THALLIUM(III) NITRATE MEDIATED SYNTHESIS OF ERYTHRININ-A, DIHYDROPYRANO- AND PYRANOISOFLAVONES

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Abstract —— Oxidative rearrangement of dihydropyranochalcones using thallium(III) nitrate-trimethylorthoformate (TTN-TMOF) reagent followed by acid catalysed cyclization yields the corresponding dihydropyranoisoflavones in good yields. Dehydrogenation of these isoflavones gave pyranoisoflavones. Demethylation of isoflavone (7) followed by dehydrogenation gave erythrinin-A (16).

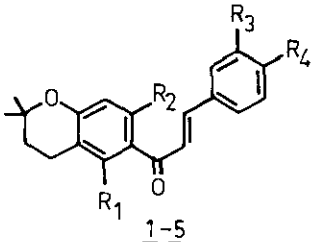
Pyranoisoflavonoids are plant secondary metabolites exhibiting insecticidal[1], antifungal[2] and antibacterial[3] properties. The methods of synthesis for pyranoisoflavones, which are the biogenetic precursors of several pyranoisoflavonoids, involve (i) ortho C-prenylation of phenolic isoflavones followed by cyclodehydrogenation[4], (ii) O-propargylation followed by Claisen rearrangement[5] and (iii) oxidative rearrangement of pyranochalcones using TTN-MeOH followed by cyclization[6]. While methods (i) and (ii) suffer from the formation of complex isomeric mixtures[4,5] from which separation of the required isomer by chromatography becomes cumbersome, method (iii) suffers from oxidative rearrangement of the chromene ring as enunciated in the synthesis of corylin[7] resulting in ring contracted products.

Recently[8], TTN-TMOF reagent has found wide use in cleanly brining about oxidations that either fail or are not cleanly proceeding with TTN-MeOH. However, the general applicability of this reagent for oxidative rearrangement of chalcones has hitherto been untested.

We now report a convenient general method for the synthesis of pyranoisoflavones in high yields starting from dihydropyranochalcones using TTN-TMOF reagent. The methodology involves building up of the γ-pyrone ring on a chroman nucleus ;

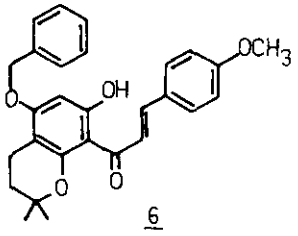
by doing so (i) the specificity of the pyran ring is defined at the beginning of the reaction series and (ii) as a result, the formation of isomeric products does not arise. Also conventional methods involving C-prenylation of 7-hydroxyisoflavones followed by cyclodehydrogenation predominantly yield pyrano-isoflavones with (1,2-b ; 5,6-b') fusion. The present method, however, provides access for (1,2-b ; 5,4-b') fused pyranoisoflavones exclusively which have erythrinin-A based nucleus. In contrast, this method involves phenyl migration whereas the method reported in our earlier communication[9] makes use of the migration of dihydropyranobenzoyl moiety. These reactions when carried out using TTN-MeOH gave relatively less yields of the products[10] as compared to TTN-TMOF method.

Using this method differently substituted dihydropyranochalcones (1-6) were converted to the corresponding dihydropyranoisoflavones (7-13) using TTN-TMOF reagent. Isoflavones 7 and 11 were dehydrogenated to 15 (erythrinin-A methyl ether) and 17 using both DDQ-benzene and NBS-pyridine. Demethylation of isoflavone 7 using HBr gave dihydroerythrinin-A (8) which on dehydrogenation using DDQ-benzene gave the natural product, erythrinin-A (16)[11]. This is the first reported synthesis of erythrinin-A.



