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PII: S0040-4039(19)31280-8
DOI: https://doi.org/10.1016/j.tetlet.2019.151481
Reference: TETL 151481

To appear in: *Tetrahedron Letters*

Received Date: 8 September 2019
Revised Date: 19 November 2019
Accepted Date: 2 December 2019

Please cite this article as: Thi Tran, M-N., Thi Nguyen, X-T., Truong Nguyen, H., Nguyen Chau, D-K., Hoang Tran, P., Deep eutectic solvent: an efficient and green catalyst for the three-component condensation of indoles, aromatic aldehydes, and activated methylene compounds, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151481

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Deep eutectic solvent: an efficient and green catalyst for the three-component condensation of indoles, aromatic aldehydes, and activated methylene compounds

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Deep eutectic solvent;
3-Substituted indoles;
Sonication;
Multicomponent reaction

ABSTRACT

The deep eutectic solvent-catalyzed multicomponent reaction of aldehydes, indoles, and activated methylene compounds under sonication has been developed. The method proceeded well for a wide scope of substrates under mild condition to afford 3-substituted indoles in moderate to good yields. Interestingly, no additives or solvents are used for the protocol. Moreover, the deep eutectic solvent (zinc chloride and choline chloride) is an inexpensive and recyclable catalyst making the protocol more efficient, facile, and cost-effective.

Keywords: Deep eutectic solvent; 3-substituted indoles; sonication; multicomponent reaction.
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molecule have attracted considerable attention for the preparation of biologically active compounds due to the synthetic simplicity of reducing the number of steps and the improvement of synthetic efficiency.[1, 2] 3-Substituted indoles are valuable structural motifs because they exhibit potential biological activities in pharmaceutical and agrochemical fields. Accordingly, the development of efficient methods for the preparation of 3-substituted indoles *via* Yonemitsu-type trimolecular condensation has received significant attention (Scheme 1).[3] Nevertheless, a large excess of unrecyclable Lewis acids, high temperatures, or long reaction times were employed in these reactions.[4, 5] Consequently, the search for more efficient, simple, low cost, and environmentally benign methods for the preparation of 3-substituted indoles remains a challenging task. Recently, a novel copper(II) sulfonato salen catalyst was utilized for the multicomponent reaction of indoles, malononitrile, and benzaldehydes to afford 3-substituted indoles in good yields.[6] However, the use of expensive catalysts, additives, and long reaction times are not suitable for industrial processes.

Green methods using water or solvent-free conditions have been extensively studied due to their economic efficiency and waste reduction.[7] Thus, deep eutectic solvents (DESs), a type of ionic liquids formed by mixing a typical ammonium halide salt and hydrogen bond donors or metal salts, have received increased interest.[8-10] DESs are green solvents/catalysts with unique properties and can be designed by changing the salt or hydrogen bond donor.[11] DESs are non-toxic, non-volatile, thermostable, recyclable, and biodegradable.[12, 13] However, there have fewer reports on the use of DESs as catalysts for multicomponent reactions. In continuation of our efforts in developing green processes, we report herein the multicomponent reactions of aldehydes, indoles, and active methylene compounds in a DES formed from choline chloride and zinc chloride. The method is simple, efficient, and cost-effective for the preparation of 3-substituted indoles. The reaction proceeded smoothly under solvent-free conditions, and the desired products were obtained in good yields.

[CholineCl][$ZnCl_2$]$_3$ was synthesized following a literature procedure (see ESI).[14] Next, we focused on screening for an effective catalyst using the model reaction of indole, benzaldehyde, and diethyl malonate. Among the various metal halides and DESs tested (Table 1), [CholineCl][$ZnCl_2$]$_3$ showed the best catalytic activity (Table 1, entry 8). Meanwhile, the reaction did not afford the desired product when other DESs were employed as catalysts (Table 1, entries 9-11). Control experiments using only choline chloride or zinc chloride were also tested. Lower yields were obtained under these conditions (Table 1, entries 12-13).

Then, the effect of the catalyst loading was investigated (Table 2). No product was obtained in the absence of [CholineCl][$ZnCl_2$]$_3$ (Table 2, entry 1). The optimal loading was attained at 30 mol% [CholineCl][$ZnCl_2$]$_3$ (Table 2, entry 6). When the catalyst loading was decreased from 30% to 5%, the yields decreased from 67% to 25% (Table 2, entries 2-5). However, at the catalyst loading of 50%, only a slightly increased yield was observed (Table 2, entry 7). Further optimization showed that the current method was most effective at room temperature for 6 h under sonication.

