Tetrahedron Letters Vol. 21, pp 2123 - 2124
0040-4039/80/0522-2123$02.00/0

A NOVEL SYNTHESIS OF 4-CYCLOHEPTENONES

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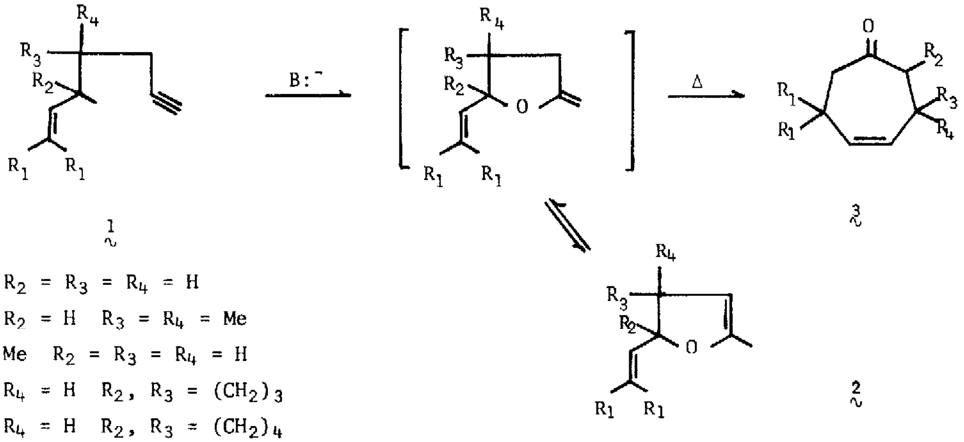
4-Cycloheptenones, mono and bicyclic, can be prepared by a base catalyzed thermal reaction of 1-hepten-6-yn-3-ols.

A broad variety of sesquiterpenes, mono and bicyclic, either incorporate or are readily accessible from compounds having a 4-cycloheptenone moiety.[1] It appeared that the synthesis of Demole and Enggist,[2] studied in detail by Rhoads,[3] would be very useful if generalized. The major problem rests in the preparationof 2-methylene-5-vinyltetrahydrofurans. We describe here a novel solution to the problem, its advantages and some limitations. The approach is dependent on the base catalyzed cyclization of 4-pentyn-1-ols first described by Paul and Tchelitcheff[4] and exploited further by Eglinton, Jones and Whiting.[5] This cyclization uses catalytic amounts (3-5%) of a strong base (NaH) and since an added vinyl group should not interfere the resulting 2-methylene-5-vinyltetrahydrofuran should be thermally convertible to a 4-cycloheptenone. In some cases the process can be accomplished in a single step while in others it may be preferable to carry out the reaction in two steps.



a. $R_1 = R_2 = R_3 = R_4 = H$
b. $R_1 = R_2 = H \quad R_3 = R_4 = Me$
c. $R_1 = Me \quad R_2 = R_3 = R_4 = H$
d. $R_1 = R_4 = H \quad R_2, R_3 = (CH_2)_3$
e. $R_1 = R_4 = H \quad R_2, R_3 = (CH_2)_4$

For example **1a** shows no tendency to form **2a** when heated at 125° for 8 hrs., but is converted in 30% yield (not optimized) to **3a** at 170° for 24 hrs. Conversely **1b** is readily converted to **2b** in 80% yield under the milder conditions above, and **2b** gives **3b** (81%) when heated at 225° in quinoline for 24 hrs. Presence of two methyls on the terminal carbon of the vinyl group prevents the reaction entirely. Bicyclic compounds **1d** and **1e** are converted to **3d** and **3e** in a single step in diphenyl ether solution. At 195° for 12 hrs. **1d** gives **3d** in 51% yield, and at 185° (12 hrs) **1e** is converted to **3e** in 78% yield. We attribute the failure of **1c** to react to steric inhibition of the Claisen rearrangement step, but otherwise the scheme is adapted to the preparation of a wide variety of substituted cycloheptenones.

The single step procedure is simple and convenient. For example a solution containing 1g (6.1 mmol) of **1e** in 3 ml of diphenyl ether was placed in a 10 ml round-bottomed flask under nitrogen. After 0.19 ml of 1.6 M methyllithium in ether (0.3 mmol) had been added, the mixture was stirred at 185° for 12 hrs. The product was separated on silica gel (pentane/ether) and the crude liquid was distilled in a Kugelrohr giving 0.84 g (84%) of **3e**, NMR (CCl_4)δ 1.30 (m, 3H) 1.78(m, 8H), 2.26(m, 5H), 2.68(m, 2H) 5.54(m, 1H).

Acknowledgement: This work was supported in part by award of a Tartar Fellowship to D. T. The HA 100 and FT80 NMR spectrometers used in this research were purchased with the aid of NSF instrument grants.

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(Received in USA 25 January 1980)