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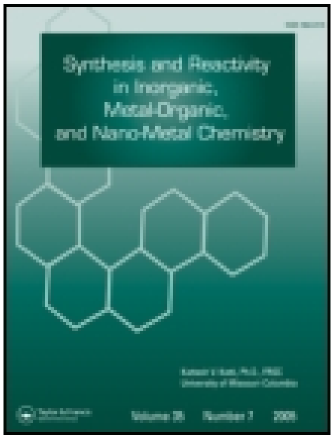

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$ZnCl_2$/Urea as a Deep Eutectic Solvent for the Preparation of Bis(indolyl)methanes Under Ultrasonic Conditions

Neda Seyedi[a], Hojatollah Khabazzadeh[b] & Samira Saeednia[c]
[a] Department of Chemistry, University of Jiroft, Jiroft, I. R. Iran
[b] Department of Chemistry, Shahid Bahonar University of Kerman, Kerman, I. R. Iran
[c] Department of Chemistry, Faculty of Science, Vali-e-Asr University, Rafsanjan, I. R. Iran
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$ZnCl_2$/Urea as a Deep Eutectic Solvent for the Preparation of Bis(indolyl)methanes Under Ultrasonic Conditions

NEDA SEYEDI[1], HOJATOLLAH KHABAZZADEH[2], and SAMIRA SAEEDNIA[3]

[1]*Department of Chemistry, University of Jiroft, Jiroft, I. R. Iran*
[2]*Department of Chemistry, Shahid Bahonar University of Kerman, Kerman, I. R. Iran*
[3]*Department of Chemistry, Faculty of Science, Vali-e-Asr University, Rafsanjan, I. R. Iran*

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This work describes the synthesis of bis(indolyl)methanes by using effective combination of ultrasound and deep eutectic solvent. This methodology offers momentous improvements over various options for the synthesis of bis(indolyl)methanes with regard to yield of products, simplicity in operation, and green aspects by avoiding toxic catalysts and solvents. Further, the deep eutectic solvent can be reused and recovered for several times without loss of activity.

Keywords: deep eutectic, bis(indolyl)methanes, ultrasound, $ZnCl_2$, indole

Introduction

Deep eutectic solvents (DESs) are materials consisting of components that form a low melting point much lower than each of the individual components. This system provides a unique substance for developing advanced materials and usually cheaper with less time-consuming than the development of new materials.

Abbott et al.[1,2] pioneered the development of these solvents, which are low-melting liquids derived from the mixture of a solid organic salt and a suitable organic complexant, typically a hydrogen-bond donating species such as a polyol or urea derivatives.

DESs exhibit similar physicochemical properties to the traditionally used ionic liquids, while being much cheaper and environmentally friendlier. Compared to ionic liquids DESs have some significant advantages. They are easier and cheaper to prepare, nonreactive with water and many are biodegradable, but still exhibit chemical stability, nonflammability, and conductivity.[3,4]

Application of ultrasound in organic transformation has proved to be an important tool in enhancing reaction rates and improving yields.[5,6] It promotes the reaction under milder conditions where drastic conditions are required conventionally.

Ultrasound irradiation, by virtue of cavitational collapse, is able to activate numerous organic reactions.[7]

Compared to the thermal methods in this technique, the reaction is carried out normally at lower temperature therefore the possibility of formation of by-products is reduced, and the reaction workup is easier.[8]

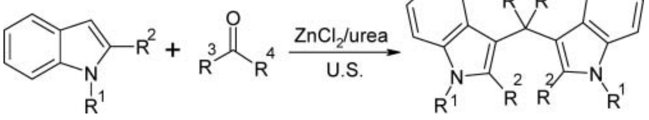
Bis(indolyl)methanes have been obtained by the reaction of indoles with various carbonyl compounds in the presence of either protic or Lewis acids.[9,10] Most of the previously reported methods suffer from several disadvantages such as using of expensive and toxic catalysts or toxic solvents such as benzene.[11]

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

In this investigation a green, convenient, mild, and efficient procedure for the synthesis of bis(indolyl)methanes is reported using a deep eutectic mixture of $ZnCl_2$/urea (1:3.5) as solvent in ultrasonic (US) conditions (Scheme 1).

