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A Novel Oxidative Cyclization of 2'-Hydroxychalcones to 4-Methoxyaurones by Thallium (III) Nitrate

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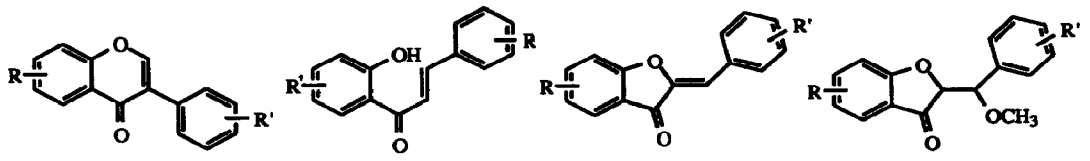
Abstract: *An unusual oxidative cyclization of chalcones by thallium (III) trinitrate (TTN) to 4-methoxyaurones has been studied. A key feature of this reaction is the introduction of a methoxyl group into the aurone skeleton. Several reactions have been performed to understand the mechanism and regiochemistry of cyclization.*

The use of thallium (III) reagents has recently evolved as a new and exceptionally versatile methodology in organic synthesis.[1] Due to our current interest in the synthesis of isoflavones **1** as potential protein-tyrosine kinase inhibitors, the conversion of 2'-hydroxychalcones **2** to the corresponding isoflavones **1**[1] was investigated. Certain 2'-hydroxychalcones **2** are also known to react with TTN in an alternative mode to give aurones **3** through the corresponding α-methoxybenzylcoumaranones **4**.[2] This has provided important insights into the behaviour of thallium (III) trinitrate (TTN) in the oxidative cyclization of 2'-hydroxychalcones as well in the oxidative rearrangement of chalcones without hydroxyl groups.[3]



1 **2** **3** **4**

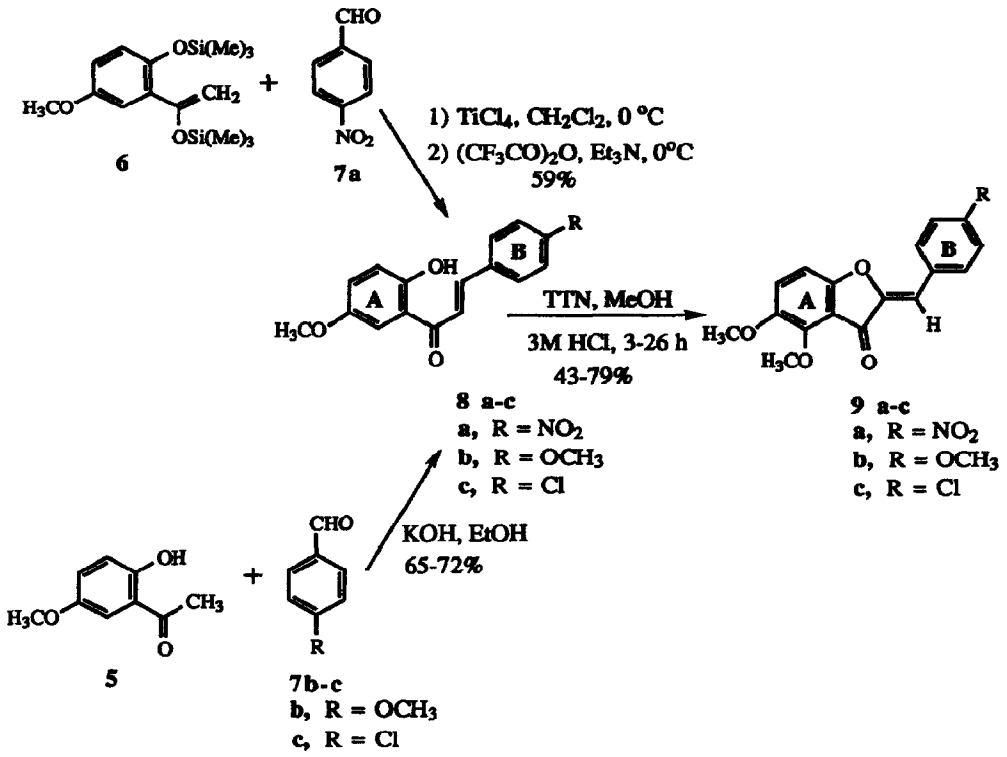
Two methods were used to prepare various chalcones **2** for attempted conversion to isoflavones **1**. In the first method, 2'-hydroxy-5'-methoxy-4-nitrochalcone (**8a**) was synthesized by an efficient modified Mukaiyama crossed aldol condensation route.[4-6] In this method, 2-hydroxy-5-methoxyacetophenone (**5**) was converted to the corresponding silyl enol ether **6**,[4] which under the modified Mukaiyama aldol condensation with *p*-nitrobenzaldehyde **7a** gave the corresponding chalcone **8a** in good yield (Scheme 1).[5,6] In the second method, the classical aldol condensation was utilized more effectively for the synthesis of chalcones **8b-c**.

