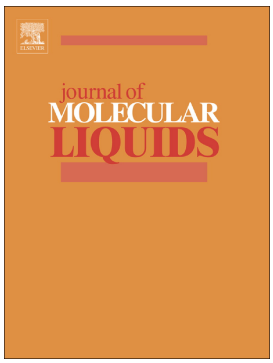

Choline chloride and lactic acid: A natural deep eutectic solvent for one-pot rapid construction of spiro[indoline-3,4′-pyrazolo[3,4-b]pyridines]

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Choline chloride and lactic acid: A natural deep eutectic solvent for one-pot rapid construction of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridines]

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ABSTRACT

The application of natural eutectic solvent (NDDES) in organic synthesis has received more and more attention. In this work, a green protocol for one-pot synthesis of spiro[indoline-3,4'-pyrazolo[3,4-b]pyridines] via three-component reactions of 1*H*-pyrazol-5-amin, isatin and enolizable C−H activated compound is achieved by the combination of microwave irradiation with choline chloride and lactic acid based NDDES. This novel method is clean, cheap, simple, high yield, chromatography-free and scalable. The use of choline chloride and lactic acid as a biodegradable, recycled and reusable media meets most of the criteria to be considered as a sustainable and environmentally benign process.

Keywords:

Natural deep eutectic solvents, Choline chloride/lactic acid, Multicomponent reaction, Isatin, Spirooxindoles, Pyrazolo[3,4-*b*]quinoline

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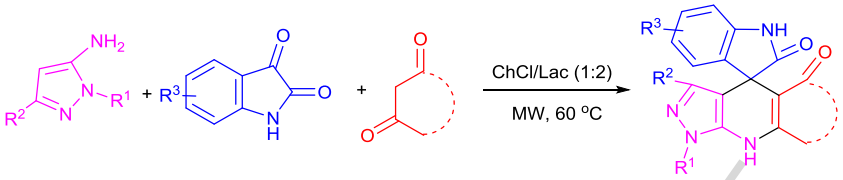
1. Introduction

Solvents occupy a strategic place in the chemical industry. Developing new green solvents to replace current harsh organic solvents is one of the key subjects. In recent years, deep eutectic solvents (DES) have attracted attention due to their excellent biodegradability, low volatility, non-toxicity, ease of preparation, and low cost [1-3]. DESs are conveniently prepared by mixing two or more components that are inexpensive, easily degradable, and environmentally friendly. Most DESs are liquids at room temperature, mainly because these components are capable of self-association through strong hydrogen bonding interactions to generate an eutectic mixture with a much lower melting point than that of any of its individual components [4-6]. When the compound that constitutes DES is primary metabolite, such as polyols, amino acid, organic acid, sugar, urea or choline derivatives, DESs are called natural deep eutectic solvents (NADESs) [7-9]. So far, these solvents have been applied to many chemical processes such as extraction and separation [10], biomass processing [11], polymerization and materials science [12] as well as organic synthesis [13-26]. Thus, the development of new NADESs and extension of research on the use of these solvents to replace harmful traditional solvents in organic reaction is highly desirable.

Pyrazolo[3,4-*b*]pyridines represent an important class of heterocyclic compounds and have found in many active biological products, natural products, and functional materials. Structures embedded with pyrazolo[3,4-*b*]pyridine units display potential medicinal properties such as antiplatelet [27], antifungal [28], anticancer [29], antimicrobial and antiproliferative [30]. They have also been found to behave as potent dual orexin receptor antagonists [31], c-Met [32], and selective FGFR kinase inhibitors [33]. Moreover, spirooxindole are also attractive structural units and are encountered in the core structure of bioactive naturally alkaloids as well as they were considered as privileged scaffolds for antiviral drug development [34-36]. According to current research, merging pyrazolo[3,4-*b*]pyridine backbones and spirooxindole motif into one molecular structure may result in a series of structural and biologically interesting compounds that will have all the properties of the moiety and enhance the pharmacological activity. For these reasons, there have been some methods for the synthesis of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridines] via three-component reactions of isatins with aminpyrazoles and reactive dicarbonyls [37-41], β-ketonitriles [42-43] or enol derivatives [44]. Despite these advances, there are only a few reports about the synthesis of spirooxindole derivatives in deep eutectic solvents [45-47].

Given these considerations and as a part of our constant interest in developing efficient and environmentally friendly synthetic methods [48-50], we herein focus on the development of a highly efficient, clean, quick, and scalable protocol for the preparation of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridines] and other similar

spiroheterocycles via three-component one-pot reaction of 1*H*-pyrazol-5-amin, isatin and enolizable C−H activated compound by combining the microwave-assisted organic synthesis (MAOS) with natural deep eutectic solvent (Scheme 1).



Scheme 1. Synthesis of pyrazolo[3,4-*b*]quinoline spirooxindoles in ChCl/Lac

2. Experimental section

2.1 General

All reagents were commercially available and used without further purification. Melting points were determined on an X-5 digital melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Scientific Nicolet iS50 spectrometer using KBr disks. ^{1}H NMR and ^{13}C NMR (500 MHz and 125 MHz, respectively) spectra were recorded on a Bruker DRX-500 spectrometer using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. The mass spectra were obtained on a 3200 Qtrap instrument (ESI). High-resolution mass spectroscopy (HRMS) was recorded on Thermo Scientific LTQ FT Ultra FT-MS.

