Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2629-2630, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00345-0

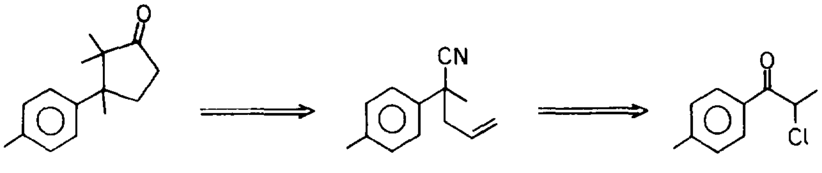
An Efficient Synthesis of α-Cuparenone

**Subhash P. Chavan*, T. Ravindranathan*, Sachindra S. Patil,
Vijay D. Dhondge and Shubhada W. Dantale**

Division of Organic Chemistry : Technology
National Chemical Laboratory, Pune - 411 008.

Abstract : *Synthesis of α-Cuparenone is described. The key step involved are photorearrangement of α-halo aryl ketone (4) to 1-methyl-1-(p-tolyl)acetic acid (5) and extremely mild, essentially neutral, room temperature /3-aza-claisen reaction of N-allylamide (6).*

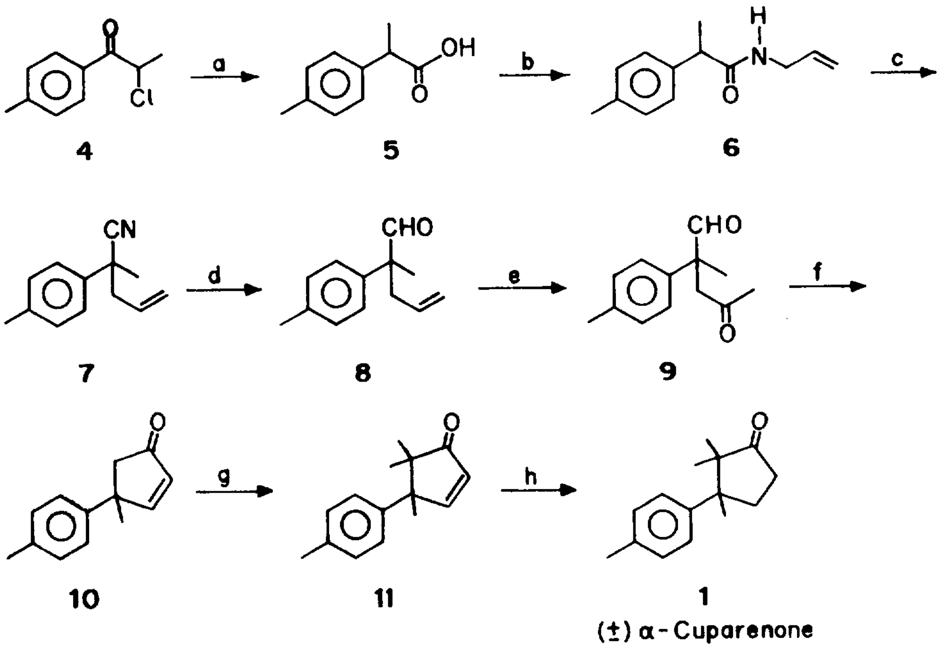
α-Cuparenone (**1**) a bicyclic terpene isolated from *Thuja Orientallis (Mayurpankhi) by Sukh Dev*[1] and co-workers is a synthetic challenge to organic chemists as it contain two contigious quaternary centers in a cyclopentane ring and it has been constructed in variety of the ways[2]. As a part of our interest in cyclopentane rings[3] in naturally occurring pentanoids, we became interested in the synthesis of α-Cuparenone. Although variety of methods for the synthesis of five membered rings are reported in literature, there still exists a need to develop efficient and simple synthesis of cyclopentane rings. In this paper we describe an alternate solution to this problem exemplified in a new total synthesis of α-Cuparenone (**1**), which involves mild neutral photochemical rearrangement of α-haloketone to aryl-propionic acid[4] and an extremely mild 3-aza-Claisen reaction[5] for the conversion of simple N-allyl amide (**6**) to nitrile (**7**).



1, α - Cuparenone 7 4

As is obvious from the retrosynthesis, our strategy was to prepare the key intermediate nitrile (**7**), by aza-Claisen rearrangement from N-allyl amide (**6**). **6** in turn was prepared from tolylaceticacid (**5**). The 1-methyl-1-(*p*-tolyl)acetic acid (**5**) was prepared by the Friedel-Craft's acylation of α-chloropropionylchloride (**3**) with toluene to furnish α-chloro-4-methyl propiophenone (**4**). This α-chloro-4-methyl propiophenone (**4**) underwent facile photochemical rearrangement, in the presence of propylene oxide as an acid scavenger, in aqueous acetone to give 1-methyl-1-(*p*-tolyl)acetic acid (**5**)[4] in 70% yield. The acid was quantitatively converted to corresponding N-allyl amide (**6**). This N-allyl amide (**6**) underwent facile 3-aza-Claisen reaction[5] in 80% yield to furnish nitrile (**7**). Reduction of nitrile (**7**) with DIBAL-H in benzene gave 70% allyl aldehyde (**8**). Wacker oxidation of allyl aldehyde gave 2-methyl-4-oxo-2(*p*-tolyl)pentanal (**9**)[6]. This 2-methyl-4-oxo-2(*p*-tolyl)pentanal (**9**) on base catalysed aldol condensation gave 2-methyl-4(*p*-tolyl)-2-cyclopentenone (**10**) in 98% yield. Alkylation of this ketone with MeI and NaH gave 4-(*p*-tolyl)-4,5,5-trimethyl-2-cyclopentenone, which on Palladium catalysed hydrogenation led to α-Cuparenone.[6,7]

Scheme-I



(a) hν, , Aq. Acetone, 6 hrs, 70 %; (b) $SOCl_2$, Benzene, Allylamine, Et_3N, Quantitative; (c) PPh_3, CH_3CN, CCl_4, Et_3N, 24 hrs, 80 %; (d) DIBAL-H, Benzene, Ambient Temp, 70 % (e) Wacker-oxidation, 63 %; (f) KOH, EtOH, RT, 98 %; (g) NaH, MeI (excess), 65 % (h) Pd-C, H_2 atm. RT, 98 %

Thus all reaction sequence are very simple, essentially mild and proceed with excellent yields and are easy to perform. We believe this is the first application of aza-Claisen rearrangement for the synthesis of cyclopentanes and would be of general utility to synthetic organic chemist.

Acknowledgement: SSP, VDD and SWD thank CSIR, New Delhi for award of fellowships. We are thankful to Dr. H. R. Sonawane for fruitful discussions.

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7. All the compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral analyses.

(*Received in UK* 13 *December* 1995; *revised* 21 *February* 1996; *accepted* 23 *February* 1996)