Chapter 1

Tandem Wittig reaction with Sigmatropic rearrangement and Diels-Alder reaction
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The recent advances in vitro and enzyme based bioassays have generated heavy demand for large number of new chemical entities (both natural products and synthetic compounds) from pharmaceutical and agrochemical industries, forcing chemists to explore new synthetic methodologies. One such method employs tandem or domino reactions for the facile synthesis of different complex molecules. According to Tietze, a Domino reaction is a process involving two or more bond forming transformations which takes place under same condition without additional reagents or catalysts and in which subsequent reaction results as a consequence of the functionality formed in the previous step. Thus, tandem reactions are ‘single pot, multi-step reactions’, wherein the starting materials are converted into their final products through sequential multi reaction steps with dramatic increase in molecular complexity and impressive selectivity. These reactions also reduce requirement of costly protecting groups and tedious purification steps.

In fact several natural compounds are biosynthesized in tandem manner. For instance, conversion of squalene epoxide into lanosterol (Scheme I) proceeds through an intramolecular iterative cationic cyclisation, forming four new C-C bonds and six stereogenic centers.

Scheme I
Perhaps the first example of domino reaction in the laboratory is the synthesis of tropinone by Schopf and Robinson\textsuperscript{3a-f} (Scheme II), involving a double Mannich reaction of succinaldehyde, methyl amine and acetonedicarboxylic acid. Tropane is an important part of several bioactive alkaloids such as cocaine, atropine, etc.

![Scheme II](image)

We were interested in synthesizing natural products using tandem sequences of Wittig reaction with sigmatropic rearrangement and Diels-Alder reaction, developed in our laboratory. Wittig reaction, well known in the preparation of alkenes, has often been used in tandem with several other reactions for the synthesis of complex scaffold.\textsuperscript{3c} In its simplest form this involves the reaction of a phosphorane (ylide) with either an aldehyde or a ketone, yielding an alkene and a phosphine oxide as products (Scheme III).

![Scheme III](image)
Tandem Wittig reaction and Sigmatropic rearrangement:

a) Schobert et al.\textsuperscript{4} used the domino concept for the synthesis of $\delta$-lactones (Scheme IV). A three step sequence involves a new Wittig reagent preparation, intramolecular Wittig olefination and 3,3-sigmatropic rearrangement.

b) In yet another report, Schobert et al.\textsuperscript{5} described the synthesis of racemic blastamycinone, a degradation product of the antibiotic antimycin A\textsubscript{3} using tandem Wittig reaction with Claisen rearrangement (Scheme V).
c) Kawasaki et al.\textsuperscript{6} exploited tandem Wittig reaction and aromatization induced Cope rearrangement for the synthesis of 3-indole acetate from 2-allyl-1,2-dihydro-indol-3-ones and phosphorane (Scheme VI). Later, the same laboratory reported\textsuperscript{7} tandem HWE reaction, isomerisation of the double bond and Claisen rearrangement (Scheme VII) for the synthesis of a marine pyrallo [2,3-\textit{b}] indole alkaloid, flustramine C.

![Scheme VI](image)

d) Rama Rao et al.\textsuperscript{8} described the intramolecular Wittig reaction and Claisen rearrangement for the synthesis of benzofuran (Scheme VIII). Later, the same laboratory reported\textsuperscript{9,10} its preparation using microwave irradiation.

![Scheme VII](image)
e) Mali et al.\textsuperscript{11} reported tandem intermolecular Wittig reaction and Claisen rearrangement for the synthesis of 8-allyl coumarin from ortho allyloxy benzaldehydes. Subsequently, synthesis of natural coumarins nieshutin, methyl ether of balsamiferone, sesalin and angelicin derivatives were also reported from the same laboratory using similar strategies (Scheme IX).
Scheme IX
f) A tandem three step process for the conversion of aldehyde into β-substituted-2-oxohex-5-enoic acid by using HWE olefination and Claisen rearrangement is used by Ernesto & Taylor\textsuperscript{12} (Scheme X).

