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Isolable Analogues of the Breslow Intermediate Derived from Chiral Triazolylidene Carbenes

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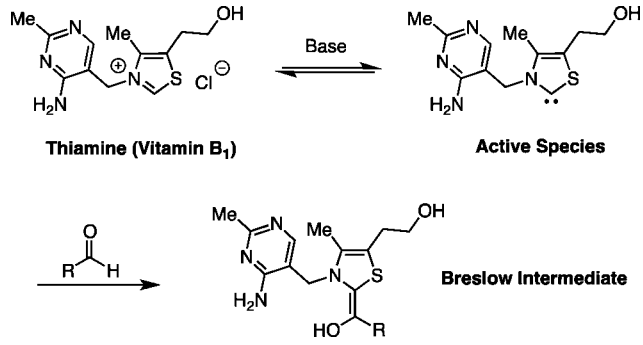
Supporting Information

ABSTRACT: Since Breslow's initial report on the thiamine mode of action, the study of catalytic acyl carbanion processes has been an area of immense interest. With the advent of azolylidene catalysis, a plethora of reactivtiy has been harnessed, but the crucial nucleophilic intermediate proposed by Breslow had never been isolated or fully characterized. Herein, we report the isolation and full characterization of nitrogen analogues of the Breslow intermediate. Both stable and catalytically relevant, these species provide a model system for the study of acyl carbanion and homoenolate processes catalyzed by triazolylidene carbenes.

Nature has long been a source of inspiration for the development of chemical synthesis. The understanding of biological processes has, in many cases, led to the direct realization of modern chemical reactions. One captivating example pertains to the mode of action of thiamine pyrophosphate, a coenzyme in a variety of biological processes responsible for vital functions in life.[1] Thiamine is thus an essential vitamin in humans and deficiency is associated with diseases such as beriberi and Wernicke-Korsakoff syndrome.[2] The common thread in these processes is the formation of an acyl-carbanion equivalent, which is responsible for thiamine's unique mode of action. In 1958, Breslow disclosed his work pertaining to the thiamine mode of action, in which he showed the thiazolium moiety to be responsible for its unique activity, not the amino group which had been proposed previously.[3] On the basis of his mechanistic studies, Breslow described that the thiazolium moiety could be deprotonated under relatively mild conditions, forming an ylide or carbene. Reaction of this active species with a pyruvic acid unit in biological systems, or an aldehyde, would then lead to a nucleophilic enaminol as the relevant carbanion equivalent, similar to Lapworth's originally proposed mechanism of the cyanide catalyzed benzoin reaction (Scheme 1).[4] Unfortunately, Breslow was not able to isolate this proposed intermediate.

With a renaissance in azolylidene catalysis of organic reactions in recent years, much effort has been expended searching for this intermediate, and until recently, no structural information had been disclosed.[5] Berkessel, Teles, and co-workers have reported an investigation of the Breslow intermediate derived from a triazolylidene carbene,[6] but after extensive investigation, only the keto-form could be identified spectroscopically. Most recently, Jacobi von Wangelin and co-workers have shown that more nucleophilic imidazolylidene

Scheme 1. Breslow's Proposed Thiamine Mode of Action



carbenes can be alkylated with alkyl bromides, leading to the formation of ene-diamines.[7] While these reports have provided enormous insight, they have neither confirmed nor debunked the existence of the species in question due to their lack of catalytic relevance in acyl-carbanion processes. Importantly, these intermediates are formed irreversibly and do not lead to catalyst release, and thus, one questions their relevance to catalysis in either a biological or a chemical setting.

Triazolylidene carbenes have proven to be workhorses for asymmetric *N*-heterocyclic carbene (NHC) catalyzed transformations, potentially due to their similarities to thiazolylidene carbenes.[8] We were interested in identifying isolable intermediates derived from our family of chiral triazolylidene carbenes to more closely study both their formation and fundamental reactivity. Because of the proven difficulty in isolating aldehyde-derived Breslow intermediates, we hypothesized that the enol moiety may be responsible for the inherent transient nature of this species. We envisioned that if the enol were replaced with a more chemically inert but electronically similar group,[9] a relevant longer-lived intermediate may result. To that end, we identified iminium ion electrophiles, which should react analogously to aldehydes producing a Breslow intermediate with similar reactivity but lacking the acidic X−H bond (Scheme 2).[10] As a further design element, we realized that the crystallinity of these intermediates would be crucial and structures that could limit degrees of freedom may increase the chance for isolation.

