Nitroketene $N,S$-acetal route to functionalized $4H$-chromenes and further transformation into hybrid amino acids and DOPA isomers

1. Introduction

Heterocyclic compounds constitute the largest and diverse family of organic compounds. A substantial number of them occur widely in nature and exhibit profound biological activity. As a consequence, many of the drug molecules used in therapy today are heterocycles. Among the heterocyclic compounds, oxygen heterocycles are special because of their wide occurrence as a part structure of carbohydrates. The low molecular weight oxygen heterocycles find application as solvents and synthetic intermediates. Some of the fundamental small ring oxygen heterocycles are epoxide (3-member), oxetane (4-member), tetrahydrofuran (THF; 5-member) and tetrahydropyran (6-member). We have been interested in the synthesis and structural studies of the six-member oxygen heterocycles fused to benzene ring. The compound in which benzene ring is fused to a $4H$-pyran ring is known as $4H$-chromene ($4H$-1-benzopyran) $1$. Its dihydro-derivative, chroman $2$ is a fragrance compound with peppermint like odor.

![Figure 1.1]

Figure 1.1

Far more important than the parent $4H$-chromene $1$, is chromone (benzpyrone) $3$, which occurs as a part structure of flavones (2-aryl chromones). Flavones are polyphenolic compounds occurring in all the plants. Flavonoids and closely related oxygen heterocycles are primarily responsible for color of plant constituents like flowers, leaves etc. In addition, flavones are phytoalexins, a property that allows plants to survive in harsh environment. Many chromene derivatives have industrial applications. Unlike flavones, they have restricted occurrence among natural product scaffolds. Sometimes, they are found in vegetables and fruits and also as a part structure of alkaloids and anthocyanins. Often presence of the chromene-based
structure in a molecule is associated with its capacity to prevent diseases.\textsuperscript{9} A few naturally occurring chromenes exhibit antimicrobial,\textsuperscript{10} antitumor,\textsuperscript{11} antiviral,\textsuperscript{12} mutagenic\textsuperscript{13} antiproliferative\textsuperscript{14} and central nervous system (CNS) activities.\textsuperscript{15} Some chromenes are sex pheromones.\textsuperscript{16} Numerous synthetic derivatives of naturally occurring chromene found use as pharmaceuticals,\textsuperscript{17} particularly as antifungal\textsuperscript{7,18} and antimicrobial\textsuperscript{19} agents. Certain 2-aminochromene derivatives are used in cosmetic and pigments industry.\textsuperscript{20} Furthermore, many bioactive molecules (eg. antioxidants,\textsuperscript{21} enzyme inhibitors\textsuperscript{22}) incorporate this key heterocycle.

Out of diverse array of chromenes, 4\textit{H}-chromenes are of interest to present research workers. They are seldom encountered as a part of natural product structures. Few natural products, which possess 4\textit{H}-chromene structural motifs are gathered in Figure 1.2.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure12.png}
\caption{Figure 1.2}
\end{figure}

6-Methoxy-4\textit{H}-1-benzopyran-7-ol \textsuperscript{4} and 6,7-dimethoxy-4\textit{H}-benzopyran \textsuperscript{5} isolated from the flowers of \textit{Wisteria sinensis} plant exhibit organoliptic property.\textsuperscript{23,24} Another 4\textit{H}-chromene natural product uvafzelin \textsuperscript{6} isolated from the stems of \textit{Uvaria afzelii} showed significant antimicrobial activity against gram-positive and acid-fast bacteria.\textsuperscript{25}

2. Biological activities of 4\textit{H}-chromenes

The 4-aryl-4\textit{H}-chromenes are potent apoptosis (controlled cell death) inducing agents.\textsuperscript{26} Since cancer cells grow faster, apoptosis inducing agents act on cancer cells to restrict their abnormal cell division. Cai and coworkers discovered the use of the 4-aryl-4\textit{H}-chromene \textsuperscript{7} as a lead compound for the development of anticancer drugs.\textsuperscript{27} By systematically changing substituents on the C4 aryl ring, they found that 4\textit{H}-