Available online at www.sciencedirect.com
ScienceDirect
Catalysis Communications 8 (2007) 1550–1555
CATALYSIS COMMUNICATIONS
www.elsevier.com/locate/catcom

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

J.G. Chandorkar [a], S.B. Umbarkar [c], C.V. Rode [b], V.B. Kotwal [a], M.K. Dongare [c,*]

[a] *Aarti Drugs Ltd., Mumbai, India*
[b] *Homogeneous Catalysis, National Chemical Laboratory, Pune 411 008, India*
[c] *Catalysis Division, National Chemical Laboratory, Pune 411 008, India*

Received 18 October 2006; received in revised form 1 January 2007; accepted 2 January 2007

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

* Corresponding author. Tel.: +91 20 25902044; fax: +91 20 25902633.
E-mail address: mk.dongare@ncl.res.in (M.K. Dongare).

1566-7367/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.catcom.2007.01.001

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.

3. Results and discussion

3.1. Catalyst characterization

The XRD patterns of MoO_3/SiO_2 catalysts with MoO_3 loading varying from 1 to 20 mol%, prepared by sol–gel technique are shown in Fig. 1. For comparison, the XRD pattern of pure silica is also included in Fig. 1a. The patterns show the amorphous nature of the material at lower (1–10%) Mo loading (Fig. 1b–d). Catalysts with 15% and 20% Mo loading (Fig. 1e and f) show highly crystalline nature with intense peaks at $2\theta = 12.9°$, 23.42°, 25.76° and 27.40° corresponding to α-MoO_3 in orthorhombic phase. No β-MoO_3 phase was observed in the structure as the samples were calcined at 500 °C, at which β-MoO_3 phase was not stable [14]. It was interesting to note that even though the MoO_3 was in the crystalline form at higher Mo loading, the reflections due to crystalline silica were not seen indicating a high dispersion of MoO_3 on the amorphous silica support.

The surface area of all the catalysts determined using BET method is given in Table 1. As expected, a very high surface area of 606 m^2/g was observed in case of pure silica because of sol–gel synthesis using ethyl silicate-40 as the silica source. Ethyl silicate-40 is a polymeric form (trimeric and tetrameric) of tetraethyl orthosilicate monomer, which on controlled hydrolysis yields the silica of a very high surface area [15]. On controlled hydrolysis of ethyl silicate-40, the trimeric and tetrameric species form the corresponding trimeric and tetrameric silica structure, with controlled growth leads to the formation of smaller particle size. The surface area was found to decrease with increase in MoO_3 loading. During the sol–gel synthesis, an aqueous solution of ammonium molybdate was added to ethyl silicate-40, which hydrolyzed ethyl silicate-40. However, the control on the rate of hydrolysis was difficult because of

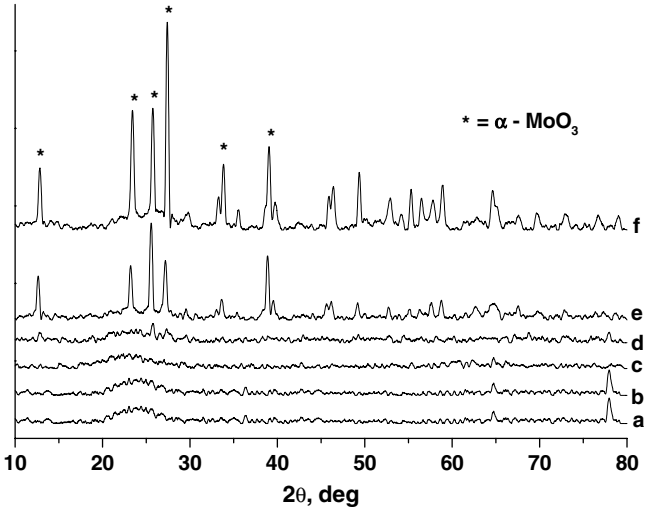


Fig. 1. XRD of (a) silica and MoO_3/SiO_2 with (b) 1%, (c) 5%, (d) 10%, (e) 15%, (f) 20% MoO_3 loading on SiO_2.

