Tetrahedron Letters 53 (2012) 5004–5007

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A clean and expedient synthesis of spirooxindoles in aqueous media catalyzed over nanocrystalline MgO

Bikash Karmakar[a,c], Anupam Nayak[b], Julie Banerji[c,*]

[a] Gobardanga Hindu College, Department of Chemistry, Khantura, North 24, Parganas 743273, India
[b] Bagnan College, Department of Chemistry, Bagnan, Howrah 711303, India
[c] Centre of Advances Studies on Natural products including Organic Synthesis, Department of Chemistry, University of Calcutta, 92, A.P.C. Road, Kolkata 700009, India

ARTICLE INFO

Article history:
Received 25 April 2012
Revised 7 July 2012
Accepted 9 July 2012
Available online 15 July 2012

Keywords:
Multicomponent synthesis
Spirooxindoles
4*H*-Chromene
Nanocrystalline MgO
Water chemistry

ABSTRACT

An efficient and eco-friendly method for the synthesis of spirooxindoles with fused tetrahydrochromenes has been demonstrated using basic nanocrystalline MgO catalyst in aqueous condition. The method has been applied for the synthesis of a range of compounds with variable functionalities in excellent yield and selectivity.

In the last few years, considerable effort is being made on the advancement of green chemistry using protocols having less environmental impact, maintaining higher atom-economy and recyclability. Multicomponent reactions have become popular for constructing complex molecules involving atom-economic way.[1] The green effect becomes more enhanced when the reactions are performed in water and over reusable heterogeneous catalysts. The importance of indoles and their derivatives is well recognized by the synthetic as well as natural product chemists due to their profound medicinal implications. As a result there has been an urge to prepare a variety of indole skeletons following easy and effective methodology.[2] Spiro compounds represent a distinguished class of molecules which are present in many naturally occurring substances.[3] Indoles being involved in these spiro nuclei enhance the biological activity to a significant extent. Examples that include this class are some cytostatic alkaloids like spirotryprostatins and pteropodines. They are effective inhibitors of microtubule activity and modulators of the function of muscarinic serotonin receptors.[4] Among the spirooxindole compounds those with substituted fused 4*H* chromenes have immense importance due to their spasmolitic, diuretic, anticoagulant, anticancer, and antinaphylactic activities.[5] Especially the nitrile substituted 4*H* chromenes are significant as they are effective drugs in human neurodegenerative disorders.[6] In view of these important implications, our current focus has been targeted on the facile synthesis of these moieties in a green pathway.

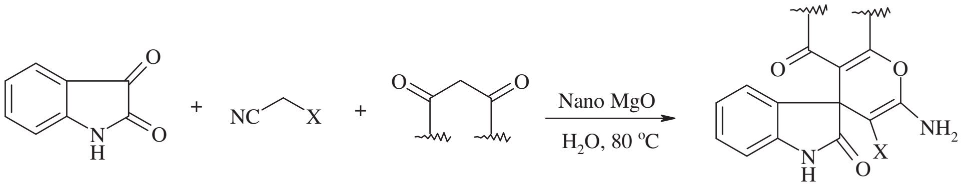
There have been several reports available in the literature on the multicomponent synthesis of fused spirochromenes. The conventional procedure constitutes the three component condensation of isatin, active methylene component, and 1,3-dicarbonyl compound. The methodology involves the use of $InCl_3$ in refluxing acetonitrile or $InCl_3/SiO_2$ composite in microwave,[7] applying the use of electrogenerated base[8] or the water mediated surfactant catalyzed synthesis.[9] However, most of the reported methods are associated with drawbacks like the use of carcinogenic organic solvents, applying high temperatures, use of expensive, and sometime non-commercially available catalysts. Those methods involving water mediated synthesis, lack the reusability property of the catalyst. A very recent method has been published on the synthesis over nanoparticular ZnS catalyst in water.[10] However, keeping in mind their own merits of the reported methods, we believe that there is scope for further development on the environmental and economical impact of the reaction.

