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**To be cited as:** *Eur. J. Org. Chem.* 10.1002/ejoc.201601354

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# Aromatic Claisen Rearrangements of Benzyl Ketene Acetals: Conversion of Benzylic Alcohols to (*ortho*-Tolyl)Acetates

Jed M. Burns, Elizabeth H. Krenske and Ross P. McGeary*

**Abstract:** Claisen rearrangements of benzyl vinyl ethers are much less facile than those of aliphatic allyl vinyl ethers, and their synthetic utility has remained relatively unexplored. A one-pot procedure is reported for the generation and Claisen rearrangement of benzyl vinyl ethers that contain an activating α-alkoxy substituent on the vinyl group. A [3,3]-sigmatropic mechanism is supported by trapping of the intermediate isotoluene in an intramolecular Alder-ene reaction.

## Introduction

The Claisen rearrangement of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds (Scheme 1a), first reported in 1912,[1] is a fundamentally important organic transformation.[2] The wide utility of the Claisen rearrangement and its variants, including the Ireland–Claisen,[3] Johnson–Claisen[4] and Eschenmoser–Claisen[5] rearrangements, has led to many applications in natural products synthesis.[2, 6]

Claisen rearrangements of aliphatic allyl vinyl ethers **1** are well known, as are the "aromatic" Claisen rearrangements of allyl phenyl ethers **3**.[2] Much less is known about the rearrangements of benzyl vinyl ethers **6**, which in principle represents a "missing" substrate class. For benzyl vinyl ethers, the high energy of the intermediate isotoluene **7** disfavors the Claisen rearrangement relative to other thermal reactions such as [1,3]-sigmatropic rearrangement and polymerization.[5, 7] McElvain's conversion of **9** to **11** (Scheme 1b) upon distillation at 150 °C is one of the few reported examples of a Claisen rearrangement of a benzyl vinyl ether derivative.[8] Until now, no broadly applicable solution-phase methodology for the rearrangement of this class of substrates has been identified.[9]

Herein we report the development of methodology for aromatic Claisen rearrangements of benzyl vinyl ethers which utilizes the activating effect of an α-alkoxy substituent on the vinyl group (i.e., benzyl ketene acetals). We describe the substrate scope and regioselectivity of the process, which may be conveniently conducted in one pot starting from the α-bromoacetal. We report trapping studies that provide evidence for a concerted [3,3]-sigmatropic mechanism.

[a] School of Chemistry and Molecular Biosciences,
The University of Queensland,
St Lucia, Brisbane, QLD, 4072, Australia
E-mail: r.mcgeary@uq.edu.au.

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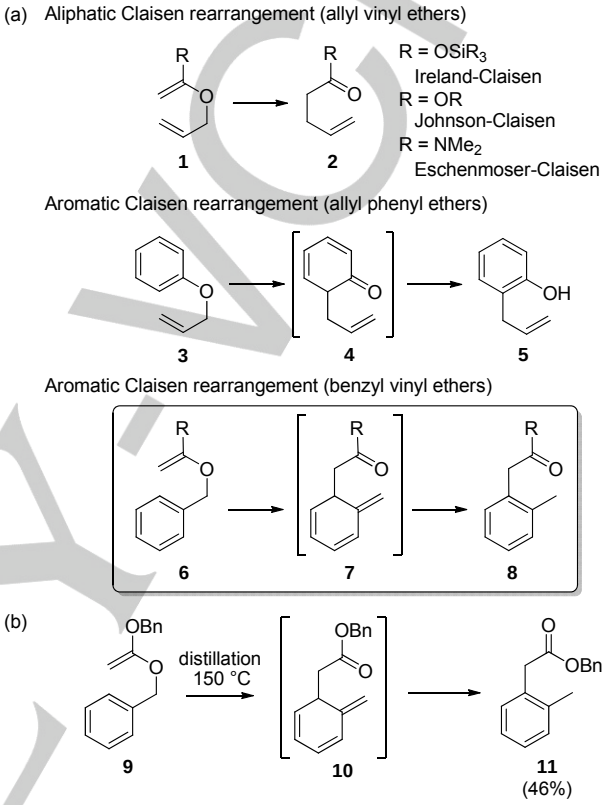


