Tetrahedron Letters 55 (2014) 2061–2064

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Michael addition of indoles to β-nitrostyrenes catalyzed by HY zeolite under solvent-free conditions

Mariappan Jeganathan [a], Kuppusamy Kanagaraj [a], Amarajothi Dhakshinamoorthy [a,b], Kasi Pitchumani [a,b,*]

[a] School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India
[b] Centre for Green Chemistry Processes, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

ARTICLE INFO

Article history:
Received 4 January 2014
Revised 22 January 2014
Accepted 24 January 2014
Available online 1 February 2014

Keywords:
Michael addition
HY zeolite
Indole
β-Nitrostyrenes
C–C bond formation

ABSTRACT

Michael addition of indoles to β-nitrostyrenes is reported using HY zeolite as catalyst under mild reaction conditions. This methodology allows the synthesis of various indole derivatives in good to high yields at 50 °C under solvent-free conditions. The short reaction time and achieving high yield of the desired products are the main advantages of the present work. The catalyst can be easily recovered and reused for six successive runs without considerable changes in yields. This Michael addition catalyzed by HY zeolite is operationally simple and can be considered as a greener protocol as it avoids the use of corrosive acids and toxic reagents.

Michael addition is one of the most important reactions for the construction of carbon–carbon bonds in organic reactions.[1] Among the Michael acceptors, nitroolefins are very attractive, since the nitro moiety is a strong electron-withdrawing group that can be readily transformed into a range of different functionalities.[2,3] Indole and many of its derivatives are relevant units in many naturally occurring compounds, because of their pharmacological and biological properties.[4] Due to the increased nucleophilic reactivity of C_3 position of indole ring, it is often used for the subsequent transformations leading to different indole alkaloids. In general, indole 3-derivatives were prepared by the Michael addition of indoles in the presence of samarium(III) iodide,[5] $CeCl_3{\cdot}7H_2O$–NaI/SiO_2,[6] Yb(OTf)$_3$,[7] $InCl_3$,[8] $InBr_3$,[9] iodine,[10] sulfamic acid,[11] boric acid,[12] Bi(OTf)$_3$,[13] $H_3PW_{12}O_{40}$,[14] basic alumina,[15] carbohydrate-based tolylsulfonyl hydrazines,[16] K10 montmorillonite,[17] β-cyclodextrin,[18] silica sulfuric acid,[19] and Sc(OTf)$_3$[20] as catalysts. Recently catalyst-free conjugate addition of indole to β-nitrostyrene was reported in aqueous medium[21] at 100 °C with 5–15 h of extended reaction time. Many of these reported procedures involve strongly acidic conditions, expensive reagents, and longer reaction times, and involve tedious procedures for the isolation of product. Also in some cases lower yield of products were observed due to dimerization of indole or polymerization of the nitroalkene. To overcome these problems, developing a simple and efficient method is always desirable for the conjugate addition of indoles to electron-deficient olefins.

Zeolites are microporous, crystalline aluminosilicates built from infinitely extending three-dimensional network of SiO_4 and AlO_4 tetrahedra that are linked together through oxygen bridges. By virtue of their structure, crystallinity, and variable stoichiometry, zeolite catalysts have well defined pore size distributions, adjustable acidity, very high surface area and good thermal stability.[22] Zeolites are also efficient inorganic solid acids, which are cheap and show high activities in organic reactions under heterogeneous reaction conditions.[23] They have been extensively used as solid heterogeneous catalysts in organic synthesis[24] due to their non-corrosive and non-toxic nature. In particular, HY zeolite has been reported as catalyst for the synthesis of heterocyclic compounds like imidazoles,[25a] tetrahydrocarbazoles,[25b] bis(indolyl)methanes,[25c] benzimidazoles,[25d] polyhydroquinolines,[25e] 1,4-dihydropyridines,[25f] and quinzolin-4(3*H*)ones.[25g] In continuation of our interest on the development of heterogeneous catalysts for organic transformations,[26] herein we report a new and efficient method for the Michael addition of indoles to β-nitrostyrenes in the presence of HY zeolite as a catalyst under mild and solvent-free conditions. Although zeolites have been used as catalysts for the synthesis of many heterocycles as mentioned above, this is the first report where the synthesis of indole derivatives being carried out in the presence of HY zeolite.

