# Oxidation of Flavanones using Thallium(III) Salts: A New Route for the Synthesis of Flavones† and Isoflavones‡

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When treated with thallium(III) acetate in acetic acid or acetonitrile, flavanones undergo facile dehydrogenation to afford flavones whereas, upon treatment with thallium(III) toluene-*p*-sulfonate or thallium(III) nitrate in propionitrile or acetonitrile, respectively, they undergo oxidative 2,3-aryl migration to give isoflavones in high yield.

Oxidation of flavanones with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[1] selenium dioxide,[2] dimethyl sulfoxide–$I_2$–sulfuric acid[3] and dimethyl sulfoxide–$I_2$ systems[4] gives flavones, whilst lead tetraacetate (LTA)[5] affords a mixture of flavones, 3-acetoxyflavones and isoflavones.

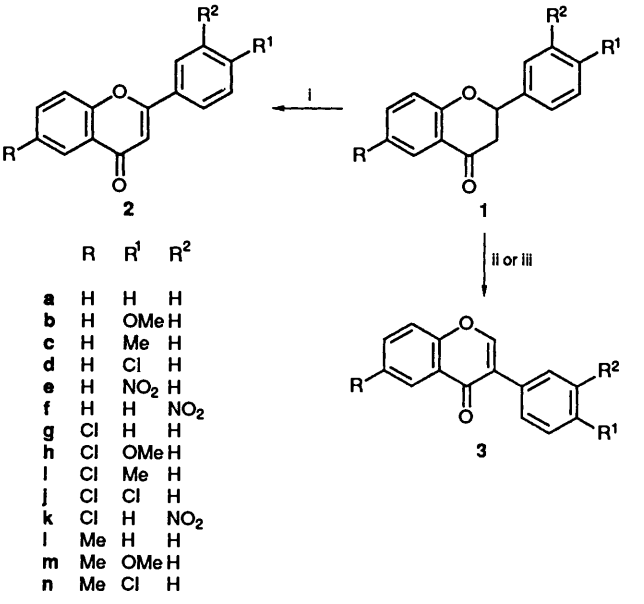
Thallium(III) salts, versatile reagents in organic synthesis,[6] in methanol smoothly oxidize 2′-hydroxychalcones to isoflavones,[7,8] and flavanones to flavones.[9] In our preliminary communication,[10] we reported that flavanones on treatment with thallium(III) acetate (TTA) in acetic acid–methanol–acetonitrile afforded flavones, while with thallium(III) toluene-*p*-sulfonate (TTS) in propionitrile they gave isoflavones. Here we describe a detailed study of the oxidation of flavanones **1a–n** and α-naphthoflavanone **7** with TTA, thallium(III) nitrate (TTN) and TTS under a variety of conditions.

## Results and Discussion

Flavanones **1a–n** were oxidized with TTA in acetic acid, with TTN in acetonitrile and with TTS in propionitrile at reflux. In oxidations using TTN 50–75% molar excess of the reagent was required for completion of reaction while with that of TTA and TTS equimolar amounts of the reagents were needed (Scheme 1).

Flavanones **1a–n** were oxidized with TTA in acetic acid to give the flavones **2a–n** almost quantitatively with, in contrast to their oxidation with LTA, no side-products.[5] Similarly, with thallium(III) oxide **1a** in refluxing acetic acid also gave the flavone **2a** almost quantitatively. A slight excess (*i.e.*, 0.012 mol with respect to **1a**) of $Tl_2O_3$ was needed, presumably because TTA (formed from acetic acid and $Tl_2O_3$)[11] oxidized the acetic acid to acetoxyacetic acid.[12] Similarly, treatment of **1a–n** with TTS in propionitrile afforded isoflavones **3a–n** almost quantitatively, except for compounds having an electron-withdrawing substituent [*e.g.* **1d, j, n** ($R^1$ = Cl), **1e** ($R^1$ = $NO_2$) and **1f, k** ($R^2$ = $NO_2$)], when a mixture of products **2** and **3** (Table 1) was obtained. TTN in acetonitrile also gave closely similar results to TTS. Compounds having 2-ArOMe, *e.g.*, **1b,h,m** ($R^1$ = OMe) behaved differently affording a mixture of flavones and isoflavones.