2.2. Preparation of choline chloride (ChCl) and lactic acid (Lac) based natural deep eutectic solvent

A mixture of ChCl (100 mmol) and Lac (100 mmol or 200 mmol)) were ground with a mortar and pestle in an argon-filled glove box, transferred to a round bottom flask and heated at 60 °C to give a clear liquid.

2.3. General procedure for preparation of pyrazolo[3,4-b]quinoline spirooxindoles

A mixture of 1*H*-pyrazol-5-amin (1 mmol), isatin (1 mmol) and enolizable C−H activated compound (1 mmol) in NDDES (1.5 ml) was stirred under microwave irradiation at 60 °C for an appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and cold water was added to the reaction mixture. The precipitated solid was isolated by filtration, washed with water and purified by recrystallization from ethanol.

3. Results and Discussion

In this work, ChCl/Lac systems were prepared by mixing ChCl and Lac at different molar ratios 1:1 and 1:2 in an argon-filled glove box. The mixture was kept under constant stirring and at 60 °C until a homogeneous

liquid was formed. Then, the mixture was cooled to room temperature, and the resulting NDDES was used directly in the organic reaction without further purification.

Subsequently, the NDDES-promoted three-component reaction of 1,3-diphenyl-1*H*-pyrazol-5-amine, isatin and 5,5-dimethylcyclohexane-1,3-dione was evaluated under microwave irradiation. Control experiments showed that no reaction was observed when the reaction was performed in the absence of solvent or catalyst at 60 °C for 1 h (Table 1, entry 1). Reaction was performed in H_2O or *N*,*N*-dimethylformamide (DMF), only trace of product was formed (entry 2 and 3). Switching the solvent to PEG 400 or EtOH, the desired product **4a** was isolated in 15% and 18%, respectively (Table 1, entries 4 and 5). The use of ethyl lactate (EL) as solvent resulted in 25% yield (Table 1, entry 6). In EL/H_2O only 20% yield was observed (Table 1, entry 7). Because ChCl is a low toxicity, biodegradable, inexpensive and ton-scale available substance, DESs derived from ChCl with several classes of hydrogen bond donor (HBD) such as renewable polyols, carbohydrates, alcohols, amides and carboxylic acids are liquids at room temperature and can be used as solvent and catalyst in different organic synthsis processes, we decided to optimize the reaction conditions using DESs. It was found that ChCl/$ZnCl_2$, ChCl/$ZnBr_2$, ChCl/ glycerol (G), and ChCl/ proline (Pro) gave the low yield of product (entries 8-11). The use of ChCl/malonic acid (MA), ChCl/ethylene glycol (EG), ChCl/1,3-dimethylurea (DU), ChCl/tartaric acid (TA) increased the yield of the desired **4a** (entries 12-15). Further exploration showed when the reaction was carried out in ChCl/Lac (1:1), product **4a** was formed in 86% yield (entry 16). Encouraged by these result, we further carried out this reaction with varied rations of ChCl and Lac. It was found high yield (95%) could be achieved in ChCl/Lac (1:2) (entry 17). Notably, the reaction can proceed in pure ChCl or Lac, but only low yield of the product was formed (Table 1, entry 18 and 19).

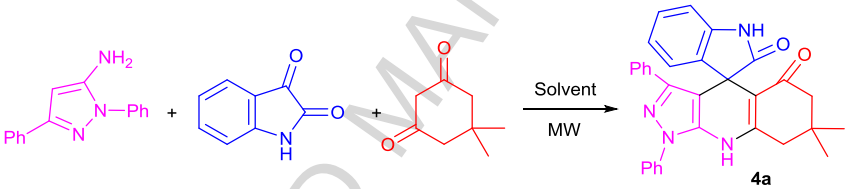
The reaction was also monitored under different amount of ChCl/Lac and the results revealed that 1.5 ml ChCl/Lac was the optimum amount for completing the reaction. Moreover, slight decrease in the product yield was observed when the reactions were performed at lower temperature (entries 20 and 21). In addition, we also studied the effect of microwave irradiation on this reaction. It was found that the reaction required a longer reaction time under simple heating conditions, and the yield of product is relatively lower than under microwave irradiation (entry 27). The effect of microwave power on the reaction was also tested. The results showed that 500 W was the proper power for this three-component reaction. These results indicated that microwave irradiation effectively accelerated the progress of this reaction. It should be pointed out that low yield was obtained when HCl was used in the absence of ChCl/Lac (entry 31). In addition, the reaction time is not shortened and the yield

is not increased when 1 drop of HCl was added in ChCl/Lac (entry 32). It was indicated that the formation of HCl during the preparation of DDES has little effect on the reaction [2].

To further showcase the practical utility of this newly developed system, the model reaction was evaluated on a larger scale. Reassuringly, the reaction was found to proceed smoothly on a 100-mmol scale and the excellent yield of **4a** was maintained (entry 33). On the same scale, the recovery and recyclability of NDDES were also investigated. After the reaction is completed, the reaction mixture was cooled to room temperature and then cold water was added, shacked vigorously and solid was separated by simple filtration followed by washing with water. The soluble NDDES in water could be easily recovered through evaporating the water at 80 °C under vacuum and was reused for the next batch. After eight consecutive recycles, it still afforded target product **4a** in 78% yield (entry 34). A slight decrease in the yield of the target product may be a little loss of deep eutectic solvent during the work-up process.