Nanocrystalline metal oxides find excellent application as active adsorbent for gases, for destruction of hazardous chemicals,[11] and as catalyst in various organic reactions.[12] In continuation of our efforts for the development of synthetic methodologies for the production of various biologically important moieties using mesoporous heterogeneous and reusable catalysts,[13] we wish to report for the first time the use of nanocrystalline MgO catalyzed one-pot three-component synthesis of spirooxindoles with fused

---

* Corresponding author. Tel.: +91 33 2350 8386; fax: +91 33 2351 9755.
E-mail address: juliebanerji47@gmail.com (J. Banerji).

0040-4039/$ - see front matter Crown Copyright © 2012 Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.030



Scheme 1. Multicomponent synthesis of spirooxindoles.

chromenes in water with excellent yields (Scheme 1).[14] Our main focus in this work was to develop a methodology which would involve inexpensive and easily available reagent, fast and high yield reaction, and clean and eco friendly pathway.

At the outset of our study, we investigated the three-component reaction between isatin, malononitrile, and cyclohexane-1,3-dione in equimolar ratio as a model reaction in water at 80 °C, both in the absence and presence of catalysts as additives. The results have been shown in Table 1. We obtained a poor result in the absence of any catalyst even after 10 h of the reaction (entry 1, Table 1). Considering the reaction being base catalyzed, a variety of basic catalysts were employed under the same condition. Easily available and cheap bases like $NaHCO_3$, K_2CO_3, and $MgCO_3$ were found to promote the reaction in shorter reaction time along with moderate yield of the product (entry 2–4). Being encouraged with this result, we decided to go on with the surface active heterogeneous catalyst, viz., nanocrystalline MgO (5 mol %). Interestingly, it afforded an improved yield of 84% of the spirooxindole derivative within 2 h of the reaction (entry 5). A further better result was obtained with an increase in catalyst loading (entry 6–7). We wish to mention here that bulk MgO did not prove to be as efficient as its nano counterpart (entry 8). Finally the reaction condition was optimized with 15 mol % nanocrystalline MgO in water at 80 °C.

In a separate study we examined the probe reaction with a variation of temperature. At room temperature (25 °C) fruitful amount of conversion was not observed. However the productivity increased by raising the temperature. As shown in Table 2, the yield of spirooxindole gradually improved at 40 and 60 °C and reached a maximum at 80 °C. With further rise in temperature the yield did not improve.

On obtaining the optimized condition, a series of spirooxindoles with fused tetrahydro chromene derivatives were synthesized by combining isatin, different nitrilo active methylene components, and 1,3 dicarbonyl compounds in order to delineate the approach. In Table 3 the detailed study following the results has been given. This method is compatible with a wide variety of substrates. Three different cyano containing active methylene components viz., malononitrile, ethyl cyanoacetate, and cyano acetamide were used (**2a**–**c**). Similarly, a variety of 1,3 dicarbonyl compounds (both cyclic and acyclic) were used in the reactions (**3a**–**f**). In all the cases high yield of the products were observed in short reaction time. Meanwhile, 4-hydroxycoumarin (**3g**) was used instead of 1,3 dicarbonyl compounds to utilize its nucleophilic center and also here the corresponding spirooxindole derivative was generated in excellent yield. In all the cases the products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and elemental analysis and correlated with authentic data.

Recyclability of nanocrystalline MgO was examined through the reaction of isatin, malononitrile, and cyclohexane-1,3-dione in water. After completion of the reaction, the crude solid reaction mixture was filtered. It was then dissolved in hot methanol and filtered to separate the catalyst. The recovered MgO was washed with methanol several times and dried in an oven at 80 °C before being reused with a fresh batch of reactants. A comparison of morphology as well as internal chemical structure of the reused MgO with the fresh batch have been performed with SEM analysis and X-ray diffraction study.[15] The study revealed that the similar spongy porous structure and same crystal planes were still retained after reuse which is a major concern in retaining similar catalytic activity. Thus it was found that MgO could be recycled three times without much significant loss of activity. The reusability test has been shown in Table 4. The gradual reduction in activity might be exclaimed due to agglomeration of small particles.