The recyclability of catalyst is the most critical feature for its upscaled application in industrial processes. The recovery of [CholineCl][$ZnCl_2$]$_3$ could be easily accomplished through liquid-liquid extraction. The recycling test was conducted using the reactions of indole and diethyl malonate with benzaldehyde, 4-nitrobenzaldehyde or 4-methoxybenzaldehyde, only indicating a slight loss of catalytic activity over four cycles (Fig. 1). FT-IR spectra of freshly prepared and recovered [CholineCl][$ZnCl_2$]$_3$ showed no significant structural changes.

With the optimized conditions in hand, the reaction scope was studied with a number of aldehydes and indoles (Table 3). The electronic effects of the benzaldehydes had little impact on the yield. Benzaldehydes bearing electron-donating groups (4-methoxy, 4-methyl, 4-hydroxy, and 4-*tert*-butyl) on the aromatic ring were beneficial and provided the desired products in good yields. Benzaldehydes bearing electron-withdrawing groups, including 4-nitrobenzaldehyde and 4-fluorobenzaldehyde, gave the desired products **4g** (35%) and **4b** (49%), respectively. The influence of substituents at the C5 position of the indole ring was also examined. Good yields were obtained with an electron-rich methyl group. However, slightly lower yields were observed with 5-halogen substituents (**4m**-**t**), which are deactivating. To further investigate the scope and limitations of the method, malononitrile was used as a reagent. Remarkably, malononitrile reacted smoothly with indoles and aldehydes affording the desired products in higher yields and shorter reaction times than diethyl malonate.

To study the reaction mechanism, some control experiments were tested. As presented in Table 1, the multicomponent reaction in the presence of either choline chloride or $ZnCl_2$ provided the desired product **4a** in 0% and 34% yield, respectively. Based on the control experiments and literature reports,[4] a plausible mechanism was proposed (Scheme S1, ESI). We believe that formation of the desired product could be explained by the role of [CholineCl][$ZnCl_2$]$_3$ in the following processes. The first step involves an interaction between [CholineCl][$ZnCl_2$]$_3$ and dimethyl malonate. This coordination increases the acidity of the α-hydrogen allowing an enolate intermediate to be easily formed. Next, the reactive intermediate attacks the benzaldehyde to generate intermediate (**A**) *via* Knoevenagel adduct formation. Finally, the Friedel-Crafts alkylation of indole by the alkylidene malonate leads to the expected product.

In conclusion, we have successfully developed a green and efficient method for the three-component reaction of indoles, aromatic aldehydes, and active methylene compounds to synthesize the 3-substituted indoles. Mild reaction conditions, simple workup protocol, no additives, and no toxic solvent are the notable features of the method. Moreover, the DES could be recovered

Acknowledgments

The Vietnam National Foundation for Science and Technology Development (NAFOSTED) is acknowledged for financial support through project code 104.01-2019.26

References and notes

1. Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958.
2. Gu, Y. *Green Chem.* **2012**, *14*, 2091.
3. Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.
4. Renzetti, A.; Dardennes, E.; Fontana, A.; De Maria, P.; Sapi, J.; Gérard, S. *J. Org. Chem.* **2008**, *73*, 6824.
5. Renzetti, A.; Boffa, E.; Colazzo, M.; Gérard, S.; Sapi, J.; Chan, T.-H.; Nakazawa, H.; Villani, C.; Fontana, A. *RSC Adv.* **2014**, *4*, 47992.
6. Rosatella, A. A.; Simeonov, S. P.; Frade, R. F. M.; Afonso, C. A. M. *Green Chem.* **2011**, *13*, 754.
7. Clarke, C. J.; Tu, W. C.; Levers, O.; Brohl, A.; Hallett, J. P. *Chem. Rev.* **2018**, *118*, 747.
8. Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Chem. Commun.* **2003**, 70.
9. Abbott, A. P.; Boothby, D.; Capper, G.; Davies, D. L.; Rasheed, R. K. *J. Am. Chem. Soc.* **2004**, *126*, 9142.
10. Carriazo, D.; Serrano, M. C.; Gutierrez, M. C.; Ferrer, M. L.; del Monte, F. *Chem. Soc. Rev.* **2012**, *41*, 4996.
11. Ruß, C.; König, B. *Green Chem.* **2012**, *14*, 2969.
12. Zhang, Q.; De Oliveira Vigier, K.; Royer, S.; Jerome, F. *Chem. Soc. Rev.* **2012**, *41*, 7108.
13. del Monte, F.; Carriazo, D.; Serrano, M. C.; Gutierrez, M. C.; Ferrer, M. L. *ChemSusChem* **2014**, *7*, 999.
14. Nguyen, H. T.; Tran, P. H. *RSC Adv.* **2016**, *6*, 98365.

