



A novel approach to bis(indolyl)methanes using nickel nanoparticles as a reusable catalyst under solvent-free conditions

ABOLFAZL OLYAEI^{1*}, MOHSEN VAZIRI¹, REZA RAZEGHI¹,
BAHAREH SHAMS¹ and HASAN BAGHERI²

¹Department of Chemistry, Payame Noor University, P. O. Box 19395–3697, Tehran, Iran and

²Department of Chemistry, Takestan Branch, Islamic Azad University, Takestan, Iran

(Received 6 May, revised 10 July 2012)

Abstract: Nano-sized nickel as a catalyst has been developed for the electrophilic substitution reactions of indole with various aromatic aldehydes under solvent-free conditions to afford the corresponding bis(indolyl)methanes in high to excellent yields. The described method has promising features, such as no hazardous organic solvents or catalysts, short reaction time, high product yields, simple work-up procedure, reusable catalyst and easy product separation without further purification with column chromatography.

Keywords: indole; aldehyde; electrophilic substitution; Nickel.

INTRODUCTION

The efficiency of heterogeneous catalysis in organic synthesis can be improved by employing nano-sized catalysts because of their extremely small size and large surface to volume ratio. It was recently demonstrated that Ni nanoparticles as catalysts offer great opportunities for a wide range of applications in organic synthesis and chemical manufacturing processes, including the chemoselective oxidative coupling of thiols,¹ reduction of aldehydes and ketones,^{2–4} hydrogenation of olefins⁵ and supports for hydrogen adsorption.⁶ Thus, the remarkable catalytic activity and easy synthesis, simplicity and reusability of Ni nanoparticles encouraged the present utilization of them as a catalyst for the synthesis of bis(indolyl)methanes (BIM).

Development of bis(indolyl)alkane (BIA) derivatives has been of considerable interest in organic synthesis because of their wide occurrence in various natural products possessing biological activity⁷ and usefulness for drug design. BIM are substances found in cruciferous plants that exhibit activity promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells.⁸ Consequently, a number of synthetic methods for the preparation of BIA deri-

* Corresponding author. E-mail: Olyaei_a@pnu.ac.ir

doi: 10.2298/JSC120506076O



vatives by reaction of indole with various aldehydes and ketones in the presence of either a Lewis acid or a protic acid have been reported in the literature.^{9–16} In recent years, environmentally safer synthetic methods have received considerable attention and some solvent-free protocols have been developed. The synthesis of BIM under solvent-free conditions may be performed using catalysts such as I₂¹⁷ and ZrOCl₂·8H₂O/silica gel.¹⁸ These previous methods generally involved difficult handling, a stoichiometric amount of catalyst may be needed, and require tedious aqueous work-up, along with the use of environmentally harmful organic solvents.

In view of the importance of BIA derivatives, the use of nano-sized nickel¹⁹ as catalyst in the reaction of indole with aromatic aldehydes under solvent-free conditions is reported herein. As such, the method provides the product *via* easy work-up and is in accord with green sustainable chemistry principles.

EXPERIMENTAL

All commercially available chemicals and reagents were used without further purification. Melting points were determined using an electrothermal model 9100 apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 4300 spectrophotometer. The ¹H- and ¹³C-NMR spectra were recorded in DMSO-*d*₆ on Bruker DRX-500 Avance spectrometer. Chemical shifts (δ) are reported in ppm and are referenced to the NMR solvent. Mass spectra of the products were obtained with an HP 5937 (Agilent Technologies) mass selective detector. Elemental analyses were performed using a CHN–O–Rapid Heraeus elemental analyzer (Wellesley, MA, USA).

General procedure for the synthesis of bis(indolyl)methanes 3

To a mixture of indole (2 mmol) and aromatic aldehyde (1 mmol) was added nickel nanoparticle powder (10 mol %). The reaction mixture was magnetically stirred on a pre-heated oil bath at 80 °C for the appropriate time as indicated in Table I. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to room temperature. Then, ethanol (5 mL) was added. The nanoparticles were recovered by centrifuging the organic layer and reutilized for the same reaction. The solution was poured into water (50 mL). The precipitate that formed was filtered, washed with water and dried. The crude product was stirred for 5 min in boiling *n*-hexane and the resulting precipitate was filtered. The thus obtained product **3** was found to be pure upon TLC examination.

