RSC Advances

This article can be cited before page numbers have been issued, to do this please use: H. Veisi, B. Maleki, F. Hosseini Eshbala, H. Veisi, R. Masti, S. Sedigh Ashrafi and M. Baghayeri, *RSC Adv.*, 2014, DOI: 10.1039/C4RA03194F.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C4RA03194F

In Situ Generated of Iron(III) Dodecyl Sulfate as Lewis Acid-Surfactant Catalyst for Synthesis of Bis-indolyl, Tris-indolyl, Di(bis-indolyl), Tri(bis-indolyl), Tetra(bis-indolyl)methanes and 3-Alkylated Indole Compounds in Water

Hojat Veisi,[a] Behrooz Maleki,*[b] Fereshteh Hosseini Eshbala,[a] Hamed Veisi,[c] Ramin Masti,[a] Samaneh Sedigh Ashrafi,[b] Mehdi Baghayeri[b]

[a]*Department of Chemistry, Payame Noor University, 19395-4697 Tehran, I.R. of Iran*

Fax +98(838)4227463; E-mail: hojatveisi@yahoo.com

[b]*Department of Chemistry, Hakim Sabzevari University, Sabzevar* 96179-76487, *Iran. E-mail:b.maleki@hsu.ac.ir; malekibehrooz@gmail.com*; *Fax: +98-571-4410300; Tel: +98-571-4002643*

[c]*School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.*

Abstract

Iron(III) dodecyl sulfate as Lewis acid-surfactant catalyst was prepared *in situ*, and effectively used in the synthesis of bis(indolyl)methanes and Michael reactions of indoles with α,β-unsaturated carbonyl compounds in water. Also, this method was used for the synthesis of 1,1,3-tri-indolyl compounds in good to excellent yield at room temperature.

Key words: Iron(III) dodecyl sulfate; Lewis acid-surfactant catalyst; Indole; Water

View Article Online
DOI: 10.1039/C4RA03194F

Introduction

The investigation performed on the chemistry of indole has led to its becoming one of the most active research areas of heterocyclic chemistry.[1,2] Various biological and pharmaceutical activities have been reported for this class of compounds.[3] Bis(indolyl)methanes are cruciferous substances useful for promoting beneficial estrogen metabolism in men and women. They are also effective in the prevention of cancer due to their ability to modulate certain cancer causing estrogen metabolites. Moreover, these compounds may normalize abnormal cell growth associated with cervical dysplasia. As bis(indolyl)methanes are important compounds in pharmaceutical chemistry, their synthesis has received increasing attention.

3-Position of indole is the preferred site for electrophilic substitution reaction and 3-substituted indoles are versatile intermediates for the synthesis of a wide range of indole compounds.[4] One of the simple and direct methods for the synthesis of 3-substituted indoles involve the conjugate addition of them to α,β-unsaturated carbonyl compounds or reaction of 2 equiv. of indoles with the carbonyl group in the presence of either protic [5,6] or Lewis acids.[7-9] However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are deactivated by the nitrogen atom of indoles.[10] Developing environmentally benign and economical syntheses is an area of research that is being vigorously pursued, and avoiding the use of harmful organic solvents is a fundamental strategy to achieving this. One of the most attractive alternatives to organic solvents is water, which has witnessed increasing popularity due to being inexpensive, readily available and environmentally benign. In

View Article Online
DOI: 10.1039/C4RA03194F

addition, reactions in aqueous media illustrate unique reactivities and selectivities that are not usually observed in organic media.[11] However, organic reactions in water are often limited in scope due to poor solubility of the organic compounds. A possible new way to improve the solubility of substrates is the use of surface-active compounds that can form micelles.[12] Under ambient conditions, surfactant molecules can aggregate in an aqueous phase to form micelles with a hydrophobic core and a hydrophilic corona. The use of micelle surfactants as catalysts is widespread, and has been investigated in detail for various reactions in aqueous solutions.[13] Recently, a new type of catalyst, a Lewis acid-surfactant-combined catalyst (LASC), has been developed. This acts both as a Lewis acid to catalyze the reaction and as a surfactant to solubilize organic substrates in water.[14]

Result and Discussions

In our continued interest in the development of a highly expedient methodology[15] for the synthesis of fine chemicals and heterocyclic compounds of biological importance, we reported here the in situ generation of iron(III) dodecyl sulfate as Lewis acid-surfactant catalyst (LASC) for synthesis of indole derivatives in water at room temperature.

