

The benzoin condensation: Charge tagging of the catalyst allows for tracking by mass spectrometry



Hao Zeng, Kai Wang, Yuan Tian, Yijie Niu, Landon Greene, Zhichao Hu, Jeehiun K. Lee *

Department of Chemistry and Chemical Biology Rutgers, The State University of New Jersey, New Brunswick, NJ 08901, United States

ARTICLE INFO

Article history:

Received 29 May 2014

Received in revised form 5 June 2014

Accepted 10 June 2014

Available online 12 June 2014

Dedicated to Professor Veronica M. Bierbaum.

Keywords:

Benzoin condensation

Charge tag

N-heterocyclic carbene

Thiazolylidene

Organic reactivity

ESI–MS/MS

ABSTRACT

A novel thiazolium with a sulfonate charge tag was synthesized to test the feasibility of tracking the progress of a thiazolylidene-catalyzed benzoin condensation reaction using electrospray ionization–mass spectrometry (ESI–MS). Intermediates in the benzoin condensation were “fished” out of a reaction mixture and detected using MS. Tandem MS and calculations were used to support structural assignments. The results are consistent with the Breslow mechanism. These data show the viability of synthesizing negatively charged compounds that will both catalyze and track reactions involving *N*-heterocyclic carbene organocatalysis, which are becoming increasingly prevalent in organic synthesis.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Electrospray ionization (ESI) is now a well-established method for the transfer of ions from solution to the gas phase [1–3]. Coupled with mass spectrometry (MS), ESI opens the door to tracking the progress of organic reactions that involve nonvolatile intermediates [4–6].

To use ESI–MS to track the progress of a reaction, the relevant species must be charged. This is often achieved by tracking reactions that either already involve charged species, or have intermediates that are in equilibrium with their respective protonated forms [4–9]. If relevant species are not charged, then a charge tag can be used [10,11]. For example, Vikse et al. used a negative charge tag on a palladium phosphine ligand to follow a palladium-catalyzed Sonogashira reaction by MS [9].

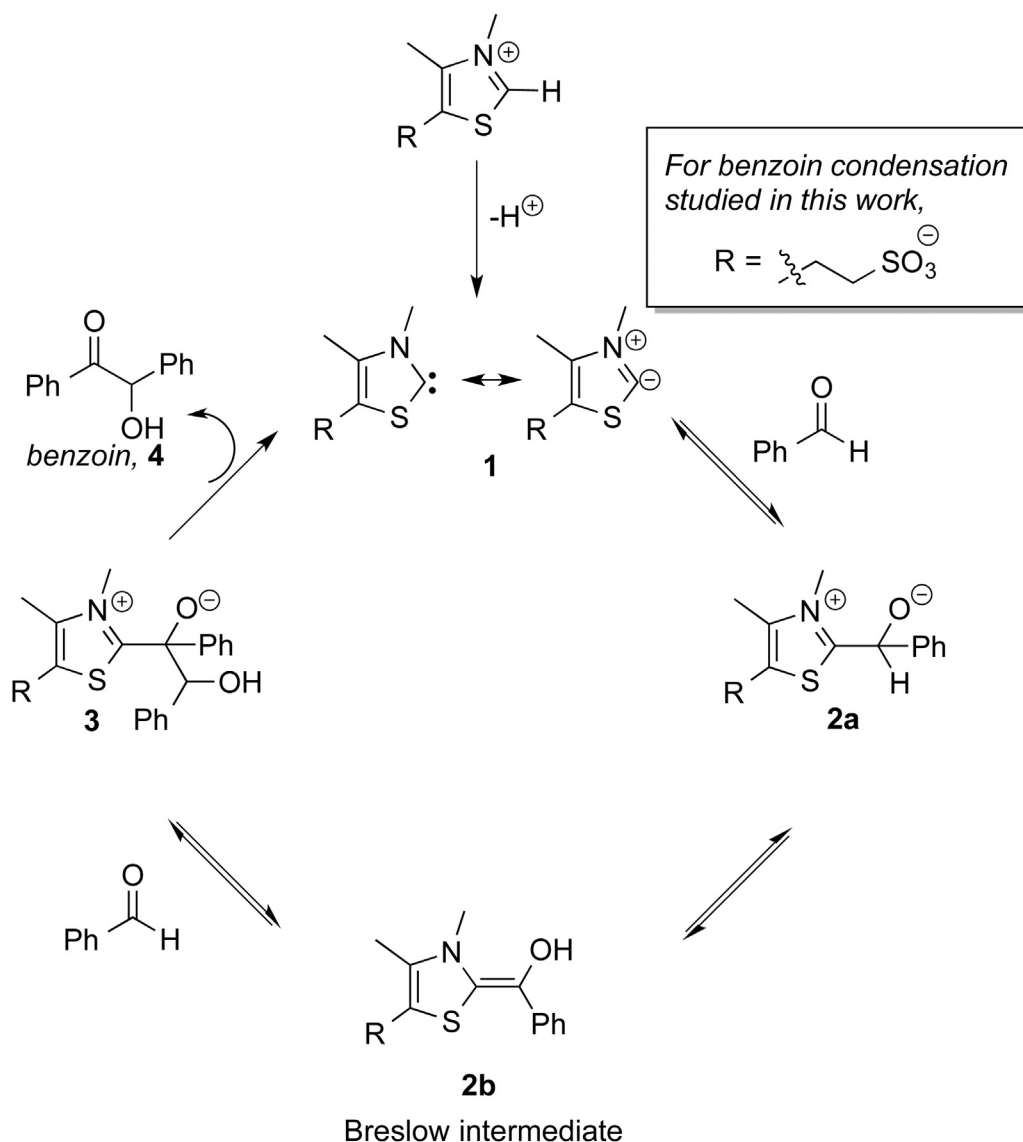
A particularly intriguing class of reactions in organic synthesis is the *umpolung*, which involves the reversal of the polarity of a functional group [12]. A classic example is the benzoin condensation, first reported by Wöhler and Liebig in 1832 with a proposed mechanism in 1903 by Lapworth; cyanide is used as a catalyst to effect the dimerization of two benzaldehyde units [13]. In 1943, Ukai et al. discovered the ability of thiazolium salts to catalyze the

