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SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS.
XV. ISOMERIZATION OF 2′-HYDROXYCHALCONES INTO FLAVANONES USING TRIETHYLAMINE

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A simple and effective method for preparing synthetic analogs of natural flavanones via isomerization of 2′-hydroxychalcones with triethylamine was proposed.

Key words: flavanone, method, triethylamine, isomerization.

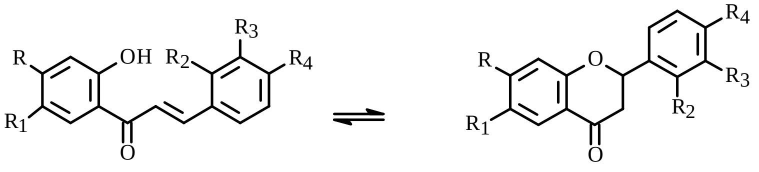
Flavanones are a large group of flavonoids, the structures of which are based on the unstable dihydro-γ-pyrone ring. They convert to the corresponding chalcones in the presence of base.

Flavanones contain one assymetric C atom (C-2). They are usually found in plants as the levorotary isomers. Flavanones are known to possess hepato-protective, anti-edemic, anti-inflammatory, estrogenic, and other types of activity [1-3].

Flavanones are prepared via isomerization of chalcones in acidic or alkaline medium. The conditions that shift the equilibrium toward flavanone formation cannot be predicted.

Known methods for isomerizing 2′-hydroxychalcones into the corresponding flavanones utilize dilute alkali or hot ethanolic solution of sulphuric or phosphoric acid. Methanolic HCl, sodium acetate, and amberlyst ion-exchange resin [4, 5] are also often used for these conversions. Sometimes, pyridine and glacial acetic acid are used [6].

Boiling 2-hydroxy-3′-iodo-4,4′,6′-trimethoxychalcone in the presence of nickel chloride, zinc powder, and KI produces the flavone and traces of 5-hydroxy-7,4′-dimethoxyflavanone [7].



1a - y

2a - y

a: $R = R_1 = R_2 = R_3 = R_4 = H$
b: $R_1 = CH_3$, $R = R_2 = R_3 = R_4 = H$
c: $R_1 = OCH_3$, $R = R_2 = R_3 = R_4 = H$
d: $R_1 = Cl$, $R = R_2 = R_3 = R_4 = H$
e: $R_1 = F$, $R = R_2 = R_3 = R_4 = H$
f: $R = R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$
g: $R_1 = CH_3$, $R_4 = OCH_3$, $R = R_2 = R_3 = H$
h: $R_1 = OCH_3$, $R_4 = OCH_3$, $R = R_2 = R_3 = H$
i: $R = R_1 = R_2 = H$, $R_3 - R_4 = -OCH_2O-$
j: $R = R_1 = R_2 = H$, $R_3 - R_4 = -OCH_2CH_2O-$
k: $R = R_1 = R_2 = H$, $R_3 - R_4 = -O(CH_2)_5O-$
l: $R_1 = CH_3$, $R = R_2 = H$, $R_3 - R_4 = -OCH_2CH_2O-$
m: $R_1 = OCH_3$, $R = R_2 = H$, $R_3 - R_4 = -O(CH_2)_3O-$
n: $R = CH_3$, $R_1 = R_2 = H$, $R_3 = R_4 = OCH_2O$, X = Cl
o: $R = CH_3$, $R_1 = R_2 = H$, $R_3 = R_4 = OCH_2$, X = Br
p: $R = OCH_3$, $R_1 = R_2 = H$, $R_3 = R_4 = OCH_2O$, X = COOH
q: $R = R_2 = CH_3$, $R_1 = H$, $R_3 = R_4 = OCH_2O$, X = COOH
r: $R = CH_3$, $R_1 = R_2 = H$, $R_3 = R_4 = OCH_2CH_2O$
s: $R = OCH_3$, $R_1 = R_2 = H$, $R_3 = R_4 = OCH_2CH_2O$
t: $R = R_2 = CH_3$, $R_1 = H$, $R_3 = R_4 = OCH_2CH_2O$
u: $R = Cl$, $R_1 = R_2 = H$, $R_3 = R_4 = OCH_2CH_2O$
v: $R = CH_3$, $R_1 = R_2 = H$, $R_3 = R_4 = O(CH_2)_3O$
w: $R = OCH_3$, $R_1 = R_2$, $R_3 = R_4 = O(CH_2)_3O$
x: $R = R_2 = CH_3$, $R_1 = H$, $R_3 = R_4 = O(CH_2)_3O$
y: $R = Cl$, $R_1 = R_2 = H$, $R_3 = R_4 = O(CH_2)_3O$

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TABLE 1. Properties of **2a-y**