In the present attempt to synthesize isoflavones **1** by oxidative rearrangement of 2'-hydroxychalcones **2**, a novel and unusual oxidative cyclization to 4-methoxyaurones **9a-c** was observed instead (Scheme 1). The key features of this reaction are: 1) the incorporation of a methoxyl group at the 4 position of the aurone

skeleton, 2) the exclusive formation of the Z-configuration of the olefinic double bond of the aurones **9a-c**, and 3) the tolerance of the reaction for electron donating groups as well as electron withdrawing groups in the para position of the B ring of the chalcones.

The typical experimental conditions are as follows. The oxidation of chalcones **8a-c** was carried out with 3 equivalents of TTN in methanol. After 20 min, HCl was added at room temperature and the reaction mixture was allowed to stir for 2 h. This was followed by heating the reaction mixture at reflux in methanol for 3-26 h or until all the thallium (I) nitrate had precipitated. Filtration of the reaction mixture and evaporation of the filtrate, followed by column chromatography, gave the novel 4-methoxyaurones **9a-c**. The structures of the 4-methoxyaurones **9a-c** have been determined by X-ray crystallography, elemental analysis, mass spectrometry, and ^{1}H NMR as well as ^{13}C NMR analysis.

Scheme 1

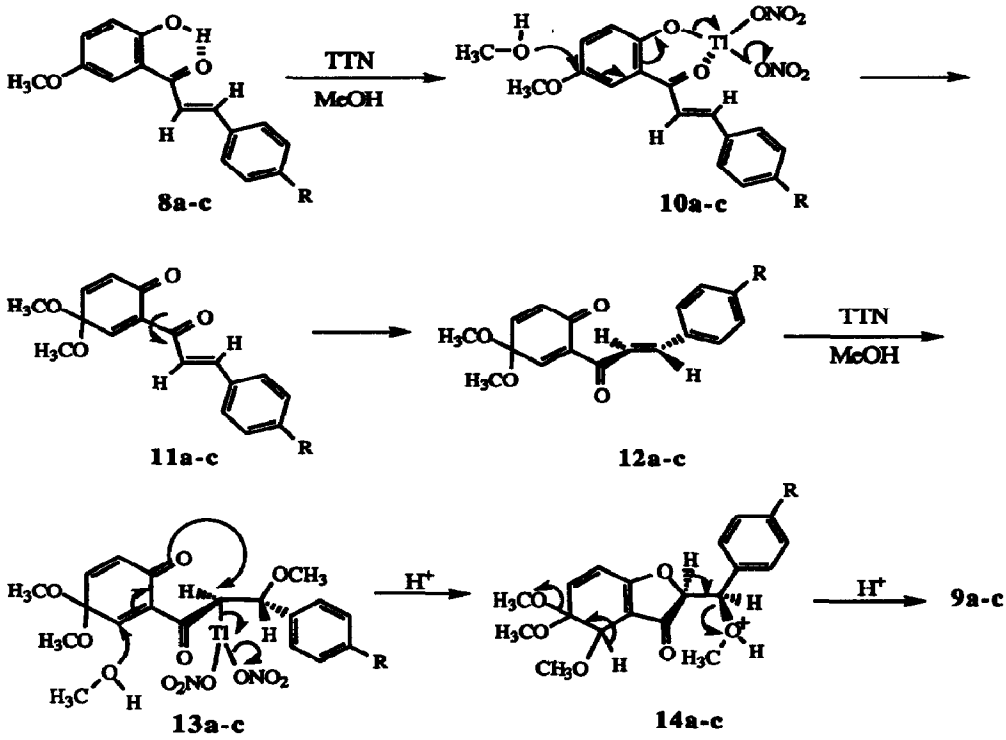


Chalcones **8a-c** were selected for synthesis in order to examine the electronic effects of substituents in the para position of ring B on 4-methoxyaurone formation. The presence of electron donating vs. electron attracting groups in the para position of the B ring of the chalcones **8a-c** had little effect on formation of 4-

methoxyaurones **9a-c**. Additional experiments involving different substitution patterns of the B ring of the chalcone are currently being investigated.

To investigate the possible effects of ring A substituents on cyclization to aurones, 4-chloro-2'-hydroxy-4'-methoxychalcone and 4-chloro-2'-hydroxy-3'-methoxychalcone were synthesized. Under identical reaction conditions used for formation of **9c**, intractable reaction mixtures were obtained and no aurone formation was detected. This unique formation of aurones seems only to occur from chalcones having a similar substitution pattern as **8a-c**, in which the methoxyl group is para to the phenolic hydroxyl group in ring A.

Scheme 2



