HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2017 January 04.

Published in final edited form as:

Angew Chem Int Ed Engl. 2016 January 4; 55(1): 355–358. doi:10.1002/anie.201508368.

Radical [1,3]-Rearrangements of Breslow Intermediates

Dr. Sefat Alwarsh[a], **Yi Xu**[b], **Prof. Steven Qian**[b], and **Prof. Matthias C. McIntosh**[a]

Matthias C. McIntosh: mcintosh@uark.edu

[a]Department of Chemistry and Biochemistry, University of Arkansas, 345 N Campus Dr., Fayetteville, AR 72701

[b]Qian Department of Pharmaceutical Sciences, NDSU Dept 2665, 208B Sudro Hall, P.O. Box 6050, North Dakota State University, Fargo, ND 58108-6050

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 CO_2 to provide unstable enaminol **2**. This and related heterocyclic enaminols 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.

Correspondence to: Matthias C. McIntosh, mcintosh@uark.edu.

Supporting information for this article is given via a link at the end of the document.

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 ^{1}H 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 CO_2.[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

This work was supported by Grant Number P30 GM103450 from the National Institute of General Medical Sciences of the National Institutes of Health (NIH), and by the Arkansas Biosciences Institute.

We thank Gregory Dudley, Florida State University, for helpful discussions.

References

1. Bunik VI, Tylicki A, Lukashev NV. FEBS J. 2013; 280:6412–6442. [PubMed: 24004353]
2. Jordan, F.; Patel, MS. Thiamine - Catalytic Mechanisms in Normal and Disease States. Marcel Dekker, Inc; New York: 2004. p. 588
3. Breslow R. J Am Chem Soc. 1958; 80:3719–3726.
4. Enders D, Breuer K, Teles JH. Helv Chim Acta. 1996; 79:1217–1221.
5. Berkessel A, Elfert S, Yatham VR, Neudoerfl J-M, Schloerer NE, Teles JH. Angew Chem Int Ed. 2012; 51:12370–12374.Berkessel A, Yatham VR, Elfert S, Neudorfl J-M. Angew Chem Int Ed. 2013; 52:11158–11162.
6. Meyer D, Neumann P, Koers E, Sjuts H, Lüdtke S, Sheldrick GM, Ficner R, Tittmann K. Proc Natl Acad Sci USA. 2012; 109:10867–10872. [PubMed: 22730460]
7. Rehbein J, Ruser S-M, Phan J. Chem Sci. 2015 ahead of print.
8. Alwarsh S, Ayinuola K, Dormi SS, McIntosh MC. Org Lett. 2013; 15:3–5. [PubMed: 23214715]
9. For a recent review of the Claisen rearrangement, see: Martin-Castro AM, Tortosa M. Claisen Rearrangements. Comprehensive Organic Synthesis II. Knochel P, Molander GA. Elsevier2014; 5:912–977.
10. For some reviews of NHC catalyzed reactions of aldehydes, see: Enders D, Niemeier O, Henseler A. Chem Rev. 2007; 107:5606–5655. [PubMed: 17956132] Biju AT, Kuhl N, Glorius F. Acc Chem Res. 2011; 44:1182–1195. [PubMed: 21751790] Bugaut X, Glorius F. Chem Soc Rev. 2012; 41:3511–3522. [PubMed: 22377957] Enders D, Grossmann A. Angew Chem Int Ed. 2012; 51:314–325.Okano T. Heterocycl Commun. 2013; 19:311–326.Flanigan DM, Romanov-Michailidis F, White NA, Rovis T. Chem Rev. 2015; 2015:9307–9387. [PubMed: 25992594]
11. Yano Y, Tamura Y, Tagaki W. Bull Chem Soc Jpn. 1980; 53:740–744.Matsumoto T, Yamamoto H, Inoue S. J Am Chem Soc. 1984; 106:4329–4832.Matsumoto T, Ohishi M, Inoue S. J Org Chem. 1985; 50:603–606.Matsumoto T, Enomoto T, Kurosaki T. J Chem Soc Chem Commun. 1992:610–611.Raghunadh A, More SS, Chaitanya TK, Kumar YS, Meruva SB, Rao LV, Kumar UKS. Beilstein J Org Chem. 2013; 9:2129–2136. [PubMed: 24204425]
12. Oka Y, Kishimoto S, Hirano H. Chem Pharm Bull. 1970; 18:527–533;.:534–541. ibid.
13. In our hands, we were only able to isolate the fragmentation products and benzoin; no [1,3]-rearrangement product was detected
14. The [1,3]-rearrangement of appropriately substituted ketimines to nitriles was demonstrated by Singer and others to be a radical process. Rearrangement of a benzhydryl ketimine occurred at ambient temperature. Lee K-W, Horowitz N, Ware J, Singer LA. J Am Chem Soc. 1977; 99:2622–2627.Neuman RC Jr, Sylwester AP. J Org Chem. 1983; 48:2285–2287.Clarke LF, Hegarty AF, O'Neill P. J Am Chem Soc. 1992; 57:362–366.
15. Baldwin has reported ambient temperature [1,3]-rearrangements that proceed via C-N bond homolysis of tetraheteroatom substituted alkenes: Baldwin JE, Walker JA. J Am Chem Soc. 1974; 96:596–597.Baldwin JE, Branz SE, Walker JA. J Org Chem. 1977; 42:4142–4144.
16. Tian and Lee recently reported collision-induced ionization (CID) mass spectrometric experiments of *N*-methyl- and *N*-ethyl-*O*-silyl Breslow intermediates in which they proposed that the same N-C homolytic cleavage was occurring: Tian Y, Lee JK. J Org Chem. 2015; 80:6831–6838. [PubMed: 26066314]
17. DFT methods tend to underestimate bond dissociation energy by ca. 1–4 kcal/mol on average: Feng Y, Liu L, Wang J-T, Huang H, Guo Q-X. J Chem Inf Comput Sci. 2003; 43:2005–2013. [PubMed: 14632451] However, the calculated energies are remarkably low even within that error range. See also: Cattoën X, Gornitzka H, Tham FS, Miqueu K, Bourissou D, Bertrand G. Eur J Org Chem. 2007:912–917.
18. See Supporting Information
19. For a review, see: Bagryanskaya EG, Marque SRA. Chem Rev. 2014; 114:5011–5056. [PubMed: 24571361]
20. For a discussion of radical cage effects, see: Koenig T, Fischer H. "Cage" Effects. Free Radicals. Kochi J. Wiley-InterscienceNew York1973; 1:157–189.Leffler JE. Radical Pairs. An Introduction to Free Radicals. WileyNew York1993:287.

