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Room temperature synthesis of 1,5-benzodiazepine and its derivatives using cage type mesoporous aluminosilicate catalysts

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ABSTRACT

Here we demonstrate for the first time the synthesis of 1,5-benzodiazepine using AlKIT-5 catalyst through a condensation reaction between *o*-phenylenediamine (OPDA) and ketones using acetonitrile as solvent at room temperature. The catalyst was found to be highly active and selective, affording a high yield of benzodiazepines. The effect of the aluminium content of the catalyst and the catalyst concentration on the above process was investigated. The catalyst was also successfully employed for the preparation of various derivatives of 1,5-benzodiazepine using substituted OPDAs and various ketones. In all cases, the reactions are highly selective and are completed within 1–2.5 h. The catalyst showed excellent activity in all the cases, showing 85–97% isolated yield of the corresponding derivatives of 1,5-benzodiazepine. The high activity of the catalyst is mainly due to its high acidity, excellent textural parameters such as high surface area, large pore volume, and cage type 3D porous structure.

1. Introduction

Benzodiazepines constitute an important class of biologically active compounds and their synthesis has been receiving much attention in the field of medicinal and pharmaceutical chemistry owing to their application as anticonvulsant, anti-inflammatory, analgesic, hypnotic, sedative agents, and hypnotic activity [1–6]. The derivatives of 1,5-benzodiazepines are also used as dyes for acrylic fibers in photography [7]. In addition, benzodiazepines are the useful precursors for the synthesis of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines [8–11]. Benzodiazepines are generally synthesized by the condensation of *o*-phenylenediamine (OPDA) with α,β-unsaturated carbonyl compounds, β-haloketones or with ketones [12] using acidic catalysts which are critical to enhance the condensation process. Different reagents such as BF_3-etherate, polyphosphoric acid, $NaBH_4$, $MgO/POCl_3$, $Yb(OTf)_3$, $Ga(OTf)_3$, lead nitrate, L-proline, acetic acid under microwave conditions, molecular iodine, and in ionic liquids have been also used for the synthesis of benzodiazepines [13–23]. Recently the synthesis of benzodiazepines was also reported using different solid acid catalysts such as sulfated zirconia, Al_2O_3/P_2O_5, $Ag_3PW_{12}O_{40}$, PVP-$FeCl_3$, and zeolite catalysts [24–28]. Unfortunately, many of these catalysts suffer from one or more limitations, such as long reaction times, occurrence of several side reactions, drastic reaction conditions, low yields, and tedious work-up procedure. In addition, the solid oxide catalyst used previously had poor textural parameters such as low surface area, and pore volume which do not support a better performance in the synthesis of benzodiazepines. These factors stimulate the search for a better catalyst, which should offer a high activity for the synthesis of 1,5-benzodiazepines under mild reaction conditions.

In recent years, mesoporous materials with different structure and tunable pore diameters have been receiving much attention in the field of adsorption and catalysis owing to their excellent textural characteristics [29–35]. Particular interest was focused on the design and fabrication of highly ordered mesoporous materials with three-dimensional (3D) pore structures such as SBA-1 and KIT-5 as they are believed to be more advantageous for catalytic applications than phases having a 1D array of pores [34,36–38]. Moreover, these materials can offer more resistant to pore locking and allow faster diffusion of reactants which are highly necessary to obtain a stable and a high catalytic activity. Recently, Vinu et al. reported the preparation of various mesoporous metallosilicate catalytic materials with 3D cage type structure and investigated their catalytic activity in the alkylation and acylation of aromatics [34,36–38]. They found that the activity of the 3D mesoporous catalysts is much better than the catalysts with unidimensional mesoporous structure. Among the 3D metallosilicate catalysts, aluminium supported mesoporous KIT-5 material (Al-KIT-5) was found to be interesting as it possesses 3D mesostructure with Fm3m symmetry and large cage type pores, a high

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acidity which mainly comes from the Brönsted acid sites on the surface of the catalyst, and a large pore diameter [37]. These features are clearly reflected in its high catalytic activity towards various acid catalyzed reactions [37,38]. Although these materials possess interesting textural and catalytic properties, unfortunately, with the best of our knowledge, there has been no report available on the synthesis of benzodiazepines using such materials as catalysts in the open literature so far.

