A FACILE AND CHEAP METHOD FOR THE CONVERSION OF FLAVONES INTO 4-THIOFLAVONES USING PHOSPHORUS PENTASULFIDE AND SODIUM HYDROGEN CARBONATE

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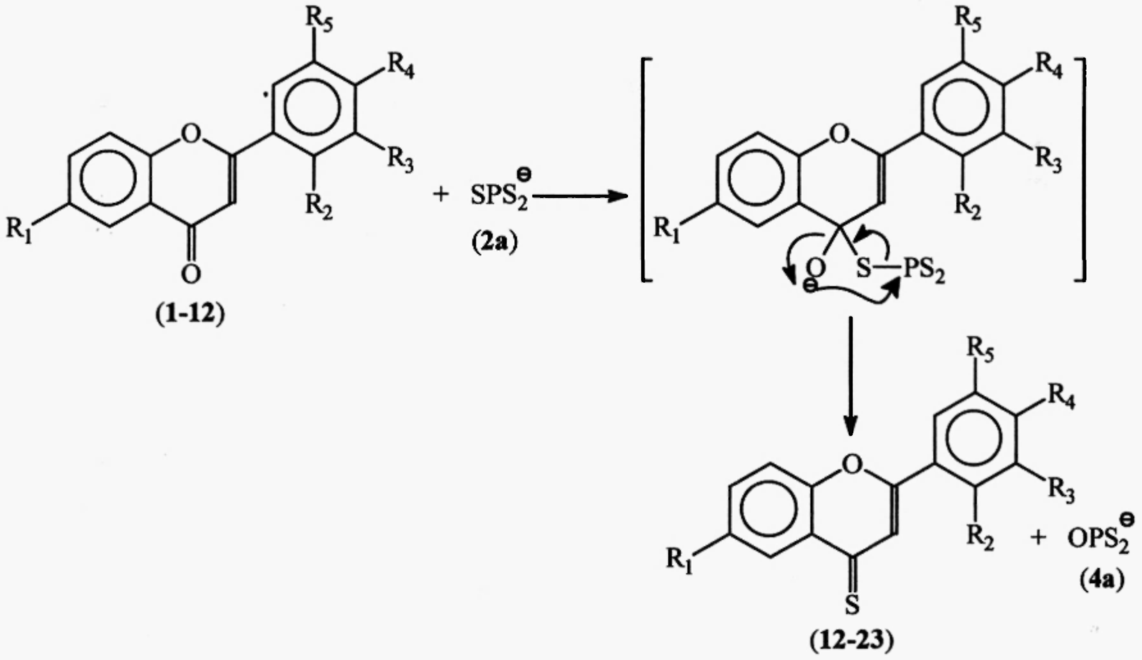
Abstract: A facile, rapid, high yielding and relatively cheaper method has been developed for the synthesis of 4-thioflavones by using phosphorus pentasulfide and sodium hydrogen carbonate. Seven new and five known substituted 4-thioflavones prepared by this method are reported

Introduction

Flavones (2-phenyl-benzo-γ-pyrone) are well known naturally occurring polyphenolic compounds [1-3]. These have been reported to possess a vast range of biological properties [4-5]. However, the corresponding 4-thio analogues of flavones have received less attention due to limited methods available for their preparation, although these sulfurated flavones may offer new and pronounced biological properties. They may also be used as precursors for the synthesis of a variety of other organic compounds. The un-substituted flavones have been transformed into 4-thio analogues by several research groups [6-12]. For this purpose, phosphorus pentasulfide was used as the thiation agent. In one case [10] this source of sulfur-atom was replaced by silicon disulfide or boron sulfide, but these two reagents proved to be highly sensitive to water. The data available in some other reports about the conversion of substituted flavones into substituted 4-thioflavones via 4,4-dicholorflavenes [11, 13, 15] does not provide information to evaluate the influence of substitution on the thiation of the flavones. Then again an efficient, high yielding and effective procedure [17] was worked out for the preparation of 4-thioflavones by the reaction of flavones with Lawesson's reagent [18, 19] without affecting the substitution pattern of the starting flavone. This method however requires excess of the reagent (0.5-3.0 molar equiv); the reaction time is lengthy (2-25h) and is conducted in dry non-polar hydrocarbon solvents at elevated temperatures that usually results in generation of side products. For the purification of thioflavones, column chromatography has to be employed. Lawesson's reagent is not suitable for flavones having low melting points. This reagent has high water sensitivity, high price and difficult to handle Moreover, the mechanism of this reagent has not been properly proposed. In 1973, Scheeren et al. [20] reported that carbonyl compounds could be converted into the corresponding thiocarbonyls by the use of phosphorus pentasufide and sodium bicarbonate in acetonitrile or ether solvents. However, when we applied this procedure to the un-substituted and substituted flavones, an interesting reaction occurred to give 4-thioflavones with high yield and having no influence on substitution pattern on flavones. We report herein the synthesis of seven new and five known variably substituted thioflavones by this method that is less time consuming, occurs at low temperature and thus no complex side products are generated. This process is very simple, relatively cheaper, easy to handle and offers higher yields.