Experimental

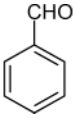
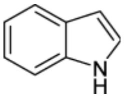
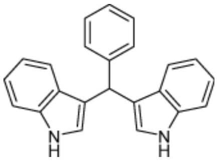
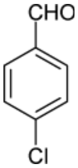
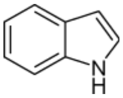
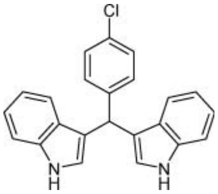
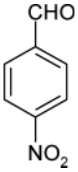
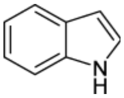
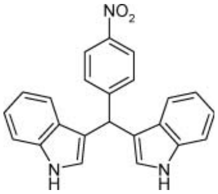
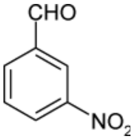
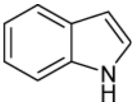
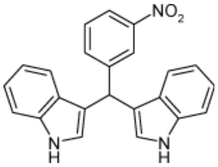
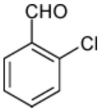
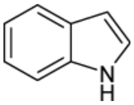
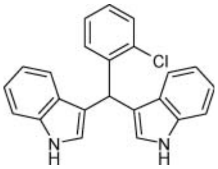
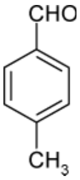
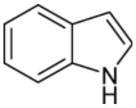
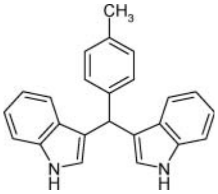
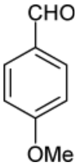
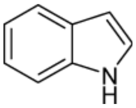
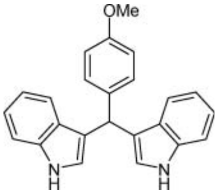
Carbonyl compounds, indole, $ZnCl_2$, urea, and organic solvents were purchased from Merck chemical company and used without further purification. All products are known and identified by comparison of their spectral data and physical properties with those of the authentic samples. Melting points were recorded on an Electrothermal-9100 apparatus and are uncorrected. All the



Sch. 1. Ultrasound assisted synthesis of bis(indolyl)methane derivatives using deep eutectic solvent as reaction medium.

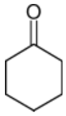
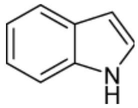
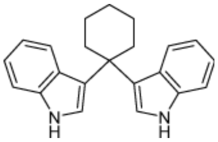
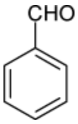
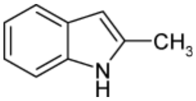
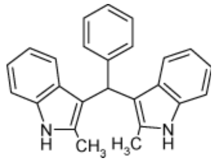
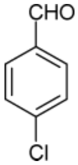
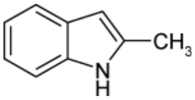
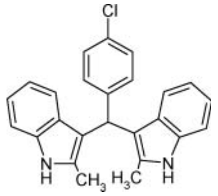
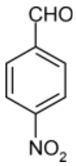
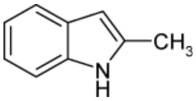
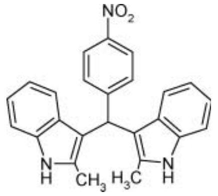
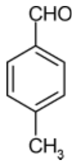
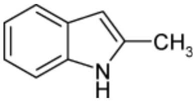
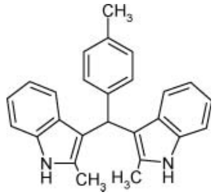
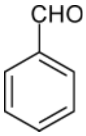
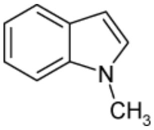
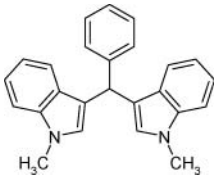
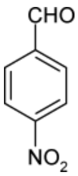
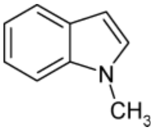
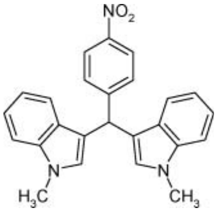
Address correspondence to Hojatollah Khabazzadeh, Department of Chemistry, Shahid Bahonar University of Kerman, 76169, I. R. Iran. E-mail: hkhabazzadeh@uk.ac.ir

