

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

Raghava Venkataramanna Suresh, (Mrs.) Chandrashekarapuram
Subramanyam Rukmani Iyer, and Parameswaran Ramasubramonia Iyer*
Department of Chemistry, Indian Institute of Technology,
Bombay-400 076, India

Abstract — Oxidative rearrangement of dihydropyrano-chalcones using thallium(III) nitrate-trimethylorthoformate (TTN-TMOF) reagent followed by acid catalysed cyclization yields the corresponding dihydropyrano-isoflavones 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 insecticidal¹, antifungal² and antibacterial³ properties. The methods of synthesis for pyrano-isoflavones, which are the biogenetic precursors of several pyranoisoflavonoids, involve (i) ortho C-prenylation of phenolic isoflavones followed by cyclodehydrogenation⁴, (ii) O-propargylation followed by Claisen rearrangement⁵ and (iii) oxidative rearrangement of pyranochalcones using TTN-MeOH followed by cyclization⁶. 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 corylin⁷ resulting in ring contracted products.

Recently⁸, TTN-TMOF reagent has found wide use in cleanly bringing 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 dihydropyrano-chalcones 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 pyranoisoflavones 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 communication⁹ makes use of the migration of dihydropyranobenzoyl moiety. These reactions when carried out using TTN-MeOH gave relatively less yields of the products¹⁰ 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.

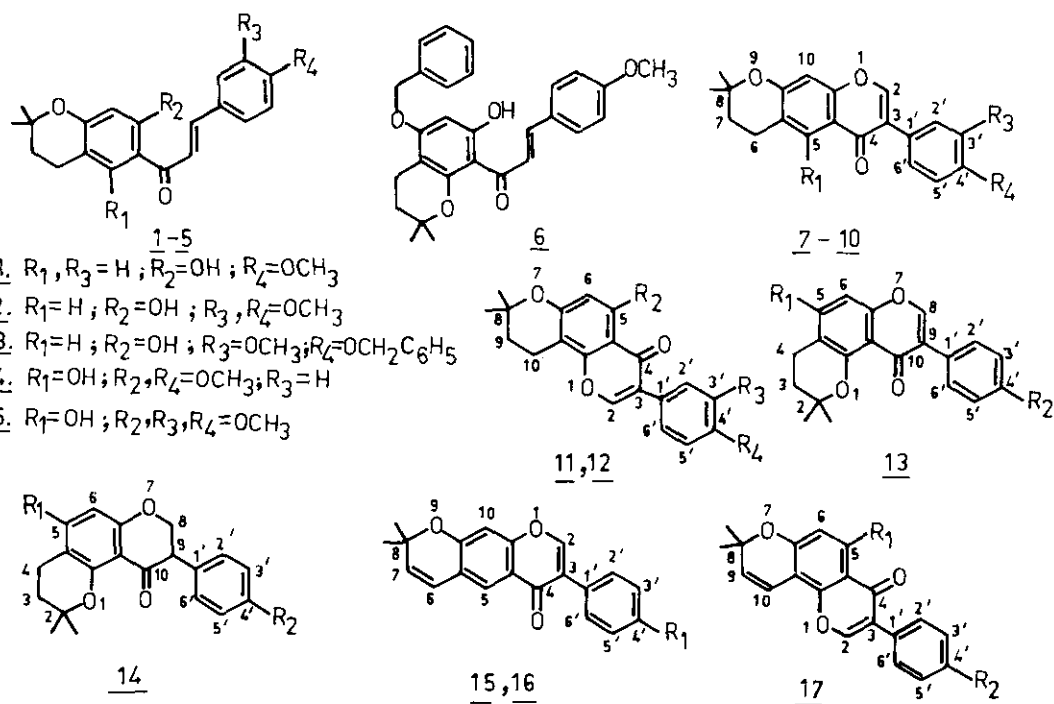


TABLE I^a

Compound No.	R ₁	R ₂	R ₃	R ₄	NMR(CDCl ₃ /TMS _{int}) of the product δ	ms m/e M ⁺
<u>7</u>	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
<u>8</u> ^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 ₂ O exchangeable).	322
<u>9</u>	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
<u>10</u>	H	-	OCH ₃	OCH ₂ Ph	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-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 ⁺
<u>11</u>	-	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
<u>12</u>	-	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
<u>13</u>	OCH ₂ Ph	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-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
<u>14</u> ^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
<u>15</u>	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
<u>16</u>	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
<u>17</u>	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 dihydropyranochalcons has been communi-
cated⁹.

b - PMR spectrum was recorded using acetone-d₆.

c - PMR spectrum was recorded using DMSO-d₆.

TABLE II

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

Compound No.	Yields %	Mp °C	Lit. Mp °C	$\nu_{\max}$ (nujol)
<u>17</u>	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 H₂ (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 dehydropyran products were characterized by ir, pmr and elemental analysis.

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