**Scheme 1.** (a) Claisen Rearrangements. (b) McElvain's Rearrangement of a Benzyl Ketene Acetal.[8].

## Results and Discussion

Quantum mechanical computations reveal the extent to which the Claisen rearrangement of a benzyl vinyl ether is disfavored with respect to that of an aliphatic analogue (Figure 1). The barrier ($\Delta G^{\ddagger}$) for rearrangement of benzyl vinyl ether **6a**, computed with CBS-QB3, is 40.1 kcal/mol, which is about 10 kcal/mol higher than the barrier for rearrangement of allyl vinyl ether **1a** (29.8 kcal/mol).[10] [11] Isotoluene intermediate **7a** is 13 kcal/mol higher in energy than **6a**, but subsequent rearomatization to **8a** is favorable and the overall conversion of **6a** to **8a** has $\Delta G$ = –20 kcal/mol. We surmised that, similar to the Johnson–Claisen rearrangement,[12] an α-alkoxy substituent on the vinyl group would activate a benzyl vinyl ether toward rearrangement. Computations supported this idea, predicting that the barrier for rearrangement of methoxy-substituted benzyl ketene acetal **6b** is 29.9 kcal/mol, almost the same as the barrier for allyl vinyl ether **1a**. Furthermore, the alkoxy substituent renders isotoluene intermediate **7b** 5 kcal/mol more stable than reactant **6b**.

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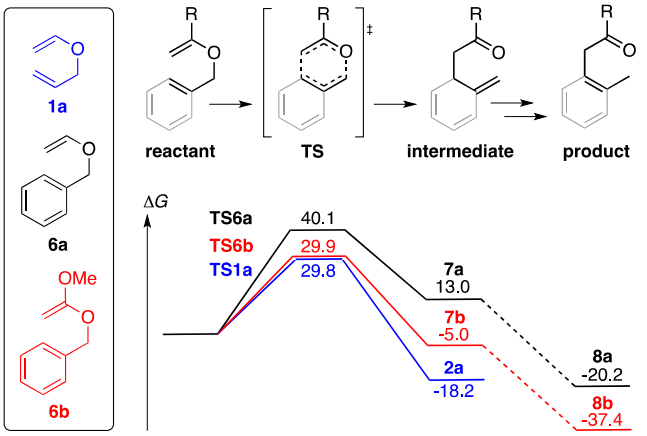
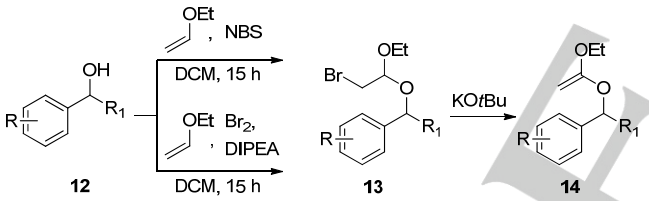



**Figure 1.** Free Energy Profiles for Claisen Rearrangements of **1a**, **6a**, and **6b**, Computed with CBS-QB3 (Δ*G* in kcal/mol).

Accordingly, we focused our attention on the rearrangements of benzyl ketene acetals (general structure **14**, Scheme 2). The synthesis of **14** required access to α-bromoacetals **13**, which were prepared by two routes (Table 1). Bromoacetalization[13] utilizing ethyl vinyl ether (EVE) and *N*-bromosuccinimide (NBS) in DCM proved to be operationally simple, but gave only moderate yields of **13** (~60%).[14] Alternatively, bromination with $Br_2$/DIPEA provided **13** in superior yields (64–99%).[15]




**Scheme 2.** Synthetic Routes to Benzyl Ketene Acetals **14**.

Bromoacetal **13a** was converted to ketene acetal **14a**[8, 14, 16] by treatment with KO*t*Bu in THF (1 M), typically under reflux to drive the elimination of HBr to completion (Table 2, Method A). The crude ketene acetal **14a** could be isolated by diluting the reaction mixture with hexanes, filtering off the inorganic salts, and evaporating the filtrate, as per the procedure of Middleton and Simpkins.[14] Due to instability toward hydrolysis, the ketene acetals were generally carried forward without further purification.

