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A ligand-free copper(II)-catalyzed three-component reaction in poly(ethylene glycol) medium: a versatile protocol for the preparation of selected 3-indole derivatives

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ABSTRACT

An efficient and eco-friendly method has been developed for the synthesis of selected 3-indole derivatives via a copper-catalyzed condensation between indole, aldehydes, and malononitrile in polyethylene glycol. The reagent system (PEG solvent plus catalyst) could be recycled up to 5 times for reaction with the same aldehyde and it was used also with at least three different aldehydes successively. This multicomponent reaction (MCR) occurs first through Knoevenagel condensation followed by Michael addition of indole.

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Multi-component reactions (MCRs) are offering many advantages, as they allow more than two simple and flexible building blocks to assemble in order to access archetypical molecules with high variability.¹ Indole structural motif represents a 'privileged scaffold' in drug discovery.² Indole alkaloids from medicinal plants and its derivatives have taken on considerable pharmacological importance.³ Multi-component reactions have emerged as an efficient tool in the synthesis of structurally diverse indole derivatives of high biological relevance.⁴ However, the development of simple and efficient multi-component reactions for the synthesis of indole 3-derivatives still remains an active research area.

Recently poly(ethylene glycol) has received greater attention in organic synthesis as an efficient and sustainable reaction media,⁵ including for MCRs.⁶ Due to the importance of eco-friendly systems in organic synthesis, we have considered the development of selected MCRs and tandem one-pot reactions in poly(ethylene glycol) [PEG].⁷

Since 3-substituted indole derivatives have been widely found in biologically active compounds, several research groups have turned their attention to access those indole 3-derivatives by simple synthetic methods, both in racemic and optically pure forms.⁸ In 1978, Yonemitsu and co-workers have reported a new multicomponent reaction of indole, aldehydes, and Meldrum's acid to give indole 3-derivatives, those were used as intermediates in the synthesis of complex indole alkaloids.^{9,10}

Usually this type of condensation has been carried out with organic bases but recently Curini et al. have exploited the Lewis acid [Yb(OTf)₃] catalyzed three-component reaction of indole, aldehydes, and dimethyl malonate under solvent-free conditions furnishing the desired adducts in moderate to good yields.¹¹ On the other hand, Sapi and Gérard described the one-pot synthesis of indole 3-derivatives by a TiCl₄/Et₃N promoted trimolecular condensation,¹² while Fontana and Re studied the mechanism of this reaction.^{12c} More recently, Zhou and co-workers have reported the three component reaction of indole, aldehydes, and malononitrile in water, catalyzed by a copper(II) sulfonato Salen complex, affording 3-indole derivatives in good to excellent yields.¹³ However, low yields were obtained in the absence of ligand and preparation of the disodium sulfonato Salen complex (ligand) required several synthetic steps. We envisioned, based on our previous work with PEG as the solvent medium,⁷ that the PEG may act as an external ligand to perform this MCR reaction (Scheme 1).

To check our hypothesis, initially we attempted a three-component coupling with indole, benzaldehyde, and malononitrile using 5 mol % Cu(OAc)₂ as the catalyst and KH₂PO₄ as an additive in PEG-400 at 70 °C. To our satisfaction, we observed a clean formation of the desired product in excellent yield (90%) after simple work up (Table 1, entry 1). To explore the scope of this methodology, a number of aldehydes were used to perform this reaction under





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Scheme 1. Synthesis of 3-indoles in PEG-400.

Table	1
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Cu(OAc)₂-catalyzed ligand-free synthesis of 3-indole derivatives

Entry	Indole	Aldehyde RCHO (R=)	Reactant (2)	Product (4) ^a	Time (h)	Yield ^b (%)
1	3a	C ₆ H ₅	2a	4a	15	90
2	3a	$4-NO_2C_6H_4$	2a	4b	15	98
3	3a	$4-NO_2C_6H_4$	2a	4b	24	51 ^c
4	3a	$4-NO_2C_6H_4$	2a	4b	24	55 ^d
5	3a	$2-NO_2C_6H_4$	2a	4c	15	82
6	3a	3-NO ₂ C ₆ H ₄	2a	4d	15	79
7	3a	2-BrC ₆ H ₄	2a	4e	15	70
8	3a	4-BrC ₆ H ₄	2a	4 f	15	88
9	3a	$4-FC_6H_4$	2a	4g	15	86
10	3a	4-OMeC ₆ H ₄	2a	4h	15	68
11	3a	2-OMeC ₆ H ₄	2a	4i	15	48
12	3a	$(CH_3)_2CH$	2a	4j	24	62
13	3a	$4-NO_2C_6H_4$	2 b	4k	24	95
14	3b	$4-NO_2C_6H_4$	2a	41	40	63
15	3c	$4-NO_2C_6H_4$	2a	4m	40	70
16	3d	$4-NO_2C_6H_4$	2a	4n	40	78

^a All products were characterized by ¹H, ¹³C, and mass spectroscopy.

^b Isolated yield.

^c The reaction was carried out in ethanol.

