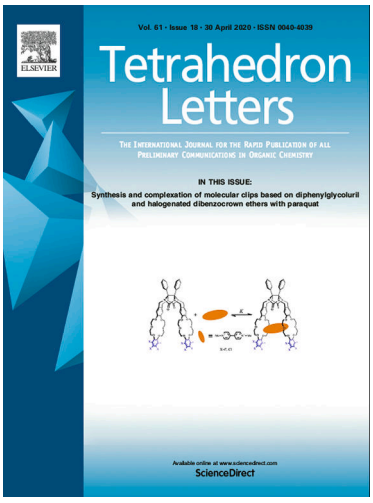
Journal Pre-proofs



Nano indium oxide-catalyzed domino reaction for the synthesis of *N*-alkoxylated benzimidazoles

Satyajit Samanta, Sachinta Mahato, Rana Chatterjee, Sougata Santra, Grigory V. Zyryanov, Adinath Majee

PII: S0040-4039(20)30637-7
DOI: https://doi.org/10.1016/j.tetlet.2020.152177
Reference: TETL 152177

To appear in: *Tetrahedron Letters*

Received Date: 24 April 2020
Revised Date: 22 June 2020
Accepted Date: 24 June 2020

Please cite this article as: Samanta, S., Mahato, S., Chatterjee, R., Santra, S., Zyryanov, G.V., Majee, A., Nano indium oxide-catalyzed domino reaction for the synthesis of *N*-alkoxylated benzimidazoles, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152177

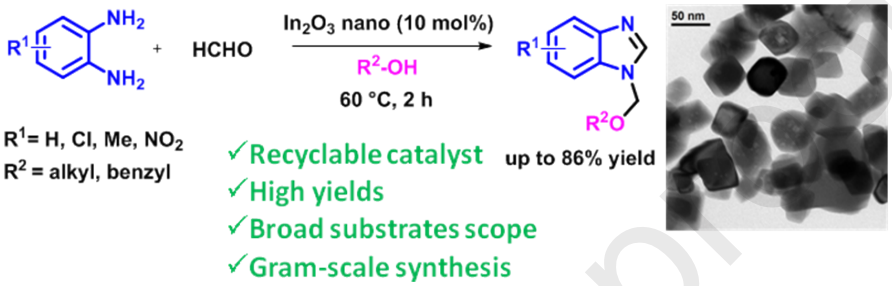
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Nano indium oxide-catalyzed domino reaction for the synthesis of *N*-alkoxylated benzimidazoles

Leave this area blank for abstract info.

Satyajit Samanta, Sachinta Mahato, Rana Chatterjee, Sougata Santra, Grigory V. Zyryanov, and Adinath Majee*



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Nano indium oxide-catalyzed domino reaction for the synthesis of *N*-alkoxylated benzimidazoles

Satyajit Samanta,[a] Sachinta Mahato,[a] Rana Chatterjee,[a] Sougata Santra,[b] Grigory V. Zyryanov,[b,c] and Adinath Majee[a,]*

[a] *Department of Chemistry; Visva-Bharati (A Central University), Santiniketan 731235, India*
[b] *Department of Organic and Biomolecular Chemistry, Chemical Engineering Institute, Ural Federal University, 19 Mira Street, 620002, Yekaterinburg, Russian Federation*
[c] *I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, 620219 Yekaterinburg, Russian Federation*

ARTICLE INFO

* Corresponding author. e-mail: adinath.majee@visva-bharati.ac.in

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Nano indium oxide
N-Alkoxylated benzimidazoles
ortho-Phenylenediamine
Formaldehyde
Reusable catalyst

ABSTRACT

A convenient method has been developed for the selective synthesis of *N*-alkoxylated benzimidazole derivatives by the cyclocondensation reaction of simple *ortho*-phenylenediamine, formaldehyde and alcohols in presence of indium oxide nanoparticles as catalyst. The alcohol acts as reactant as well as solvent in this reaction. No other solvents or additives have been used for this reaction. The catalyst can be reused several times without significant loss of catalytic activity. A probable reaction mechanism has been proposed based on some control experiments.

