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cis-β-Bromostyrene derivatives from cinnamic acids via a tandem substitutive bromination-decarboxylation sequence

Khanh G. Tang, Greggory T. Kent, Ihsan Erden *, Weiming Wu *

Department of Chemistry and Biochemistry, San Francisco State University, 1600 Holloway Avenue, San Francisco, CA 94132, USA

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Dedicated to Professor James R. Keeffe on the occasion of his 80th birthday.

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ABSTRACT

cis-β-Bromostyrene derivatives were synthesized stereospecifically from cinnamic acids through β-lactone intermediates. The synthetic sequence did not require the purification of the β-lactone intermediates although they were found to be stable and readily purified in most cases.

Introduction

Vinyl bromides are very useful synthetic intermediates in organic synthesis; they are used as precursors in the formation of vinyl carbanions[1] and as substrates in many transition metal-catalyzed cross-coupling reactions.[2–4] Vinyl bromides have also been used to synthesize styrene and stilbene derivatives and heterocyclic compounds.[5–9] Therefore, development of methods for the stereoselective synthesis of *E*- or *Z*-vinyl bromides is of considerable importance.

Most methods for the stereoselective preparation of vinyl bromides involve organometallic or related compounds.[10] The Hunsdiecker-type bromodecarboxylation and decarboxylation of brominated cinnamic acids have been reported for the synthesis of both *E*- or Z-vinyl bromides.[10–19]

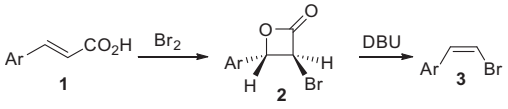
We recently reported on the reductive debromination or dehydrobromination of *vic*-dibromides by anisidines (*o* and *m*) and trimethylamine, respectively.[20,21] Recently, during our attempt to prepare a vicinal dibromide from cinnamic acid, we isolated a stable β-lactone instead.

In this *Letter*, we report on the stereospecific synthesis of *cis*-β-bromostyrene derivatives **3** from cinnamic acids **1** through the formation of isolable β -lactone intermediates **2,** as shown in Scheme 1.

Results and discussion

Bromination of cinnamic acids in methylene chloride produced a rather non-polar compound, which was identified as β-lactone **2** by NMR spectroscopy. It is presumably formed through the ring-opening nucleophilic attack on the bromonium intermediate **4** by the carboxylic acid functionality as shown in Scheme 2.[14,22] In most cases, the β-lactone intermediates can be readily isolated and even purified by column chromatography, though their purification is not required for synthetic purposes.

When lactones **2** were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), β-bromostyrenes **3** were isolated as the predominant products. Their structures and the *cis*-stereochemistry were determined by NMR spectroscopy. The ^{1}H–^{1}H coupling constant J_{cis} was used to assign the stereochemistry since *cis*-isomers have



Scheme 1. Synthesis of *cis*-β-bromostyrenes from cinnamic acids.

* Corresponding authors.
E-mail addresses: ierden@sfsu.edu (I. Erden), wuw@sfsu.edu (W. Wu).

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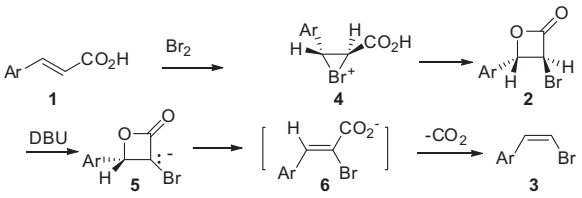


Scheme 2. Mechanism of the decarboxylative bromination.

smaller coupling constants than *trans*-isomers.[10,14,19,23] Triethylamine was found to be a much less effective base, as expected, requiring elevated temperatures and resulting in lower yields.

The mechanism of the sequence of reactions was also shown in Scheme 2. DBU deprotonates the α-proton to give **5**, which displaces the C—O bond with concomitant C=C formation leading to the carboxylate **6** in an E1cB-like mechanism. Compound **6** then decarboxylates to form the corresponding *Z*-vinyl carbanion (structure **7** in Fig. 1), which is protonated to produce (*Z*)- β-bromostyrenes **1**. The fact that only the Z isomer is formed indicates that the decarboxylation of β-lactone **2** is not a thermal nor concerted process (only the *E*-isomer would be expected from such a pathway). Instead, after the deprotonation of the acidic α-proton, the resulting enolate stereospecifically undergoes a well-known "forbidden" β-elimination by a E1cB mechanism to give the *Z*-alkene as concluded by the detailed study of lactone enolates like **5** by Mulzer et al.[24] An enthalpy of −18 kcal/mol was reported for the isomerization of β-lactone enolates of the type **5** to the more stable *Z* carboxylates like **6**.[24] The study concluded that enolates of the type **5** represent equivalents of vinyl anions of the type **7** with fixed stereochemistry (Fig. 1).[24] The carboxylate intermediate **6** decarboxylates with ease in the present case because the resulting 1-bromovinyl carbanion is stabilized by the bromine. Therefore, our mechanism rationalizes both the formation of the β-lactone intermediate and the observed *Z* stereochemistry of the product and is entirely consistent with the findings of Mulzer et al. (Scheme 2).[24]