^d The reaction was carried out in ethylene glycol.

previous conditions to yield the corresponding 3-substituted indoles (Table 1). 4-Nitrobenzaldehyde (entry 2) gave the product 4b in 98% yield, which was comparable to the reaction using copper(II) sulfonato Salen complex as a catalyst. The 2- and 3-nitrobenzaldehydes (entries 5 and 6) underwent a three-component coupling reaction to afford the products 4c and 4d in 82% and 79% yields, respectively. The bromo and fluoro substituted benzaldehydes were also well compatible substrates for the MCR (entries 7, 8, and 9). In the case of 4-methoxybenzaldehyde (entry 10) the product yield was slightly decreased (68%), while 2-methoxy also reacted but gave adduct 4i in 48% yield only (entry 11). The aliphatic aldehyde isobutyraldehyde also provided the MCR product in moderate yield (62%, entry 12), which is still better than using [Yb(OTf)₃].¹¹ Then, to diversify this reaction malononitrile has been replaced with ethyl 2-cyano acetate. Indole, 4-nitrobenzaldehyde and ethyl 2-cyano acetate were coupled under optimized conditions to provide the desired product **4k** as inseparable diastereomeric mixture (1:1) in 95% yield (entry 13).

Next, the MCR was performed with substituted indoles providing the desired products in reasonably good yields. *N*-methyl indole **3b**, 2-methyl indole **3c**, and 5-methoxy indole **3d** (entries 14–16) were participating in the three component coupling reaction with 4-nitrobenzaldehyde and malononitrile under optimized reaction conditions to afford the desired products **4l–4n** in 63%, 70%, and 78% yields, respectively.

Attempts to expedite this MCR in two related solvents, ethanol and ethylene glycol, provided the desired product **4b** however in lower yields 51% and 55%, respectively (entry 3 and 4). This result demonstrates that PEG plays a key role in this catalytic process but complementary studies will be required to better understand this mechanistic aspect.¹⁴

Table 2

Recyclability for the same substrate (synthesis of 4b)

Aldehyde	Yield ^a (%)				
	1st	2nd	3rd	4th	5th
1b	95%	90%	88%	80%	75%

^a Isolated yield after column chromatography.

Table 3	
Recyclability for	different aldehydes

	Aldehyde	Product	Yield ^a (%)
1 st Run	1b	4b	95
2 nd Run	1f	4f	70
3 rd Run	1a	4a	65

^a Isolated yield after column chromatography.

With regard to sustainable chemistry issues, the recyclability was an important question. We were pleased to find that the entire reagent [catalyst Cu(OAc)₂ and KH₂PO₄ in PEG-400] could be successfully recycled up to five runs with limited loss of activity (Yield decreased from 95% to 75% after 5 runs, Table 2). Furthermore, it has been demonstrated that the same system [PEG with Cu(OAc)₂ and KH₂PO₄] can be recycled several times by using different aldehydes as substrates (Table 3). Therefore, this new catalytic process does not require organic solvents, except those used for extraction and purification of final products.

To the best of our knowledge, there are very few literature precedents on the mechanism for this multicomponent reaction.^{12c} Initially, we hypothesized two possible pathways (path A and path B in Scheme 2) to access the MCR product.

To reveal the mechanism of this reaction, we performed several control experiments, under different conditions, in PEG-400.

- In the first series of experiments, 4-nitro benzaldehyde treated with malononitrile gave Knoevenagel adduct I in excellent yield. The same reaction, carried out in the absence of catalyst [Cu(OAc)₂ and KH₂PO₄] in PEG at room temperature, provided similar results. Therefore the copper catalyst has no key role in this first step.
- In the second series of experiments, indole and Knoevenagel adduct I treated with Cu(OAc)₂ and KH₂PO₄ in PEG-400 at 70 °C for 15 h provided the MCR product in high yield.¹⁵
- In the third series of experiments, it was demonstrated that the MCR could be performed with Cu(OAc)₂ only affording **4b** in 72% yield. Alternatively, the use of KH₂PO₄ only also gave **4b** in 88% yield, but the combination of Cu(OAc)₂ and KH₂PO₄ gave the best yield (98%). However, there was no reaction between indole and adduct-I in the absence of Cu(OAc)₂ and KH₂PO₄.
- Finally, in the last series of experiments, it was demonstrated that no reaction was taking place between indole and 4-nitro benzaldehyde under the same reaction conditions. No evidence could be found for adduct II in the scheme (path B).

Thus this MCR proceeds very likely via Knoevenagel condensation between aldehyde and malononitrile, followed by the Michael addition of indole to adduct I catalyzed by $Cu(OAc)_2$ and KH_2PO_4 in PEG-400 (path A).

In conclusion, we have successfully demonstrated a MCR reaction as an operationally simple and efficient method for the condensation of indole, aldehydes, and malononitrile using PEG as the reaction medium in the presence of KH_2PO_4 , and using $Cu(OAc)_2$ as the catalyst under ligand-free conditions. Furthermore, in this



Scheme 2. Proposed mechanism for MCR.

new process, both the solvent and the catalytic system can be recycled efficiently. Finally, we revealed the mechanistic pathway for this MCR and the importance of both Cu(OAc)₂ and KH₂PO₄ for the Michael addition to provide desired indole 3-derivatives with high yield and variability.

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Supplementary data

Supplementary data (experimental procedures and compound characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.008.

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