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Reprint of "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

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Dedicated to Professor Veronica M. Bierbaum.

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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.

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].

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

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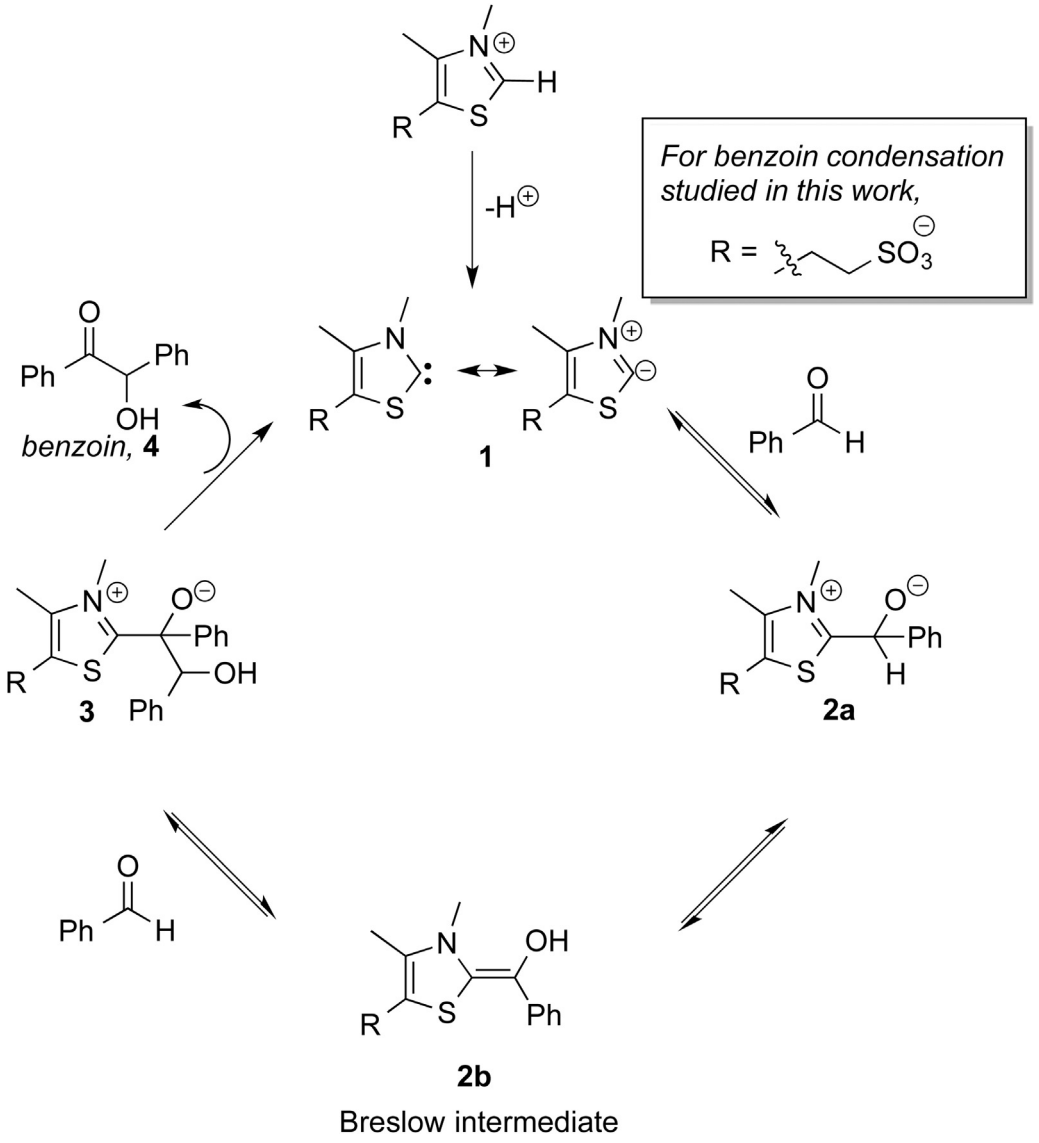


Scheme 1. Breslow mechanism for the benzoin condensation.