With this in mind, we reacted highly crystalline NHC precatalyst **1** with iminium salt **2** in the presence of Hünig's base (Figure 1). After resting undisturbed for 12 h, a yellow material crystallized from the reaction mixture. Analysis by X-

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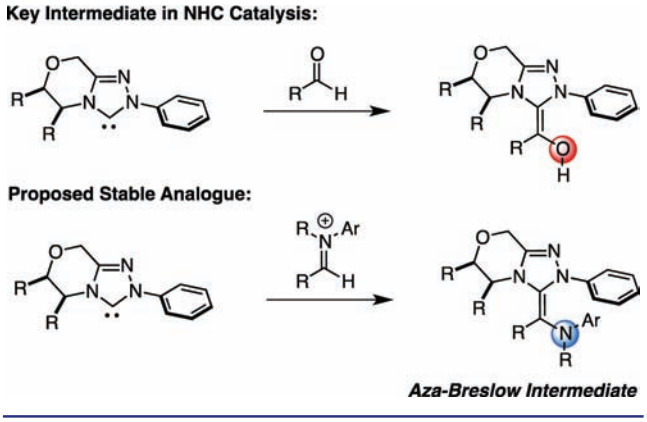
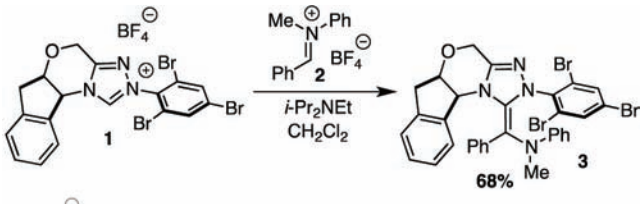
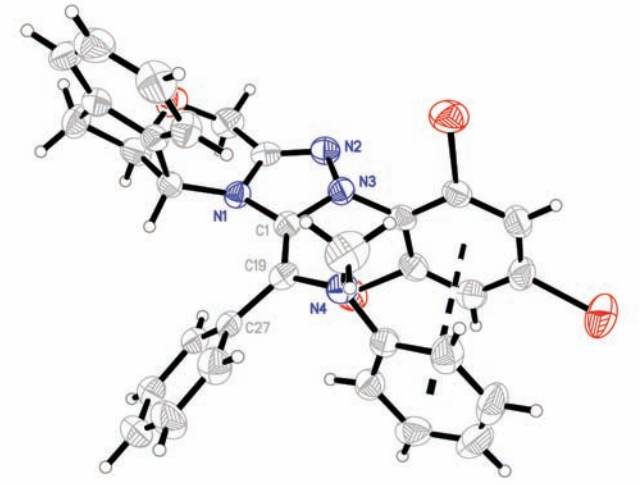
Scheme 2. Intermediates in NHC Catalysis





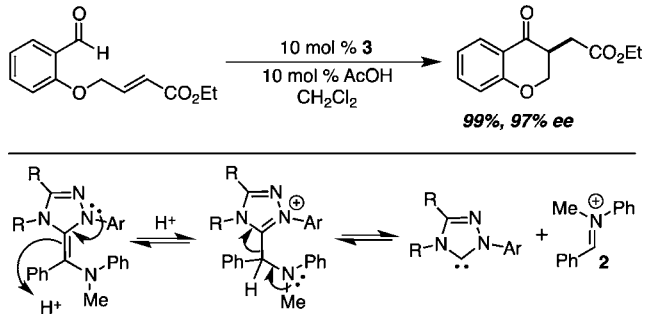


Bond	Length (Å)	Bond	Length (Å)
C1-C19	1.360	N3-C1	1.394
C19-N4	1.427	C19-C27	1.471
N1-C1	1.412	Ar-Ar	3.535

Figure 1. Synthesis and X-ray structure of an aza-Breslow intermediate. Ellipsoids are shown at the 50% probability level.