The reaction conditions were optimized for the Michael addition between indole and β-nitrostyrene under various parameters

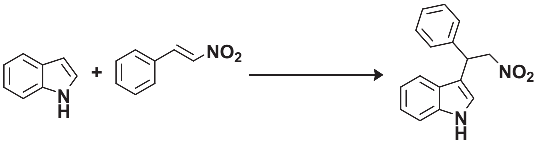
---

* Corresponding author. Tel.: +91 452 2456614; fax: +91 452 2459181.
E-mail address: pit12399@yahoo.com (K. Pitchumani).

http://dx.doi.org/10.1016/j.tetlet.2014.01.112
0040-4039/© 2014 Elsevier Ltd. All rights reserved.

Table 1

Optimization of reaction conditions for the Michael addition of indole to beta-nitrostyrene under different conditions[a]



Entry	Catalyst	Solvent	Time (h)	*T* (°C)	Yield[b] (%)
1	—	Neat	3	RT	—
2	—	Neat	3	50	9
3	NaY	Neat	1	RT	11
4	NaY	Neat	1	50	40
5	HY	Acetonitrile[c]	3	50	45
6	HY	Acetone[c]	3	50	41
7	HY	Ethanol[c]	3	50	38
8	HY	Tetrahydrofuran[c]	3	50	48
9	HY	Neat	2	RT	25
10	HY	Neat	0.5	50	51
11	HY	Neat	1	50	55[d]
12	HY	Neat	1	50	78[e]
13	HY	Neat	1	50	93[f]
14	HY	Neat	1	50	93[g]
15	HY	Neat	1	75	91

[a] Reaction conditions: indole (1 mmol), β-nitrostyrene (1 mmol), catalyst (100 mg).

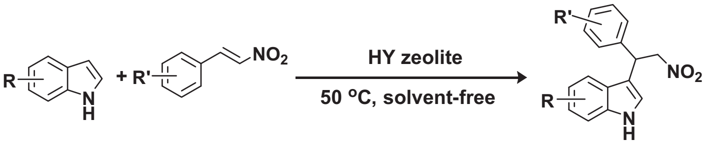
[b] Isolated yield.

[c] Solvent (5 mL).

[d–g] 20, 50, 100, and 200 mg of catalyst, respectively.

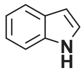
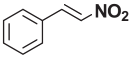
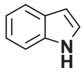
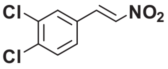
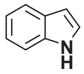
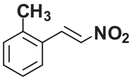
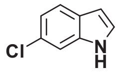
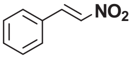
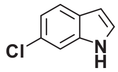
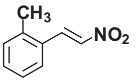
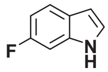
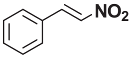
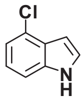
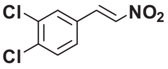
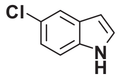
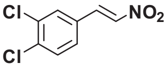
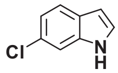
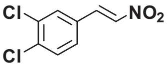
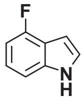
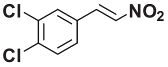
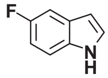
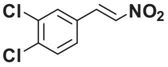
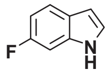
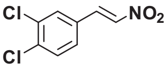
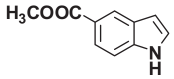
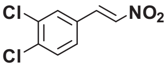
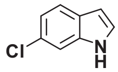
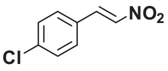
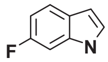
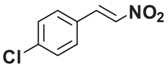
Table 2