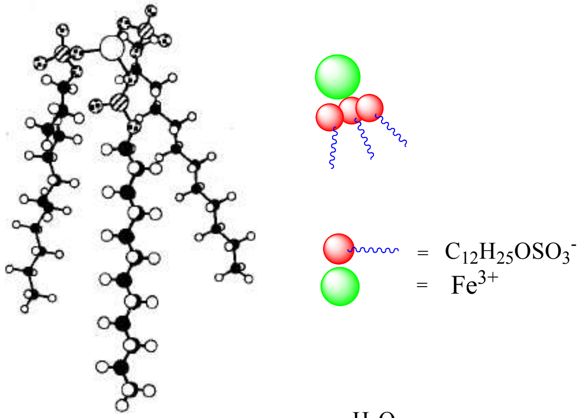
First, encouraged by the effect of a protic solvent and to reduce the reaction time in the synthesis of bis(indolyl)methane, we studied the reaction using water as the solvent. In a simple experimental procedure, 2 equiv. of indole with 1 equiv. of benzaldehyde in water were allowed to react with stirring at room temperature. Unfortunately, it was observed that indoles were insoluble in water and no reaction occurred even after stirring the reaction mixture for a long time. Presuming the insolubility of the reactant was the problem, we considered the use of SDS (sodium dodecylsulfate) as a surfactant, since it forms micelles in water and can solubilize organic compounds, which are otherwise

View Article Online
DOI: 10.1039/C4RA03194F

insoluble in water. Then, we repeated the reaction in the presence of SDS as surfactant, but we could not observe any product after 3 hours.

In recent times, iron(III) chloride has been used as a Lewis acid catalyst in many important organic transformations.[16] In addition, We have also shown that $FeCl_3.6H_2O$ is a good Lewis acid catalyst in the synthesis of bis(indolyl)methanes under organic solvent conditions. Although Lewis acid-catalyzed reactions are of great current interest because of their unique reactivities, selectivities, and mild conditions used, Lewis acids have been believed to be unstable in water and therefore not to be used in aqueous media. Some of these problems were solved with the discovery of water-tolerant Lewis acids by Kobayashi et al.[14] However, it is necessary to synthesize new types of cheap and powerful water active Lewis acids.

In continuation of our studies in this area, we decided to combine two effects together: Lewis acidity of $FeCl_3.6H_2O$ and surfactant effect of SDS. Iron tris(dodecyl sulfate) $Fe(DS)_3.nH_2O$ was synthesized by adding a solution of sodium dodecyl sulfate to an aqueous solution of $FeCl_3.6H_2O$ (Scheme 1).[17]



$$FeCl_3.6H_2O + C_{12}H_{25}OSO_3Na \xrightarrow{H_2O} Fe(DS)_3.\ nH_2O$$

Scheme 1 In situ generated of iron(III) dodecyl sulfate.

View Article Online
DOI: 10.1039/C4RA03194F

The iron dodecyl sulfate was precipitated immediately. we believe that this new type of "combined Lewis acid-surfactant catalyst (LASC)'', would act in dual role both as a catalyst to activate the substrate molecules and as a surfactant to increase the concentration of organic reactants to form micelle particles.

We described here the first example of the in situ generated of iron(III) dodecyl sulfate as Lewis acid-surfactant catalyst (LASC) for synthesis of bis(indolyl)methanes in water at room temperature. The optimum conditions were indole (2 mmol) and aldehyde (1 mmol), in the presence of SDS (0.3 mmol) and $FeCl_3.6H_2O$ (0.1 mmol) (SDS and $FeCl_3.6H_2O$ should be added together at same time) in water at 25 °C (Fig. 1) (Scheme 2).

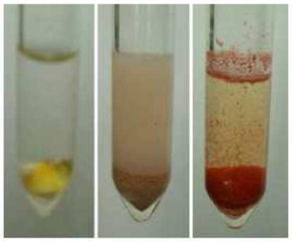
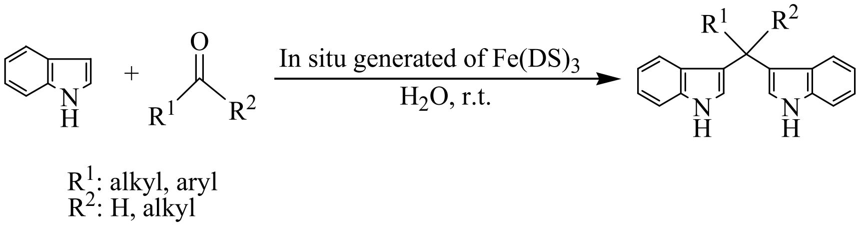


Fig. 1 Photographs of the reaction of indole with benzaldehyde in the presence of SDS and $FeCl_3.6H_2O$ in H_2O at 25 °C: (left side) at the start of the reaction; (middle side) after 10 second; and (right side) at the end of the reaction (after 5 min., 98% yield).