Compound	Yield, %	mp, °C	Empirical formula	Solvent for crystallization
2a	47.6	76-78	$C_{15}H_{12}O_2$	EtOH
2b	48.2	104-105	$C_{16}H_{14}O_2$	EtOH
2c	75.2	97-98	$C_{16}H_{14}O_3$	EtOH
2d	78.5	96-97	$C_{15}H_{11}ClO_2$	EtOH
2e	72.1	76-77	$C_{15}H_{11}FO_2$	EtOH
2f	58.8	94-95	$C_{16}H_{14}O_3$	EtOH
2g	69.4	109-110	$C_{17}H_{16}O_3$	EtOH
2h	80.2	158-159	$C_{17}H_{16}O_4$	MeOH
2i	85.2	127-128	$C_{16}H_{12}O_4$	MeOH
2j	73.3	108-109	$C_{17}H_{14}O_4$	EtOH
2k	60.5	94-96	$C_{18}H_{16}O_4$	MeOH
2l	62.3	76-78	$C_{18}H_{16}O_4$	EtOH
2m	84.9	87-89	$C_{19}H_{18}O_5$	EtOH
2n	38.0	180-181	$C_{18}H_{15}O_4$	MeOH
2o	46.9	149-151	$C_8H_{15}O_4$	EtOH
2p	41.5	226-227	$C_{19}H_{16}O_7$	iso-PrOH
2q	36.4	226-227	$C_{20}H_{18}O_6$	iso-PrOH/$(CH_3)_2CO$
2r	31.2	76-78	$C_{18}H_{16}O_4$	EtOH
2s	40.0	116-117	$C_{18}H_{16}O_5$	EtOH
2t	28.9	113-115	$C_{19}H_{18}O_4$	MeOH
2u	36.5	116-118	$C_{17}H_{14}O_4$	MeOH
2v	31.8	92-94	$C_{19}H_{18}O_4$	EtOAc/C_7H_{14}
2w	42.1	87-89	$C_{19}H_{18}O_5$	EtOH
2x	37.8	142-144	$C_{20}H_{20}O_4$	MeOH
2y	45.4	83-85	$C_{18}H_{16}ClO_4$	EtOH

A simple method for isomerizing 2′-hydroxychalcones that uses silica gel in the presence of conc. H_2SO_4, ethylenediamine, and hydroxylamine hydrochloride has been described [8].

Condensation of 2-hydroxyacetophenones with certain aromatic or heteroaldehydes forms the target chalcones and sometimes flavanones [9-14].

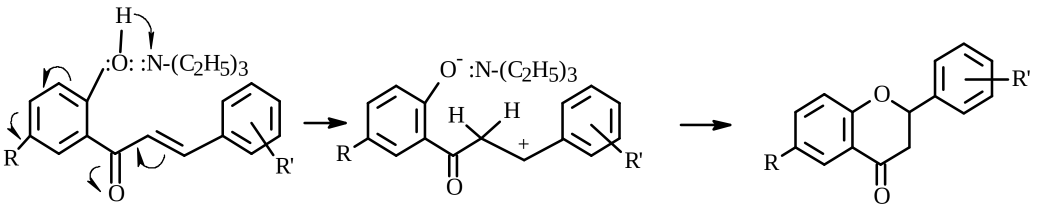
We proposed an effective method for isomerizing 2′-hydroxychalcones into the corresponding flavanones by boiling with triethylamine.

The ease of isomerizing chalcones into flavanones as a function of the position and nature of the substituents on the A and B rings has been noted (Table 1).

We now present the proposed mechanism for cyclization of chalcones into flavanones in alcohol in the presence of triethylamine.

Apparently release of a proton from the 2′-hydroxyl, which is accelerated by substituents in the 5′-position of the chalcone and the presence of a catalyst, and its subsequent attack on the chalcone α-C atom occur simultaneously. Further attack of the phenoxide oxygen on the positively charged β-C atom of the chalcone results in flavanone formation. The course of the reaction is monitored using TLC.

Isomerization of chalcones using triethylamine showed that mainly flavanones are formed. However, we were unable to prove this in some instances owing to the difficulty of separating the chalcone—flavanone mixtures, which are isolated as oils. In such instances, column chromatography over silica gel (benzene eluent) was effective for separating the mixtures. We were able to isolate some flavanones (*2c*, *-d*, *-e*, and *-g-m*) in high yields by fractional crystallization from the appropriate solvents.



The structures of the synthesized flavanones were confirmed by elemental analyses, TLC, and melting points of mixtures. The properties of the synthesized flavanones are listed in Table 1.

EXPERIMENTAL

The purity of the synthesized compounds was monitored by TLC on Silufol UV-254 plates using benzene—ethanol (9:1). Analyses of all compounds corresponded to those calculated.

Synthesis of Flavanones 2a-y. A solution of the appropriate 2′-hydroxychalcone (2 mmole) and triethylamine (0.28 mL, 2 mmole) in alcohol (25 mL) was boiled for 2-3 h. The reaction mixture was poured into cold water containing HCl (1 mL, 10%). The resulting precipitate was filtered off, washed with water, and crystallized from a suitable solvent. If TLC indicated the presence of chalcone and flavanone in the reaction products, the mixture was separated using fractional crystallization or column chromatography over silica gel with benzene eluent.

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