RESULTS AND DISCUSSION

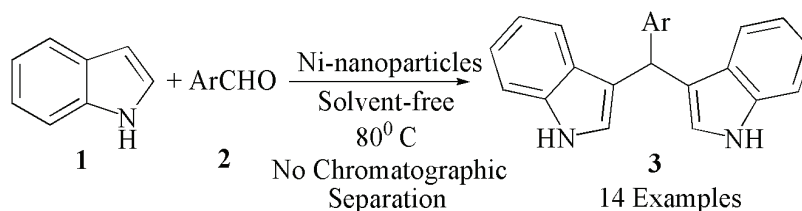
In continuation of work on the development of solvent-free conditions in one-pot, multi-component reactions,^{20–24} it was observed that the treatment of indole with aromatic aldehydes in the presence of nickel catalyst under solvent-free conditions afforded the corresponding BIM derivatives. As a model reaction, the reaction of indole (2 mmol) with benzaldehyde (1 mmol) was initially examined at 70–120 °C in the presence of nano-sized nickel powder (10 mol %) as catalyst under solvent-free conditions. The investigation demonstrated that the best result was obtained when the temperature was fixed at 80 °C and the reaction was completed in 1 h. Thereby, an excellent yield of bis(3-indolyl)phenyl-

methane (**3a**) was obtained (95 %). To determine the appropriate concentration of the Ni nanoparticles catalyst, the model reaction of benzaldehyde and indole was investigated at different concentrations of the catalyst. This indicated that 10 mol % of nano-sized Ni produced the best results with respect to product yield (Table I).

TABLE I. Comparison of the amount of Ni and yields for the synthesis of BIM

Entry	Catalyst amount, mol %	Time, min	Yield, %
1	1	90	55
2	2.5	90	65
3	5.0	90	70
4	7.5	60	84
5	10	60	95

In order to show the general applicability of the method for other substrates and derivatives, the same reaction conditions were applied for the reactions of 2 equiv. indole and 1 equiv. of an aromatic aldehyde **2** in the presence of nickel nanoparticle catalyst under solvent-free conditions at 80 °C for an appropriate time, which directly afforded BIM derivatives (**3a–n**) in good to excellent yields (Scheme 1). The reaction times and yields of the synthesized BIM derivatives are given in Table II, which shows that the yields were almost quantitative in most cases. It was found that aromatic aldehydes with electron donating or electron withdrawing groups were converted to the corresponding products within some hours.



Scheme 1. Synthesis of bis(indolyl)methanes.

The recovery and reusability of the catalyst was examined. The catalyst was recovered by a simple work-up using the centrifugation method and reused during four consecutive runs without any apparent loss of activity for the same reaction. It is noteworthy that the yields of the product in the second, third, and fourth runs were almost the same as that in the first run.

All products were well characterized by ¹H-NMR, ¹³C-NMR, FTIR, mass spectroscopy, elemental analyses and melting point determination. The data are given in the Supplementary material to this paper. To the best of our knowledge, the synthesis of compounds **3j–n** has not been previously reported in the literature. The ¹H-NMR spectra of compounds **3j–n** showed a sharp singlet for the

indole-NH at about δ 10.80 ppm. The methine protons appeared as a singlet at about δ 6.20 ppm and the aromatic protons were displayed in the region of 6.68–7.86 ppm. Hydroxyl protons in compounds **3k** and **3l** were observed at δ 11.30 and 9.76 ppm, respectively. The ^{13}C -NMR, FTIR, mass spectra and elemental analyses confirmed the structures of the synthesized compounds.

TABLE II. Ni nanoparticles-catalyzed synthesis of BIM under solvent-free conditions at 80 °C

Entry	Ar	Product	Time, min	Yield, %	M.p. / °C	
					Found	Reported
1	C ₆ H ₅	3a	60	95	148–150	149–150 ²⁵
2	4-NO ₂ C ₆ H ₄	3b	20	92	220–222	217–220 ²⁵
3	3-NO ₂ C ₆ H ₄	3c	30	89	264–265	265–266 ²⁶
4	2-NO ₂ C ₆ H ₄	3d	60	88	137–139	139–141 ²⁷
5	2-ClC ₆ H ₄	3e	20	91	74–75	70–71 ²⁵
6	4-ClC ₆ H ₄	3f	100	90	80–82	76–77 ²⁵
7	4-BrC ₆ H ₄	3g	100	88	116–117	110–112 ²⁸
8	4-OHC ₆ H ₄	3h	120	85	136–137	122–124 ²⁵
9	4-CH ₃ C ₆ H ₄	3i	90	85	96–97	93–94 ²⁵
10	4-Cl-3-NO ₂ C ₆ H ₃	3j	70	89	183–184	–
11	2-OH-5-NO ₂ C ₆ H ₃	3k	20	94	194–196	–
12	2-Br-5-OHC ₆ H ₃	3l	110	88	141–142	–
13	2-Cl-6-FC ₆ H ₃	3m	60	92	94–95	–
14	2-OCH ₂ PhC ₆ H ₄	3n	70	88	206–208	–

CONCLUSIONS

In summary, for the first time, it was found that Ni in the form of nanoparticles is a potential alternative to the use of noble-metal-based catalysts for the synthesis of BIM derivatives. Compared to other procedures previously reported in the literature, the present method provides some advantages such as omitting an organic solvent, efficient and experimental simplicity, compatibility with various functional groups, generality, clean, easy work-up and high yields. Moreover, there is no necessity for dry solvents or protecting gas atmospheres. Product purification by column chromatography is not necessary and the catalyst could be easily recovered from the reaction mixture by simple centrifugation.

SUPPLEMENTARY MATERIAL

IR, ^1H - and ^{13}C -NMR data for obtained compounds are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

Acknowledgment. The authors thank the Research Council of Payame Noor University for financial support.

