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

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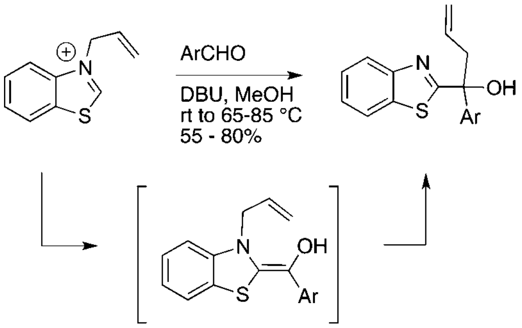
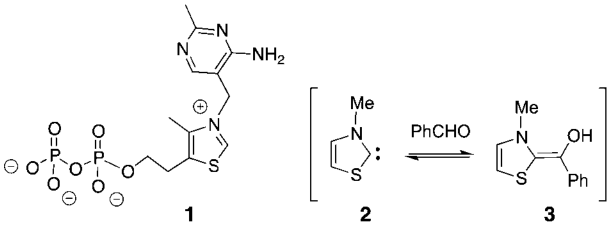
ABSTRACT



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 (NHC) 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.[6−8]



1 **2** **3**

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

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

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[†] These authors contributed equally.

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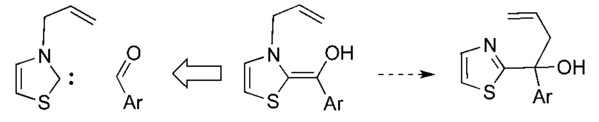
may also view the intermediate as a hydroxy-substituted *N*, *S*-ketene acetal. From that perspective, a conceptually novel disconnection for a Claisen rearrangement precursor emerges (Scheme 1).[9−12]

Scheme 1. Novel Retrosynthetic Approach to Claisen Rearrangement Precursor **6**

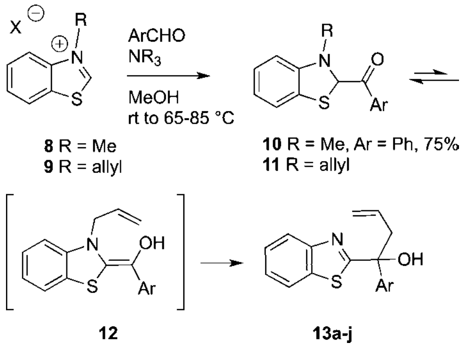


4 **5** **6** **7**

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 the 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 = OSO$_3$Me) with benzaldehyde in the presence of NEt$_3$ 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.

Scheme 2. Metzger Condensation and Claisen Rearrangement



However, no rearrangement product was detected upon extended heating. Further experimentation revealed that use of DBU in place of NEt$_3$ 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*.[15−17] 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 the Cannizarro 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**).

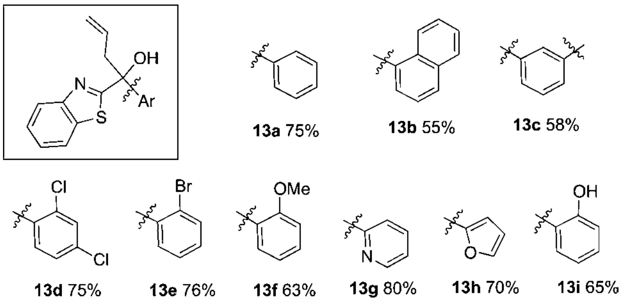


Figure 2. Claisen rearrangement products and yields from **9**.

There were notable differences in reactivity of electron-poor and -rich aldehydes. Electron-poor aldehydes reacted more rapidly in both the Metzger condensation and the

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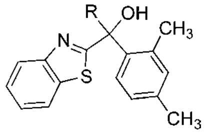
Claisen rearrangement based on TLC analysis of the reaction mixture. For example, ketone formation had begun within 30 min for 2-Br benzaldehyde, while 2,4-dimethylbenzaldehyde required 24 h for the ketone to begin to appear. Similarly, the electron-poor or -neutral aldehydes were heated at ca. 60−65 °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] First, 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]

Second, 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 economy[25] 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.



AC-265347, R=CH_3
13j, R = allyl, 50%

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

Third, 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 two steps under mild conditions without the use of any organometallic reagents. We continue to investigate the scope of the reaction.

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

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The authors declare no competing financial interest.