A Convenient Triisobutylaluminium (TIBAL)-Promoted Johnson–Claisen Approach to γ,δ-Unsaturated Alcohols

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Received 5 March 2009

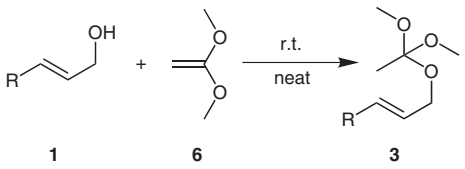
Abstract: Mixed ortho esters derived from allylic alcohols undergo methanol elimination in the presence of triisobutylaluminium (TIBAL) at room temperature to form mixed ketene acetals. TIBAL then promotes immediate Claisen rearrangement of these intermediates, and subsequent reduction of the ester products, to give unsaturated γ,δ-primary alcohols in a convenient, one-pot procedure.

Key words: triisobutylaluminium, mixed ortho esters, ketene dimethyl acetal, Johnson–Claisen rearrangement, γ,δ-unsaturated alcohols

The Johnson–Claisen rearrangement is a valuable method for the formation of new carbon–carbon bonds.[1] The effectiveness of the approach can be attributed, at least in part, to the execution of several steps in a one-pot procedure. Typically, an allylic alcohol is heated in the presence of a large excess of ortho ester and a catalytic amount of a weak protic acid at temperatures ranging from 140–200 °C.[1] The reaction sequence involves an allylic alcohol **1** condensing with an ortho ester **2** to form a mixed ortho ester intermediate **3**, which is generally not isolated. Subsequent acid-catalysed alcohol elimination results in formation of a mixed ketene acetal **4**, which immediately undergoes a Claisen rearrangement to give a γ,δ-unsaturated ester **5** (Scheme 1).[2] Despite the fact that this reaction suffers from high reaction temperatures and prolonged reaction times, the Johnson–Claisen rearrangement is regularly employed in natural product syntheses, an extensive review of which was recently reported by Langlois.[1] Additionally, an excellent discussion on the various Claisen rearrangements can be found in the reviews of Ziegler[3] and Castro.[4]

We wish to expand upon the versatility of this reaction and we now report a one-pot, room temperature, Lewis acid catalysed method for the Johnson–Claisen rearrangement in which the intermediate γ,δ-unsaturated ester **5** is further reduced to the corresponding γ,δ-unsaturated alcohol. γ,δ-Unsaturated alcohols are useful intermediates in natural product syntheses, particularly as precursors for molecular constructs containing tetrahydrofurans and tetrahydropyrans.[5–7]

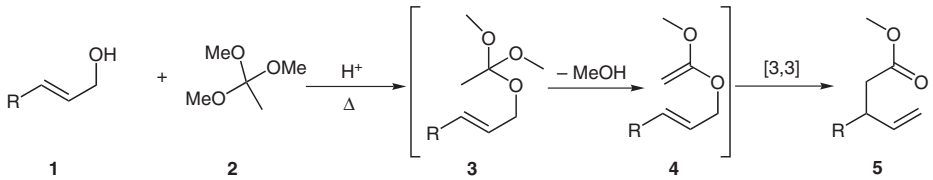
As part of our studies on the Johnson–Claisen rearrangement we recently reported a mild, solvent-free, uncatalysed, quantitative procedure for the synthesis of mixed ortho esters (Equation 1).[8]



1 6 3

Equation 1 Primary and secondary allylic alcohols react with ketene dimethyl acetal to form mixed ortho esters at room temperature without the need for solvent or catalyst[8]

Having developed an attractive route to mixed ortho esters, we sought to develop a comparably mild method for converting these into mixed ketene acetals and promoting their subsequent Claisen rearrangement. TIBAL caught our attention because it is a Lewis acid and reducing agent which has previously been shown to promote methanol elimination in dimethoxyalkanes.[9] The [3,3]-sigmatropic rearrangement of allyl vinyl ethers and the Ketal–Claisen rearrangement are also known to be promoted by TIBAL.[10,11] As envisioned, we successfully converted a mixed ortho ester derived from an allylic alcohol **3** into a γ,δ-unsaturated alcohol **7** via TIBAL-mediated Johnson–



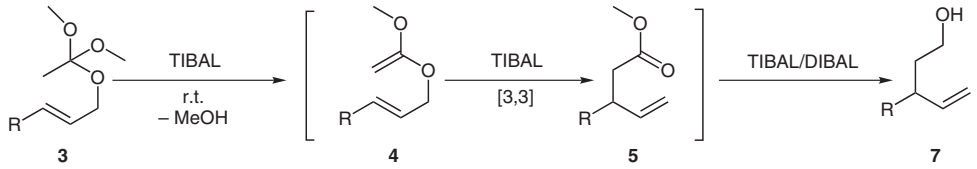
1 2 3 4 5

Scheme 1 The Johnson–Claisen rearrangement

SYNLETT 2009, No. 11, pp 1749–1752
Advanced online publication: 16.06.2009
DOI: 10.1055/s-0029-1217382; Art ID: D06609ST

Claisen rearrangement. Further reduction of the intermediate γ,δ-unsaturated ester **5** was accomplished by the action of TIBAL, along with subsequent addition of DIBAL. To the best of our knowledge there are no reports in the literature of TIBAL promoting the Johnson–Claisen rearrangement. We are pleased to report a TIBAL-catalysed Johnson–Claisen rearrangement using a one-pot procedure that has been applied to a variety of allylic alcohols (Table 1).