Here we demonstrate for the first time the synthesis of 1,5-benzodiazepine using AlKIT-5 catalyst through a condensation reaction between OPDA and ketones under acetonitrile condition. The effect of the aluminium content of the catalyst and the catalyst concentration on the above process has been also investigated in detail. We also demonstrate the preparation of various derivatives of 1,5-benzodiazepine using substituted OPDAs and various ketones.

2. Experimental section

All chemicals and solvents were obtained from Aldrich and used without further purification. Column chromatographic separations were carried out on silica gel 100–200 mesh size. The ^{1}H NMR spectra of samples were recorded on a JEOL 300-MHz NMR spectrometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on a MALDI-MS. FT-IR spectra of all the final products were recorded on a Nicolet Nexus 670 instrument by averaging 50 scans with a resolution of 2 cm^{-1} measuring in transmission mode by using the KBr self-supported pellet technique.

2.1. Preparation of the catalyst

The AlKIT-5 materials with different n_{Si}/n_{Al} ratios were synthesized using polymeric Pluronic F127 as a template, and tetraethyl orthosilicate (TEOS) and aluminium isopropoxide as the sources of silicon and aluminium, respectively. In a typical synthesis, pluronic F127 (5 g) was dissolved in conc. HCl (3 g, 35 wt.%) and distilled water (240 g). To this mixture, TEOS (24 g) and the required amount of the aluminium source were added, and the resulting mixture was stirred for 24 h at 45 °C. Subsequently, the reaction mixture was heated for 24 h at 100 °C under static condition for hydrothermal treatment. After hydrothermal treatment, the final solid product was filtered off and then dried at 100 °C without washing. The white colored product was calcined at 540 °C for 10 h. The samples are denoted as AlKIT-5(x) where x denotes the n_{Si}/n_{Al} ratio in the final product. The molar gel composition of the reaction mixture was 1.0:0.041 – 0.071:0.0035:0.25:116.6 SiO_2:Al_2O_3:F127:HCl:H_2O [37,38].

2.2. Characterization of the catalysts and the products

The powder X-ray diffraction (XRD) patterns of the AlKIT-5 catalysts with different Al contents were collected on a Rigaku diffractometer using Cu Kα (λ = 0.154 nm) radiation. The diffractograms were recorded in the 2θ range of 0.8–10° with a 2θ step size of 0.01° and a step time of 10 s. Nitrogen adsorption and desorption isotherms were measured at −196 °C on a Quantachrome Autosorb 1C sorption analyzer. All samples were outgassed at 250 °C for 24 h. The specific surface area was calculated using the Brunauer–Emmett–Teller (BET) method. The pore size distributions were obtained from the adsorption branch of the nitrogen isotherms by Barrett–Joyner–Halenda method. The ^{1}H NMR spectra of samples were recorded on a JEOL 300-MHz NMR spectrometer using TMS as an internal standard in $CDCl_3$. Elemental composition of the materials was determined by inductively coupled plasma atomic emission spectrometry (ICP-AES). The temperature-programmed desorption (NH_3-TPD) was carried out on a Micromeritics Autochem 2910 instrument. Approximately 0.2 g of a fresh sample was placed in a U-shaped, flow-through, quartz microreactor for each experiment. The catalyst was activated at 500 °C for 6 h under He flow (20 ml/min) and then cooled to 100 °C before being exposed to ammonia. The sample was flushed again in He for 2 h to remove any physisorbed ammonia, and desorption profile was then recorded by increasing the sample temperature from 100 to 550 °C at a ramp rate of 5 °C/min.