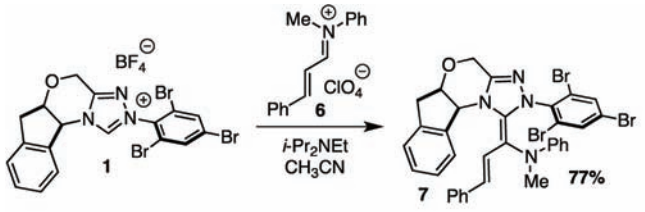
ray crystallography identified the species to be a nitrogen analogue of the Breslow intermediate. We were excited that **3** was isolable, but we questioned whether this compound was catalytically relevant. It seemed reasonable that protonation of the nucleophilic olefin would allow for regeneration of active catalyst while reforming the iminium salt (Scheme 3). Addition of excess HBF_4 to intermediate **3** leads to complete conversion to triazolium salt **1** and iminium salt **2** by ^1H NMR. With the assumption that this could be a reversible process with weak acid, we subjected the Breslow intermediate to the well-studied intramolecular Stetter reaction in the presence of a catalytic amount of AcOH. After 48 h, complete conversion to ketone **5** was achieved, in excellent enantioselectivity (Scheme 3).[11] This

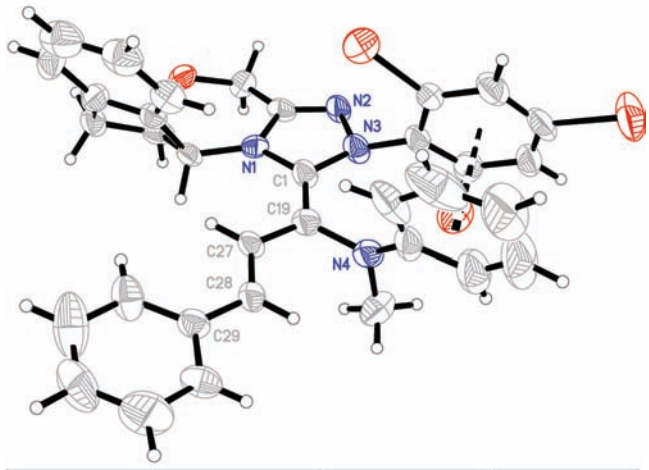
Scheme 3. Catalytic Activity of Aza-Breslow Intermediate 3



result confirms the relevance of this type of structure as a precatalyst for NHC catalyzed reactions.[12]

While Breslow analogue **3** is a good model system for acyl anion reactivity, we were also interested in probing the homoenolate reactivity commonly displayed with chiral triazolylidene carbenes.[13,14] Subjection of triazolium salt **1** to cinnamaldehyde derived iminium salt **6** leads to the generation of another yellow crystalline solid. X-ray analysis confirmed the identity of this species to be homoenolate equivalent **7** (Figure 2). To demonstrate the extended nucleophilicity of this intermediate, it was subjected to a weak D^+ source (AcOD). By ^1H NMR, complete deuterium incorporation is observed at the γ-position.[15]





Bond	Length (Å)	Bond	Length (Å)
C1-C19	1.367	C19-N4	1.449
C19-C27	1.441	N3-C1	1.406
C27-C28	1.355	N1-C1	1.406
C28-C29	1.458	Ar-Ar	3.558

Figure 2. Synthesis and X-ray structure of a homoenolate equivalent. Ellipsoids are shown at the 50% probability level.

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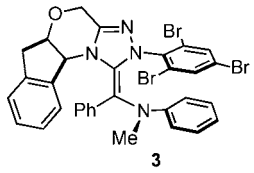
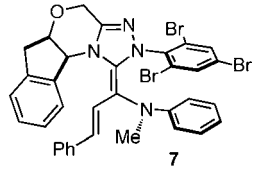
DFT studies have suggested the E-olefin geometry to be favored in aldehyde-derived systems.[16,17] Solid-state analysis of both isolated aza-Breslow intermediates indicates a preferred Z-olefin geometry as seen in the X-ray structures. This contradiction may arise from stabilizing interactions exhibited by the electron rich/electron deficient aryl substituents present in these analogues. Since the geometry of this nucleophilic olefin likely plays a significant role in determining the stereochemical outcome of NHC catalyzed processes, we were interested in probing these intermediates in solution. ^{1}H NMR analysis of **3** reveals at least four distinct species present, which we attribute to both the C1−C19 olefin isomers as well as rotamers around the C19−N4 bond. At room temperature, a ∼1:1 ratio of two major isomers is present which does not change significantly at elevated temperatures. EXSY NMR experiments at room temperature do not show appreciable exchange on the NMR time scale, but at 100 °C interconversion is observed. In the absence of a catalyst, interconversion provides evidence of rotation around the formal C1−C19 double bond, speaking to its nucleophilicity and partial single bond character.[18] NMR studies of homoenolate equivalent **7** show similar characteristics.