A probable mechanism for the above transformation is depicted in Scheme 2. Initial enolization of compound **1** followed by electrophilic attack by the thallium(III) reagent at the face of the molecule *syn* to 2-Ar in the case of TTA and *anti* to 2-Ar in the case of TTS, gives the intermediates **4** and **5** respectively, which undergo subsequent dethalliation *via* two different mechanistic pathways. Whereas, in the case of species




| | R | $R^1$ | $R^2$ |
|---|---|---|---|
| **a** | H | H | H |
| **b** | H | OMe | H |
| **c** | H | Me | H |
| **d** | H | Cl | H |
| **e** | H | $NO_2$ | H |
| **f** | H | H | $NO_2$ |
| **g** | Cl | H | H |
| **h** | Cl | OMe | H |
| **i** | Cl | Me | H |
| **j** | Cl | Cl | H |
| **k** | Cl | H | $NO_2$ |
| **l** | Me | H | H |
| **m** | Me | OMe | H |
| **n** | Me | Cl | H |

**Scheme 1** *Reagents and conditions:* i, TTA, AcOH reflux 2–3 h; ii, TTS, EtCN, reflux 2–3 h; iii, TTN, MeCN, reflux 2–3 h

**4**, the reductive cleavage of the C(3)–Tl bond is accompanied by a concomitant loss of the *trans* proton 2-H to afford the flavone, a similar cleavage in the case of **5** is assisted by the neighbouring 2-Ar ring to form a bridged carbocation **6**, which loses 3-H accompanied by the migration of 2-Ar ring to yield compound **3**. In this case, the 2,3-aryl shift is a favoured path because of anchimeric assistance from the 2-Ar group. The possibility of a two-step process involving the initial formation of a carbocation by reductive C–Tl bond cleavage is ruled out in both cases because the formation of such an intermediate would develop a positive charge on the carbon atom in the vicinity of a carbonyl group. In addition, formation of a free carbocation intermediate, would have given a mixture of flavones and isoflavones by the oxidation of flavanones with TTA in acetic acid as well as TTS in propionitrile; such is not the case (Table 1).

Substituents in the 2-Ar ring had the expected effect on the ease of migration. Thus, 4′-methoxy- and 4′-methyl-flavanones underwent 2,3-aryl migration smoothly giving the corresponding isoflavones in better yields than 4′-chloro- (**1d,j,n**) as well as 3′- and 4′-nitroflavanones (**1k,e,f**). The inhibitory effect of electron-withdrawing groups on the ease of migration was so pronounced that only 20–30% of nitroisoflavones were obtained from the corresponding nitro substituted flavanones. This is, however, contrary to the results reported recently.[13]

† 2-Phenylchromones.
‡ 3-Phenylchromones.

