CLAISEN REARRANGEMENT OF 5- OR 7-PROPARGYLOXYFLAVONES: FORMATION OF PYRANOFLAVONES

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Abstract — The Claisen rearrangement of 7-propargyloxy-5-hydroxy-3-phenylflavone, 7-propargyloxy-5-hydroxy-3-methylflavone and 7-methoxy-5-propargyloxy-3-methylflavone in N,N-dimethylaniline at 195°C resulted in the formation of angular 2H-[1]-pyranoflavones, 2,3-diphenyl-5-hydroxy-8H-4-oxobenzo-[1,2-b:5,6-b']dipyran, 5-hydroxy-3-methyl-2-phenyl-8H-4-oxobenzo-[1,2-b:5,6-b']dipyran and 9-methoxy-3-methyl-2-phenyl-6H-4-oxobeno-[1,2-b:3,4-b']dipyran, respectively in 50% yields. The structures were determined by spectral characteristics.

The Claisen rearrangement of aryl propargyl ethers, brought thermally in various high boiling solvents, was found to give 2H-[1]-benzopyrans[1,2,3]. The rearrangement is not regiospecific since *m*-substituted arylpropargyl ethers on rearrangement were found to give the two possible isomeric 2H-[1]-benzopyrans[4]. Further it is noticed that aryl propargyl ethers containing electron donating groups yield 2H-[1]-benzopyrans and those containing electron withdrawing groups yield 2-methylbenzofurans[5,6].

The Claisen rearrangement of heterocyclic propargyl ethers does not seem to have been well studied. The rearrangement of 3-pyridyl propargyl ethers gave the two possible linear-and angular-fused 2-methylfuro compounds as well as linear 2H-[1]-pyran suggesting there is no regioselectivity or product selectivity[5]. Mixtures of fused 2-methylfuro and 2H-[1]-pyrano compounds were also found on the rearrangement of 1,3-dimethyl-5-(2-propargyloxy)uracil[7]. On the other hand 3-propargyl ether of kojic acid furnished exclusively fused 2-methylfuro derivative[8].

In some instances it is observed that Claisen rearrangement of arylpropargyl ethers in the presence of mild base in a high boiling solvent gave exclusively

fused a 2-methylfuro derivative while in the absence of such a base, the corresponding 2H-[1]-pyrano derivative was resulted[9]. Claisen rearrangement of *propargyloxybenzene in the silver borofluorate* ($AgBF_4$)/benzene gave exclusively a fused 2-methylfuro derivative[10].

We report herein the Claisen rearrangement of 7-propargyloxy-and 5-propargyloxy-flavones. Such rearrangement studies on propargyl ethers of flavones were not investigated earlier.

5,7-Dihydroxy-3-phenyl[11]-(Ia) and 5,7-dihydroxy-3-methylflavone[12](Ib) were monopropargylated by refluxing with an equimolar amount of propargyl bromide in acetone-anhydrous potassium carbonate medium for 4 h to yield the corresponding 7-propargyloxy derivatives (IIa, mp 174-175°C and IIb, mp 130-132°C).

Monomethylation of Ib with equimolar amount of dimethyl sulphate in acetone-anhydrous potassium carbonate for 6 h yielded 5-hydroxy-7-methoxy-3-methylflavone (Ic, mp 157°C), whose monopropargylation with propargyl bromide in refluxing acetone-anhydrous potassium carbonate medium for 80 h furnished 7-methoxy-3-methyl-5-propargyloxyflavone (IIc, mp 128-129°C). The yield of propargyloxy-flavones, IIa,b and c, from Ia,b and c, respectively, are about 85%.

The Claisen rearrangement of monopropargyloxyflavones (IIa-c) was carried out in N,N-dimethylaniline at 195°C. The products on chromatography furnished angularly fused 2H-[1]-pyranoflavones (IVa-c) in 50% yields. The structures were assigned on the basis of the following considerations:

In the ^1H nmr spectrum (270 MHz in $CDCl_3$) of the product (IVa) the two methylene protons were observed as double doublets at δ 4.947 ($J_{8H,9H}$=3.574 and $J_{8H,10H}$= 1.600Hz,2H). The C_9-proton (α-proton was observed as two triplets at δ 5.729 ($J_{9H,8H}$=3.574 and $J_{9H,10H}$=9.000Hz,1H) and C_{10} proton (β) as doublet δ 6.828 ($J_{10H,9H}$=9.000Hz). This data are in agreement with the earlier reported values for 2H-[1]-benzopyrans[13]. Compounds, IV and IVc, also exhibited these characteristics in ^1H nmr spectrum.

