Tetrahedron Letters 57 (2016) 4866–4868

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereospecific synthesis of *cis*-stilbenes from benzaldehydes and phenylacetic acids via sequential Perkin condensation and decarboxylation

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ARTICLE INFO

Article history:
Received 23 August 2016
Revised 16 September 2016
Accepted 19 September 2016
Available online 20 September 2016

Keywords:
cis-Stilbene
α-Arylcinnamic acid
Stereospecific
Decarboxylation
Perkin condensation

ABSTRACT

cis-Stilbenes were synthesized stereospecifically in high yields from the cuprous oxide-catalyzed decarboxylation of α-aryl-*trans*-cinnamic acids that were prepared from the Perkin condensation of benzaldehydes and phenylacetic acids.

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Introduction

Stilbene derivatives have many applications in industry as dyes, optical brighteners, phosphors, and scintillators.[1] Stilbene moieties are also common in natural products such as resveratrol and pterostilbene.[2,3] The *trans*- and *cis*-stilbenes are also used for the study of the transmission of substituent effects from one benzene ring to another through a double bond.[4–6]

The synthesis of stilbene has been extensively studied and discussed.[7] The common methods include the Wittig reaction and related reactions[8–10], the reduction of benzoins[11,12], the reaction of benzaldehydes with benzylmagnesium halides followed by dehydration[13], the Meerwein reaction of cinnamic acids with aromatic diazonium salt[14–17], and the decarboxylation of α-arylcinnamic acids from the Perkin condensation of benzaldehydes with phenylacetic acids.[18–20] These methods do not usually give exclusively one isomer.

The decarboxylation of α-arylcinnamic acids have recently been revisited as a method to prepare resveratrol derivatives.[21–23] In this Letter, we describe an improved method for the stereospecific synthesis of *cis*-stilbene derivatives.

Results and discussion

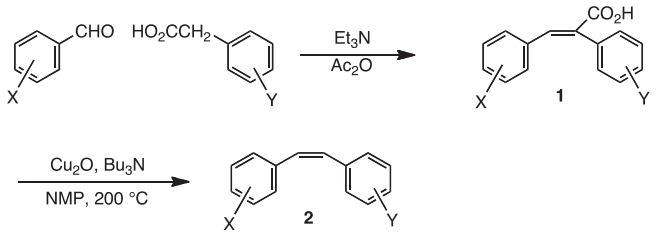
The Perkin condensation between benzaldehydes and phenylacetic acids to form α-arylcinnamic acids (Scheme 1) has been found to be moderate in yield and stereospecific in some cases[18,20] but not others.[21–23] In this work, the yields were improved by adding triethylamine slowly and by designing a simpler purification procedure.[24] The reaction was complete in about five hours, but overnight reaction did not seem to hurt the yield. A dilute HCl solution was added to the reaction mixture to precipitate the product α-arylcinnamic acids **1**. Upon filtration and drying in the same Buchner funnel, the solid was washed with a 9:1 mixture of hexanes and ethyl acetate to remove the trace amount of unreacted aldehydes. The solids thus isolated were found to be pure as judged by NMR spectroscopy. Only the α-aryl substituted *trans*-cinnamic acids **1** were produced. The stereochemistry of **1** was deduced from that of the product stilbene **2**.

The yields were generally excellent for various substituents as seen in Table 1. Benzaldehydes and phenylacetic acids with strong electronwithdrawing *p*-substituents such as cyano and nitro groups were not examined because they were reported to form stilbene product under Perkin condensation conditions.[7,17] The 3-cyano derivatives were used in many cases due to our interest in the property of the stilbene-3-carboxylic acids in connection with another project.

The reported decarboxylation of α-arylcinnamic acids **1** to stilbenes **2** was usually carried out in quinoline using copper or

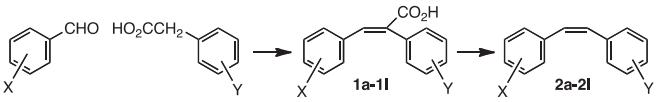
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http://dx.doi.org/10.1016/j.tetlet.2016.09.069
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Scheme 1.