Scheme 2 Synthesis of bis(indolyl)methanes in water.

View Article Online
DOI: 10.1039/C4RA03194F

These results showed that the combination of a Lewis acid moiety (cationic part) and a surfactant (anionic part) in $Fe(DS)_3.nH_2O$ is important for the reactions to proceed in water. The Lewis acid part of the catalyst activates the substrate molecules and the surfactant part, affecting the solubility of the substrates in water at the same time. When these two factors are in play together, a drastic enhancement of the rates and the yields of the products are observed. We have also tried to use prepared $Fe(DS)_3$ instead of in situ generated $Fe(DS)_3$ in the same conditions, but we could not get better results than in situ in situ generated $Fe(DS)_3$ for the synthesis of bis(indolyl)methanes.

These results promoted us to investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions. As shown in Table 1, a series of aromatic, aliphatic and heterocyclic aldehydes underwent electrophilic substitution reaction with indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields (Table 1, entries 1-22). Ketones required longer reaction times, which is most probably due to the electron-donating and steric effects of the methyl group.

Table 1
Synthesis of bis(indolyl)methanes in the presence of iron(III) dodecyl sulfate as Lewis acid-surfactant catalyst (LASC) in water

Entry	R^1	R^2	Time/min	Yield (%)[a]	Ref.
1	C_6H_5	H	5	98	18
2	$4\text{-}MeC_6H_5$	H	5	96	19
3	$4\text{-}MeOC_6H_5$		5	98	20
4	$2\text{-}MeOC_6H_5$	H	5	98	20
5	$4\text{-}ClC_6H_5$	H	5	96	20
6	$2\text{-}ClC_6H_5$	H	5	98	19
7	$4\text{-}BrC_6H_5$	H	10	96	21
8	$4\text{-}OHC_6H_5$	H	10	95	22
9	$4\text{-}NO_2C_6H_5$	H	15	90	19
10	$3\text{-}NO_2C_6H_5$	H	15	90	23

View Article Online
DOI: 10.1039/C4RA03194F

11	$4\text{-}(Me_2N)C_6H_5$	H	15	90	20
12	$C_6H_5\text{-}CH{=}CH$	H	10	96	19
13	2-Furyl	H	10	92	19
14	2-Thienyl	H	10	95	19
15	$CH_3(CH_2)$	H	12	85	21
16	$CH_3(CH_2)_8$	H	15	85	21
17	Indol-3-carbaldehyde	-	15	90	24[a]
18	terephthaldialdehyde	-	10	90	25
19	isatin	-	15	85	24[b]
20	C_6H_5	CH_3	20	96	21
21	$4\text{-}NO_2C_6H_5$	CH_3	25	90	21
22	Cyclohexanone	-	20	85	29

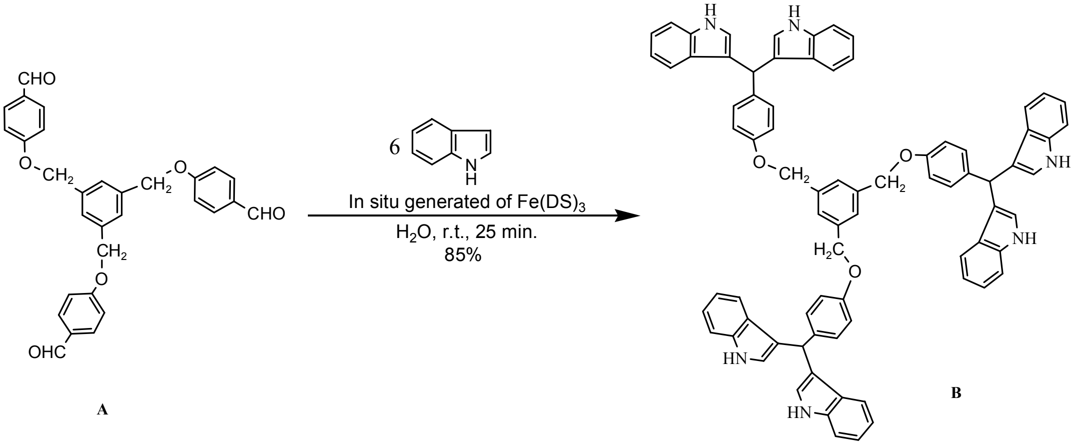
[a] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

