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SUSTAINABLE CONSTRUCTION OF PYRANOPYRAZOLES UTILIZING $HClO_4$-SiO_2 AS AN EFFICIENT SOLID CATALYST AND DOCKING STUDIES

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ABSTRACT

This article introduces a highly proficient and environmentally friendly process for producing pyranopyrazole-5-carbonitriles with outstanding yields. This involves a multicomponent synthesis using commonly available aldehydes, malononitrile, ethyl acetoacetate, and phenylhydrazine, conducted in ethanol with perchloric acid supported on silica ($HClO_4$-SiO_2) as a solid catalyst. Utilizing $HClO_4$-SiO_2 as a reusable catalyst underscores the sustainability of this approach, offering a valuable green chemical strategy for pyranopyrazole synthesis. Characterization of the synthesized compounds was achieved using FTIR, ^{1}H NMR, ^{13}C NMR, and Mass spectrometry. Additionally, molecular docking studies revealed significant binding energies of the compounds to receptor-active sites, further validating their potential pharmacological relevance.

Keywords: Pyranopyrazole-5-carbonitriles; multi-component; $HClO_4$-SiO_2; Heterogeneous Catalyst; Greeprotocol; Docking studies

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INTRODUCTION

Pyranopyrazoles are a fascinating class of fused heterocycles widely utilized in medicinal chemistry and sustainable agriculture.[1-3] Distinguished for their diverse therapeutic properties, including anti-dysplasia, hypoglycemia, antimicrobial, and anticancer effects, they have spurred innovative organic synthesis methods.[4-11] Furthermore, pyrazole core units are used to make several pharmaceuticals that are sold commercially.[12-14] Because of this, it has opened up new avenues for organic synthesis and sparked the creation of creative methods for creating pyranopyrazole molecules. Multicomponent reaction (MCR) is the most effective method among all those that have been explored for creating the target skeleton compound in a single step. Numerous synthesis efforts for pyranopyrazoles and the development of multicomponent methods were reported in a review by Mamaghani *et al.*[15] In the field of catalytic conversions, organo catalysts are metal-free simple organic compounds that act as potent and selective catalysts for massive transformations. The progress of eco-friendly, non-hazardous, cost-effective, recyclable, and reusable catalyst systems provides great output under mild organic reaction environments.[16,17] However, solid-supported catalysts have attracted a lot of consideration because they offer several significant benefits as heterogeneous catalysts. They possess inherent economic and environmental profits, high catalytic activity, ease of work, thermal stability, chemical stability, ease of separation, reusability, and moreover environmentally non-toxic catalysts.[18,19] The $HClO_4$-SiO_2 as a solid-supported heterogeneous catalyst, possesses green chemistry criteria for an extensive variety of organic transformations.[20-22] The Ras/Raf/MEK/ERK mitogen-activated protein kinase (MAPK) waving route, implicated in various malignancies, features the tyrosine/threonine protein kinase MEK1.[23] Constitutively activated MEK1 induces cellular transformation, and constitutively activated MAPK pathways are

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prevalent in over 35% of human malignancies. Structural analyses reveal that the MgATP-binding site is adjacent to a distinct inhibitor-binding pocket shared by MEK1 and MEK2. The unphosphorylated forms of MEK1 and MEK2 are conformationally locked in a closed, catalytically inactive state by pyranopyrazoles, inducing numerous conformational changes in the enzymes. As a part of our ongoing attempt to introduce a new method for the construction of heterocyclic analogs,[24,25] we constructed pyranopyrazoles *via* the MCR process in the occurrence of $HClO_4$-SiO_2 and the constructed pyranopyrazoles were imperiled to theoretical docking studies.

EXPERIMENTAL

Preparation of Pyranopyrazoles

Aldehyde (4.5 mmol), malononitrile (4.5 mmol), perchloric acid supported on silica (Purchased from Aldrich, Pcode: 1002217783) (30.0 mg), and EtOH (10 ml) were mixed in a round bottom container. The combination was stirred for about 10 mins at room temperature and then phenyl hydrazine (4.5 mmol) and ethyl acetoacetate (4.5 mmol) were added and refluxed for a suitable time as presented in Table 2 at 60-80°C. The end of the reaction was observed every 10 mins with the help of TLC (EtOAc / hexane 4:1). The solution was brought to rt and the impurities were removed with dichloromethane followed by filtration to separate the $HClO_4$-SiO_2 solid. The filtrate was rinsed with water, desiccated over anhydrous Na_2SO_4, and subsequently subjected to solvent evaporation, resulting in the formation of the crude compound. The crude was recrystallized using EtOH to acquire a pure compound as a pale-yellow solid (5a). The recovered $HClO_4$-SiO_2 acid catalyst was rinsed with dichloromethane and the solvent was removed thus, the catalyst was reused for the next cycles. Above mentioned procedure was applied for the synthesis of 5b-5f compounds where the benzaldehyde is substituted with other derivatives as shown in scheme-1 and table 2. The prepared compounds are characterized by FTIR, ^{1}HNMR, ^{13}CNMR, and Mass spectrometry. The characterization of the compounds 5a-5f is represented in supplementary data.