Benzimidazole is fused aromatic heterocyclic compound (i.e. a couple of benzene and imidazole ring) which is mainly a derivative of imidazole framework. Among heterocyclic pharmacophores [1], benzimidazole and its derivatives are very much highlighted in the synthesis of pharmacologically and biologically active compounds [2-4]. Benzimidazoles with different functional group(s) at position(s) on the interior framework display a wide range of biological activities like anti-HBV (**A**) [5], antitubercular (**B**) [6], non-seadating antihistamine (**C**) [7], ($GABA_A$ agonists (**D**) [8], anti-viral (**E**) [9], anti-inflammatory and analgesic (**F**) [10] (Figure 1).

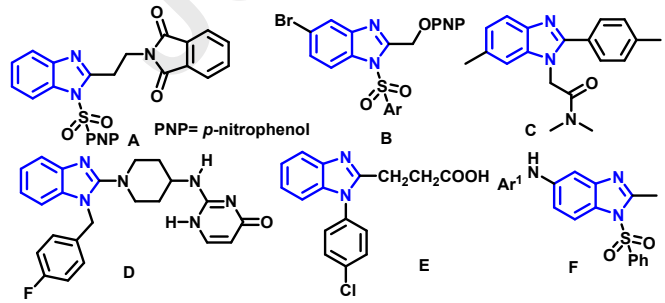


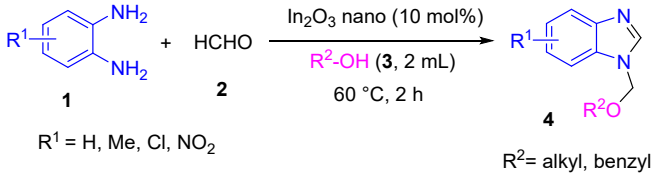
Figure 1. Some biologically active *N*-protected benzimidazole scaffold.

Domino reactions are one of the most powerful and atom economical methodologies in organic synthesis [11]. These reactions usually proceed in a more efficient and environmentally benign manner than conventional procedures by omitting the steps of separation and purification of the reaction intermediates.

Classically, benzimidazoles are prepared by the two ways *i.e.* first, by different cyclocondensation reaction and secondly by cross dehydrogenative coupling (CDC) via C-H functionalization and C-N bond formation. Moreover, 2-substituted benzimidazoles were synthesized from various *ortho*-phenylenediamines (OPDs) which subjected to react with different functional groups via cyclocondensation pathways [12-14] or CDC coupling [15-17]. A few protocols have been reported in the last decade to synthesize 1,2-disubstituted benzimidazoles like *N*-alkylation of ortho-nitro [18,19] ortho-bromo anilide [20,21] followed by cyclocondensation / reductive cyclization pathway or direct coupling of *ortho*-phenylenediamines with aryl, alkyl aldehydes using a variety of catalysts such as SDS micelles [22], cobalt(II) chloride [23], trimethylsilyl chloride [24], organocatalyst like L-proline [25], DMF/TMSCl [26], also indium oxide nano [27] and dehydrogenative coupling between aromatic diamines and alcohols using different catalyst like Ir(III) [28], Mn(I) [29], Ni(II) [30]. In addition, water-assisted tandem *N*-alkylation-reduction-condensation process was also developed [31]. Very recently, several convenient methods have been reported, such as Fe-catalyzed CDC reaction and aromatization of diarylmethyl- and dialkyl- benzimidazole precursors [32], dodecylimidazolium hydrogen sulfate-catalyzed condensation reaction between OPDs and aldehydes [33], metal-free, aerobic oxidative C-O and C-C

cle the [34], cascade oxidation/cyclization/alkylation reaction of meso-hydrobenzoin or benzyl alcohols with OPD and 2,6-difluorobenzyl bromide [35], I_2-mediated intramolecular C–H amidation reaction [36] and hydrotalcite supported BINAP-copper-catalyzed reaction between OPDs and benzyl alcohols [37]. Most of these methodologies used substituted diamines, aromatic aldehydes rather than aliphatic aldehydes and also product selectivity is a major problem due to the formation of three types of substituted benzimidazole derivatives (*N*-1 substituted, 2- substituted, 1,2-disubstituted benzimidazoles).