It was reported in literature[14] that in linear chromene, 5-hydroxy-2,2-dimethyl-chromene (VI) on acetylation, the β-proton (C_4-H) suffers an upfield shift (δ +0.280) while the α-proton (C_3-H) suffers a down field shift (δ -0.070). On the other hand in the angular chromene, 7-hydroxy-2,2-dimethylchromene (VII) both α-and β-protons suffer a down field shift of the magnitude (δ -0.050) upon acetylation. Therefore compound IVa was acetylated with acetic anhydride-pyridine

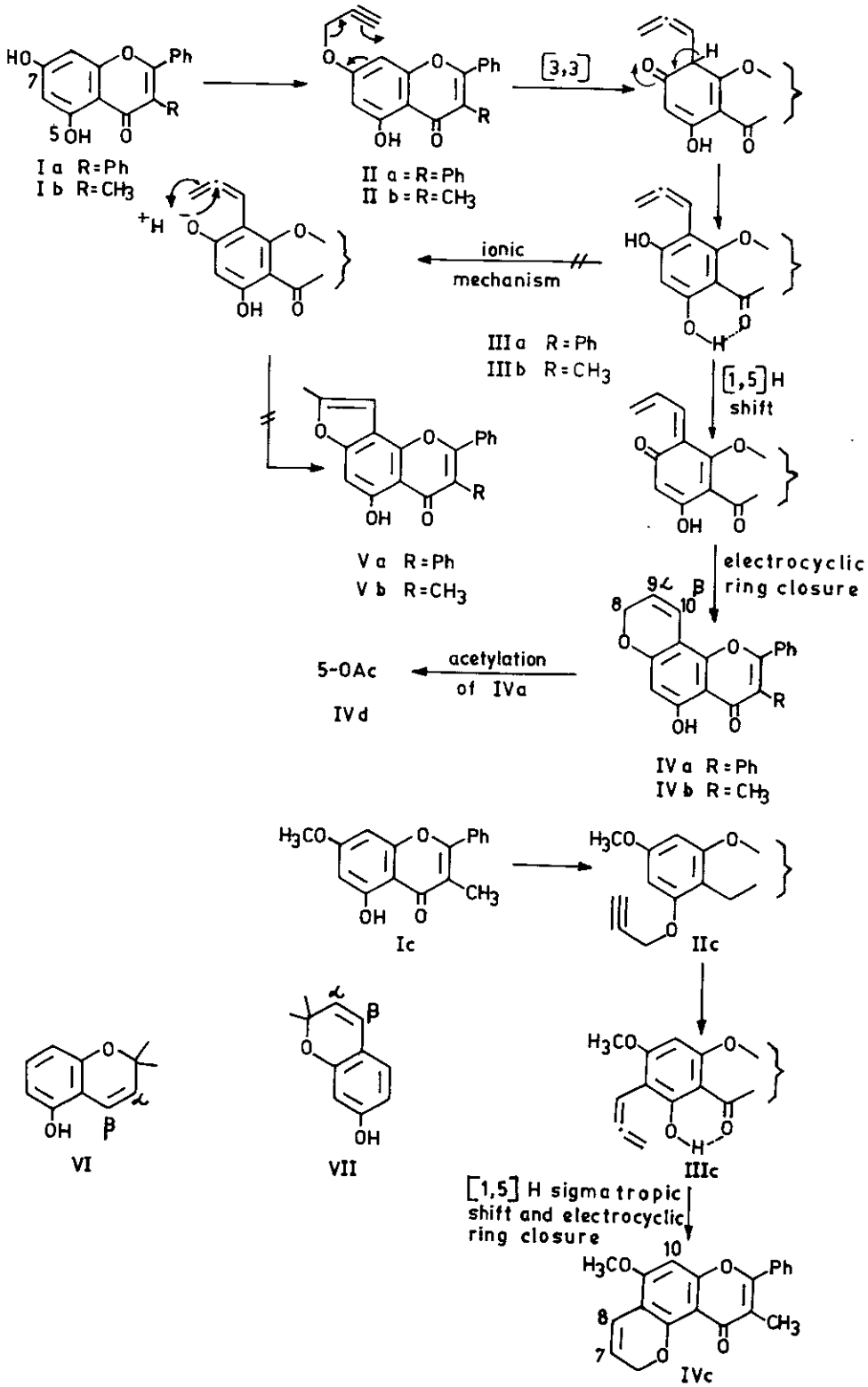
to give 5-O-acetyl compound (IVd, mp 198-200°C). The acetate shift observed in the compounds (IVa and IVd) reveals that both α-and β-protons suffered down field shift [β-proton, δ -0.055, α-proton, δ -0.104], suggesting the angular 2H-[1]-pyrano ring in IVa. Further IVa did not give positive Gibb's test suggesting <u>para</u> to hydroxyl (position C-8 of flavone) is substituted.

