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SBA-Pr-SO_3H Catalyzed Synthesis, and Molecular Docking Study of Aryltetrahydrodipyrazolopyridine Derivatives as PDK1 Inhibitors

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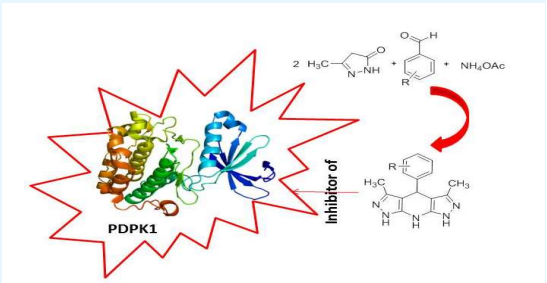
Abstract: Hantzsch reaction is a popular procedure for the synthesis of dihydropyridines (DHPs) through the reaction of two equivalents of a *β*-ketoester with one equivalent of aldehyde in the presence of an ammonia source. The Hantzsch reaction of pyrazolone, aromatic aldehydes and ammonium acetate was studied in the presence of SBA-Pr-SO_3H, as the catalyst, to gain tetrahydrodipyrazolopyridines. The high yield of products (80-95%) within a short reaction time (6-15 min) proves the efficiency of this methodology. Finally, molecular docking studies were used to show the binding mode of these compounds in the active site of 3-phosphoinositide-dependent kinase 1 (5OOT). Docking computation studies show the Gold Score value and the binding mode of resulting complexes. The synthesized compounds can bind to the receptor's residues by forming hydrogen bonds and π interactions. The detailed analysis of the binding mode of the best-docked molecule exhibited a hydrogen bond between NH substituent and Tyr20. Moreover, π-π and π-cation interactions can be seen with the residues Tyr20 and Lys38, respectively.



Keywords: Hantzsch reaction, SBA-Pr-SO_3H, Pyrazolone, Tetrahydrodipyrazolopyridines, Molecular docking

1. Introduction

Hantzsch reaction is a popular procedure for the synthesis of dihydropyridines (DHPs) through the reaction of two equivalents of a *β*-ketoester with one equivalent of aldehyde in the presence of ammonia source.[1] So far, several pharmaceuticals having DHP scaffolds have been discovered such as Aranidipine, Nisoldipine, Isradipin, and so on.[2] Furthermore, DHPs have been evaluated for diverse biological activities including antimicrobial,[3] anticancer,[4] anti-inflammatory,[5] analgesic,[6] anti-HIV,[7] and antitubercular[8] activities.

In recent decades, mesoporous silica compounds have been found as the appropriate substrate for the preparation of heterogeneous catalysts. The most famous and applicable substrates are Mobil Composition of Matter (MCM-41) and Santa Barbara Amorphous (SBA-15). These materials have a high surface area, ordered pores and modifiable surface.[9] However, SBA-15 has higher hydrothermal stability than the MCM-41. So far, SBA-15 has been functionalized with varied organic functional groups and used as a chemosensor,[10] catalyst,[11,12] adsorbent,[13] and so on. Sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) is an efficient solid acid catalyst which has been used for the synthesis of different organic compounds isoindigo,[14] *α,β*-substituted nitroalcohols,[15] quinazolinones,[16] isatinhydrazones,[17] and furfural.[18] In this paper, we want to study the Hantzsch reaction of pyrazolone compounds in the presence of SBA-Pr-SO_3H as a catalyst for the preparation of tetrahydrodipyrazolopyridine.

2. Experimental

Melting points (M.P.) were measured using the capillary tube method with an electrothermal 9200 apparatus. FT-IR spectra were recorded from the KBr disk using a FT-IR Bruker Tensor 27 instrument. The ^1H and ^{13}C NMR were run on a 250 and 62.5 MHz Bruker, respectively. SEM image was obtained on a Philips XL-30 field-emission scanning electron microscope operated at 16 kV, while TEM was carried out on a Tecanai G^2 F30 at 300 Kv.

Synthesis and functionalization of SBA-15

The mesoporous SBA-Pr-SO_3H was prepared and functionalized according to our previous report[17] and then, the obtained was used as a heterogeneous acid catalyst in the mentioned reactions.