1-5

1. $R_1, R_3 = H$; $R_2 = OH$; $R_4 = OCH_3$
2. $R_1 = H$; $R_2 = OH$; $R_3, R_4 = OCH_3$
3. $R_1 = H$; $R_2 = OH$; $R_3 = OCH_3$; $R_4 = OCH_2C_6H_5$
4. $R_1 = OH$; $R_2, R_4 = OCH_3$; $R_3 = H$
5. $R_1 = OH$; $R_2, R_3, R_4 = OCH_3$



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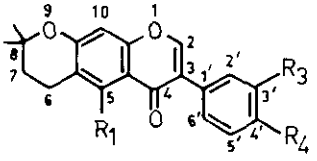

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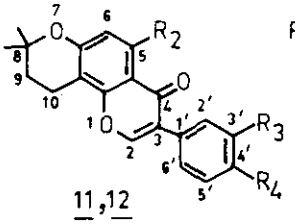

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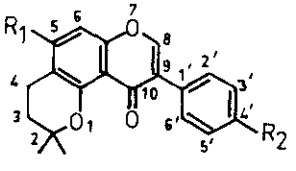

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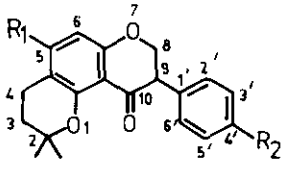

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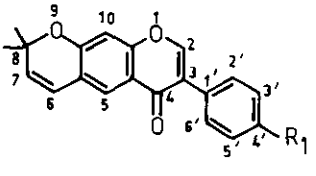

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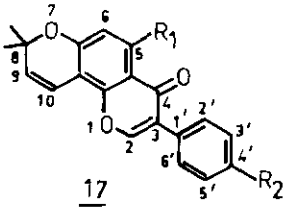

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TABLE I[a]

Compound No.	R_1	R_2	R_3	R_4	NMR($CDCl_3$/TMS_{int}) of the product δ	ms m/e M^+
7	H	-	H	OCH_3	1.42(6H,s,C_8-gem dimethyl), 1.9(2H,t, C_7-H,J = 7 Hz), 2.94(2H,t,C_6-H,J = 7 Hz), 3.88(3H,s,C_4,-OCH_3), 6.82(1H,s,C_{10}-H), 7.0(2H,d,C_3,-H and C_5,-H,J = 8 Hz), 7.52(2H,d,C_2,-H and C_6,-H,J = 8 Hz), 7.9(1H,s,C_5-H), 8.04(1H,s,C_2-H).	336
8[b]	H	-	H	OH	1.44(6H,s,C_8-gem dimethyl), 1.94(2H,t, C_7-H,J = 8 Hz), 2.9(2H,t,C_6-H,J = 8 Hz), 6.84(1H,s,C_{10}-H), 7.0(2H,d,C_3,-H and C_5,-H,J = 8 Hz), 7.48(2H,d,C_2,-H and C_6,-H,J = 8 Hz), 7.98(1H,s,C_5-H), 8.16(1H,s,C_2-H), 8.72(1H,s,C_4,-OH, D_2O exchangeable).	322
9	H	-	OCH_3	OCH_3	1.42(6H,s,C_8-gem dimethyl), 1.86(2H, t,C_7-H,J = 7 Hz), 2.88(2H,t,C_6-H, J = 7 Hz), 4.02 and 4.04 (6H,2s, C_3,-OCH_3 and C_4,-OCH_3), 6.78(1H,s, C_{10}-H), 6.82(1H,d,C_5,-H, J = 9 Hz), 7.3(1H,d,C_2,-H,J = 3 Hz), 7.74(1H,dd,C_6,-H, J = 3 and 9 Hz), 7.88(1H,s,C_5-H), 7.98(1H,s,C_2-H).	366
10	H	-	OCH_3	OCH_2Ph	1.4(6H,s,C_8-gem dimethyl), 1.88(2H, t,C_7-H,J = 7 Hz), 2.9(2H,t,C_6-H, J = 7 Hz), 4.02(3H,s,C_3,-OCH_3), 5.22(2H, s,-O-$\underline{CH_2}$-Ph), 6.84(1H,s,C_{10}-H), 6.9(1H, d,C_5,-H,J = 9 Hz), 6.96(1H,d,C_2,-H, J = 3 Hz), 7.2-7.9(7H,m,aromatic-H), 8.06(1H,s,C_2-H).	442

