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Synthesis of tinidazole by condensation–oxidation sequence using MoO_3/SiO_2 bifunctional catalyst

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Abstract

Antimicrobial drug, tinidazole has been synthesized by condensation of 2-methyl,5-nitro-imidazole and 2-ethyl-thio-ethanol over MoO_3/SiO_2 catalyst to obtain 1-(2-ethyl-thio-ethanol)-2-methyl-5-nitro-imidazole which is further oxidized using hydrogen peroxide using the same MoO_3/SiO_2 catalyst to obtain tinidazole. MoO_3/SiO_2 catalyst (20%), synthesized by sol–gel process showed the highest acid strength and was successfully demonstrated to catalyze both condensation and oxidation in the synthesis of tinidazole. Due to the bifunctional activity of the catalyst, the use of acetic acid for condensation step and tungstic acid or ammonium molybdate for oxidation step in the conventional synthesis of tinidazole could be eliminated, thus making it an environmentally benign process. The catalysts could be recycled five times without any appreciable loss in the conversion and selectivity showing the potential for the use of MoO_3/SiO_2 as bifunctional catalyst for the production of this industrially important compound.

Keywords: Tinidazole; Antimicrobial drug; Solid acid catalyst; MoO_3/SiO_2; Condensation; Oxidation

1. Introduction

Substituted compounds derived from imidazole ring systems form the basis of several important drugs exhibiting novel biological activities [1,2]. Among these, metronidazole, tinidazole are well-known antimicrobial drugs as well as sensitizers of hypoxic tumors in conjunction with radiotherapy and 1-(2-ethyl-sulfonyl-ethyl)-2-methyl-5-nitro-imidazole (tinidazole) particularly, is known to be useful for the treatment of amebiasis while other derivatives with substitutions on the imidazole ring either on nitrogen or on the carbon also show a wide spectrum of clinical activity for microbial diseases [1,2]. The conventional manufacturing process of tinidazole involves first, a condensation step in the presence of sulfuric and acetic acids to give an intermediate, 1-(2-ethyl-thio-ethyl)-2-methyl-5-nitro-imidazole which in the second step undergoes oxidation with H_2O_2 in presence of ammonium molybdate or tungstic acid. Like several other processes practiced in pharma industry, the above process also results in the production of large amount of wastes due to (i) use of stoichiometric quantities of both acetic and sulfuric acids, and hence the work up as well as recovery of the intermediate becomes tedious (ii) use of ammonium molybdate or tungstic acid in the oxidation step, which gets converted to ammonium tungstate due to addition of liquor ammonia for work up of the reaction [3]. In order to overcome these problems, the development of an environmentally benign catalytic route is highly desirable and the use of a bi-functional catalyst with acidic as well as oxidation properties would be an attractive alternative. The use of solid acids such as zeolites, clays and metal oxides with Lewis acid sites and/or Bronsted acidity have been well established for developing 'green' processes [4]. Various solid acids such as zeolites, mesoporous materials, supported and unsupported metal oxides have been used as

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catalysts for several types of reactions like alkylation, oxidation, condensation, isomerization, etc. [5,6]. In particular, molybdenum oxide as such or supported on silica is a well-known solid acid catalyst which possesses both strong Lewis and Bronsted acidity [7]. In our earlier studies, 20% MoO_3/SiO_2 catalyst prepared by sol–gel synthesis using ethylsilicate-40 as silica source has been found to be highly active in various acid catalyzed reactions such as nitration, esterification and acylation [8–12]. MoO_3/SiO_2 catalyst is also used in catalytic oxidation reactions [13]. Considering the bi-functional nature of the 20% MoO_3/SiO_2 catalyst, we thought it to be an appropriate catalyst for the two-step synthesis of tinidazole. Both condensation and oxidation steps in the reaction sequence were carried out successfully using the same catalyst (MoO_3/SiO_2). Considering the pharmaceutical importance of tinidazole the condensation/oxidation reactions were carried out as per the conventional synthetic procedure followed in the pharmaceutical industry and the results are presented here.

