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An efficient green procedure for the synthesis of bis (indolyl) methanes in water

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Abstract

In this work, a green, simple and highly efficient procedure for the synthesis of bis(indolyl)methanes is described. The condensation of indoles with carbonyl compounds catalyzed by citric acid in water affords bis(indolyl)methanes in high yields and relatively short reaction times. The advantages of this method are using of water as a low cost solvent and efficient recyclability of the catalyst.

Keywords: Bis(indolyl) methane; Indole; Citric acid; Water

Introduction

Solvents play essential roles in chemical processes serving to put reactants into contact by dissolution and also affecting rates of the reactions. Solvents are also used in the later stages of a reaction for extraction and purification of the products.

In the past years, organic solvents were the most common and perhaps the only choices of solvents among chemists. This scenario has been substantially changed during the last decade or so due to the intensive research towards environmentally benign substitutes for volatile and toxic organic solvents. Now chemists have to deal with the challenge of reducing the environmental impact of the processes without loosing their efficiency by using the so-called green solvents under the concepts of Green Chemistry, which has emerged as an important area of chemistry and has achieved outstanding progresses towards the development of green reaction processes [1].

A green solvent must ideally have a high boiling point, a low vapor pressure, be non-toxic, dissolve a great range of organic compounds, be inexpensive and of course be recyclable. All these things put together tend to narrow the possibilities of finding a compound or a class of compounds that can effectively be called a green solvent. However, many efforts from research groups all around the world have enabled the appearance of some good alternatives for organic solvents, which include: supercritical fluids, ionic liquids, low melting polymers, perfluorinated solvents and water.

Water is a solvent with unique physical-chemical properties. Its use as a solvent or co-solvent has unique synthetic advantages leading in some cases to exceptionally high selectivities or reaction rates. Furthermore, organic reactions in water may lead to the development of environmentally friendly chemical

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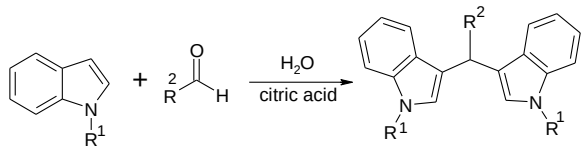


Scheme 1. Citric acid catalyzed condensation of indoles with carbonyl compounds in water.

processes.

Indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties [2].

Several bis(indolyl)methanes have been isolated from natural sources [3]. Some members from this class have shown promising biological activity [4].

Because of these interesting biological activities and other uses, development of protocols for the synthesis of bis (indolyl)methanes is of current interest.

Bis(indolyl)methanes have been obtained by the reaction of indoles with various carbonyl compounds in the presence of either protic or Lewis acids [5-10]. Most of the previously reported methods suffer from several disadvantages such as using of expensive and toxic catalysts or toxic solvents such as benzene [11].

Hence a more efficient and practical alternative method using an inexpensive and environmentally friendly reagent and solvent is still warranted.

In this investigation a green, convenient, mild and efficient procedure for the synthesis of bis (indolyl) methanes is reported using citric acid as catalyst and water as solvent (Scheme 1).

Materials and Methods

Carbonyl compounds, indole, N-methyl indole and citric acid were purchased from Merck chemical company and used without further purification. All products are known and identified by comparison of their spectral data and physical properties with those of the authentic samples. Melting points were recorded on an Electrothermal-9100 apparatus and are uncorrected. NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using $CDCl_3$ as solvent.

General procedure for preparation of bis-indolylmethanes

To a mixture of indole (2 mmol), aldehydes or ketones (1mmol) and water (5 mL), citric acid (0.5 mmol) was added and stirred vigorously at reflux temperature until the disappearance of the starting indole, checked by TLC. When the reaction was completed, the reaction mixture was filtrated and washed with water. Then, the reaction mixture was recrystalized using ethanol.

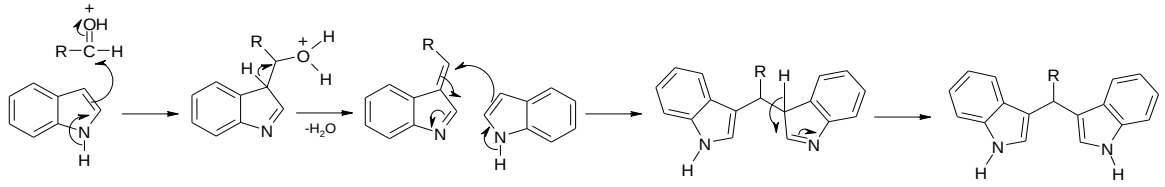
Selected data

3, 3′-Bis-indolyl phenylmethane (Table 1, entry 1): ^{1}H NMR: δ (ppm) 5.94 (s, 1H, CH), 6.68 (d, J = 1.6 Hz, 2H), 7.06 (t, J = 7.2 Hz, 4H), 7.21–7.46 (m, 9H, arom), 7.89 (s, br, 2H, NH).