Table 1
Surface area and NH_3 desorption measurement of MoO_3/SiO_2 catalysts

Catalyst	Surface area (m^2/g)	NH_3 desorbed (mmol/g)
Silica	606	0.0317
1% MoO_3/SiO_2	583	0.1830
5% MoO_3/SiO_2	432	0.5562
10% MoO_3/SiO_2	284	0.7056
15% MoO_3/SiO_2	275	0.863
20% MoO_3/SiO_2	180	0.937

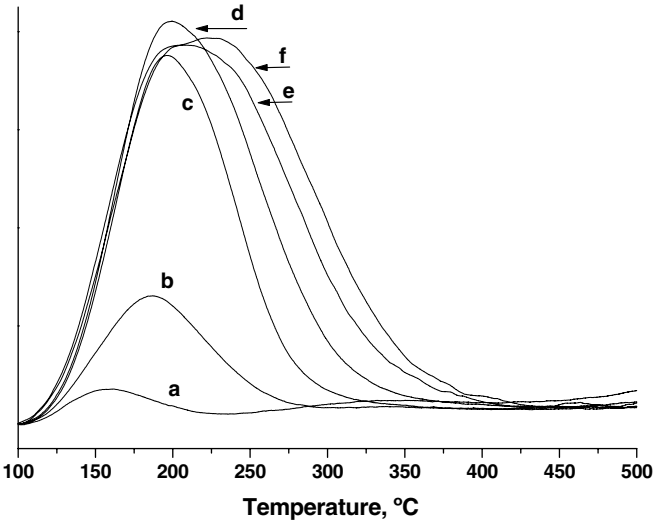


Fig. 2. NH_3 TPD of (a) silica and MoO_3/SiO_2 with (b) 1%, (c) 5%, (d) 10%, (e) 15%, (f) 20% MoO_3 loading on SiO_2.

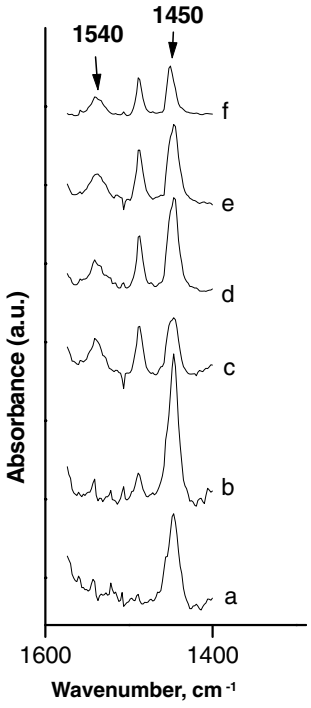
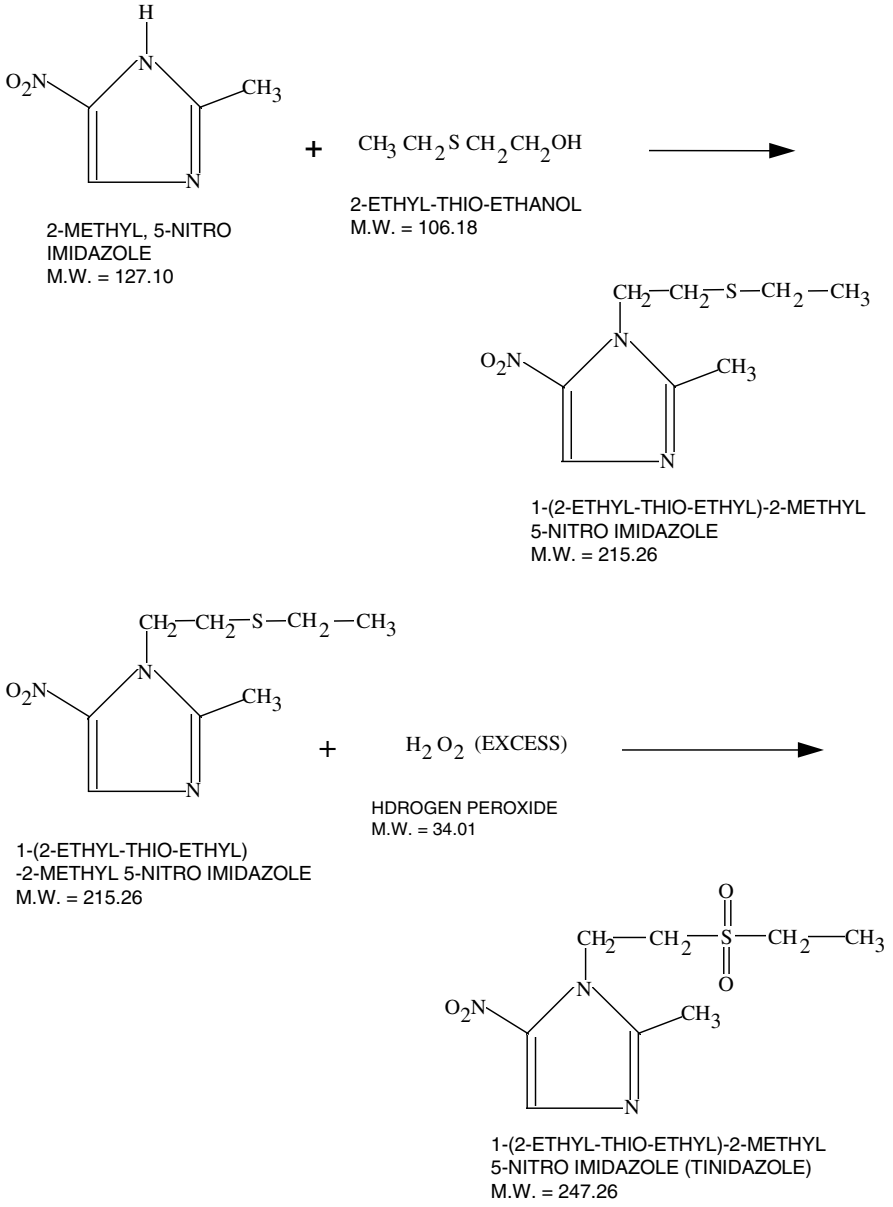


