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

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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 SiO$_2$-Pr-SO$_3$H 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-4H-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 spasmyloytic, diuretic, antianaphylactin, antisterility and anticancer agents. The polyfunctionalized benzopyrans were used as cosmetics, pigments and biodegradable agrochemicals. 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 approaches. The simplest method involves one-pot, three-component condensation of malononitrile, an aldehyde and dimedone in different conditions. Various catalysts such as Na$_2$SeO$_3$, hexadecyldimethylbenzyl ammonium bromide, NaBr, tetramethyl ammonium hydroxide (CH$_3$)$_4$N$^+$OH$^-$, TEBA, KF-montmorillonite, KF-alumina, organocatalysts, acetic acid, diammonium hydrogen phosphate and hexadecyltrimethyl...
ammonium bromide 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 (SiO$_2$-Pr-SO$_3$H) 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 $^1$H 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 Kα 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 SiO$_2$ (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 H$_2$O$_2$ (excess) in methanol (20 mL) for 24 h at room temperature and then the mixture was filtered and washed with H$_2$O and acetone to obtain SiO$_2$-Pr-SO$_3$H catalyst. The modified SiO$_2$-Pr-SO$_3$H 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), dimeredon (1 mmol) and catalyst (SiO$_2$-Pr-SO$_3$H) (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 H$_2$O. 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-tetrahydro-benzopyran (4b)**

IR (KBr): $\nu_{max}=3390, 3290, 3180, 2190, 1660, 1584$ cm$^{-1}$. $^1$H NMR (250 MHz, DMSO-d$_6$): $\delta= 1.08$ (s, 3H, CH$_3$), 1.12 (s, 3H, CH$_3$), 2.26 (s, 2H, CH$_2$-8), 2.46-2.48 (m, 2H, CH$_2$-6), 4.43 (s, 1H, CH-4), 6.58 (s, 2H, NH$_2$), 7.18-7.28 (m, 4H, Ar-H) ppm.

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

IR (KBr): $\nu_{max}=3380, 3323, 3182, 2188, 1676, 1634, 1490, 1405, 1365, 1216, 1032, 830$ cm$^{-1}$. $^1$H NMR (250MHz, DMSO-d$_6$): $\delta= 0.89$ (s, 3H, CH$_3$), 1.05 (s, 3H, CH$_3$), 2.06-2.28 (d,d, 2H, CH$_2$-8), 2.50 (2H, CH$_2$-6), 4.20 (s, 1H, CH-4), 7.07 (s, 2H, NH$_2$), 7.91- 7.157 (d, 2H, Ar-H), 7.36-7.33 (d, 2H, Ar-H) ppm.
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2-Amino–3–cyano–7,7–dimethyl–4-(4-methylphenyl)–5–oxo–4H-5,6,7,8-tetrahydro benzopyran (4d)

IR (KBr): $\nu_{\text{max}}$ = 3426, 3329, 2956, 2191, 1673, 1639, 1601, 1510, 1462, 1439, 1321, 1248, 1206, 1140, 1032, 976 cm$^{-1}$. $^1$H NMR (250 MHz, DMSO-d$_6$): $\delta$ = 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): $\nu_{\text{max}}$ = 3375, 3318, 2962, 2193, 1684, 1655, 1605, 1508, 1368, 1252, 975 cm$^{-1}$. $^1$H NMR (250 MHz, DMSO-d$_6$): $\delta$ = 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), 6.82-6085 (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 Kα radiation ($\lambda$ = 0.71073 Å). 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 reflections. 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 correction. The structure was solved by direct methods using SHELXS-97, and refined using full-matrix least-squares method on $F^2$, SHELXL-97. Molecular graphics were drawn by Diamond programs and PLATON 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 $U_{\text{iso}}$(H) = 1.2 $U_{\text{eq}}$(C/N) and for methyl group $U_{\text{iso}}$(H) = 1.5 $U_{\text{eq}}$(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$_2$O (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.
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 $\alpha$-cyanocinnamonitrile 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.

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, $^1$H 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 | 228-230⁷   |
| 2     | 4-ClC₆H₄ | 4b      | 20        | 90      | 237-239 | 239-241⁵ᵃ  |
| 3     | 3-NO₂C₆H₄| 4c      | 15        | 90      | 210-212 | 213-214⁵ᵃ  |
| 4     | 4-CH₂C₆H₄| 4d      | 25        | 98      | 214-216 | 220-222⁵ᵃ  |
| 5     | 4-OCH₂C₆H₄| 4e     | 25        | 98      | 190-192 | 196-198⁵ᵃ  |
| 6     | 2,4-Cl₂C₆H₄| 4f      | 20        | 92      | 118-119 | 116-118¹⁴ᵇ⁻ᶜ |
| 7     | 4-NO₂C₆H₄| 4g      | 15        | 93      | 176-178 | 176-178⁵ᵃ  |
| 8     | 3,4-(OCH₃)₂C₆H₄| 4h | 35        | 85      | 170-172 | 170-173³ᵇ  |
| 9     | 4-OHC₆H₄ | 4i      | 30        | 90      | 205-207 | 206-208⁷    |

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
Temperature, $^\circ$C

Weight, %

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Figure 2. Thermal gravimetric analysis of the SiO$_2$-Pr-SO$_3$H in N$_2$ flow

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

| Name                | Surface area, m$^2$/g | Total pore volume, cm$^3$/g | Average pore diameter, nm |
|---------------------|-----------------------|-----------------------------|---------------------------|
| SiO$_2$             | 499                   | 0.737                       | 6.4                       |
| SiO$_2$-Pr-SO$_3$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 SiO$_2$-Pr-SO$_3$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     | H$_2$O/EtOH      | 30 min  | 78-98   | [13b] |
| 3     | HDMBAB$^*$      | H$_2$O           | 7-8 h   | 84-93   | [5a] |
| 4     | Na$_2$SeO$_4$   | EtOH/H$_2$O      | 0.75-3 h | 80-98 | [4] |
| 5     | TMAH$^{**}$     | H$_2$O           | 0.5-2 h | 79-93   | [7] |
| 6     | TBAF$^{***}$    | H$_2$O           | 30-300 min | 73-98 | [14d] |
| 7     | MgO             | EtOH/H$_2$O      | 22-33 min | 90-96 | [14c] |
| 8     | SiO$_2$-Pr-SO$_3$H | H$_2$O     | 8-20 min | 88-97 | This work |

$^*$Hexadecylidimethylbenzyl ammonium bromide, $^{**}$Tetra-methyl ammonium hydroxide, $^{***}$Tetrabutyl ammonium fluoride

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 (SiO$_2$-Pr-SO$_3$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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