**Table 1** Oxidation of flavanones **1a–n** and **7** with TTA, TTN and TTS

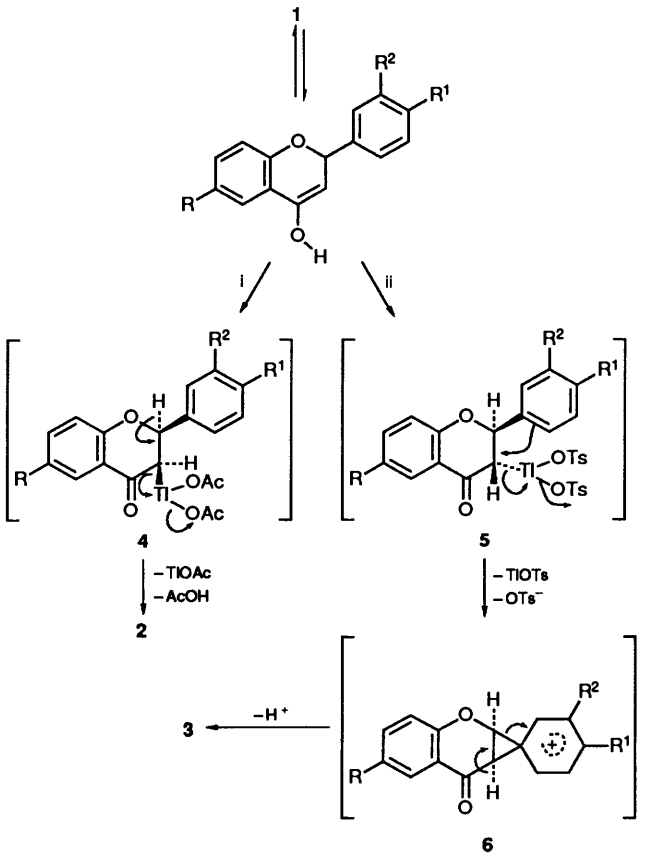
| Compound | Thallium(III) salts | Solvent | Flavone:Isoflavone[a] | Yield (%)[b] Flavone | Yield (%)[b] Isoflavone | M.p./°C (lit.) Flavone | M.p./°C (lit.) Isoflavone |
|---|---|---|---|---|---|---|---|
| **1a** | TTA[g] | AcOH | 100:0 | 96[c] | | 98 (98)[14] | |
| | TTN | MeCN | 5:95 | | 80[c] | | 131–2 (132)[15] |
| | TTS[g] | EtCN | 0:100 | | 94[c] | | |
| **1b** | TTA | AcOH | 100:0 | 95[c] | | 156–7 (156)[14] | |
| | TTN | MeCN | 38:62 | | 50[c] | | |
| | TTS | EtCN | 0:100 | | 96[c] | | 138–9 (138)[16] |
| **1c** | TTA | AcOH | 100:0 | 96[c] | | 110 (110–12)[17] | |
| | TTN | MeCN | 5:95 | | 82[d] | | |
| | TTS | EtCN | 0:100 | | 95[c] | | 153–4[f] |
| **1d** | TTA | AcOH | 100:0 | 98[c] | | 188 (188–9)[18] | |
| | TTN | MeCN | 15:85 | | 74[d] | | |
| | TTS | EtCN | 10:90 | | 84[d] | | 182[f] |
| **1e** | TTA | AcOH | 100:0 | 96[c] | | 246–7 (244–6)[19] | |
| | TTN | MeCN | *e* | 70[d] | 20[d] | | |
| | TTS | EtCN | *e* | 70[d] | 20[d] | | 216–7[f] |
| **1f** | TTA | AcOH | 100:0 | 98[c] | | 194–5 (201–2)[19] | |
| | TTN | MeCN | *e* | 60[d] | 30[d] | | |
| | TTS | EtCN | *e* | 60[d] | 30[d] | | 185–6[f] |
| **1g** | TTA | AcOH | 100:0 | 96[c] | | 182 (182–4)[20] | |
| | TTN | MeCN | 10:90 | | 78[d] | | |
| | TTS | EtCN | 0:100 | | 96[c] | | 174–5[f] |
| **1h** | TTA | AcOH | 100:0 | 98[c] | | 180–1 (180–1)[21] | |
| | TTN | MeCN | 40:60 | 20[d] | 45[d] | | |
| | TTS | EtCN | 0:100 | | 94[c] | | 194–5[f] |
| **1i** | TTA | AcOH | 100:0 | 98[c] | | 183–4[f] | |
| | TTN | MeCN | 5:95 | | 80[c] | | |
| | TTS | EtCN | 0:100 | | 94[c] | | 173–4 (173–4)[22] |
| **1j** | TTA | AcOH | 100:0 | 96[c] | | 226–7 (226)[23] | |
| | TTN | MeCN | 45:55 | — | — | | |
| | TTS | EtCN | 20:80 | | 72[d] | | 195–6[f] |
| **1k** | TTA | AcOH | 100:0 | 96[c] | | 235–6[f] | |
| | TTN | MeCN | *e* | 55[d] | 30[d] | | |
| | TTS | EtCN | *e* | 60[d] | 20[d] | | 181–2[f] |
| **1l** | TTA | AcOH | 100:0 | 98[c] | | 121–2 (122)[24] | |
| | TTN | MeCN | 5:95 | | 74[c] | | |
| | TTS | EtCN | 0:100 | | 92[c] | | 108–9 (108)[25] |
| **1m** | TTA | AcOH | 100:0 | 96[c] | | 167–8 (167)[26] | |
| | TTN | MeCN | 40:60 | — | — | | |
| | TTS | EtCN | 0:100 | | 94[c] | | 123–4[f] |
| **1n** | TTA | AcOH | 100:0 | 96[c] | | 198–9[f] | |
| | TTN | MeCN | 20:80 | | 68[d] | | |
| | TTS | EtCN | 10:90 | | 85[d] | | 205–6[f] |
| **7** | TTA | AcOH | 100:0 | 94[c] | | 156–8 (156–9)[27] | |
| | TTN | MeCN | *e* | | 74[c] | | |
| | TTS | EtCN | 0:100 | | 92[c] | | 165–6[f] |