A plausible mechanism for explaining the geometry of the aurone olefinic double bond as well as addition of a 4-methoxy group in the aurone skeleton is shown in Scheme 2. Initially, TTN in methanol reacts with the chalcones **8a-c** to give the corresponding *O*-thallated complex **10a-c**. This is based on the studies of the oxidation of 2-hydroxyacetophenones conducted by Horie *et al.*[7] The nucleophilic attack of methanol leading to elimination of the thallium moiety in **10a-c** would afford the corresponding quinone monoacetals

11a-c. Alternatively, **11a-c** might arise by ipso thallation of **8a-c** followed by methanolysis of the C-Tl bond.[8] Conformers **12a-c** can then form from **11a-c** by rotation of the bond between the quinone monoacetal ring and the ketone. The methoxythallation of the olefinic double bond of quinone monoacetal **12a-c** by TTN would give the quinone monoacetal thallium adducts **13a-c** by antarafacial methoxythallation of the trans double bond.[9] Michael addition of methanol to **13a-c**, followed by cyclization, would yield the desired dethallated α-methoxycoumaranones **14a-c**. The observed regiochemistry of Michael addition of methanol is facilitated by two carbonyl groups in conjugation with the reactive double bond as opposed to one carbonyl group in the alternative mode. Under the acidic conditions, the α-methoxycoumaranones **14a-c** could eliminate two equivalents of methanol to re-aromatize to give the corresponding 4-methoxyaurones **9a-c** with the olefinic double bond in the Z-configuration only, resulting from anti periplanar elimination of methanol. Although the proposed mechanism is logical and would account for the observed Z-alkene stereochemistry of the product, the structure of the product is not conclusive with regard to the stereochemistry of the methoxythallation of **12a-c** and subsequent elimination since the Z-alkene is the thermodynamically more stable isomer and could therefore result from equilibration of the E-isomer under the acidic conditions of the reaction.[10]

In order to investigate the scope of this reaction, 4-chloro-2'-hydroxy-5'-methoxychalcone (**8c**) was reacted with TTN in ethanol. 4'-Chloro-3,4-diethoxyaurone and 4'-chloro-4-ethoxy-3-methoxyaurone were isolated. This result is consistent with the proposed mechanism (Scheme 2). Additional experiments involving different solvents are currently being conducted.

The nucleophilic introduction of a methoxyl group in ring A of chalcones followed by cyclization to give the corresponding aurones is unique and to our knowledge has never been reported before.

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