Results and Discussions

Phosphorus pentasulfide [20,21-23] proved to be the choice of thiation agent especially for the conversion of chromones, flavones and 1-thiochromones into their 4-thio analogues. We report herein on utilization of this thiation agent for the conversion of flavones into 4-thioflavones. Little is known about the interaction of P_2S_5 with inorganic salts in organic solvents, but it may be assumed that such solutions contain the anion $X_2PS_2^-$ (X^- is the monovalent anion in the salt used) in monomeric or polymeric form [24, 25]. In solutions prepared from P_2S_5 and sodium carbonate or hydrogen-carbonate, which evolve carbon dioxide, OPS_2^- and SPS_2^- (**2a**) should thus be present. For sulfurization reactions, such solutions have to be used when freshly prepared, because they become syrupy on standing or heating, probably due to polymerization. Sulfurization may be due to nucleophilic attack of these anions on the carbonyl C-atom followed by elimination of O_2PS^- or OPS_2^- (4a), respectively [20] (Scheme-1).



	R_1	R_2	R_3	R_4	R_5
1, 13	H	H	H	H	H
2, 14	H	H	–OMe	H	H
3, 15	H	H	H	–Me	H
4, 16	H	H	H	$-NO_2$	H
5, 17	H	H	H	–OMe	H
6, 18	H	$-NO_2$	H	H	$-NO_2$
7, 19	H	H	$-NO_2$	H	H
8, 20	–F	–I	H	H	H
9, 21	–F	H	H	H	H
10,22	–Cl	–I	H	H	H
11, 23	–Br	–I	H	H	H
12, 24	H	H	H	F	H

Scheme-1

Flavones (**1-12**) were allowed to react with P_2S_5/$NaHCO_3$ in dry THF at low temperature with constant stirring for 1-2 hrs, to give 4-thioflavones (**13-24**) (Scheme-1).

The structures of synthesized compounds were elucidated by microanalysis, IR, EIMS and ^{1}H- and ^{13}C NMR spectroscopies.

In IR spectra, the disappearance of the C=O bond and appearance of a C=S bond at around 1120-1190 cm^{-1} unequivocally prove the replacement of the oxygen by a sulfur atom. This finding was corroborated by the C=S signal observed in their ^{13}C-NMR spectra between 200-206 ppm. The structures of these compounds wee also confirmed by EIMS. The molecular weight of the 4-thioflavones was confirmed from molecular ion peaks which are the base peaks. The whole ^{1}H- and ^{13}C-NMR and EIMS were in complete harmony with the presence of a 4-thioflavone skeleton.

Conclusions

In conclusion, we have developed a facile and very simple method for the synthesis of 4-thio analogues of un-substituted and substituted flavones which may have very useful bioactivities [26].This eco-friendly method avoids the use of expensive Lawesson's reagent, use of excess time in purification of the samples through column chromatography and precludes the use of high temperature. All 4-thioflavones were obtained in very good yields indicating that conversion is not influenced by the substitution pattern of the 2-phenyl ring as well as ring-A of the flavone.