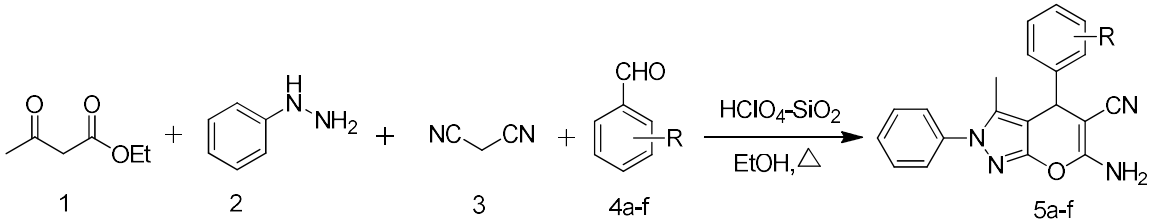
Docking Analysis

The docking analysis is extensively utilized in molecular modeling studies to discover the interface between two molecules (receptor and ligand) and aids in finding suitable drugs.[26] 2-dimensional structures of all the constructed derivatives (ligand) of pyranopyrazoles were drawn by using Chem Draw software. Open Bable GUI version 2.3.2 was employed to convert the 2D structures to 3D structures. The energy minimization module of the Schrodinger program Maestro Tool was used to reduce molecular energy.[27] The three-dimensional core of human mitogen-activated protein kinase kinase 1 (MEK1) was obtained from Protein Data Bank (PDB ID: 1S9J.pdb).[28] The protein core was established, followed by correction of protein was done by means of a protein preparation group, where the targeted protein sequence was set by separating the structural H_2O molecules, hetero atoms, and co-factors and by adding polar hydrogens. Additionally, a grid was prepared for the active site, and docking studies were conducted using the Glide docking module. The acquired outcomes were examined on the basis of maximum dock score, and the number of H-bonds was visualized using Pymol.[29]

RESULTS AND DISCUSSION

We introduced a heterogeneous acid catalyst to optimize the reaction environment to produce a clean multicomponent protocol for the construction of pyranopyrazoles. In a model study, ethyl acetoacetate (4.5 mmol), phenyl hydrazine (4.5 mmol), malononitrile (4.5 mmol), benzaldehyde 4a (4.5 mmol), and $HClO_4$-SiO_2 in EtOH as a solvent (Scheme-1) are used. The target compound was not formed after 7 hours in ethanol at 25 ± 2°C without the SiO_2 catalyst (Table-1, entry 1) and with the SiO_2 catalyst (Table-1, entry 5). But when the temperature is increased to 70°C the compound formation observed was 55% without using a SiO_2 catalyst (Table-1, entry 2) and 69% yield with a SiO_2 catalyst (Table-1, entry 6). Keeping in mind the purpose of green chemistry, a trial reaction was carried out in water as solvent at 70°C, where no product was noticed (Table-1, entry 3). Further, another trial reaction was conducted by adding NaOH in water as a catalyst at room temperature, even then the compound was not acquired (Table-1, entry 4). Then we introduced $HClO_4$-SiO_2, a heterogeneous acid catalyst in this four-component reaction, but the target product was not produced at room temperature (Table-1, entry 7). Finally, the preferred compound obtained was 84% when the temperature was raised to 70°C in ethanol after 5 h in the presence of the heterogeneous catalyst $HClO_4$-SiO_2 (Table-1, entry 8). Table-1 acutely shows that $HClO_4$-SiO_2 is an efficient catalyst in

words of compound yield and reaction duration time. To find out the ideal mass of the catalyst, the four-component reaction was conducted with 20, 30, and 40 mg of $HClO_4$-SiO_2, and the product yields were found 84, 90, and 92% respectively (Table-1, entries 8-10). The efforts suggested that 30 mg of $HClO_4$-SiO_2 catalyst was sufficient to perform the reaction under the elected reaction conditions. After the standardization of reaction conditions, various reactions were performed with different aromatic aldehydes, malononitrile, phenylhydrazine, and ethyl acetoacetate. Thus, the compounds synthesized by using the MCR process and standard reaction conditions are summarized in Table-2. ^{1}H NMR, ^{13}C NMR, FTIR, and Mass spectrometric techniques were used to confirm the final target products (Supplementary data).