Fig. 3. Pyridine adsorption spectra of (a) silica, and MoO_3/SiO_2 with (b) 1%, (c) 5%, (d) 10%, (e) 15%, (f) 20% MoO_3 loading on SiO_2.

use of excess water for dissolving ammonium molybdate, which led to decrease in the surface area. The highly basic pH of the solution also led to the formation of the product with lower surface area. It was expected that as MoO_3 loading increased, the crystalline molybdenum oxide clusters were formed covering the amorphous silica support and reducing the total surface area of the catalyst. However, the catalysts prepared by sol–gel techniques showed a very high surface area as compared to the catalysts prepared by impregnation method. For 1% Mo loading, the catalyst prepared by sol–gel technique showed surface area of 583 m^2/g whereas the catalyst prepared by impregnation method showed surface area of only 155 m^2/g [16].

Ammonia-TPD experiments were carried out to determine the acid strength of the MoO_3/SiO_2 catalysts for various loadings of MoO_3. The results are shown in Fig. 2 and amount of NH_3 desorbed is given in Table 1. The pure silica catalyst showed the lowest acidity with 0.0317 mmol/g of ammonia desorbed at comparatively lower temperature indicating the presence of few weaker acid sites. Addition of 1% MoO_3 to the silica support by sol–gel increased the acidity almost six times (0.183 mmol/g) with respect to the number of acid sites as well as acid strength. The temperature for total desorption of ammonia increased from 175 to 275 °C with increase in MoO_3 loading showing the increase in acid strength as well as number of acid sites. Catalyst with 20% Mo loading showed the maximum number of acid sites (NH_3 desorbed: 0.937 mmol/g) as well as the highest acid strength.

Pyridine adsorption studies for determination of the nature of acidity revealed the presence of Lewis acidity in all the catalysts. Fig. 3 shows the IR spectra of adsorbed



Scheme 1.