To gain further insight into the nature of these intermediates, oxidation potentials were measured by cyclic voltammetry. Intermediate **3** undergoes a highly reversible oxidation at +0.17 eV (vs SSCE in CH_2Cl_2), while **7** is oxidized irreversibly at +0.49 eV (vs SSCE in CH_2Cl_2) (Figure 3). The irreversible



3

E^{o}_{ox} = + 0.17 eV vs SSCE
λ= 238, 346 nm
$[\alpha]_D^{23}$= +242



7

E^{o}_{ox} = + 0.49 eV vs SSCE
λ= 409, 230 nm
$[\alpha]_D^{23}$= +754

Figure 3. Physical data for aza-Breslow intermediates.

oxidation of **7** is most likely due to dimerization or other degradation pathways.[19] Given the numerous examples of oxidative NHC catalyzed transformations, direct information about the oxidation potential of the Breslow intermediate is useful in the judicious choice of oxidants.[20]

In summary, we have identified stable isolable Breslow intermediate analogues derived from the reaction of chiral triazolylidene carbenes and iminium salts. These structures are arguably the most relevant model systems for studying both asymmetric acyl anion reactivity, as well as homoenolate reactivity. In solution, both olefin geometries are observed which can interconvert by two pathways. In the presence of an acid catalyst, dissociation and recombination of the carbene iminium ion pair is rapid. We have also provided evidence of interconversion by bond rotation at elevated temperatures. These compounds not only serve as stable resting states in NHC catalyzed reactions, but also hold promise for the rational design of new catalytic reactions. The isolation and analysis of these reactive species provides the most direct evidence for the role of Breslow intermediates in carbene catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, crystallographic data, and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Nilsson, U.; Meshalkina, L.; Lindqvist, Y.; Schneider, G. *J. Biol. Chem.* **1997**, *272*, 1864.
(2) Combs, G. F. Jr. *The vitamins: Fundamental Aspects in Nutrition and Health*, 3rd ed.; Elsevier Academic Press: Ithaca, NY, 2008.
(3) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
(4) Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.
(5) For early studies on thiamine related intermediates see: Jordan, F.; Kudzin, Z. H.; Rios, C. B. *J. Am. Chem. Soc.* **1987**, *109*, 4415.
(6) Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7120.
(7) Knappke, C. E. I.; Neudörfl, J. M.; Jacobi von Wangelin, A. *Org. Biomol. Chem.* **2010**, *8*, 1695.
(8) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *290*, 77.
(9) The electronic character of the OH should be analogous to a NPh group. Witness the respective pK_a's of H_2O (31.2) and $PhNH_2$ (30.6) in DMSO; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(10) For an example of the intramolecular reaction of imidazolylidene carbenes with imines see: Simonovic, S.; Frison, J.-C.; Koyuncu, H.; Whitwood, A. C.; Douthwaite, R. E. *Org. Lett.* **2009**, *11*, 245.
(11) As a point of comparison, the same reaction catalyzed by **1** with Hünig's base provides product in 98% yield, 98% ee while the use of the free carbene derived from **1** delivers product in 96% yield, 96% ee.
(12) Teles has demonstrated that a protonated derivative of the Breslow intermediate is also a competent precatalyst for acyl anion catalysis; see: Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61.
(13) Chiang, P.-C.; Bode, J. W. *N-Heterocyclic Carbenes as Organic Catalysts, in N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*; Díez-González, S., Ed.; RSC Catalysis Series No. 6; Royal Society of Chemistry: Cambridge, 2011; pp 399−435.
(14) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182.
(15) See Supporting Information for details.
(16) Hawkes, K. J.; Yates, B. R. *Eur. J. Org. Chem.* **2008**, 5563.
(17) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5770.
(18) A situation also observed by Jacobi von Wangelin and coworkers in their more simplified system; see ref 7.
(19) Barletta, G.; Chung, A. C.; Rios, C. B.; Jordan, F.; Schlegel, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 8144.
(20) (a) Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727. (b) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266.