

Silica Supported V_2O_5 as a Catalyst Promoted the Synthesis of 4h-Pyrans Through Multicomponent Reaction Under Solvent Free Conditions

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Abstract

Silica supported V_2O_5 was synthesized and elucidated by X-ray diffraction; using scanning electron microscopy and Fourier transform infrared spectroscopy. From the data obtained crystalline phase of V_2O_5 overlapped over the silicate amorphous matrix. V_2O_5/SiO_2 has been used as an efficient and eco-friendly catalyst in the synthesis of 4H-pyran derivatives. A series of 2-amino-3-cyano-4H-pyran derivatives was synthesized through one-pot reaction of ethylacetoacetate (EAA), malononitrile and aldehydes. In the presence of catalytic amount of V_2O_5/SiO_2 the reactions occurred under stirring at $80^\circ C$ temperature in solventless conditions.

Keywords: SiO_2 ; V_2O_5 ; One-pot; Multicomponent; Malononitrile; 4H-pyran

Introduction

4H-Pyran derivatives have been considered as a main unit in most oxygen-containing heterocyclic compounds. 4H-Pyrans are synthesized through one-pot Knoevenagel-Michael cyclo-condensation reaction. In addition, they have been attracted a great deal of interest related to their biological and pharmaceutical properties such as antibacterial, antitumor, antitubercular, pigments, antiviral and spasmolytic activities [1]. So that, a lot of researchers have been developed many protocols for 4H-Pyrans synthesis by reacting aldehydes, malonitrile and 1,3-dicarbonyl compounds using various catalysts, such as $SnCl_2/SiO_2$, MgO, hexadecyldimethylbenzyl ammonium bromide, potassium phthalimide, silica nanoparticles and silica-bonded N-propylpiperazine sodium n-propionate [2].

Multicomponent reaction (MCR) or multicomponent process (MCP) are considered as one of the most important synthetic methodology in which three or more reactants attached together in a one-pot reaction to form targeted products. The

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characteristic advantage of MCRs is that the targeted products contain nearly all portions of substrates, generating chiefly no by-products. That makes MCRs really ideal, green and eco-friendly reactions system. Targeted products can be obtained in one-pot with much less steps. Therefore, MCRs have been attracted much attention in many research fields, such as discovery of key compounds in medicinal chemistry, or combinatorial chemistry [3,4].

The heterogenous catalytic reactions have played important role in developing organic synthesis. Because of their, operational simplicity, environmental compatibility, reusability, non-toxicity, economic and easy removal from reaction mixture [5,6], so we have presented the following catalytic system from V_2O_5/SiO_2 in the synthesis of some important 4H-pyran."

Experimental

Instruments and analysis

Melting points were determined by open capillary method and were uncorrected. IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer using KBr pellet. 1H NMR spectra were obtained on a Bruker instrument (400 MHz) and ^{13}C NMR spectra were (100 MHz) recorded in DMSO- d_6 as solvent with TMS as internal standard. Chemical shifts are reported in ppm. Mass spectra were measured using high resolution GC–MS (DFS) thermo spectrometers with EI (70 EV). Molecular ion peak was observed in agreement with molecular weight of respective compound. Reactions have been monitored by thin layer chromatography on 0.2-mm pre-coated plates of silica gel G60 F254 (Merck).

Catalyst preparation

To a suspension of SiO_2 (for column chromatography, mesh 70-230, 0.06-0.2 mm, 2 g) in 50 ml $CHCl_3$, V_2O_5 (1 g) was added. The mixture stirred at room temperature for 90 min. The solvent was evaporated at room temperature overnight to obtain a brown solid of 50% (W/W) V_2O_5/SiO_2 . The catalyst was characterized using XRD diffraction scans and collective FTIR spectra (FIG.1).