3, 3′-Bis-indolyl (4-methoxyphenyl) methane (Table 1, entry 8): ^{1}H NMR: δ (ppm) 3.84 (s, 3H, OCH_3), 5.90 (s, 1H, CH), 6.64 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, arom), 7.07 (t, J = 7.4 Hz, arom), 7.23 (t, J = 7.2 Hz, arom), 7.30 (t, J = 6.7 Hz, arom), 7.37 (d, J = 8.1 Hz, arom), 7.45 (d, J = 7.9 Hz, arom), 7.82 (s, br, 2H, NH).

Table 1. Synthesis of bis(indolyl)methanes using the citric acid as catalyst in water

Entry	R^1	R^2	Time (min)	Yield (%)	Mp (observed)	Mp (reported)	Reference
1	H	C_6H_5	20	93	143-146	140-142	12
2	H	4-Cl-C_6H_4	15	92	80-84	78-80	13
3	H	4-NO_2-C_6H_4	10	95	220-223	221-223	14
4	H	4-HO-C_6H_4	30	80	125-127	123-125	14
5	H	2-Cl-C_6H_4	20	88	77-79	74-76	12
6	H	2-MeO-C_6H_4	25	80	138-141	138	15
7	H	2,4-di-Cl-C_6H_3	15	90	100-102	103-105	16
8	H	4-MeO-C_6H_4	25	85	192-195	191-193	14
9	CH_3	C_6H_5	15	95	190-192	185-187	17
10	CH_3	4-NO_2-C_6H_4	10	94	222-225	219-220	13
11	CH_3	3-NO_2-C_6H_4	10	92	158-160	156-158	18
12	CH_3	4-Cl-C_6H_4	15	90	144-147	142-145	18
13	CH_3	2,4-di-Cl-C_6H_3	15	88	125-128	120-123	18
14	H	cyclohexanone	40	76	158-161	148-150	18



Scheme 2. A plausible mechanism for the preparation of bis(indolyl)methanes

Results and Discussion

First, the reaction of benzaldehyde with indole (1:2 molar ratios) was studied to optimize the reaction conditions with respect to molar ratio of catalyst to the substrate and reusability of catalyst. It was found that 50 mol% of catalyst was sufficient to obtain the desired bis(indolyl)methane in 93% yield within 20 min in water at reflux.

Encouraged by these successful results, various aldehydes were studied under optimized conditions to better understand the scope and generality of this procedure (Table 1).

Table 1 shows a significant difference in the yield and reaction time for different substrates. Aromatic aldehydes bearing an electron withdrawing substituent (entry 3) undergo reaction at a much faster rate as compared to aromatic aldehydes with electron releasing groups appended (entry4), and gave bis (indolyl) methanes in excellent yields.

The following sequence of reactions appears to afford a satisfactory explanation of the mode of formation of products for the synthesis of bis(indolyl)methanes catalyzed by citric acid from carbonyl compounds (Scheme 2). An aldehyde was first activated by proton and carried out an electrophilic substitution reaction at C-3 of an indole. After loss of water, an intermediate was generated. The intermediate was further activated by proton and served as an electrophile to attack a second molecule of indole to form the final product.

In order to assess the efficiency of the present method in comparison with the reported methods for the preparation of bis(indolyl)methanes from indoles and carbonyl compounds, the results of present method was compared with reported methods which used water as solvent (Table 2). As it is clear from Table 2, the present method is more efficient when all terms including yields, reaction times, conditions and catalyst are taken into account.

Ease of recycling of the catalyst is a valuable advantage of this method. After cooling of the reaction mixture the product separated by filtration and the aqueous solution was used again for the same reaction. For the reaction of indole with 4-nitrobenzaldehyde (as a model reaction), no significant loss of the catalyst activity was observed when the aqueous solution of citric acid was used after several times of recycling (Table 3).

Acknowledgements

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Table 2. Synthesis of bis(indolyl)methanes in the presence of different catalysts in water as solvent

Carbonyl compound	Catalyst	Catalyst extent ratio	Conditions	Time	Yield (%)	Reference
C_6H_4CHO	squaric acid	10mg	H_2O/RT	2h	90	18
	Meldrum's acid	0.02 mol	H_2O/ultrasonic	4h	95	19
	aminosulfonic acid	1.5 mol	H_2O/ultrasonic	30 min	93	6
	citric acid	0.5 mol	H_2O/reflux	20 min	93	Present work

Table 3. The reaction of indole with 4-nitrobenzaldehyde in the presence of recycled citric acid

Entry	cycle	Time (min)	Yield (%)
1	1st run	10	95
2	2nd run	10	93
3	3rd run	15	90
4	4th run	15	90