\[
\begin{align*}
R_1\text{CHO} + \text{EtOPO(OEt)}_2\text{CH}_2\text{CH}_2\text{CH}_2& \xrightarrow{\text{K}_2\text{CO}_3/\text{H}_2\text{O}, \text{MW 55 °C, 30 min}} \text{EtOPO(OEt)}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2R_1 \\
& \xrightarrow{\text{K}_2\text{CO}_3/\text{H}_2\text{O}, \text{MW 105 °C, 10 min}} \text{CH}_2\text{CH}_2\text{OCH}_2\text{CO}\text{R}_1 \\
& \xrightarrow{\text{heat}} \text{CH}_2\text{CH}_2\text{OCH}_2\text{CO}\text{R}_1 \\
& \xrightarrow{\text{Toluene, reflux}} \text{CH}_2\text{CH}_2\text{OCH}_2\text{CO}\text{R}_1
\end{align*}
\]

\text{Scheme X}

g) Begue \textit{et al.}\textsuperscript{13} have synthesized γ,δ-unsaturated perfluoro alkyl ketones using Wittig olefination of allyl perfluoroalkanoates, followed by Claisen rearrangement of the fluorinated (Rf) enol ethers in one pot (Scheme XI). The authors also synthesized stereoisomeric mixture of the 1,5-diene using Wittig reaction, Claisen rearrangement and Wittig reaction in a domino sequence.

\[
\begin{align*}
\text{O} & \xrightarrow{\text{Ph}_3\text{P}=\text{CHR}_2, \text{THF}} \text{O} \\
\text{CH}_3 & \xrightarrow{\text{Claisen}} \text{H}_2\text{C} & \text{CH}_3 \\
\text{Rf} & = \text{CF}_3, \text{C}_2\text{F}_5 \\
\text{Ph}_3\text{P}^+\text{CH}_2\text{RBr}^- & \xrightarrow{\text{NaNH}_2, (\text{Me}_3\text{Si})_2\text{NH}} \text{Rf} & \text{R}
\end{align*}
\]

\text{Scheme XI}
h) Loffler and Schobert described the synthesis of furoquinolones, by treating substituted allylic esters of anthranilic acid with cumulated ylide by using tandem Wittig reaction and Claisen rearrangement (Scheme XII).

\[
\begin{align*}
\text{R1} & \quad \text{R2} \\
\text{R3} & \quad \text{R4}
\end{align*}
\]

\[
\begin{align*}
\text{Ph3P}=\text{C}=\text{C}=\text{O} & \quad \text{Toluene} & \quad 180 \, ^{\circ}\text{C} \\
\text{MeCN} & \quad \text{Wittig-Claisen} \\
\end{align*}
\]

Scheme XII

i) Schobert et al. have synthesized bisspirolactones via 3-allyltetronic acids, which are precursors of 5-spiro-3-(α-cyclopropylbenzyl)tetronic acid using domino Wittig olefination-Claisen rearrangement (Scheme XIII) and Conia cyclisation. The same group has shown the abnormal rearrangement of allyl and benzyl tetronates for the construction of various types of 3, 5-disubstituted tetronic acids (Scheme XIV).

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
\text{Ph3P}=\text{C}=\text{C}=\text{O} & \quad \text{Toluene} & \quad 180 \, ^{\circ}\text{C} \\
\text{MeCN} & \quad \text{Wittig-Claisen} \\
\text{Toluene} & \quad 180 \, ^{\circ}\text{C} \\
\text{Conia}
\end{align*}
\]

Scheme XIII
Tandem Wittig reaction and Diels-Alder reaction:

a) Kozikowski and Jung\textsuperscript{18} have used tandem Wittig intramolecular Diels-Alder reaction for the construction of a tricyclic structure from a monocyclic precursor (Scheme XV).
b) Jarosz\textsuperscript{19} has developed a route for optically active highly oxygenated decalines using tandem Wittig-Diels-Alder reaction between sugar derived phosphoranes and sugar aldehyde (Scheme XVI). The same laboratory\textsuperscript{20} reported the synthesis of complex perhydroindene derivatives with the \textit{trans} junction between the five and six membered rings using tandem Wittig-Diels-Alder reaction between sugar derived phosphonates and dienoaldehydes. These authors also achieved synthesis of enantiomerically pure, highly oxygenated decaline system from the corresponding sugar derived dieno-phosphorane or phosphonates (Scheme XVII and XVIII).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme_xvi.png}
\caption{Scheme XVI}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme_xvii.png}
\caption{Scheme XVII}
\end{figure}
c) Ramachary et al.\textsuperscript{21} have shown the use of organocatalyst for the synthesis of spiro compounds using tandem Wittig reaction, Knoevenagel reaction and Diels-Alder reaction (Scheme XIX).
d) Holmes et al.\textsuperscript{22} have synthesized eunicelline analogues by using tandem Wittig-intramolecular Diels-Alder reaction (Scheme XX).

