An Efficient Synthesis of Tetrahydrobenzo[*b*]pyran Derivatives Using Sulfonic Acid Functionalized Silica as an Efficient Catalyst

GHODSI MOHAMMADI ZIARANI^{§*}, ALIREZA ABBASI,
ALIREZA BADIEI and ZEINAB ASLANI[§]

[§]Department of Chemistry
Alzahra University, Vanak Square, Tehran, Iran
School of Chemistry, College of Science
University of Tehran, Tehran, Iran
gmziarani@gmail.com

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Abstract: Tetrahydrobenzo[*b*]pyran derivatives were efficiently synthesized by the reaction of appropriated aromatic aldehydes, malononitrile and dimedone in the presence of SiO₂-Pr-SO₃H as a nanoporous and recoverable solid acid catalyst, in good to excellent yields. Single crystal x-ray analysis conclusively confirmed the structure of the 2-amino-3-cyano-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-4*H*-5,6,7,8-tetrahydro-benzopyran.

Keywords: Tetrahydrobenzo[*b*]pyran, Dimedone, Aromatic aldehyde, Malononitrile, Sulfonic acid functionalized silica.

Introduction

Benzopyrans and their derivatives, in particular have shown several biological and pharmacological properties, such as spasmolytic, diuretic, antianaphylactin, antisterility and anticancer agents¹. The polyfunctionalized benzopyrans were used as cosmetics, pigments and biodegradable agrochemicals². Due to their applications, the syntheses of heterocyclic derivatives of these ring systems have great importance in medicinal chemistry and organic synthesis. Strategies for the synthesis of these compounds have varied from one-pot to multi-step approaches³. The simplest method involves one-pot, three-component condensation of malononitrile, an aldehyde and dimedone in different conditions. Various catalysts⁴ such as Na₂SeO₄, hexadecyldimethylbenzyl ammonium bromide⁵, NaBr⁶, tetramethyl ammonium hydroxide (CH₃)₄ N⁺OH⁻,⁷ TEBA,⁸ KF-montmorillonite⁹, KF-alumina¹⁰, organocatalysts¹¹, acetic acid¹², diammonium hydrogen phosphate¹³ and hexadecyltrimethyl

ammonium bromide¹⁴ have been used in this synthesis. Each method has own advantages and disadvantages, however, because of wide range of biological activities of Tetrahydrobenzo[*b*]pyran derivatives, we would like to explore the catalytic activity of the silica based sulfonic acid (SiO₂-Pr-SO₃H) as heterogenous nanoporous acid catalyst towards the synthesis of these products.

Experimental

IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The ¹H NMR (250MHz) was run on a Bruker DPX, 250 MHz. x-ray crystallography were collected at ambient temperature by means of a STOE IPDS II, using graphite-monochromated Mo K α radiation ($\lambda = 0.71073$ Å). Weight change curve in nitrogen were measured on a TA instrument TGA Q50 V6.3 with maximum heating rate of 20 °C/min. Nitrogen adsorption and desorption isotherms were measured at -196 °C using a Japan Belsorb II system after the samples were vacuum dried at 150 °C overnight.

Preparation of catalyst

To SiO₂ (20 g) in dry toluene (50 mL), (3-mercaptopropyl)trimethoxysilane (25 mL) was added and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropylsilica which was washed with acetone and dried. 3-mercaptopropylsilica was oxidized with H₂O₂ (excess) in methanol (20 mL) for 24 h at room temperature and then the mixture was filtered and washed with H₂O and acetone to obtain SiO₂-Pr-SO₃H catalyst. The modified SiO₂-Pr-SO₃H was dried and used as solid acid catalyst in the synthesis of tetrahydrobenzo[*b*]pyran derivatives.