With ketene acetals **14** in hand, conditions for the Claisen rearrangement to arylacetates **15** were explored (Table 2). Initial experiments employed xylenes as a non-polar, high boiling point solvent. Heating a solution of **14a** (R = $R^1$ = H) in xylenes at reflux for 15 h led to the formation of a complex mixture which did not contain any of the expected Claisen rearrangement product **15a**. Among the components identified by GCMS analysis were diethyl succinate, bibenzyl and ethyl 3-phenylpropionate, which are thought to be products of radical fission/recombination reactions of **14a**. A solvent screen revealed that these undesired homolytic processes could be suppressed and the [3,3]-sigmatropic rearrangement could be promoted by performing the reaction in anhydrous DMF.[17] Thus, heating **14a** in DMF at reflux for 15 h provided rearranged product **15a** in 48% yield after purification by column chromatography, with no homolysis products detectable by GCMS. Diglyme was also found to be a permissible solvent.

**Table 1.** Synthesis of Bromoacetals **13**.

| entry | 12 | R | $R^1$ | yield **13** (%) |
|---|---|---|---|---|
| 1 | **12a** | H | H | 89,[a] 96[b] |
| 2 | **12b** | 4-Me | H | 61,[a] 99[b] |
| 3 | **12c** | 4-$C_6H_5$ | H | 96[b] |
| 4 | **12d** | 4-Cl | H | 65[a] |
| 5 | **12e** | 4-Br | H | 64[b] |
| 6 | **12f** | 4-OMe | H | 64[a] |
| 7 | **12g** | 4-SMe | H | 71[b] |
| 8 | **12h** | $(CH)_4$ (1-naphthyl) | H | 94[b] |
| 9 | **12i** | $(CH)_4$ (2-naphthyl) | H | 72[b] |
| 10 | **12j** | H | Me | 40,[a] 99[b] |
| 11 | **12k** | 4-F | H | 23,[a] 90[b] |
| 12 | **12l** | 3-OMe | H | 40,[a] 82[b] |
| 13 | **12m** | 3-Br | H | 54,[a] 92[b] |
| 14 | **12n** | H | $(CH_2)_3CH=CH_2$ | 43[a] |
| 15 | **12o** | H | $(CH_2)_4CH=CH_2$ | 53[a] |
| 16 | **12p** | 4-$NMe_2$ | H | 87[b] |
| 17 | **12q** | 4-$SO_2Me$ | H | 80[b] |
| 18 | **12r** | 4-COOBn | H | 85[b] |
| 19 | **12s** | 4-$NO_2$ | H | 55[a] |
| 20 | **12t** | 4-CN | H | 60[a] |
| 21 | **12u** | 4-$CF_3$ | H | 68[b] |
| 22 | **12v** | H | $Me_2$ | 58[b] |

[a] NBS used as the brominating agent. [b] $Br_2$/DIPEA used as the brominating agent.

Rather than isolating ketene acetals **14** prior to conducting their Claisen rearrangements, we found that the procedure could be simplified by combining the elimination of HBr from bromoacetal **13** and the rearrangement of ketene acetal **14** into a one-pot operation (Table 2, Method B). Such procedures are commonplace in the Ireland variant of the Claisen rearrangement. Results of the elimination/rearrangement sequence involving a range of bromoacetals are given in Table 2. Purification of the arylacetate esters **15** by column chromatography proved tedious, due to the presence of benzyl acetates (hydrolytic side products of ketene acetals **14**).