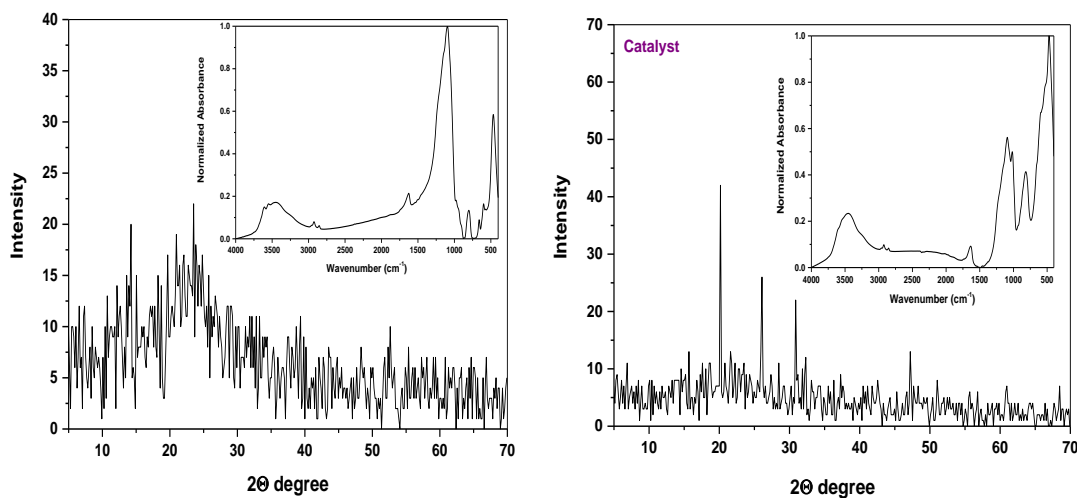


FIG.1. XRD diffraction scans and collective FTIR spectra of received silica and vanadium dioxide before the catalyst preparation and after interaction.

General procedure for the preparation of 2-amino-3-cyano-4H-pyrans derivatives (2a-2m).

A mixture of aldehyde 1a-1 (0.5 mmol), malononitrile (0.5 mmol), ethyl acetoacetate (0.5 mmol) and catalyst (0.5 mmol) was placed in a 25 mL round-bottom flask equipped with a condenser. The mixture was stirred at 70 °C, under solvent-free conditions, until the consumption of the substrates. The reaction was monitored by TLC. After cooling, the catalyst was removed from reaction mixture by dissolving in hot ethanol and filtration. The product mixture was directly submitted to recrystallization from water/ethanol (90:10), affording the corresponding pure 4H-pyran derivatives **2a-2m**.

Data of selected compounds:

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (4a): White Solid, m.p. 190-192 °C; IR (KBr): ν_{max} : cm^{-1} ; 3409, 3337 (NH₂), 2191 (C≡N), 1686 (CO), 1619 (C=C). ¹H NMR (500 MHz, CDCl₃) δ = 1.27 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 2.23 (s, 3H, CH₃), 4.22 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.29 (s, 1H, CH), 4.59 (s, 2H, NH₂, D₂O-exchangeable), 6.76–7.16 (m, 5H, Ar-H) ppm. MS (EI) [M]⁺ = 284. Anal. calcd. for C₁₆H₁₆N₂O₃ (284.32): C=67.59; H, 5.67; N, 9.85. Found: 67.54; H, 5.61; N, 9.80.

Ethyl 6-amino-5-cyano-2-methyl-4-(3-(nitrooxy)phenyl)-4H-pyran-3-carboxylate (2h): Yellow crystals; m.p. 176–178 °C. IR (KBr) (ν_{max} : cm^{-1}); 3406, 3333 (NH₂), 2193 (C≡N), 1688 (CO), 1610 (C=C). ¹H NMR (500 MHz, CDCl₃) δ = 1.29 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 2.24 (s, 3H, CH₃), 4.2 (q, J = 7.2 Hz, 2H, CO₂CH₂CH₃), 4.29 (s, 1H, CH), 4.59 (s, 2H, NH₂, D₂O-exchangeable), 6.76–7.16 (4H, Ar-H) ppm. MS (EI) [M]⁺ = 345. Anal. calcd. for C₁₆H₁₅N₃O₆ (345.31): C=55.65; H, 4.38; N, 12.17. Found: 55.60; H, 4.31; N, 12.10.

