SYNTHESIS OF BIOACTIVE CYCLOHEXENYL CHALCONES AND FLAVONOID DERIVATIVES

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Abstract

Flavonoids are a class of natural products that are well known to possess a wide range of pharmacological properties. Due to their recent discovery in modulating muscarinic receptor activity and its inhibitory effect against dengue-2 virus NS3 protease, flavonoids are idea candidates for drug development. This dissertation describes the syntheses of several flavones and some Diels-Alder adducts derived from chalcones.

A modified Baker-Venkataraman method has been developed where flavones were prepared in a one-pot procedure from the corresponding 2′-hydroxyacetophenones and acyl chlorides under different conditions. When 2′-hydroxyacetophenone is heated with a stoichiometric amount of acyl chloride, either in a DBU/pyridine system or in an open K_2CO_3/acetone system, only the flavone is obtained, albeit in modest yield. However, when it is heated with an excess of acyl chloride in a DBU/pyridine system, the 3-acylflavone is the only product, while treatment in an open K_2CO_3/acetone system afforded the flavone as the major product and a smaller amount of 3-aroylflavone.

Panduratin A and its regioisomer isopanduratin A have been synthesized in four steps from (*E*)-ocimene, [(*E*)-3,7-dimethyl-1,3,6-octatriene] via a Diels–Alder cycloaddition reaction. An overall yield of 75% was achieved from 2′,6′-dihydroxy,4′-methoxyacetophenone.

The mulberry Diels-Alder adducts pentamethyl ethers of the kuwanon V and dorsterone have been synthesised via a biomimetic intermolecular [4+2] cycloaddition reaction between a highly electron-rich dienophile and a Lewis acid sensitive diene derived from chalcone. Cycloaddition reaction under thermal condition afforded the

kuwanon V and dorsterone in a 3:2 ratio. Cycloaddition catalysed by AgOTf/Bu_4NBH_4 gave higher yield of adducts.

Abstrak

Flavonoid merupakan satu kelas sebatian semulajadi yang dikenalpasti dengan pelbagai sifat farmakologinya. Penemuan terbaru flavonoid dalam penyelarasan aktiviti reseptor muscarinik dan kesan penghambatannya terhadap protease denggi-2 virus NS3 menjadikan flavonoid sebagai suatu idea untuk menghasilkan ubat yang sesuai. Disertasi ini menggambarkan sintesis beberapa flavonoid dan produk Diels-Alder yang berasal dari chalcon.

Satu kaedah Baker-Venkataraman telah diubahsuai di mana sintesis flavon dilakukan dalam prosedur satu-bakul (one-pot) dari 2′-hidroksiasetofenon dan asid klorida di bawah keadaan-keadaan yang berbeza. Semasa 2′-hidroksiasetofenon dipanaskan dengan stoikiometri kuantiti asid klorida, baik dalam sistem DBU/piridin atau dalam sistem K_2CO_3/aseton terbuka, hanya flavon dihasilkan, walaupun dalam kuantiti yang sederhana. Namun demikian, apabila 2′-hidroksiasetofenon dipanaskan dengan asid klorida yang berlebihan dalam sistem DBU/piridin, hanya 3-asilflavon dihasilkan. Sebaliknya tindak balas yang sama dalam sistem K_2CO_3/aseton terbuka menghasilkan flavon sebagai produk utama dan 3-asilflavon sebagai hasil sampingan.

Panduratin A dan regioisomernya isopanduratin A telah disediakan dalam empat langkah dari (*E*)-ocimene, [(*E*)-3,7-dimetil-1,3,6-octatriene] melalui tindak balas Diels-Alder. Hasil keseluruhannya adalah 75% dari 2′,6′-dihidroksi,4′-metoksiasetofenone.

Produk Diels-Alder kuwanon V dan dorsterone pentametil eter telah disediakan melalui biomimitik tindak balas Diels-Alder antara kedua-dua dienophile dan diene yang berasal dari chalcon dimana dienophile itu kaya dengan electron dan diene itu sensitif terhadap acid Lewis. Tindak balas Diels-Alder yang dilakukan di bawah keadaan termal menghasilkan kuwanon V dan dorsterone dalam nisbah 3:2. Tindak balas Diels-Alder yang dilakukan di bawah pemangkin AgOTf/Bu_4NBH_4 memberi hasil yang lebih tinggi.

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List of Abbreviations

Ac	Acetyl
BDNF	Brain-Derived Neurotrophic Factor
cAMP	Cyclic Adenosine MonoPhosphate
CO	Carbon monoxide
COX	Cyclo-oxygenase
CREB	cAMP Response-Element Binding protein
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
EI	Electron Ionisation
ESI	ElectroSpray Ionisation
ERK	Extracellular Signal-Regulated Kinase
GCMS	Gas Chromatography-Mass Spectrometry
KO*t*Bu	Potassium *tert*-butoxide
MEM-Cl	Methoxyethoxymethyl chloride
mp	melting point
MW	Microwave
NaH	Sodium hydride
NMR	Nuclear Magnetic Resonance
NMS	*N*-methylscopolamine
NOE	Nuclear Overhauser Effect
OAc	Acetate
OBz	Benzoyloxy
OTf	Trifluoromethanesulfonate

PA-Ph	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane
$Pd_2(dba)_3$	Tris[dibenzylideneacetone]dipalladium(0)
PPh_3	Triphenylphosphine
SAR	Structure-Activity Relationship
TBAF	Tetra-*n*-butylammonium fluoride
THF	Tetrahydrofuran

Research Publications

1. Chee, C. F.; Abdullah, I.; Buckle, M. J. C.; Rahman, N. A. (2010) An efficient synthesis of (±)-panduratin A and (±)-isopanduratin A, inhibitors of dengue-2 viral activity. *Tetrahedron Lett.* 51, 495-498.

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