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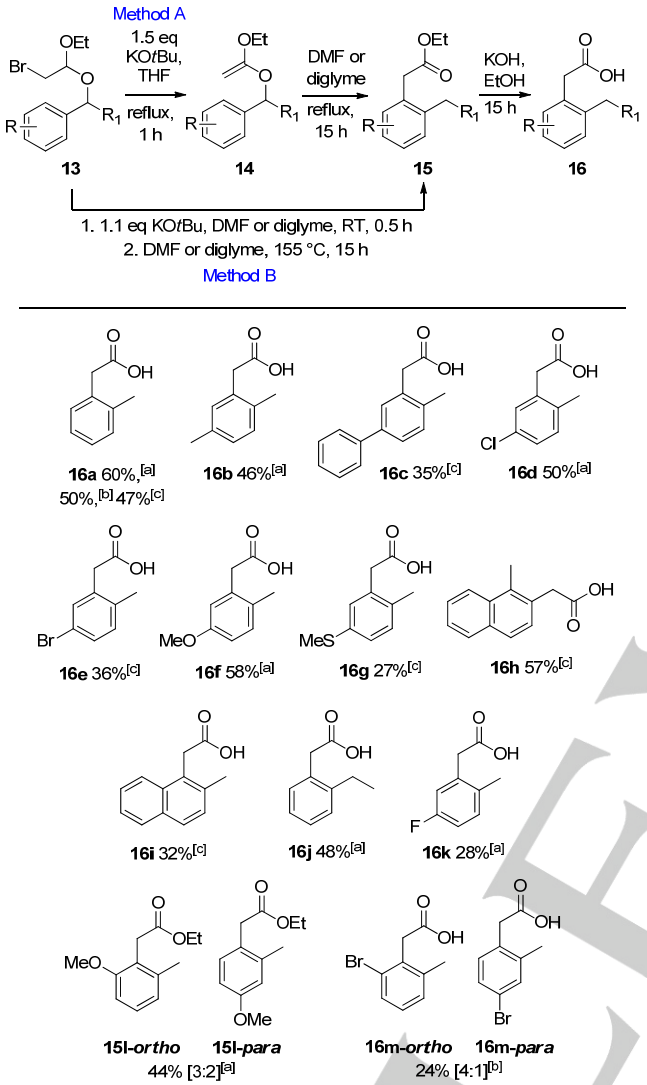
However, saponification of the crude reaction mixtures with ethanolic KOH allowed ready isolation of the corresponding carboxylic acids **16** (Table 2) in pure form.

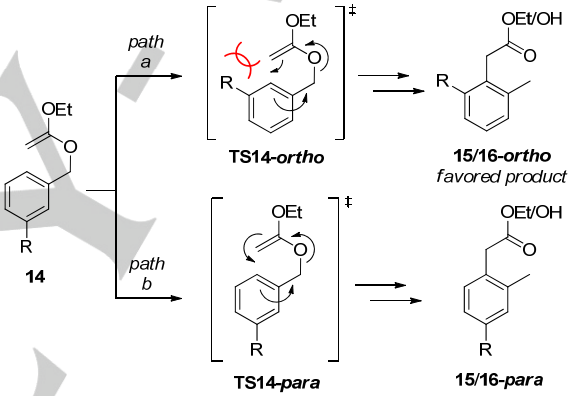
**Table 2.** Synthesis and Claisen Rearrangements of Benzyl Ketene Acetals **14**




[a] Method A, DMF [b] Method B, DMF [c] Method B, diglyme.