Michael addition of substituted indoles to substituted β-nitrostyrenes catalyzed by HY zeolite under solvent-free conditions[a]



R = H, 6-Cl, 6-F, 4-Cl, 5-Cl, 4-F, 5-F, 5-COOCH$_3$

R' = H, 3,4-di-Cl, 2-CH$_3$, 4-Cl

Entry	Substituted Indole	Substituted β-Nitrostyrene	Time (h)	Yield[b] (%)
1			1	95
2			1	93
3			1.5	89
4			1	92
5			1.5	87
6			1	93
7			2	85
8			1.5	88
9			1.5	90
10			2	83
11			1.5	87
12			1.5	89
13			2	84
14			1.5	90
15			1.5	85

[a] Reaction conditions: substituted indole (1 mmol), substituted β-nitrostyrene (1 mmol), HY zeolite (100 mg), 50 °C under solvent-free conditions.

[b] Isolated yield.

like temperature, solvent, and catalyst loading. The observed results are given in Table 1. Control experiments in the absence of catalyst showed 0% and 9% yields in 3 h at room temperature and at 50 °C, respectively under neat conditions. On the other hand, NaY zeolite[27] resulted in 11% and 40% yields of the desired product at room temperature and at 50 °C in 1 h, respectively under neat conditions. HY zeolite gave moderate yields in the presence of organic solvents like acetonitrile, acetone, ethanol, and THF at 50 °C. In contrast, HY zeolite[27] showed a promising yield of 93% at 50 °C under neat conditions. Table 1 shows the influence of catalyst loading on the product yield. The high yield was achieved with 100 mg of HY zeolite and increasing its loading further to 200 mg failed to increase the yield. Also, it was found that high yield was achieved at 50 °C under the present experimental conditions.

The present methodology will be highly useful to synthesize a series of indole derivatives as it employs milder conditions and no solvent is required for this transformation. These encouraging results obtained in the preliminary experiments prompted us to expand the generality of this catalytic system to various other substituted indoles and β-nitrostyrenes and the observed results are given in Table 2.[28] In general, mono/di-substituted indole derivatives were readily reacted with mono/di-substituted β-nitrostyrenes in very high yields at short reaction times. This catalytic system allowed us to synthesize a series of indole derivatives containing fluoro, chloro, methyl, and ester groups and interestingly they are not affected during the course of reaction. This is yet another example to demonstrate nicely the catalytic activity of HY zeolite through its Bronsted acidity to promote this transformation.

In order to check the stability of catalyst under the present experimental conditions, reusability experiments were performed in the reaction between indole and β-nitrostyrene. Thus, after completion of the Michael addition, product was extracted with ethyl acetate. The catalyst was filtered, washed with ethyl acetate, and dried under vacuum. The recovered catalyst was reused in the next cycle. As it is shown in Table 3, the catalyst maintains its activity up to 6 reuses without much loss in its activity. This test clearly demonstrates the stability of catalyst over multiple runs and supporting its stability over extended duration.

Table 3
Reusability of HY zeolite in Michael addition of indole to β-nitrostyrene[a]

