Research Article

Nanorod-Shaped Basic Al₂O₃ Catalyzed N,N-Diformylation of Bisuracil Derivatives: A Greener “NOSE” Approach

Vijay K. Das and Ashim J. Thakur

Department of Chemical Sciences, Tezpur University (A Central University), Napaam, Assam 784028, India

Correspondence should be addressed to Ashim J. Thakur; ajt.tezu03@gmail.com

Received 14 May 2013; Accepted 10 June 2013

1. Introduction

The exercise of metal/metal oxide nanoparticles as a frontier between the homogeneous catalysis and heterogeneous catalysis [1] in organic synthesis has invoked tremendous interests [2] in the recent times. The interesting features inherited with these small particle sizes are their large surface area along with more edges and corners and distinct electronic, optical, magnetic, thermal, and chemical properties [3–5]. The crucial role of nanoparticles in organic transformations is their excellent catalytic activity, straightforward recoverability, better selectivity, criteria of evolution, and their versatile role in green chemistry [6–10]. Thus, the domain of metal nanoparticle catalysis [11–13] should offer opportunities for mining new chemical reactions [14–16] which include the synthesis of biologically important and synthetically challenging natural products. In the context of green chemistry [17], organic synthesis in solvent-free reaction condition [18–21] has occupied a significant position in the recent years since solvent-free reaction condition involves the best reaction medium with “no medium” [22].

One of the key motifs present in the biopolymer RNA [23–26] is uracil, a nucleobase of the pyrimidine family which participates in various functions in our life processes [27]. Uracil derivatives also have several potent medicinal properties such as bronchodilators and anticancer [28, 29], antiallergic [30, 31], antiviral [32, 33], antihypertensive, and adenosine receptor antagonists [34, 35]. Recently, our research group reported a greener protocol for the synthesis of bisuracil derivatives [36]. Bisuracil and their analogues have also been isolated from marine sea hare Dolabella auricularia [37]. Some of the N-substituted bisuracil analogues have been screened for bioactivities against several diseases [38].

To explore the possible applications of the metal/metal oxide nanoparticles in organic synthesis, we have been focusing on the advancement of a protocol termed “NOSE” (nanoparticles-catalyzed organic synthesis enhancement) [39–41] chemistry in our laboratory. To the best of our knowledge, there has been no report on nano-rod-shaped Al₂O₃ catalysis for the N,N-diformylation of bisuracil derivatives. Recently, we reported N-formylation of amines catalyzed by nano-Al₂O₃ under solvent-free reaction condition [39]. This work inspired us to focus on nano-Al₂O₃ catalysis for the N,N-diformylation of bisuracil analogues. Therefore, in this paper, we wish to account for the same (Scheme 1).

Nano-Al₂O₃ draws our attention due to its crystalline size and shape, abrasive and insulating properties, less toxicity, large surface area, basic surface characteristics, high resistant towards bases and acids and excellent wear resistance [40–44].

2. Materials and Methods

2.1. General Experimental Methods. Rod-shaped nano-Al₂O₃ (the average particle diameter is 8.12 nm and average length
Scheme 1: N,N-diformylation of bisuracil derivatives I(a–k).

Scheme 2: Optimization of reaction condition.

2.2. General Procedure for N,N-Diformylation of Bisuracil Derivatives. In a two-neck round bottom flask (50 mL), nanorod-shaped basic Al₂O₃ (7.0 mol%, 7.12 mg) were taken, and then 1g (1.0 mmol, 414 mg) and formic acid (98%, 6.0 mmol, 0.23 mL) were added. After that, it was allowed to stir on a pre heated oil bath at 40°C for the required time (the progress of the reaction was judged by TLC). The reaction mixture was brought to room temperature after its completion, and ethyl acetate (3 × 10 mL) was added and then centrifuged (3,000 r.p.m) to recover the nanocatalyst. Having done this, the reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, and concentrated in a rotary evaporator, and finally the crude product was purified by column chromatography (30% ethyl acetate: hexane as an eluent). The recovered catalyst was washed with hot ethanol (3 × 10 mL) to remove the organic impurities, decanted, dried in an oven at 80°C for 6 h, and reused for evaluating the performance in the next run in the reaction as shown in Scheme 2.

