Published in final edited form as:

Org Lett. 2013 January 4; 15(1): 3–5. doi:10.1021/ol303053c.

Intercepting the Breslow Intermediate via Claisen Rearrangement: Synthesis of Complex 3° Alcohols without Organometallic Reagents

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Abstract

A novel Claisen rearrangement in which the Breslow intermediate is engaged as a hydroxy-substituted N,S-ketene acetal to provide complex 3° alcohols without the use of organometallic reagents is reported. The reaction constitutes an unprecedented reactivity mode for the Breslow intermediate.

Thiamine diphosphate (**1**) is an essential cofactor for several enzymes, including transketolase, acetolactate synthase, and pyruvate oxidase, decarboxylase, and oxidoreductases (Figure 1).¹ In 1958, as a part of an investigation of the mechanism of thiamine action, Breslow proposed carbene **2** and enol **3** as transient intermediates in the N-methylthiazolium-catalyzed benzoin condensation of benzaldehyde.² The so-called Breslow intermediate **3**, and other azole-based variants, has been implicated in a variety of N-heterocyclic carbene catalyzed processes involving aldehydes.³ While a stable thiazolyl carbene analogous to **2** has been characterized,^{4,5} the corresponding Breslow intermediate **3** has thus far eluded even spectroscopic detection.^{6,7,8}

Most NHC-catalyzed reactions involving aldehydes are thought to proceed via mechanisms in which intermediates such as **3** behave as nucleophilic enamines.³ However, one may also view the intermediate as a hydroxy-substituted N,S-ketene acetal. From that perspective, a conceptually novel disconnection for a Claisen rearrangement precursor emerges (Scheme 1).^{9,10,11,12}

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Supporting Information Available Supporting Information. Experimental procedures, compound characterization data, and ¹H and ¹³C NMR spectra of **13a-j**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Rearrangement of an N-allyl-hydroxy-N,S-ketene acetal **6** would provide tertiary alcohol **7**. Such an approach would require that intermediate **6** undergo rearrangement in preference to participating in benzoin condensation. Since the rearrangement would be intramolecular, and benzoin condensation intermolecular, it seemed plausible that rearrangement might be kinetically favored.

In 1964, Metzger reported the condensation of N-methyl benzothiazolium salt **8** (X = OSO₃Me) with benzaldehyde in the presence of NEt₃ in methanol under reflux to provide ketone **10** in 75% yield (Scheme 2).¹³ Using the Metzger conditions, we found that reaction of benzothiazolium salt **9** (X = Br)¹⁴ likewise afforded the analogous N-allyl ketone **11** in comparable yield.

However, no rearrangement product was detected upon extended heating. Further experimentation revealed that use of DBU in place of NEt₃ provided ketone **11** at ambient temperature. More importantly, heating of the reaction mixture to 60–65 °C provided Claisen rearrangement product **13a** in 75% yield.^{15,16,17} No benzoin was detected by TLC analysis of the crude reaction mixture upon comparison to an authentic sample.

We probed the steric and electronic influences on the reaction by surveying a variety of aromatic and heteroaromatic aldehydes (Figure 2). The reaction tolerated ortho substitution to the aldehyde (**13b,d–f,i**), reacting even with 1-naphthaldehyde, albeit in somewhat diminished yield. Both electron rich (**13f,i,j**) and electron poor (**13c–e**) aldehydes participated in the reaction. However, 4-nitrobenzaldehyde gave only products of Cannizzaro reaction.¹⁸

Pyridine-2-carboxaldehyde and 2-furaldehyde also provided good yields of rearrangement products (**13g,h**). We were pleased to find that even an *unprotected* phenol was tolerated (**13i**).

There were notable differences in reactivity of electron poor and electron rich aldehydes. Electron poor aldehydes reacted more rapidly in both the Metzger condensation and the Claisen rearrangement based on TLC analysis of the reaction mixture. For example, ketone formation had begun within 30 min for 2-Br benzaldehyde, while 2,4-dimethylbenzaldehyde required 24 h for the ketone to begin to appear. Similarly, the electron poor or neutral aldehydes were heated at ca. 60–65 °C for 16 h to effect the rearrangement step, while the 2,4-dimethylbenzaldehyde-derived ketone **11j** required 48 h, and the 2-oxy substituted ketones **11f,i** required 72 h at ca. 80–85 °C.

