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Xiang-Wei Du
Iowa State University

Levi M. Stanley
Iowa State University, lstanley@iastate.edu

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Tandem Alkyne Hydroacylation and Oxo-Michael Addition: Diastereoselective Synthesis of 2,3-Disubstituted Chroman-4-ones and Fluorinated Derivatives

Xiang-Wei Du and Levi M. Stanley*

Department of Chemistry, Iowa State University, 1605 Gilman Hall, Ames, Iowa 50014, United States

Supporting Information

ABSTRACT: Tandem reactions involving Rh-catalyzed intermolecular hydroacylations of alkynes with salicylaldehydes followed by intramolecular oxo-Michael additions are described for the diastereoselective synthesis of 2,3-disubstituted chroman-4-ones. The tandem hydroacylation/oxo-Michael additions occur to form 2,3-disubstituted chroman-4-ones in high yields from a range of 1,2-disubstituted acetylenes and substituted salicylaldehydes. The resulting 2,3-disubstituted chroman-4-ones are readily fluorinated to form trans-3-fluoro-2,3-disubstituted chroman-4-ones in high yields with excellent diastereoselectivity.

Tandem processes involving atom-economic, transition-metal-catalyzed alkene or alkyne hydroacylation have been developed as efficient routes to a variety of ketones. However, examples of these tandem processes to form valuable heterocyclic ketones are rare. The paucity of tandem reactions involving alkenes and alkyne hydroacylation to form heterocyclic ketones is surprising because a variety of heteroatom-functionalized aldehydes, particularly 2-hydroxybenzaldehydes (salicylaldehydes), 2-aminobenzaldehydes, 2-mercaptopbenzaldehydes, and derivatives, are established as privileged substrates in transition-metal-catalyzed alkene and alkyne hydroacylation reactions. The presence of heteroatom substitution in the aldehyde substrates is often viewed as a limitation of alkene and alkyne hydroacylation necessary to suppress catalyst deactivation pathways and minimize the formation of undesired products often observed in reactions of simple aldehydes. However, these heteroatom functional groups offer a handle to rapidly generate complex heterocycles when olefin hydroacylation reactions are coupled with additional reaction manifolds (Scheme 1). To this end, Willis developed a stepwise protocol for hydroacylation of alkynes with 2-aminobenzaldehydes followed by Lewis acid catalyzed, intramolecular aza-Michael addition to rapidly generate dihydroquinolones (Scheme 1A). The development of related intermolecular hydroacylation of alkynes with salicylaldehydes followed by intramolecular oxo-Michael addition offers the potential to streamline traditional syntheses of chroman-4-ones. However, tandem alkyne hydroacylation/oxo-Michael addition processes to form chroman-4-ones are limited to two examples reported by Miura. Hydroacylations of activated alkynes, ethyl hept-2-ynoate and 1-phenylhept-2-yn-1-one, and the subsequent oxo-Michael additions occur to form approximately 1:1 mixtures of chroman-4-one and benzofuran-3-(2H)-one products. To our knowledge, a general catalyst system to generate chroman-4-ones with high regio- and diastereoselectivity by a tandem alkyne hydroacylation/oxo-Michael addition strategy has not been reported.

We now report a one-pot process to synthesize 2,3-disubstituted chroman-4-ones by hydroacylation of 1,2-disubstituted alkynes with salicylaldehydes followed by an intramolecular oxo-Michael addition (Scheme 1B). The 2,3-disubstituted chroman-4-one products of these tandem reactions are readily converted to trans-3-fluoro-2,3-disubstituted chroman-4-ones.
tuted chroman-4-ones by a highly diastereoselective enolate fluorination.

2,3-Diarylcroman-4-ones are core structures present in a wide variety of flavonoids and are valuable precursors to 2,3-diaryl-2H-1-benzopyrans that exhibit potent antitryptic activity. To develop a rapid entry into the 2,3-diarylcroman-4-one core, we studied the reaction of salicylaldehyde 1a with 1,2-diphenylacetylene 2a in the presence of a variety of bases and 5 mol % of catalyst prepared in situ from [Rh(COD)Cl]2 and dppf (Table 1). The hydroacylation of

Table 1. Identification of Reaction Conditions for Tandem Alkyne Hydroacylation/Oxo-Michael Addition