[a] Ratio determined by $^1$H NMR spectroscopy by integration of 2-H and 3-H proton signals of isoflavones and flavones, respectively. [b] Yield based upon isolated solid products with respect to flavanones used. [c] Crystallization of reaction mixture using ethyl acetate–hexane. [d] Separated by column chromatography. [e] Ratio could not be determined. [f] Satisfactory C and H analyses were obtained. [g] Similar results were obtained with $Tl_2O_3$ in the presence of AcOH–*p*-TSA.

**Table 2** Oxidation of compound **1** with TTA (1 mol) in the presence of *p*-TSA in refluxing propionitrile

| *p*-TSA (mol) | Flavone:isoflavone |
|---|---|
| 0 | 100:0 |
| 1 | 70:30 |
| 2 | 40:60 |
| 3 | 5:95 |
| >3 | 0:100 |

The formation of isoflavones from flavanones in the presence of TTA and toluene-*p*-sulfonic acid (*p*-TSA) in propionitrile can be rationalized, by considering the *in situ* formation of TTS by the action of TTA with *p*-TSA (Scheme 3), on the basis of following observations (Table 2): (i) the treatment of **1** with TTA in acetonitrile or propionitrile yields only product **2**;[10] (ii) treatment of **1** with TTA and *p*-TSA (1 equiv.) affords a mixture of products **2** and **3** in the ratio of 70:30, probably due to the partial conversion of TTA into TTS, both reacting with **1** giving rise to the mixture; (iii) treatment of **1** with TTA and *p*-TSA (2 equiv.) also affords a mixture of products **2** and **3** in the ratio 40:60; (iv) treatment of **1** with TTA and *p*-TSA ($\geq$3 equiv.) results in the exclusive formation of product **3**. The last was observed on treatment of **1** with $Tl_2O_3$ and *p*-TSA (6



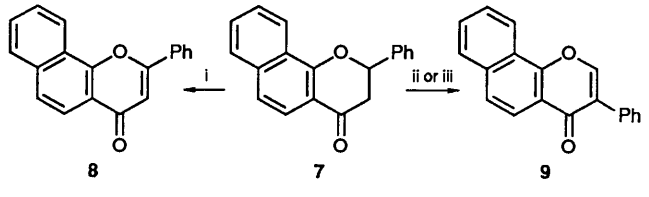
**Scheme 2** *Reagents:* i, TTA; ii, TTS

$$Tl(OCOMe)_3 + 3\,p\text{-}MeC_6H_4SO_3H \longrightarrow Tl(OSO_2C_6H_4\,Me\text{-}p)_3 + 3\,MeCOOH$$

**Scheme 3**

$$Tl_2O_3 + 6\,p\text{-}MeC_6H_4SO_3H \longrightarrow 2\,Tl(OSO_2C_6H_4Me\text{-}p)_3 + 3\,H_2O$$

**Scheme 4**



**Scheme 5** *Reagents and conditions:* i, TTA, AcOH, reflux 2–3 h; ii, TTS, EtCN, reflux 2–3 h; iii, TTN, MeCN, reflux 2–3 h

equiv.) in refluxing propionitrile when **3** was obtained in almost quantitative yield (Scheme 4).