General procedure for the synthesis of pyrazolopyridine 6a-i

A mixture of pyrazolone **3** (2 mmol, 0.196 g), aldehyde derivative **4** (1 mmol), ammonium acetate (3 mmol) and activated SBA-Pr-SO_3H (0.02 g) was stirred and heated under the solvent-free condition at 120 °C. After completion of the

reaction, as indicated by TLC, the crude product was dissolved in hot EtOH and subsequently filtered for removal of the catalyst. The pure products (**5a-i**) were obtained after cooling the filtrates. The spectral data for the new compounds are given below.

4-(2,3-dimethoxyphenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b:4',3'-e]pyridine:

White powder (yield 85%); mp: 275-277 °C; ^{1}H NMR (250 MHz, DMSO-d_6): 2.01 (s, 6H), 3.51 (s, 3H), 3.71 (s, 3H), 5.02 (s, 1H), 6.81-7.06 (3H), 10.92 (br., 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): 10.84, 27.96, 55.96, 59.72, 104.49, 111.02, 121.85, 123.13, 137.56, 139.84, 146.09, 152.45, 161.71., FT-IR (KBr) (ν_{max}/cm^{-1}): 3590, 3472, 3234, 2931, 1583, 1472, 1275, 1178, 1080, 1033, 980, 898, 822.

4-(3-methoxyphenyl)-3,5-dimethyl-1,4,7,8-tetrahydro-dipyrazolo[3,4-b:4',3'-e]pyridine:

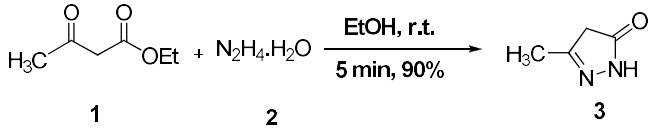
White powder (yield 95%); mp: 276-278 °C; ^{1}H NMR (250 MHz, DMSO-d_6): 2.06 (s, 6H), 3.47 (s, 3H), 4.78 (s, 1H), 6.69-7.14 (4H), 10.09 (br., 3H); ^{13}C NMR (62.5 MHz, DMSO-d_6): 10.82, 33.26, 55.24, 104.57, 110.51, 114.48, 120.46, 129.15, 140.24, 145.54, 159.44,161.49., FT-IR (KBr) (ν_{max}/cm^{-1}): 3380, 2995, 1588, 1484, 1310, 1218, 1178, 1080, 1033, 980, 898, 822.

Molecular docking

The crystal structure of 3-phosphoinositide-dependent kinase 1 (5OOT) was taken from the RCSB protein databank (http://www.pdb.org). In the protein databank, this protein is complexed with the ligand 4K4, so the ligand was removed and then the structure of our synthesized compounds was docked in the active site of protein one by one. Discovery Studio 2.5 (Accelrys Inc, San Diego, CA, USA) was employed to dock the compounds to protein. All molecules were sketched and typed with CHARMm force field then partial charges were calculated by the Momany-Rone option.[19] Then the minimization step was performed. For the preparation step of protein, CHARMm force field was used, hydrogen atoms were added, all water molecules were removed and the pH of protein was adjusted to almost neutral, 7.4, using protein preparation protocol. The protein active site was defined as a sphere with a radius of 11 Å around the bounded ligand (4K4) to confirm atoms of the ligand and the side-chains of the residues of the receptor within 9 Å from the center of the binding site are free to move. Afterwards, the bounded ligand was removed from the binding site, so that our compounds could bind in the cavity. Other parameters were set by default protocol settings. The GOLD program was used to dock the compounds into receptors.[20]

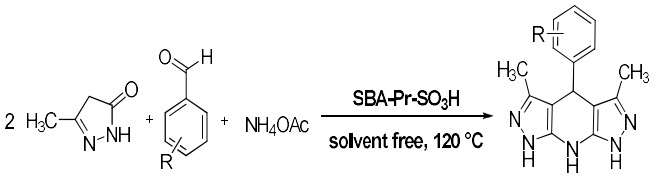
3. Results and Discussion

In this research, pyrazolone **3** was initially synthesized through the reaction of ethyl acetoacetate **1** and hydrazine hydrate **2** in EtOH at room temperature (Scheme 1). When the structure of pyrazolone **3** was confirmed by melting point and FT-IR, it participated in the multicomponent reaction with aromatic aldehydes **4a-i** and ammonium acetate **5** (Scheme 2). The optimization of reaction conditions was performed in the presence of the nanocatalyst SBA-Pr-SO_3H, or in the absence of a catalyst or a solvent, as well as in the presence of absolute EtOH as a solvent, under different temperature conditions (reflux and room temperature) (Table 1). Based on the highest yield achieved for the products and the shortest reaction time, solvent-free conditions in the presence of the SBA-Pr-SO_3H catalyst were selected for conducting this reaction. Therefore, final products **6a-i** were produced in high yields under solvent free conditions at 120 °C within 8-15 min (Table 2).