Table 2
Activity results of 20% MoO_3/SiO_2 for tinidazole synthesis

S. no.	Catalyst (g)	H_2SO_4 (g)	AcOH (g)	Temperature (°C)	Conversion (%)	Selectivity for tinidazole (%)
1[a]	–	300	200	85	50	68.6
2	MoO_3/SiO_2 (12)	–	–	80	20	100
3	MoO_3/SiO_2 (12)	215	–	80	50	69.3
4	MoO_3/SiO_2 (8)	215	–	80	50	70
5	–	215	–	80	4	2.1
6	MoO_3/SiO_2 (8)	215	–	75	50	67.9
7	MoO_3/SiO_2 (8)	215	–	70	50	65.1

[a] Conventional process using ammonium molybdate or tungstic acid in catalytic quantities.

pyridine on the catalyst surface for various MoO_3 loadings. The spectrum of pure silica (Fig. 3a) shows the presence of only Lewis acidity (peak at 1450 cm^{-1}) with low acidity and 1% MoO_3/SiO_2 sample (Fig. 3b) shows increase in Lewis acidity as well as the acid strength. As the MoO_3 loading was further increased the samples showed presence of both Brønsted (peak at 1540 cm^{-1}) as well as Lewis acid sites (Fig. 3c–f).

3.2. Activity results

It was clear from the characterization studies that 20% MoO_3/SiO_2 showed the highest acid strength with Brønsted acid sites. In a conventional process for tinidazole, condensation of 2-methyl,5-nitro-imidazole with 2-ethyl-thio-ethanol is carried out in presence of sulfuric and acetic acids and subsequent oxidation of the intermediate is done in presence of tungstic acid or ammonium molybdate to give tinidazole Scheme 1. As can be seen from Table 2, in the conventional process (entry 1) the conversion obtained was 50% and the selectivity for tinidazole was 70%. As per the conventional process followed in the pharmaceutical industry, the unreacted 2-methyl,5-nitro-imidazole (about 50%) in the first condensation reaction was recovered and the remaining 50% 2-methyl,5-nitro-imidazole was converted further to the intermediate. The oxidation of the intermediate product, 1-(2-ethyl-thio-ethyl)-2-methyl-5-nitro-imidazole using hydrogen peroxide and tungstic acid resulted in the product which on isolation showed the formation of tinidazole with 70% selectivity and other 30% impurities were not identified. The purity of tinidazole was matched with the standard pharmacopial quality, which involved the assay determination by non-aqueous titration [17]. Since 20% MoO_3/SiO_2 catalyst showed highest acid strength and Brønsted acidity, it was used as a catalyst in the first step of condensation. When the reaction was carried out using catalytic amount of 20% MoO_3/SiO_2 without sulphuric and acetic acids, ammonium molybdate and tungstic acid, 100% selectivity was obtained for tinidazole however the conversion dropped down to 20% (entry 2) indicating the bifunctional activity of the catalysts. Thus, the first step of condensation involving protonation of hydroxyl group of the thio alcohol was possible even in absence of acetic acid due to acid sites of a solid catalyst, MoO_3/SiO_2 to form a carbocation facilitating the nucleophilic attack of nitrogen of the imidazole ring. The role of sulphuric acid is protonation of tertiary nitrogen atom at third position of 2-methyl,5-nitro-imidazole to form quaternary ammonium salt and avoid tautomerism to facilitate the condensation reaction at secondary nitrogen atom only. The results of reaction carried out in absence of sulphuric acid and acetic acid clearly indicates the ability of MoO_3/SiO_2 to protonate nitrogen to avoid tautomerism. The same catalyst also showed oxidation activity for oxidation of the intermediate, 1-(2-ethyl-thio-ethyl)-2-methyl-5-nitro-imidazole to give 1-(2-ethyl-sulfonyl-ethyl)-2-methyl-5-nitro-imidazole (tinidazole) in the second step. In absence of sulphuric acid the conversion dropped down to 20% which may be due to lesser extent of protonation of tertiary nitrogen atom to form quaternary ammonium salt, hence addition of sulphuric acid increased the conversion to 50%. The use of catalytic amount of 20% MoO_3/SiO_2 without acetic acid and with lower amount of sulphuric acid (Table 2, entry 3) also gave 69.30% selectivity for tinidazole with 50% conversion of 2-methyl,5-nitro-imidazole (Table 2, entry 3). A blank run (Table 2, entry 5) without MoO_3/SiO_2 but in presence of sulfuric acid showed only 4% conversion with 2.1% selectivity for tinidazole, which clearly confirmed the role of MoO_3/SiO_2 as a catalyst in condensation as well as subsequent oxidation of the intermediate to tinidazole. Decrease in reaction temperature from 80 to 70 °C did not affect the conversion but the yield of final product, tinidazole decreased by about 6–7%, hence the optimum temperature was found to be 80 °C. Thus, the synthesis of tinidazole involving condensation–oxidation steps could be successfully achieved using a solid 20% MoO_3/SiO_2 catalyst.