Experimental

All melting points were determined in open capillaries using Gallenkemp melting point apparatus and are un-corrected. The IR spectra were recorded on Bio-red spectrophotometer using KBr discs. ^{1} H- and 13C-NMR spectrum was recorded on Bruker (400 MHz) AM-250 in DMSO solution using TMS as internal standard. EIMS was recorded on MAT-311-A machine. Purity of each compound was monitored on Shimadzu LC-6A, HPLC. TLC was performed on Kieselgel 60 F_{254} (Merck) plates using hexane : acetone (4:1 v/v) as the developing solvent . Flavones (**1-12**) were synthesized by the Baker-Venkataraman Reaction [27], starting from 5-substituted 2-hydroxyacetophenone and substituted benzoyl chlorides [27-30].

General Procedure for the Preparation of Compounds (13-24)

To the stirred solution of flavones (2.5 mmL) in anhydrous THF (6 mL), a solution of P_2S_5 (1.5 equiv.) in the same solvent (5 mL) was added. Solid sodium hydrogen carbonate (6 equiv.) was then added to the stirred mixture Stirring was then continued for 1-2 hrs and regularly monitored by TLC at 30°C under dried conditions. The reaction mixture was then poured into water. The solid 4-thioflavones (**13-24**) were isolated by filtration, washed several times with water and crystallized from ethanol.

4-Thioflavone (13): This compound was obtained as dark red needles in 81% yield, m.p. 86-87°C, lit. 87-88°C [31]. IR (ν cm^{-1}): 1165 (C=S), 1595 (C=C). ^{1}H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 7.05-8.21 (m, 3H + 9H). ^{13}C NMR δ (ppm): 202.01 (C-4), 128.8 (C-3), 156.1 (C-2). EIMS (70 eV) m/z (%): 238 ($M^{+\bullet}$, 100), 237 (45), 194 (29), 108 (10), 165 (13), 92 (11), 105 (42), 77 (35). Anal. Calcd. for $C_{15}H_{10}OS$: C, 75.63; H, 4.20. Found: C, 75.59, H, 4.18.

3′-Methoxy-4-thioflavone (14): This substance was prepared as red crystals in 77% yield, m.p. 105-106°C; lit. m.p. 107-108°C [17]. IR (ν cm^{-1}): 1178 (C=S), 1606 (C=C). ^1H NMR (400 MHz, DMSO δ(ppm), J(Hz): 3.88 (s, 3H, OMe), 8.43 (t, 1H, J = 8.86, 5′-H), 7.69 (s, 1H, 3′-H), 7.22 (dd, 1H, J = 8.2, 2.3, 4′-H), 7.95 (s, 1H, 2′-H). ^{13}C NMR δ (ppm): 129 (C–3), 157.5 (C–2), 202.2 (C–4). EIMS (70 eV) m/z(%): 268 ($M^{+\bullet}$, 100), 237 (7), 224 (20), 134 (8), 108 (10), 92 (5). Anal. Calcd. for $C_{18}H_{12}O_2S$: C, 71.64; H, 4.52. Found, 71.66; H, 4.50.

4′-Methyl-4-thioflavone (15): This compound was obtained as purple crystals in 80% yield, m.p. 139-141°C; lit. m.p. 145-146°C [15]. IR (ν cm^{-1}): 1167 (C=S), 1601 (C=C). ^1H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 2.38 (s, 3H, Me), 7.50 (s, 1H, 3H), 8.42 (d, 1H, J = 8.14, 5-H), 8.08 (d, 2H, J = 8.15, 2′H + 6′H), 7.40 (d, 2H, J = 8.06, 3′H + 5′H), 7.54 (dd, 1H, J = 7.84, 7.17, 7H), 7.89 (ddd, J = 8.27, 6.02, 1.17, 6H + 8H). ^{13}C NMR δ (ppm): 127.9 (C–3), 155.1 (C–2), 202.4 (C–4). EIMS (70 eV) m/z(%): 252 ($M^{+\bullet}$, 100), 237 (20), 208 (30), 165 (4), 108 (25), 92 (7). Anal. Calcd. for $C_{16}H_{12}OS$: C, 76.18; H, 4.78. Found, 76.02; H, 4.69.