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 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.

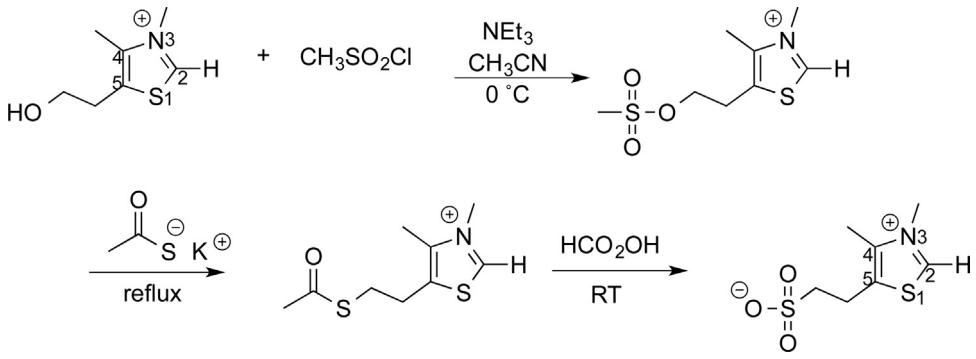
2. Material and methods

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. ^{1}H 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



Scheme 2. Synthesis of charge tagged thiazolium.

diluted to make a 100 uM (in thiazolium) solution, which was then injected into the ESI source.

An electrospray needle voltage of ~4 kV and flow rate of 25 μl/min was used to volatilize the reaction mixture. Full scan spectra are an average of forty scans. For MS/MS, the ions were isolated and activated for 30 ms, at varying (5–30%) collision energies. Fragmentations at 25% (isolation width of 2) are reported herein. Ten scans were averaged for the product ions.

2.3. Calculational method

Calculations were conducted at B3LYP/6-31+G(d) using Gaussian09; the geometries were fully optimized and frequencies were calculated [42–46]. All the values reported are at 298 K. No scaling factor was applied. For the solvation calculations, the integral equation formalism variant of the polarizable continuum model, using radii and non-electrostatic terms for Truhlar and coworkers SMD solvation model, was utilized [47–49].

3. Results and discussion

3.1. Charge-tagged catalyst

The intermediates in the benzoin condensation are uncharged; in order to track the benzoin condensation by ESI–MS, we synthesized a thiazolium with a sulfonate tag (Scheme 2). This molecule has not heretofore been synthesized. A commercially available thiazolium with a hydroxyl side chain was allowed to react with methanesulfonyl chloride to yield the sulfonic ester. Reaction with potassium thioacetate yields the thioester. The final step is oxidation by performic acid to yield the sulfonate-tagged thiazolium product.

3.2. Benzoin condensation reaction and MS

The charge-tagged thiazolium was allowed to react with benzaldehyde in the presence of triethylamine (to ensure that both the sulfonic acid moiety and C2 are deprotonated, to yield catalyst 1, Scheme 1). The mass spectrum of the reaction after 5 min of reaction time is shown in Fig. 1. The *m*/*z* signals corresponding to the catalyst (1, *m*/*z* 220), the intermediate resulting from addition of one benzaldehyde (2, *m*/*z* 326), and thiazolylidene-thiazolium dimer (5, *m*/*z* 441) are observed. We also see *m*/*z* 121, which is deprotonated benzoic acid, resulting from the facile air oxidation of the benzaldehyde reactant. As the reaction proceeds, oxidation products (benzoate at *m*/*z* 121, as well as oxidized catalyst (*m*/*z* 236)) become increasingly prevalent. No appreciable signal for the second intermediate (3, Scheme 1, *m*/*z* 432) nor the deprotonated product (deprotonated 4, *m*/*z* 211) is observed.