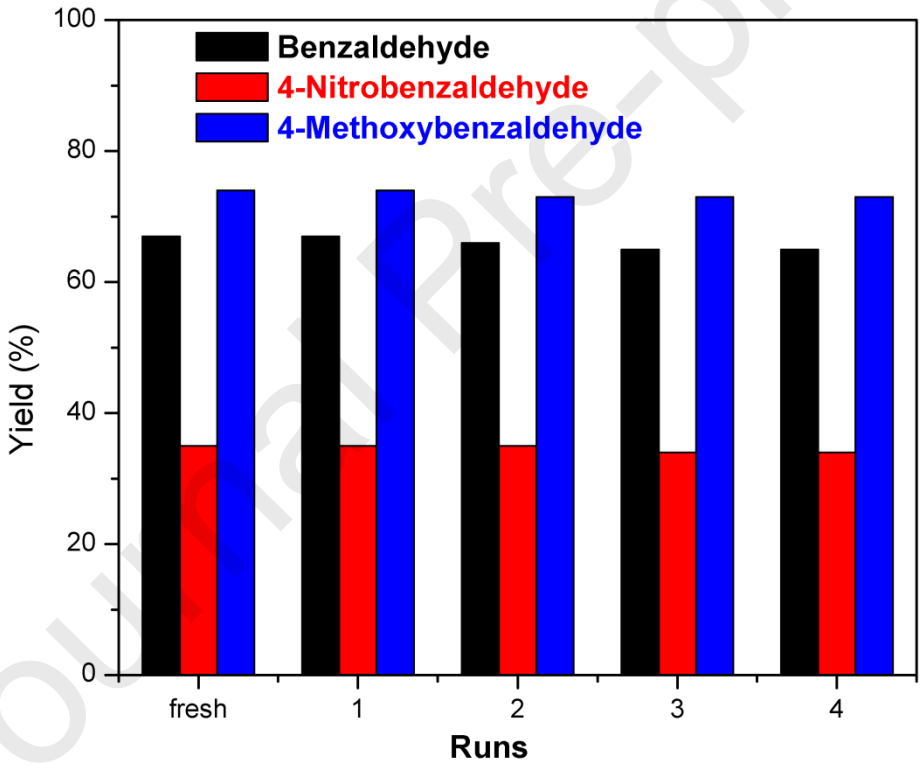
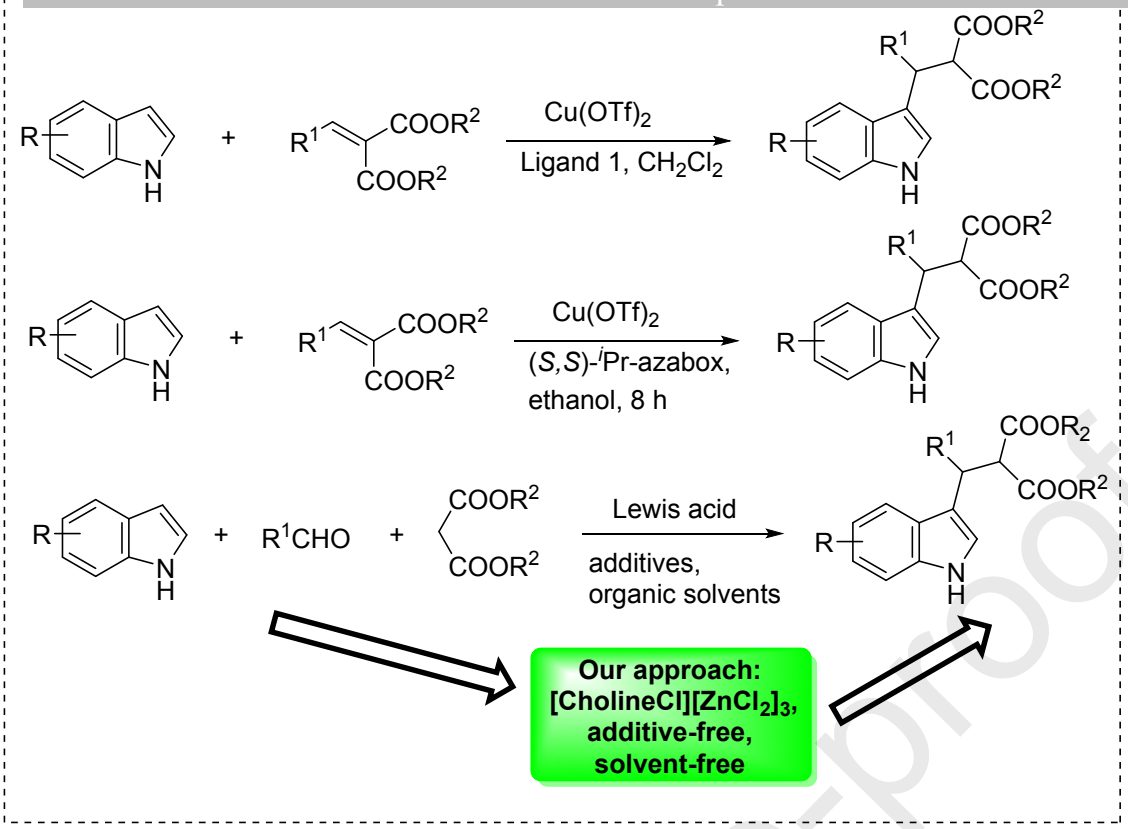
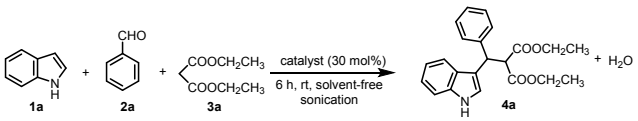