21. Low levels of escape of radical pairs from the solvent cage have been noted in Stevens rearrangements: Ollis WD, Rey M, Sutherland I. J Chem Soc Perkin Trans 1. 1983:1009–1027.

22. Toluene and diphenylmethane have significantly weaker C-H bonds than that of methanol ($PhCH_2$-H, 85 kcal/mol; $HOCH_2$-H, 93 kcal/mol [Gordon AJ, Ford RA. The Chemist's Companion: a Handbook of Practical Data, Techniques, and References. WileyNew York1972]). Hence C-H abstraction from solvent would be endothermic by 8 kcal/mol in the case of benzyl radical, and higher still for cinnamyl and diphenylmethyl radical. Unsurprisingly, no D-atom transfer was observed upon performing the reactions in CD_3OH

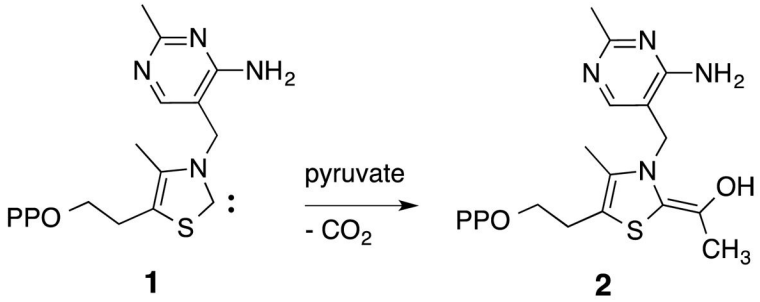
23. For radicals similar to **8**, see: Leaver IH, Ramsay GC. Tetrahedron. 1969; 25:5669–5675.

