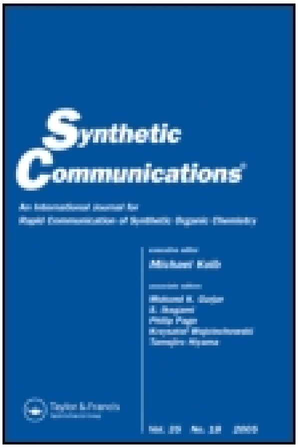

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Manganese(III) Acetate Mediated Oxidation of Flavanones: A Facile Synthesis of Flavones

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To cite this article: Om V. Singh , M. Muthukrishnan & Gopan Raj (2005) Manganese(III) Acetate Mediated Oxidation of Flavanones: A Facile Synthesis of Flavones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:20, 2723-2728

To link to this article: http://dx.doi.org/10.1080/00397910500214490

Synthetic Communications®, 35: 2723–2728, 2005
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ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500214490

Manganese(III) Acetate Mediated Oxidation of Flavanones: A Facile Synthesis of Flavones

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Abstract: Oxidation of flavanones (**1a**–**o**) with manganese(III) acetate by heating in acetic acid in presence of perchloric acid afforded exclusively flavones (**2a**–**o**) by dehydrogenation in almost quantitative yields.

Keywords: Manganese(III) acetate, flavanone, oxidation, flavone, dehydrogenation

Flavones are one of the important subgroups of flavonoids, which are widely distributed in nature from ferns to higher plants and also have diverse biological activities.[1] Over the years many synthetic methods have been developed for their synthesis and have been reviewed from time to time.[1] The most widely used approach for their synthesis is either oxidative cyclization of 2′-hydroxychalcones or nondegradative oxidation of flavanones. The oxidation of flavanones to flavones has been reported using different reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[2] DMSO/I_2,[3] selenium dioxide,[4] nickel peroxide,[5] disulfide,[6] thallium(III) salts,[7] and hypervalent iodine reagents.[8] The oxidation of flavanone with lead(IV) acetate[9] gave a mixture of 3-acetoxyflavanone, flavone, and isoflavone with former being the major product.

Received in the USA May 18, 2005

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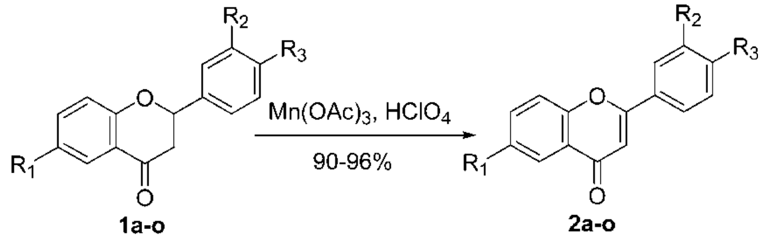
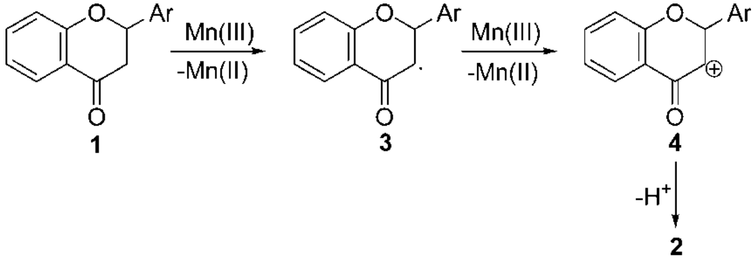
Mangnese(III) acetate (MTA), a one-electron oxidant, has been utilized for the synthesis of numerous natural products via oxidative radical cyclizations.[10] MTA generates α-oxo and α,α-dioxoalkyl radicals by regioselective oxidation of carbonyl compounds, which leads to different products by radical cyclization to other functional groups.[10b] The α-acylation of ketones and enolizable α,β-unsaturated ketones with MTA have also been reported.[10c,11] Furthermore, the oxidation of flavanone with MTA gave a mixture of 3,3-dichloroflavanone and 3-chloroflavone in the presence of potassium chloride as chloride source, with the former being the major product[12] and the later formed by dehydrohalogenation of the former. We have reported the oxidation of flavanones with thallium(III) acetate, which exclusively gave flavones[7a] and isoflavones[13] by the addition of perchloric acid to the reaction mixture. As the addition of perchloric acid has changed the course of this reaction, it was thought worthwhile to investigate the effect of perchloric acid for the oxidation of flavanones with MTA. We describe the results of our findings.

Treatment of flavanone (**1a**) with MTA in acetic acid at 100°C for 10 h afforded flavone (**2a**) in only 20% yield (based on ^{1}H NMR of the reaction mixture). After addition of perchloric acid to the reaction mixture, **1a** was completely converted to **2a** and no trace of **1a** could be detected by ^{1}H NMR (Scheme 1). Hence, the addition of perchloric acid to the reaction mixture increases the conversion (20% to 100%) and also decreases the reaction time (10 h to 1 h). The generality of this transformation was checked by treating different flavanones (**1b–o**) with MTA under similar reaction conditions. In all the cases flavones (**2b–o**) were obtained as the sole product. The identities of all flavones were established by ^{1}H NMR and IR spectral data by comparison with those reported in the literature.