The oxidation of flavanones with TTN gave rise to isoflavones along with small amounts of flavones demonstrating that in this case there is the formation of both the *syn* as well as *anti* thalliated intermediates, the latter being formed in major quantity.

Similarly, α-naphthoflavanone **7** on oxidation with TTA in acetic acid, TTS in propionitrile and TTN in acetonitrile at reflux temperature afforded the α-naphthoflavone **8** and α-naphthoisoflavone **9** in excellent yields (Scheme 5).

## Conclusion

The oxidation with $Tl^{III}$ salts of flavanones to flavones and isoflavones constitutes a new and convenient procedure for synthesizing the latter. Thus TTA in acetic acid and TTS in EtCN, give, almost quantitatively, flavones and isoflavones, respectively. More conveniently, $Tl_2O_3$ under different conditions may be used to give the same products. TTN is a less good reagent since the isoflavones are always contaminated with flavones (Table 1). Although TTS is an excellent reagent for the synthesis of isoflavones, it cannot be used for those having electron-withdrawing groups in the 2-Ar ring.

## Experimental

M.p.s were taken in open capillaries in a sulfuric acid bath and are uncorrected. IR spectra were recorded on a Beckman spectrophotometer (IR-20) and Perkin-Elmer 842 IR spectrophotometer in Nujol mulls. $^1H$ NMR spectra were scanned on Perkin-Elmer R-32 or JEOL Fx-90Q MHz machine using $CDCl_3$ as solvent and $Me_4Si$ as an internal standard. TLC was carried out on silica gel coated plates using benzene as solvent and the compounds were separated over a silica gel (100–200 mesh) column using ethyl acetate–hexane (1:9) as eluent.

Flavanones **1a–n** and **7** with various substituents in both aromatic rings were prepared by acid-catalysed cyclization of the corresponding chalcones in 60–80% yields, according to the procedure described in the literature.[28] Solvents were distilled before use. Thallium(III) nitrate, thallium(III) acetate and thallium(III) oxide were commercial products and were obtained from Aldrich.

*Thallium*(III) *Toluene*-p-*sulfonate.*—To a solution of *p*-TSA (5 mol) in dry acetonitrile (20 $cm^3$) was added TTN (1.5 mol); a colourless solid separated in approximately 10 min and the residue left after decanting the solvent was washed with dry hexane (3 × 10 $cm^3$) and dried (m.p. 166–167 °C).

*Oxidation of Flavanones with Thallium*(III) *Acetate. General Procedure.*—TTA (0.011 mol) was added to a solution of appropriate flavanone (0.01 mol) in acetic acid (20 $cm^3$). The reaction mixture was refluxed for 2–3 h, cooled to room temperature and poured into ice-cold water with stirring. The solid so obtained was extracted with $CH_2Cl_2$ (3 × 50 $cm^3$). The organic layer was washed with water (2 × 50 $cm^3$), followed by saturated aqueous sodium hydrogen carbonate (2 × 100 $cm^3$) and dried ($Na_2SO_4$). The solvent was then distilled off under reduced pressure to yield a solid product which on crystallization with ethyl acetate–hexane gave the pure flavone (Table 1).