MgO has a three-dimensional polyhedral structure, which having the presence of high surface concentrations of edge/corner and various exposed crystal planes (such as 200, 100 and 111) leads to inherently high surface reactivity per unit area.[15] Besides this, the NC MgO has a Lewis acid site Mg^{2+}, Lewis basic sites O^{2-} and O^{-}, lattice bound and isolated Bronsted hydroxyls, and anionic and cationic vacancies. A cascade reaction mechanism follows in the synthesis of spirooxindoles. Initial step involves a Knoevenagel condensation between isatin and malononitrile. The intermediate isatylidene malononitrile then undergoes Michael reaction via the enolic nucleophilic center of 1,3-dicarbonyl compound. Both these steps are known to be promoted by bases. Therefore the surface hydroxyls and oxide anions (basic sites) are expected to play their roles here. The final step is supposed to be catalyzed by Lewis acid site Mg^{2+} which involves the cyclization of hydroxyl group to cyano function affording the spirooxindole with fused tetrahydro chromene.

In conclusion, we have described a novel and highly efficient green protocol for the synthesis of diverse spirooxindole

Table 1
Evaluation of catalysts in the synthesis of spirooxindole by combining isatin, malononitrile and cyclohexane-1,3-dione[a]

Entry	Catalyst (mol%)	Time (h)	Yield (%)
1	None	10	33
2	$NaHCO_3$ (10)	6	57
3	K_2CO_3 (10)	6	61
4	$MgCO_3$ (10)	6	67
5	NC MgO (5)	2	84
6	NC MgO (10)	2	88
7	NC MgO (15)	2	93
8	bulk MgO (15)	2	78

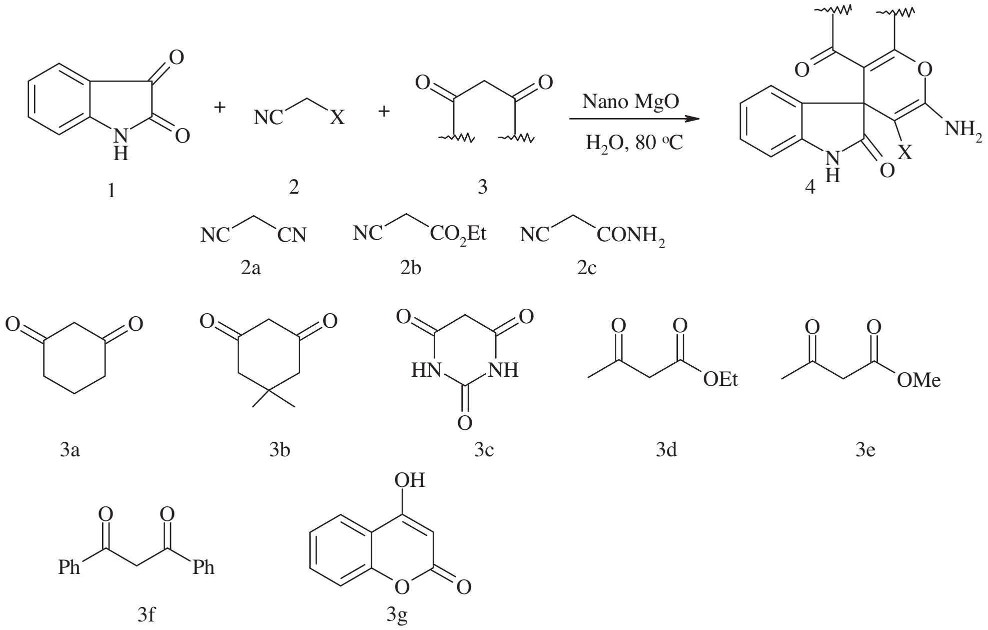
[a] Reaction condition: Isatin: malononitrile: cyclohexane-1,3-dione = 1:1:1, H_2O, 80 °C; Isolated yield; NC stands for nanocrystalline.