The elimination/Claisen rearrangement protocol was compatible with a range of electron-neutral and donor groups on the aromatic ring. Thus, the *para*-Me, Ph, Cl, Br, OMe and SMe derivatives **13b–g** gave arylacetates **16b–g**, respectively, in yields of 27–58% for three steps in the one pot (Table 2), comparable to the yield obtained with the unsubstituted system **13a** (50%). Replacement of the benzyl group by 1- or 2-naphthyl (**13h** and **13i**) or by a secondary benzylic group (**13j**) was also tolerated. However, while elimination/Claisen rearrangement/saponification of the 1-naphthyl-bromoacetal **13h** gave **16h** as the sole product, analogous reactions of the 2-naphthyl-bromoacetal **13i** gave mainly **16i**, accompanied by 3-(naphthalene-2-yl)propionic acid, the product of a [1,3]-sigmatropic shift (See Supporting Information). Powerful donor or acceptor groups were not compatible with the transformation; *para*-$NMe_2$, $NO_2$, CN, $CO_2Bn$, $SO_2Me$ and $CF_3$ derivatives all decomposed under the reaction conditions. However, the fluoro-substituted substrate **13k** did provide a 28% yield of rearranged product. The failure to obtain rearranged products from ketene acetals bearing strong donor or acceptor groups is not necessarily due to a higher rearrangement barrier, but more likely reflects the incompatibility of such substrates towards the conditions of the elimination/rearrangement protocol.

The rearrangements of *meta*-substituted benzyl ketene acetals were found to be moderately regioselective (Scheme 3). For the *meta*-methoxy and *meta*-bromo substituted ketene acetals **14l** and **14m**, products **15/16-*ortho*** were favored over **15/16-*para*** with a selectivity of 3:2–4:1. The preference for the more sterically crowded regioisomer is surprising, and is not observed in normal aromatic Claisen rearrangements of allyl phenyl ethers.[18] However, comparable regioselectivity has previously been noted in rearrangements of fused aromatic systems similar to **14i**.[19]




| 14 | R | product | *ortho*:*para* |
|---|---|---|---|
| **14l** | OMe | **15l** (44%) | 3:2 |
| **14m** | Br | **16m** (24%) | 4:1 |

**Scheme 3.** Regioselective Claisen Rearrangements of *meta*-Substituted Benzyl Vinyl Ethers.

Trapping studies were conducted to probe the mechanism of the benzyl ketene acetal Claisen rearrangement. Based on the known reactivity of isotoluenes[20] and dearomatized furans[21] towards Alder-ene reactions, we designed ketene acetal **14n** (Scheme 4), for which the isotoluene intermediate **17n** could undergo either tautomerization to **15n** or an intramolecular Alder-ene reaction with the tethered alkene (red arrows) giving **18n**. Rearrangement of **14n** under the standard reaction conditions was found to give Alder-ene product **18n** and regular product **15n** in a ratio of 2:1 (41% yield), supporting the proposed involvement of isotoluene **17n**. As expected,[22] the length of the tether was crucial to the Alder-ene reaction. With an additional methylene group in the tether, none of the cyclohexyl homologue of **18n** was detected, and only the regular tautomerization product was obtained (see the Supporting Information).

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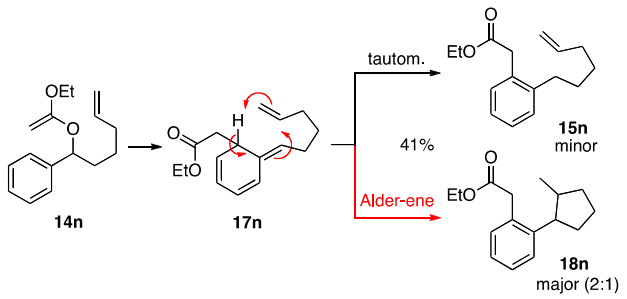


**Scheme 4.** Tandem Claisen Rearrangement/Alder-Ene Reaction of **14n** Showing Evidence for Formation of Isotoluene Intermediate **17n**. Conditions are Method B, DMF (see Table 2).

## Conclusions

We have demonstrated the successful implementation of Claisen rearrangements involving benzyl vinyl ether derivatives. These substrates are intrinsically much less prone to Claisen rearrangements than are allyl vinyl ethers **1** or allyl phenyl ethers **3**, but we have shown that their rearrangements are promoted by an α-alkoxy substituent on the vinyl group, similar to the Johnson–Claisen rearrangement. These results expand the applicability of Claisen rearrangements to a challenging and previously little-studied substrate class. Studies of the mechanism of the rearrangement will be reported in due course.