The most plausible mechanism for this transformation is depicted in Scheme 2. The electophillic attack of MTA at the enol form of **1** afforded flavanone-Mn(III) adduct either by Mn(III)-O bond or Mn(III)-C_3 bond formation. The reductive elimination of Mn(II) from flavanone-Mn(III) adduct generated α-oxoradical **3**,[10c] which on further reaction with second molecule of MTA furnished carbocation **4**. The deprotonation of carbocation



Scheme 1.



Scheme 2.

4 under reaction conditions produced the respective flavone **2**. The formation of **3** through enol form **1** can be explained by the fact that the addition of perchloric acid to the reaction mixture enhanced the reaction rate several fold (≈50 times).

In summary an efficient method has been developed for the synthesis of flavones by oxidation of flavanones using manganese(III) acetate in presence of perchloric acid, which replaces the toxic reagents such as thallium(III), selenium dioxide, and nickel peroxide for this transformation. Furthermore, the method has been utilized for the synthesis of bioactive flavones such as 6-chloro-3′-nitroflavone (**2i**)[17] and 6-methyl-3′-nitroflavone (**2o**),[16] which have been demonstrated as potent ligands for the benzodiazepine binding site of $GABA_A$ receptor.

EXPERIMENTAL

General

Melting points were taken in open capillaries in a sulfuric acid bath and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on Perkin Elmer 283 IR spectrophotometer, ^1H NMR spectra were recorded on JEOL FX90Q (90 MHz) using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Manganese(III) acetate was purchased from Aldrich Chemical Co (USA). Substituted flavanones (**1 a–n**) were prepared by cyclization of respective 2′-hydroxychalcones using literature procedure.[18]

Oxidation of Flavanones with Manganese(III) Acetate in Presence of Perchloric Acid, General Procedure

Perchloric acid (70%, 0.1 mL) and flavanones (1 mmol) were added to a solution of manganese(III) acetate (0.563 g, 2.1 mmol) in acetic acid (5 mL). The resultant mixture was heated at 100°C for 1 h, then cooled to room

Table 1. Oxidation of flavanones (**1a–n**) with manganese(III) acetate

Entry	Products	Yields[a] (%)	Mp (lit. mp) (°C)
1	**2a**, $R_1 = R_2 = R_3 = H$	92	97–98 (98)[14]
2	**2b**, $R_1 = R_2 = H$, $R_3 = Cl$	95	188–189 (188)[14]
3	**2c**, $R_1 = R_2 = H$, $R_3 = CH_3$	90	110 (110)[14]
4	**2d**, $R_1 = R_2 = H$, $R_3 = NO_2$	96	245–246 (246)[14]
5	**2e**, $R_1 = R_3 = H$, $R_2 = NO_2$	95	199–200 (194–195)[14]
6	**2f**, $R_1 = Cl$, $R_2 = R_3 = H$	95	182–183 (182)[14]
7	**2g**, $R_1 = R_3 = Cl$, $R_2 = H$	96	226–227 (226–227)[14]
8	**2h**, $R_1 = Cl$, $R_3 = CH_3$, $R_2 = H$	92	183–184 (183–184)[14]
9	**2i**, $R_1 = Cl$, $R_2 = NO_2$, $R_3 = H$	94	235–236 (235–236)[14]
10	**2j**, $R_1 = Cl$, $R_2 = H$, $R_3 = NO_2$,	96	>285 (>285)[14]
11	**2k**, $R_1 = CH_3$, $R_2 = R_3 = H$	90	122 (121–122)[14]
12	**2l**, $R_1 = CH_3$, $R_2 = H$, $R_3 = Cl$	92	198–199 (198–199)[14]
13	**2m**, $R_1 = R_3 = CH_3$, $R_2 = H$	92	150–151 (151)[15]
14	**2n**, $R_1 = CH_3$, $R_2 = NO_2$, $R_3 = H$	94	222–223 (221–223)[16]
15	**2o**, $R_1 = CH_3$, $R_2 = H$, $R_3 = NO_2$	92	275–277 (276–278)[16]

[a] Yield are based on isolated products.

temperature, and added slowly to ice cold water with constant stirring. The obtained solid was filtered, washed with water, dried, and recrystallized from ethanol to afford the respective flavones (**2a–o**). The characterization data of flavones (**2a–o**) are given in Table 1.

ACKNOWLEDGMENTS

Authors are grateful to the International Foundation of Science, Sweden, and State Committee on Science, Technology and Environment, Thiruvananthapuram, Government of Kerala, India, for financial support.

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