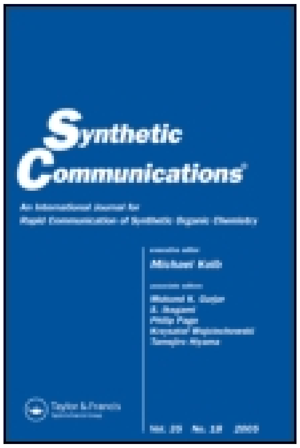

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ABSTRACT

A protocol for one-pot Claisen rearrangement with *n*-butyl vinyl ether is described. Upon heating allylic alcohols with excess *n*-butyl vinyl ether with catalytic amount of $Hg(OAc)_2$ and NaOAc, Claisen rearrangement takes place through in situ formation of the requisite allyl vinyl ether.

The Claisen rearrangement of allyl vinyl ether is a convenient tool for preparation of γ,δ-unsaturated aldehydes from allylic alcohols.[1] In conventional protocol, a two-step transformation, consisting of acid[2] or mercury acetate-catalyzed[3] vinylation of allylic alcohols with a large excess of ethyl vinyl ether and the subsequent thermolysis at high temperature, is employed. Since the vinyl ether formation is an equilibrium process, the reaction is usually slow and low yielding. Although this two-step transformation has been carried out in a one-pot procedure, use of a pressure-proof

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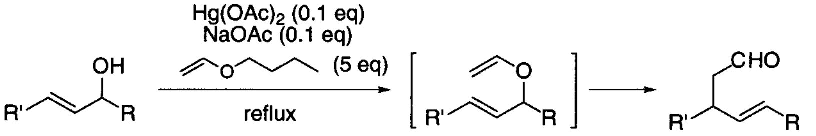
*Corresponding author.

reaction vessel or a sealed tube was required due to the high volatility of ethyl vinyl ether.[2,4] To date, several modified protocols have been developed,[5–8] but none of them seems to be practical enough for preparation of a large quantity of γ,δ-unsaturated aldehydes. During the study of natural products synthesis, we have found that one-pot transformation involving vinylation and Claisen rearrangement was quite effectively performed in *n*-butyl vinyl ether at refluxing temperature. While *n*-butyl vinyl ether has occasionally been used for vinyl ether formation,[3a–9] to the best of our knowledge, no examples of its application to one-pot Claisen rearrangement has been reported. We report herein a highly practical protocol for one-pot Claisen rearrangement with *n*-butyl vinyl ether, which is practically suited for a large-scale preparation of γ,δ-unsaturated aldehydes (scheme).



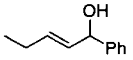
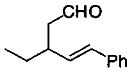
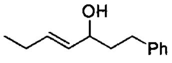
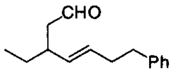
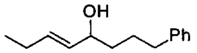
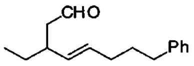
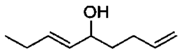
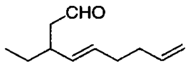
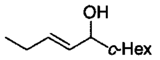
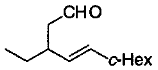
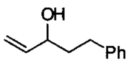
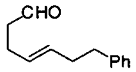
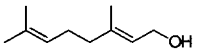
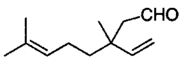
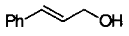
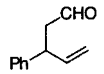
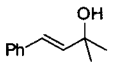
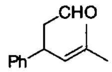
Scheme.

Allylic alcohols were directly converted to the corresponding γ,δ-unsaturated aldehydes in high overall yields by a quite simple procedure. Thus, a mixture of allylic alcohol, five equivalents of *n*-butyl vinyl ether, and catalytic $Hg(OAc)_2$ (0.1 eq.) and NaOAc (0.1 eq.) was stirred at reflux for 10 to 40 h. The irreversible Claisen rearrangement of the vinyl ether at refluxing temperature shifted the equilibrium of the reaction to vinyl ether side, allowing us to reduce the amount of *n*-butyl vinyl ether down to five equivalents. The other advantage of using *n*-butyl vinyl ether is that excess *n*-butyl vinyl ether could easily be removed by concentration on a rotary evaporator.