Scheme-1: Preparation of Pyranopyrazoles

Table-1: Enhancement of Reaction Circumstances for the Construction of Pyranopyrazoles (5a)

S.No.	Catalyst	Quantity (mg)	Solvent	Temp (°C)	Time (hr)	Yield
1	-	-	EtOH	rt	7.0	No product
2	-	-	EtOH	70	6.0	55
3	-	-	H_2O	70	6.0	No product
4	NaOH	300	H_2O	rt	6.0	Trace
5	SiO_2	20	EtOH	rt	7.0	No product
6	SiO_2	20	EtOH	70	8.0	69
7	$HClO_4$-SiO_2	20	EtOH	rt	8.0	No product
8	$HClO_4$-SiO_2	20	EtOH	70	5.0	84
9	$HClO_4$-SiO_2	30	EtOH	70	4.0	90
10	$HClO_4$-SiO_2	40	EtOH	70	4.0	92

Plausible reaction mechanism for the construction of Pyranopyrazoles. **The stepwise reaction mechanism is as follows:**

Step-1: Formation of arylidenemalononitrile (A)

The nucleophilic nature of $HClO_4$-SiO_2 facilitates the formation of arylidenemalononitrile (A) from the aldehyde and malononitrile reactions. The catalyst is capable of providing optimal conditions to carry Knoevenagel reaction by removing protons from the reactants

Step-2: Formation of Compound B

The 3-methyl-1-phenyl-pyrazol-5-ol (B) is formed from the standard reaction of phenylhydrazine with ethyl acetoacetate.

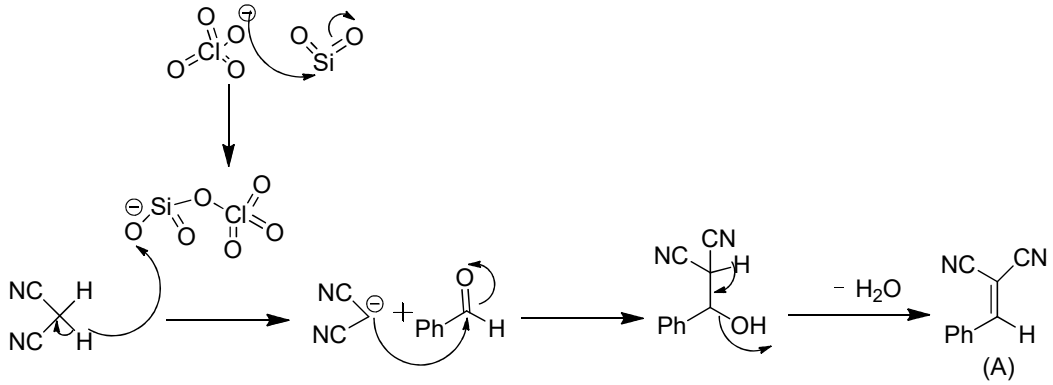
Step-3: Formation of Pyranopyrazole

Both intermediates, A, and B, undergo Michael-type addition followed by intramolecular nucleophilic cyclization and tautomerization in the presence of $HClO_4$-SiO_2 to yield the target compound.

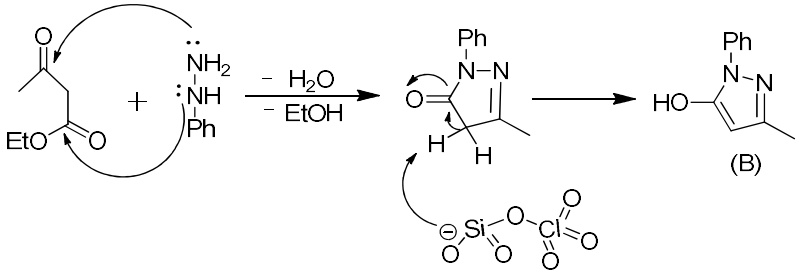
Molecular Docking Studies

Our Insilco readings showed that all the constructed derivatives exhibited outstanding binding energies against the active sites of the receptor protein. Docking results were recognized on the basis of maximum ligand binding poses employing the great docking score -86.712 kcal/mol, -85.75 kcal/mol. The number of H-bonding and hydrophobic interactions of molecule 5b (Fig.-1) & molecule 5a (Fig.-2) with receptor are shown. The Table-3 exhibits the docking energies, interacting atoms along with H-bond distances.