The use of indium oxide nano (In_2O_3) mediated in the area of organic synthesis is very much limited [38-40]. As a continuation of our previous work on indium oxide nano [27,39,40], here we are pleased to report a convenient synthesis of *N*-substituted benzimidazole derivatives (*N*-alkoxylated benzimidazoles) by the multicomponent reaction (MCR) of *ortho*-phenylenediamines (OPDs) with formaldehyde and alcohol in presence of indium oxide nano particles (In_2O_3) *via* intermolecular cyclization (Scheme 1). To the best of our knowledge, this is the first time report for the synthesis of *N*-alkoxylated benzimidazoles derivatives synthesized in a one pot domino fashion.

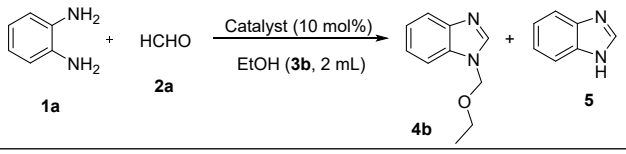


Scheme 1. Synthesis of *N*-substituted benzimidazole derivatives.

We initiated our observation by using *ortho*-phenylenediamine (**1a**, 0.5 equiv.) and 37% formaldehyde (**2a**, 2 equiv.) in presence of In_2O_3 nano (5 mol%) in ethanol solvent (**3b**, 2 mL) at 60 °C under the open air. To our delight, the reaction underwent smoothly and 50% of 1-(ethoxymethyl)-1*H*-benzo[*d*]imidazole (**4b**) and 15% of 1*H*-benzo[d]imidazole (**5**) were isolated within 2 h (Table 1, entry 1). Inspired by this result when we increased the amount of In_2O_3 nano to 10 mol% the yield of the reaction increased significantly with 76% of **4b** and 20% of **5** (Table 1, entry 2). Further increase of catalyst loading did not improve the yield of the reaction (Table 1, entry 3). Again, the yield of the reaction did not improve appreciably by increasing the reaction time but with reducing the reaction time the yield of both **4b** and **5** decreased considerably (Table 1, entry 6 & 7). Increasing temperature from 60 °C to 80 °C no considerable improvement has been noticed whereas, decreasing the temperature decreased the yield of both **4b** and **5** (Table 1, entry 4 & 5). We examined other indium catalysts like $InCl_3$, $In(OTf)_3$ and also other catalysts like $Zn(OTf)_2$, CuO nano but the yields are not impressive (Table 1, entry 8-11). But in the absence of any catalyst, the reaction did not proceed at all (Table 1, entry 12).

Next, for enrichment of our present methodology and to get a better knowledge of the solvent effects, we have screened a series of mix-solvent as summarized in Table 2. For polar aprotic solvents like DCE, THF, 1,4-dioxane and DCM in the presence of ethanol (**3b**) the targeted product (**4b**) was found in 20-35% yields (Table 2, entry 1-4). When we used nonpolar aprotic solvent like toluene, DCB and also polar aprotic solvent like DMSO with ethanol (**3b**) we got lower and a trace amount of yield of the products (Table 2, entry 5-7). We acquired the best result affording 76% yield of our desired product (**4b**) when we optimized condition was considered by using 10 mol% of In_2O_3 nano and ethanol as solvent as well as reactant (**3b**, 2 mL) at 60 °C for 2 h.

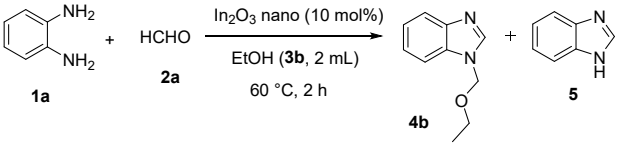
Table 1. Optimization of the reaction conditions [a]



Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield of **4b** (%)[b]	Yield of **5** (%)[b]
1	In_2O_3 nano (5)	60	2	50	15
2	In_2O_3 nano (10)	60	2	76	20
3	In_2O_3 nano (20)	60	2	76	20
4	In_2O_3 nano (10)	80	2	70	20
5	In_2O_3 nano (10)	40	2	45	10
6	In_2O_3 nano (10)	60	4	72	20
7	In_2O_3 nano (10)	60	1	60	15
8	$InCl_3$ (10)	60	2	58	21
9	$In(OTf)_3$ (10)	60	2	55	20
10	$Zn(OTf)_2$ (10)	60	2	<10	NR[c]
11	CuO nano (10)	60	2	55	20
12	-	60	2	NR[c]	NR[c]

[a]Reaction conditions: All the reactions were carried out on 1 mmol scale, **1a** (1 equiv.), 37% HCHO (**2a**, 2 equiv.) in presence of catalyst and ethanol (**3b**, 2 mL). [b]Isolated yield. [c]NR = no reaction.

Table 2. Screening of the solvent effects[a]



Entry	Solvents (2 mL)	Yield of **4b** (%)[b]	Yield of **5** (%)[b]
1	DCM	25	<10
2	DCE	35	15
3	THF	20	<5
4	1,4- dioxane	20	<8
5	DMSO	trace	ND[c]
6	Toluene	15	<8
7	DCB	20	<8
8	EtOH	76	20

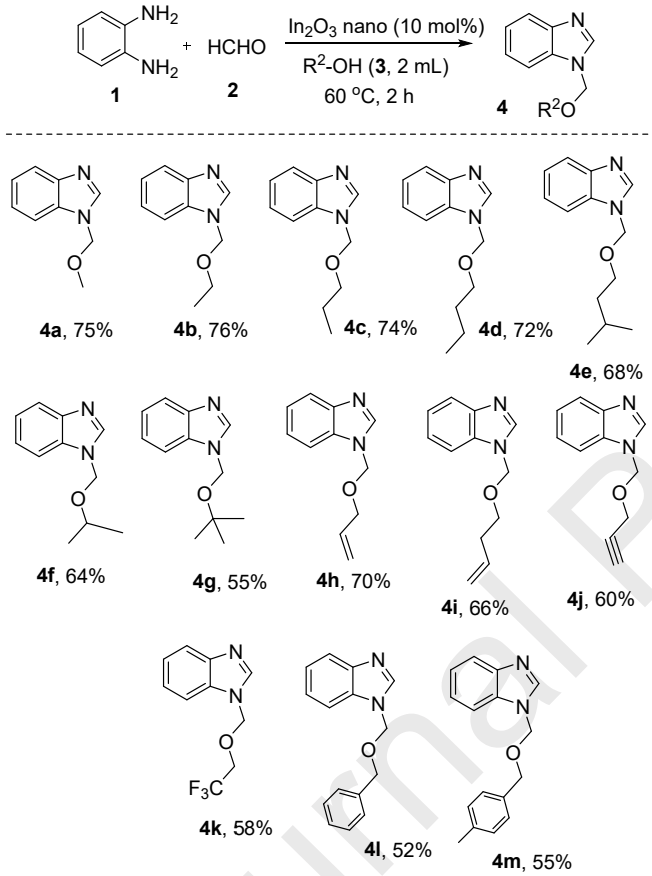
[a]Reaction conditions: All the reactions were carried out on 1 mmol scale, **1b** (1 equiv.), 37% HCHO (**2a**, 2 equiv.) in presence of different solvent (2 mL). [b]Isolated yield. [c]ND = not detected in TLC.

After optimization, we explored the substrate scope of this methodology and the results are summarized in Table 3 & 4. A library of *N*-alkoxylated benzimidazole derivatives was synthesized by varying different alcohols. At first, we used different primary as well as saturated alcohols like methanol (**3a**), propanol (**3c**), butanol (**3d**) and isobutanol (**3e**) which were

subj

observed that the corresponding desired products were obtained in 68-76% yields (Table 3, **4a**-**4e**). Next, in case of secondary and tertiary alcohols (**3f** & **3g**), the corresponding desired products were obtained in moderate yields (Table 3, **4f** & **4g**). Remarkably, unsaturated alcohols like prop-2-en-1-ol (**3h**), but-3-en-1-ol (**3i**) and propargyl alcohol (**3j**) were also examined and the reactions underwent without any difficulty to produce the products (60-70% yields) (Table 3, **4h**-**4j**). Even, trifluoroethanol (**3k**) responded for this present protocol affording moderate yield (**4k**). Moreover, benzyl alcohol and 4-methyl benzyl alcohol also gave the alkoxylated products in 52% and 55% yields (**4l, 4m**). For all these reactions no additional solvent was needed but the alcohols themselves acted as solvent and reactant.