*Oxidation of Flavanones with Thallium*(III) *Nitrate. General Procedure.*—TTN (0.025 mol) was added to the solution of flavanone (0.01 mol) in acetonitrile (15 $cm^3$). The resulting reaction mixture was refluxed for 2–3 h. It was then cooled to room temperature, diluted with $CH_2Cl_2$ (50 $cm^3$) and the precipitated thallium(I) nitrate was filtered off and washed with $CH_2Cl_2$ (2 × 20 $cm^3$). The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 $cm^3$), followed by water and dried ($Na_2SO_4$). The solvent was distilled off under reduced pressure. The gummy mass so obtained was purified either by crystallization or by column chromatography over silica gel 'G' using ethyl acetate–hexane (1:9) as eluent (Table 1).

*Oxidation of Flavanones with Thallium*(III) *Toluene*-p-*sulfonate. General Procedure.*—Toluene-*p*-sulfonic acid (0.035 mol) was dissolved in propionitrile (15–20 $cm^3$) containing TTA (0.011 mol). The resulting solution was warmed for 5 min, after

which the flavanone (0.01 mol) was added. The mixture was then refluxed for 2–3 h, cooled to room temperature and diluted with $CH_2Cl_2$ (50 $cm^3$). The separated thallium(I) salt was filtered off and washed with $CH_2Cl_2$ (20 $cm^3$). The filtrate was washed with aqueous sodium hydrogen carbonate (2 × 50 $cm^3$) followed by water (2 × 50 $cm^3$) and dried ($Na_2SO_4$). The solvent was then distilled off under reduced pressure and the residue purified either by crystallization or by column chromatography on silica gel 'G' using ethyl acetate–hexane (1:9) as an eluent (Table 1). In an alternate procedure addition of flavanone to the preformed TTS (*vide supra*) in refluxing propionitrile gave the same result.

*Oxidation of Flavanones with Thallium*(III) *Oxide. General Procedure.*—Thallium(III) oxide (0.012 mol) was added to a solution of flavanone (0.01 mol) in acetic acid (20 $cm^3$) containing 3–4 drops of water. The reaction mixture was refluxed for 3–4 h, cooled to room temperature and poured into ice-cold water. The mixture was extracted with $CH_2Cl_2$ (2 × 50 $cm^3$), washed with water (2 × 50 $cm^3$), followed by saturated aqueous sodium hydrogen carbonate (2 × 50 $cm^3$) and dried ($Na_2SO_4$). The solvent was distilled off under reduced pressure and the solid, so obtained, was crystallized with ethyl acetate–hexane (Table 1).

*Oxidation of Flavanones with Thallium*(III) *Oxide in the Presence of Toluene-*p*-sulfonic Acid. General Procedure.*—Thallium(III) oxide (0.01 mol) was added to a solution of flavanone (0.01 mol) in propionitrile (15 $cm^3$) containing toluene-*p*-sulfonic acid (0.065 mol). The resulting dark brown mixture was refluxed until it became colourless (1–2 h). It was then cooled to room temperature, diluted with $CH_2Cl_2$ (50 $cm^3$) and the separated thallium(I) salt was filtered off and washed with $CH_2Cl_2$ (20 $cm^3$). The filtrate was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 $cm^3$) and water and dried ($Na_2SO_4$). The solvent was then distilled off under reduced pressure and the residue was recrystallized from ethyl acetate–hexane (1:9) (Table 1).

