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Radical [1,3]-Rearrangements of Breslow Intermediates

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Abstract

Breslow intermediates that bear radical stabilizing *N*-substituents including benzyl, cinnamyl, and diarylmethyl undergo facile homolytic C-N bond scission under mild conditions to give products of formal [1,3]-rearrangement rather than benzoin condensation. EPR experiments and computational analysis support a radical mechanism. Implications for thiamine based enzymes are discussed.

Keywords

N-heterocyclic carbene; Breslow intermediate; radical; rearrangement; thiamine

Thiamine diphosphate (TDP) is an essential cofactor for all living things. It is involved in several critical metabolic processes, including the tricarboxylic acid cycle, the pentose phosphate pathway, and amino acid catabolism.^{1,2} In 1958, Ronald Breslow postulated that key intermediates in thiamine catalyzed enzymatic pathways included an *N*-heterocyclic carbene (**1**) and an enaminol, e.g. **2** (Scheme 1).³ In pyruvate decarboxylation, for example, addition of the TDP carbene to pyruvate is followed by extrusion of CO₂ to provide unstable enaminol **2**. This and related heterocyclic enamins have collectively been called “Breslow intermediates.”⁴ Only recently have such compounds been rigorously characterized,^{5,6} and new chemistry continues to be revealed.⁷

We recently reported that Breslow intermediates such as **2a** derived from *N*-allyl benzothiazolium bromide and aromatic aldehydes could be captured in a unique Claisen rearrangement to provide 2-butenyl benzothiazoles (Scheme 2, R=H).^{8,9} In the course of examining the scope of the reaction, we were surprised to find that *N*-cinnamyl substituted salt **3b** provided principally [1,3]-rearrangement product **4b** upon reaction with benzaldehyde, accompanied by only ca. 5% of the nominal [3,3]-product. The [1,3]-rearrangement product clearly implied a stepwise process in competition with the concerted rearrangement.

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Reaction of *N*-benzyl and *N*-diphenylmethyl benzothiazolium salts under the same conditions also yielded [1,3]-rearrangement products, albeit in diminished yield in the case of benzyl salt **3c** (Scheme 3). The structures were confirmed by X-ray crystallography.

Many NHC catalyzed reactions of aldehydes are presumed to proceed via a Breslow intermediate,¹⁰ so these observations are relevant to NHC catalysis and catalyst design. Since benzothiazolium salts are only occasionally employed as NHC catalysts,¹¹ we exposed thiazolium and triazolium salts to the reaction conditions (Scheme 4). Reaction of thiazolium salt **3e** with benzaldehyde gave high yield of [1,3]-rearrangement product **4e**, as well as a few percent of ketone **5e**. Treatment of symmetrically substituted 1,2,4-triazole **3f** provided rearrangement product **4f** in low yield as the only isolable product, although interestingly as a single regioisomer resulting from migration of the *N*-4 substituent. No significant amount of benzoin was detected in the crude reaction mixtures based on TLC and ¹H NMR analysis. In both cases *the rearrangements occurred at ambient temperature*.

In 1970 Oka et al reported a similar [1,3]-rearrangement in which thiamine and related compounds underwent reaction with substituted benzaldehydes in methanol under reflux to provide rearranged 3° alcohol products, albeit in very low yield (3–12%, highest yielding example shown, Scheme 5).¹² The rearrangement products were accompanied by larger amounts of ketone and pyrimidine products resulting from cleavage of the benzylic C-N bond, as well as “considerable” benzoin. Hence thiamine was serving for a limited period during the reaction as a benzoin catalyst, but ultimately decomposing into rearrangement and fragmentation products. Oka proposed a rather elaborate polar mechanism that engaged the ortho amino group of the pyrimidine substituent to explain both the ketone and 3° alcohol products, since derivatives lacking the amino group failed to provide the products.¹³

Based on the similarity of the rearrangement and fragmentation products in the Oka reports and our results, we propose that all of the products can be explained by the same *radical* mechanism. C-N bond homolysis of the Breslow intermediate initially forms a geminate radical pair (Scheme 6). The rearrangement product forms by radical recombination, while the ketone and pyrimidine products result from disproportionation, i.e. β-hydrogen atom abstraction of the hydroxyl hydrogen by the carbon radical.^{14–16}

DFT calculations (B3LYP/6-31G*)¹⁷ of the enthalpy of the homolysis reactions of Breslow intermediates **2b–e** corresponding to the benzyl, cinnamyl, and diarylmethyl radicals and carbinol radicals **6** were +20.9, 13.0, 8.8, and 6.6 kcal/mol, respectively (Scheme 7).¹⁸ The extraordinarily low enthalpies of reaction are likely due to the highly delocalized nature of carbinol radical **6** and its nominal recovery of aromaticity upon homolysis. The trend in enthalpies for the benzothiazole based intermediates correlates with the increasing radical stabilizing ability of the *N*-substituent R.