There are several practical benefits to this Claisen-based method for the synthesis of complex diaryl 3° alcohols such as **13a–j**.^{19,20} Firstly, benzothiazoles are very common heteroaromatic motifs in medicinal chemistry.²¹ AC-265347 and analogs thereof, for example, have been reported to be calcium sensing receptor agonists (Figure 3).²² They were prepared in the traditional fashion by addition of 2-lithiobenzothiazole to the corresponding ketones at –78 °C. By contrast, we prepared allyl analog **13j** in 50 % yield over two steps from benzothiazole using our all-organic Claisen approach.^{15b}

Secondly, 2-lithiothiazole and -benzothiazole have been employed extensively in synthesis as acyl anion equivalents.²³ These organometal reagents are not compatible with a large number of comparatively acidic and/or electrophilic functional groups.²⁴ This necessitates the deployment of protective groups, with the attendant decrease in step economy²⁵ and process efficiency.²⁶ The mildness of the Claisen-based approach avoids the need for protective groups for hydroxyl and phenoxy groups, and will presumably tolerate many other comparatively acidic functionalities.

Thirdly, unlike organometal-based approaches that require ethereal solvents, the above transformations were carried out in methanol. Methanol is generally considered to be a green solvent,²⁷ which is an important consideration for process and/or production scale synthesis.

Finally, the conventional approach to 3° alcohol synthesis employing highly reactive organo Li or Mg nucleophiles generally requires cryogenic conditions. This can be problematic on production scale, and requires more expensive reactor equipment and careful monitoring of reaction temperature due to the danger of exotherms.²⁸ By contrast, only mild heating is necessary to effect the Metzger condensation/Claisen rearrangement sequence. Increasing the scale of the reaction to 10 g of benzothiazolium salt **9** provided a 77% yield of **13a** with no alteration of reaction conditions.

In conclusion, we have prepared a variety of benzothiazole-based complex 3° alcohols in 2 steps under mild conditions without the use of any organometallic reagents. We continue to investigate the scope of the reaction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the NSF (CHE0911638), the NIH (P30RR031154 and P30GM103450), and the Arkansas Biosciences Institute for support of this work, and the Ministry of Education of Saudi Arabia for a graduate fellowship for S.A.

References

1. Jordan, F.; Patel, MS. Thiamine - Catalytic Mechanisms in Normal and Disease States. Marcel Dekker, Inc.; New York: 2004. p. 588
2. Breslow R. J. Am. Chem. Soc. 1958; 80:3719–3726.
3. Enders D, Niemeier O, Henseler A. Chem. Rev. 2007; 107:5606–5655. [PubMed: 17956132] Nair V, Vellalath S, Babu BP. Chem. Soc. Rev. 2008; 37:2691–2698. [PubMed: 19020682] Vora HU, Rovis T. Aldrichimica Acta. 2011; 44:3–11. Biju AT, Kuhl N, Glorius F. Angew. Chem. Int. Ed. 2011; 44:1182–1195. Bugaut X, Glorius F. Chem. Soc. Rev. 2012; 41:3511–3522. [PubMed: 22377957]
4. Arduengo AJ, Goerlich JR, Marshall WJ. Liebigs Ann. 1997:365–374.
5. Vignolle J, Cattoen X, Bourissou D. Chem. Rev. 2009; 109:3333–3384. [PubMed: 19368393]
6. DiRocco DA, Oberg KM, Rovis T. J. Am. Chem. Soc. 2012; 134:6143–6145. [PubMed: 22455368]
7. Berkessel has recently reported the spectroscopic characterization of an analogous intermediate formed from a 1,2,4-triazolylidene carbene and several aromatic aldehydes: Berkessel A, Elfert S, Yatham VR, Neudoerfl J-M, Schloerer NE, Teles JH. Angew. Chem. Int. Ed. 2012; 51:1–6..
8. Mayr has recently reported the isolation of several O-methylated Breslow intermediates: Maji B, Mayr H. Angew. Chem. Int. Ed. 2012; 51:10408–10412..
9. Hollóczki O, Kelemen Z, Nyulászi L. J. Org. Chem. 2012; 77:6014–6022. [PubMed: 22731396]
10. For other approaches to *N*-allyl-*N*,*X*-ketene acetals derived from azoles or azolines, see: Ireland RE, Willard AK. J. Org. Chem. 1974; 39:421–424.. Baldwin JE, Walker JA. J. Am. Chem. Soc. 1974; 96:596–597.. Kurth MJ, Decker OHW, Hope H, Yanuck MD. J. Am. Chem. Soc. 1985; 107:443–448.; Kurth MJ, Decker OHW. J. Org. Chem. 1986; 51:1377–1383.. Waetzig SR, Tunge JA. J. Am. Chem. Soc. 2007; 129:4138–4139. [PubMed: 17371027] .
11. For another Claisen rearrangement of an enol, see: Wood JL, Moniz GA, Pflum DA, Stoltz BM, Holubec AA, Dietrich H-J. J. Am. Chem. Soc. 1999; 121:1748–1749..

