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Full Paper

Sn-PILC: A novel Efficient and Recyclable Catalyst for One-pot Three Component Povarov's Inverse-electron-demand Hetero Diels-Alder Reaction for a Facile Synthesis of Tetrahydropyranoquinoline Derivatives under Neat Conditions

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Abstract: The Povarov's inverse-electron-demand hetero Diels–Alder one-pot three components reaction of aromatic aldehyde, aromatic amine with DHF has been developed using Sn-PILC as a catalyst under a neat condition which may helpful to society to get pharmacologically more active compounds. In the present study a novel series of tetrahydroquinoline **4(a-f)** were synthesized and characterized by IR, ^{1}HNMR, ^{13}CNMR, Mass spectral analysis and elemental analysis. The synthetic details and characterization results are discussed.

Keywords: Sn-PILC; Povarov reaction; aza-Diels-Alder; THQ; neat condition

1. INTRODUCTION

Tetrahydroquinolines (THQ) have gained a tremendous amount of attention in recent years because many drug molecules and pharmaceutical agents are reported to possess tetrahydroquinoline scaffold as a core structure. They exhibit interesting biological activities such as antitumor activity, anti-malarial, antiasthma, anti-allergic and psychotropic activity [1]. Many efforts have been made to synthesize substituted tetrahydroquinoline derivatives. But Povarov's inverse-electron-demand hetero Diels–Alder reaction [2], has received considerable interest among synthetic chemists for providing an easy access to substituted tetrahydroquinolines by employing aromatic aldehydes, aromatic amines, and nucleophilic olefins in the presence of suitable catalysts. A variety of catalysts have been explored for these transformations such as BF_3-EtO_2 $SbCl_3$, $NbCl_5$, $InCl_3$, silica chloride, $GdCl_3$, $CuBr_2$, prolinetriflate, lanthanide triflates, $Cu(OTf)_2$. $Yb(OTf)_3$, SmI_2 and trifluoroacetic acidetc [3].

Nevertheless, the drawbacks associated with most of these methods are the exercise of expensive catalysts, lack of reusability for the catalyst, use of excess catalyst, low product yield, longer reaction and tedious workup. Consequently simple, efficient, safer and greener catalytic system is highly demanded. Herein, we report Sn-PILC as a solid acid catalyst for one pot three component synthesis of tetrahydroquinolins. Montmorillonite clays (2:1 clay mineral) have been used as efficient solid acid catalysts for a number of organic and liquid phase reactions and offer several advantages over classic acids. Pillaring of clays by a suitable pillaring agent leads to high permanent porosity by separating the clay sheets, a two dimensional channel system comparable to that of zeolites [4]. Furthermore, particular large pillaring agents can establish channels wider than those of zeolites (5–20 A ° compared to 3–11 A°) and increasing the accessibility of reactant molecules to the interlamellar catalytic sites. Which make pillared clays suitable catalysts for the synthesis of larger molecules that cannot penetrate into the pore system of zeolites. Moreover, the pillar can exert a shape-selective effect, which controls diffusion rates of reactants and products or formation of reaction intermediates [5]. The acidic character of pillared clays is attributed to Bronstd acidity associated with the liberation of protons during dehydroxylation of the pillars and the clay sheets, while Lewis acidity is attributed to the metal oxide pillars. In contrast to the reactions using homogeneous catalysis the experimental conditions are non-polluting [6-7].

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In considering the factor discussed above and as part of our ongoing research on the chemical synthesis and biological properties of tetrahydroquinoline derivatives, it is proposed to synthesize of tetrahydropyranoquinoline derivatives by using Sn-PILC as a catalyst via one-pot three components Aza-Diels-Alder reactions under neat conditions which may helpful to society to get pharmacologically more active compounds. In the present study a novel series of tetrahydroquinoline were synthesized and characterized by means of IR, ^{1}HNMR, ^{13}CNMR, Mass spectral analysis and elemental analysis.