Compound No.	R_1	R_2	R_3	R_4	NMR($CDCl_3$/TMS_{int}) of the product δ	ms m/e M^+
11	-	OCH_3	H	OCH_3	1.42(6H,s,C_8-gem dimethyl), 1.88(2H, t,C_9-H,J = 7 Hz), 2.8(2H,t,C_{10}-H, J = 7 Hz), 3.88 and 3.94 (6H,2s, C_5-OCH_3 and C_4,-OCH_3), 6.32(1H,s, C_6-H), 6.96(2H,d,C_3,-H and C_5,-H, J = 8 Hz), 7.52(2H,d,C_2,-H and C_6,-H, J = 8 Hz), 7.84(1H,s,C_2-H).	366
12	-	OCH_3	OCH_3	OCH_3	1.44(6H,s,C_8-gem dimethyl), 1.94(2H, t,C_9-H,J = 7 Hz), 2.9(2H,t,C_{10}-H, J = 7 Hz), 3.94 and 4.02(9H,3s, C_5-OCH_3,C_3,-OCH_3 and C_4,-OCH_3), 6.98(1H,s,C_6-H), 7.02(1H,d,C_2,-H, J = 3 Hz), 7.12(1H,d,C_5,-H, J = 9 Hz), 7.83(1H,dd,C_6,-H, J = 3 and 9 Hz), 7.92(1H,s,C_2-H).	396
13	OCH_2Ph	OCH_3	-	-	1.46(6H,s,C_2-gem dimethyl), 1.84(2H,t, C_3-H,J = 7 Hz), 2.76(2H,t,C_4-H,J = 7 Hz), 3.86(3H,s,C_4,-OCH_3), 5.18(2H,s, -O-$\underline{CH_2}$-Ph), 6.46(1H,s,C_6-H), 6.94(2H,d, C_3,-H and C_5,-H,J = 8 Hz), 7.3-7.6(7H, m,aromatic-H), 7.72(1H,s,C_8-H).	442
14[c]	OH	OCH_3	-	-	1.28(6H,s,C_2-gem dimethyl), 1.7(2H,t, C_3-H,J = 7 Hz), 2.5(2H,t,C_4-H,J = 7 Hz), 3.68(1H,t,C_9-H,J = 6 Hz), 4.52(2H,d, C_8-H,J = 6 Hz), 6.02(1H,s,C_6-H), 6.9(2H, d,C_3,-H and C_5,-H,J = 8 Hz), 6.98(2H,d, C_2,-H and C_6,-H,J = 8 Hz).	354
15	OCH_3	-	-	-	1.52(6H,s,C_8-gem dimethyl), 3.88(3H,s, C_4,-OCH_3), 6.12(1H,d,C_7-H,J = 10 Hz), 6.82(1H,s,C_{10}-H), 7.0(2H,d,C_3,-H and C_5,-H,J = 10 Hz), 7.43(1H,d,C_6-H,J = 10Hz),	

Compound No.	R_1	R_2	R_3	R_4	NMR($CDCl_3$/TMS_{int}) of the product δ	ms m/e M^+
					7.52(2H,d,C_2,-H and C_6,-H, J = 10 Hz), 7.9(1H,s,C_5-H), 8.36(1H,s,C_2-H).	334
16	OH	-	-	-	1.42(6H,s,C_8-gem dimethyl), 5.66(1H, d,C_7-H,J = 10 Hz), 6.46(1H,d,C_6-H, J = 10 Hz), 6.36(1H,s,C_{10}-H), 6.94(2H, d,C_3,-H and C_5,-H,J = 8 Hz), 7.48(2H, d,C_2,-H and C_6,-H,J = 8 Hz), 7.84(1H, s,C_5-H), 7.86(1H,s,C_2-H).	320
17	OCH_3	OCH_3	-	-	1.6(6H,s,C_8-gem dimethyl), 3.82 and 3.92(6H,2s,C_4,-OCH_3 and C_5-OCH_3), 6.32(1H,s,C_6-H), 6.92(2H,d,C_3,-H and C_5,-H,J = 8 Hz), 7.1(1H,d,C_9-H, J = 10 Hz), 7.28(1H,d,C_{10}-H,J = 10Hz), 7.48(2H,d,C_2,-H and C_6,-H,J = 8 Hz), 7.78(1H, s, C_2-H).	364