ИЗВОД

НОВ ПРИСТУП СИНТЕЗИ БИС(ИНДОЛИЛ)МЕТАНА УПОТРЕБОМ НАНОЧЕСТИЦА
НИКЛА КАО КАТАЛИЗАТОРА БЕЗ ПРИСУСТВА РАСТВОРАЧАABOLFAZL OLYAEI¹, MOHSEN VAZIRI¹, REZA RAZEGHI¹, VAHAREH SHAMS¹ и HASAN BAGHERI²¹Department of Chemistry, Payame Noor University, P. O. Box 19395–3697, Tehran, Iran и²Department of Chemistry, Takestan Branch, Islamic Azad University, Takestan, Iran

Развијене су наночестице никла које су употребљене као катализатор у реакцији електрофилне супституције индола и различитих ароматичних алдехида у одсуству растварача. Добијени су одговарајући бис(индолил)метани у добром до одличном приносу. Предности ове методе су одсуство органских растварача, кратко реакционо време, висок принос производа реакције, једноставан поступак обраде реакционе смеше, олакшано изоловање производа и могућност регенерације и вишеструке употребе катализатора.

(Примљено 6. маја, ревидирано 10. јула 2012)

REFERENCES

1. A. Saxena, A. Kumar, S. Mujumdar, *J. Mol. Catal.*, A **269** (2007) 35
2. F. Alonso, P. Riente, M. Yus, *Tetrahedron* **64** (2008) 1847
3. F. Alonso, P. Riente, M. Yus, *Tetrahedron Lett.* **49** (2008) 1939
4. F. Alonso, P. Riente, M. Yus, *Synlett* (2008) 1289
5. A. Dhakshinamoorthy, K. Pitchumani, *Tetrahedron Lett.* **49** (2008) 1818
6. L. Zank, J. Zielinsky, *Appl. Catal.*, A **334** (2008) 268
7. R. Bell, S. Carmeli, N. Sar, *J. Nat. Prod.* **57** (1994) 1587
8. X. Ge, S. Yannai, G. Rennert, N. Gruener, F. A. Fares, *Biochem. Biophys. Res. Commun.* **228** (1996) 153
9. B. V. Gregorovich, K. Liang, M. Clugston, S. MacDonald, *Can. J. Chem.* **46** (1968) 3291
10. A. Chatterjee, S. Manna, J. Benerji, C. Pascard, T. Prange, J. Shoolery, *J. Chem. Soc. Perkin Trans. 1* (1980) 553
11. W. E. Noland, M. R. Venkiteswaran, G. Richards, *J. Org. Chem.* **26** (1961) 4241
12. G. Babu, N. Sridhar, P. T. Perumal, *Synth. Commun.* **30** (2000) 1609
13. H. Firouzabadi, N. Iranpoor, A. A. Jafari, *J. Mol. Catal.*, A **244** (2005) 168
14. M. A. Zolfigol, P. Salehi, M. Shiria, *Phosphorus, Sulfur Silicon Relat. Elem.* **179** (2004) 2273
15. P. Srinivasan, J. Amalraj, *J. Mol. Catal.*, A **242** (2005) 168
16. M. Chakrabarty, A. Mukherji, S. Karmakar, S. Arima, Y. Harigaya, *Heterocycles* **68** (2006) 331
17. S. J. Ji, S. Y. Wang, Y. Zhang, T. P. Loh, *Tetrahedron* **60** (2004) 2051
18. H. Firouzabadi, N. Iranpoor, M. Jafarpour, A. Ghaderi, *J. Mol. Catal.*, A **253** (2006) 249
19. S. H. Wu, D. H. Chen, *J. Colloid Interface Sci.* **259** (2003) 282
20. A. Shockravi, M. Sadeghpour, A. Olyaei, *Synth. Commun.* **39** (2009) 2347
21. A. Shockravi, M. Sadeghpour, A. Olyaei, *J. Chem. Res.* (2009) 556
22. A. Olyaei, E. Chehrehgosha Parashkuhi, S. Raoufmoghaddam, M. Sadeghpour, *Synth. Commun.* **40** (2010) 3609
23. A. Olyaei, B. Shams, M. Sadeghpour, F. Gesmati, Z. Razaziane, *Tetrahedron Lett.* **51** (2010) 6086

24. A. Olyaei, S. Raoufmoghaddam, M. Sadeghpour, B. Ebadzadeh, *Chin. J. Chem.* **28** (2010) 825
25. Z. C. Ma, Z. H. Zhang, *Synth. Commun.* **35** (2005) 1997
26. G. Penieres-Carrillo, J. G. Garcia-Estrada, J. L. Gutierrez-Ramirez, C. Alvarez-Tolendano, *Green Chem.* **5** (2003) 337
27. R. Tayebee, F. Nehzat, E. Rezaei-Seresht, F. Z. Mohammadi, E. Ezzat Rafiee, *J. Mol. Cat. A: Chem.* **351** (2011) 154
28. S. M. Vahdat, S. Khaksar, S. Baghery, *World Appl. Sci. J.* **15** (2011) 877.