2. MATERIAL AND METHODS

Experimental

General procedure for the synthesis of tetrahydroquinoline derivatives

A mixture of aromatic aldehyde 1 mmol, and aniline 1 mmol was taken into a 25mL round bottom flask Then, both 3,4-dihydrofuran (2 mmol), and Sn-PILC catalyst (10 wt% with respect to aldehyde) were added successively into the above reaction mixture was refluxed for an appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by filtration and usual work-up procedure was followed to obtain the crude products. The products eluted in ethyl acetate/hexane. At the onset of this work 4-chlorobenzaldehyde, 4-chloroaniline, and 3, 4-dihydropyran was chosen as model reaction to optimize the reaction parameters (Scheme 1).

The chemicals used were of laboratory grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra (KBr disks) were recorded on Brukar FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Brukar DRX-300 and 400 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on a Brukar DRX-75 and 100 MHz NMR in $CDCl_3$/DMSO-d6 using (TMS) as an internal standard and chemical shifts are in δ(ppm). High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument. The purity of each of the compound was checked by thin-layer chromatography (TLC) using silica-gel, $60F_{254}$ aluminium sheets as an adsorbent, and visualization was accomplished by iodine/ultraviolet light.

Characterization

2,3,3a,4,5,9b-hexahydro-4-(4-nitrophenyl)furo[3,2,-c]quinoline (4a): White needles (EtOH) (this compound was prepared by the reaction aniline, p-nitrobenzaldehyde and DHF in the presence of Sn-PILC catalyst. It was obtained as a white solid); mp 218–220 ^{0}C; IR (KBr): 3,190, 3,010, 1,680, 1520, 1,420, and 1340 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6) δ = 7.06-7.36 (m, 4H, Ar-proton), 6.09-6.90 (m, 4H, Ar-proton), 5.10 (d, 1H, -CH-quinoline proton), 4.59 (d, 1H, NH proton), 3.77 (m, 1H, N-CH-C proton), 3.21-3.50 (m, 2H, O-CH_2-THF proton), 2.35 (m, 1H, C-CH-c proton), 1.68-1.93 (m, 2H, C-CH_2-C proton). ^{13}CNMR (100 MHz, DMSO-d6) δ = 112.11, 112.47, 116.54, 125.99, 127.14, 127.61, 128.74, 129.94, 131.09, 130.79, 133.54, 136.75 (ar-C), 74.52, 65.87, 44.41, 24.14 (THF-C), 56.19 (βC-quinoline). HRESIMS m/e (pos): 296.3201 [M $^{+}$] for $C_{17}H_{16}N_2O_3$

8-Chloro-4-(4-chlorophenyl)-2,3,3a,4,5,9b hexahydrofuro[3,2,-c]quinolone (4b): White needles (EtOH) (this compound was prepared by the reaction p-chloroaniline, p-chlorobenzaldehydeand DHF in the presence of Sn-PILC catalyst. It was obtained as a white solid); mp 213–214 ^{0}C; IR (KBr): 3,150, 3,012, 1,690, 1,425, and 610 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6) δ = 7.06-7.40 (m, 4H, Ar-proton), 6.09-6.70 (m, 3H, Ar-proton), 5.10 (d, 1H, -CH-quinoline proton), 4.59 (d, 1H, NH proton), 3.77 (m, 1H, N-CH-C proton), 3.21-3.50 (m, 2H, O-CH_2-THF proton), 2.35 (m, 1H, C-CH-c proton), 1.68-1.93 (m, 2H, C-CH_2-C proton). ^{13}CNMR (100 MHz, DMSO-d6) δ = 112.15, 112.45, 116.44, 125.99, 127.14, 127.61, 128.74, 129.94, 130.09, 130.79, 133.54, 136.85 (ar-C), 74.55, 65.89, 44.41, 24.16 (THF-C), 56.23 (βC-quinoline). HRESIMS m/e (pos): 320.0609[M $^{+}$] for $C_{17}H_{15}Cl_2NO$.