Table 1

Optimization of the reaction conditions[a]



4a

Entry	solvent	Temperature (°C)	MW (W)	Time (min)	Yield (%)[b]
1	No	60	500	60	0
2	H_2O	60	500	60	trace
3	DMF	60	500	60	trace
4	PEG 400	60	500	60	15
5	EtOH	60	500	60	18
6	EL	60	500	60	25
7	EL/H_2O (1:1)	60	500	60	20
8	ChCl/$ZnCl_2$ (1:2)	60	500	20	21
9	ChCl/$ZnBr_2$ (1:2)	60	500	20	28
10	ChCl/G (1:1)	60	500	20	20
11	ChCl/Pro(1:2)	60	500	20	30
12	ChCl/MA (1:2)	60	500	20	50
13	ChCl/EG (1:1)	60	500	20	56
14	ChCl/DU (1:1)	60	500	20	58
15	ChCl/TA (2:1)	60	500	20	64
16	ChCl/Lac (1:1)	60	500	20	86

17	ChCl/Lac (1:2)	60	500	20	95
18	ChCl	60	500	60	35
19	Lac	60	500	60	20
20[c]	ChCl/Lac (1:2)	60	500	20	30
21[d]	ChCl/Lac (1:2)	60	500	20	71
22[e]	ChCl/Lac (1:2)	60	500	20	93
23[f]	ChCl/Lac (1:2)	60	500	20	91
24	ChCl/Lac (1:2)	40	500	20	81
25	ChCl/Lac (1:2)	50	500	20	90
26	ChCl/Lac (1:2)	70	500	20	93
27	ChCl/Lac (1:2)	60	0	120	82
28	ChCl/Lac (1:2)	60	300	40	91
29	ChCl/Lac (1:2)	60	400	40	93
30	ChCl/Lac (1:2)	60	600	20	95
31[g]	no	60	500	20	12
32[h]	ChCl/Lac (1:2)	60	500	20	95
33[i]	ChCl/Lac (1:2)	60	500	20	94
34[j]	ChCl/Lac (1:2)	60	500	20	93, 90, 88, 86, 83, 80, 80, 78

[a] Reaction conditions: 1,3-diphenyl-1H-pyrazol-5-amine (1 mmol), isatin (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (1 mmol) in solvent (1.5 ml) at 60 °C under microwave irradiation (500 W) unless otherwise specified in the table.

[b] Isolated yield.

[c] The reaction was performed in 0.50 ml ChCl/Lac.

[d] The reaction was performed in 0.75 ml ChCl/Lac.

[e] The reaction was performed in 1.25 ml ChCl/Lac.

[f] The reaction was performed in 1.75 ml ChCl/Lac.

[g] 1 ml HCl (1 mol/l) was used.

[h] 1 Drop of HCl was added.

[i] The reaction was carried out in 100 mmol scale.

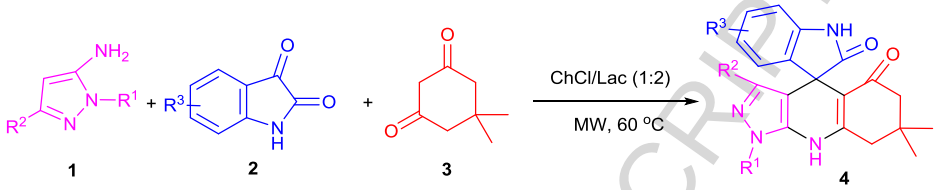
[j] ChCl/Lac was reused for 8 times.

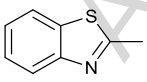
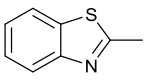
After the optimal reaction conditions were identified, the scope and generality of this domino process were evaluated. As shown by the results in Table 2, various isatins reacted with 1,3-diphenyl-1*H*-pyrazol-5-amine and 5,5-dimethylcyclohexane-1,3-dione to produce the expected products in excellent yields, no matter the presence of substituents bearing electron-rich or electron-poor groups in various positions. Various functional groups were well tolerated on the isatin moiety including methyl (**4b**, **4f** and **4i**), fluoro (**4g**), chloro (**4h**), bromo (**4c** and **4e**),

and nitro (**4d**) groups. Additionally, diversified 1*H*-pyrazol-5-amines were also surveyed. Regarding the upper aromatic ring, various substituents, including electron-donating methyl group, and electron-withdrawing groups such as chloro and nitro groups were tolerated. Moreover, 1*H*-pyrazol-5-amine with benzo[d]thiazole ring behaved quite well in this domino process to afford the corresponding products **4p** and **4q** in high yields, thereby expanding the range of functional groups tolerated with this novel method.