In continuation of our efforts to synthesize bis(indolyl)methanes, in a similar way with $Fe(DS)_3$, the reaction between indole (2 mmol) and benzaldehyde (1 mmol) was carried out with $Fe(DS)_2$ (0.1 mmol) in water (5 mL) at room temperature. The product of this reaction was obtained in lower yield and longer time (yield: 50%, time: 60 minutes). In order to examine the catalytic activity of lauric acid and n-hexyl alcohol in this reaction, benzaldehyde and indole were selected as the model. It showed that nearly no product could be detected when a mixture of benzaldehyde (1 mmol) and indole (2 mmol) were stirred at room temperature for 2 hours in presence of n-hexyl alcohol (1 mL). Also, the reaction between benzaldehyde (1 mmol) and indole (2 mmol) and lauric acid in water (5 mL) at room temperature was carried out with a yield 32% and 60 minutes.

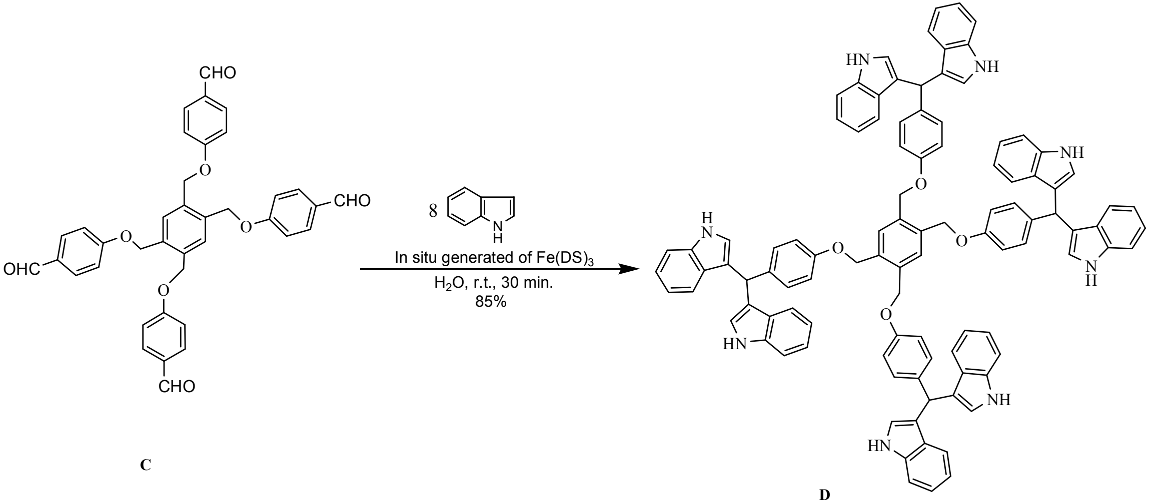
The catalytic effect of the in situ generated of iron(III) dodecyl sulfate in this reaction can be explained as follows. This 'Lewis acid–surfactant-combined catalyst (LASC)' form stable colloidal dispersion system with organic substrates in water and have been used for Lewis acid-catalyzed reactions. It has been suggested that LASCs generate hydrophobic reaction fields in water while an active Lewis acidic site is close to the

View Article Online
DOI: 10.1039/C4RA03194F

hydrophobic sites. On the other hand, This system was further explored for the synthesis of tri(bis-indolyl)methane (**B**) and tetra(bis-indolyl)methanes (**D**) as new tri- and tetra-arylmethanes, by the condensation of aldehyde (**A**) with 6 equivalents indole and aldehydes (**C**) with 8 equivalents indole under similar condition in high yields (Scheme 3 and 4).



Scheme 3 Synthesis of tri(bis-indolyl)methane (**B**).

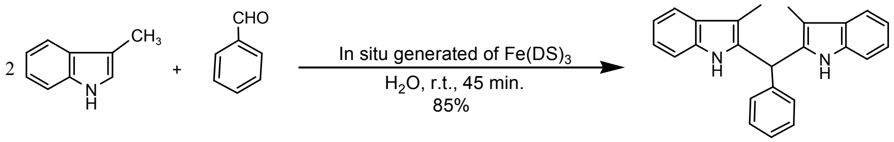


Scheme 4 Synthesis of tetra(bis-indolyl)methanes (**D**).

3-Substituted indole was examined for this reaction under the above reaction conditions with aldehydes (Scheme 5). Since the more active site (C-3) in indole was

View Article Online
DOI: 10.1039/C4RA03194F

blocked in this case electrophilic substitution took place at C-2 in indole giving the corresponding bis(indolyl)methane in high yield under same conditions.