In order to lend support to our structural assignments, we also conducted MS/MS experiments. We presume *m*/*z* 220 is the catalyst 1, although a doubly charged dimerized structure could also

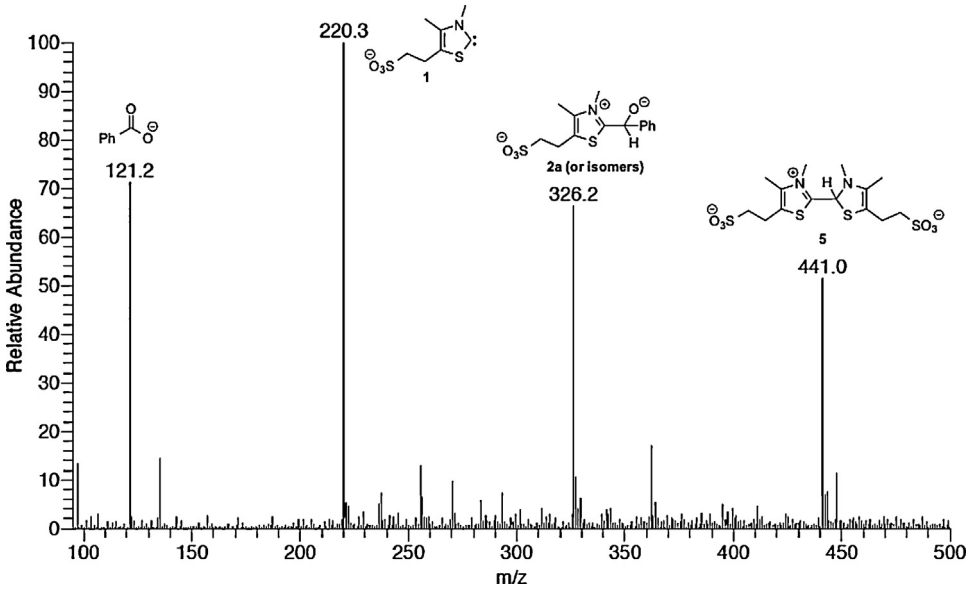


Fig. 1. Mass spectrum of reaction mixture after 5 min.

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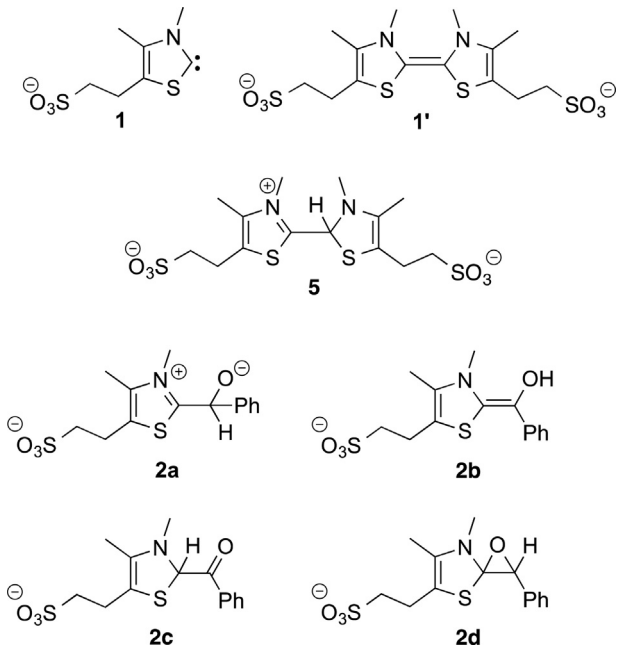


Fig. 2. Possible structures for observed *m*/*z* signals.

be possible (1' or a noncovalent analog, Fig. 2). MS/MS of *m*/*z* 220 yields only *m*/*z* 81, corresponding to HSO_3^- (Fig. 3). If *m*/*z* 220 were a dimer, loss of HSO_3^- would leave behind an ion of *m*/*z* 359, which we do not observe. Also, exposing *m*/*z* 220 to increasingly higher collision energies results in the decrease and eventual disappearance of *m*/*z* 220; a dimer might be expected to break apart to produce *m*/*z* 220 as a daughter ion. For these reasons we attribute *m*/*z* 220 to the catalyst 1. The ion at *m*/*z* 441 is presumably the overall singly charged thiazolylidene-thiazolium dimer 5 (Fig. 2, or a noncovalent equivalent). MS/MS yields *m*/*z* 220, which corresponds to loss of thiazolium.

