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ONE-STEP CONVERSION OF FLAVANONES INTO ISOFLAVONES: A NEW FACILE BIOMIMETIC SYNTHESIS OF ISOFLAVONES

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Summary: One-step chemical conversion of flavanones into isoflavones by use of thallium trinitrate (TTN) is reported, and the mechanism of a 2,3-aryl migration in this reaction is discussed in relation to *in vivo* rearrangement process of flavanone precursors in the isoflavone biosynthesis.

The isoflavonoids are a subgroup of the flavonoids mainly occurring in species of the Leguminosae family. One of the characteristic features of the flavonoids in nature is that many isoflavonoids act as phytoalexins which play a key role in defense against fungal infection.[1] According to recent detailed enzymological studies, the isoflavonoids share a common biosynthetic pathway with the flavonoids as far as flavanone intermediates, but then a 2,3-aryl migration occurs to give the rearranged skeleton.[2,3] However, details of this rearrangement still remain unknown. In this paper we describe the one-step chemical conversion of flavanones into isoflavones, a laboratory analogy for *in vivo* rearrangement process to give the characteristic skeleton of the isoflavonoid phytoalexins.

Flavanones with various substituents in both aromatic rings were prepared by the acid-catalized cyclization of corresponding chalcones in 60% to 80% yields. The chemical conversion of flavanones into isoflavones was accomplished as follows: a flavanone was added to a solution of thallium trinitrate (TTN) in methanol-$CHCl_3$ containing 70% perchloric acid,[4] and the reaction mixture was stirred at 25°C for 5 -12 hr. Experimental data for representative conversions are summarized in Table I. Of interest to note is that in all cases flavones were

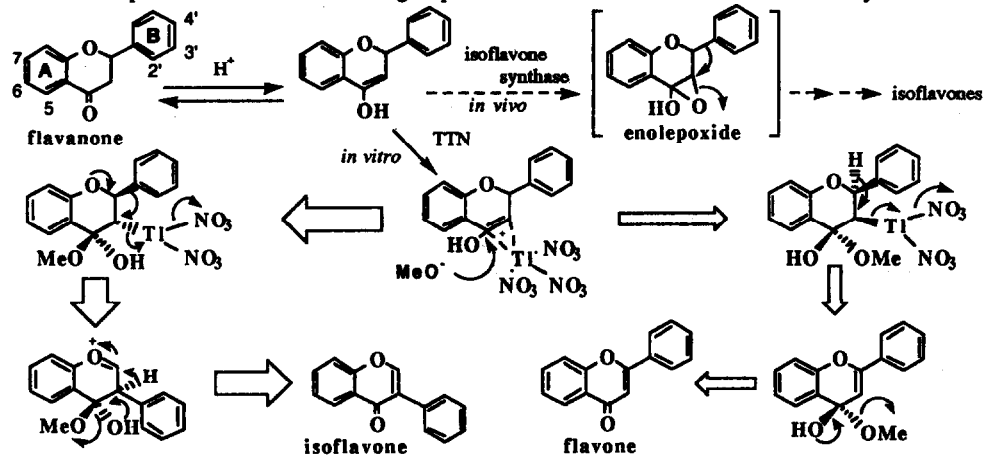
Table I. Conversion of Substituted Flavanones into Corresponding Isoflavones and Flavones

Substitution[a]						Yields (%)[b]	
5	6	7	2'	3'	4'	isoflavone	flavone
H	H	H	H	H	H	65	13
H	H	H	H	H	CH_3	63	15
H	H	H	H	H	OMe	59	9
H	H	H	H	H	F	75	10
H	H	H	H	H	Cl	65	7
H	H	H	H	H	Br	73	8
H	H	OMe	H	H	OMe	28	6
H	H	OMe	H	H	H	48	10
H	H	OMe	H	H	F	57	14
H	H	OMe	OMe	H	OMe	34[c]	5
OMe	H	OMe	H	H	OMe	28	6
H	H	OBz	H	H	OMe	29	7
H	OMe	OMe	H	OMe	OMe	25	6

[a] see scheme 1 for the numbering of flavanone rings; [b] calculated on pure recrystallized materials; [c] yield of 5'-nitro-2', 4', 7-trimethoxyisoflavone. 5'-Nitro group is derived from nitric acid released from TTN.

obtained as byproducts in much reduced yields as compared to those of isoflavones. The possibility that the reaction proceeds *via* chalcones is ruled out by the following evidences: when a chalcone was treated with TTN under identical condition the corresponding isoflavone was obtained only in much poorer yield, and the formation of a flavone was not observed. The mechanism of this conversion may be depicted as shown in scheme 1. In the first step, acid-catalized enolization of flavanone followed by alkoxythallation leads to two unstable intermidiate thallium adducts (*syn* and *anti* to the aryl group, respectively). On stereochemical grounds the *anti* adducts are

predominant, and dethalliation proceeds *via* migration of the aryl group, resulting in formation of corresponding isoflavones. In the minor intermediate *syn* adducts dethalliation occurs only to give flavones accompanying elimination of a proton *anti* to the thallate group. It is of interest to note that the alkoxythallate adduct is



Scheme 1. Plausible Mechanism of Chemical Conversion of Flavanone by TTN

chemically equivalent to the enolepoxide postulated as an intermediate in the hypothetical rearrangement sequence of flavanones by isoflavone synthase.[2] Since both the acid-mediated opening of the enolepoxide and heterolysis of the alkoxythallate adduct can develop similar carbonium cation adjacent to the ketal or hemiketal group, the development of this cation can be postulated as the driving force for 2,3-aryl migration. However, it appears that heterolysis of the carbon-thallium bond occurs simultaneously with aryl migration because an isoflavone will be produced from a *syn* adduct as well as an *anti* adduct if carbon-thallium heterolysis is complete before aryl migration. As long as it is assumed that the rearrangement proceeds through the ionic mechanism, the thallium-promoted conversion of flavanones into isoflavones can be looked upon as a mimic of *in vivo* rearrangement process catalyzed by isoflavone synthase. As for the effect of the substitution on the aromatic ring, 4'-haloflavanones underwent 2,3-aryl migration smoothly to give rise to corresponding isoflavones in slightly better yields than other analogs, which is contrary to expectations that the presence of electron-withdrawing substituents at the *para* position may inhibit the migratory aptitude of the aryl group. Indirect rearrangement process *via* the spirodienone intermediate was postulated for *in vivo* rearrangement,[2] but this finding indicates that *in vivo* 2,3-aryl migration could also occur by concerted mechanism as seen in the above reaction.

The yield of isoflavone synthesis by the above method is comparable to the one reported by Farkas *et al* [5] which involves initial alkoxythallation of the olefinic double bond of chalcones for the skeletal conversion and requires two further steps. This method may find practical value in the synthesis of isoflavones since the procedure is far more facile than the previous methods.[1b]

References and note

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4. The reaction did not proceed without $HClO_4$ in the reaction medium. The addition of such strong acid is presumed to be indispensable to induce the enol form of flavanone as described later.
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