3. Results and Discussion

With the previously reported catalyst characterizations in hand [39], to begin with, reaction of 6,6'-diamino-1,1',3,3'-tetramethyl-5,5'-(benzylidene)bis[pyrimidine-2,4 (1H, 3H)-dione] [36] (1a, 1 mmol) with formic acid (6 mmol) was chosen as the model reaction (Scheme 2).

The optimization of the various parameters of this reaction is elaborated in Table 1. Initially, the reaction was carried out without using catalyst under solvent-free reaction condition at 40°C and 80°C which did not yield any product (Table 1, entries 1 and 2). Various solvents were also tested under the mentioned condition, but they all failed (Table 1, entries 3–11) to provide any product. These negative results suggested that we look for an effective catalyst in the present study. Next, various Lewis acid-base catalysts (Table 1, entries 12–14) along with the nanocatalysts (Table 1, entries 15–18) were surveyed to observe the influence on rate and yield of N,N-diformylation of 1a which were not fruitful. Interestingly, nanorod-shaped basic Al₂O₃ stood out as a choice of catalyst at 7 mol% loading (Table 1, entry 15) under solvent-free reaction condition at 40°C. During the course of our experiment, we observed that at higher temperature...
Table 1: Optimization of the reaction conditions for the N,N-diformylation of 1a (Scheme 1).

| Entry | Catalyst | Solvent       | Temp. (°C) | Time (h) | Yield (%) b |
|-------|----------|---------------|------------|----------|-------------|
| 1     | None     | Solvent-free  | 40         | 9        | NR c        |
| 2     | None     | Solvent-free  | 80         | 9        | NR c        |
| 3     | None     | H₂O           | 40         | 12       | NR c        |
| 4     | None     | CH₃CN         | 40         | 12       | NR c        |
| 5     | None     | MeOH          | 40         | 12       | NR c        |
| 6     | None     | EtOH          | 40         | 12       | NR c        |
| 7     | None     | THF           | 40         | 12       | NR c        |
| 8     | None     | Toluene       | 40         | 12       | NR c        |
| 9     | None     | DMSO          | 40         | 12       | NR c        |
| 10    | None     | Xylene        | 40         | 12       | NR c        |
| 11    | None     | DMF           | 40         | 12       | NR c        |
| 12    | K₂CO₃    | Solvent-free  | 40         | 12       | NR c        |
| 13    | PPh₃     | Solvent-free  | 40         | 12       | NR c        |
| 14    | Imidazole| Solvent-free  | 40         | 10       | Trace       |
| 15    | Nano-Al₂O₃ᵢ | Solvent-free | 40         | 45 min   | 70          |
| 16    | Nano-MgO | Solvent-free  | 40         | 3        | 34          |
| 17    | Nano-Fe₃O₄ᵢ | Solvent-free | 40         | 5        | 12          |
| 18    | Nano-TiO₂ᵢ | Solvent-free | 40         | 4        | 8           |
| 19    | Nano-Al₂O₃ᵢ | Solvent-free | 80         | 2        | 43          |
| 20    | Nano-Al₂O₃ᵢ | Solvent-free | 40         | 3        | 25          |
| 21    | Nano-Al₂O₃ᵢ | Solvent-free | 40         | 4        | 17          |
| 22    | Nano-Al₂O₃ᵢ | Solvent-free | 40         | 6        | 8           |

aReaction conditions: bisuracil 1a (1 mmol, 0.454 g), formic acid (6 mmol, 0.66 mL), and solvent (5 mL). bIsolated yields. cNo reaction was observed. d7 mol% catalyst was used. e5 mol% catalyst was used. f3 mol% catalyst was used. g10 mol% catalyst was used. h1 mol% catalyst was used. iParticles size (17.4–16.4 nm). jParticles size (<50 nm). kParticles size (12 nm). lParticles size (<80 nm).