The signal at *m*/*z* 326 corresponds to the first intermediate formed upon addition of the thiazolylidene catalyst to benzaldehyde (2a, Scheme 1, Fig. 2). The subsequent step of the Breslow mechanism is the formation of the Breslow intermediate 2b, which also has a *m*/*z* ratio of 326. Other possible structures include the ketone 2c and the epoxide 2d (Fig. 2) [28,30,41,50–54]. MS/MS of *m*/*z* 326 yields *m*/*z* 311 (loss of $CH_3^\bullet$) and *m*/*z* 220 (catalyst 1) as the two strongest signals, with the *m*/*z* 311 signal being more than twice that of *m*/*z* 220. While these fragments do not aid in the differentiation of the possible structures for *m*/*z* 326, we did conduct calculations to lend further insight. Our calculations indicate that of the four possible structures for 2 (*m*/*z* 326), the ketone 2c is the most stable, by 7 kcal/mol over the Breslow intermediate 2b, 14 kcal/mol over the initial intermediate 2a and 19 kcal/mol over the epoxide 2d (Fig. 4). The calculated high stability of 2c is consistent with the isolation of a ketone structure in benzoin condensation studies by Berkessel and co-workers in 2010 [28,50,53,54].

3.3. Mechanistic comments

Previous mechanistic studies indicate that addition of the first benzaldehyde, formation of the Breslow intermediate, and addition of the second benzaldehyde are all "partially rate determining" [55]. By mass spectrometry, we see the deprotonated thiazolium (catalyst 1) at *m*/*z* 220 and the ion corresponding to the Breslow intermediate at *m*/*z* 326. Calculations indicate that 2c is the most stable structure for *m*/*z* 326 (Fig. 4); however, we cannot discount the presence of the catalytically active Breslow intermediate 2b. It probably is present, though not isolable nor detectable by mass spectrometry [4,27,28]. The lack of *m*/*z* 432 (after addition of the second benzaldehyde, 3 in Scheme 1) may be because once formed, the release of the final stable benzoin product (4) provides a driving force for the reaction such that intermediate 3 is relatively short-lived. The lack of *m*/*z* 211 (deprotonated benzoin, 4) is not too surprising as ketones have pK_a values of 19–20 and triethylamine is not a strong enough base to significantly deprotonate the benzoin product.

Also interesting to consider is how the sulfonate charge tag might affect the catalytic activity of 1. We calculated the proton affinity of the thiazolylidene 1 and its neutral counterpart (1H). In the gas phase, the negatively charged sulfonate group renders 1 71 kcal/mol more basic than 1H at the reactive carbene center. However, this difference essentially disappears when solvation is considered (calculations in a water dielectric). In fact, in water, 1H is calculated to be more basic than 1, though not by much (3 kcal/mol). Therefore, in water, our negatively charge-tagged catalyst is probably not different enough in basicity as compared to more commonly used neutral counterparts to significantly affect catalytic ability.