2. Experimental

2.1. Catalyst preparation

A series of MoO_3/SiO_2 catalysts with varying molybdenum molar concentration (1–20 mol%) was prepared by sol–gel technique. Ammonium molybdate and ethyl silicate-40 (CAS registry no. 18945-71-7) were used as molybdenum and silica source, respectively. In a typical synthesis of 1% MoO_3/SiO_2, 0.353 g ammonium molybdate was dissolved in 20 ml water at 80 °C. This hot solution was added dropwise to the dry isopropyl alcohol solution (20 ml) of ethyl silicate-40 (29.7 g) with constant stirring. The resultant greenish gel was air dried and calcined at 500 °C in air in a muffle furnace for 8 h. Similarly catalysts with 5, 10, 15 and 20 mol% molybdenum loading were prepared. Pure silica catalyst was also prepared by adding 52 g ethyl silicate-40 to 30 g dry isopropyl alcohol to which 0.02 g ammonia solution (25%) was added with constant stirring. The transparent white gel thus obtained was air dried and calcined in muffle furnace at 500 °C for 8 h.

2.2. Catalyst characterization

The X-ray diffraction analysis was carried out using Rigaku X-ray diffractometer (Model DMAX IIIVC) with Cu Kα (1.542 Å) radiation. Temperature programmed desorption of ammonia (TPD-NH_3) was carried out using Micromeritics Autochem 2910. BET surface area was determined using NOVA 1200 Quanta chrome.

Acidity of the samples was determined by pyridine adsorption studies using Shimadzu 8000 series FTIR spectrometer using DRIFT technique. The sample was placed in the DRIFT cell and heated to 400 °C in flow of inert gas (N_2) for 2 h. It was cooled to 100 °C and pyridine was adsorbed on the sample in N_2 flow. The physisorbed pyridine was removed by flushing the cell with N_2 for 45 min at the same temperature and the spectrum was recorded. Then pyridine was desorbed for 45 min at 200, 300 and 400 °C and spectra were recorded at each temperature. The spectrum of the neat catalyst (before pyridine adsorption) at 100 °C was subtracted from all the spectra.

2.3. Conventional tinidazole preparation

2-Methyl,5-nitro-imidazole (800 g) was taken in a 2 l round bottom flask fitted with a reflux condenser and stirring arrangement. To this 200 ml of acetic acid was added along with 300 ml 98% sulfuric acid and this mixture was kept under stirring for 9 h at 80–85 °C with the addition of 440 g 2-ethyl-thio-ethanol. The unreacted 2-methyl,5-nitro-imidazole was precipitated by adjusting the pH to 3.0 by adding 24% liquor ammonia solution and isolated by filtration. Filtrate obtained was a mixture of aqueous solution of salts and organic layer, which contains intermediate product. The aqueous layer was discarded and organic layer was extracted using 15% hydrochloric acid. The intermediate product 1-(2-ethyl-thio-ethyl)-2-methyl-5-nitro-imidazole was separated as a hydrochloride in aqueous solution from organic layer and oxidized using stoichiometric quantities of 50% H_2O_2 and tungstic acid or ammonium molybdate (8 g) as catalyst at 50–55 °C. During work up, 25% aqueous ammonia was added to precipitate tinidazole, which was isolated by filtration while tungstic acid was converted to ammonium tungstate which goes in filtrate.

2.4. Tinidazole preparation using MoO_3/SiO_2 catalyst

2-Methyl,5-nitro-imidazole (800 g) was taken in a 2 l round bottom flask fitted with a reflux condenser and stirring arrangement. To this 12 g 20% MoO_3/SiO_2 was added along with either 215 ml 98% sulfuric acid or without sulphuric acid. This mixture was kept under stirring for 9 h at 80–85 °C with the addition of 440 g 2-ethyl-thio-ethanol. The solid catalyst was separated by filtration. The unreacted 2-methyl,5-nitro-imidazole was isolated from filtrate by initially diluting the mass with water followed by adjusting the pH to 3.0 using 24% liquor ammonia solution. The precipitated 2-methyl,5-nitro-imidazole was isolated by filtration. This filtrate obtained was a mixture of aqueous solution of salts and organic layer, which contains intermediate product. The aqueous layer was discarded and organic layer was extracted using 15% hydrochloric acid. The intermediate product 1-(2-ethyl-thio-ethyl)-2-methyl-5-nitro-imidazole was separated as a hydrochloride in aqueous solution from organic layer and further used in oxidation step at 50–55 °C with stoichiometric quantity of 50% H_2O_2 and 20% MoO_3/SiO_2 catalyst isolated form first step. During work up, 25% aqueous ammonia was added to precipitate tinidazole, which was isolated by filtration. Thus both the steps, condensation as well as oxidation were carried out using same MoO_3/SiO_2 catalyst without using acetic acid, ammonium molybdate or tungstic acid.