24. For a radical similar to **9**, see: Zhao WY, Huang ZT. Chin Chem Lett. 1991; 2:501–504.

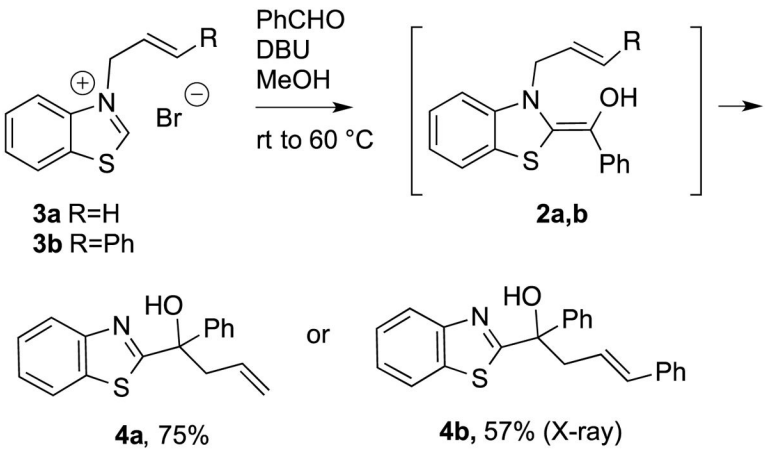
25. Kluger, R.; Hu, Q.; Moore, IF. Thiamine: Catalytic Mechanisms in Normal and Disease States. Marcel Dekker, Inc; New York: 2004. Benzoylformate Decarboxylase: Intermediates, Transition States, and Diversions; p. 291-308.

26. (a) Kluger R, Lam JF, Kim C-S. Bioorg Chem. 1993; 21:275–283.(b) Kluger R, Lam JF, Pezacki JP, Yang C-M. J Am Chem Soc. 1995; 117:11383–11389.(c) Kluger R, Moore IF. J Am Chem Soc. 2000; 122:6145–6150.(d) Moore IF, Kluger R. Org Lett. 2000; 2:2035–2036. [PubMed: 10891223] (e) Moore IF, Kluger R. J Am Chem Soc. 2002; 124:1669–1673. [PubMed: 11853442] (f) Hu Q, Kluger R. J Am Chem Soc. 2002; 124:14858–14859. [PubMed: 12475322] (g) Ikeda G, Kluger R. J Phys Org Chem. 2004; 17:507–510.(h) Ikeda G, Kluger R. Can J Chem. 2005; 83:1277–1280.(i) Mundle SOC, Howe GW, Kluger R. J Am Chem Soc. 2012; 134:1066–1070. [PubMed: 22122780]

27. For a review, see: Kluger R, Tittmann K. Chem Rev. 2008; 108:1797–18. [PubMed: 18491870]

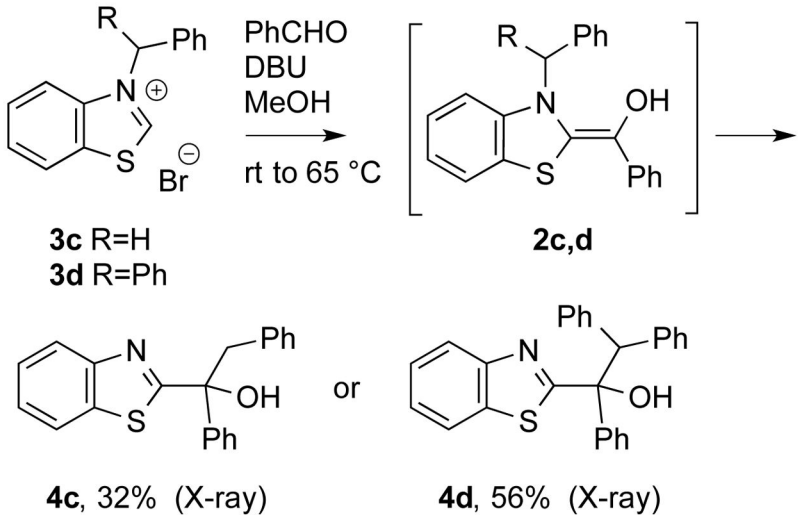


Scheme 1.
Formation of TDP-derived Breslow Intermediate **2**.