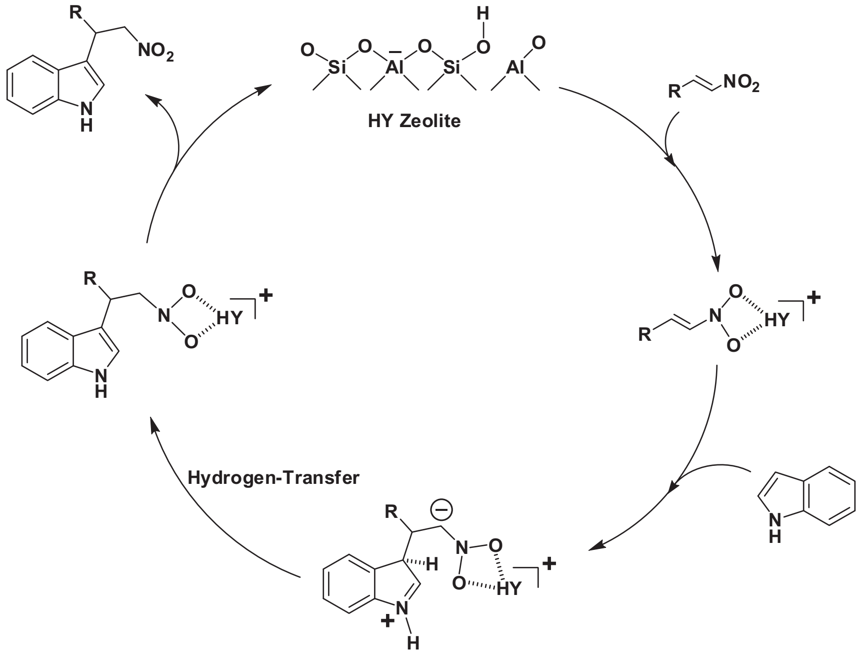
Run	1st	2nd	3rd	4th	5th	6th
Yield[b] (%)	95	93	91	90	88	85

[a] Reaction conditions: indole (1 mmol), β-nitrostyrene (1 mmol), HY zeolite (100 mg), 50 °C, 1 h under solvent-free conditions.
[b] Isolated yield.

The following mechanism is proposed for the Michael addition of indole and nitroalkene using HY zeolite as catalyst (Scheme 1). The nitroalkene was activated by chelation to HY zeolite to form a four-membered intermediate, which underwent nucleophilic addition of indole via its 3-position to provide the Michael adduct. Subsequent hydrogen-transfer, followed by dissociation affords the product regenerating the HY zeolite catalyst. This recovered catalyst was reused for the next cycle of reaction.

Data on the reaction conditions, as well as the activity and efficiency of the different catalysts reported in the literature for the Michael addition are given in Table 4. A comparison of these results indicates that our catalytic system (Table 4, entry 10) exhibits comparatively better activity compared to conventional catalysts which require higher reaction time (entries 2–6, 8, and 9), higher temperature (entries 5 and 7), and poor reusability of the catalyst (entries 1–3, 5, 6, and 8).

In conclusion, we have demonstrated the efficient catalytic activity of HY zeolite for Michael addition of indoles to β-nitrostyrene derivatives under mild and solvent-free conditions. In most of the cases, high yields of Michael adduct were achieved at short reaction times. The catalyst was recovered and reused with no noticeable changes in the yield. The salient features of this protocol are reusability, cost-effectiveness, environmentally benign nature, use of metal-free heterogeneous solid acid catalysts with high stability, shorter reaction time, tolerance toward wide range of



Scheme 1. Proposed mechanism for Michael addition of indole to β-nitroalkene catalyzed by HY zeolite.

Table 4
Comparison of the present catalytic system with the earlier reported procedures for the Michael addition from substituted indole and substituted β-nitrostyrene

Entry	Catalyst (weight)	Supporting reagent (weight)	Solvent	Temp (°C)	Time	Yield (%)	Reusability	Ref.
1	SmI_3 (0.1 mmol)	Silica gel (0.25 g)	ACN	Microwave	2 min	94–96	NR	5
2	$CeCl_3{\cdot}7H_2O$ (30 mol %)	NaI supported on Silica gel (30 mol %)	Neat	RT	4–24 h	74–96	NR	6
3	$InCl_3$ (10 mol %)	NR	DCM	RT	3.5 h	78	Reused[a]	8
4	$InBr_3$ (5 mol %)	NR	Water–THF	RT	2–24 h	28–99	5(93)	9
5	Sulfamic acid (0.01 g)	NR	Neat	60	0.5–6 h	80–99	NR	11
6	$H_3PW_{12}O_{40}$ (10 mg)	NR	Water	RT	14–18	74–93	NR	14
7	K10-Montmorillonite (200 mg)	NR	Neat	60	20–75 min	83–92	4(89)	17
8	Silica sulfuric acid (30 mg)	NR	Dichloroethane	RT	2.2–4 h	71–93	NR	19
9	$Sc(OTf)_3$ (2.5 mmol %)	NR	Water	30	10–1440 min	87–97	5(88)	20
10	HY zeolite (100 mg)	NR	Neat	50	1–2 h	83–95	6(85)	Present system

[a] Data were not reported.

functional groups, operational simplicity, and easy separation of products in high yield. A tentative mechanism is also proposed.