Table 2: Nano-Al₂O₃ catalyzed N,N-diformylation of uracil and bisuracil derivatives.

| Entry | "R" in 1 | Product 2 | Time (min) | Yield (%) ab |
|-------|----------|-----------|------------|--------------|
| 1     | C₆H₅      | 2a        | 45         | 70           |
| 2     | p-OMeC₆H₅ | 2b        | 60         | 68           |
| 3     | p-CIC₆H₅  | 2c        | 75         | 58           |
| 4     | p-OHOC₆H₅ | 2d        | 90         | 55           |
| 5     | p-NOC₆H₅  | 2e        | 90         | 52           |
| 6     | p-MeC₆H₅  | 2f        | 70         | 60           |
| 7     | o-OHOC₆H₅ | 2g        | 100        | 52           |
| 8     | m-NOC₆H₅  | 2h        | 90         | 65           |
| 9     | CH₃        | 2i        | 100        | 52           |
| 10    | CH₃(CH₂)₃ | 2j        | 120        | 44           |
| 11    | 2-furyl    | 2k        | 150        | 57           |

a6 mmol of formic acid was used. bIsolated yield. cProducts were characterized by IR and NMR (¹H and ¹³C) spectroscopy, MS, and also melting points.

Table 3: Recycling study of nano-Al₂O₃.

| Entry | No. of cycles | Time (min) | Yield (%) b | TONs |
|-------|---------------|------------|-------------|------|
| 1     | Fresh         | 45         | 70          | 88   |
| 2     | 1st run       | 45         | 70          | 88   |
| 3     | 2nd run       | 45         | 70          | 88   |
| 4     | 3rd run       | 45         | 70          | 88   |
| 5     | 4th run       | 45         | 70          | 88   |
| 6     | 5th run       | 60         | 58          | 76   |
| 7     | 6th run       | 180        | 40          | 70   |

aReaction conditions: 2 mmol of 2b, 12 mmol formic acid, and 7 mol% basic nano-Al₂O₃, 40°C. bYields refer to the isolated pure products.
(Table 1, entry 19) and at lower/higher catalyst loading the yield of the products was poor (Table 1, entries 20–22). Thus, the yield of N,N-diformylation product of bisuracil derivatives is highly dependent upon the temperature and catalyst loading.

With this supportive optimized reaction condition in hand, a series of bisuracil derivatives (entries 1–11) bearing different aliphatic, aromatic, and heterocyclic moieties were examined to explore the scope and limitations of this reaction and the outcomes are presented in Table 2. It is clear from Table 2 that bisuracil derivatives carrying both electron donating and electron withdrawing groups in benzene ring underwent N,N-diformylation reaction smoothly producing good yields (Table 2, entries 1–8). However, longer reaction time was required for bisuracil derivatives substituted with furan and alkyl groups (Table 2, entries 9–11). It is worth mentioning that 6-amino-1,3-dimethyluracil when treated with formic acid under the current condition gave N,N-diformylation product in lower yield (26%, 9 h). The reactions were found to be clean, and no side products were formed.

To test the recyclability (vide Scheme 2) of nano-Al$_2$O$_3$, it was separated from the reaction mixture by adding ethyl acetate (10 mL), centrifuged at 3,000 rpm, to pellet out the catalyst. The separated particles were washed with hot ethanol (3 × 10 mL) to remove the organic impurities, decanted, dried in an oven at 80°C for 6 h, and reused for further reactions. The efficiency of the catalyst was found to be unaffected up to 4th run, and after that, its action started to decrease as shown in Table 3. The TONs were also retained from fresh up to the 5th cycle, and after that it decreased considerably.

The recovered catalyst was also investigated through powder XRD and it was compared with the fresh nano-Al$_2$O$_3$ (Figure 1). In the powder XRD of the recovered catalyst after 6th run (Figure 1), the intensity of the peaks (4 0 0) and (1 0 0) weakened and became broad. It might be due to the blockage of the pores of the catalyst which caused a decrease in effective active sites and also due to the dislocation of the crystal planes after each run which in turn decreased the yield.

The SEM micrograph of the fresh nano-Al$_2$O$_3$ previously reported by us [39] was also compared with the recycled one (Figure 2) under the present study. As indicated in Figure 2, the recycled nano-Al$_2$O$_3$ revealed the aggregation of the particles responsible for reducing its surface area and hence deactivated the catalyst after 4th run which caused the lower yield of product.