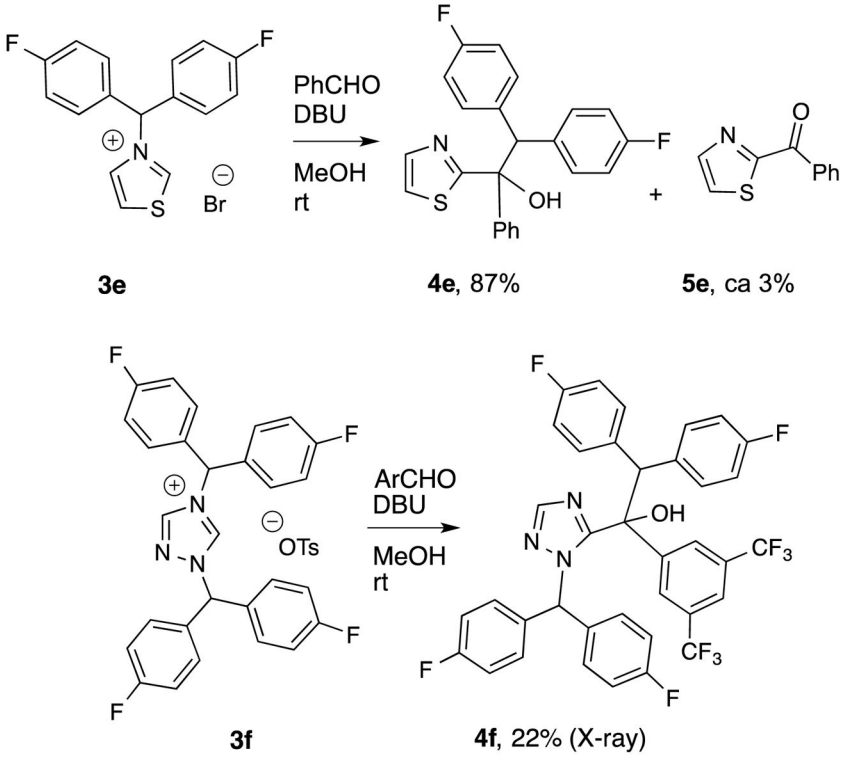
Scheme 2.

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



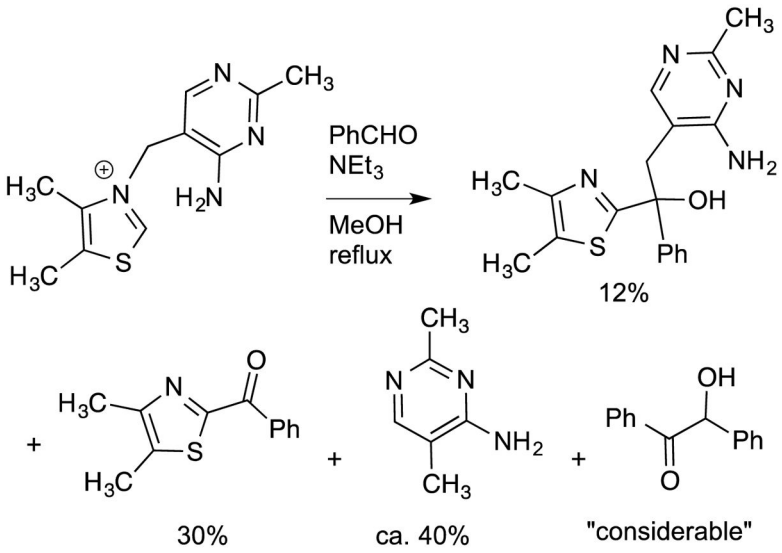
Scheme 3.

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



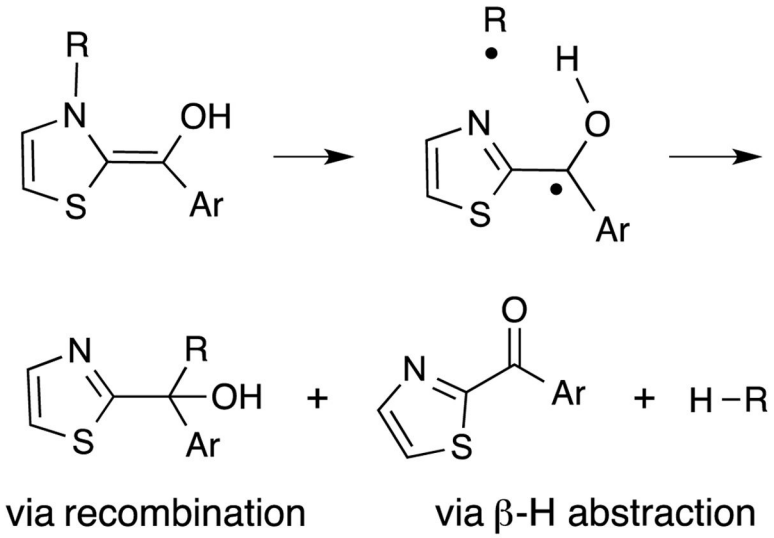
Scheme 4.