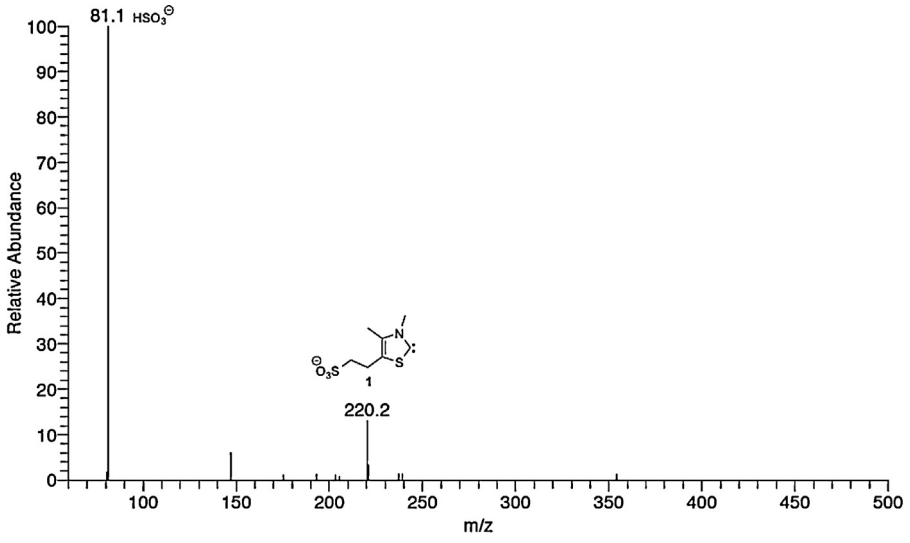


Fig. 3. MS/MS spectrum of *m*/*z* 220.

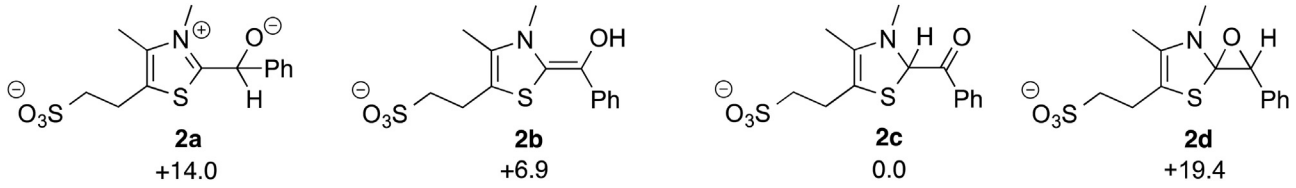
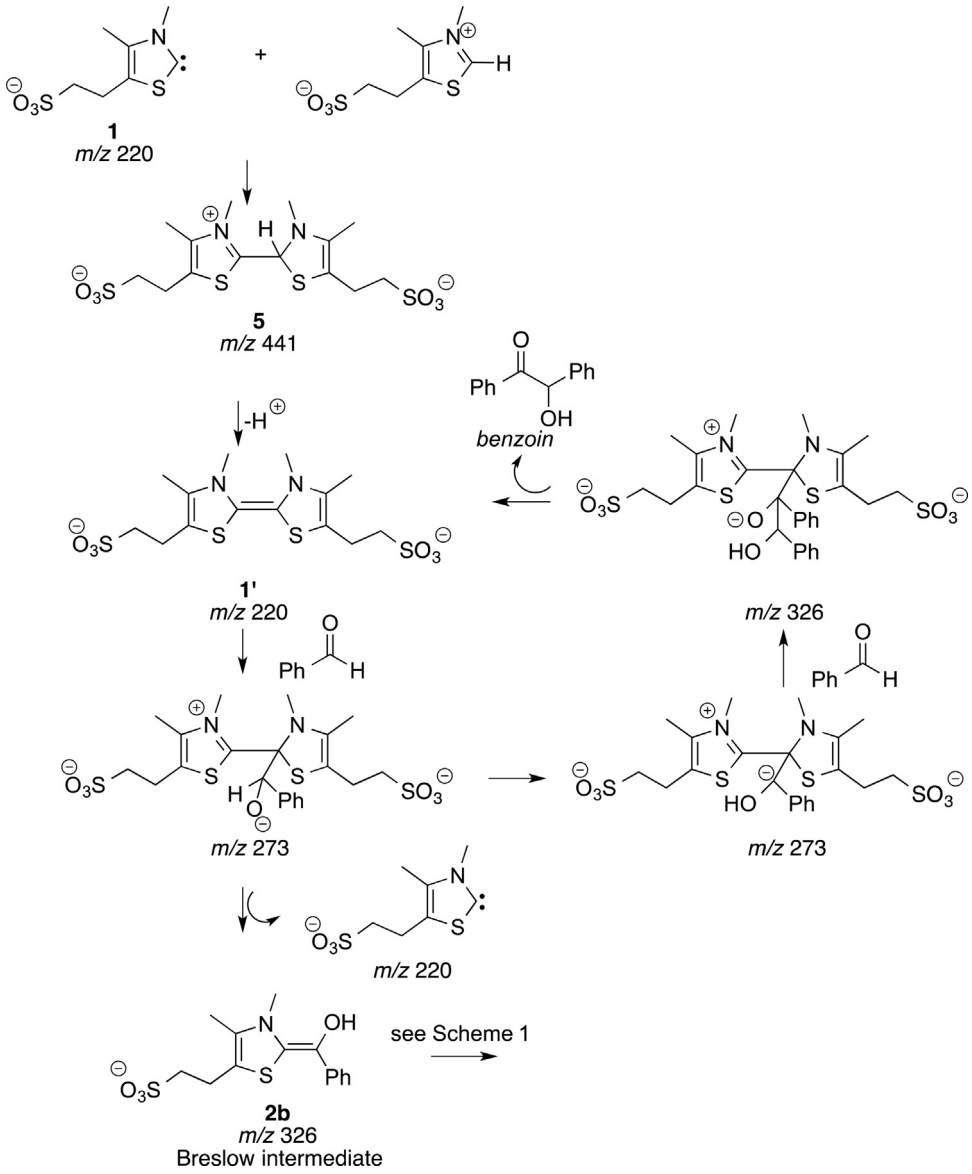
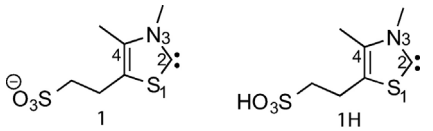