**4. Conclusions**

In conclusion, we have demonstrated a novel method for synthesis the N,N-diformylation of bisuracil derivatives in good yield under solvent-free reaction condition at 40°C catalyzed by recyclable nano-Al$_2$O$_3$ rods. Nano-Al$_2$O$_3$ catalyzed organic transformations are less explored. We believe that this work would find wide applications for new chemical transformations, including those which enable the synthesis of complex natural products and derivatives.

**Conflict of Interests**

The authors declare no financial conflict of interests.

**Acknowledgments**

Vijay K. Das thanks UGC for a Rajiv Gandhi National Fellowship given to him. The authors would also like to acknowledge Mr. Prakash Kurmi, Department of Physics, Tezpur University, for carrying out XRD studies and fruitful discussions.

**References**

[1] D. Astruc, F. Lu, and J. R. Aranzaes, “Nanoparticles as recyclable catalysts: the frontier between homogeneous and heterogeneous catalysis,” Angewandte Chemie—International Edition, vol. 44, no. 48, pp. 7852–7872, 2005.

[2] J. Grunes, J. Zhu, and G. A. Somorjai, “Catalysis and nanoscience,” Chemical Communications, vol. 9, no. 18, pp. 2257–2260, 2003.

[3] J. Rautio, P. Perämäki, J. Honkamo, and H. Jantunen, “Effect of synthesis method variables on particle size in the preparation of homogeneous doped nano ZnO material,” Microchemical Journal, vol. 91, no. 2, pp. 272–276, 2009.
[4] M. T. Reetz and E. Westermann, “Phosphane-free palladium-catalyzed coupling reactions: the decisive role of Pd nanoparticles,” Angewandte Chemie—International Edition, vol. 39, no. 1, pp. 165–168, 2000.

[5] C. Ramarao, S. V. Ley, S. C. Smith, I. M. Shirley, and N. DeAlmeida, “Encapsulation of palladium in polyurea microcapsules,” Chemical Communications, no. 10, pp. 1132–1133, 2002.

[6] J. A. Gladysz, ” Recoverable catalysts. Ultimate goals, criteria of evaluation, and the green chemistry interface,” Pure and Applied Chemistry, vol. 73, no. 8, pp. 1319–1324, 2001.

[7] J. A. Gladysz, ” Introduction: recoverable catalysts and reagents—perspective and prospective,” Chemical Reviews, vol. 102, no. 10, pp. 3215–3216, 2002.

[8] G. Pacchioni, "Quantum chemistry of oxide surfaces: from CO chemisorption to the identification of the structure and nature of point defects on MgO" Surface Review and Letters, vol. 7, no. 3, pp. 277–306, 2000.

[9] D. M. Cox, D. J. Trevor, R. L. Whetten, and A. Kaldor, "Alumina clusters: ionization thresholds and reactivity toward deuterium, water, oxygen, methanol, methane, and carbon monoxide," Journal of Physical Chemistry, vol. 92, no. 2, pp. 421–429, 1988.

[10] V. Polshettiwar and R. S. Varma, "Green chemistry by nanocatalysis," Green Chemistry, vol. 12, no. 5, pp. 743–754, 2010.

[11] V. Polshettiwar, B. Baruwati, and R. S. Varma, "Self-assembly of metal oxides into three-dimensional nanostructures: synthesis and application in catalysis," ACS Nano, vol. 3, no. 3, pp. 728–736, 2009.

[12] V. Polshettiwar, M. N. Nadagouda, and R. S. Varma, "The synthesis and applications of a micro-pine-structured nanocatalyst," Chemical Communications, no. 47, pp. 6318–6320, 2008.

[13] A. Fihri, R. Sougrat, R. B. Rakhi et al., "Nanoroses of nickel oxides: synthesis, electron tomography study, and application in CO oxidation and energy storage," ChemSusChem, vol. 5, no. 7, pp. 1241–1248, 2012.

[14] K. Shimizu, R. Sato, and A. Satsuma, "Direct C–C cross-coupling of secondary and primary alcohols catalyzed by a γ-alumina-supported silver subnanocluster," Angewandte Chemie—International Edition, vol. 48, no. 22, pp. 3982–3986, 2009.