## Experimental Section

**Typical procedure for the synthesis of bromoacetals 13:** To a round-bottom flask (under argon and cooled in an ice bath) was added 50 mL DCM and 0.5 mL (9.4 mmol) bromine (dissolved in approximately 4 mL DCM). Ethyl vinyl ether (1.00 mL, 10.3 mmol) was then added dropwise, the mixture changed from red-brown to clear (indicating complete consumption of bromine). The mixture was left to stir at 0 °C for 5 minutes before DIPEA (1.8 mL, 10.3 mmol) was added in one portion followed by the requisite alcohol **12** (6.3 mmol) dropwise. Once addition was complete, the reaction flask was removed from the ice bath and allowed to stir at room temperature under argon. After stirring overnight, the mixture was washed with 30 mL saturated $NaHCO_3$ solution then 30 mL brine. The organic phase was dried with $Na_2SO_4$, filtered and evaporated in vacuo to a brown oil. Products were purified by silica gel chromatography.

**Typical procedure for one-pot elimination-Claisen rearrangement:** To a round-bottom flask, equipped with a reflux condenser, under argon was placed the requisite bromoacetal **13** and DMF (to form a 0.5 M solution). To this was added 1.1 eq KO*t*Bu. The reaction mixture became warm and a cloudy precipitate formed.[23] The mixture was allowed to stir at RT for 30 minutes before being heated at 155 °C (oil bath temperature) overnight. The reaction mixture was then poured into 20 mL distilled water and extracted with 5 × 20 mL hexanes. The organic layer was washed with 2 × 20 mL distilled water and 20 mL brine, then dried ($Na_2SO_4$), filtered and evaporated in vacuo to give the crude product. Hydrolysis of the crude product with ethanolic KOH yielded the product acid **16**.

## Acknowledgements

We thank the Australian Research Council (FT120100632 to E.H.K.) for financial support. Computational resources were provided by the National Computational Infrastructure National Facility (Australia) and The University of Queensland Research Computing Centre.

