CHEMISTRY LETTERS, pp. 1537-1538, 1982.

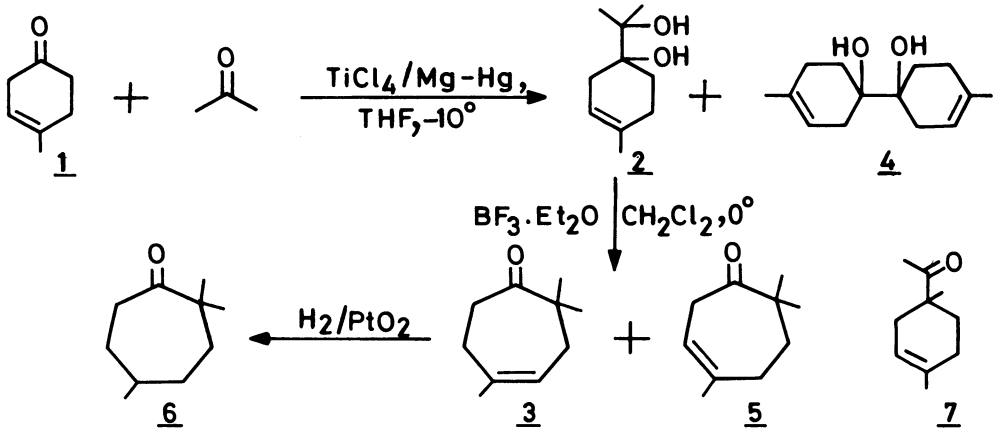
LEWIS ACID CATALYSED PINACOL REARRANGEMENT - A SHORT SYNTHESIS OF KARAHANAENONE

Vidya BHUSHAN and Srinivasan CHANDRASEKARAN*
Department of Chemistry, Indian Institute of Technology, Kanpur-208016, U.P., India

The pinacolic coupling reaction has been effectively used to prepare the unsymmetrical pinacol 2 and this key intermediate underwent a smooth ring enlargement to the monoterpene karahanaenone 3, an odoriferous constituent of Japanese hop and Cypress oil.

Our interest in the chemistry of low valent transition metal reagents prompted us to look into the scope and effectiveness of the pinacolic coupling reaction of carbonyl compounds mediated by Ti(II) species generated by the reaction of titanium tetrachloride and amalgamated magnesium.[1] We have now extended these studies to the synthesis of the unsymmetrical pinacol 2 and its rearrangement which results in a very short synthesis of the 7-ring monoterpene, karahanaenone 3, an odoriferous constituent of Japanese hop and Cypress oil Cupressus sempervirens.[2]

Reductive coupling of readily available 4-methyl-3-cyclohexenone 1[3] (1 equiv.) and acetone (4 equiv.) in the presence of titanium tetrachloride (4 equiv.) and amalgamated magnesium (8 equiv.) (THF, -10°, 0.75 hr)[1] resulted in the formation of the unsymmetrical pinacol (2, 57%), which was easily separated by flash column chromatography as an oil. ν_{max}: 3425 cm^{-1}; $\delta_H(CDCl_3)$: 1.2 (s, 6 H), 1.7 (s, 3 H), 1.4 - 2.34 (m, 8 H), 5.32 (br, 1 H) . A small amount of the symmetrical pinacol (4, 5%) was also obtained. The mineral acid catalysed pinacol rearrangement of 2 did not give any of the desired ring enlarged ketone 3. However, treatment of 2 with $BF_3.Et_2O$ (1 equiv., CH_2Cl_2, 0°, 12 hr) yielded a mixture of two isomeric products (82%). The GC-Mass analysis (10% SE-30, 140°) showed the presence of two components with molecular weight of 152, in the ratio of 70:30. Hydrogenation of the crude reaction mixture gave rise to a single product (GC) 6[2a] (M^+= 154). The crude reaction mixture from the Lewis acid catalysed rearrangement was purified by preparative gas chromatography to yield karahanaenone 3 (70%) as a pleasant smelling oil. The synthetic karahanaenone 3, ν_{max}: 1710 cm^{-1}; $\delta_H(CDCl_3)$: 1.09 (s, 6 H), 1.67 (s, 3 H), 2.25 (br, 4 H), 2.74 (br, 2 H), 5.43 (br, 1 H); (semicarbazone, m.p. $164-68^{\circ}$),



showed spectral data closely similar to those reported for the natural product.[4] The minor component 5 (30%) had ν_{max}: 1710 cm^{-1}; $\delta_H(CDCl_3)$: 1.12 (s, 6 H), 1.66 (s, 3 H), 1.78 - 2.4 (br, 4H), 3.18 (br, d, 2H), 5.32 (br, 1 H).

It is of interest to note that the Lewis acid catalysed rearrangement of 2 did not give any of the methyl ketone 7 although methyl ketones of this type were the major products under similar conditions.[1] Attempts to effect this ring enlargement using other Lewis acids and mineral acids led to complex mixtures of products. The simple route leading to 2 together with the crucial ring expansion has resulted in a very short synthesis of the monoterpene karahanaenone.

Acknowledqements. We thank the Department of Science and Technology, New Delhi for financial assistance.

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(Received August 6, 1982)