In 5,7,8-trisubstituted flavones, such as vitexin, the C_6-proton resonates at an upfield (δ 6.310) while the C_8-proton of isomeric 5,6,7-trisubstituted flavone-saponaretin, at down field (δ 6.580). Therefore in compounds IVa and IVb -- the lone aromatic signal at δ 6.296 and δ 6.200 respectively, are assignable to C_6-proton of flavone while in IVc the relatively upfield aromatic singlet at δ 6.410 is assignable to C_8-proton of flavone skeleton (i.e. C-10 in IVc). Thus in the Claisen rearrangement of IIa and IIb migration of propargyl group to C_8-position took place rather than to C_6-position. In the Claisen rearrangement of 7-allyloxyflavones also migration took place to C_8-position in preference to C_6-position and a satisfactory explanation was provided by Dean[16].

Based on the mechanism provided by various workers[2,7], the initial step in the Claisen rearrangement of 5-hydroxy-7-propargyloxyflavones (IIa and IIb) is the migration of propargyl unit to C_8-position by 3,3-sigmatropic shift to give unisolable 5,7-dihydroxy-8-allenylflavones (IIIa and IIIb) intermediates. These intermediates by 1,5-sigmatropic hydrogen shift give rise to reactive trienes which on electrocyclization lead to the formation of 2H-[1]-pyranoderivative (IVa and IVb).

On the other hand in some instances fused α-methylfuro compounds formed presumably by ionic mechanism. In these cases the ionisation of hydroxyl group of o-hydroxy phenylallene takes place under the influence of added bases, or by markedly acidic nature of the o-hydroxyphenylallene and subsequent ring closure[7]. Further even if the central allenic carbon atom is electron deficient as in the case of N-heterocyclic uracil, α-methylfuro derivatives will be formed. α-methylfuro derivatives, Va and Vb were not formed even in traces, suggesting that ionic mechanism is not operating.

The reason for the exclusive formation of 2H-[1]-benzopyrano compounds may be, although C7-hydroxyl is expected to be acidic by virtue of its conjugation with C4-carbonyl, its acidity is greatly reduced since the carbonyl is involved in chelation with C5-hydroxyl. Therefore by 1,5-H-sigmatropic shift and


I a R=Ph
I b R=CH3
II a = R=Ph
II b = R=CH3
[3,3]
ionic
mechanism
III a R=Ph
III b R=CH3
[1,5] H
shift
electrocyclic
ring closure
V a R=Ph
V b R=CH3
acetylation
of IVa
5-OAc
IV d
IV a R=Ph
IV b R=CH3
Ic
IIc
IIIc
[1,5] H sigmatropic
shift and electrocyclic
ring closure
IVc
VI
VII

electrocyclic ring closure 2H-/¯1_7-pyranoflavones 2,3-diphenyl-5-hydroxy-8H-4-oxobenzo/¯1,2-b:5,6-b'_7dipyran (IVa, mp 249-251°C) and 5-hydroxy-3-methyl-2-phenyl-8H-4-oxobenzo/¯1,2-b:5,6-b'_7dipyran (IVb) mp 158-160°) are resulted as shown in the chart.

Similar mechanism is presumably operating in the formation of IVc from IIc. Due to decreased acidic character of C5-hydroxyl in IIIc as a result of its chelation with C4-carbonyl, ionic mechanism is not operative and by 1,5-sigmatropic shift and electrocyclic ring closure yielded 2H-/¯1_7-pyrano compound, 9-methoxy-3-methyl-2-phenyl-6H-4-oxobenzo /¯1,2-b:3,4-b'_7dipyran (IVc, mp 218-220°C). All the new compounds gave satisfactory analytical and spectral data.

ACKNOWLEDGEMENTS

One of us (K.N.) thanks Prof. K.V.N. Rao and U.G.C., New Delhi for financial assistance. The authors thank N.M.R. facility, I.I.Sc. Bangalore. The authors also thank ICAR, New Delhi for financial assistance.

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Received, 7th July, 1986