4′-Nitro-4-thioflavone (16): This substance was obtained as purple crystals in 77% yield, m.p. 246-248°C; lit. m.p. 145-146°C [17]. IR (ν cm^{-1}): 1170 (C=S), 1604 (C=C). ^1H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 7.3 (s, 1H, 3H), 8.40 (d, 1H, J = 8.08, 5-H), 8.38 (d, 2H, J = 8.16, 2′H + 6′H), 8.60 (d, 2H, J = 8.31, 3′H + 5′H), 7.51 (dd, 1H, J = 7.84, 7.16, 7H, 7.87 (ddd, 2H, J = 8.21, 7.01, 1.18, 6H + 8H). ^{13}C NMR δ(ppm): 131 (C–3), 150 (C–2), 205 (C–4). EIMS (70 eV) m/z(%): 283 ($M^{+\bullet}$, 100), 239 (31), 238 (27), 165 (13), 92 (9), 108 (19). Anal. Calcd. for $C_{15}H_9NO_3S$: C, 63.62; H, 3.21. Found: 63.54; H, 3.17.

4′-Methoxy-4-thioflavone (17): This compound was obtained as light red plates in 85% yield, m.p. 135-136°C; lit. m.p. 137°C [14]. IR (ν cm^{-1}): 1185 (C=S), 1590 (C=C). ^1H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 3.85 (s, 3H, Ome), 7.41 (s, 1H, 3H), 8.41 (d, 1H, J = 8.20, 5H), 8.01 (d, 2H, J = 7.99, 2′H + 6′H), 8.35 (d, 2H, J = 8.21, 3′H + 5′H), 7.50 (dd, 1H, J = 7.85, 7.15, 7H), 7.81 (ddd, 2H, J = 8.20, 6.99, 1.50, 6H + 8H). ^{13}C NMR δ(ppm): 129 (C–3), 150 (C–2), 202.1 (C–4). EIMS (70 eV) m/z(%): 268 ($M^{+\bullet}$, 10), 237 (20), 224 (13), 134 (100), 108 (12), 92 (7). Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.64; H, 4.52. Found: C, 71.53; H, 4.48.

2′,5′-Dinitro-4-thioflavone (18): This compound was obtained as maroon powder in 70% yield, m.p. 232-233°C. IR (ν cm^{-1}): 1179 (C=S), 1602 (C=C). ^1H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 7.20 (s, 1H, 3H), 8.35 (s, 1H, 6′H), 8.55 (d, 1H, J = 8.24, 3′H), 8.45 (d, 1H, J = 8.12, 4′H), 7.40-8.02 (m, ArH). ^{13}C NMR δ(ppm): 131 (C–3), 159 (C–2), 202.6 (C–4). EIMS (70 eV) m/z(%): 328 ($M^{+\bullet}$, 100), 236 (21), 282 (34), 284 (45), 108 (23), 92 (10). Anal. Calcd. for $C_{15}H_8O_5S$: C, 54.88; H, 2.44. Found: C, 54.70; H, 2.35.

3′-Nitro-4-thioflavone (19): This substance was obtained as bright red crystals in 81% yield, m.p. 150-151°C. IR (ν cm^{-1}): 1170 (C=S), 1619 (C=C). ^1H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 6.99 (s, 1H, 3H), 8.91 (s, 1H, 2′H), 8.66 (d, 1H, J = 7.95, 4′H), 7.00-8.55 (m, 5′H + 6′H + A-ring H). ^{13}C NMR δ(ppm): 133 (C–3), 153 (C–2), 201

(C–4). EIMS (70 eV) m/z(%): 283 ($M^{+\bullet}$, 100), 239 (30), 238 (40), 165 (9), 105 (19), 92 (10), 105 (6), 77 (50). Anal. Cald. for $C_{15}H_9NO_3S$: C, 63.60; H, 3.20. Found: C, 63.55; H, 3.21.

6-Fluoro -2′-Iodo-4-thioflavone (20): This compound was obtained as dull orange crystals in 83% yield, m.p. 162-163°C. IR (ν cm^{-1}): 1169 (C=S), 1696 (C=C). ^{1}H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 7.03 (s, 1H, 3H), 7.54-8.30 (m, 8 ArH). ^{13}C NMR δ(ppm): 130.2 (C–3), 154 (C–2), 203.0 (C–4). EIMS (70 eV) m/z(%): 363 ($M^{+\bullet}$, 100), 227 (40), 230 (75), 202 (60), 194 (35). Anal. Calcd. for $C_{15}H_9IOS$: C, 49.58; H, 2.48. Found: C, 49.10; H, 2.31.