12. For reviews, see: Nubbemeyer U, Hiersemann M. The Claisen Rearrangement – Methods and Applications. 2007:591. Wiley-VCH Weinheim additional reviews cited therein.
13. (a) Metzger J, Larive H, Dennilaule R, Baralle R, Gaurat C. Bull. Soc. Chim. Fr. 1964:2857–2867. (b) Doughty MB, Risinger GE. Bioorg. Chem. 1987; 15:1–14.
14. Yen SK, Koh LL, Huynh HV, Hor TSA. Dalton Trans. 2007:3952–3958. [PubMed: 17893793]
15. (a) Troisi has previously prepared **13a** via Wittig rearrangement: Capriati V, Florio S, Ingrosso G, Granito C, Troisi L. Eur. J. Org. Chem. 2002:478–484. (b) Troisi's preparation of **13a** employed organolithium reagents and cryogenic temperatures in both steps.
16. There has recently been a renaissance of interest in stoichiometric reactions of NHCs: Arduengo AJ, Calabrese JC, Davidson F, Dias HVR, Goerlich JR, Krafczyk R, Marshall WJ, Tamm M, Schmutzler R. Helv. Chim. Acta. 1999; 82:2348–2364.; Coady DJ, Bielawski CW. Macromolecules. 2006; 39:8895–8897.; Hudnall TW, Moorhead EJ, Gusev DG, Bielawski CW. J. Org. Chem. 2010; 75:2763–2763. [PubMed: 20297836] ; Moerdyk JP, Bielawski CW. J. Am. Chem. Soc. 2012; 134:6116–6119. [PubMed: 22463070] .
17. The capture of thiazolyl intermediates **12** via Claisen rearrangement is arguably the most direct structural evidence yet for the Breslow intermediate's existence, since all of the elements of the intermediate are retained in the rearranged product.
18. Maki BE, Chan A, Scheidt KA. Synthesis. 2008:1306–1315. [PubMed: 22347730] . Mojtahedi MM, Akbarzadeh E, Sharifi R, Abaee MS. Org. Lett. 2007; 9:2791–2793. [PubMed: 17580879] . However, exchange of the bromide counterion of **9a** for a tosylate resulted in no significant change in the reaction outcome, suggesting the Cannizzaro reaction is NHC catalyzed.
19. For less conventional anionic approaches to related compounds, see: Popov I, Do H-Q, Daugulis O. J. Org. Chem. 2009; 74:8309–8313. [PubMed: 19827765] ; Hirono Y, Kobayashi K, Yonemoto M, Kondo Y. Chem. Commun. 2010:7623–7624..
20. For other non-metallic approaches to similar compounds, see: Burns NZ, Hackman BM, Ng PY, Powelson IA, Leighton JL. Angew. Chem. Int. Ed. 2006; 45:3811–3813.. Khodakovskiy PV, Mykhailiuk PK, Volochnyuk DM, Tolmachev AA. Synthesis. 2010:1633–1638..