**Keywords:** Claisen rearrangement • Benzyl-Claisen • Ketene acetal • Density Functional Theory • Alder-ene

[1] L. Claisen, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157-3166.
[2] A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939-3002.
[3] a) R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.* **1972**, *94*, 5897-5898; b) R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.
[4] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
[5] a) A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425-2429; b) D. Felix, K. Gschwend-Steen, A. E. Wick, A. Eschenmoser, *Helv. Chim. Acta* **1969**, *52*, 1030-1042.
[6] a) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423-1452; b) M. Hiersemann, U. Nubbemeyer, Eds, *The Claisen Rearrangement*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2007**.
[7] a) A. W. Burgstahler, L. K. Gibbons, I. C. Nordin, *J. Chem. Soc.* **1963**, 4986-4989; b) I. Shiina, H. Nagasue, *Tetrahedron Lett.* **2002**, *43*, 5837-5840; c) S. Raucher, A. S. T. Lui, *J. Am. Chem. Soc.* **1978**, *100*, 4902-4903; d) W. J. le Noble, P. J. Crean, *J. Am. Chem. Soc.* **1964**, *86*, 1649-1650; e) V. Valerio, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2011**, *17*, 4742-4745.
[8] S. M. McElvain, H. I. Anthes, S. H. Shapiro, *J. Am. Chem. Soc.* **1942**, *64*, 2525-2531.
[9] For Claisen rearrangements of benzyl propargyl ethers, see Tudjarian, A. A.; Minehan, T. G. *J. Org. Chem*. **2011**, *76*, 3576–3581.
[10] For previous CBS-QB3 calculations on the Claisen rearrangements of **1a** and **3**, see: S. Osuna, S. Kim, G. Bollot, K. N. Houk, *Eur. J. Org. Chem.* **2013**, *2013*, 2823-2831.
[11] Several previous computational studies of the aromatic Claisen rearrangement of **3** have proposed that the tautomerization step (**4**→**5**) may be rate limiting in certain media. See (a) Yamabe, S.; Okumoto, S.; Hayashi, T. *J. Org. Chem*. **1996**, *61*, 6218; (b) Zheng, Y.; Zhang, J. *J. Phys. Chem. A* **2010**, *114*, 4325; (c) Ghadari, R.; Shaabani, A.; *J. Mol. Model.* **2012**, *18*, 319.
[12] For previous theoretical studies of substituent effects on the Claisen rearrangement, see: (a) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 2877. (b) Aviyente, V.; Yoo, H. Y.; Houk, K. N. *J. Org. Chem* **1997**, *62*, 6121–6128. (c) Aviyente, V.; Houk, K. N. *J. Phys. Chem. A* **2001**, *105*, 383–391.
[13] a) Y. Ueno, O. Moriya, K. Chino, M. Watanabe, M. Okawara, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351-1356; b) G. Stork, P. M. Sher, H. L. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6384-6385.
[14] D. S. Middleton, N. S. Simpkins, *Synth. Commun.* **1989**, *19*, 21-29.
[15] P. Magnus, N. Sane, B. P. Fauber, V. Lynch, *J. Am. Chem. Soc.* **2009**, *131*, 16045-16047.
[16] a) W. J. Bailey, L.-L. Zhou, *Tetrahedron Lett.* **1991**, *32*, 1539-1540; b) Q.-H. Zheng, J. Su, *Synth. Commun.* **1999**, *29*, 3467-3476.
[17] Eschenmoser has noted a similar effect when applying the Eschenmoser-Claisen rearrangement to benzyl alcohol. See: Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.
[18] a) F. C. Gozzo, S. A. Fernandes, D. C. Rodrigues, M. N. Eberlin, A. J. Marsaioli, *J. Org. Chem.* **2003**, *68*, 5493-5499; b) W. N. White, C. D. Slater, *J. Org. Chem.* **1961**, *26*, 3631-3638.
[19] 2-Naphthylmethanol **12i** leads to **19** as the sole product when submitted to Eschenmoser-Claisen conditions. See: Felix, D.;

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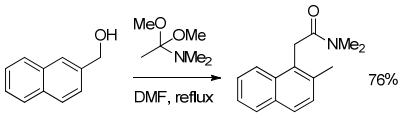
Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.




**12i** **19**

[20] a) J. J. Gajewski, A. M. Gortva, *J. Am. Chem. Soc.* **1982**, *104*, 334-335; b) J. J. Gajewski, A. M. Gortva, *J. Org. Chem.* **1989**, *54*, 373-378; c) W. D. Graham, J. G. Green, W. A. Pryor, *J. Org. Chem.* **1979**, *44*, 907-914.

[21] W. H. Miles, E. A. Dethoff, H. H. Tuson, G. Ulas, *J. Org. Chem.* **2005**, *70*, 2862-2865.

[22] W. Oppolzer, V. Snieckus, *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476-486.

[23] The cloudy precipitate (KBr) is also observed when the reaction is run in diglyme.

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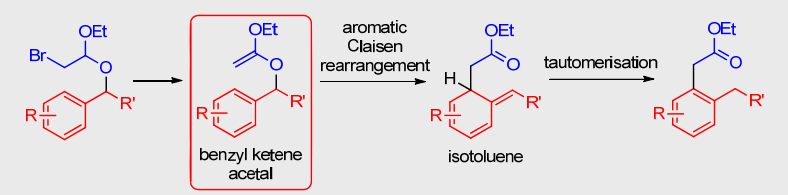


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**Benzylic Claisen rearrangements***

*Jed M. Burns, Elizabeth H. Krenske and Ross P. McGeary**

***Page No. – Page No.***

**Aromatic Claisen Rearrangements of Benzyl Ketene Acetals: Conversion of Benzylic Alcohols to (Ortho-Tolyl)Acetates**

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[4] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741-743.
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[6] a) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423-1452; b) M. Hiersemann, U. Nubbemeyer, Eds, *The Claisen Rearrangement*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2007**.