6-Fluoro-4-thioflavone (21): This substance was prepared as fully red crystals in 85% yield, m.p. 112-113°C. IR (ν cm^{-1}): 1180 (C=S), 1615 (C=C). ^{1}H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 7.48 (s, 1H, 3H), 7.60-8.22 (m, 8 ArH). ^{13}C NMR δ(ppm): 128.8 (C–3), 159 (C–2), 202.2 (C–4). EIMS (70 eV) m/z(%): 256 ($M^{+\bullet}$, 100), 212 (38), 194 (4), 183 (20), 154 (8), 126 (14), 77 (16). Anal. Calcd. for $C_{15}H_9FOS$: C, 70.32; H, 3.52. Found: C, 70.01; H, 3.48.

6-Chloro-2′-Iodo-4-thioflavone (22): This compound was obtained as red crystals in 82% yield, m.p. 158-160°C. IR (ν cm^{-1}): 1163 (C=S), 1620 (C=C). ^{1}H NMR (400 MHz, DMSO) δ(ppm), J(Hz): 7.19 (s, 1H, 3H), 8.37 (d, 1H, J = 2.23, 5H), 8.08 (d, 1H, J = 7.89, 7H), 7.97 (dd, 1H, J = 8.35, 2.36, 3′H), 7.83 (d, 1H, J = 8.90, 6′H), 7.76 (d, 1H, J = 7.48, 8H), 7.61 (dd, 1H, J = 7.47, 7.50, 5′H), 7.33-7.48 (m, 1H, 4′H). ^{13}C NMR δ(ppm): 129.5 (C–3), 152.5 (C–2), 202.7 (C–4). EIMS (70 eV) m/z(%): 397 ($M^{+\bullet}$, 100), 397 ($M^{+\bullet}$ + 2, 100), 353 (13), 271 (100), 236 (38), 208 (45), 149 (42), 78 (62). Anal. Calcd. for $C_{15}H_8ClIOS$: C, 45.28; H, 2.01. Found: C, 45.20; H, 1.97.

6-Bromo-2′-Iodo-4-thioflavone (23): This substance was synthesized as dark red crystals in 78% yield, m.p. 152-153°C. IR (ν cm^{-1}): 1160 (C=S), 1616 (C=C). ^{1}H NMR (500 MHz, DMSO) δ(ppm), J(Hz): 7.01 (s, 1H, 3H), 8.42 (d, 1H, J = 2.51, 5H), 8.20 (d, 1H, J = 7.91, 7H), 7.96 (dd, 1H, J = 8.35, 2.36, 3′H), 7.85 (d, 1H, J = 8.92, 6′H), 7.87 (d, 1H, J = 7.62, 8H), 7.60 (dd, 1H, J = 7.68, 7.51, 5H). ^{13}C NMR δ(ppm): 129.3 (C–3), 153 (C–2), 202.3 (C–4). EIMS (70 eV) m/z(%): 441 ($M^{+\bullet}$, 100), 443 ($M^{+\bullet}$ + 2, 100), 397 (16), 315 (95), 236 (40), 208 (47), 78 (62), 63 (71). Anal. Calcd. for $C_{15}H_8BrIOS$: C, 40.72; H, 1.80. Found: C, 40.40; H, 1.75.

4′-Fluoro-4-thioflavone (24): This substance was synthesized as dark brown crystals in 82% yield, m.p. 154-156°C.IR (ν cm^{-1}): 1173 (C=S), 1618 (C=C). ^{1}H NMR (500 MHz, DMSO) δ(ppm), J(Hz): 7.33 (s, 1H, 3H), 8.22 (d, 2H, J = 7.56, 2′H + 6′H), 8.31 (d, 2H, J = 7.67, 3′H + 5′H), 7.40-8.01 (m, A-ring H). ^{13}C NMR δ(ppm): 131.0 (C–3), 151.0 (C–20, 202.8 (C–4). EIMS (70 eV) m/z(%): 256 ($M^{+\bullet}$, 100), 212 (41), 194 (18), 123 (47), 119 (8), 104 (27), 76 (31). Anal. Calcd. for $C_{15}H_9FOS$: C, 66.05; H, 3.32. Found: C, 66.13; H, 3.25.