Table 1 Reaction of Various Mixed Ortho Esters with TIBAL to Yield γ,δ-Unsaturated Primary Alcohols



3 **4** **5** **7**

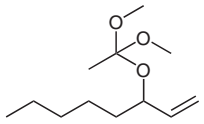
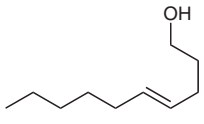
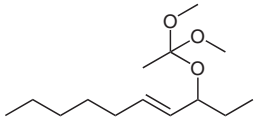
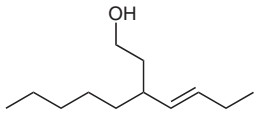
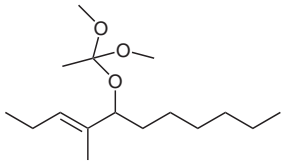
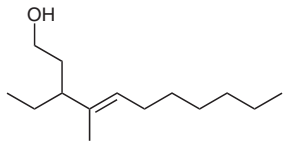
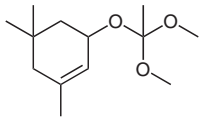
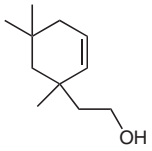
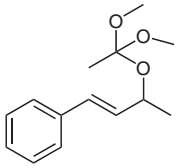
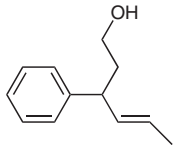
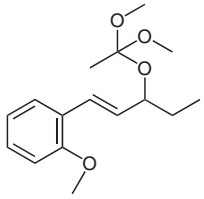
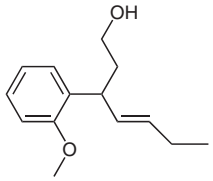
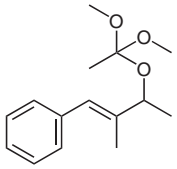
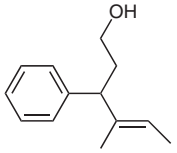
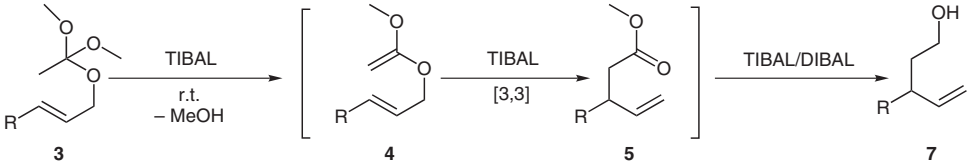
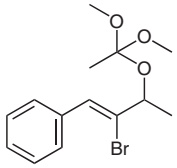
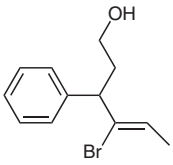
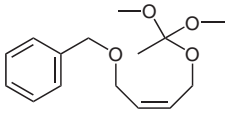
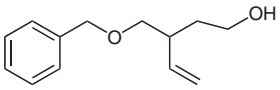
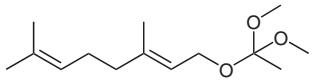
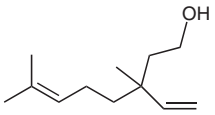
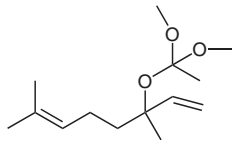
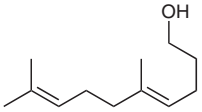
Entry	Substrate	Product	Ratio *Z*/*E*[a]	Yield (%)[b]
1	 **8**	 **9**	14:86	70
2	 **10**	 **11**	15:85	79
3	 **12**	 **13**	17:83	77
4	 **14**	 **15**	1	23[c]
5	 **16**	 **17**	14:86	75
6	 **18**	 **19**	15:85	67
7	 **20**	 **21**	16:84	71

Table 1 Reaction of Various Mixed Ortho Esters with TIBAL to Yield γ,δ-Unsaturated Primary Alcohols (continued)



Entry	Substrate	Product	Ratio *Z*/*E*[a]	Yield (%)[b]
8	 **22**	 **23**	92:8	64
9	 **24**	 **25**	N/A	52
10	 **26**	 **27**	N/A	54
11[12]	 **28**	 **29**	43:57[d]	81

[a] The *E*/*Z* ratio was measured by ^{1}H NMR spectroscopy.
[b] Isolated uncorrected yields.
[c] Lower yield due to evaporative losses.
[d] The *E*/*Z* ratio was measured by GCMS.