Ethyl 6-amino-5-cyano-4-(4-(dimethylamino) phenyl)-2-methyl-4H-pyran-3-carboxylate (4i): Yellow crystals; m.p. 184–186 °C. IR (KBr) (ν_{max} : cm^{-1}); 3410, 3343 (NH₂), 2209 (C≡N), 1669 (CO), 1630 (C=C). ¹H NMR (500 MHz, CDCl₃) δ : 1.24 (t, J = 7.2 Hz, 3H, CH₃CH₂), 2.95 (s, 6H, N(CH₃)₂), 2.28 (s, 3H, CH₃), 4.15 (q, J = 7.2 Hz, 2H, CH₃CH₂), 4.92 (s, 1H, CH), 5.22 (s, 2H, NH₂), 7.13 (d, J = 7.2 Hz, 2H, Ar-H), 7.41 (d, J = 7.2 Hz, 2H, Ar-H) ppm. MS (EI) [M]⁺ = 327. Anal. calcd. for C₁₈H₂₁N₃O₃ (327.38): C = 66.04; H, 6.47; N, 12.84. Found 66.00; H, 6.41; N, 12.78.

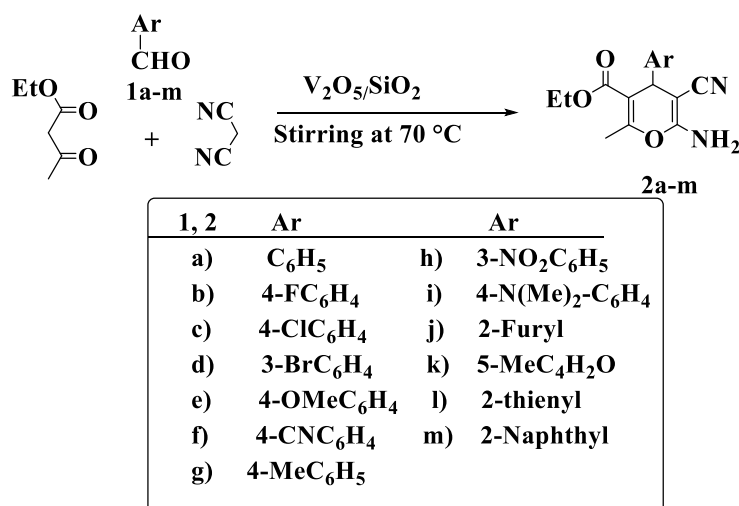
Results and Discussions

The catalytic reactions Study attracted our group interest [7-10] and so we presented this work. Silica supported V₂O₅ was tested as an efficient and ecofriendly catalyst in the synthesis of 4H-pyrans. Firstly, the reaction was optimized starting from measure the effect of catalyst molar ratio. As a model example we mixed benzaldehyde, malononitrile and EAA under solvent less condition and different ratios (5,10,15 mol%) of the prepared catalyst after the appropriate time the products 2a was obtained in the (60,81,82 yield %) respectively. And so, the reaction proceeds well in the presence of 10 mol% of V₂O₅/SiO₂ catalyst. Also, the temperature degree was examined as in **TABLE 1**. Thus, the optimized reaction conditions include the use of 10 mol% of the silica supported V₂O₅ catalyst at 70 °C.

TABLE 1. Effect of temperature on synthesis of 2a.

	Temp.(°C)	Time (h)	Yield (%)
1	r.t.	12	70
2	50	8	76
3	60	7	78
4	70	4	81
5	80	6	82
6	90	6	82

The reaction was extended by the synthesis of a series from 2-amino-3-cyano-4H-pyran derivatives 2a–2m (**TABLE 2**) from a diversity of aromatic aldehydes 1a-1m. The efficacy of the catalyst was examined on all multicomponent reactions with malononitrile and ethyl acetoacetate to afford tetrahydrobenzo [b] pyrans 2a-2m in good to excellent yields (Scheme 1). All reactions were done under solvent free and 70°C conditions. The reaction time ranged between 1–6 h to produce targeted products. Various aldehydes 1, including electron-donating and electron-withdrawing groups, and from this we noticed that the presence of electron releasing group give less effect in improving the reaction time and the reaction yield compared with the aromatic aldehydes bearing electron-withdrawing groups. As shown in (**TABLE 2**) nitro and halogens that act as electron withdrawing groups give more good yields than those substituted by electron-donating groups such as methoxy or methyl. The final products were purified by classical recrystallization method in ethanol as solvent then dried under vacuum oven conditions. The structures were confirmed by compared with the literatures melting points also the products were further confirmed by their spectroscopic data (FT-IR, 1H NMR and Mass data).



