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An Efficient Synthesis of α-Cuparenone

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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). Copyright © 1996 Published by Elsevier Science Ltd

 α -Cuparenone (1) a bicyclic terpene isolated from *Thuja Orientallis (Mayurpankhi)* by Sukh Dev¹ 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 ways². As a part of our interest in cyclopentane rings³ 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 acid⁴ and an extremely mild 3-aza-Claisen reaction⁵ for the conversion of simple N-allyl amide (6) to nitrile (7).



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 reaction⁵ 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}



(a) hy, Aq. Acetone, 6 hrs, 70%; (b) SOCl₂, Benzene, Allylamine, Et₃N, Quantitative;
(c) PPh₃, CH₃CN, CCl₄, Et₃N, 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, H₂ 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.

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

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