\begin{align*}
&\begin{array}{c}
\text{H}\text{C} \quad \text{C}\text{H} \\
\text{CH}_2
\end{array}
\xrightarrow{\text{Ph}_3\text{P} = \text{CH}_3}
\begin{array}{c}
\text{H}\text{C} \quad \text{C}\text{H} \\
\text{CH}_2
\end{array}
\end{align*}

Scheme XX

e) One pot synthesis of Mikanecic acid derivatives from allylic phosphonates via a tandem HWE-Diels-Alder reaction is described by Bodre and Colligton\textsuperscript{23} (Scheme XXI).

\begin{align*}
&\begin{array}{c}
\text{H}\text{C} \quad \text{C}\text{H}_2
\end{array}
\xrightarrow{\text{i) LDA/ THF/ -78 °C}}
\begin{array}{c}
\text{H}\text{C} \quad \text{C}\text{H}_2
\end{array}
\xrightarrow{\text{ii) CICO}_2\text{Et}}
\begin{array}{c}
\text{H}\text{C} \quad \text{C}\text{H}_2
\end{array}
\xrightarrow{\text{iii) HCHO}}
\begin{array}{c}
\text{H}\text{C} \quad \text{C}\text{H}_2
\end{array}
\end{align*}

Scheme XXI
f) Bestman & Schobert\textsuperscript{24} achieved the synthesis of substituted cyclohexene ester by reacting butanol, butyraldehyde, cumulated ylide and 1,3 diene in domino sequence of Wittig reaction, esterification and intermolecular Diels-aldor reaction (Scheme XXII).

\[ \text{Scheme XXII} \]

\[ \begin{align*}
\text{n BuOH} & + \text{n BuCHO} + \text{Ph}_3\text{P}=\text{C}=\text{C}=\text{O} \\
\text{Toluene, 120 deg. C, 12 hrs} & \rightarrow \text{products} 
\end{align*} \]

g) Yvonne Martin\textsuperscript{25} synthesized substituted heterocyclic core of the pseudodistomin C and E by using tandem Wittig reaction and (2+3) cycloaddition (Scheme XXIII).

\[ \text{Scheme XXIII} \]

\[ \text{Et}_3\text{N} \] pivaloylformylanhydride

\[ \text{hydrogenation} \]
h) Dai & co-workers\textsuperscript{26} used tandem Wittig-intramolecular Diels-Alder reaction for a modular synthesis of the bicyclic lactones with α-bromoacetates and α-oxo carbonyl compounds as the building blocks (Scheme XXIV).

\[
\begin{align*}
\text{CHO} & \quad \text{PPPh}_3 \\
\text{C=O} & \\
\text{Br} & \\
\text{R}_4 & \\
\text{2, 6 Lutidine} & \\
\text{MeCN, 180 °C} & \\
\end{align*}
\]

Scheme XXIV

i) Herdeis & co-workers\textsuperscript{27} have reported diastereoselective synthesis of non-racemic 2-alkyl-5-hydroxypiperidines with \((2R, 5S)\)-configuration via a tandem Wittig reaction and \((2+3)\) cycloaddition reaction. Syntheses of related alkaloids, prosopsis, cassia alkaloids and azasugars were achieved in this manner (Scheme XXV). Later on the same authors have synthesized natural (-)-cassine by using HWE and \((3+2)\) cycloaddition process, starting with L-rhamnose, a cheap starting material. The HWE-\((3+2)\) \& 1,3-dipolar cycloaddition reaction is the pivotal step in this reaction sequence and makes the synthesis highly efficient (Scheme XXVI).