21. See, for example: Rai G, Vyjayanti VN, Dorjsuren D, Simeonov A, Jadhav A, Wilson DM III, Maloney DJ. J. Med. Chem. 2012; 55:3101–3112. [PubMed: 22455312] ; Ochiai K, Takita S, Eiraku T, Kojima A, Iwase K, Kishi T, Fukuchi K, Yasue T, Adams DR, Allcock RW, Jiang Z, Kohno Y. Bioorg. Med. Chem. 2012; 20:1644–1658. [PubMed: 22336247] ; Spadaro A, Frotscher M, Hartmann RW. J. Med. Chem. 2012; 55:2469–2473. [PubMed: 22277094] ; Li K, Frankowski KJ, Belon CA, Neuenswander B, Ndjomou J, Hanson AM, Shanahan MA, Schoenen FJ, Blagg BSJ, Aube J, Frick DN. J. Med. Chem. 2012; 55:3319–3330. [PubMed: 22409723] ; Arasappan A, Bennett F, Girjavallabhan V, Huang Y, Huelgas R, Alvarez C, Chen L, Gavallas S, Kim S-H, Kosinski A, Pinto P, Rizvi R, Rossman R, Shankar B, Tong L, Velazquez F, Venkatraman S, Verma VA, Kozlowski J, Shih N-Y, Piwinski JJ, MacCoss M, Kwong CD, Clark JL, Fowler AT, Geng F, S. K. H III, Roychowdhury A, Reynolds RC, Maddry JA, Ananthan S, A. S. J III, Li C, Chase R, Curry S, Huang H-C, Tong X, Njoroge FG. Bioorg. Med. Chem. Lett. 2012; 22:3229–3234. [PubMed: 22472692] ; Sharma AK, Pavlova ST, Kim J, Finkelstein D, Hawco NJ, Rath NP, Kim J, Mirica LM. . Am. Chem. Soc. 2012; 134:6625–6636.; Ward RA, Brassington C, Breeze AL, Caputo A, Critchlow S, Davies G, Goodwin L, Hassall G, Greenwood R, Holdgate GA, Mrosek M, Norman RA, Pearson S, Tart J, Tucker JA, Vogtherr M, Whittaker D, Wingfield J, Winter J, Hudson K. J. Med. Chem. 2012; 55:3285–3306. [PubMed: 22417091] .
22. Gustafsson M, Jensen J, Bertozzi SM, Currier EA, Mab J-N, Burstein ES, Olsson R. Bioorg. Med. Chem. Lett. 2010; 20:5918–5921. [PubMed: 20727747] ; Ma J-N, Owens M, Gustafsson M, Jensen J, Tabatabaei A, Schmelzer K, Olsson R, Burstein ES. J. Pharmacol. Exp. Therap. 2011; 337:275–284. [PubMed: 21239511]
23. Dondoni A, Marra A. Chem. Rev. 2004; 104:2557–2599. [PubMed: 15137800]
24. There is a single report of a 2-organolanthanide benzothiazole addition to a ketone: Wunderlich SH, Knochel P. Chem. Eur. J. 2010; 16:3304–3307. [PubMed: 20187042] .
25. Wender PA, Verma VA, Paxton TJ, Pillow TH. Acc. Chem. Res. 2008; 41:40–49. [PubMed: 18159936]
26. Henderson, RK.; Constable, DJC.; Jimenez-Gonzalez, C. Green Chemistry in the Pharmaceutical Industry. Dunn, PJ.; Wells, AS.; Williams, MT., editors. Wiley-VCH; Weinheim: 2010. p. 21–48.

27. Constable DJC, Jimenez-Gonzalez C, Henderson RK. *Org. Process Res. Dev.* 2007; 11:133–137.
28. See, for example: Copp RR, Abraham BD, Farnham JG, Twose TM. *Org. Process Res. Dev.* 2011; 15:1344–1347..

Figure 1.
Thiamine diphosphate and Breslow intermediate **3**.

Figure 2.
Claisen rearrangement products and yields from **9**.

AC-265347, R=CH₃
13j, R = allyl, 50%

Figure 3.
Calcium sensing AC-265347 and allyl analog **13j**.

Scheme 1.

Novel retrosynthetic approach to Claisen rearrangement precursor **6**.

Scheme 2.
Metzger condensation and Claisen rearrangement.