1 2 3

Scheme 1. Synthesis of pyrazolone **3**



3 4a-i 5 6a-i

Scheme 2. Hantzsch reaction of pyrazolone for the synthesis of pyrazolopyridine derivatives

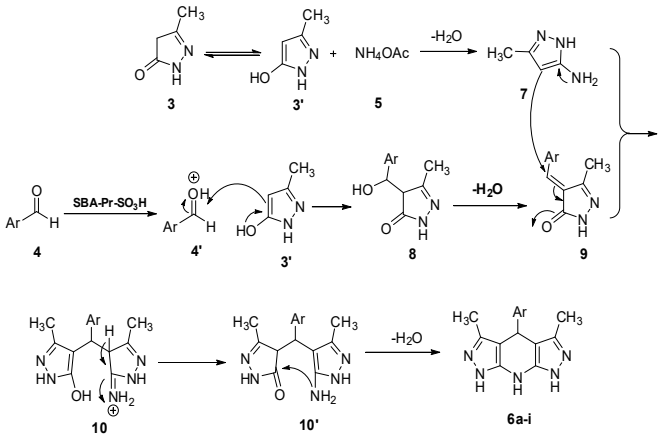
Table 1. Optimization of reaction conditions

No	Catalyst	Solvent	Condition	Time (min)	Yield (%)
1	SBA-Pr-SO_3H	-	120 °C	8	80
2	SBA-Pr-SO_3H	EtOH	reflux	60	40
3	SBA-Pr-SO_3H	EtOH	r.t.	120	20
4	-	EtOH	reflux	180	60

Table 2. Synthesis of pyrazolopyridine derivatives

Entry	No.	R	Time (min)	Yield (%)	m.p. (°C)	m.p. Lit. (°C)
1	**6a**	H	8	80	244-246	240-242 [21]
2	**6b**	4-Cl	10	93	260-262	254-256 [21]
3	**6c**	3-NO_2	15	80	288-290	286-288 [21]
4	**6d**	4-OH	10	82	270-272	266-268 [22]
5	**6e**	4-Me	6	97	252-254	244-246 [23]
6	**6f**	4-NO_2	15	80	298-300	>300 [21]
7	**6g**	4-F	10	80	265-267	258-260 [21]
8	**6h**	2,3-$(OMe)_2$	15	85	275-277	new
9	**6i**	3-OMe	15	95	276-278	new

According to the proposed mechanism as shown in Scheme 3, the enolic form of pyrazolone **3´** treats with ammonium acetate to gain aminopyrazole **7**. On the other side, the carbonyl group of aldehyde is activated by SBA-Pr-SO_3H to gain **4´** which is attacked by the enolic form of pyrazolone **3´**, followed by dehydration, intermediate **9** is obtained. Subsequently, the aminopyrazole **7** attacks the intermediated **9** through a Michael addition and after tautomerization, intramolecular cyclization and dehydration, respectively, the final product **6** is produced.



Scheme 3. The plausible reaction mechanism for the synthesis of pyrazolopyridine **6a-i**

To delight the efficiency of this methodology, its results have been compared with the literature in Table 2. As it is clear, the reaction in refluxing EtOH or H_2O in the absence of a catalyst gains the product in good yields within 0.5-10 h (Table 2, entries 1-3). While by applying a catalyst, the obtained results were improved (Table 2, entries 4-5). However, SBA-Pr-SO_3H acted more efficiently on this reaction and gave the products in shorter reaction time with high yields. Furthermore, it is a metal-free and environmentally friendly catalyst, which shows the advantages of this methodology compared to the others.