2.3. General procedure for the synthesis of 1,5-benzodiazepine

A mixture of OPDA (**1**) (1 mmol, 108.1 mg), ketone (**2**) (2.5 mmol, 145.2 mg) and AlKIT-5 (100 mg) was stirred in acetonitrile (4 ml) at room temperature until thin layer chromatography indicated the reaction was completed. Ethyl acetate (10%) in hexane was used as the mobile phase and both the reactant and the final product were spotted on the TLC plate. The product retention factor (R_f) was observed at 0.4. The disappearance of the reactant spot on the TLC place indicates the completion of the reaction. After completion of the reaction, ethyl acetate (20 ml) was added to the reaction mixture and the catalyst was recovered by filtration. The organic layer was concentrated and the crude product was purified by silica gel column chromatography using ethyl acetate-*n*-hexane (1:9) as eluent to afford the desired product (**3**). The spectral data of entry 1, 2, 4, 5, 8 and 11 [39], entry 9, 10 [40], and entry 6, 7 and 15 [41] in Table 3 are in full agreement with the reported literature and the spectral data of the other compounds are described in the following sections.

2.3.1. Entry 3 (**3c**)

Yellow solid, m.p. 140–142 °C, IR(KBr): ν_{max} 3341, 1674, 1589 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92–0.98 (m, 6H, $2CH_3$), 1.13 (s, 3H, CH_3), 1.18–1.36 (m, 4H, $2CH_2$), 1.52–1.62 (m, 1H, CH^a), 2.10–2.20 (m, 1H, CH^b), 2.51–2.59 (m, 4H, $2CH_2$), 3.05 (br s, 1H, NH), 6.70–6.73 (m, 1H, Ar-H), 6.95–6.98 (m, 2H, Ar-H), 7.12–7.14 (m, 1H, Ar-H). EIMS: m/z [M^+] = 244. Anal. Calcd. for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.50; H, 9.85; N, 11.36.

2.3.2. Entry 12 (**3l**)

Yellow solid, m.p. 94–96 °C, IR(KBr): ν_{max} 3424, 1595, 1499 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3H, CH_3), 1.24–1.25 (m, 6H, $2CH_3$), 1.60–1.65 (m, 2H, CH_2), 2.22 (m, 2H, CH_2), 2.50–2.68 (q, 2H, J = 3.23 Hz, CH_2), 3.00–3.20 (br s, 1H, NH), 6.62–6.71 (m, 1H, Ar-H), 6.88–6.93 (m, 1H, Ar-H), 7.04–7.14 (m, 1H, Ar-H). EIMS: m/z [M^+] = 250, Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; N, 11.17. Found: C, 67.00; H, 7.54; N, 11.10.

2.3.3. Entry 13 (**3m**)

Reddish yellow solid, m.p. 160–162 °C, IR(KBr): ν_{max} 3338, 1638, 1591 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82–0.92 (m, 6H, $2CH_3$), 1.15 (s, 3H, CH_3), 1.23–1.49 (m, 4H, $2CH_2$), 1.58–1.68 (m, 2H, CH_2), 2.02–2.10 (m, 2H, CH_2), 2.39–2.45 (m, 2H, CH_2), 3.10 (br s, 1H, NH), 6.51–6.60 (m, 1H, Ar-H), 6.77–6.82 (m, 1H, Ar-H), 6.93–7.02 (m, 1H, Ar-H). EIMS: m/z [M^+] = 278. Anal. Calcd. for $C_{16}H_{23}ClN_2$: C, 68.92; H, 8.31; N, 10.05. Found: C, 68.83; H, 8.21; N, 10.00.

2.3.4. Entry 14 (**3n**)

Light yellow solid, m.p. 140–142 °C, IR(KBr): ν_{max} 3197, 1623, 1590 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98–1.02 (m, 12H, $4CH_3$), 1.25 (m, 2H, 2CH), 1.30 (s, 3H, CH_3), 1.70–1.73 (m, 2H, $2CH_2$), 2.15–2.20 (m, 2H, CH_2), 2.40 (d, 2H, CH_2), 3.50 (br s, 1H, NH), 6.60–6.673 (m, 1H, Ar-H), 6.86–6.94 (m, 1H, Ar-H), 7.04–7.13 (m, 1H, Ar-H). EIMS: m/z [M^+] = 306. Anal. Calcd. for