Figure 1. Recycling test



Scheme 1. Pathways for the synthesis of 3-substituted indoles

Tab



Entry	Catalyst	Isolated yield **4a** (%)
1	$FeCl_3$	0
2	$FeCl_2$	0
3	$AlCl_3$	10
4	$CuCl_2$	12
5	[CholineCl][Oxalic acid]	0
6	[CholineCl][$ZnCl_2$]	37
7	[CholineCl][$ZnCl_2$]$_2$	51
8	**[CholineCl][$ZnCl_2$]$_3$**	**67 (55)[b]**
9	[CholineCl][Glucose]	0
10	[CholineCl][Succinic acid]	0
11	[CholineCl][3-phenylpropionic acid]	0
12	$ZnCl_2$	34 (38)[c]
13	Choline chloride	0

[a] Reagents and conditions: indole (1 mmol), benzaldehyde (1 mmol), diethyl malonate (1 mmol), [CholineCl][$ZnCl_2$]$_3$ (30 mol%), solvent-free sonication.
[b] Yield in parenthesis corresponds to the reaction carried out under stirring for 6 h at room temperature
[c] Yield in parenthesis was obtained in the presence of 90 mol% $ZnCl_2$.

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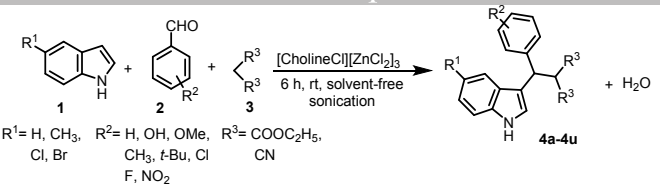
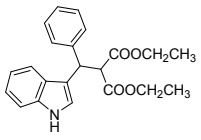
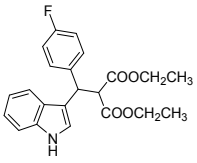
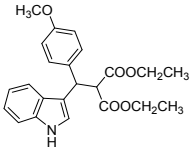
Entry	[CholineCl][$ZnCl_2$]$_3$ (mol%)	Time (h)	Isolated yield **4a** (%)
1	0	6.0	0
2	5	6.0	25
3	10	6.0	37
4	15	6.0	40
5	20	6.0	53
6	30	6.0	67
7	50	6.0	70
8	30	0.1	trace
9	30	0.5	23
10	30	1.0	34
11	30	3.0	55
12	30	8.0	69

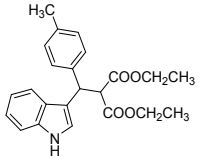
[a] Reagents and conditions: indole (1 mmol), benzaldehyde (1 mmol), diethyl malonate (1 mmol), [CholineCl][$ZnCl_2$]$_3$, room temperature, solvent-free sonication.