4-(3–bromo–4-methoxyphenyl)-8-Chloro-2,3,3a,4,5,9b-hexahydrofuro [3,2-c]quinoline (4c): Pale yellow needles (EtOH) (this compound was prepared by the reaction p-chloroaniline, 4-methoxy-3-bromobenzaldehyde DHF in the presence of Sn-PILC catalyst. It was obtained as a Pale yellow); mp211–212 ^{0}C; IR (KBr : 3,070, 3,010, 2995, 1,650, 1435 and 610 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6) δ = 6.61-7.38 (m,3H,Ar-proton), 6.36-6.98 (m, 3H, Ar-proton), 5.10 (d, 1H, -CH-quinoline proton), 4.7 (d, 1H, NH proton), 3.89 (m, 1H, N-CH-C proton), 3.77 (s, 3H, ali. proton), 3.67-3.72 (m, 2H,O -CH_2-THF proton), 2.84 (m, 1H,C -CH-C proton), 1.68-1.93 (m, 2H,C -CH_2-C proton). ^{13}CNMR (100 MHz, DMSO-d6) δ =112.11, 112.47, 116.54, 125.99, 127.14, 127.61, 128.74, 129.94, 130.09, 130.79, 133.54, 136.85 (ar-C), 74.55, 65.89, 44.41, 24.14 (THF-C), 56.23 (βC-quinoline), 54.49 (ali.-C) HRESIMS m/e (pos): 394.0124[M $^{+}$] for

$C_{18}H_{17}BrClNO_2$.

8-Chloro-2,3,3a,4,5,9b-hexahydrofuro4-(4-nitrophenyl)-[3,2-c]quinoline (4e): Off white needles (EtOH) (this compound was prepared by the reaction p-chloroaniline, p-nitrobenzaldehyde DHF in the presence of Sn-PILC catalyst. It was obtained as an off white solid); mp213–214 ^{0}C; IR (KBr): 3,150, 3,012, 1,690, 1,425, and 610 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6) δ = 8.14 (d, 2H, J= 6Hz, Ar-proton), 7.38 (d, 2H, J=6Hz, Ar-proton), 6.36-6.98 (m, 3H, Ar-proton), 5.02 (d, 1H, -CH-quinoline proton), 4.0 (d, 1H, NH proton), 3.89 (m, 1H, N-CH-C proton), 3.7-3.8 (m, 2H, O-CH_2-THF proton), 2.84 (m, 1H, C-CH-c proton), 1.68-1.93 (m, 2H, C-CH_2-C proton). ^{13}CNMR (100 MHz, DMSO-d6) δ = 112.15, 112.45, 116.44, 125.99, 127.14, 127.61, 128.74, 129.94, 130.09, 130.79, 133.54, 136.85 (ar-C), 74.55, 65.89, 44.41, 24.16 (THF-C), 56.23 (βC-quinoline). HRESIMS m/e (pos): 331.0807[M $^+$] for $C_{17}H_{15}ClN_2O_3$.

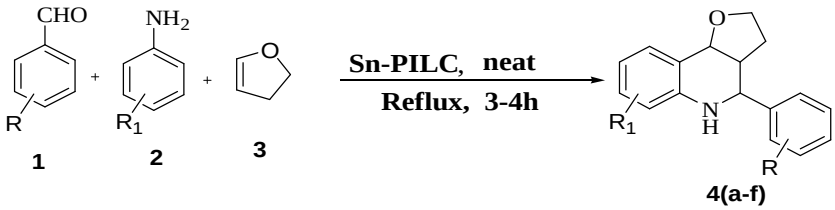
8-Fluro-2,3,3a,4,5,9b-hexahydro-4-(naphthalene-1-yl)-[3,2-c]quinoline (4f): Off white needles (EtOH) (this compound was prepared by the reaction p-fluroaniline, *p*-napthaldehyde DHF in the presence of Sn-PILC catalyst. It was obtained asoff white solid); mp233–234 ^{0}C; IR (KBr) : 3,150, 3,012, 1,690, and 610 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6) δ = 7.23-8.04 (m, 10H, Ar-proton), 5.25 (d, 1H, -CH-quinoline proton), 3.93 (d, 1H, NH proton), 3.85-3.91 (m, 1H, N-CH-C proton), 3.65-3.71 (m, 2H, O-CH_2-THF proton), 2.95-3.10 (m, 1H, C-CH-C proton), 1.85-2.15 (m, 2H, C-CH_2-C proton). ^{13}CNMR (100 MHz, DMSO-d6) δ = 112.15, 112.45, 116.44, 125.99, 127.14, 127.61, 128.74, 129.94, 130.09, 130.79, 133.54, 136.85 (ar-C), 74.55, 65.89, 44.41, 24.16 (THF-C), 56.23 (βC-quinoline). HRESIMS m/e (pos): 319.3707 [M $^+$] for $C_{21}H_{18}FNO$.