Table 1. Synthesis of bis(indolyl)methanes in DES under ultrasonic conditions

Entry	Carbonyl compound	Indole	Product	Time (min)	Yield (%)	Mp (°C) observed	Mp (°C) Reported [ref]
1				10	92	142–145	140–142[12]
2				10	90	82–83	78–80[13]
3				8	93	220–224	221–223[14]
4				12	90	261–263	264–265[9]
5				14	86	76–78	74–76[12]
6				16	85	93–96	95–97[12]
7				16	80	183–186	185–187[12]

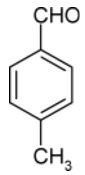
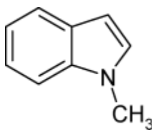
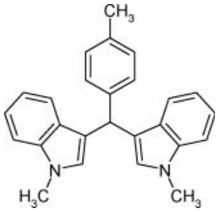
(*Continued on next page*)

Table 1. Synthesis of bis(indolyl)methanes in DES under ultrasonic conditions *(Continued)*

Entry	Carbonyl compound	Indole	Product	Time (min)	Yield (%)	Mp (°C) observed	Mp (°C) Reported [ref]
8				25	80	160–164	163–165[12]
9				12	93	244–246	247–248[12]
10				10	90	186–189	180–184[15]
11				10	92	237–240	241–243[9]
12				14	80	170–173	174–175[12]
13				8	90	202–205	201–203[9]
14				8	92	216–218	219–220 [12]

(*Continued on next page*)

Table 1. Synthesis of bis(indolyl)methanes in DES under ultrasonic conditions *(Continued)*

Entry	Carbonyl compound	Indole	Product	Time (min)	Yield (%)	Mp (°C) observed	Mp (°C) Reported [ref]
15				10	86	150–153	145–148[15]

reactions were studied using digital ultrasonic cleaner CD-4820. NMR spectra were recorded on a Bruker DRX-500 Avance NMR spectrometer using $CDCl_3$ as solvent.

Preparation of Deep Eutectic Solvent

The DES was prepared as follows: $ZnCl_2$ (1 mmol) was mixed with urea (3.5 mmol) and heated at 80°C in air with stirring until a clear colorless liquid was obtained. Then the mixture was allowed to cool to room temperature and then was used.

General Procedure for the Preparation of bis(indolyl) methanes

A mixture of a carbonyl compound (1 mmol), indole (2 mmol), and DES (1 eq) was irradiated in the water bath of the ultrasonic cleaner at 60°C for a period as indicated in Table 1. The reactions were followed by thin layer chromatography (TLC). After completion of the reaction, 10 mL of water was added to the mixture and the resulting precipitate was filtered off. The product was recrystallyzed from ethanol and the filleterd solution was evaporated to recover the DES.

Selected Spectral Data

3,3′-Bis-indolyl phenylmethane (Table 1, entry 1): ^{1}H NMR ($CDCl_3$): δ 5.92 (s, 1H), 6.60 (d, J = 1.5, 2H, Ar–H), 7.05 (d, J = 7.9 Hz, 2H, Ar–H), 7.20 (d, J = 7.9 Hz, 2H, Ar–H), 7.23−7.28 (m, 1H, Ar–H), 7.29−7.35 (m, 3H, Ar–H), 7.36−7.40 (m, 3H, Ar–H), 7.42 (d, J = 7.9 Hz, 2H, Ar–H), 7.82 (s, 2H, N–H). ^{13}C NMR ($CDCl_3$): δ 40.1, 111.1, 119.2, 119.7, 121.0, 121.9, 123.8, 126.1, 127.1, 128.2, 128.8, 136.6, 144.1.