Scheme 5 Synthesis of bis(indolyl)methanes at C-2.

We also investigated the recycling of the catalytic system under same conditions by the condensation of benzaldehyde with 2 equivalents indole. After completion of the reaction, water was added and the precipitated mixture was filtered off for separation of crude products. After washing the solid products with water completely, the water containing catalyst ($Fe(DS)_3$) was evaporated under reduced pressure and the catalyst was recovered and reused (Fig. 2). The recovered catalyst was reused four runs without any loss of their activities. Melting point of the recycled catalyst was 210 °C that corresponded to the literatures.[17] Also, the IR spectrum of recycled catalyst showed clear peaks in 1170 cm^{-1} and 1320 $cm^{-1}$for the SO_2 group. All of these are evidences for the construction of this catalyst.

View Article Online
DOI: 10.1039/C4RA03194F

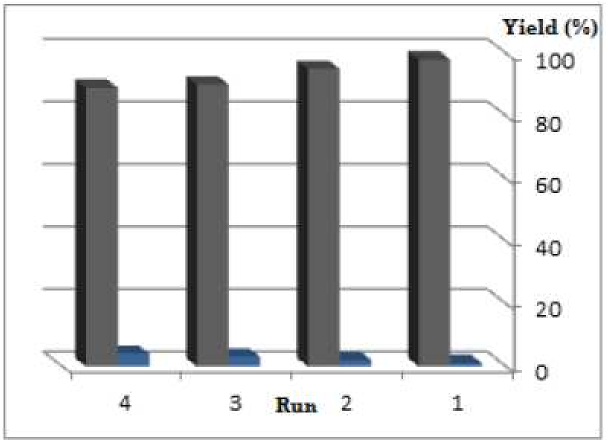
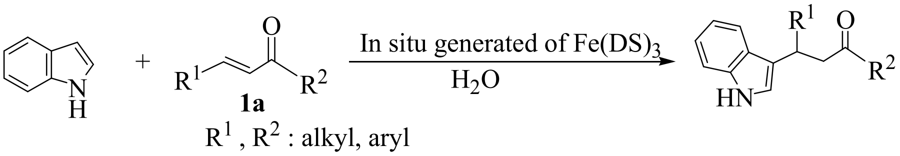


Fig. 2. The recycling of the catalyst Fe(DS)$_3$ for synthesis of bis(indolyl)methanes.

While most Michael additions are performed in organic solvents, today's environmental concerns encourage the development of "greener" conditions where possible. Then we intended to use this system in Michael reactions of indole with α,β-unsaturated compounds in water (Scheme 6). In synthesis of all products, Michael addition (1,4 addition) prevailed on 1,2 addition. The predominant product was 1,4 addition.



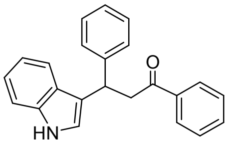
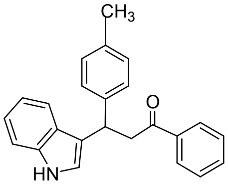
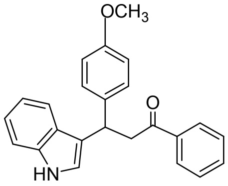
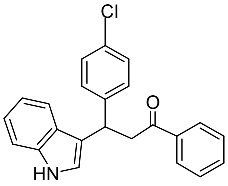
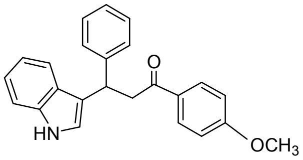
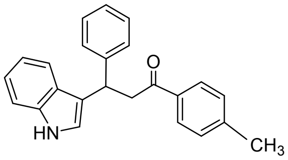
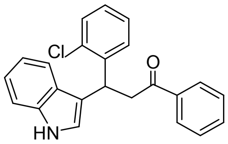
Scheme 6 Michael reactions of indole with α,β-unsaturated compounds in water.