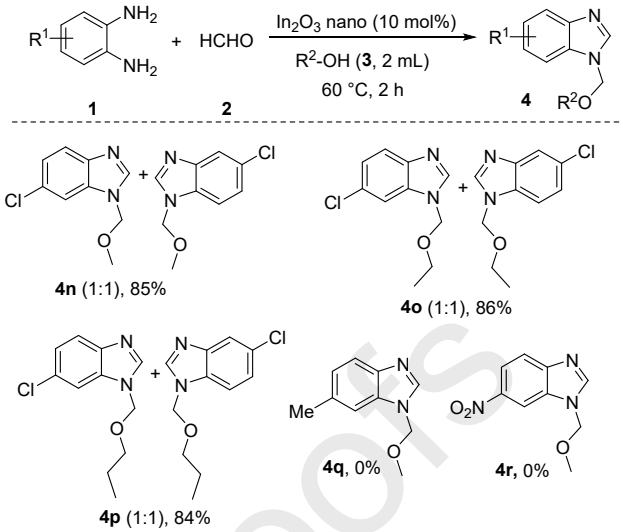
Table 3. Substrates scope using different alcohols[a,b]



[a]Reaction conditions: All reactions were carried out on 1 mmol scale, **1** (1 equiv.), 37% HCHO (**2a**, 2 equiv.) in presence of In_2O_3 nano (10 mol%) and ethanol (**3b**, 2 mL). [b]Isolated yield.

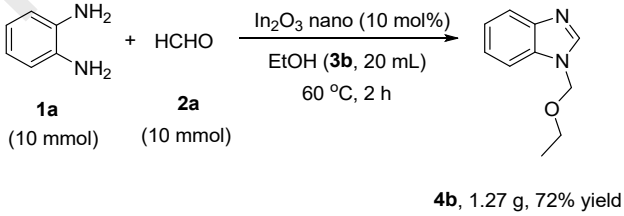
Next, our attention was turned to the use of substituted phenylenediamine to expand the general applicability of the present procedure (Table 4). Surprisingly, 4-chlorobenzene-1,2-diamine reacted well with ethanol but produced the *N*-alkoxylated product (86%) with 1:1 mixture of isomers (**4o**). We have also changed alcoholic part like methanol, propanol but we get the same mixture of the product (**4n**, **4p**) with good yields (85% and 84% respectively). However, 4-methylbenzene-1,2-diamine (**1b**) and 4-nitrobenzene-1,2-diamine (**1c**) did not undergo to afford the corresponding products under the present reaction conditions.

phenylenediamines [a,b]



[a]Reaction conditions: All the reactions were carried out on 1 mmol scale, **1** (1 equiv.), 37% HCHO (**2a**, 2 equiv.) in presence of In_2O_3 nano and ethanol (**3b**, 2 mL). [b]Isolated yield.

Moreover, the synthetic applicability of this protocol was investigated on the gram scale using the model reaction in our laboratory setup. As shown in Scheme 2, the reaction could afford 1.27 g of **4b** in 72% yield without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of *N*-alkoxylated benzimidazole derivatives.



Scheme 2. Gram-scale reaction.

To check the recyclability of the catalyst, it was separated from the reaction mixture by ultra centrifugation, washed with water, dried under vacuum followed by drying at 110 °C and reused for further reactions. The catalyst maintained its high level of activity even after being recycled five times for synthesizing **4b** as shown in Table 4.