As shown in the table, the protocol is applicable to a variety of allylic alcohols. The reaction of secondary allylic alcohols bearing *trans*-1,2-disubstituted olefins proceeded smoothly to furnish the desired aldehydes in good yields (Entries 1–5). Due to low reactivity of vinyl ethers formed, geraniol forming quarternary carbon center, styrene derivative giving deconjugated product, and a terminal olefin required prolonged reaction time (Entries 6–9). For these relatively unreactive substrates, heating the mixture up to 180°C in a sealed tube (Condition B) shortened the reaction time.

The practical utility of this protocol has been proved by a large-scale preparation of γ,δ-unsaturated aldehydes (table, Entry 1). A mixture of allylic alcohol prepared from phenyl magnesium bromide (1.2 mol) and

Table One-Pot Claisen Rearrangement Using *n*-Butyl Vinyl Ether

Entry	Substrate	Condition[a]	Time (h)	Product	Yield (%)[b]
1		A	10		72[c]-79
2		A	12		67
3		A	16		83
4		A	32		71
5		A	23		64
6[e]		A B[d]	40 5.5		56 47
7[e]		A B	36 13		61 67
8[e]		A B	40 4		47 52
9[e]		B[d]	8		53

[a]Condition A; Hg(OAc)$_2$ (0.1 eq), NaOAc (0.1 eq), *n*-butyl vinyl ether (5 eq), reflux. Condition B; Hg(OAc)$_2$ (0.1 eq), NaOAc (0.1 eq), *n*-butyl vinyl ether (5 eq), 180 °C in a sealed tube. [b]The yields are based on isolated materials. [c]Large-scale (0.82 mol) reaction. [d]After heating for four hours, an additional 0.1 equivalent of Hg(OAc)$_2$ was added. [e]Trace amount of the starting materials and the corresponding vinyl ethers were recovered. No improvement of the yields was observed after prolonged reaction time.

2-pentenal (0.82 mol), *n*-butyl vinyl ether (420 ml, 5 eq.), Hg(OAc)$_2$ (26.0 g), and NaOAc (6.7 g) was stirred at reflux for 10 h, followed by a treatment with NaSH. After an aqueous work-up, distillation gave the desired aldehyde (111 g) in 72% overall yield from the starting aldehyde.

In conclusion, we have developed a one-pot protocol for the in situ generation of allyl vinyl ether to effect direct Claisen rearrangement using inexpensive and commercially available *n*-butyl vinyl ether. The process may find a widespread use in organic synthesis.

EXPERIMENTAL

A Typical Procedure for One-Pot Claisen Rearrangement. Preparation of 3-Ethyl-5-phenyl-4-pentenal

1-Phenyl-2-penten-1-ol was prepared by addition of phenylmagnesium bromide (0.89 M in THF, 9.0 ml, 8.02 mmol) to 2-pentenal (500 mg, 5.94 mmol). After conventional aqueous work-up, the crude material was directly subjected to the one-pot Claisen rearrangement. To the solution of the crude allylic alcohol in *n*-butyl vinyl ether (4.11 ml, 31.8 mmol) were added $Hg(OAc)_2$ (202 mg, 0.635 mmol) and NaOAc (52.9 mg, 0.635 mmol). The resulting suspension was stirred at reflux for 10 h. After treatment with $NaSH{\cdot}nH_2O$ (55.9 mg) at room temperature for an hour, the reaction mixture was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, filtered through a pad of Celite®, and concentrated. Purification by flash column chromatography on silica gel (hexanes to 2.5% EtOAc in hexanes, gradient) gave 3-ethyl-5-phenyl-4-pentenyl aldehyde (0.89 g, 79%, 2 steps) as a colorless oil; IR (film, cm^{-1}): 3425, 2963, 2723, 2361, 1724, 1598, 1449, 968, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, $J = 14.8$ Hz, 1H), 1.38–1.61 (m, 2H), 2.45–2.56 (m, 2H), 2.66–2.75 (m, 1H), 6.06 (dt, $J = 7.3$, 15.9 Hz, 1H), 6.44 (d, $J = 15.9$ Hz, 1H), 7.19–7.35 (m, 5H), 9.75 (t, $J = 4.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 28.0, 39.4, 49.7, 126.0, 127.0, 129.0, 131.0, 132.0, 137.0, 202. Anal. Calcd for $C_{13}H_{16}O$: C; 82.94, H; 8.57. Found: C; 82.72, H; 8.58.

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