Acknowledgements

K.P. thanks the Department of Science and Technology, New Delhi, India for the financial assistance. A.D.M. thanks University Grants Commission, New Delhi for the award of Assistant Professorship under its Faculty Recharge Programme. K.K. thanks Council of Scientific and Industrial Research, New Delhi for the award of Senior Research Fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.112.

References and notes

1. (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695; (b) Trost, B. M. *Science* **1991**, *254*, 1471.
2. (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (b) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1; (c) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1995**, *68*, 1592.
3. Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.
4. (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, 1996. p 113; (b) *Rodd's Chemistry of Carbon compounds*; Livingstone, R., Ansell, M. F., Eds.; Elsevier: Oxford, 1984. Vol. 4.
5. Zhan, Z.-P.; Yang, R.-F.; Lang, K. *Tetrahedron Lett.* **2005**, *46*, 3859.
6. Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941.
7. Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047.
8. Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165.
9. Bandini, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Synthesis* **2002**, 1110.
10. Lin, C. C.; Hsu, J. M.; Sastry, M. N. V.; Fang, H. L.; Tu, Z. J.; Liu, J. T.; Yao, C. F. *Tetrahedron* **2005**, *61*, 11751.
11. Li-Tao, A.; Jian-Ping, Z.; Li-Li, Z.; Yong, Z. *Tetrahedron Lett.* **2007**, *48*, 4297.
12. Meshram, H. M.; Nageswara Rao, G.; Santosh Kumar, G. *Synth. Commun.* **2010**, *40*, 3496.
13. Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115.
14. Azizi, N.; Arynasab, F.; Saidi, M. R. *Org. Biomol. Chem.* **2006**, *4*, 4275.
15. Ballini, R.; Clemente, R. R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191.
16. Wu, P.; Wan, Y.; Cai, J. *Synlett* **2008**, 1193.
17. Li-Tao, A.; Li-Li, Z.; Jian-Ping, Z.; Guang-Liang, Z. *Synth. Commun.* **2010**, *40*, 1978.
18. Kumar, V. P.; Sridhar, R.; Srinivas, B.; Narender, M.; Rao, K. R. *Can. J. Chem.* **2008**, *86*, 907.
19. Sri Hari, G.; Nagaraju, M.; Marthanda Murthy, M. *Synth. Commun.* **2008**, *38*, 100.
20. Xie, J.; Zhu, X.; Huang, M.; Meng, F.; Wang, M.; Wan, Y. *Synth. Commun.* **2010**, *40*, 3259.
21. Pateliya, M. H.; Veerababurao, K.; Chun-Wei, K.; Ching-Fa, Y. *Tetrahedron Lett.* **2008**, *49*, 7005.
22. Breck, D. W. *Zeolite Molecular Sieves*; Wiley: New York, 1974; Dyer, A. *An Introduction to Zeolite Molecular Sieves*; Wiley: Chichester, 1988.
23. (a) Rama, V.; Kanagaraj, K.; Pitchumani, K. *Tetrahedron Lett.* **2012**, *53*, 1018; (b) Beneteau, V.; Olmos, A.; Boningari, T.; Sommer, J.; Pale, P. *Tetrahedron Lett.* **2010**, *51*, 3673; (c) Hong, K. B.; Lee, C. W.; Yum, E. K. *Tetrahedron Lett.* **2004**, *45*, 693; (d) Arunkumar, K.; Naresh Kumar Reddy, D.; Chandrasekhar, K. B.; Rajender Kumar, P.; Shiva Kumar, K.; Pal, M. *Tetrahedron Lett.* **2012**, *53*, 3885; (e) Tillu, V. H.; Dumbre, D. K.; Wakharkar, R. D.; Choudhary, V. R. *Tetrahedron Lett.* **2011**, *52*, 863.