[15] A. Murugadoss, P. Goswami, A. Paul, and A. Chattopadhyay, "Green’ chitosan bound silver nanoparticles for selective C–C bond formation via in situ iodination of phenols," Journal of Molecular Catalysis A, vol. 304, no. 1-2, pp. 153–158, 2009.

[16] C. A. Witham, W. Huang, C. Tsung, J. N. Kuhn, G. A. Somorjai, and F. D. Toste, "Converting homogeneous to heterogeneous in electrocatalytic catalysis using monodisperse metal nanoparticles," Nature Chemistry, vol. 2, no. 1, pp. 36–41, 2010.

[17] P. T. Anastas and J. C. Warner, Green Chemistry: Theory and Practice, Oxford Publication, New York, NY, USA, 1998.

[18] M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol, and P. Machado, "Solvent-free heterocyclic synthesis," Chemical Reviews, vol. 109, no. 9, pp. 4140–4182, 2009.

[19] P. F. Walsh, H. Li, and C. A. de Parrodi, "A green chemistry approach to asymmetric catalysis: solvent-free and highly concentrated reactions," Chemical Reviews, vol. 107, no. 6, pp. 2503–2545, 2007.

[20] K. Tanaka and F. Toda, "Solvent-free organic synthesis," Chemical Reviews, vol. 100, no. 3, pp. 1025–1074, 2000.

[21] G. Nagendrappa, "Organic synthesis under solvent-free condition: an environmentally benign procedure—II," Resonance, vol. 7, no. 10, pp. 59–68, 2002.

[22] K. Tanaka, Solvent-Free Organic Synthesis, Wiley-VCH, Weinheim, Germany, 2009.

[23] M. Fathalla, C. M. Lawrence, N. Zhang, J. L. Sessler, and J. Jayawickramarajah, “Base-pairing mediated non-covalent polymers,” Chemical Society Reviews, vol. 38, no. 6, pp. 1608–1620, 2009.

[24] S. Sivakova and S. J. Rowan, "Nucleobases as supramolecular motifs," Chemical Society Reviews, vol. 34, no. 1, pp. 9–21, 2005.

[25] M. W. Powner, B. Gerland, and J. D. Sutherland, "Synthesis of activated pyrimidine ribonucleotides in prebiotically plausible conditions," Nature, vol. 459, no. 7244, pp. 239–242, 2009.

[26] O. S. Pedersen and E. B. Pedersen, "Non-nucleoside reverse transcriptase inhibitors: the NNRTI boom," Antiviral Chemistry and Chemotherapy, vol. 10, no. 6, pp. 285–314, 1999.

[27] A. R. Dinner, G. M. Blackburn, and M. Karplus, "Uracil-DNA glycosylase acts by substrate autocatalysis," Nature, vol. 413, no. 6857, pp. 752–755, 2001.

[28] F. C. Tucci, Y. F. Zhu, Z. Guo et al., "3-(2-aminoalkyl)-1-(2,6-difluorobenzyl)-5-(2-fluoro-3-methoxyphenyl)-6-methyluracils as orally bioavailable antagonists of the human gonadotropin releasing hormone receptor," Journal of Medicinal Chemistry, vol. 47, no. 14, pp. 3483–3486, 2004.

[29] D. P. Sutherland, D. Sampath, M. Berry et al., "Discovery of (thienopyrimidin-2-yl)aminopyrimidines as potent, selective, and orally available Pan-P13-kinase and dual Pan-P13-kinase/mTOR inhibitors for the treatment of cancer," Journal of Medicinal Chemistry, vol. 53, no. 3, pp. 1086–1097, 2010.

[30] S. Manta, E. Tsoukala, N. Tzioumaki, C. Kiritsis, J. Balzarini, and D. Komitiotis, "Synthesis of 4,6-dideoxy-3-fluoro-2-keto-β-d-glucopyranosyl analogues of 5-fluorouracil, Nβ-benzoyl adenine, uracil, thymine, Nβ-benzoyl cytosine and evaluation of their antitumor activities," Bioorganic Chemistry, vol. 38, no. 2, pp. 48–55, 2010.