Step 1: Formation of arylidenemalononitrile (A)



Step 2: Formation of 3-methyl-1-phenyl-pyrazol-5-ol (B)



Step 3: Formation of Pyranopyrazole

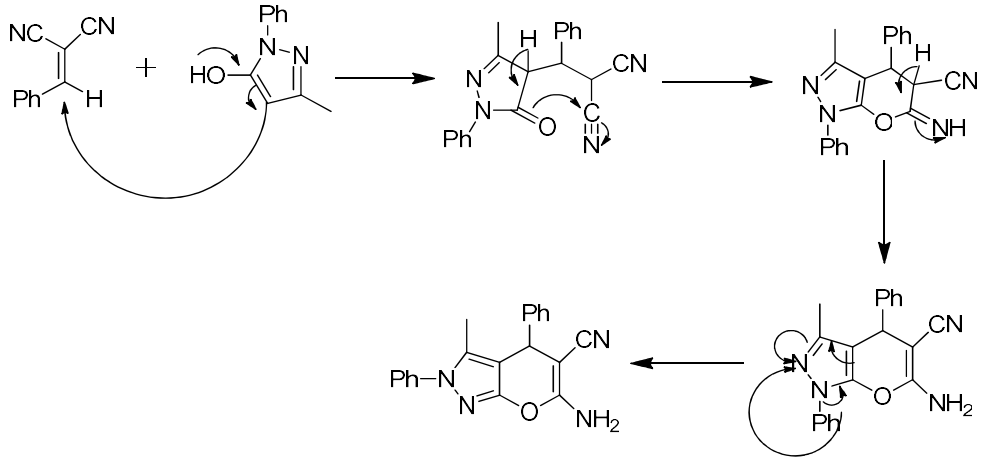
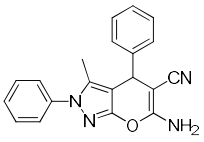
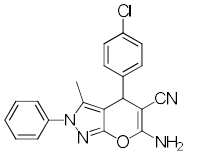


Table-2: $HClO_4$-SiO_2 Catalyzed Preparation of the Pyranopyrazoles (5a-f)

Entry	Compound No.	R	Compound	Time (h)	Yield (%)
1	5a	H		4.0	94.0
2	5b	4-Cl		4.0	92.0

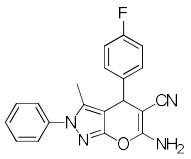
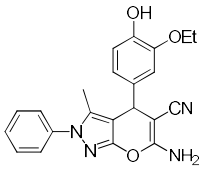
3	5c	4-F		4.5	93.0
4	5d	3-OEt, 4-OH		4.0	95.0
5	5e	4-OCH_3		3.5	90.0
6	5f	4-OEt		4.0	92.0

Table-3: Molecular Interactions of MEK1 Receptor and Synthetic Compounds

Molecule	Receptor (Connecting atoms)	Ligand (atoms)	H-bond distance (Aº)	Docking energy (kcal/mol)
5a	MET146-O	NH	2.60	-86.712
	GLN153-OE1	NH	3.14	
5b	GLN153-OE1	NH	2.63	-85.751
	SER150-OG	NH	3.02	
5c	LEU74-O	NH	3.73	-80.146
	GLN153-OE1	NH	3.22	
5d	MET146-N	O	2.79	-85.924
5e	MET146-N	O	2.79	-84.012
	LEU74-O	O	3.60	
5f	GLU144-O	NH	2.75	-82.824
	MET146-O	NH	3.27	

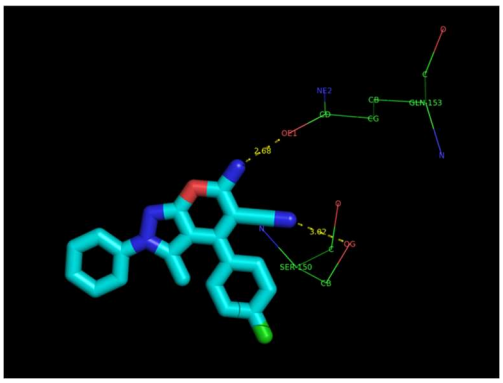


Fig.-1: Structure 5b Molecular Interactions

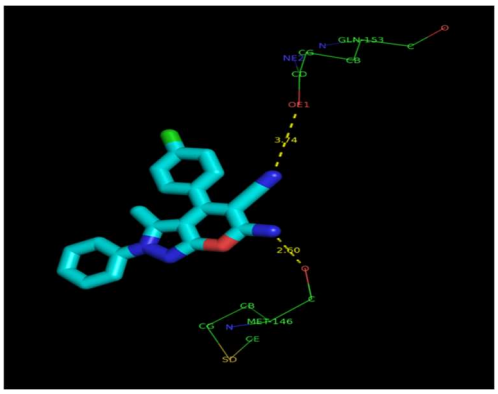


Fig.-2: Structure 5a Molecular Interactions

CONCLUSION

To conclude, an efficient process for the construction of pyranopyrazoles was developed by using simple, readily available reactants and inexpensive $HClO_4$-SiO_2 catalysts under milder reaction conditions by the MCR process. This process facilitates a broad scope for the usage of starting materials with an ecofriendly and simple workup process resulting in the construction of target compounds in a less reaction time with good yields. Insilco analysis revealed that the compounds 5a and 5b have high affinity towards the receptor. This technique finds extensive claims in the area of drug discovery, multifaceted production, and synthesis.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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