24. (a) Corma, A. *Chem. Rev.* **1995**, *95*, 559; (b) Corma, A. *Chem. Rev.* **1997**, *97*, 2373; (c) Corma, A.; Garcia, H. *Chem. Rev.* **2002**, *102*, 3837; (d) Corma, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307; (e) Corma, A.; Leyva-perez, A.; Sabater, Maria J. *Chem. Rev.* **2011**, *111*, 1657; (f) Davis, M. E. *Acc. Chem. Res.* **1993**, *26*, 111.
25. (a) Balaaie, S.; Arabanian, A. *Green Chem.* **2000**, *2*, 274; (b) Bhattacharya, D.; Gammon, D. W.; van Steen, E. *Catal. Lett.* **1999**, *61*, 93; (c) Reddy, A. V.; Ravinder, K.; Reddy, V. L. N.; Goud, T. V.; Ravikanth, V.; Venkateswarlu, Y. *Synth. Commun.* **2003**, *33*, 3687; (d) Saberi, A.; Rangappa, K. S. *Synth. React. Inorg. Met. Org. Chem.* **2009**, *39*, 425; (e) Das, B.; Ravikanth, B.; Ramu, R.; Rao, B. V. *Chem. Pharm. Bull.* **2006**, *54*, 1044; (f) Nikpassand, M.; Mamaghani, M.; Tabatabaeian, K. *Molecules* **2009**, *14*, 1468; (g) Bakavoli, M.; Sabzevari, O.; Rahimizadeh, M. *Chin. Chem. Lett.* **2007**, *18*, 533.
26. (a) Dhakshinamoorthy, A.; Pitchumani, K. *Tetrahedron Lett.* **2008**, *49*, 1818; (b) Namitharan, K.; Pitchumani, K. *Eur. J. Org. Chem.* **2010**, 411; (c) Rama, V.; Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2011**, *76*, 9090; (d) Vijaikumar, S.; Dhakshinamoorthy, A.; Pitchumani, K. *Appl. Catal. A: Gen.* **2008**, *340*, 25.
27. *General method for the preparation of cation-exchanged zeolites:* NaY zeolite powder was purchased from Sigma–Aldrich and used as received without further treatment. The physicochemical parameters of NaY zeolite are Si/Al ratio 2.43, unit cell size 24.65 Å, and surface area 900 m^2/g with supercages of a diameter of ≈1.3 nm. NH_4Y zeolite powder is purchased from Sigma–Aldrich and used as received. The physiochemical parameters of NH_4Y zeolite are Si/Al ratio 2.9, unit cell size 24.68 Å, and surface area 925 m^2/g with supercages of a diameter of ca. 1.38 nm. HY zeolite was obtained by the thermal deammonification of NH_4Y zeolite at 450 °C for 6 h.
28. *Typical procedure for the Michael addition of indole to β-nitrostyrene in the presence of HY zeolite:* Indole (1 mmol), β-nitrostyrene (1 mmol), and HY zeolite (100 mg) were mixed uniformly and kept at 50 °C for the required time in the absence of solvent. The reaction was monitored by TLC and after consumption of indole, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (15 mL). Then the catalyst was filtered, washed with ethyl acetate (3×5 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The recovered catalyst was activated at 450 °C for 6 h and reused for successive runs. The crude residue was finally purified by column chromatography using hexane–ethyl acetate (15% ethyl acetate in hexane) as an eluent to afford pure product. The products were confirmed by mass spectrometry, ^1H and ^{13}C NMR, and their melting points. HY zeolite was pre-activated at 450 °C for 6 h for all the reactions.