Table 1
Synthesis of *cis*-stilbenes **2** from benzaldehydes and phenylacetic acids through *E*-2-arylcinnamic acids **1**



Entries	X=	Y=	Yield (**1**, isolated, %)	Yield (**2**, isolated, %)
a	4-Chloro	H	80	59
b	4-Chloro	4-Methoxy	92	82
c	3-Cyano	H	100	85
d	3-Cyano	4-Fluro	99	85
e	3-Cyano	4-Chloro	86	66
f	3-Cyano	4-Bromo	99	76
g	3-Cyano	4-Iodo	86	87
h	3-Cyano	4-Methoxy	93	95
i	2-Cyano	4-Bromo	99	65
j	3-Methoxy	4-Methoxy	80	69
k	3-Methoxy	4-Bromo	99	55
l	3,5-Dimethoxy	4-Methoxy	94	76

copper chromite catalysts at high temperatures (~260 °C).[7,19,22] At these temperatures, the decarboxylation product could be transformed into the more stable *trans*-isomer. Thus, the formation of a mixture of *cis*- and *trans*-stilbenes had been observed.[7,22]

A somewhat milder condition for the decarboxylation would preserve the *cis*-configuration. It has been reported that cuprous oxide is an efficient catalyst for the decarboxylation of benzoic acids.[25] Different amines were thus tested as base with cuprous oxide as catalyst for the efficient decarboxylation of α-arylcinnamic acids. Tributylamine turned out to be the best since it has a boiling point of slightly higher than the reaction temperature and is easily removed by washing with dilute acid. *N*-Methyl-2-pyrrolidone (NMP) was found to be an excellent solvent for the reaction.

The reaction condition was thus applied to various α-arylcinnamic acids. Good to excellent yields were obtained regardless of the properties of the substituents as seen in Table 1. The stereochemistry of the stilbenes was established by the chemical shifts and the characteristic vicinal ^{1}H–^{1}H-coupling constants of the stilbene double bond protons. The two protons of the *cis*-isomers have lower chemical shifts and smaller coupling constants (about 12 Hz) than the *trans*-isomers. All isolated stilbenes were found to be *cis*-isomers and were judged to be pure by thin-layer chromatography (TLC) and NMR. The *cis*-stilbene products can be conveniently converted to the *trans*-isomer if desired.[7,22] The described method can be useful in the synthesis of derivatives of resveratrol, as evident from the synthesis of resveratrol precursor **2l**. It should also be pointed out that this synthetic method is flexible in terms of substitution patterns of benzaldehydes and phenylacetic acids starting material. In *cis*-stilbene products, substituents X and Y may stem from either benzaldehydes or phenylacetic acids, depending on the availability of these starting materials.

Conclusion

In summary, *cis*-stilbenes were synthesized stereospecifically from the decarboxylation of α-aryl-*trans*-cinnamic acids, which was formed from the Perkin condensation of benzaldehydes and phenylacetic acids. The synthetic method allows the mix-and-match of different substituents on the two phenyl groups. Overall, the two-step sequence represents a convenient, stereospecific, flexible and high-yielding method for the synthesis of symmetrically and especially unsymmetrically substituted *cis*-stilbenes.

Acknowledgments

This investigation was supported by the San Francisco State University Office of Research and Sponsored Programs (W.W.) and the Department of Chemistry and Biochemistry Summer Research Fellowship (C.M.T.). The NMR facility was funded by the National Science Foundation, United States (DUE-9451624 and DBI 0521342). We also thank Professor Ihsan Erden for helpful discussions and ACS Project SEED student Junyi Liu for technical assistance.

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24. *Experimental details*: All reagents were obtained from commercial sources and used without further purification. Typical experimental procedures are described below using the syntheses of α-phenyl-3-cyano-*trans*-cinnamic acid (**1c**) and 3-cyano-*cis*-stilbene (**2c**) as examples. In some cases, the crude cinnamic acids appeared as oil and liquid–liquid extraction was necessary to separate the product. Upon removal of solvent, the crude product was washed with 9:1 hexane/ethyl acetate solution to yield the products as solids.
α-Phenyl-3-cyano-trans-cinnamic acid (**1c**): Phenylacetic acid (274 mg, 2 mmol) and 3-cyanobenzaldehyde (264 mg, 2 mmol) were mixed with acetic anhydride (300 mg, 3 mmol) in a round-bottom flask. The mixture was heated at 65 °C for 15 min before triethylamine (400 mg, 4 mmol) was added dropwise. The reaction mixture was heated overnight at 65 °C. Upon cooling to room temperature, the reaction mixture was poured into a dilute aqueous HCl solution. The solid precipitated was suction-filtered and washed with water, suction-dried on the Buchner funnel under vacuum for 1 h, and washed with a hexane/ethyl acetate solution (9:1) to remove trace starting materials. An off-white solid (501 mg, 100%) was obtained and was found to be pure by NMR.

3-Cyano-cis-stilbene (**2c**): The acid **1c** (495 mg, 2 mmol) was mixed with cuprous oxide (15 mg, 5 mol%), tributylamine (185 mg, 1 mmol) in 3 mL of *N*-methyl-2-pyrrolidone (NMP). The reaction mixture was heated at 200 °C for 90 min. Upon cooling to room temperature, the reaction was partitioned between a dilute HCl solution in brine and ethyl acetate. The organic layer was washed with water three times, dried over anhydrous sodium sulfate, and concentrated to give a crude product. The product was further purified by column chromatography to give the product as a clear oil (346 mg, 85%).

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