The generality of the procedure was evaluated by the reaction of a number of α,β-unsaturated compounds with indole under same conditions at room temperature. The

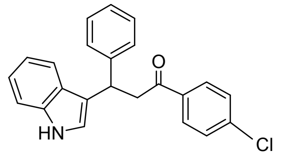
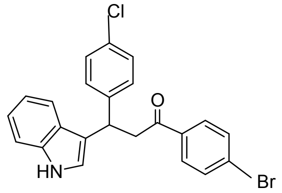
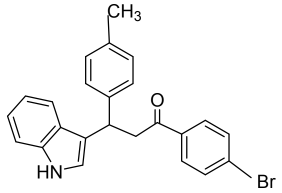
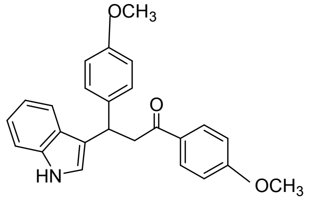
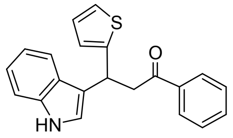
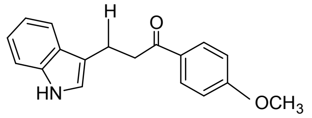
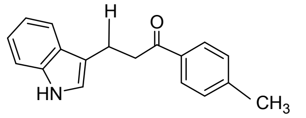
View Article Online
DOI: 10.1039/C4RA03194F

reactions proceeded easily, and the products were isolated in comparable yields in short reaction times (Table 2, entries 1–15).

Table 2
Michael addition of indole to Michael acceptors in the presence of iron(III) dodecyl sulfate as Lewis acid-surfactant catalyst (LASC) in water

Entry	Products	Time/min	Yield (%)[a]	Ref.
1		15	96	26
2		15	95	26
3		10	98	26
4		10	98	26
5		15	96	27
6		20	92	26
7		10	96	28

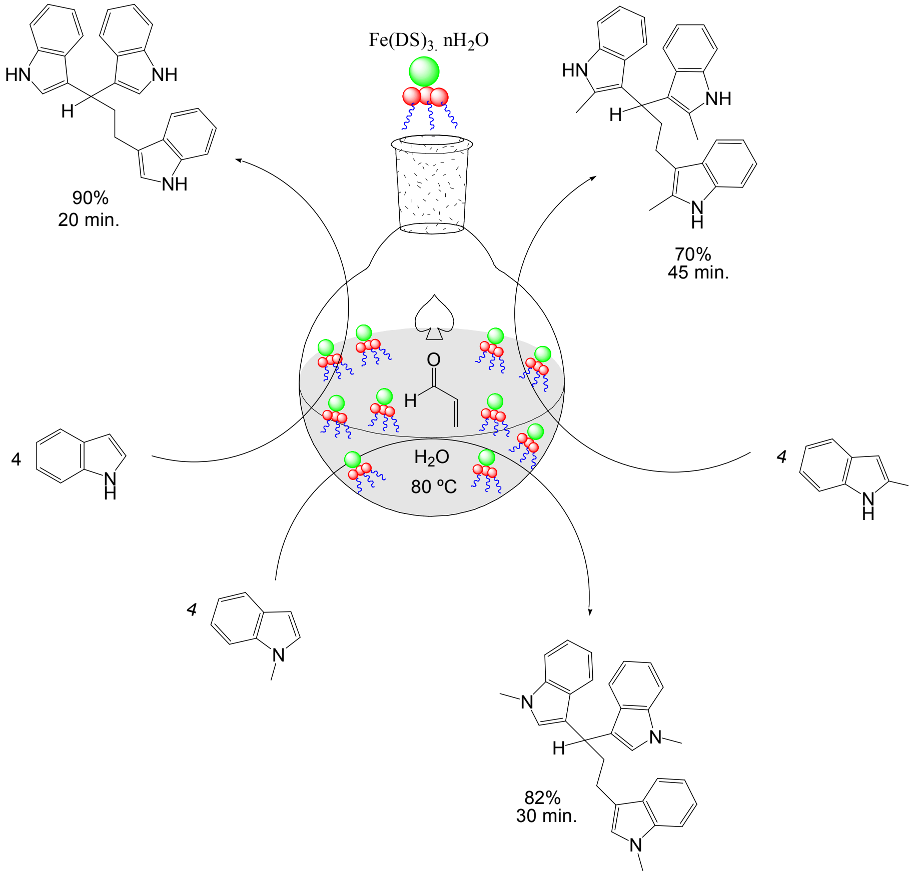
View Article Online
DOI: 10.1039/C4RA03194F

8		15	86	28
9		10	95	29
10		15	90	29
11		10	98	27
12		25	90	26
13		20	80	30
14		20	90	30

[a] Products were characterized from their physical properties, comparison with authentic samples and by spectroscopic methods.

Based on the results of above study, we planned to synthesis of 1,1,3-triindolyl compounds using in situ generation of iron(III) dodecyl sulfate as Lewis acid-surfactant catalyst (LASC) in water under thermal conditions through the tandem Michael addition and Friedel-Crafts reaction of α,β-unsaturated aldehyde and indoles (Scheme 7). Three variety of 1,1,3-tri(1H-indol-3-yl)butanes in 70-90% yield was prepared from crotonaldehyde as starting material.