Table 2

Synthesis of spiro[indoline-3,4'-pyrazolo[3,4-*b*]quinoline]-2,5'(6'*H*)-diones in ChCl/Lac



Entry	R^1	R^2	R^3	Product	Time (min)	Yield (%)[a]
1	Ph	Ph	H	**4a**	20	95
2	Ph	Ph	5-Me	**4b**	15	94
3	Ph	Ph	5-Br	**4c**	20	93
4	Ph	Ph	5-NO_2	**4d**	25	95
5	Ph	Ph	6-Br	**4e**	20	94
6	Ph	Ph	7-Me	**4f**	18	95
7	Ph	Ph	7-F	**4g**	16	94
8	Ph	Ph	7-Cl	**4h**	17	93
9	Ph	Ph	1-Me	**4i**	20	92
10	Ph	4-FC_6H_4	H	**4j**	20	95
11	4-MeC_6H_4	Ph	H	**4k**	15	94
12	3-ClC_6H_4	Ph	H	**4l**	20	93
13	4-$NO_2C_6H_4$	Ph	H	**4m**	16	93
14	4-$NO_2C_6H_4$	Ph	5-Me	**4n**	15	94
15	4-$NO_2C_6H_4$	Ph	7-Me	**4o**	16	93
16		Ph	H	**4p**	22	92
17		Ph	5-Me	**4q**	18	91

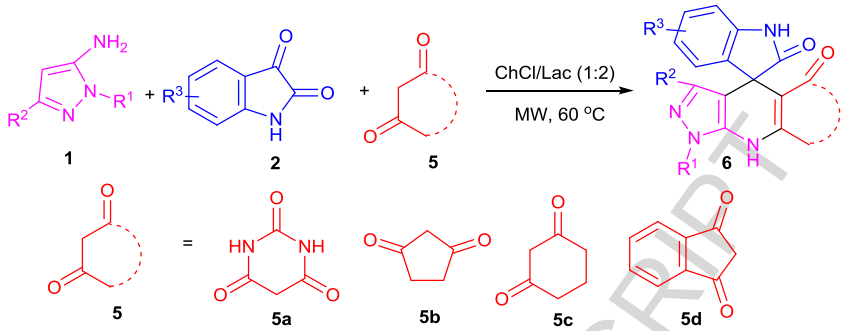
[a] Isolated yield.

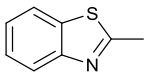
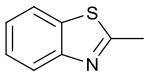
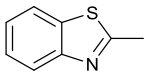
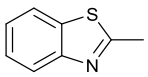
To further investigate the scope of this reaction, various enolizable C−H activated compounds such as barbituric acid, cyclopentane-1,3-dione, cyclohexane-1,3-dione, and 1,3-indanedione were assessed in this three-component reaction. Gratifyingly, these reactions proceeded smoothly, leading to the formation of the

anticipated pyrazolo[3,4-*b*]quinoline spirooxindoles **6a**–**6ah** in excellent yields. The above results clearly demonstrated that the present procedure can be extended to a wide variety of substrates to construct a library of diversified orientations of functionalized spirooxindoles.

Table 3

Synthesis of pyrazolo[3,4-*b*]quinoline spirooxindoles in ChCl/Lac.



Entry	R^1	R^2	R^3	1,3-Dicarbonyl	Product	Time (min)	Yield (%)[a]
1	Ph	Ph	H	**5a**	**6a**	20	95
2	Ph	Ph	5-Me	**5a**	**6b**	20	95
3	Ph	Ph	7-Cl	**5a**	**6c**	18	93
4	3-FC_6H_4	Ph	H	**5a**	**6d**	25	94
5	3-ClC_6H_4	Ph	H	**5a**	**6e**	20	92
6	3-ClC_6H_4	Ph	5-Me	**5a**	**6f**	15	95
7	3-ClC_6H_4	Ph	7-Cl	**5a**	**6g**	20	95
8	4-MeC_6H_4	Ph	H	**5a**	**6h**	20	94
9	4-$NO_2C_6H_4$	Ph	H	**5a**	**6i**	20	93
10	2,6-$Me_2C_6H_3$	Ph	H	**5a**	**6j**	19	93
11	Ph	4-FC_6H_4	H	**5a**	**6k**	25	94
12		Ph	H	**5a**	**6l**	30	94
13		Ph	5-Me	**5a**	**6m**	30	93
14	Ph	Ph	H	**5b**	**6n**	17	94
15	Ph	Ph	7-Me	**5b**	**6o**	13	93
16	Ph	Ph	7-Cl	**5b**	**6p**	15	95
17	3-ClC_6H_4	Ph	H	**5b**	**6q**	14	95
18	3-ClC_6H_4	Ph	5-Me	**5b**	**6r**	15	95
19	3-ClC_6H_4	Ph	7-Cl	**5b**	**6s**	15	94
20	Ph	4-FC_6H_4	H	**5b**	**6t**	20	93
21	Ph	Ph	H	**5c**	**6u**	20	94
22	Ph	Ph	5-Me	**5c**	**6v**	20	93
23	3-ClC_6H_4	Ph	H	**5c**	**6w**	20	94
24	3-ClC_6H_4	Ph	5-Me	**5c**	**6x**	20	95
25	4-$NO_2C_6H_4$	Ph	H	**5c**	**6y**	18	94
26	4-$NO_2C_6H_4$	Ph	5-$NO_2C_6H_4$	**5c**	**6z**	18	95
27	Ph	4-FC_6H_4	H	**5c**	**6aa**	25	93
28		Ph	H	**5c**	**6ab**	30	94
29		Ph	5-Me	**5c**	**6ac**	30	90
30	Ph	Ph	H	**5d**	**6ad**	21	93
31	Ph	Ph	5-OMe	**5d**	**6ae**	25	91
32	Ph	Ph	7-Cl	**5d**	**6af**	20	94
33	3-ClC_6H_4	Ph	H	**5d**	**6ag**	20	92