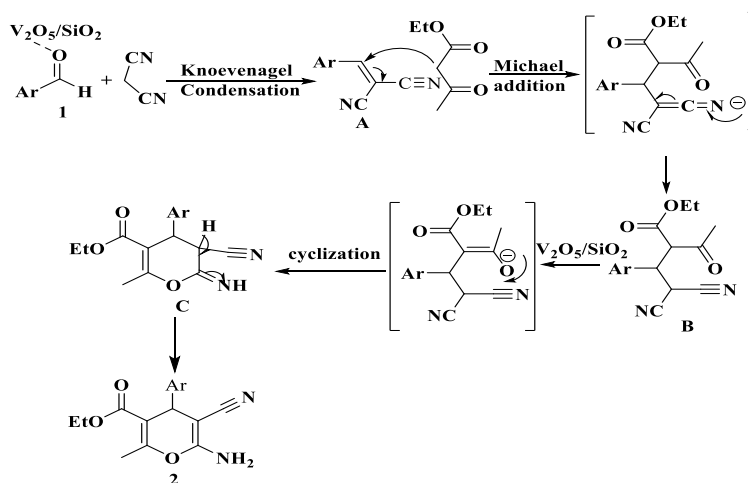
Scheme 1. Synthesis of ethyl 6-amino-4-phenyl-5-cyano-2-methyl-4H-pyran-3-carboxylates 2a-m via multicomponent reaction.

TABLE 2. Synthesis of various 4H-pyrans.

Entry	R	Products	Time (hr)	Yield (%)	Mp (°C)	
					Obs	Lit
1	C ₆ H ₅ -	2a	4	81	190-192°C	192-194°C ⁽¹³⁾
2	4-F-C ₆ H ₄ -	2b	2	82	162-164°C	158-160°C ⁽¹²⁾
3	4-Cl-C ₆ H ₄ -	2c	2.5	85	174-176°C	170-172°C ⁽¹²⁾
4	3-Br-C ₆ H ₄ -	2d	3	80	160-162°C	156-158°C ⁽¹³⁾
5	4-MeO-C ₆ H ₄	2e	6	80	144-146°C	198-200 ⁽¹²⁾
6	4-CN-C ₆ H ₄ -	2f	2	88	156-158°C	156-158°C ⁽¹³⁾
7	4-Me-C ₆ H ₅ -	2g	5	76	177-175	177-179 ⁽¹²⁾
8	3-NO ₂ -C ₆ H ₅ -	2h	3	90	176-178°C	176-178°C ⁽¹³⁾
9	4-N(Me) ₂ -C ₆ H ₄	2i	4	75	184-186	181-183 ⁽¹⁴⁾
10	Furyl-	2j	6	65	212-114°C	216-118°C ⁽¹³⁾

11	5-Me-furul-	2k	6	70	200-202°C	196-198°C ⁽¹⁵⁾
12	2-thienyl	2l	6	60	175-177°C	175-177°C ⁽¹³⁾
13	2-Naphthyl	2m	6	57	154-156°C	150-152°C ⁽¹⁴⁾

The suggested mechanism based on the idea of common reactions like Michael addition, Knoevenagel and ThorpeZiegler reaction on the way of synthesis the targeted product 2. Firstly, the reaction was suggested to ongoing by electrophilic activation of carbonyl group in aldehyde by the prepared catalyst V_2O_5/SiO_2 to increase its electrophilicity. The aryl aldehydes and malononitrile formed corresponding arylidene (Knoevenagel product) A, which undergoes nucleophilic attack from EAA anion to give the Michael adduct B, then an intermolecular cyclization occurs through the formation of [1,3] sigmatropic proton shift of the iminopyrans C and this converted into a stable 2-amino-4H-pyran ring system. In conclusion, the synthesis of 2-amino 4H-pyran ring considered as regioselective reaction (Scheme 2 explaining the plausible reaction mechanism) [11-15].



Scheme 2. Suggested reaction mechanism

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