Table 2
Effect of temperature in the synthesis of spirooxindole by combining isatin, malononitrile and cyclohexane-1,3-dione[a]

Entry	Temperature (°C)	Time (h)	Yield (%)
1	25	12	27
2	40	6	51
3	60	2	87
4	80	2	93

[a] Reaction condition: Isatin: malononitrile: cyclohexane-1,3-dione = 1:1:1, H_2O, 15 mol % NC MgO; Isolated yield.

Table 3
Synthesis of spirooxindoles with varying reaction components in water over nanocrystalline MgO[a]



Entry	2	3	Product	Time (h)	Yield (%)
1	**2a**	**3a**	**4a**	2	93
2	**2a**	**3b**	**4b**	2	95
3	**2a**	**3c**	**4c**	1.5	88
4	**2a**	**3d**	**4d**	2	87
5	**2a**	**3e**	**4e**	2	84
6	**2a**	**3f**	**4f**	2.5	83
7	**2a**	**3g**	**4g**	1.2	91
8	**2b**	**3a**	**4h**	2	90
9	**2b**	**3b**	**4i**	2	92
10	**2b**	**3d**	**4j**	2.5	85
11	**2b**	**3f**	**4k**	3.0	80
12	**2b**	**3g**	**4l**	1.5	88
13	**2c**	**3a**	**4m**	2.5	84
14	**2c**	**3b**	**4n**	2	85
15	**2c**	**3d**	**4o**	3.0	80

[a] Reaction condition: All three reactants in equimolar ratio, H_2O, 80 °C; 15 mol % NC MgO; Isolated yield.

Table 4
Reusability study of NC MgO in the synthesis of spirooxindole by combining isatin, malononitrile and cyclohexane-1,3-dione[a]

Entry	Yield[a] (%)
1	93
2	92
3	85
4	83

[a] Isolated yield after each run.

derivatives catalyzed effectively by nanocrystalline MgO in aqueous medium. This method offers several advantages which includes high yield, short reaction time, a simple work-up procedure, ease of separation, and recyclability of the catalyst, as well as the ability to sustain a wide variety of reactants.

Acknowledgements

This work was financially supported by UGC, New Delhi and J.B. thanks them.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.030.

References and Notes

1. (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
2. (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic press: New York, 1970; (b) Lo, K. K.-W.; Tsang, K. H.-K.; Hui, W.-K.; Zhu, N. *Chem. Commun.* **2003**, *21*, 2704; (c) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **1891**, *2003*, 10.
3. (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127; (b) Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, 273.
4. (a) Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715; (b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666; (c) Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39.
5. (a) Skommer, J.; Wlodkowic, D.; Matto, M.; Eray, M.; Pelkonen, J. *Leuk. Res.* **2006**, *30*, 322.; (b) Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. *Tetrahedron Lett.* **2000**, *41*, 6993; (c) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517; (d) Witte, E.C.; Neubert, P.; Roesch, A. Ger. Offen. DE 3427985, 1986. *Chem. Abstr.* **1986**, *104*, 224915.; (e) Andreani, L. L.; Lapi, E. *Bol. Chim. Farm.* **1960**, *99*, 583.
6. Konkoy, C.S.; Fick, D.B.; Cai, S.X.; Lan, N.C.; Keana, J.F.W. PCT Int. Appl. WO0075123, 2000. *Chem. Abstr.* **2001**, *134*, 29313a.

7. Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057.
8. (a) Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron* **2007**, *63*, 10543; (b) Fotouhi, L.; Heravi, M. M.; Fatehi, A.; Bakhtiari, K. *Tetrahedron Lett.* **2007**, *48*, 5379.
9. (a) Zhu, S.-L.; Ji, S.-J.; Zhang, Y. *Tetrahedron* **2007**, *63*, 9365; (b) Gao, S.; Tsai, C. H.; Tseng, C.; Yao, C.-F. *Tetrahedron* **2008**, *64*, 9143; (c) Wang, L.-M.; Jiao, N.; Qiu, J.; Yu, J.-J.; Liu, J.-Q.; Guo, F.-L.; Liu, Y. *Tetrahedron* **2010**, *66*, 339.
10. Dandia, A.; Parewa, V.; Jain, A. K.; Rathore, K. S. *Green Chem.* **2011**, *13*, 2135.
11. (a) Lucas, E.; Decker, S.; Khaleel, A.; Seitz, A.; Fultz, S.; Ponce, A.; Li, W.; Carnes, C.; Klabunde, K. J. *Chem. Eur. J.* **2001**, *7*, 2505; (b) Schlogl, R.; Abd Hamid, S. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 1628; (c) Bell, A. T. *Science* **2003**, *299*, 1688; (d) Carnes, C. L.; Klabunde, K. J. *Langmuir* **2000**, *16*, 3764.
12. (a) Choudary, B. M.; Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Sreedhar, B. *J. Am. Chem. Soc.* **2004**, *126*, 3396; (b) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167; (c) Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Kantam, M. L. *Tetrahedron Lett.* **2005**, *46*, 1369; (d) Choudary, B. M.; Mahendar, K.; Ranganath, K. V. S. *J. Mol. Catal. A: Chem.* **2005**, *234*, 25; (e) Choudary, B. M.; Mahendar, K.; Kantam, M. L.; Ranganath, K. V. S.; Athar, T. *Adv. Synth. Catal.* **1977**, *2006*, 348; (f) Kantam, M. L.; Ranganath, K. V. S.; Mahendar, K.; Chakrapani, L.; Choudary, B. M. *Tetrahedron Lett.* **2007**, *48*, 7646.
13. (a) Karmakar, B.; Nayak, A.; Chowdhury, B.; Banerji, J. *Arkivoc* **2009**, *XII*, 209; (b) Postole, G.; Chowdhury, B.; Karmakar, B.; Pinki, K.; Banerji, J.; Auroux, A. *J. Catal.* **2010**, *269*, 110; (c) Karmakar, B.; Chowdhury, B.; Banerji, J. *Catal. Commun.* **2010**, *11*, 601; (d) Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2010**, *51*, 3855; (e) Karmakar, B.; Sinhamahapatra, A.; Panda, A. B.; Banerji, J.; Chowdhury, B. *Appl. Catal. A: Gen.* **2010**, *392*, 111; (f) Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2011**, *52*, 4957; (g) Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2011**, *52*, 6584.
14. *(i) Procedure for the synthesis of nanocrystalline Mgo*: The catalyst was prepared by non-hydrothermal sol-gel approach. Anhydrous $MgCO_3$ was used as the Mg source. Triethanolamine was used as a surfactant and structure directing template. $MgCO_3$ was dissolved in triethanolamine with stirring at room temperature. Deionised water was added to form a gel. Then another co-surfactant triethyl ammonium hydroxide was added dropwise to the mixture to maintain a pH 12. This was aged at room temperature for 24 h to obtain a white gel. The gel was dried at 120 °C for another 24 h and finally the cake was calcined at 600 °C for 6 h to obtain a fine white powder. The material has been characterized by SEM, TEM, and X-ray diffraction study (Supplementary data).
    (ii) Typical Procedure for the synthesis of spirooxindoles: A mixture of isatin, malononitrile, and cyclohexane-1,3-dione in equimolar ratio was heated (5 mL) in water at 80 °C. After completion of the reaction a precipitate was observed which was filtered. The solid thus obtained was dissolved in hot methanol to separate the catalyst. Pure product was obtained by recrystallization of the filtrate. The products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and elemental analysis. The characteristic spectroscopic data have been provided in the Supplementary data.
15. The comparison studies have been shown in Supplementary data.