34	3-ClC_6H_4	Ph	5-Me	**5d**	**6ah**	20	94

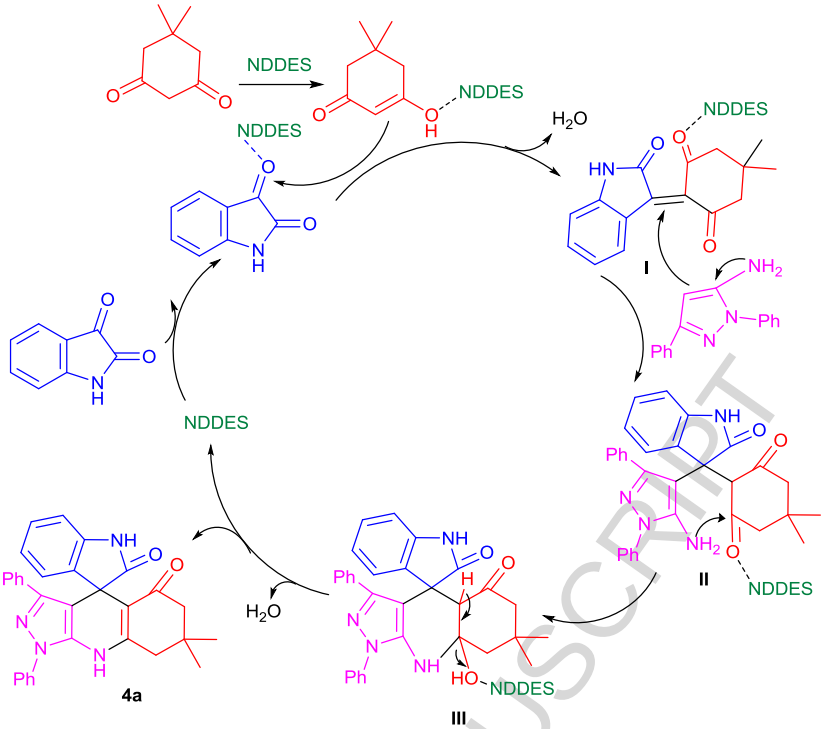
[a] Isolated yield.

To illustrate the advantages and limitations of this work, we summarize some of the results for the synthesis of **6a** and compare them with other reported methods in the literatures. As can be seen from this Table 4, the present work is an equally or more efficient than those previously reported.

Table 4
Comparison of different methods for synthesis of **6a**

Entry	Reaction condition	Yield (%)	Ref.
1	*p*-Toluenesulfonic acid, H_2O, reflux, 24 h	90	39
2	Alum, [Bmim]PF_6, 100 °C, 30 min	95	40
3	A tin complex immobilized on silica gel, H_2O, reflux, 90 min	83	41
4	ChCl/Lac (1:2), microwave irradiation, 60 °C, 20 min	95	This work

The tentative reaction mechanism for the NDDES-based formation of 7',7'-dimethyl-1',3'-diphenyl-1',7',8',9'-tetrahydrospiro[indoline-3,4'-pyrazolo[3,4-*b*]quinoline]-2,5'(6'*H*)-dione (**4a**) is well established (Scheme 2). With the understanding from the literatures [37, 39] and based on the results obtained, the first step involved Knoevenagel condensation of isatin and 5,5-dimethylcyclohexane-1,3-dione to give intermediate **I** in the presence of a NDDES. The subsequent a Michel-type addition of 1,3-diphenyl-1*H*-pyrazol-5-amine to the C=C bond of intermediate **I** occurred, resulting in the formation of the adduct **II**. Afterwards, an intramolecular cyclic condensation between the amino and the carbonyl groups of the Michael adduct **II** took place to produce intermediate **III**, which upon elimination of water to provide the expected product **4a**. The NDDES acts as the solvent as well as participates as a hydrogen-bonding catalyst, the strong hydrogen bond interaction of NDDES with carbonyl group is responsible for formation of Knoevenagel condensation product as well as for assisting to enhance electrophilic character of carbonyl carbons in both intermediate **I** and intermediate **II**.



Scheme 2. A plausible mechanism for the formation of product **4a**

4. Conclusion

In summary, we have disclosed a novel, general, highly efficient, economical method for the fast and divergent assembly of a new class of pyrazolo[3,4-*b*]quinoline spirooxindoles via a three-component reaction involving 1*H*-pyrazol-5-amin, isatin and enolizable C−H activated compound under microwave irradiation in ChCl and Lac based NDDES for the first time. This environmentally friendly process features broad substrate scope, high yield, short reaction time, easy scalability with the use of NDDES as a biodegradable, recycled and reusable media and catalyst.

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References

[1] E.L. Smith, A.P. Abbott, K.S. Ryder, Deep eutectic solvents (DESs) and their applications, Chem. Rev. 114 (2014) 11060-11082.

[2] C. Florindo, F.S. Oliveira, L.P.N. Rebelo, A.M. Fernandes, I.M. Marrucho, Insights into the synthesis and

properties of deep eutectic solvents based on cholinium chloride and carboxylic acids. ACS Sustainable Chem. Eng. 2 (2014) 2416-242.

[3] C. Florindo, M.M. Oliveira, L.C. Branco, I.M. Marrucho, Carbohydrates-based deep eutectic solvents: Thermophysical properties and rice straw dissolution. J. Mol. Liq., 247 (2017) 441-447.

[4] S. Khandelwal, Y.K. Tailor, M. Kumar, Deep eutectic solvents (DESs) as eco-friendly and sustainable solvent/catalyst systems in organic transformations. J. Mol. Liq. 215 (2016) 345-386.