We sought to obtain direct chemical evidence of radical intermediates, albeit without success. Trapping experiments with TEMPO gave no isolable addition products.¹⁹ This could be due to more rapid recombination of radicals than escape from the solvent cage.^{20,21} Deuterium labeling experiments were problematic due to the relative unreactivity of the intermediate radicals relative to a labeling source.²² However, EPR experiments gave solid

evidence of a radical pathway. The EPR spectrum of the reaction of **3e** with benzaldehyde in the presence of the radical trap 2-methyl-2-nitrosopropane (MNP) was consistent with nitroxyl adducts **7**, **8**,²³ and **9**²⁹ in an approximately 29:4:1 ratio (Scheme 8).¹⁸

The [1,3]-rearrangement proved to be a general process across a variety of aromatic and heteroaromatic aldehydes. We prepared a variety of benzyl, cinnamyl, and diarylmethyl substituted tertiary alcohols in 2 steps from the corresponding azole in moderate to good yields (Scheme 9). Both electron rich and poor aldehydes participated in the reaction. Thiazole, benzothiazole, 1,2,4-triazole and a 1,3,4-thiadiazole (**4p**) all participated in the rearrangement. From a synthetic perspective, this reaction extends the scope of complex 3° alcohols that can be prepared via Breslow intermediates beyond those that can participate in a Claisen rearrangement.⁸

We note that the radical homolysis of Breslow intermediates may have implications in enzymology as well. Benzoylformate decarboxylase is a thiamine containing enzyme that catalyzes the conversion of benzoylformate to benzaldehyde and CO₂.²⁵ In model studies of the enzyme, Kluger and coworkers found that the rate of fragmentation of the derived Breslow intermediate **12** to ketone **13** and pyrimidine **14** is competitive with the rate of formation of benzaldehyde and thiamine (Scheme 10), yet how the enzyme avoids the unproductive fragmentation pathway is unknown.^{26,27}

Kluger et al have been studying the so-called “Oka fragmentation” for some years and have considered several concerted and ionic mechanisms for the reaction.^{26,27} It seems likely to us, based on the results described above, that the process occurs via homolysis of the C-N bond of Breslow intermediate **12** followed by disproportionation (cf Scheme 6). Kluger and Ikeda reported a deuterium labeling experiment that was argued to be consistent with a polar mechanism,^{26h} but the labeling result is equally consistent with a radical disproportionation reaction. (cf. Schemes 5,6).

In summary, we describe a facile [1,3]-radical rearrangement of appropriately substituted Breslow intermediates at temperatures from ambient to ca. 65 °C. While the phenomenon places limits on NHC catalyst structure, it opens a novel means of generating a radical pair that can be exploited for organic synthesis. The proposed radical mechanism may also help elucidate how the fragmentation pathway is avoided in Breslow intermediates in thiamine containing enzymes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Formation of TDP-derived Breslow Intermediate **2**.

Scheme 2.[3,3]- and [1,3]-Rearrangements of *N*-Allyl Substituted Breslow Intermediates.

Scheme 3.

[1,3]-Rearrangements of *N*-Benzyl and *N*-Diphenylmethyl Breslow Intermediates.

Scheme 4.

Ambient Temperature [1,3]-Rearrangements of *N*-Di(4-fluorophenyl)methyl Breslow Intermediates.

Scheme 5.

[1,3]-Rearrangement and Fragmentation Products of Thiamine Derivatives Reported by Oka et al.

Scheme 6.
Proposed Radical Reaction Mechanism.

Scheme 7.

Calculated Enthalpies of Homolysis for Intermediates **2b–e** (B3LYP/6-31G*).

Scheme 8.

MNP-Trapped Radicals Consistent with Observed EPR Spectrum.

4k, R=2,4-diCl-phenyl, 62%

4l, R=2-pyridyl, 61% (X-ray)

4m, R=2-furyl, 45%

4n, R=2-OH-phenyl, 59%

4o, 73% (X-ray)

4p, 67% (X-ray)

Scheme 9.

Azole-containing 3° Alcohols Prepared by Radical [1,3]-Rearrangement.

Scheme 10.
Competitive Reaction Pathways for the Breslow Intermediate from Benzoyl Formate Decarboxylase.