<table>
<thead>
<tr>
<th>entry</th>
<th>base (mol %)</th>
<th>solvent</th>
<th>yield 3a (%)</th>
<th>dr (trans/cis)</th>
<th>yield 4a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na2CO3 (200)</td>
<td>toluene</td>
<td>14</td>
<td>1.8:1</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>CsF (200)</td>
<td>toluene</td>
<td>78</td>
<td>3.6:1</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>CsF (20)</td>
<td>toluene</td>
<td>84</td>
<td>3.9:1</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>CsF (20)</td>
<td>DCE</td>
<td>85</td>
<td>3.2:1</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>CsF (20)</td>
<td>1,4-dioxane</td>
<td>65</td>
<td>2.6:1</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>CsF (20)</td>
<td>DMF</td>
<td>91</td>
<td>3.8:1</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>CsF (20)</td>
<td>MeCN</td>
<td>93</td>
<td>5.7:1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>CsF (20)</td>
<td>MeNO2</td>
<td>81</td>
<td>1.8:1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>CsF (20)</td>
<td>MeCN</td>
<td>70</td>
<td>3.0:1</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>CsF (10)</td>
<td>MeCN</td>
<td>95</td>
<td>5.0:1</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>CsF (8)</td>
<td>MeCN</td>
<td>94</td>
<td>5.0:1</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>CsF (8)</td>
<td>MeCN</td>
<td>94 (92)</td>
<td>5.4:1</td>
<td>4</td>
</tr>
</tbody>
</table>

aReaction conditions: 1a (1.0 equiv), 2a (1.2 equiv), [Rh(COD)Cl]2 (2.5 mol %), dppf (5 mol %), base, solvent (0.20 M), 100 °C. bDetermined by 1H NMR spectroscopy of the crude reaction mixture with dibromomethane as the internal standard. cCombined yield of trans-3a and cis-3a. dReaction conducted with 2 mol % of Rh catalyst (0.5 M in MeCN). eCombined yield of trans-3a and cis-3a.

2a in the presence of a variety of inorganic bases occurs in high yields (entries 1–3). These reactions form 2,3-diphenylchroman-4-one 3a and (E)-1,2-bis(phenylethynyl)-1,2-diphenylprop-2-en-1-one 4a in combined yields of ≥90% with 2 equiv of Na2CO3, K2PO4, or CsF as the base. However, the efficiency of the oxo-Michael addition to form 3a is significantly impacted by the identity of the base. Product 3a was generated in higher yield and with higher diastereoselectivity when CsF (20 mol %) was used as the base (entry 3).

The improved yield and diastereoselectivity observed with CsF as the base guided attempts to improve the yield and selectivity of the model reaction. To improve the diastereoselectivity of the intramolecular oxo-Michael addition of 4a to 3a, we evaluated the tandem reaction in a range of solvents (entries 4–9) and found the yield (93%) and diastereomeric ratio (5.7:1) of 3a to be the highest in acetonitrile (entry 7). Conducting the model reaction in acetonitrile enabled us to lower the loading of CsF to 8 mol % with only a modest decrease in selectivity (entry 11). The loading of the Rh catalyst was reduced from 5 to 2 mol % without significantly impacting the yield or diastereoselectivity of the tandem reaction sequence (compare entry 12 with entry 11).

The scope of the tandem reaction sequence with regard to 1,2-disubstituted alkenes was then examined (Scheme 2).

Reactions of 1a with a variety of 1,2-diarylacetylenes occur to form the corresponding 2,3-dialkylnchroman-4-ones 3a–f in good to excellent yields (55–92%). The diastereomeric ratio of 2,3-diarylcroman-4-ones 3a–f was influenced by substitution on the alkyne. 2,3-Diarylcroman-4-ones derived from 1,2-diarylacetylenes with electron-neutral (R = Ph, 4-ClC6H4) or bulky (R = 2-MeOC6H4) aryl groups were isolated with greater than 5:1 diastereomeric ratios favoring trans-3a, 3b, and 3f. Tandem reactions of 1a with 1,2-diarylacetylenes containing strongly electron-withdrawing (R = 4-F, 3-C6H4) or bulky (R = 2-MeOC6H4) aryl groups were isolated with greater than 5:1 diastereomeric ratios favoring trans-3a, 3b, and 3f. Tandem reactions of 1a with 1,2-diarylacetylenes containing strongly electron-donating (R = 4-MeOC6H4) and meta-substituted (R = 4-MeOC6H4) aryl groups formed the corresponding 2,3-dialkylnchroman-4-ones 3c–e with modest diastereoselectivities (2.0–3.1:1 trans:cis-3).

Although the tandem reactions form mixtures of trans:cis diastereoisomers, pure trans-3 (>20:1) can be isolated by recrystallization or column chromatography. For example, trans-3a was isolated in 74% yield (2.22 g) after recrystallization from the reaction of 1a (10.0 mmol, 1.22 g) with 2a. trans-3b and trans-3c were isolated in 74% yield and 48% yield after column chromatography.

A tandem alkyne hydroacylation and oxo-Michael addition involving an unsymmetrical alkyne also occurs to form 2,3-disubstituted chroman-4-ones with modest levels of regio- and diastereoselectivity (eq 1). The reaction of 1-phenyl-1-propyne with salicylaldehyde occurs to form a 3.4:1 mixture of regioisomeric products 3-methyl-2-phenylchroman-4-one and 2-methyl-3-phenylchroman-4-one in 88% combined yield. 3-Methyl-2-phenylchroman-4-one is formed with a 3.8:1 diastereomeric ratio of trans and cis isomers, and 2-methyl-3-
phenylchroman-4-one is formed with a 2.5:1 diastereomeric ratio of trans and cis isomers.