[5] P. Liu, J.W. Hao, L.P. Mo, Z.H. Zhang, Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. RSC Adv. 5 (2015) 48675-48704.

[6] N. Guajardo, C.R. Muller, R. Schrebler, C. Carlesi, P.D. de Maria, Deep eutectic solvents for organocatalysis, biotransformations, and multistep organocatalyst/enzyme combinations. ChemCatChem 8 (2016) 1020-1027.

[7] Y. Liu, J.B. Friesen, J.B. McAlpine, D.C. Lankin, S.N. Chen, G.F. Pauli, Natural deep eutectic solvents: properties, applications, and perspectives. J. Nat. Prod., 81 (2018) 679-690.

[8] I.M. Aroso, A. Paiva, R.L. Reis, A.R.C. Duarte, Natural deep eutectic solvents from choline chloride and betaine - Physicochemical properties. J. Mol. Liq. 241 (2017) 654-661.

[9] R. Craveiro, I. Aroso, V. Flammia, T. Carvalho, M.T. Viciosa, M. Dionisio, S. Barreiros, R.L. Reis, A.R.C. Duarte, A. Paiva, Properties and thermal behavior of natural deep eutectic solvents. J. Mol. Liq. 215 (2016) 534-540.

[10] X.X. Li, K.H. Row, Development of deep eutectic solvents applied in extraction and separation. J. Sep. Sci.

[11] X. Tang, M. Zuo, Z. Li, H. Liu, C.X. Xiong, X.H. Zeng, Y. Sun, L. Hu, S.J. Liu, T.Z. Lei, L. Lin, Green processing of lignocellulosic biomass and its derivatives in deep eutectic solvents, ChemSusChem 10 (2017) 2696-2706.

[12] X. Li, J. Choi, W.S. Ahn, K.H. Row, Preparation and application of porous materials based on deep eutectic solvents. Crit. Rev. Anal. Chem. 48 (2018) 73-85.

[13] D.A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I.M. Pastor, D.J. Ramon, Deep eutectic solvents: the organic reaction medium of the century. Eur. J. Org. Chem. (2016) 612-632.

[14] B.L. Gadilohar, G.S. Shankarling, Choline based ionic liquids and their applications in organic transformation. J. Mol. Liq. 227 (2017) 234-261.

[15] J. Lu, X.T. Li, E.Q. Ma, L.P. Mo, Z.H. Zhang, Superparamagnetic $CuFeO_2$ nanoparticles in deep eutectic solvent: an efficient and recyclable catalytic system for the synthesis of imidazo[1,2-*a*]pyridines. ChemCatChem 6 (2014) 2854-2859.

[16] D. Chandam, A. Mulik, P. Patil, S. Jagdale, D. Patil, S. Sankpal, M. Deshmukh, Oxalic acid dihydrate: proline (LTTM) as a new generation solvent for synthesis of 3,3-diaryloxindole and chromone based bis(indolyl)alkanes: Green, chromatography free protocol. J. Mol. Liq. 207 (2015) 14-20.

[17] H.C. Hu, Y.H. Liu, B.L. Li, Z.S. Cui, Z.H. Zhang, Deep eutectic solvent based on choline chloride and malonic acid as an efficient and reusable catalytic system for one-pot synthesis of functionalized pyrroles. RSC Adv. 5 (2015) 7720-7728.

[18] N. Azizi, F. Shirdel, Task specific dicationic acidic ionic liquids catalyzed efficient and rapid synthesis of

benzoxanthenones derivatives. J. Mol. Liq. 222 (2016) 783-787.

[19] S. Khandelwal, Y.K. Tailor, M. Kumar, Deep eutectic solvents (DESs) as eco-friendly and sustainable solvent/catalyst systems in organic transformations. J. Mol. Liq. 215 (2016) 345-386.

[20] G. Gao, P. Wang, P. Liu, W.H. Zhang, L.P. Mo, Z.H. Zhang, Deep eutectic solvent catalyzed one-pot synthesis of 4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles. Chin. J. Org. Chem. 38 (2018) 846-854.

[21] D.R. Chandam, A.G. Mulik, D.R. Patil, A.P. Patravale, D.R. Kumbhar, M.B. Deshmukh, Oxalic acid dihydrate and proline based low transition temperature mixture: An efficient synthesis of spiro diindenopyridine-indoline triones derivatives. J. Mol. Liq. 219 (2016) 573-578.

[22] N. Azizi, T.S. Ahooie, M.M. Hashemi, Multicomponent domino reactions in deep eutectic solvent: An efficient strategy to synthesize multisubstituted cyclohexa-1,3-dienamines. J. Mol. Liq. 246 (2017) 221-224.

[23] C.T. Ma, P. Liu, W. Wu, Z.H. Zhang, Low melting oxalic acid/proline mixture as dual solvent/catalyst for efficient synthesis of 13-aryl-13*H*-benzo[g]benzothiazolo[2,3-*b*] buinazoline-5,4-diones under microwave irradiation. J. Mol. Liq. 242 (2017) 606-611.

[24] D.R. Chandam, A.A. Patravale, S.D. Jadhav, M.B. Deshmukh, Low melting oxalic acid dihydrate: proline mixture as dual solvent/catalyst for synthesis of spiro[indoline-3,9´-xanthene]trione and dibarbiturate derivatives. J. Mol. Liq. 240 (2017) 98-105.