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

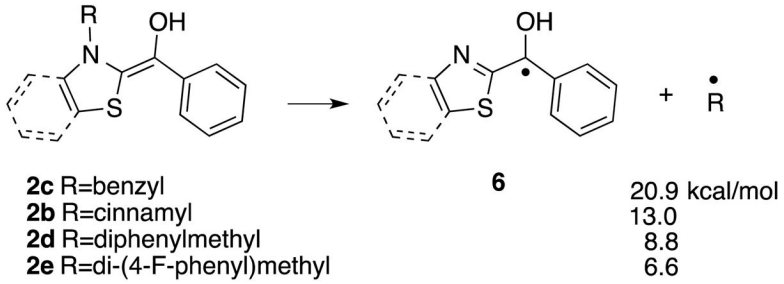


Scheme 5.

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

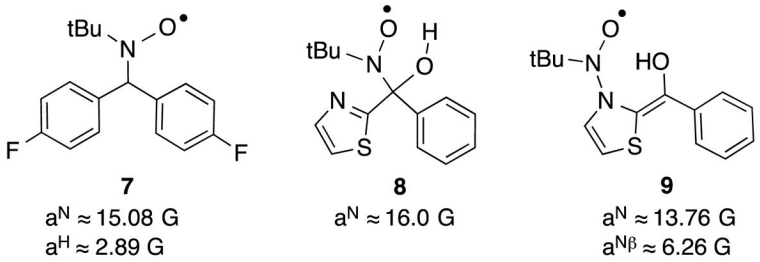


Scheme 6.
Proposed Radical Reaction Mechanism.



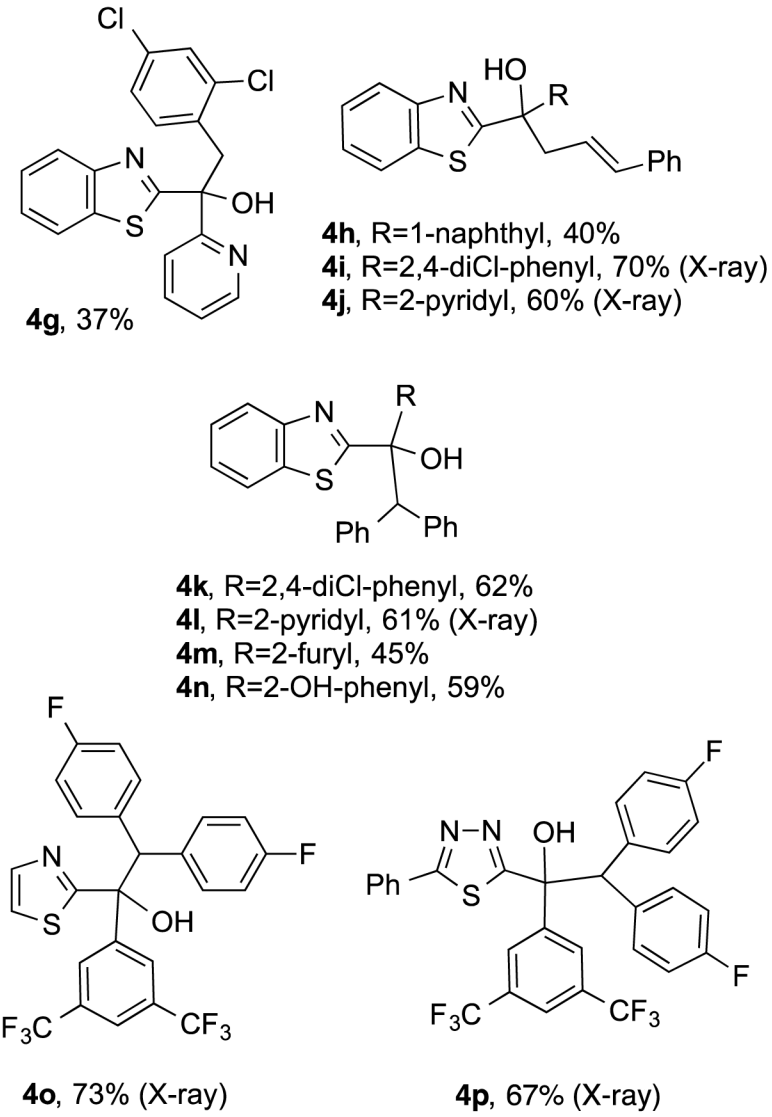
Scheme 7.