View Article Online
DOI: 10.1039/C4RA03194F



Scheme 7 Synthesis of 1,1,3-triindolyl compounds.

Experimental

Materials and Methods

All chemicals were commercially purchased and used without further purification. All products were identified by comparison of their spectral and physical data with those previously reported.[15-27] Progress of the reactions was monitored by Thin-layer Chromatography (TLC). Melting points were recorded on a Bamstead electrothermal type 9200 melting point apparatus. IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). NMR spectra were obtained using Jeol FT NMR 90 MHz and spectrometer in $CDCl_3$ or DMSO using TMS as an internal reference.

View Article Online
DOI: 10.1039/C4RA03194F

Synthesis of bis(indolyl)methanes

The aldehyde or ketone (1 mmol) and indole (2 mmol) were added to a solution of $FeCl_3.6H_2O$ (0.1 mmol) and SDS (0.3 mmol) in H_2O (5 mL), and the mixture stirred at room temperature for the time given (Table 1). The progress of the reaction was monitored by TLC (eluent: 4:1 *n*-hexane-acetone). After completion of the reaction, the resulting precipitate of product filtered off. Finally, the crude product was recrystallized in ethanol-water (85-98% Yield). All of the products are known compounds, and their identity was easily confirmed by comparison with authentic samples (^{1}H NMR, ^{13}C NMR, and Mp).

Michael addition of indole to α,β-unsaturated carbonyl compounds

The α,β-unsaturated carbonyl compound (1 mmol) and indole (1 mmol) were added to a solution of $FeCl_3.6H_2O$ (0.1 mmol) and SDS (0.3 mmol) in H_2O (5 mL), and the mixture stirred at room temperature for the time given (Table 2). The progress of the reaction was monitored by TLC (eluent: 3:1 *n*-hexane-acetone). After completion of the reaction, the resulting precipitate of product filtered off. Finally, the crude product was recrystallized from ethanol-water (70:30) afforded pure Michael adducts (80-98% Yield), which were characterized by spectral methods.

Conclusion

In conclusion, we have developed a new type *in situ* generated of ‘‘combined Lewis acid-surfactant catalyst (LASC)’’, derived from $FeCl_3.6H_2O$ and SDS, would act in dual role both as a catalyst to activate the substrate molecules and as a surfactant to increase the concentration of organic reactants to form stable colloidal dispersion system for synthesis

View Article Online
DOI: 10.1039/C4RA03194F

of bis(indolyl)methanes and Michael reactions of indoles with α,*β*-unsaturated carbonyl compounds in water. The operational simplicity, excellent yields of the products, and high chemoselectivity are the main advantages of this method, and furthermore, this procedure is cheap, safe and environmentally benign. This novel concept is expected to contribute to the development of more benign reactions in water, and the related work is underway in our group.

Acknowledgements

We are thankful to Payame Noor University (PNU), and Hakim Sabzevari university for partial support of this work.

References

1 T. L. Gilchrist, *Heterocyclic Chemistry*., Academic Press, London, 1997, p. 231.
2 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875.
3 M. A. Zeligs, *J. Medicinal Food*., 1998, **67**.
4 F. He, P. Li, Y. Gu, G. Li, *Green Chem*., 2009, **11**, 1767.
5 A. V. Reddy, K. Ravinder, V. L. N. Reddy, T. V. Goud, V. Ravikanth, Y. Venkateswarlu, *Synth. Commun*., 2003, **33**, 3687.
6 M. Roomi, S. MacDonald, *Can. J. Chem*., 1970, **48**,139.
7 F. Rajabi, S. Razavi, R. Luque, *Green Chem*., 2010, **12**, 786.
8 L. Wang, J. H. Han, T. Sheng, J. Z. Fan, X. Tang, *Synlett*., 2005, 337.
9 . Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, *J. Org. Chem*., 2002, **67**, 4594.
10 S. Kobayashi, M. Araki, M. Yasuda, *Tetrahedron Lett*., 1995, **36**, 5773.
11 S. Kobayashi, Y. Mori, S. Nogayama, K. Manabe, *Green Chem*., 1999, **1**, 175.