Table 4. Recycling of In_2O_3 nanoparticles for synthesizing **4b**[a]

No. of cycle	Yields (%)[b]	Catalyst recovery (%)
1	76	97
2	75	95
3	75	93
4	72	90
5	71	87

[a]Carried out with 1 mmol of **1a** and 1 mmol of **2a** in the presence of catalyst in ethanol (2 mL) at 60 °C for 2 h. [b]Isolated yields.

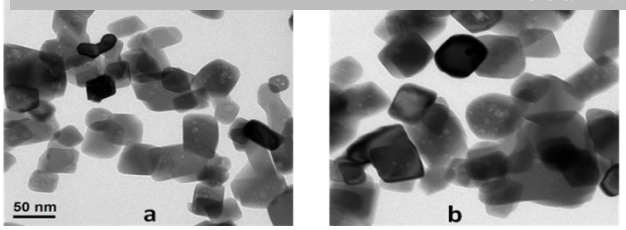
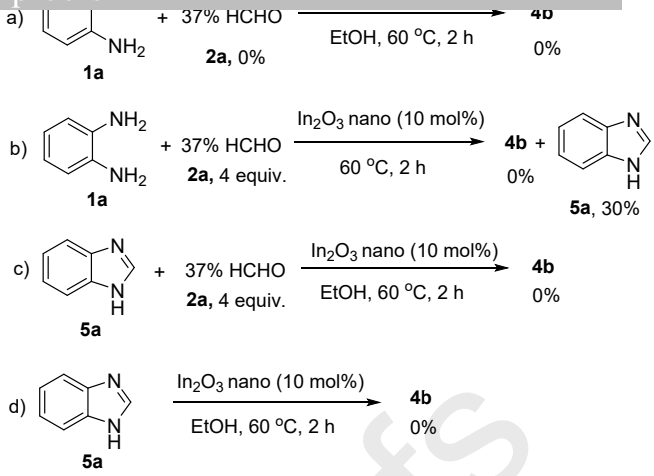


Figure 2. HRTEM images of (a) fresh In_2O_3 nanoparticles and (b) In_2O_3 nanoparticles after the fifth cycle.

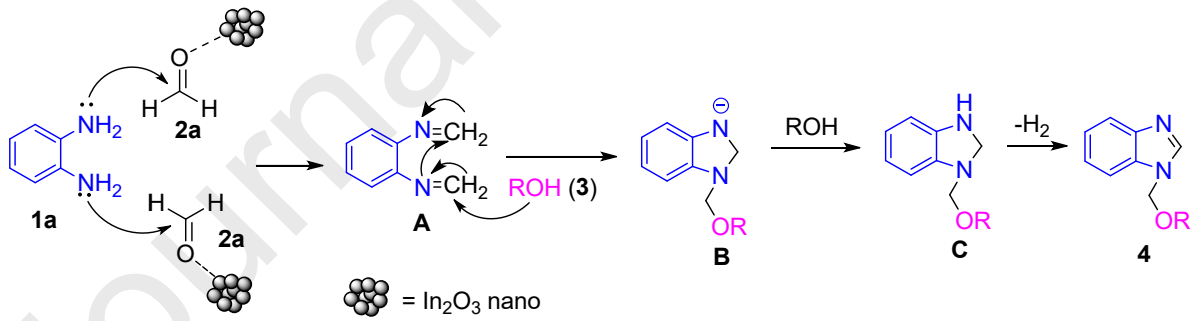
The morphology of nano-In_2O_3 was determined by HRTEM. A comparative study of the HRTEM of the fresh catalyst and the recovered catalyst after five cycles shows that the catalyst does not undergo agglomeration during the recycling process (Figure 2).

For the mechanistic investigation of our present protocol, we performed some control experiments (Scheme 3). When the reaction was carried out in absence of formaldehyde no desired product was obtained (Scheme 3a). Again, the targeted product was not formed in the absence of ethanol but we got only benzimidazole product (**5a**) in 30% yield (Scheme 3b). Next, by taking only synthesized benzimidazole (**5a**) instead of 1,2-phenylenediamine (**1a**) and formaldehyde, no desired product was obtained under the optimized reaction conditions (Scheme 3c). Similarly, the present reaction did not proceed when benzimidazole (**5a**) reacted with ethanol in the absence of formaldehyde under the same reaction conditions (Scheme 3d). So, from the above observations, it is clear that the reaction does not proceed via the formation of benzimidazole as intermediate.