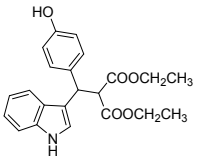


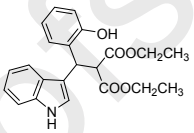

4a, 67%

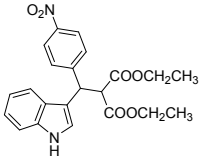

4b, 49%

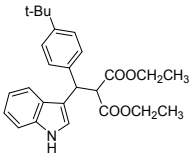

4c, 74%

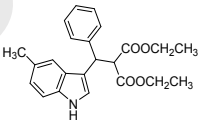

4d, 70%

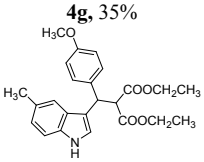

4e, 72%

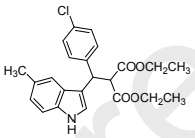

4f, 57%

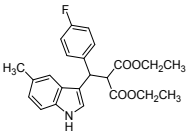

4g, 35%


4h, 75%


4i, 73%


4j, 85%


4k, 75%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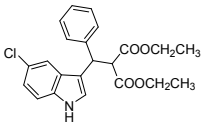
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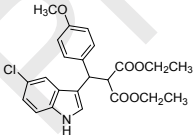
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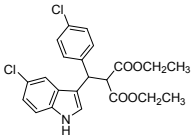
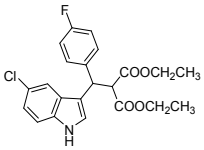
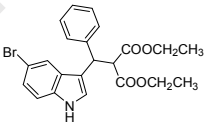
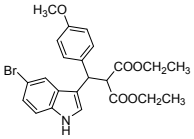

4o, 70%


4p, 75%


4q, 80%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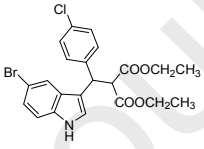
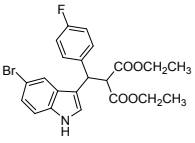
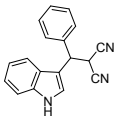

4s, 69%


4t, 62%


4u, 90%

[a] Reagents and conditions: indole (1 mmol), aldehyde (1 mmol), diethyl malonate or malonitrile (1 mmol), $[CholineCl][ZnCl_2]_3$ (30 mol%), solvent-free sonication.

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Deep eutectic solvent: an efficient and green catalyst for three-component condensation of indoles, aromatic aldehydes, and activated methylene compounds

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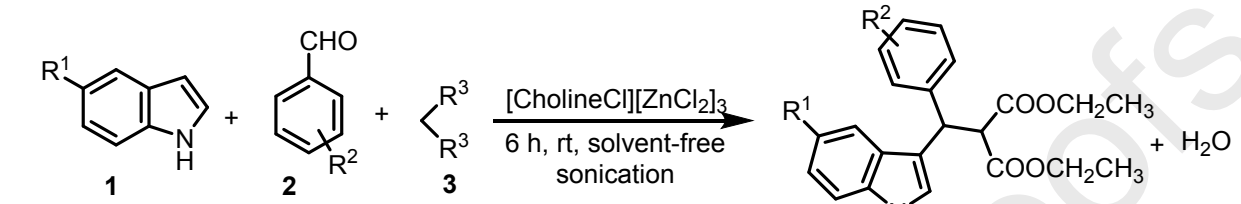

R^1= H, CH_3, Cl, Br R^2= H, OH, OMe, CH_3, *t*-Bu, Cl F, NO_2 R^3= $COOC_2H_5$, CN

Highlights

- Deep eutectic solvent-catalyzed multicomponent reaction of aldehydes, indoles, and activated methylene compounds is described.
- Inexpensive, non-toxic, and recyclable catalyst.
- Simple, efficient, and cost-effective method.

Declaration of Interest Statement

All authors declare that **there are no conflicts of interest to declare.**