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References

1. T.A. Geissman, *The Chemistry of Flavonoid Compounds*, Pergamon Press, Oxford (1962).
2. J.B. Harborne, T.J. Mabry and J. Mabry, *The Flavonoids*, Chapman and Hall, London (1975).
3. J.B. Harborne, *The Flavonoids: Advances in Research Since 1980*, Chapman and Hall, London (1988).

4. B. Havsteen, *Biochem. Pharmacol.* **32**, 1141 (1983).
5. M. Gabor, *The Pharmacology of Benzopyran Derivatives and Related Compounds*, Akademiai Kiado, Budapest (1988).
6. I. Kraemer and W. Schunaek, *Arch. Pharm. (Weinheim Ger)* **319**, 1091 (1986).
7. B.K. Bhattacharya, H.H. Singh, L.D.S. Yadav and G. Hoornaert, *Acta Chim. Acad. Sci. Hung.* **110**, 133 (1982).
8. G.F. Meijs, E. Rizzardo, T.P.T. Le and Y. Chen, *Makromol. Chem.* **190**, 369 (1992).
9. W. Baker, J.B. Harborne and W.D. Ollis, *J. Chem. Soc.* 1294 (1952).
10. A. Schonberg, H. Kal Schmitt and H. Schulten, *Chem. Berg.* 66, 245 (1933).
11. I. Fancas, B. Costisella, M. Rakosi, H. Gross and R. Bognar, *Chem. Bar.* **102**, 1333 (1969).
12. R. Bognar, J. Baliant and M. Rakosi, *Liebigs Ann. Chem.* 1529 (1977).
13. F.M. Dean, J. Coodchild and A.W. Hill, *J. Chem. Soc. (C)* 2192 (1962).
14. W. Baker, G.G. Clarke and J.D. Harborne, *J. Chem. Soc.* 998 (1954).
15. Z. Witezak and M. Krolikowska, *Polish J. Chem.* **55**, 763 (1981).
16. M.T. Biggs, G.J.S. Puncan, C.W. Thornber and C.R. Cooper, *J. Chem. Research (M)* 2458 (1982).
17. A. Levai, *Heterocycl. Commum.* **5**, 5 (1999).
18. H.Z. Lecher, R.A. Greenwood, K.C. Whitehouse and T.H. Chao, *J. Am. Chem. Soc.* **78**, 5018 (1956).
19. B.S. Pedersen, S. Schibye, H.H. Nilsson and S.O. Lewesson, *Bull. Soc. Chem. Belges* **87**, 223 (1978).
20. J.W. Scheeren, P.H.J. Ooms and R.J.F. Nivard, *Synthesis* 149 (1973).
21. B. Dash, E.K. Dora and C.S. Panda, *Heterocycles* 19, 2093 (1982).
22. D.H.R. Barton, U.S. Patent, 4, 011, 36 (1977); *Chem. Abstr.* **87**, 53490n (1977).
23. T. Machiguchi, M. Hoshino and Y. Kitahara, *Jpn. Kokai Tokkoy Koho,* 77, 23, 066 (1977); *Chem. Abstr.* **82**, 102153r (1977).
24. *Mellor's Comphrehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. VIII, Supp. III, Longmans, London, p. 427 (1970).
25. E. Thilo and G. Ladwig, *Monatsber. Deutsch. Akad. Wiss. Berlin* 4, 720 (1962).
26. R.H. Peters, D.F. Crowe, M.A. Avery, W.K.M. Chong, M. Tanabe, *J. Med. Chem.* **32**, 1642 (1988).
27. J. Staunton, in: D.H.R. Barton and W.D. Ollis, *Comprehensive Organic Chemistry,* Vol. 4, Pergamon Press, London, p.659 (1979).
28. F.M. Dean, *Naturally Occurring Oxygen Ring Compounds,* Butterworths, London, p.251, 280 (1963).
29. H.S. Mahal and K. Venkataraman, *J. Chem. Soc.* 1767 (1934).
30. W. Baker, *J. Chem. Soc.* 1381 (1933).
31. W. Baker and J.B. Harborne, *J. Chem. Soc.* 1303 (1952).

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