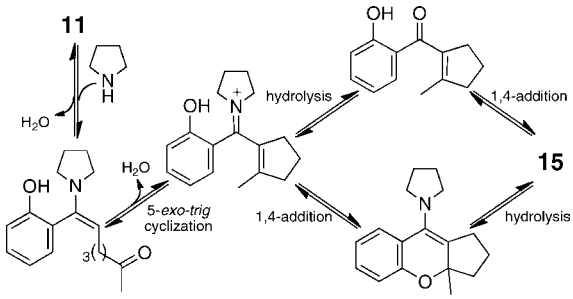

Figure 6. Proposed mechanism of tetrahydro-cyclopenta[*b*]chromanone formation.

E−G, the **16a**/**16b** mixture was treated with KOH in MeOH. Through a presumed E1cB mechanism, the **16a**/**16b** mixture was quantitatively converted to enone phenol **26**. No reaction of **26** was observed in MeOH alone (Expt. E). Upon addition of pyrrolidine, **26** was cleanly converted back to a 9:1 mixture of **16a** and **16b** (Expt. F). However, **26** treated with catalytic Et_3N afforded the same ratio of **16a**:**16b**.

These experiments give insight into the possible dual role played by the pyrrolidine catalyst in this tandem aldol/oxa-Michael reaction and confirm that 1,4-addition to the iminium (Figure 6) is not a requirement. In addition, Michael addition reversibility was corroborated.

This reversibility allows for the preparation of a single diastereomer by iterative separation and resubjection of the minor isomer to the reaction conditions. It unfortunately also means that enantioselective chromanone formation from an achiral diketo phenol fails (attempts on **11** with L-proline and L-prolinol gave racemic **15**). We suspect this equilibration occurs via an E1cB mechanism where the pyrrolidine catalyst (Expts. B, C, and F) or Et_3N (Expts. D and G) acts simply as a base.

Ultimately, our goal of developing an organocatalyzed aldol/oxa-Michael reaction to deliver ring-fused chromanones of synthetic and biological importance has been realized. This reaction sequence was probed and revealed evidence as to

(18) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

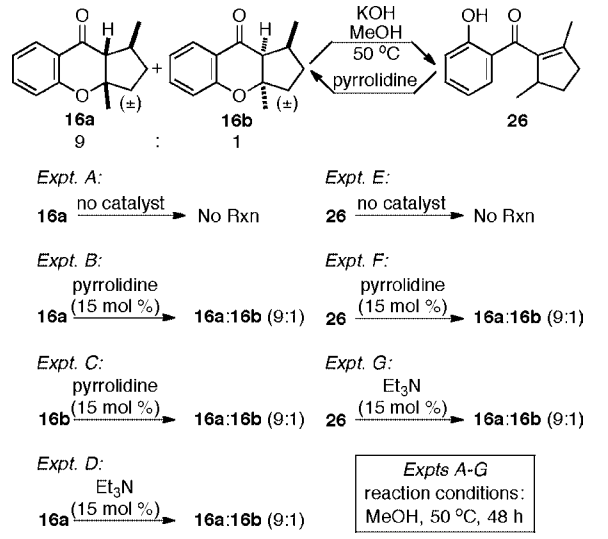

Figure 7. Experiments performed to investigate Michael reversibility and catalyst function.

the roles of the pyrrolidine catalyst. In addition, our synthetic strategy revealed interesting anti-Saytzeff dehydration products, whose isomerization led to the discovery of an intriguing Pd-mediated intramolecular Friedel−Crafts alkylation. Current efforts in our laboratory are focused on this unique cyclization and these results will be the topic of a future report.

Acknowledgment. The authors dedicate this letter to Professor Thomas R. Hoye (University of Minnesota), a mentor and friend, on the occasion of his 60th birthday. Financial support provided by the National Science Foundation (CHE-0910870, CHE-0449845) and the National Institutes of Health (GM089153).

Supporting Information Available: Full experimental details, characterization data (^{1}H NMR, ^{13}C NMR, IR, and LC/MS) for all new compounds, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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