Fig. 4. Relative stabilities for the possible structures for 2, *m*/*z* 326 (ΔH at 298 K, B3LYP/6-31+G(d).



Scheme 3. Dimer mechanism for benzoin condensation.



Last, we consider the "dimer mechanism," which over the years has been invoked as a possible alternate to the Breslow mechanism (Scheme 3) [29–41]. Several ions have the same *m*/*z* ratios (220, 326) as other ions in the Breslow mechanism. We do see *m*/*z* 441 (5), but it may not be catalytically active. The unique identifying ion, resulting from the addition of one benzaldehyde to the dimer, is *m*/*z* 273. We do not see this ion under our conditions.[56] While the lack of *m*/*z* 273 cannot be used as definitive proof against the dimer mechanism (since it may be short-lived), it certainly implies that this may not be an operative path under our conditions.

[56] A reviewer raised the concern that if we do not see *m*/*z* 211 (deprotonated benzoin), how would we expect to see m/z 273, as both are relatively basic ions. However, benzoin is a neutral product that has to be deprotonated for detection, whereas *m*/*z* 273 is generated via reaction as an already-charged species.

4. Conclusions

A new negatively charge-tagged catalyst has been synthesized and used to probe the benzoin condensation for the first time. The tag allows intermediates to be "fished out" of the reaction mixture. The results indicate that under these conditions, the Breslow mechanism is likely, but not a dimer mechanism. We detect the presence of an ion consistent with the Breslow intermediate. Calculations indicate that the detected intermediate may be the tautomerized structure 2c. No ions corresponding to the dimer mechanism are observed. These results show the viability of synthesizing negatively charged catalysts to track reactions involving *N*-heterocyclic carbene organocatalysis, which are becoming increasingly prevalent in organic synthesis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijms.2014.06.008.

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