4. Conclusion

Tinidazole, an important pharmaceutical compound was synthesized by condensation/oxidation reaction using MoO_3/SiO_2 catalyst without any use of acetic acid, tungstic acid or ammonium molybdate used in the conventional process. The MoO_3/SiO_2 showed appreciable activity both in acid catalyzed condensation reaction as well as in subsequent oxidation reaction indicating bi-functional nature of the MoO_3/SiO_2 catalyst. The MoO_3/SiO_2 catalyst could be recycled five times without any appreciable loss of conversion and selectivity indicating the potential for the use of

this bi functional catalyst for the development of environmentally benign process for the production of tinidazole.

References

[1] J.G. Lombardino, E.H. Wiseman, J. Med. Chem. 17 (1974) 1182;
J. Chen, M. Pattarawarapan, A. Zhang, K. Burgess, J. Comb. Chem. 2 (2000) 276.
[2] A.I. Kodair, P. Bertrand, Tetrahedron 54 (1998) 4859.
[3] A.A. Upcroft, R.W. Campbell, K. Benakli, P. Upcroft, P. Vanelle, Antimicrob. Agents Chemother. 43 (1999) 73;
P. Vanelle, J. Maldonado, M.P. Crozet, K. Senouki, F. Delmas, M. Gasquet, P. Timon-David, Eur. J. Med. Chem. 26 (1991) 709.
[4] K. Butler, W. Conn, US Patent 3376311 to Pfizer and Co., USA, 1968.
[5] A. Mitsutani, Catal. Today 73 (2002) 57.
[6] P. Beltrame, G. Zuretti, Green Chem. 6 (2004) 7;
C.R. Holmquist, E.J. Rosekamp, J. Org. Chem. 54 (1898) 3258;
C.B. Dartt, M.E. Davis, Catal. Today 19 (1994) 151;
W.F. Holderich, H. van Bekkum, Stud. Surf. Sci. Catal. 58 (1991) 631;
H. Sato, Catal. Rev. Sci. Eng. 39 (1997) 395.
[7] A. Auroux, A. Gervasini, J. Phys. Chem. 94 (1990) 6371;
M. Kawai, M. Tsukuda, K. Tamaru, Surf. Sci. 111 (1981) L176.
[8] L. Letti, G. Ramis, G. Busca, F. Bregani, P. Forzetti, Catal. Today 61 (2000) 187;
Y. Ono, Z.H. Fu, J. Mol. Catal. A 118 (1997) 293;
S. Narayan, B. Prasad, Chem. Commun. (1991) 1204;
N.C. Martinez, J.A. Dumesic, J. Catal. 127 (1991) 706.
[9] M.K. Dongare, P.T. Patil, K.S. Malshe, US Patent 6,791,000, 2004.
[10] S.K. Maurya, M.K. Gurjar, K.M. Malshe, P.T. Patil, M.K. Dongare, E. Kemnitz, Green Chem. 5 (2003) 720.
[11] M.K. Dongare, V.V. Bhagvat, C.V. Ramana, M.K. Gurjar, Tetrahedron Lett. 45 (2004) 4759.
[12] P.T. Patil, K.M. Malshe, S.P. Dagde, M.K. Dongare, Catal. Commun. 4 (2003) 429.
[13] N. Ohler, A.T. Bell, J. Catal. 231 (2005) 115.
[14] A. Kido, H. Iwamoto, N. Azuma, A. Ueno, Catal. Surv. Jpn. 6 (2002) 45.
[15] M.K. Dongare, P.T. Patil, K.M. Malshe, EP Patent EP 1386907, 2004.
[16] X. Ma, J. Gong, S. Wang, N. Gao, D. Wang, X. Yang, F. He, Catal. Commun. 5 (2004) 101.
[17] Indian Pharmacopoeia, vol. II, Controller of Pub., New Delhi, 1996, p. 764.