Table 2. Comparing different conditions used for the synthesis of pyrazolopyridine **6**

Entry	Catalyst	Solvent	Conditions	Yield (%)	Time	Year
1	-	EtOH	Reflux	84-94	2-10 h	2011 [21]
2	-	EtOH	Reflux	60-78	4-8 h	2014 [23]
3	-	H_2O	))),* 50 °C	90-96	30-120 min	2015 [22]
4	Nano $CdZr_4(PO_4)_6$	EtOH	Reflux	80-94	40-50 min	2016 [24]
5	Nano $FeNi_3$/ILs**	EtOH	Reflux	78-92	40-55 min	2016 [25]
6	SBA-Pr-SO_3H	-	120 C	80-95	8-15 min	This work

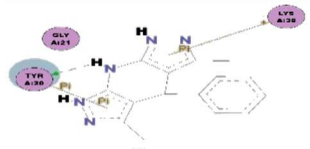
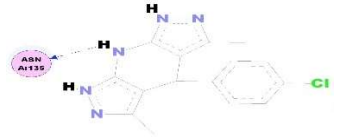
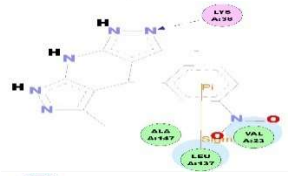
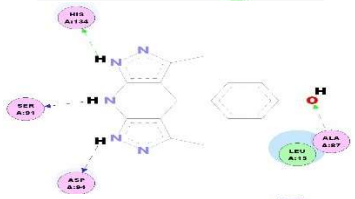
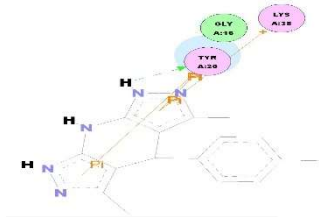
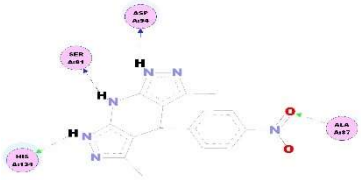
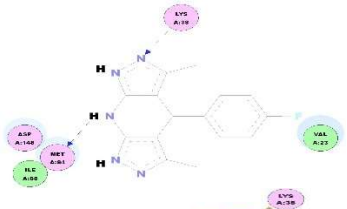
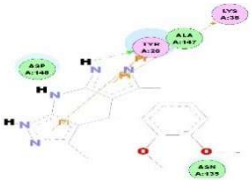
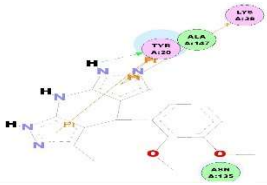
*Ultrasonic irradiation
**Ionic liquid supported on $FeNi_3$ nanoparticles

Docking results

Docking computations were used to find the possible binding conformations of all molecules. Table 3 shows the Gold Score value and the binding mode of resulting complexes.

The synthesized compounds can bind to the receptor's residues by forming hydrogen bonds and π interactions. For example, a detailed analysis of the binding mode of the best docked pose of molecule **6a** shows a hydrogen bond between NH substituent and Tyr20. Moreover, π-π and π-cation interactions can be seen with the residues Tyr20 and Lys38, respectively. Another example is compound **6i,** which shows π interactions with Tyr20 and Lys38 (Figure 1).

Table 3. The calculated Gold value for the synthesized pyrazoles

Compound	Gold Score	Interaction
6a	43.57	
6b	47.71	
6c	42.19	
6d	42.80	
6e	42.77	
6f	42.80	
6g	44.93	
6h	48.52	
6i	45.33	

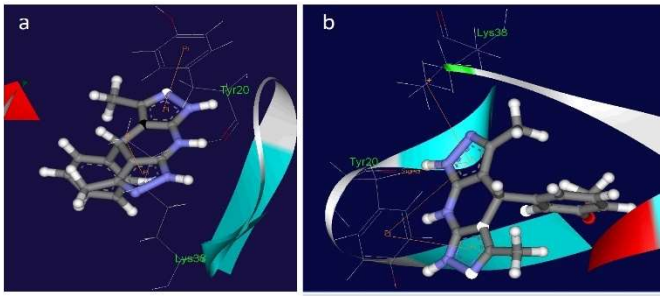


Figure 1. The best-docked conformation of 2 synthesized compounds in the binding site of the kinase domain (5OOT). (a) Molecule 5a, and (b) molecule 5i.