Scheme 3. Control experiments.

On the basis of these experimental observations, literature reports [41] and our previous experience in In_2O_3 nano [27,39,40], a probable mechanistic pathway has been proposed for the synthesis of *N*-alkoxylated benzimidazole derivatives as shown in Scheme 4. Initially, *ortho*-phenylenediamine (**1a**) reacts with formaldehyde (**2a**) to form 1,2-diimine intermediate (**A**). In_2O_3 nano might activate the formaldehyde through the co-ordination with the oxygen of the corresponding carbonyl group which facilitates the subsequent nucleophilic attack by the nitrogen atom on the carbonyl carbon. The addition of alcohol (**3**) with one imine produces the nucleophilic nitrogen which by intra-molecular imine cyclization furnish the intermediate (**B**). The intermediate **B** after protonation gives intermediate (**C**) which on aromatization by dehydrogenation produce the final product.



Scheme 4. Plausible mechanistic pathway.

In conclusion, a convenient method has been developed for the synthesis of *N*-alkoxylated benzimidazoles by the reaction between readily available 1,2-phenylenediamine, formaldehyde and alcohol in the presence of indium oxide nano as catalyst. To the best of our knowledge, this is the first-time report for the synthesis of *N*-alkoxylated benzimidazoles derivatives synthesized in a one-pot tandem fashion. Furthermore, the present methodology is also applicable for the gram-scale synthesis without any significant loss of its efficiency, demonstrating the potential applications of the present method for a large-scale synthesis of *N*-alkoxylated benzimidazole derivatives. Easily accessible reagents, gram-scale synthesis, general applicability, simple operation, mild reaction conditions and reusability of the catalyst are the remarkable advantages of the present methodology. We believe that our new protocol using In_2O_3 nano will find widespread applications in academic laboratories and industry.

Acknowledgments

A. Majee acknowledges financial support from the CSIR-Major Research Project (Ref. No. 02(0383)/19/EMR-II). S. Santra acknowledges the Russian Science Foundation – Russia (Ref. # 18-73-00301) for funding. We are thankful to the DST-FIST and UGC-SAP programmes.