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[7] a) A. W. Burgstahler, L. K. Gibbons, I. C. Nordin, *J. Chem. Soc.* **1963**, 4986-4989; b) I. Shiina, H. Nagasue, *Tetrahedron Lett.* **2002**, *43*, 5837-5840; c) S. Raucher, A. S. T. Lui, *J. Am. Chem. Soc.* **1978**, *100*, 4902-4903; d) W. J. le Noble, P. J. Crean, *J. Am. Chem. Soc.* **1964**, *86*, 1649-1650; e) V. Valerio, C. Madelaine, N. Maulide, *Chem. Eur. J.* **2011**, *17*, 4742-4745.

[8] S. M. McElvain, H. I. Anthes, S. H. Shapiro, *J. Am. Chem. Soc.* **1942**, *64*, 2525-2531.

[9] For Claisen rearrangements of benzyl propargyl ethers, see Tudjarian, A. A.; Minehan, T. G. J. Org. Chem. 2011, 76, 3576–3581.

[10] S. Osuna, S. Kim, G. Bollot, K. N. Houk, *Eur. J. Org. Chem.* **2013**, *2013*, 2823-2831.

[11] The proton transfer step of the aromatic Claisen rearrangement is proposed to be rate limiting. See (a) Yamabe, S.; Okumoto, S.; Hayashi, T. J. Org. Chem. 1996, 61, 6218; (b) Zheng, Y.; Zhang, J. The Journal of Physical Chemistry A 2010, 114, 4325.

[12] Previous theoretical studies of substituent effects on the Claisen rearrangement: (a) Yoo, H. Y.; Houk, K. N. J. Am. Chem. Soc. 1997, 119, 2877–2884. (b) Aviyente, V.; Yoo, H. Y.; Houk, K. N. J. Org. Chem. 1997, 62, 6121–6128. (c) Aviyente, V.; Houk, K. N. J. Phys. Chem. A 2001, 105, 383–391.

[13] a) Y. Ueno, O. Moriya, K. Chino, M. Watanabe, M. Okawara, *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351-1356; b) G. Stork, P. M. Sher, H. L. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6384-6385.

[14] D. S. Middleton, N. S. Simpkins, *Synth. Commun.* **1989**, *19*, 21-29.

[15] P. Magnus, N. Sane, B. P. Fauber, V. Lynch, *J. Am. Chem. Soc.* **2009**, *131*, 16045-16047.

[16] a) W. J. Bailey, L.-L. Zhou, *Tetrahedron Lett.* **1991**, *32*, 1539-1540; b) Q.-H. Zheng, J. Su, *Synth. Commun.* **1999**, *29*, 3467-3476.

[17] Eschenmoser has noted a similar effect when applying the Eschenmoser-Claisen rearrangement to benzyl alcohol. See: Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. Helv. Chim. Acta 1969, 52, 1030.

[18] a) F. C. Gozzo, S. A. Fernandes, D. C. Rodrigues, M. N. Eberlin, A. J. Marsaioli, *J. Org. Chem.* **2003**, *68*, 5493-5499; b) W. N. White, C. D. Slater, *J. Org. Chem.* **1961**, *26*, 3631-3638.

[19] 2-naphthyl methanol 13m leads to 22 as the sole product when submitted to Eschenmoser-Claisen conditions. See: Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. Helv. Chim. Acta 1969, 52, 1030.

[20] a) J. J. Gajewski, A. M. Gortva, *J. Am. Chem. Soc.* **1982**, *104*, 334-335; b) J. J. Gajewski, A. M. Gortva, *J. Org. Chem.* **1989**, *54*, 373-378; c) W. D. Graham, J. G. Green, W. A. Pryor, *J. Org. Chem.* **1979**, *44*, 907-914.

[21] W. H. Miles, E. A. Dethoff, H. H. Tuson, G. Ulas, *J. Org. Chem.* **2005**, *70*, 2862-2865.

[22] W. Oppolzer, V. Snieckus, *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476-486.

[23] The cloudy precipitate (KBr) is also observed when the reaction is run in diglyme.

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