Preparation of SBA-Pr-SO_3H

The SBA-Pr-SO_3H was synthesized through the previously reported method.[26] BET analysis proved that the propylsulfonic acid groups were immobilized in the pores of SBA-15. The average pore diameter, surface area and pore volume of SBA-Pr-SO_3H, obtained by BET and BJH, were 440 m^2 g^{-1}, 6.0 nm and 0.660 cm^3 g^{-1}, respectively. These data are smaller than those of SBA-15 due to the functionalization of the SBA-Pr-SO_3H pores. The SEM image of SBA-Pr-SO_3H (Figure 2-left) indicated uniform particles about 1µm; the identical morphology was observed for SBA-15. It can be concluded that the morphology of the acid catalyst was saved without any changes during the process of surface modification. Besides this, the TEM image (Figure 2-right) distinguishes the parallel channels, which are similar to the pores configuration of SBA-15. This shows that the pore of SBA-Pr-SO_3H did not collapse during two-step reactions.

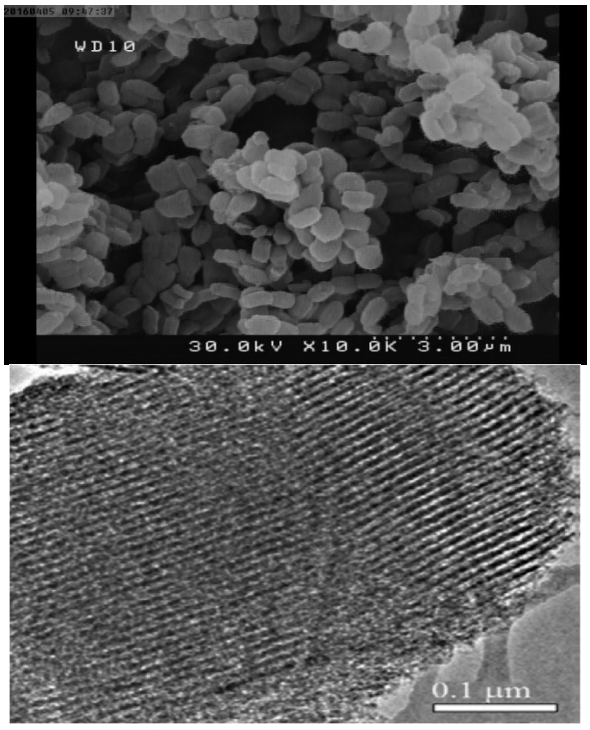


Figure 2. The SEM (left) and TEM (right) images of SBA-Pr-SO_3H.

The catalyst was washed subsequently with H_2SO_4 diluted acid solution, distilled H_2O, and then acetone, dried under vacuum and re-used four times without significant loss of activity. The reusability of the catalyst was investigated under optimized conditions in this synthesis. As shown in Figure 3, the process of recycling was completed four times and no significant decrease in activity was observed. The yields for the four runs were found to be 98%, 97%, 93%, and 90%, respectively.

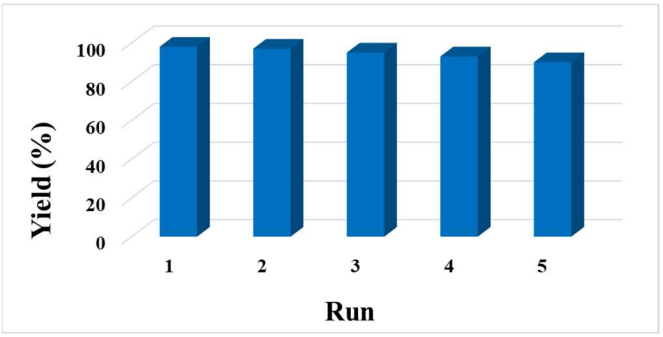


Figure 3. Reusability of SBA-Pr-SO3H in the synthesis of compound **6e**.

4. Conclusions

In this paper, the role of SBA-Pr-SO_3H in the synthesis of pyrazolopyridines was investigated. It was found that the reaction of pyrazolone, aldehydes and ammonium acetate catalyzed by SBA-Pr-SO_3H is more efficient than that catalyzed by the other nanocatalysts.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships , which could have appeared to influence the work reported in this paper.

Acknowledgements

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