Ref

1. Alaqeel SI. *J Saudi Chem Soc*. 2017; 21: 229–237.
2. Bhattacharya S, Chaudhuri P. *Curr Med Chem*. 2008; 15: 1762–1777.
3. Boiani M, González M. *Mini Rev Med Chem*. 2005; 5: 409–424.
4. Horton DA, Bourne GT, Smythe ML. *Chem Rev*. 2003; 103: 893–930.
5. Li Y-F, Wang G-F, He P-L, Huang W-G, Zhu F-H, Gao H-Y, Tang W, Luo Y, Feng C-L, Shi L-P. *J Med Chem*. 2006; 49: 4790–4794.
6. Ranjith PK, Rajeesh P, Haridas KR, Susanta NK, Row TNG, Rishikesan R, Kumari NS. *Bioorg Med Chem Lett*. 2013; 23: 5228–5234.
7. Prakash A, Lamb HM. *BioDrugs*. 1998; 10: 41–63.
8. Yuen J, Fang Y-Q, Lautens M. *Org Lett*. 2006; 8: 653–656.
9. Tewari AK, Mishra A. *Indian J. Chem., Sect. B* 2006; 45: 489–493.
10. Gaba M, Singh D, Singh S, Sharma V, Gaba P. *Eur J Med Chem*.
11. Tietze LF, Brasche G, Gericke K., in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.
12. Wright JB. *Chem Rev*. 1951; 48: 397–541.
13. Li L, Luo Q, Cui H, Li R, Zhang J, Peng T. *ChemCatChem*. 2018; 10: 1607–1613.
14. Sharma R, Abdullaha M, Bharate SB. *Asian J Org Chem*. 2017; 6: 1370–1374.
15. Daw P, Ben-David Y, Milstein D. *ACS Catal*. 2017; 7: 7456–7460.
16. Tateyama K, Wada K, Miura H, Hosokawa S, Abe R, Inoue M. *Catal Sci Technol*. 2016; 6: 1677–1684.
17. Chaudhari C, Siddiki SMAH, Shimizu K. *Tetrahedron Lett*. 2015; 56: 4885–4888.
18. Takeuchi K, Bastian JA, Gifford-Moore DS, Harper RW, Miller SC, Mullaney JT, Sall DJ, Smith GF, Zhang M, Fisher MJ. *Bioorg Med Chem Lett*. 2000; 10: 2347–2351.
19. Evindar G, Batey RA. *Org Lett*. 2003; 5: 133–136.
20. Brain CT, Steer JT. *J Org Chem*. 2003; 68: 6814–6816.
21. Saha P, Ali MA, Ghosh P, Punniyamurthy T. *Org Biomol Chem*. 2010; 8: 5692–5699.
22. Bahrami K, Khodaei MM, Nejati A. *Green Chem*. 2010; 12: 1237–1241.
23. Khan AT, Parvin T, Choudhury LH. *Synth Commun*. 2009; 39: 2339–2346.
25. Varala R, Nasreen A, Enugala R, Adapa SR. *Tetrahedron Lett*. 2007; 48: 69–72.
26. Ryabukhin S V, Plaskon AS, Volochnyuk DM, Tolmachev AA. *Synthesis (Stuttg)*. 2006; 2006: 3715–3726.
27. Santra S, Majee A, Hajra A. *Tetrahedron Lett*. 2012; 53: 1974–1977.
28. Sharma AK, Joshi H, Bhaskar R, Singh AK. *Dalt Trans*. 2017; 46: 2228–2237.
29. Das K, Mondal A, Srimani D. *J Org Chem*. 2018; 83: 9553–9560.
30. Bera A, Sk M, Singh K, Banerjee D. *Chem Commun*. 2019; 55: 5958–5961.
31. Kommi DN, Kumar D, Bansal R, Chebolu R, Chakraborti AK. *Green Chem*. 2012; 14: 3329-3335.
32. Thapa P, Palacios PM, Tran T, Pierce BS, Foss FW, Jr. *J. Org. Chem*. 2020, 85: 1991-2009.
33. Senapak W, Saeeng R, Jaratjaroonphong J, Promarak V, Sirion U. *Tetrahedron* 2019, 75: 3543-3552.
34. Senadi GC, Kudale VS, Wang J-J. *Green Chem* .2019, 21: 979-985.
35. Bi X, Meng X, Chen G, Chen B, Zhao P. *Catal. Commun*. 2018, 116: 27-31.
36. Hu Z, Zhao T, Wang M, Wu J, Yu W, Chang J. *J. Org. Chem*. 2017, 82: 3152-3158.
37. Xu Z, Yu X, Sang X, Wang D. *Green Chem*. 2018, 20: 2571-2577.
38. Reddy VP, Kumar AV, Swapna K, Rao KR. *Org Lett*. 2009; 11: 1697–1700.
39. Santra S, Majee A, Hajra A. *Catal. Commun.* 2014; 49: 52-57.
40. Mitra S, Bagdi AK, Majee A, Hajra A, *Tetrahedron Lett*. 2013; 54: 4982-4985.
41. Xu Z, Yu X, Sang X, Wang D, *Green Chem*. 2018; 20: 2571-2577.

Supplementary Material

Click here to remove instruction text...

Highlights

- Nano-In_2O_3 is found to be an efficient catalyst for three-component condensation.
- In_2O_3 nanoparticles are recyclable without significant loss of catalytic activities.
- Applicable to gram-scale synthesis of *N*-alkoxylated benzimidazoles.
- Control experiments were done for mechanism studies.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Nano indium oxide-catalyzed domino reaction for the synthesis of *N*-alkoxylated benzimidazoles

Leave this area blank for abstract info.

Satyajit Samanta, Sachinta Mahato, Rana Chatterjee, Sougata Santra, Grigory V. Zyryanov, and Adinath Majee*