These reactions work well for various substituting groups on the aromatic moiety as shown in Table 1. Although lactone **3** was stable and readily isolated, it can be used in the second reaction without purification. The methylene chloride solvent and excess bromine were stripped off in vacuo to leave the crude lactone product behind which was treated with DBU in CH_2Cl_2. The product can be isolated by simple extraction of the reaction residue with hexanes or column chromatography if necessary.[25]

Careful examination of the reactions of different substrates provides further support for the proposed mechanism and hints to an alternative mechanism for reactions with a strong electron-donating group present. As shown in Table 1, reactions with strong electron-donating groups are less stereoselective. In these cases, the initial bromonium ion opens up to a stabilized benzylic carbocation intermediate **8** which is subject to rotation before being captured intramolecularly by the ester oxygen to the β-lactone **2f** as a mixture of both diastereomers (Scheme 3). Decarboxylation with DBU thus gives both the *cis*-isomer **3f** and the *trans*-isomer **9f**. Furthermore, when a substrate was used carrying a strong electron-donating group (i.e., 2-and 4-methoxy) on the aryl group, and ether was employed as solvent, the bromination reaction produced a mixture of lactones **2** as well as both *cis*- and *trans*- β -bromostyrenes.

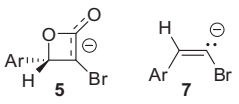
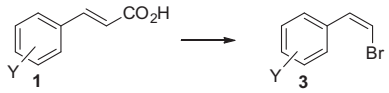


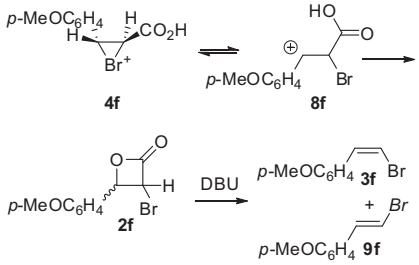
Fig. 1. Enolate **5** as an equivalent of vinyl anion **7**.

Table 1
Conversion of cinnamic acids to β-bromostyrenes.



Entries	Y	Combined Yield % (isolated)
a	H	99
b	4-Methyl	70
c	4-Fluoro	72
d	4-Chloro	75
e	4-Bromo	92
f	4-Methoxy	70[a]
g	2-Methoxy	75[b]
h	4-Nitro	75
i	2-Nitro	65

[a] 5:1 mixture of *cis*- to *trans*-isomers.
[b] 1:1 mixture of *cis*- to *trans*-isomers.



Scheme 3. Mechanism for the nonstereoselective formation of styrene bromides from **1f**.

In support of this mechanism is the fact that bromine additions to styrenes in CH_2Cl_2 change from near nonstereoselective for the most reactive styrene (*p*-methoxy) to antistereospecific for the least reactive one (3,5-$(CF_3)_2$).[26]

Conclusions

In summary, cinnamic acids are converted to β-lactones upon bromination, which are subsequently transformed to *cis*-β-bromostyrenes in a stereospecific manner. The β-lactone intermediates can be readily isolated and identified except when strong electron-donating groups are present on the aromatic ring. However, isolation and purification of the lactone intermediates is not necessary. The tandem substitutive bromination-decarboxylation sequence presented herein thus provides an efficient and stereospecific method for the conversion of cinnamic acids to *cis*-β-bromostyrenes.

Acknowledgments

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25. *Experimental details*: All reagents were obtained from commercial sources and used without further purification. Typical experimental procedures are described below using the syntheses of 4-bromo-*cis*-β-bromostyrenes (**3e**) as an example. Bromination of the nitrocinnamic acids (Entries **h** and **i**) took overnight to complete. To a mixture of 4-bromocinnamic acid (228 mg, 1 mmol) in 5 mL of methylene chloride in a round-bottom flask in an ice bath was added excess bromine dropwise until color remained dark orange. The reaction was allowed to react for 2 h. The solvent and excess bromine were evaporated to yield a white solid (**2e**) in quantitative yield, which was used without further purification.
To a solution of lactone **2e** in 5 mL of anhydrous THF in a round-bottom flask in an ice bath was added DBU (300 mg, 2 mmol). The reaction was allowed to warm up to room temperature overnight. The reaction mixture was partitioned between hexanes and water. The aqueous layer was extracted with hexanes two more times and the combined organic layer was dried with sodium sulfate to yield 4-bromo-*cis*-β-bromostyrenes (**3e**) as a clear liquid (241 mg, 92%).
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