condensation. Fifteen years later, Breslow proposed the deprotonated thiazolium – the thiazolylidene (which can also be thought of as a thiazolium zwitterion) – as the catalytic species [14–17]. His proposed mechanism (Scheme 1) involves deprotonation of the thiazolium to yield thiazolylidene/thiazolium zwitterion, which attacks a benzaldehyde, followed by a proton transfer to form the so-called Breslow intermediate, which can then display the *umpolung* reactivity (the aldehyde becomes nucleophilic rather than electrophilic, adding to a second aldehyde). This reaction, as well as its related counterpart, the Stetter (addition to an enone), has seen a renaissance in the last decade, with chiral versions catalyzed by a variety of *N*-heterocyclic carbenes (thiazolylidenes, imidazolylidenes, and triazolylidenes) [18–25].

The Breslow mechanism is commonly accepted, with many attempts to isolate the Breslow intermediate, which had proven to be elusive until 2012, when both an analogue and the intermediate itself were observed and characterized spectroscopically [26–28]. Mechanisms involving a thiazolylidene dimer (first proposed by Lemal) have also been proposed; data both in support of and against such mechanisms exist [29–41].

Because of the ever-growing prevalence and synthetic utility of reactions catalyzed by ylidenes, we sought to explore the potential of using ESI–MS to track such reactions, focusing on the classic benzoin condensation. Because the intermediates are not charged, the reaction is potentially difficult to track using mass spectrometry. An imidazolylidene-catalyzed conjugate *umpolung* reaction to form a

* Corresponding author. Tel.: +1 8484456562; fax: +1 8484455312.
E-mail address: jee.lee@rutgers.edu (J.K. Lee).



Scheme 1. Breslow mechanism for the benzoin condensation.

lactone was successfully studied using ESI-MS by Glorius and co-workers in 2007, who relied on the protonation of the intermediates in the electrospray process, enabling the use of positive ion mass spectrometry for detection [4]. To explore the possibility of charging the catalyst itself in order to track all steps involving the catalyst in the benzoin condensation, we successfully synthesized a thiazolium with a sulfonate charge tag. The synthesized compound was used to catalyze the benzoin condensation, and intermediates were detected using negative ion ESI-MS. Calculations and MS/MS were also used to aid in interpretation of results.

2. Material and methods

2.1. Synthesis details

A mixture of 1,5-dimethyl-4-(hydroxyethyl) thiazolium iodide (2.5 mmol, 700 mg), methylsulfonyl chloride (3 mmol, 0.25 ml) and triethylamine (5 mmol, 0.35 ml) in CH_3CN (20 ml) was stirred at 0°C for 2 h, under argon. After rotary evaporation, the crude product was dissolved in ethanol (25 ml). Potassium thioacetate (3 mmol, 343 mg) was added dropwise and the

mixture was allowed to reflux for 72 h. The product mixture was rotary evaporated to dryness, then the resultant crude solid was dissolved in formic acid (5 ml). Performic acid was generated by stirring hydrogen peroxide (14 mmol, 1.8 ml) and formic acid (30 mmol, 1.4 ml) at room temperature for 1 h. The performic acid solution was cooled to 0°C and added to the reaction mixture. The mixture was left stirring for 48 h. Excess solvent was removed by rotary evaporation and the final crude product was purified by HPLC. ^1H NMR (300 MHz, DMSO-d_6) δ 9.90 (s, H), 4.05 (s, 3 H), 3.14–3.19 (t, $J=7.1$ Hz, 2 H), 2.70–2.75 (t, $J=7.0$ Hz, 2 H), 2.41 (s, 3 H).

2.2. Benzoin condensation reaction conditions

The synthesized thiazolium was dissolved in methanol to make a 0.1 M solution. Argon was bubbled in for 5 min to expel oxygen. Ten equivalents of benzaldehyde and 2.5 equivalents of triethylamine were added to the reaction solution. The reaction was stirred at room temperature and tracked over time. To track the reaction by mass spectrometry, an aliquot from the reaction mixture was diluted to make a 100 μM (in thiazolium) solution, which was then injected into the ESI source.

Download English Version:

<https://daneshyari.com/en/article/1193103>

Download Persian Version:

<https://daneshyari.com/article/1193103>

[Daneshyari.com](https://daneshyari.com)