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

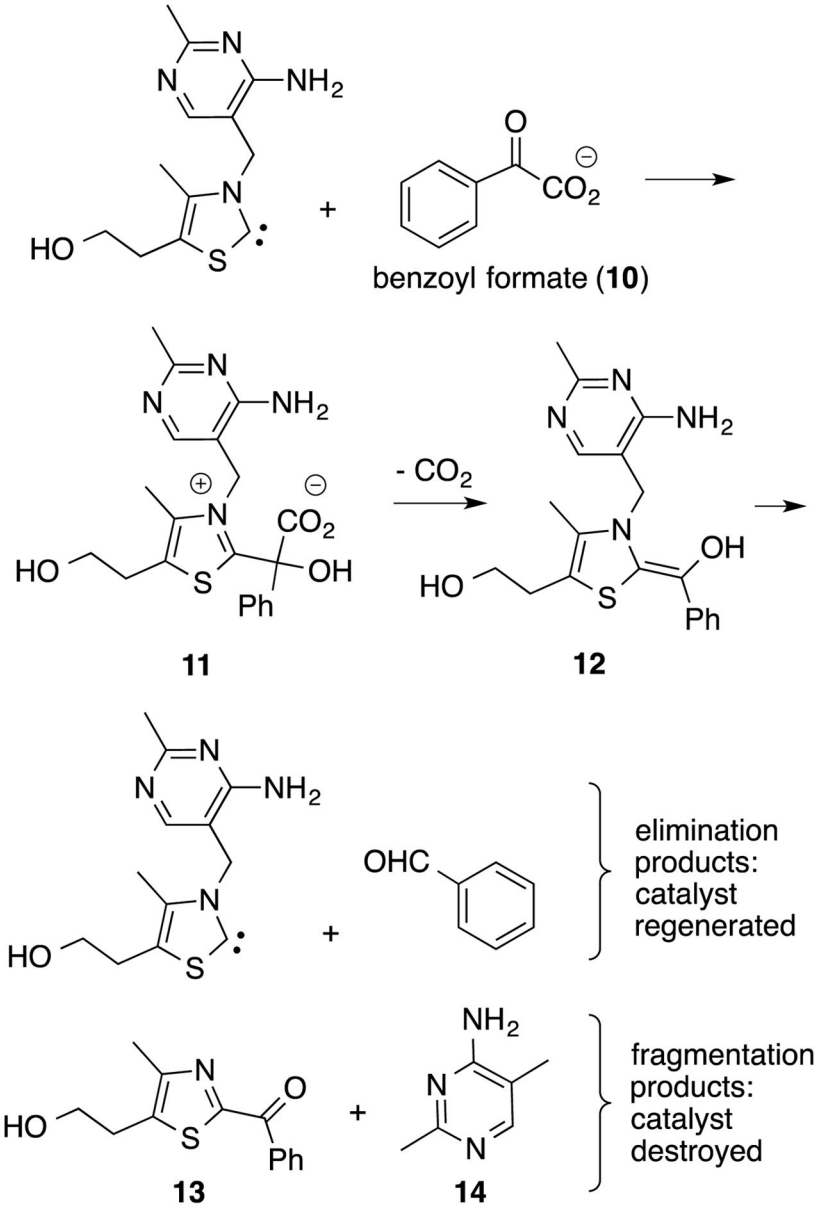


Scheme 8.

MNP-Trapped Radicals Consistent with Observed EPR Spectrum.



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.