Electronic supplementary information available (NMR ^{1}H of compounds 4b, 4c, 4d and 4f): ***http://www.orbital.ufms.br/index.php/Chemistry/article/downloadSuppFile/801/191***

3. RESULTS AND DISCUSSION

In our initial studies synthesis of tetrahydropyranoquinoline through one-pot three component Povarov's inverse-electron-demand hetero Diels–Alder reaction of 4-chlorobenzaldehyde, 4-chloroaniline, and 3,4-dihydropyran was chosen as model reaction to optimize the reaction parameters by using Sn-PILC catalyst.

Scheme 1



Sn-PILC was found to be the suitable catalyst which shows excellent catalytic activity without any byproduct formation. Using this catalyst under neat condition the model reaction furnished 88%of the desired product within 3 h at the expense of catalytic amount of Sn-PILC (Scheme 1). The optimum amount of the catalyst in this one-pot three component reaction, was found to be 5 mg by lowering the catalyst amount the desired product was obtained in lower yield, while as increased catalyst amount above has no significant effect on reaction rate and isolated yield of product. XRD pattern of catalyst Sn-PILC shown in graph (Figure 1) which indicates crystalline nature of the catalyst as well as the catalyst Sn-PILC is thermally stable, as it is evident from Figure 2.

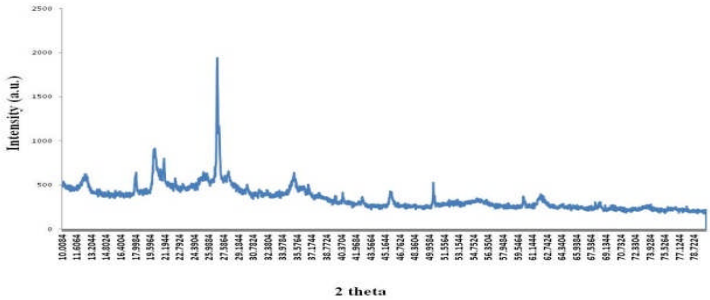


Figure 1. XRD of catalyst Sn-PILC.

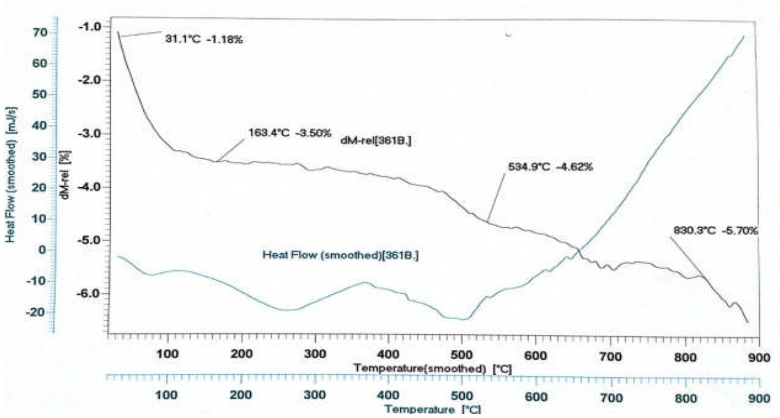


Figure 2. TGA-DTA of catalyst Sn-PILC.