*General procedure for the synthesis of tetrahydrobenzo[*b*]pyran derivatives*

A mixture of appropriated aromatic aldehydes (1 mmol), malononitril (1 mmol), dimedon (1 mmol) and catalyst (SiO₂-Pr-SO₃H) (0.03 g), in water (4 mL) and ethanol (1 mL) were refluxed for appropriated time as mentioned in Table 2. The progress of reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to room temperature; the crude product was filtered off and washed with H₂O. Then the resulting solid was dissolved in hot ethanol, after filtration of catalyst and cooling of the filtrate, the pure crystals of tetrahydrobenzo[*b*]pyran derivatives will be obtained. The recovered catalyst can be washed consequently with diluted acid solution, water and then acetone. After drying, it can be reused without noticeable loss of reactivity. Spectral data for selected compounds:

2-Amino-4-(4-Chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzopyran (4b)

IR (KBr): $\nu_{\max}$ =3390, 3290, 3180, 2190, 1660, 1584 cm⁻¹. ¹H NMR (250 MHz, DMSO-d₆): δ = 1.08 (s, 3H, CH₃), 1.12 (s, 3H, CH₃), 2.26 (s, 2H, CH₂-8), 2.46-2.48 (m, 2H, CH₂-6), 4.43 (s, 1H, CH-4), 6.58 (s, 2H, NH₂), 7.18-7.28 (m, 4H, ArH) (ppm).

2-Amino-3-cyano-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-4H-5,6,7,8-tetrahydrobenzopyran (4c)

IR (KBr): $\nu_{\max}$ = 3380, 3323, 3182, 2188, 1676, 1634, 1490, 1405, 1365, 1216, 1032, 830 cm⁻¹. ¹H NMR (250MHz, DMSO-d₆): δ = 0.89 (s, 3H, CH₃)-1.05 (s, 3H, CH₃), 2.06-2.28 (d.d, 2H, CH₂-8), 2.50 (2H, CH₂-6), 4.20 (s, 1H, CH-4), 7.07 (s, 2H, NH₂), 7.91- 7.157 (d, 2H, Ar-H), 7.36-7.33 (d, 2H, Ar-H) ppm.

2-Amino-3-cyano-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-4H-5,6,7,8-tetrahydro benzopyran (4d)

IR (KBr): $\nu_{\max}$ = 3426, 3329, 2956, 2191, 1673, 1639, 1601, 1510, 1462, 1439, 1321, 1248, 1206, 1140, 1032, 976 cm^{-1} . ^1H NMR (250 MHz, DMSO- d_6): δ = 1.02 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.16-2.20 (q, AB, 2H, CH_2 -8), 2.28 (s, 3H, 3H), 2.47 (br, 2H, CH-6), 4.24 (s, 1H, CH-4), 6.16 (s, 2H, NH_2), 7.06 (m, 4H, Ar-H) ppm.

2-Amino-3-cyano-7,7-dimethyl-4-(4-methoxyphenyl)-5-oxo-4H-5,6,7,8-tetrahydro benzopyran (4e)

IR (KBr): $\nu_{\max}$ = 3375, 3318, 2962, 2193, 1684, 1655, 1605, 1508, 1368, 1252, 975 cm^{-1} . ^1H NMR (250 MHz, DMSO- d_6): δ = 0.94 (s, 3H, CH_3)-1.03 (s, 3H, CH_3), 2.05-2.27 (dd, 2H, CH_2 -8), 2.49-2.50 (brs, 2H, CH-6), 3.71 (s, 3H, OCH_3), 4.11 (s, 1H, CH-4), 6.82-6.085 (d, 2H, Ar-H), 6.96 (s, 2H, NH_2), 7.06-7.032 (d, 2H, Ar-H) ppm.