References

1. Anastas P.T., Kirchhoff M. M. Origins, Current Status, and Future Challenges of Green Chemistry. *Acc. Chem. Res.* **35**: 686-694 (2002).
2. Sundberg R. J. *The Chemistry of Indoles*; Academic Press: New York, 113-114 (1996).
3. Osawa T., Namiki M. Structure elucidation of streptindole, a novel genotoxic metabolite isolated from intestinal bacteria. *Tetrahedron Lett.* **2**:4719-4723 (1983).
4. Hong C., Firestone G. L., Bjeldanes L. F. Bcl-2 family-mediated apoptotic effects of 3, 3′-diindolylmethane (DIM) in human breast cancer cells. *Biochem. Pharmacol.* **63**:1085-1094 (2002).
5. Mishra S., Ghosh R. Ecofriendly and sustainable efficient synthesis of bis(indolyl)methanes based on recyclable Bronsted (CSA) or Lewis ($ZrOCl_2.8H_2O$) acid catalyst. *Indian J. Chem.* **50B**:1630-1636 (2011).
6. Li J., Dai H., Xu W., Li T. An efficient and practical synthesis of bis(indolyl)methanes catalyzed by aminosulfonic acid under ultrasound. *Ultrason. Sonochem.* **13**:24–27 (2006).
7. Das P. J., Das J. Synthesis of aryl/alkyl(2, 2′-bis-3-methylindolyl)methanes and aryl(3,3′-bis indolyl)methanes promoted by secondary amine based ionic liquids and microwave irradiation, *Tetrahedron Lett.* **53**:4718-4720 (2012).
8. Azizi N., Manocheri Z. Eutectic salts promote green synthesis of bis(indolyl) methanes, *Res. Chem. Intermed.* **38**:1495-1500 (2012).
9. Rani V. J., Vani K. V., Rao C. V. PEG-SO_3H as a Catalyst for the Preparation of Bis-Indolyl and Tris-Indolyl Methanes in Aqueous Media, *Synth. Commun.* **42**:2048-2057 (2012).
10. Tekale S. U., Shisodia S. S., Kauthale S. S., Jadhav V. B., Kanhe N. S., Bhoraskar S. V., Pawar R. P. Micron Particles of AlN/Al: Efficient, Novel, and Reusable Heterogeneous Catalyst for the Synthesis of Bis(indolyl)methanes, *Synth. Commun.* 43:1849-1858 (2013).
11. Qu H., Xiao C., Wang N., Yu K., Hu Q., Liu L. $RuCl_3{\cdot}3H_2O$ Catalyzed Reactions: Facile Synthesis of Bis(indolyl)methanes under Mild Conditions. *Molecules*, **16**:3855-3868 (2011).
12. Hasaninejad A., Zare A., Sharghi H., Niknam K., Shekouhya M. P_2O_5/SiO_2 as an efficient, mild, and heterogeneous catalytic system for the condensation of indoles with carbonyl compounds under solvent-free conditions. *ARKIVOC*, **xiv**:39-50 (2007).
13. Deb M. L., Bhuyan P. J. An efficient and clean synthesis of bis(indolyl)methanes in a protic solvent at room temperature.*Tetrahedron Lett.* **47**:1441-1443 (2006).
14. Sadaphal S. A., Shelke K. F., Sonar S. S., Shingare M. S. Ionic liquid promoted synthesis of bis(indolyl) methanes. *Cent. Eur. J. Chem.* **6**:622-626 (2008).
15. Kargar Behbahani F., Sasani M., Facile synthesis of bis(indolyl)methanes using iron(III) phosphate. *J. Serb. Chem. Soc.* **77**:1157-1163 (2012).
16. Ghorbani-Vaghei R., Veisi H., Keypour H., Dehghani-Firouzabadi A. A. A practical and efficient synthesis of bis(indolyl)methanes in water, and synthesis of di-, tri-, and tetra(bis-indolyl)methanes under thermal conditions catalyzed by oxalic acid dihydrate. *Mol. Divers.* **14**:87-96 (2010).
17. Firouzabadi H., Iranpoor N., Jafarpour M., Ghaderi A. $ZrOCl_2{\cdot}8H_2O$/silica gel as a new efficient and a highly water–tolerant catalyst system for facile condensation of indoles with carbonyl compounds under solvent-free conditions. *J. Mol. Catal. A: Chem.* **253**:249-251 (2006).
18. Azizi N., Gholibeghlo E., Manocheri Z. Green procedure for the synthesis of bis(indolyl)methanes in water. *Scientia Iranica C* **19**:574–578 (2012).
19. Wang S., JI S., Su X. A Meldrum's Acid Catalyzed Synthesis of Bis(indolyl)methanes in Water under Ultrasonic Condition. *Chin. J. Chem.* **26**:22-24 (2008).

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یک روش موثر سبز برای سنتز بیس (ایندولیل) متان ها در آب

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چکیده

در این مقاله، یک روش سبز، ساده، و خیلی موثر برای سنتز بیس (ایندولیل) متان ها توضیح داده شده است. تراکم کاتالیز شده ایندول ها با ترکیبات کربونیل توسط اسید سیتریک در آب بیس (ایندولیل) متانها را با راندمان و زمان های نسبتا" کوتاه تولید می کند. مزایای این روش استفاده از آب بعنوان یک حلال ارزان و قابلیت بالای بازیافت کاتالیزور می باشند.

واژه‌های کلیدی: بیس (ایندولیل) متان؛ ایندول؛ سیتریک اسید؛ آب