SYNTHESIS OF TRANS ELECTRON-RICH SUBSTITUTED ISOFLAVANS FROM ISOFLAVANOL

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ABSTRACT

Synthesis of **trans-isoflavans** from **isoflavanol**, 4-(7-acetoxy-4-hydroxy chroman-3-yl)phenyl acetate, and its hydrolysis had been carried out. Then, a stereoselective conversion of the **trans-isoflavan** into **cis-isoflavan** had been attempted. However, this was proven to be unsuccessful.

The synthesis of **trans-isoflavans** was done by mixing **isoflavanol** with the electron-rich substituent, i.e. 3,4,5-trimethoxyphenol, 1,3-dimethoxybenzene or anisole with the presence of $BF_3.OEt_2$ in anhydrous dichloromethane (DCM) at room temperature and inert atmosphere of argon for 3 h, to produce 4-((3*S*,4*S*)-7-acetoxy-4-(6-hydroxy-2,3,4-trimethoxyphenyl)chroman-3-yl)phenyl acetate (**trans-isoflavan 1**), 4-((3*S*,4*R*)-7-acetoxy-4-(2,4-dimethoxyphenyl)chroman-3-yl) phenyl acetate (**trans-isoflavan 2),** and 4-((3*S*,4*R*)-7-acetoxy-4-(4-methoxy phenyl)chroman-3-yl)phenyl acetate (**trans-isoflavan 3**), respectively. The hydrolysis of the acetyl ends of the **trans-isoflavans** into hydroxyl ends was done by mixing each of the synthesised **trans-isoflavans** with potassium hydroxide in methanol, followed by quenching it in acetic acid, to give out (3*S*,4*S*)-4-(6-hydroxy-2,3,4-trimethoxyphenyl)-3-(4-hydroxyphenyl)chroman-7-ol (**hydroxylated trans-isoflavan 1**), (3*S*,4*R*)-4-(2,4-dimethoxyphenyl)-3-(4-hydroxyphenyl)chroman-7-ol (**hydroxylated trans-isoflavan 2**), and (3*S*,4*R*)-3-(4-hydroxyphenyl)-4-(4-methoxyphenyl)chroman-7-ol (**hydroxylated trans-isoflavan 3**). While the attempt to convert **trans-isoflavans** into their **cis-isoflavans** counterparts was done by trying to oxidise the **trans-isoflavans** into **isoflavenes** and followed by its reduction by using H_2(g) in the presence of Pd/C catalyst to obtain the **cis-isoflavans**. All the synthesised products were characterised by using ^{1}H- and ^{13}C-NMR, IT-ESI or FT-NSI MS, and FTIR.

From the synthesis of **trans-isoflavan**, it was found that **trans-isoflavan 1**, **trans-isoflavan 2** and **trans-isoflavan 3** had been successfully synthesised with the yield of 64.8%, 43.3% and 41.6%, respectively from 500 mg **isoflavanol** starting material. While its hydrolysis had successfully produced **hydroxylated trans-isoflavan 1**, **hydroxylated trans-isoflavan 2** and **hydroxylated trans-isoflavan 3** with the yield of 85 mg (97.0%), 58 mg (94.5%) and 49 mg (86.9%), respectively. The attempt of converting **trans-isoflavans** into **cis-isoflavans** had failed in the oxidation to produce **isoflavenes**. Thus, its reduction was not carried out.

Keywords: synthesis, isoflavan, electron-rich, stereochemistry.

SINTESIS TRANS ISOFLAVAN TERSUBSTITUSI GUGUS KAYA-ELEKTRON DARI ISOFLAVANOL

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INTISARI

Sintesis **trans-isoflavan** dari **isoflavanol**, 4-(7-asetoksi-4-hidroksikroman-3-il)fenil asetat dan hidrolisisnya telah dilakukan. Konversi stereoselektif dari **trans-isoflavan** menjadi **cis-isoflavan** telah dicoba. Namun, percobaan ini telah terbukti tidak berhasil.

Sintesis **trans-isoflavan** dimulai dengan mereaksikan **isoflavanol** dengan substituen kaya-elektron, yaitu 3,4,5-trimetoksifenol, 1,3-dimetoksibenzena, atau *anisole* dengan adanya katalis BF3.OEt2 di dalam diklorometan *anhydrous* pada suhu ruangan dan atmosfir argon *inert* selama 3 jam untuk menghasilkan 4-((3*S*,4*S*)-7-asetoksi-4-(6-hidroksi-2,3,4-trimetoksifenil)kroman-3-il)fenil asetat (**trans-isoflavan 1**), 4-((3*S*,4*R*)-7-asetoksi-4-(2,4-dimetoksifenil)kroman-3-il) fenil asetat (**trans-isoflavan 2),** dan 4-((3*S*,4*R*)-7-asetoksi-4-(4-metoksifenil)kroman-3-il)fenil asetat (**trans-isoflavan 3**), secara berurutan. Hidrolisis gugus asetil pada **trans-isoflavan** menjadi gugus hidroksil dilakukan dengan mereaksikan **trans-isoflavan** yang telah disintesis dengan kalium hidroksida di dalam metanol, dan kemudian ditambahkan asam asetat untuk menghentikan reaksinya, yang menghasilkan (3*S*,4*S*)-4-(6-hidroksi-2,3,4-trimetoksifenil)-3-(4-hidroksifenil)kroman-7-ol (***hydroxylated*** **trans-isoflavan 1**), (3*S*,4*R*)-4-(2,4-dimetoksifenil)-3-(4-hidroksifenil)kroman-7-ol (***hydroxylated*** **trans-isoflavan 2**), and (3*S*,4*R*)-3-(4-hidroksifenil)-4-(4-metoksifenil)kroman-7-ol (***hydroxylated*** **trans-isoflavan 3**).

Dari sintesis **trans-isoflavan** ditemukan bahwa **trans-isoflavan 1**, **trans-isoflavan 2**, dan **trans-isoflavan 3** telah berhasil disintesis dengan rendemen sebesar 64,8%, 43,3%, dan 41,6% dari 500 mg bahan dasar **isoflavanol**. Sedangkan, proses hidrolisisnya telah berhasil menghasilkan ***hydroxylated*** **trans-isoflavan 1**, ***hydroxylated*** **trans-isoflavan 2**, dan ***hydroxylated*** **trans-isoflavan 3** dengan rendemen sebesar 85 mg (97,0%), 58 mg (94,5%), dan 49 mg (86,9%). Usaha untuk mengubah **trans-isoflavan** menjadi **cis-isoflavan** telah gagal dalam tahap oksidasi untuk menghasilkan **isoflaven**. Maka, reduksi darinya tidak dilakukan.

Kata kunci: sintesis, isoflavan, kaya-elektron, stereokimia.