a - PMR spectral data of the precursor dihydropyranochalcones has been communicated[9].

b - PMR spectrum was recorded using acetone-d_6.

c - PMR spectrum was recorded using DMSO-d_6.

TABLE II

Compound No.	Yields %	Mp °C	Lit. Mp °C	ν max (nujol)
7	82[a]	183-184	183-184[9]	1630
9	78[a]	245-246	244-246[9]	1640
10	69[a]	223-224	-	1640
11	76[a]	192-193	-	1650
12	71[a]	217-218	-	1640
13	66[a]	206-207	-	1660
15	62[b]	139-141	-	1635
16	68[b]	160-161	160-162[11]	1640,3340(br)

Compound No.	Yields %	Mp °C	Lit. Mp °C	ν max (nujol)
17	65[b]	153-154	152-155[12]	1650

a - Yields are calculated based on conversion of the chalcone to the isoflavone.

b - Yields are calculated based on conversion of the dihydropyranoisoflavone to the pyranoisoflavone and the better yield of the two methods of dehydrogenation carried out is reported.

EXPERIMENTAL

1. General procedure for oxidative rearrangement and acid-catalysed cyclization

In a typical experiment to a solution of chalcone (0.0007 M) in analytical grade methanol (15 ml), thallium(III) nitrate trihydrate (0.0008 M) in trimethylorthoformate (0.003 M) was added in aliquot portions and stirred till most of the chalcone disappeared (tlc). Removal of solvent gave a solid which was dissolved in methanol (15 ml) and refluxed for 2-3 h with 10% HCl (1/20 of the volume of methanol). Evaporation of the solvent and crystallization of the residue gave the isoflavone. The pure product was characterized by its mp and superimposable uv, ir, pmr and mass spectral data.

2. Debenzylation of isoflavone (13)

Isoflavone (13) (0.002 M) in ethyl acetate (25 ml) was subjected to hydrogenolysis using H_2 (20 psi) in presence of Pd-C (10%, 10 mg) as catalyst. Filtration and removal of solvent gave a solid which crystallised from methanol to give isoflavanone (14) (0.002 M).

3. Demethylation of isoflavone (7)

To a solution of isoflavone (7) (0.00015 M) in acetic anhydride (5 ml), HBr (1 ml, 48%) was added in drops and the mixture heated on water bath for 5 h. Work-up gave a product which crystallized from dil. methanol as colourless plates, mp 283-285°C (decomp.) (0.00012 M).

4. General procedure for dehydrogenation

i) Using DDQ and Benzene

To a solution of dihydropyranoisoflavone (0.00015 M) in dry benzene (10 ml), DDQ (0.00018 M) was added and the mixture refluxed for 30 h. Removal of the solvent followed by purification of the residue over a silica gel column using pet.ether-benzene (90:10) gave the pyranoisoflavone.

ii) Using NBS and pyridine

To a mixture of dihydropyranoisoflavone (0.00015 M), NBS (0.00018 M) and dibenzoyl peroxide (1 mg), CCl_4 (10 ml) was added and the reaction mixture refluxed for 2.5 h. Work-up gave a residue which was heated to reflux with pyridine (2 ml) for 1 h. Removal of pyridine under reduced pressure and purification of the residue by eluting with pet.ether-ethyl acetate (98:2) over silica gel column gave the required pyranoisoflavone.

The dehydroproducts were characterized by ir, pmr and elemental analysis.

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