[25] M. Zhang, P. Liu, Y.H. Liu, Z.R. Shang, H.C. Hu, Z.H. Zhang, Magnetically separable graphene oxide anchored sulfonic acid: a novel, highly efficient and recyclable catalyst for one-pot synthesis of 3,6-di(pyridin-3-yl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitriles in deep eutectic solvent under microwave irradiation. RSC Adv., 6 (2016) 106160-106170.

[26] M. Zhang, Y.H. Liu, Z.R. Shang, H.C. Hu, Z.H. Zhang, Supported molybdenum on graphene oxide/Fe_3O_4: An efficient, magnetically separable catalyst for one-pot construction of spiro-oxindole dihydropyridines in deep eutectic solvent under microwave irradiation. Catal. Commun. 88 (2017) 39-44.

[27] A. Ramzan, S. Siddiqui, A. Irfan, A.G. Al-Sehemi, A. Ahmad, F. Verpoort, A.H. Chughtai, M.A. Khan, M.A. Munawar, M.A.R. Basra, Antiplatelet activity, molecular docking and QSAR study of novel N'-arylmethylidene-3-methyl-1-phenyl-6-*p*-chlorophenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carbohydrazides. Med. Chem. Res. 27 (2018) 388-405.

[28] J. Quiroga, Y. Villarreal, J. Galvez, A. Ortiz, B. Insuasty, R. Abonia, M. Raimondi, S. Zacchino, Synthesis and antifungal in vitro evaluation of pyrazolo[3,4-b]pyridines derivatives obtained by Aza-Diels-Alder reaction and microwave irradiation. Chem. Pharm. Bull. 65 (2017) 143-150.

[29] P. Nagender, R.N. Kumar, G.M. Reddy, D.K. Swaroop, Y. Poornachandra, C.G. Kumar, B. Narsaiah, Synthesis of novel hydrazone and azole functionalized pyrazolo[3,4-b]pyridine derivatives as promising anticancer agents. Bioorg. Med. Chem. Lett. 26 (2016) 4427-4432.

[30] M.S. Salem, M.A.M. Ali, Novel pyrazolo[3,4-*b*]pyridine derivatives: synthesis, characterization, antimicrobial and antiproliferative profile. Biol. Pharm. Bull. 39 (2016) 473-483.

[31] D. Behnke, S. Cotesta, S. Hintermann, M. Fendt, C.E. Gee, L.H. Jacobson, G. Laue, A. Meyer, T. Wagner, S. Badiger, V. Chaudhari, M. Chebrolu, C. Pandit, D. Hoyer, C. Betschart, Discovery of

1*H*-pyrazolo[3,4-b]pyridines as potent dual orexin receptor antagonists (DORAs). Bioorg. Med. Chem. Lett. 25 (2015) 5555-5560.

[32] N. Liu, Y.F. Wang, G.C. Huang, C.H. Ji, W. Fan, H.T. Li, Y. Cheng, H.Q. Tian, Design, synthesis and biological evaluation of 1H-pyrrolo[2,3-b]pyridine and 1*H*-pyrazolo[3,4-*b*]pyridine derivatives as c-Met inhibitors. Bioorg. Chem. 65 (2016) 146-158.

[33] B. Zhao, Y.X. Li, P. Xu, Y. Dai, C. Luo, Y.M. Sun, J. Ai, M.Y. Geng, W.H. Duan, Discovery of substituted 1*H*-Pyrazolo[3,4-b]pyridine derivatives as potent and selective FGFR kinase inhibitors. ACS Med. Chem. Lett. 7 (2016) 629-634.

[34] M.M.M. Santos, Recent advances in the synthesis of biologically active spirooxindoles. Tetrahedron 70 (2014) 9735-9757.

[35] R.Y. Yang, J. Sun, Q. Sun, C.G. Yan, Selective construction of polycyclic spirooxindoles via a $Cu(OTf)_2$/HOTf-catalyzed domino reaction of *o*-arylalkynylacetophenones and 3-phenacylideneoxindoles. Org. Biomol. Chem. 15 (2017) 6353-6357.

[36] M.A. El-Hashash, S.A. Rizk, One-pot synthesis of novel spirooxindoles as antibacterial and antioxidant agents. J. Heterocycl. Chem. 54 (2017) 1776-1784.

[37] J. Quiroga, S. Portillo, A. Perez, J. Galvez, R. Abonia, B. Insuasty, An efficient synthesis of pyrazolo[3,4-*b*]pyridine-4-spiroindolinones by a three-component reaction of 5-aminopyrazoles, isatin, and cyclic β-diketones. Tetrahedron Lett. 52 (2011) 2664-2666.

[38] S. Kumari, J. Sindhu, J.M. Khurana, Efficient green approach for the synthesis of spiro[indoline-3,4'-pyrazolo[3,4-*b*]quinoline diones using $[NMP]H_2PO_4$ and solvatochromic and pH studies, Synth. Commun. 45 (2015) 1101-1113.

[39] R. Ghahremanzadeh, M. Sayyafi, S. Ahadi, A. Bazgir, Novel one-pot, three-component synthesis of spiro[indoline-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine] trione library, J. Comb. Chem. 11 (2009) 393-396.

[40] S.A. Shirvan, R. Ghahremanzadeh, M.M. Moghaddam, A. Bazgir, A.H. Zarnani, M.M. Akhondi, A novel method for the synthesis of spiro[indoline-pyrazolo[4',3':5,6 pyrido][2,3-*d*]pyrimidine]triones by Alum as a reusable catalyst, J. Heterocycl. Chem. 49 (2012) 951-954.