[31] T. Lundqvist, S. L. Fisher, G. Kern et al., "Exploitation of structural and regulatory diversity in glutamate racemases," Nature, vol. 447, no. 7146, pp. 817–822, 2007.

[32] J. B. Parker, M. A. Bianchet, D. J. Krosby, J. I. Friedman, L. M. Amzel, and J. T. Stivers, "Enzymatic capture of an extrahelical thymine in the search for uracil in DNA," Nature, vol. 449, no. 7161, pp. 433–437, 2007.

[33] A. Okamoto, "Chemical approach toward efficient DNA methylation analysis," Organic and Biomolecular Chemistry, vol. 7, no. 1, pp. 21–26, 2009.

[34] A. Samanta, D. D. Leonidas, S. Dasgupta, T. Pathak, S. E. Zogofrin, and N. G. Okonomokos, "Morpholin, piperedin, and pyrrolidino derivatives of pyrimidine nucleosides as inhibitors of ribonuclease A: synthesis, biochemical, and crystallographic evaluation," Journal of Medicinal Chemistry, vol. 52, no. 4, pp. 932–942, 2009.

[35] R. Rico-Gómez, J. M. López-Romero, J. Hierrezuelo, J. Brea, M. I. Loza, and M. Pérez-Gonzalez, "Synthesis of new mannosyl, galactosyl and glucosyl theophylline nucleosides with potential activity as antagonists of adenosine receptors. DEMA-induced cyclization of glycosylidineiminouracils," Carbohydrate Research, vol. 343, no. 5, pp. 855–864, 2008.

[36] S. Das and A. J. Thakur, "A clean, highly efficient and one-pot green synthesis of aryl/alkyl/heteroaryl-substituted bis(6-amino-1,3-dimethyluracil-5-yl)methanes in water," European Journal of Organic Chemistry, no. 12, pp. 2301–2308, 2011.
[37] J. W. Blunt, B. R. Copp, W. P. Hu, M. H. G. Munro, P. T. Northcotec, and M. R. Prinsep, “Marine natural products,” Natural Product Reports, vol. 26, no. 1, pp. 170–224, 2008.

[38] V. E. Semenov, V. D. Akamsin, V. S. Reznik et al., “New type of pyrimidinophanes with α,ω-bis(uracil-1-yl)alkane and bis(uracil-5-yl)methane units,” Mendeleev Communications, vol. 11, no. 3, pp. 96–97, 2001.

[39] V. K. Das, R. R. Devi, P. K. Raul, and A. J. Thakur, “Nano rod-shaped and reusable basic Al$_2$O$_3$ catalyst for N-formylation of amines under solvent-free conditions: a novel, practical and convenient ‘NOSE’ approach,” Green Chemistry, vol. 14, no. 3, pp. 847–854, 2012.

[40] V. K. Das, R. R. Devi, and A. J. Thakur, “Recyclable, highly efficient and low cost nano-MgO for amide synthesis under SFRC: a convenient and greener "NOSE" approach,” Applied Catalysis A, vol. 456, pp. 118–125, 2013.

[41] V. K. Das, M. Borah, and A. J. Thakur, “Piper-betle-shaped nano-S-catalyzed synthesis of 1-amidoalkyl-2-naphthols under solvent-free reaction condition: a greener nanoparticle-catalyzed organic synthesis enhancement approach,” Journal of Organic Chemistry, vol. 78, no. 7, pp. 3361–3366, 2013.

[42] M. Shojaie-Bahaabad and E. Taheri-Nassaj, “Economical synthesis of nano alumina powder using an aqueous sol-gel method,” Materials Letters, vol. 62, no. 19, pp. 3364–3366, 2008.

[43] C. Huang, J. Wang, and C. Huang, “Sintering behavior and microwave dielectric properties of nano alpha-alumina,” Materials Letters, vol. 59, no. 28, pp. 3746–3749, 2005.

[44] Y. Zhang, J. Liu, R. He, Q. Zhang, X. Zhang, and J. Zhu, “Synthesis of alumina nanotubes using carbon nanotubes as templates,” Chemical Physics Letters, vol. 360, no. 5-6, pp. 579–584, 2002.