DOI: 10.1039/C4RA03194F

12 D. A. Sabatini, R. C. Knox, *Surfactant-Enhanced Subsurface Remediation.*, Harwell, J. H. ACS, Washington, DC, 1994.

13 S. Kobayashi, *Chem. Lett*., 1991, 2187.

14 (a) S. Kobayashi, K. Manabe, Y. Mori, T. Wakabayashi, S. Nagayama, S. Kobayashi, *J. Am. Chem. Soc*. 2000, **122**, 7202; (b) M. A. Zolfigol, P. Salehi, A. Ghaderi, M. Shiri, Z. Tanbakouchian, *J. Mol. Catal. A: Chem.*2006, **259**, 253; (c) L. Zhang, J. Wu, *Adv. Synth. Catal.* 2007, **249**, 1047; (d) N. Aoyama, K. Manabe, S. Kobayashi, *Chem. Lett*. 2004, **33**, 312.

15 H. Veisi, *Synthesis*, 2010, 2631; (b) H. Veisi, *Tetrahedron Lett*., 2010, 2109.

16 (a) Y. V. V. Ahmed Kamal, M. Srikanth, A .Naseer Khan, S. Thokhir Basha, A. Md, *Bio.Med. Chem. Lett*., ***2010*, *20, 5229; (b)*** L. Jie, H. Tao, W. Lei, *Tetrahedron*, 2011, **67**, 3420*; (c)* L. Zhongxian, D. Zheng, K. Jianxun, W. Huaiqiu, Y. Liujian, W. Yangjie, *Tetrahedron*, 2008, **64**, 1924*; (d)* W. Guohua, Z. Lei, C. Chao, C. Shuihong, D. Yuguo, *Tetrahedron Letters*, 2008, **49**, 5488*; (e)* B. Roy, I. Ansary, S. Samanta, K.C. Majumdar, *Tetrahedron Lett.*, 2012, **53**, 5119.

17 K. Pradhan, S. Paul, A. R. Das, *Tetrahedron Lett*. 2013, **54**, 3105.

18 H. Veisi, S. Hemmati, H. Veisi, *J. Chin. Chem. Soc*. 2009, **56**, 240.

19 M. L. Deb, P. J. Bhuyan, *Tetrahedron Lett*., 2006, **47**, 1441.

20 M. M. Khodaei, I. H. Mohammadpoor-Baltork, R. Memarian, A. R. Khosropour, K. Nikofar, P. Ghanbary, *J. Heterocycl. Chem*., 2008, **45**, 1.

21 M. A. Zolfigol, P. Salehi, M. Shiri, Z. Tanbakouchian, *Catal. Commun*., 2007, **8**, 173.

22 S. A. Sadaphal, K. F. Shelke, S. S. Sonar, M. S. Shingare, *Cent. Eur. J. Chem*., 2008, **6**, 622.

23 S. -R. Sheng, Q. -Y. Wang, Y. Ding, X. -L. Liu, M. -Z. Cai, *Catal. Lett*., 2009, **128**, 418.

24 S. -Y. Wang, S. -J. Ji, *Tetrahedron*, 2006, **62**, 1527.

25 R. Ghorbani-Vaghei, H. Veisi, *J. Braz. Chem. Soc*., 2010, **21**, 193.

26 S. -J. Ji, S. -Y. Wang, *Ultrasonics Sonochem*., 2005, **12**, 339.

27 W. Zhou, L. -W. Xu, L. Yang, P. -Q. Zhao, C. -G. Xia, *J. Mol. Catal. A Chem*., 2006, **249**, 129.

28 W. J. Li, X. F. Lin, J. Wang, G. L. Li, Y. G. Wang, *Synlett*, 2005, 2003.

View Article Online
DOI: 10.1039/C4RA03194F

29 R. Ghorbani-Vaghei, H. Veisi, *Mol. Divers*., 2010,**14**, 385.

30 M. Mujahid Alam, R. Varala, S. R. Adapa, *Tetrahedron Lett*., 2003, **44**,5115.

View Article Online
DOI: 10.1039/C4RA03194F

Graphical Abstract

In Situ Generated of Iron(III) Dodecyl Sulfate as Lewis Acid-Surfactant Catalyst for Synthesis of Bis-indolyl, Tris-indolyl, Di(bis-indolyl), Tri(bis-indolyl), Tetra(bis-indolyl)methanes and 3-Alkylated Indole Compounds in Water

Hojat Veisi,[a] Behrooz Maleki,*[b] Fereshteh Hosseini Eshbala,[a] Hamed Veisi,[c] Ramin Masti,[a] Samaneh Sedigh Ashrafi,[b] Mehdi Baghayeri[b]

- ✓ In situ generated of Iron(III) dodecyl sulfate
- ✓ Efficient recycling of catalyst
- ✓ Water as solvent
- ✓ Synthesis of poly-indolyl derivatives