Carbo-/Hetero-annulations and Cyclization reactions of Propargyl alcohols

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• **Carbo/-Heterocyclic compounds:** Generally belongs to privileged-class of molecules with important Medicinal and Material applications (also in other applied fields)

• Therefore, Carbo/-hetero cyclization become an active and challenging research area for synthetic Chemists to develop new strategies

• Generally these strategies involve an inter and/or intramolecular carbon-carbon and/or carbon-hetero atom bond formations through either $S_{N}1$ or $S_{N}2$ reactions

• Despite having several Synthetic methods developed for the construction of Carbo-/Heterocyclic compounds, there is always a continuous thirst and demand to develop a better design for the efficient, economic and Controlled-construction of these molecules
Synthetic Design-Analysis

Catalyst

\[
\text{HO} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3
\]

\[\text{SN}1\]

nu

endocyclization

nu

exo-cyclization

nu

EWG

Michael addition

nu

\[
\text{CO}_2\text{Et} \quad \text{OH} \quad \text{CO}_2\text{Et} \\
\text{C} \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{O} \quad \text{C} \quad \text{O}
\]

5-exo dig

\[
\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]
Furan vs Pyran

conditions: 10 mol% Ca(OTf)$_2$/nBu$_4$NPF$_6$, 120 °C, neat, 1-3.5 h

(S. Yaragorla et al) RSC. Adv. 2016, 6, 28865
RSC. Adv. 2016, 6, 89732
Studies on Inhibition of amyloid Fibril formation of Lysozyme

• Furan derivatives have been shown to interact with amyloid plaques
• We were curious to explore the effect of our compounds on amyloid formation
• Selected compounds (3f, 5j, 5k) were able to inhibit lysozyme aggregation

Normalized ThT fluorescence intensity for lysozyme fibrils without inhibitors and with inhibitors 3f, 5j and 5k, respectively

ThT fluorescence spectra with lysozyme fibrils with and without inhibitors

ThT Fluorescence clearly indicates three compounds inhibit lysozyme aggregation by 85, 92 and 90%, respectively

(S. Yaragorla et al) RSC. Adv. 2016, 6, 89732
Strategic Analysis

Nucleophilic Cyclization

Catalyst

\[ \text{Nu} \]

\[ S_{N2'} \]

\[ \text{endo cyclization} \]

\[ \text{exo cyclization} \]

Nucleophilic Cyclization
Selectivity & Control??

Acyclic bidentate nucleophiles

5-endo dig
6-endo-trig


10 mol% Ca(NTf_2)_2
DBU (3 eq.), DCE, rt

(80%)
Synthesis of allenes

One-pot, Sequential poly-annulation

What is known about Fluorenopyrans??
• **SIX** step synthesis
• Photochromic
• Used in plastics
• Particularly Ophthalmic purposes

Fluorenofurans

One-pot, Sequential annulation

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<th>Yield (%)</th>
<th>Time (h)</th>
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Under review
Normalized ThT fluorescence intensities for lysozyme fibrils without inhibitors and with inhibitors 3a and 3v respectively.
Enyne Cycloisomerization via Allenes??

1. Ca(OTf)_2, Bu_4NPF_6 (10 mol%), 110 °C

6-endo trig cyclization

[3,3]-Sigmatropic Rearrangement

Diels-Alder

oxidative Rearrangement

Chloranil, 150 °C

12 compounds
53-77% yields
7-9 h

10 compounds; 53-72% Yields; 6-9 h

Cyclopentenylation!!

Cascade Meyer-Schuster Rearrangement & Pyrrole synthesis

Medicinally important
Accessed through a multi-step sequence

10 mol%, Ca(OTf)$_2$/ Bu$_4$NPF$_6$
Isobutanol, 90 °C

Meyer-Schuster rearrangement

(S. Yaragorla, R. Dada, P. Rajesh, M. Sharma) ACS Omega, 2018, 3, 2934-2946
Developed a **strategic approach** of *in situ* Allene synthesis and Nucleophilic Cyclization reactions

**Green Chemical Synthesis** (One-Pot, Cascade, MCRs, Solvent-Free, Calcium-catalysis)

**New Chemical Entities** (NCE’s) with synthetic, medicinal & material applications
Acknowledgements

Past PhD Students
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- Dr. Garima Singh
- Dr. Abhishek Pareek

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- Mr. Ravikrishna D
- Mr. Rajesh P
- Ms. Tabassum Khan
- Mr. Farooque Husni
- Ms. Sneha Latha
- Mr. Arun D

Thank You All

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- UGC NRC
- CSIR-India (Funding)
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- IASc Bangalore, India
Benzannulations via Iodocyclization: Concise Synthesis

37 compounds; Yields: 77%-95%


ACS Omega, 2018, 3, 15024

PhB(OH)$_2$, Pd(OAc)$_2$
Na$_2$CO$_3$, DMF:H$_2$O (1:1), 100 °C

(Suzuki reaction)

Ethyl acrylate
Pd(OAc)$_2$, Bu$_4$NBr
Na$_2$CO$_3$, DMF, 80 °C
75%, 22 h
(Heck reaction)

Phenylacetylene
Pd(OAc)$_2$, DABCO
CH$_3$CN, rt, 70%, 12 h

(Sonogashira reaction)
12 compounds; 53-77% yields; 7-9 h
The plausible mechanism for the Bu$_4$NPF$_6$ mediated regioselective synthesis of functionally embellished naphthofurans
NBO charge distribution on the activated C-C double bond. The NBO charge distribution of selected compounds was studied by performing ab initio (B3LYP/6-31g**) calculations.

Yaragorla, S.; Dada, R.; Pallava, R.; Sharma, M. Submitted
The concept of Privileged Structures in Rational Drug Design:

- The concept of 'privileged structures' has been proposed as a way of overcoming deficiencies and increasing the reliability of the drug discovery process.
- The original definition provided by Evans in 1988, the concept has greatly evolved in most cases to describe not only those structures found to be promiscuous within a given target family, but also those that modulate proteins lacking a strict target class relation.
- Due to their inherent affinity for various targets, privileged structures could offer a viable starting point in the search for novel multi-target ligands.
- From a broader perspective, they can serve as effective probes for investigating unknown but interrelated mechanisms of action.