

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- [1,7] -pyranoflavones, 2,3-diphenyl-5-hydroxy-8H-4-oxobenz- [1,2-b:5,6-b'] dipyran, 5-hydroxy-3-methyl-2-phenyl-8H-4-oxobenz- [1,2-b:5,6-b'] dipyran and 9-methoxy-3-methyl-2-phenyl-6H-4-oxobenz- [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- [1,7] -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- [1,7] -benzopyrans⁴. Further it is noticed that aryl propargyl ethers containing electron donating groups yield 2H- [1,7] -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- [1,7] -pyran suggesting there is no regioselectivity or product selectivity⁵. Mixtures of fused 2-methylfuro and 2H- [1,7] -pyrano compounds were also found on the rearrangement of 1,3-dimethyl-5-(2-propargyloxy)uracil⁷. On the other hand 3-propargyl ether of kojic acid furnished exclusively fused 2-methylfuro derivative⁸.

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- γ -pyrano derivative was resulted⁹. Claisen rearrangement of propargyloxybenzene in the silver borofluorate (Ag BF_4)/benzene gave exclusively a fused 2-methylfuro derivative¹⁰.

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-phenyl¹¹-(Ia) and 5,7-dihydroxy-3-methylflavone¹²(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- γ -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 ($J_{8\text{H},9\text{H}}=3.574$ and $J_{8\text{H},10\text{H}}=1.600\text{Hz}, 2\text{H}$). The C_9 -proton (α -proton) was observed as two triplets at δ 5.729 ($J_{9\text{H},8\text{H}}=3.574$ and $J_{9\text{H},10\text{H}}=9.000\text{Hz}, 1\text{H}$) and C_{10} proton (β) as doublet δ 6.828 ($J_{10\text{H},9\text{H}}=9.000\text{Hz}$). This data are in agreement with the earlier reported values for 2H- γ -benzopyrans¹³. Compounds, IV and IVc, also exhibited these characteristics in ^1H nmr spectrum.

It was reported in literature¹⁴ that in linear chromene, 5-hydroxy-2,2-dimethylchromene (VI) on acetylation, the β -proton ($\text{C}_4\text{-H}$) suffers an upfield shift ($\delta +0.280$) while the α -proton ($\text{C}_3\text{-H}$) suffers a down field shift ($\delta -0.070$). 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 ($\delta -0.050$) upon acetylation. Therefore compound IVa was acetylated with acetic anhydride-pyridine