Table 2. Synthesis of bis(indolyl)methanes in conventional thermal and ultrasonic methods

Entry	Solvent	Conditions	Temperature (°C)	Time (min)	Yield (%)
1	EtOH	thermal	reflux	40	65
2	$CHCl_3$	thermal	reflux	50	50
3	CH_3CN	thermal	reflux	30	70
4	$ZnCl_2$/urea	thermal	30	30	50
5	$ZnCl_2$/urea	thermal	50	20	75
6	$ZnCl_2$/urea	US	30	25	55
7	$ZnCl_2$/urea	US	50	15	80
8	$ZnCl_2$/urea	US	60	10	92
9	$ZnCl_2$/urea	US	64	10	92

3,3′-Bis-(N-methylindolyl)-(4-methylphenyl)methane (Table 1, **entry 15**): ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 3.68 (s, 6H, $2CH_3$), 5.80 (s, 1H), 6.49 (s, 2H, Ar–H), 6.09 (d, J = 7.8 Hz, 2H, Ar–H), 7.00 (d, J = 7.2 Hz, 2H, Ar–H), 7.02−7.20 (m, 4H, Ar–H), 7.23 (d, J = 7.3 Hz, 2H, Ar–H), 7.42 (d, J = 7.4 Hz, 2H, Ar–H). ^{13}C NMR ($CDCl_3$) δ 21.2, 31.2, 38.3, 109.1, 116.0, 117.0, 119.2, 120.1, 126.4, 126.8, 127.2, 127.5, 134.7, 136.2, 140.3.

Results and Discussion

Study of Significance of DES in Synthesis of Bis(indolyl) methanes by Thermal and US Methods

The reaction parameters were optimized by the reaction of benzaldehyde with indole. First deep eutectic solvent ($ZnCl_2$/urea) and common organic solvents such as ethanol, chloroform and acetonitrile in the presence of 1eq $ZnCl_2$ as a catalyst were used as reaction medium in thermal conditions. Best results were obtained with $ZnCl_2$/urea. The efficiency of deep eutectic medium ($ZnCl_2$/urea) prompted us to explore the scope for further improvement in results using ultrasound method. This method gave improved yield in shorter reaction time (Table 2).

As shown in Table 2, the combination of DES and US showed marked improvements both in terms of reaction times and yields. The impact of acoustic energy results in rapid micromixing thus reducing the processing time.

Table 3. The reaction of benzaldehyde with indole in DES

Entry	Cycle	Time (min)	Yield (%)
1	First run	10	92
2	Second run	10	90
3	Third run	12	87

Table 4. Reaction of indole with carbonyl compounds in the presence of different catalysts

Carbonyl compound	Catalyst	Solvent	Condition	Time	Yield (%)	Ref.
4-Cl-C_6H_4CHO	P_2O_5/SiO_2	Glycerin	75°C	8 h	88	[12]
	$CeCl_3.7H_2O$	Solvent-free	R. T.	30 min	92	[16]
	$FePO_4$	Glycerin	75°C	8 h	85	[17]
	$ZnCl_2$/Urea	$ZnCl_2$/Urea	60°C/US	10	90	—

This protocol accepts different carbonyl compounds and produces respective bis(indolyl)methanes in excellent yields and the results are presented in Table 1. As shown in Table 1, aromatic aldehydes with electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. As was expected the electron-donating and electron-withdrawing groups affect the activity of carbonyl group and it was observed that, the aromatic aldehydes with electron-withdrawing groups such as 4-nitro benzaldehyde reacts faster than the aromatic aldehydes with electron-donating groups such as 4-methyl and 4-methoxy benzaldehyde. It seems the lower yield of 3-nitro benzaldehyde compared to benzaldehyde is related to its lower solubility in DES.

Recyclability of DES

The DES medium was recycled and reused up to three times. Reaction of benzaldehyde with indole was selected as the model reaction. DES recycled from the previous run was reused for the next run without further purification. No significant decrease in yields was obtained as shown in Table 3. This indicates the fact that ultrasound does not have any negative effect on the eutectic combination even after three runs.

In order to show the merit of $ZnCl_2$/Urea deep eutectic system in comparison with the other catalytic systems we performed the reaction of 4-chlorobenzalehyde with indole in different conditions listed in Table 4. It appears from the results that ZnCl2/Urea is more efficient than other catalytic systems.

Conclusion

In conclusion, we have explored combination of deep eutectic solvent and ultrasonic irradiation for clean and efficient synthesis of bis(indolyl)methane derivatives. Ultrasonic irradiation also showed a significant improvement in parameters such as reaction yield and time. DES was found to be more effective than conventional organic solvents. This method has several unique merits, such as high yields, very short reaction time, efficiency, generality, the use of cheap and nontoxic solvent and catalyst, and simplicity in operation.

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