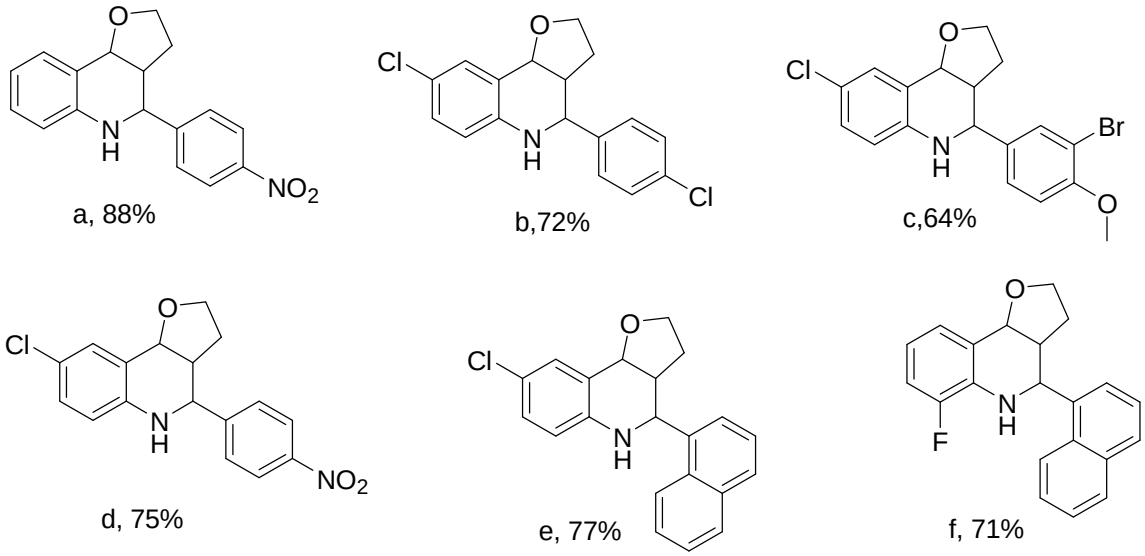


Figure 3. Sn-PILC catalyzed synthesis of THQ with isolated yield.

Reusability of the catalyst Sn-PILC

Recovery and reusability of Sn-PILC was studied for the model reaction. In this experiment the catalyst was separated by centrifuging the reaction mixture after diluting with ethyl acetate. From this experiment it was proved that the catalyst can be reused several times without any appreciable lost in activity and generates the products with purities similar to those obtained in the first run. The catalyst reusability for 5 cycles is shown in Figure 4.

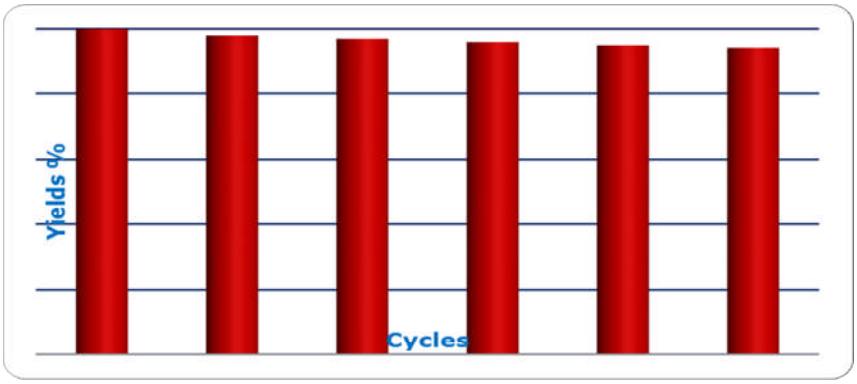


Figure 3. Reusability of cycles of the catalyst.

The IR, ^{1}HNMR and ^{13}CNMR data of synthesized compound confirm the formation of substituted tetrahydropyranoquinoline and H*igh Resolution* Mass spectra confirmed the molecular mass of the synthesized derivatives.

4. CONCLUSION

Substituted tetrahydropyranoquinoline derivatives has been successfully and congenital prepared by using Sn-PILC as catalyst via one-pot three component Povarov's inverse-electron-demand hetero Diels–Alder reaction under neat conditions which is the important class of heterocyclic compounds with a diverse pharmacological activity.

5. ACKNOWLEDGEMENTS

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