Crystallography

The data were collected at ambient temperature by means of a STOE IPDS II, using graphite-monochromated Mo $\text{K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). No intensity variations due to decomposition of the crystals were observed. Selected crystallographic and experimental details are summarized in Table 1. X-Area program packages were used for indexing and integrating the single crystal reflections¹⁵. Absorption corrections become important if the crystal is very anisotropic, *i.e.* a very thin plate. Due to a low absorption coefficient (0.081 mm^{-1}), absorption correction is not required and the current case we neglect performing the correction¹⁶. The structure was solved by direct methods using SHELXS-97, and refined using full-matrix least-squares method on F^2 , SHELXL-97¹⁷. Molecular graphics were drawn by Diamond programs¹⁸ and PLATON¹⁹ software was used to prepare materials for publication. All non-hydrogen atoms were refined anisotropically. Aromatic, methane and amine H atoms were placed in calculated positions and constrained to ride on their parent atoms, with $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C/N})$ and for methyl group $U_{\text{iso}}(\text{H}) = 1.5 U_{\text{eq}}(\text{C})$.

Results and Discussion

The synthesis of tetrahydrobenzopyran derivatives were achieved by the three-component condensation of an aromatic aldehyde (1 mmol), malonitrile (1 mmol) and dimedone (1 mmol) in the presence of 0.02 g sulfonic acid functionalized silica in the mixture of ethanol and H_2O (1:4) at reflux to give products in excellent yields (Scheme 1). For optimization of reaction conditions, 2-amino-3-cyano-7,7-dimethyl-4-(phenyl)-5-oxo-4H-5,6,7,8-tetrahydro-benzopyran (**4a**) was synthesized in different solvents. As shown in Table 1, the mixture of water and ethanol (4:1) was the most effective solvent for this reaction. The key advantages of this condition are the very short reaction time and high yield of products.

Scheme 1

Table 1. Solvent optimization in the synthesis 2-Amino-3-cyano-7,7-dimethyl-4-(phenyl)-5-oxo-4H-5,6,7,8-tetrahydro-benzopyran (**4a**)

Entry	Solvent	Time	Yield, %
1	H ₂ O	5 h	97
2	EtOH	180 min	78
3	EtOH/H ₂ O (1:1)	120 min	97
4	EtOH/H ₂ O (1:4)	15 min	97

Yields are related to isolated pure products

In the current study, tetrahydrobenzo[*b*]pyran derivatives were prepared according to the one-pot three-component Tandem Knoevenagel-cyclocondensation reaction. As it is shown in Scheme 2, the solid acid catalyst, firstly protonates the aldehyde carbonyl group, which then condenses with malononitrile via the Knoevenagel type coupling to produce the α -cyanocinnamionitrile derivatives (**5**). Michael addition reaction of **5** with dimedone followed by rearrangement and cyclization give rise to 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzopyran (**4**) in good to excellent yield.

Scheme 2

The results were shown in Table 2. The high yields of reaction are attributed to the effect of nano pore size about 5.9 nm of solid acid catalyst, which could act as nanoreactor. The products were characterized by comparison of their melting points, ¹H NMR and IR spectra with the corresponding values from the literatures. Single-crystal x-ray analysis of **4d** was conclusively confirmed by the structure of the isolated products. An ORTEP diagram of **4d** is shown in Figure 1.

Figure 1. ORTEP structure of the compound **4d**, showing 50% probability ellipsoids H atoms are shown as circles of arbitrary radii

The results in Table 2 show that, SiO₂-Pr-SO₃H is an efficient heterogeneous nanoporous solid acid in this reaction because of high yield of reaction. Karimi²⁰ and Paul²¹ have used the SiO₂-Pr-SO₃H catalyst to carry out variety of reactions. It has been used in organic synthesis by our group²².