\[
\begin{align*}
\text{PhP=CH}_3\text{COOEt} & \\
\text{N} & \\
\text{HO} & \\
\text{EtO} & \\
\text{R} & \\
\text{Scheme XXV}
\end{align*}
\]
j) Boeckmann et al.\textsuperscript{28} have used domino Wittig-intramolecular Diels-Alder reaction for the synthesis of indanomycin (Scheme XXVII).
k) Thiemann et al.\textsuperscript{29} have used tandem Wittig Diels-Alder reaction where in, Wittig olefination of cyclopropanone hemiacetal with stabilized phosphoranes was used to generate \textit{in situ} monosubstituted alkylidene cyclopropane which was further trapped by thiophene derivative to give one diastereomer (Scheme XXVIII).

\begin{center}
\includegraphics{schemeXXVIII.png}
\end{center}

Scheme XXVIII

l) Varseev & Maire\textsuperscript{30} have developed efficient route for the synthesis of neosymbioimine from citronellol. They have constructed the neosymbioimine core by using tandem HWE-intramolecular Diels-Alder reaction (Scheme XXIX).

\begin{center}
\includegraphics{schemeXXIX.png}
\end{center}

Scheme XXIX
m) Roush & co-workers\textsuperscript{31} have achieved the total synthesis of spinosyn A using tandem HWE-Diels-Alder reaction. The cascade begins from linear precursor A, which undergoes HWE macrocyclisation to give pentene adduct, which simultaneously undergoes a transannular Diels-Alder reaction to form B with correct stereochemistry for spinosyn A. Bromine substituents on the diene is used as a stereodirecting group to attain the required geometry for Diels-Alder reaction (Scheme XXX).

\[ \text{Scheme XXX} \]

n) Hilt & Hengst\textsuperscript{32} described the synthesis of substituted styrenes and stilbenes using Diels-Alder reaction and Wittig olefination in one pot. The cobalt(I) catalysed Diels-Alder reaction of propargyl phosphonium salts with 1,3-dienes led to the formation of dihydroaromatic phosphonium salt intermediates which were directly used in a Wittig type olefination reaction with aldehyde. Subsequent oxidation led to the formation of stilbenes (Scheme XXXI).
o) From our\textsuperscript{33} laboratory, tandem Wittig reaction-isomerisation-electrocyclisation reaction is described for the regioselective synthesis of carbazole precursor for the anticancer alkaloid olivacine (Scheme XXXII).

\begin{center}
\textbf{Scheme XXXII}
\end{center}

p) Another interesting tandem Wittig reaction-reductive cyclisation on \textit{o}-nitro benzaldehyde is reported for the synthesis of 2-acyl and 2-benzoyl indoles from our\textsuperscript{34} laboratory (Scheme XXXIII).

\begin{center}
\textbf{Scheme XXXIII}
\end{center}
Statement of Objectives:

Multistep synthesis of speciality chemicals normally requires stoichiometrically excess reagents, leading to high effluent loads besides adding to the cost of the final product. Hence, search is now on for clean, non-hazardous and 'green' chemical transformations, which will have negligible bi-products and high selectivity.

The broad objective of this work was to evaluate the possibility of combining Wittig reaction with Diels-Alder reaction and Sigmatropic rearrangements in tandem fashion for the synthesis of bioactive natural products and their analogues. Specifically, we were interested in synthesizing different furanesquiterpenes: furodysin 1 and furodysinin 2 besides the secofuranoelemophilane 3, using tandem Wittig reaction and Diels Alder reactions.

Yet another interest was to develop efficient methods for the synthesis of Tetrahydrocarbazole 4 and its derivatives of pharmaceutical interest.
Lignans, an ubiquitous plant metabolite are also known to possess interesting pharmacological activities. In view of their interesting biological properties, we were interested synthesizing lignans 5, 6 and heterolignans 7, 8, 9 in one pot using Wittig and Diels-Alder reactions.

Several coumarins - an important class of oxygen heterocycles - are useful for the treatment against HIV, tumor, hypertension, arrhythmia, osteoporosis, pain, asthma and sepsis. We were interested in the synthesis of naturally occurring prenylated coumarins demethylsuberosin 10, gravelliferone 11, methyl ether of 6-hydroxy-7-methoxy-3-(3,3-dimethylallyl)coumarin 12, balsamiferone 13 and cedrelropsin 14 using Wittig reaction and Claisen-Cope rearrangement in a tandem manner.

![Chemical structures](image-url)
References:


3) a) Mannich, Arch. Pharm. 1917, 255.

   b) F. F. Blicke, Org. React. 1942, 1, 303.