Reactions of salicylaldehyde with 1,2-dialkylacetylenes occur to form the corresponding 2,3-dialkylchroman-4-ones, which are found in a variety of naturally occurring chroman-4-ones\(^{11}\) in higher yields than analogous reactions of 1,2-diarylacetylenes. For example, reactions of 3-hexyne and 4-octyne with salicylaldehyde occur to form 2,3-dialkylchroman-4-ones\(^{3g}\) and\(^{3h}\) in 92% and 94% yield. However, the diastereoselectivity of these reactions is modest, and the resulting 2,3-dialkylchromanones\(^{3g}\) and\(^{3h}\) were isolated as 1.8:1 and 1.3:1 mixtures of the trans:cis diastereomers.

The scope of tandem reactions of a variety of substituted salicylaldehydes with 1,2-diphenylacetylene\(^{2a}\) is summarized in Scheme 3. Reactions of salicylaldehydes containing both electron-withdrawing and electron-donating substituents with 2a occur to form 2,3-diphenylchroman-4-ones in good yields with moderate diastereoselectivities. Reactions of 4-NO\(_2\), 4-F, and 4-Cl-salicylaldehyde with 2a form the corresponding 2,3-diphenylchroman-4-ones\(^{3i} - k\) in 64–86% yield with diastereoselectivities ranging from 2.6:1 to 5.3:1. Reactions of 3-MeO, 4-MeO, 5-MeO, and 6-MeO-salicylaldehydes with 1,2-diphenylacetylene generate 2,3-diphenylchroman-4-ones\(^{3l} - o\) in 55–90% yield with 2.9:1 to 4.6:1 dr. The reaction of 6-methoxysalicylaldehyde with 2a formed only 55% yield of 2,3-dialkyllchroman-4-one\(^{3n}\), while the initial alkyne hydroacylation product was isolated in 17% yield. The reaction of 2-hydroxy-1-naphthalddehyde with 2a formed 3p with 3.5:1 dr. Trans diastereomers (>20:1 dr) of 3 are readily obtained by column chromatography or recrystallization. trans-3i and trans-3p were isolated in 64% yield and 79% yield after recrystallization. trans-3o was isolated in 36% after column chromatography.

With a tandem reaction strategy to form trans-2,3-disubstituted chroman-4-ones 3 in hand, we sought to develop a fluorination protocol to access pseudodiastereomeric trans-3-fluoro-2,3-disubstituted chroman-4-ones in which the 2,3-diaryl or 2,3-dialkyl substituents reside on the same face of the chromanone core. A direct fluorination protocol to synthesize trans-3-fluoro-2,3-disubstituted chroman-4-ones 5 is summarized in Scheme 4.\(^{12}\) Deprotonation of diastereomeric mixtures of chroman-4-ones 3 with LiHMDS and fluorination of the resulting enolate with NFSI from the opposite face of the C2 substituent selectively generates trans-5 in high yields with excellent selectivities. Fluorinations of a variety of 2,3-diphenylchroman-4-ones 3 occur to form trans-5\(^{a}\) in 67–91% yield with nearly perfect diastereoselectivity (>20:1). The relative stereochemistry of 5a was confirmed by X-ray crystallographic analysis (Figure 1). Fluorinations of 2,3-dialkylchroman-4-ones form the corresponding trans-3-fluoro-2,3-dialkylchroman-4-ones 5g (R\(^1\) = Et) and 5h (R\(^1\) = n-Pr) in 88% and 93% yield as 14:1 and 9:1 diastereomeric mixtures.

**Scheme 3. Scope of Tandem Alkyne Hydroacylation/Oxo-Michael Addition with Substituted Salicylaldehydes**

**Scheme 4. Synthesis of 3-Fluoro-2,3-disubstituted Chroman-4-ones**

\(^{a}\)NFSI = N-fluorobenzenesulfonimide. Isolated yields are reported as mixtures of diastereomers. Diastereomeric ratios determined by \(^{19}\)F NMR spectroscopy. \(^{b}\)Reaction conducted with 3.0 equiv of LiHMDS and 4.8 equiv of NFSI.
In conclusion, we have developed a tandem alkyne hydroacylation/oxo-Michael addition process to synthesize trans-2,3-disubstituted chroman-4-ones from readily accessible starting materials in the presence of simple catalyst precursors. The 2,3-disubstituted chroman-4-one products are transformed to trans-3-fluoro-2,3-disubstituted chroman-4-ones in high yields and with excellent diastereoselectivities by a straightforward fluorination procedure. Studies to expand the scope of the tandem reaction to encompass unsymmetrical alkynes and to apply these reactions in total syntheses of natural products are ongoing in our laboratory.

ASSOCIATED CONTENT

 Supporting Information

Experimental procedures, characterization data for all new compounds, and crystallographic data for compound 5a. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01447.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lstanley@iastate.edu.

Notes

The authors declare no competing financial interest.

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