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## References

1 C. G. Shankar, B. V. Mallarah and G. Srimannarayana, *Synthesis*, 1983, 310.
2 D. Chakravarti and J. Dutta, *J. Indian Chem. Soc.*, 1939, **16**, 639.
3 W. Fatima, J. Iqbal, H. Ismail, Kh. Ishratullah, W. A. Shaida and W. Kehaman, *Chem. Ind. (London)*, 1979, 315; W. Fatima, J. Iqbal, V. Manchanda, W. A. Shaida and W. Rohaman, *J. Chem. Res. (S)*, 1984, 29; *J. Chem. Res. (M)*, 1984, 2656.
4 A. G. Doshi, P. A. Soni and B. J. Ghiya, *Indian J. Chem.*, 1986, **25B**, 259; R. P. Kapoor, Om V. Singh and C. P. Garg, *J. Indian Chem. Soc.*, 1991, **68**, 367.
5 G. W. K. Cavil, F. M. Dean, A. McGookin, B. M. Marshall and A. Robertson, *J. Chem. Soc.*, 1954, 4573.
6 A. McKillop and E. C. Taylor, *Adv. Organomet. Chem.*, 1973, **11**, 147; A. McKillop, *Pure Appl. Chem.*, 1975, **43**, 463; A. McKillop and E. C. Taylor, *Endeavour*, 1976, **35**, 88; S. Uemura, *Synthetic Reagents*, ed. J. S. Pizey, Ellis Horwood, Chichester, 1981, vol. 5, p. 165.
7 L. Farkas, A. Gottesegen and M. Nogradi, *J. Chem. Soc., Perkin Trans. 1*, 1974, 306 and references cited therein.
8 W. D. Ollis, K. L. Ormand and I. O. Sutherland, *Chem. Commun.*, 1968, 1237.
9 R. S. Varma and M. Varma, *Synth. Commun.*, 1982, **12**, 927.
10 Preliminary communications: (*a*) O. V. Singh and R. P. Kapoor, *Tetrahedron Lett.*, 1990, **31**, 1459; (*b*) O. V. Singh, C. P. Garg and R. P. Kapoor, *Tetrahedron Lett.*, 1990, **31**, 2747.
11 L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1967, **1**, 1150.
12 E. C. Taylor, H. W. Altland, G. McGillivray and A. McKillop, *Tetrahedron Lett.*, 1970, 5285.
13 When the present manuscript was in preparation a communication concerning the oxidation of flavanone to isoflavone along with flavone using TTN also appeared: T. Kinoshita, K. I. Chinose and V. Shankawa, *Tetrahedron Lett.*, 1990, **31**, 7355.
14 M. S. Mahal, H. S. Rai and K. Venkataraman, *J. Chem. Soc.*, 1935, 866.
15 P. C. Joshi and K. Venkataraman, *J. Chem. Soc.*, 1934, 513.
16 S. C. Bharara, A. C. Jain and T. R. Seshadri, *Tetrahedron*, 1965, **21**, 963.
17 U. K. Mallik, M. M. Saha and A. K. Mallik, *Indian J. Chem.*, 1989, **20B**, 970.
18 W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.*, 1952, 1294.
19 R. Ludwig and G. Hempel, *Justus Liebigs Ann. Chem.*, 1960, **625**, 184 (*Chem. Abstr.*, 1960, **54**, 3396f).
20 S. Hatori, *Bull. Chem. Soc. Jpn.*, 1927, **2**, 171.
21 C. T. Chang, F. C. Chen, T. S. Chen, K. K. Ksu, T. Ueng and M. Hang, *J. Chem. Soc.*, 1961, 3414.
22 O. Prakash, S. Pahuja, S. Goyal, S. N. Sawhney and R. M. Moriarty, *Synlett*, 1990, 337.
23 M. K. Gurgar, *Curr. Sci.*, 1978, **47**, 8878.
24 O. Dann and G. Mylius, *Justus Liebigs Ann. Chem.*, 1954, **587**, 1.
25 Le-van-Thol and Nguyen-van-Hang, *Vietnam. Chim. Acta*, 1966, 87 (*Chem. Abstr.*, 1969, **71**, 124127).
26 D. M. Fitzgerold, J. F. O'Sullivan, F. M. Phillibin and T. S. Wheeler, *J. Chem. Soc.*, 1959, 860; B. J. Ghiya and M. G. Marathy, *Indian J. Chem.*, 1963, **1**, 1389.
27 F. E. Smith, *J. Chem. Soc.*, 1946, 542.
28 D. D. Keane, K. G. Maratha, W. I. O'Sullivan, E. M. Philin, R. M. Simons and P. C. Teague, *J. Org. Chem.*, 1970, **35**, 2286.

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