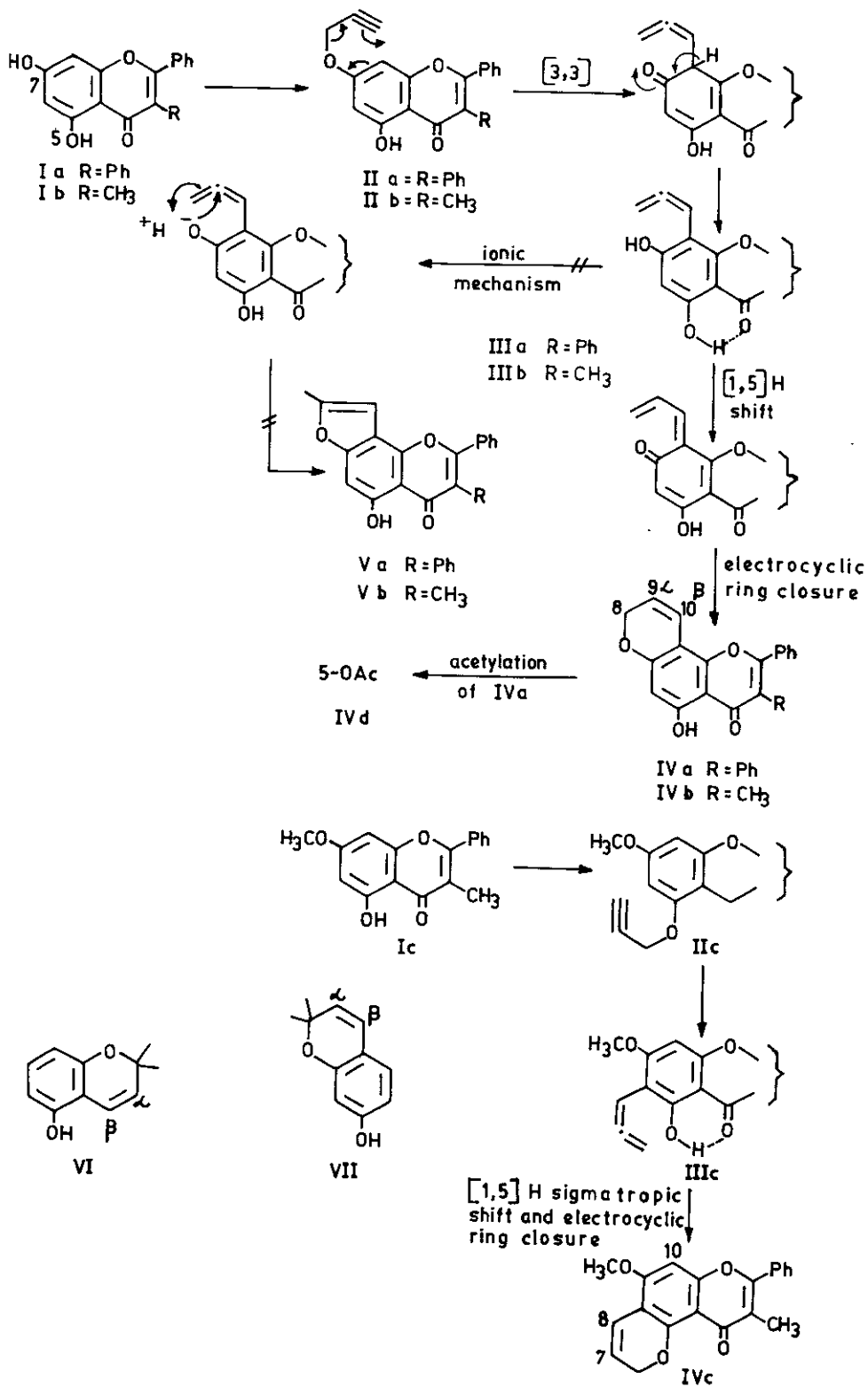
to give 5-O-acetyl compound (IVd, mp 198-200°C). The acetate shift observed in the compounds (IVa and IVd) reveals that both α - and β -protons suffered down field shift [β -proton, δ -0.055, α -proton, δ -0.104], suggesting the angular 2H- γ -pyrano ring in IVa. Further IVa did not give positive Gibb's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

In 5,7,8-trisubstituted flavones, such as vitexin, the C₆-proton resonates at an upfield (δ 6.310) while the C₈-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 C₆-proton of flavone while in IVc the relatively upfield aromatic singlet at δ 6.410 is assignable to C₈-proton of flavone skeleton (i.e. C-10 in IVc). Thus in the Claisen rearrangement of IIa and IIb migration of propargyl group to C₈-position took place rather than to C₆-position. In the Claisen rearrangement of 7-allyloxyflavones also migration took place to C₈-position in preference to C₆-position and a satisfactory explanation was provided by Dean¹⁶.

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 C₈-position by 3,3-sigmatropic shift to give unisolable 5,7-dihydroxy-8-allynylflavones (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- γ -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 closure⁷. 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- γ -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



electrocyclic ring closure 2H- γ -pyranoflavones 2,3-diphenyl-5-hydroxy-8H-4-oxobenzofluorene (IVa, mp 249-251°C) and 5-hydroxy-3-methyl-2-phenyl-8H-4-oxobenzofluorene (IVb) mp 158-160°C) 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- γ -pyrano compound, 9-methoxy-3-methyl-2-phenyl-6H-4-oxobenzofluorene (IVc, mp 218-220°C). All the new compounds gave satisfactory analytical and spectral data.

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