Isolated yields of the product unsaturated alcohols **7** range from moderate for mixed ortho esters derived from primary alcohols, to good through to excellent for mixed ortho esters derived from secondary and tertiary alcohols. The variation in yields can be explained by the bulky TIBAL coordinating to the least hindered ortho ester oxygen, which in the case of mixed ortho esters derived from secondary and tertiary alcohols, is the methoxy oxygen, making methanol elimination the favoured pathway and thereby promoting ketene acetal formation. In contrast, mixed ortho esters derived from primary alcohols are less hindered at the allylic oxygen. This is demonstrated for primary alcohol derivatives **24** and **26** which gave reaction yields of 52% and 54%, respectively, indicating that there is an almost equal likelihood of TIBAL coordinating to either the methoxy oxygen or the allylic oxygen, resulting in either ketene acetal formation and subsequent rearrangement, or ortho ester elimination to regenerate the starting allylic alcohol.

Mixed ortho esters derived from allylic alcohols possessing mono-, di- and tri-substituted alkenes, together with both *cis* and *trans*-alkenes were all capable of rearrangement. The reaction conditions are compatible with the presence of other functional groups: an additional double bond (**26** and **28**), an aromatic methyl ether **18**, a vinyl bromide **22** and, quite surprisingly, a benzyl ether **24** are all stable to TIBAL. TIBAL is regularly employed to reductively cleave benzyl ethers of carbohydrates, with the reaction typically being performed at 50 °C.[13] Even though the addition of TIBAL to mixed ortho esters is exothermic, the reaction products of substrate **24** in their entirety consisted of rearranged alcohol **25** and some recovered starting material, with no detectable trace of debenzylated alcohol.

Mixed ortho esters derived from acyclic secondary allylic alcohols predominantly lead to the *E*-isomer on rearrangement as shown in entries 1–3 and 5–7. Interestingly, the mixed ortho ester derived from the tertiary alcohol **28** gave a 43:57 *Z*/*E* mixture of reaction products; the lower than expected yield of the *E*-isomer can be attributed to the presence of an unfavourable 1,3-diaxial interaction between the methoxy group and the methyl group in the chair-like transition-state, which leads to the *E*-isomer of

29. There are no steric impediments in the alternate boat-like transition-state leading to the *Z*-isomer of **29**.

In conclusion, we have developed a straightforward, room temperature procedure[14] for the Johnson–Claisen rearrangement. This method avoids the vigorous reaction conditions of the standard method, whilst adding the further step of reducing the ester to the alcohol. The synthesis of a mixed ortho ester followed by ketene acetal formation, rearrangement and subsequent reduction of the ester to the alcohol, all occur in the one-pot to afford a γ,δ-unsaturated primary alcohol. We believe this method is a useful alternative to the standard Johnson–Claisen conditions.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

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(12) Mixed ortho esters derived from tertiary alcohols cannot be synthesised by the standard method which we employ.[8] Ketene dimethyl acetal (3.17 mL, 33 mmol) and propionic acid (~0.1 mL) were added to linalool (4 mL, 22 mmol; entry 11) and stirred at r.t. for 1.5 h. Distillation of the crude reaction mixture allowed isolation of the mixed ortho ester **28** as a clear liquid (1.5 g, 28%).
(13) Lecourt, T.; Alexandre, H.; Pearce, A. J.; Sollogoub, M.; Sinay, P. *Chem. Eur. J.* **2004**, *10*, 2960.
(14) In a typical experiment, ketene dimethyl acetal (3 mmol per hydroxyl group) was added cautiously to the anhyd allylic alcohol (1 mmol) and stirred rapidly at r.t. under argon for ~2 h. Excess ketene dimethyl acetal was removed in vacuo, giving the pure mixed ortho ester in quantitative yield.[8] To the same vessel, TIBAL (6 equiv, 1 M solution in toluene) was added at r.t. under argon over ~2 min. The reaction immediately became exothermic and was typically allowed to stir at r.t. overnight, however, the reaction was usually complete after ~6 h. DIBAL (1–2 equiv, 1 M in toluene) was added and the reaction was stirred for 2 h to reduce any remaining traces of ester. The reaction was quenched at –78 °C by the cautious addition of 5% HCl and then allowing the reaction to warm to room temperature. The aqueous layer was extracted with Et_2O (3 × 40 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and evaporated to give the crude product as a yellow oil (we found that the HCl quench worked better than aqueous NaOH[10,11] or aqueous sodium citrate solution[9] as it avoided formation of solid aluminum salts). Silica column chromatography was required to separate residual starting alcohol from the rearranged γ,δ-unsaturated primary alcohol. All new compounds were characterised by ^1H and ^{13}C NMR and/or by HRMS and elemental analysis. The spectroscopic data can be found in the supplementary information.