Table 2. SiO₂-Pr-SO₃H catalyzed the synthesis of tetrahydrobenzo[*b*]pyran derivatives

Entry	Aldehyde	Product	Time, min	Yield %	m.p.	m.p. (Lit)
1	Ph	4a	15	97	230-232	228-230 ⁷
2	4-ClC ₆ H ₄	4b	20	90	237-239	239-241 ^{5a}
3	3-NO ₂ C ₆ H ₄	4c	15	90	210-212	213-214 ^{5a}
4	4-CH ₃ C ₆ H ₄	4d	25	98	214-216	220-222 ^{5a}
5	4-OCH ₃ C ₆ H ₄	4e	25	98	190-192	196-198 ^{5a}
6	2,4-Cl ₂ C ₆ H ₄	4f	20	92	118-119	116-118 ^{14b,c}
7	4-NO ₂ C ₆ H ₄	4g	15	93	176-178	176-178 ^{5a}
8	3,4-(OCH ₃) ₂ C ₆ H ₄	4h	35	85	170-172	170-173 ^{5b}
9	4-OHC ₆ H ₄	4i	30	90	205-207	206-208 ⁷

For preparation of the catalyst, at first, the surface of silica was grafted by (3-mercaptopropyl)trimethoxysilane and then the thiol functionalities were oxidized by hydrogen peroxide into sulfonic acid groups (Scheme 3)²³⁻²⁴. The TGA of catalyst (Figure 2) shows two decomposition states: one below 100 °C (4% weight loss), assigned to loss of water surface and one more mass loss between 100 °C and 550 °C (16% weight loss), corresponded to the decomposition of organic groups (PrSO₃H) anchored onto silica and the water loss during the condensation of silanol to siloxane groups. The surface area, pore volume and average pore diameter of SiO₂-Pr-SO₃H are 440 m²g⁻¹, 0.43 cm³ g⁻¹ and 5.9 nm, respectively, which are smaller than SiO₂ due to the immobilization of organic groups (propyl sulfonic acid) into the pores (Table 3)²².

Scheme 3

Figure 2. Thermal gravimetric analysis of the $\text{SiO}_2\text{-Pr-SO}_3\text{H}$ in N_2 flow

Table 3. Surface area, pore size and pore volume of silica gel and $\text{SiO}_2\text{-Pr-SO}_3\text{H}$

Name	Surface area, m^2/g	Total pore volume, cm^3/g	Average pore diameter, nm
SiO_2	499	0.737	6.4
$\text{SiO}_2\text{-Pr-SO}_3\text{H}$	440	0.430	5.9

The efficiency of various catalysts in synthesis of 2-amino-4*H*-Benzopyran derivatives has been compared in Table 4. The best yield and short reaction time is attributed to the high efficiency of the nano-catalyst of $\text{SiO}_2\text{-Pr-SO}_3\text{H}$.

Table 4. Comparison of efficiency of various catalysts in synthesis of 2-amino-4*H*-Benzopyran derivatives

Entry	Catalyst	Solvent	Time	Yield, %	Ref.
1	NaBr	free	10-15 min	60-95	[6]
2	(S)-Proline	$\text{H}_2\text{O}/\text{EtOH}$	30 min	78-98	[13b]
3	HDMBAB*	H_2O	7-8 h	84-93	[5a]
4	Na_2SeO_4	$\text{EtOH}/\text{H}_2\text{O}$	0.75-3 h	80-98	[4]
5	TMAH**	H_2O	0.5-2 h	79-93	[7]
6	TBAF***	H_2O	30-300 min	73-98	[14d]
7	MgO	$\text{EtOH}/\text{H}_2\text{O}$	22-33 min	90-96	[14c]
8	$\text{SiO}_2\text{-Pr-SO}_3\text{H}$	H_2O	8-20 min	88-97	This work

* Hexadecyldimethylbenzyl ammonium bromide, ** Tetra-methyl ammonium hydroxide, *** Tetrabutyl ammonium fluorid

Conclusion

In conclusion we have demonstrated a novel one-pot, three-component synthesis of 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzopyran derivatives using sulfonic acid functionalized silica ($\text{SiO}_2\text{-Pr-SO}_3\text{H}$) as an efficient heterogeneous solid acid catalyst in good to excellent yield. The simplicity of reaction, recovery of catalyst without loss of reactivity, high yield products and short time of reaction offer improvements over many existing methods.

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