[41] R. Ghahremanzadeh, Z. Rashid, A.H. Zarnani, H. Naeimi, Inorganic organic hybrid silica based tin complex as a novel, highly efficient and recyclable heterogeneous catalyst for the one-pot preparation of spirooxindoles in water, Dalton Trans. 43 (2014) 15791-15797.

[42] A. Rahmati, T. Kenarkoohi, H.R. Khavasi, Synthesis of 2,6'-dioxo-1',5',6',7'-tetrahydrospiro indoline-3,4'-pyrazolo[3,4-*b*]pyridine-5'-carbonitriles via a one-pot, three-component reaction in water. ACS Comb. Sci. 14 (2012) 657-664.

[43] X. Gao, Z. Yang, W.J. Hao, B. Jiang, S.J. Tu, Three-Component synthesis of spiro indoline-3,4-pyrazolo[3,4-*b*]pyridines under microwave irradiation. J. Heterocycl. Chem. 54 (2017) 2434-2439.

[44] S. Safaei, I. Mohammadpoor-Baltork, A.R. Khosropour, M. Moghadam, S. Tangestaninejad, V. Mirkhani, H.R. Khavasi, One-pot three-component synthesis of pyrano[3,2-*b*]pyrazolo[4,3-e]pyridin-8(1*H*)-ones. ACS

Comb. Sci. 15 (2013) 141-146.

[45] N. Azizi, S. Dezfooli, M.M. Hashemi, Greener synthesis of spirooxindole in deep eutectic solvent. J. Mol. Liq. 194 (2014) 62-67.

[46] N. Yan, Y. Xiong, J. Xia, P. Rui, Z. Lei, W. Liao, B. Xiong, Green Synthesis of novel spirooxindole derivatives in deep eutectic solvent. Chin. J. Org. Chem. 35 (2015) 384-389.

[47] S. Khandelwal, A. Rajawat, Y.K. Tailor, M. Kumar, A simple, efficient and environmentally benign synthetic protocol for the synthesis of spirooxindoles using choline chloride-oxalic acid eutectic mixture as catalyst/solvent system. Comb. Chem. High Throughput Screening 17 (2014) 763-769.

[48] M. Zhang, Q.-Y. Fu, G. Gao, H.-Y. He, Y. Zhang, Y.-S. Wu, Z.-H. Zhang, Catalyst-free, visible-light promoted one-pot synthesis of spirooxindole-pyran derivatives in aqueous ethyl lactate. ACS Sustainable Chem. Eng. 5 (2017) 6175-6182.

[49] M. Zhang, Y. Han, J.L. Niu, Z.H. Zhang, A general and practical approach for the synthesis of 1,2,4-trioxanes catalyzed by silica-ferric chloride. Adv. Synth. Catal. 359 (2017) 3618-3625.

[50] Y. Han, M. Zhang, Y.-Q. Zhang, Z.-H. Zhang, Copper immobilized at covalent organic framework: an efficient and recyclable heterogeneous catalyst for Chan−Lam coupling reaction of aryl boronic acids and amines. Green Chem. 20 (2018) doi: 10.1039/C8GC02611D.

Graphical abstract

Choline chloride and lactic acid: A natural deep eutectic solvent for one-pot rapid construction of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridines]

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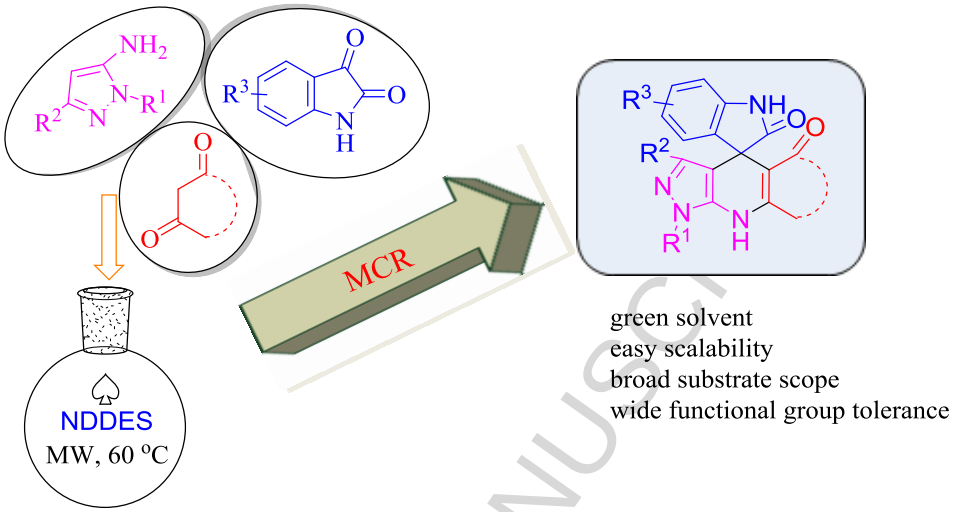

Highlights

- The synthetic procedure of choline chloride and lactic acid based on the natural eutectic solvents is very simple.
- The NDDES plays dual role as medium and catalyst for synthesis of spirooxindole derivatives.
- This new method is clean, inexpensive, high yield, chromatography-free and scalable.
- NDDES is easy to recycle and reuse.