Contents lists available at SciVerse ScienceDirect





journal homepage: www.elsevier.com/locate/apcata

# Polyethylene glycol (PEG-200)-promoted sustainable one-pot three-component synthesis of 3-indole derivatives in water



© 2012 Elsevier B.V. All rights reserved.

# Leilei Wang, Manna Huang, Xinhai Zhu, Yiqian Wan\*

School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou 510275, PR China

#### ARTICLE INFO

# ABSTRACT

Article history: Received 21 October 2012 Received in revised form 6 December 2012 Accepted 7 December 2012 Available online 20 December 2012

Keywords: Green chemistry Multicomponent reaction Aldol reaction Michael addition

# 1. Introduction

In addition to their occurrences in nature, indoles have found wide applications in materials science, organic synthesis, medicinal chemistry and agricultural chemistry [1]. Thus, a number of practical strategies based on multi-component reactions (MCRs) for the synthesis of indoles have been established since Ugi et al. reported the first four-component reactions in 1959 [1–4]. For example, the three-component reactions of indoles, aldehydes, and malononitrile are known to provide 3-substituted indole derivatives [5], which are particularly useful for furnishing biologically active chromenes [6–11].

MCRs, termed by Tsepalov in 1961 and possibly traceable to the publication of the Strecker reaction [1,4,12], have attracted significant attention in recent years due to their wide applications in medicinal chemistry [2,4,12–20], organic synthesis (especially asymmetric synthesis [21]) [22], and materials science with high atom economy and good overall yields [23].

A variety of green MCR protocols have been documented in recent years [5,7–11,24–32], utilizing unconventional solvents (such as ionic liquid, water, and PEGs) or solvent-free conditions [33]. However, it is still difficult to design "ideal" [34] MCR processes, as motivated by increasing concern about strict legislation aimed at improving the 'greenness' of synthetic pathways and processes [35]. In addition, improving already known MCRs is an interesting challenge for current organic synthesis [32,36,37].

We now wish to report a general route to 3-substituted indole derivatives via the three-component reaction of indoles, malononitrile and aldehydes in water promoted by PEG-200 without the use of metal (such as Cu [5], Zn [38], and In [10]) or L-proline [26] as catalysts.

A sustainable three-component reaction of indoles, aldehydes, and malononitrile in water promoted by

polyethylene glycol (PEG-200) afforded 3-indole derivatives in good to excellent yields.

# 2. Experimental

All starting materials and reagents are commercially available and were used as received. All reactions were carried out in 10 mL vials sealed with a septum. Flash column chromatography was performed with silica gel (200–300 mesh). Thin-layer chromatography was carried out with Merck silica gel GF<sub>254</sub> plates. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded at r.t. on a Mercury-Plus 300 or a Bruker AVANCE 400 instrument with TMS as an internal reference. LC/MS was run on an LCMS-2010A or a LCQ DECA XP instrument. Element analyses were carried out on an Elemental Analyzer vario EL cube. Melting points were determined on a WRS-1B digital melting point apparatus and are uncorrected. IR spectra were determined on an EQUINOX 55 Fourier transformation infrared spectrometer coupled with an infrared microscope.

#### 2.1. General procedure A

 $KH_2PO_4$  (136 mg, 1.0 mmol), PEG-200 (1.5 g),  $H_2O$  (1.5 mL), aldehyde (1.0 mmol), malononitrile (72.6 mg, 1.1 mmol), indole (128 mg, 1.1 mmol), and a magnetic stir bar were added to a 10 mL vial, which was then sealed. The reaction mixture was stirred at room temperature. The precipitate was collected by filtration. The



<sup>\*</sup> Corresponding author. Tel.: +86 2084113610; fax: +86 2084113610. *E-mail address*: ceswyq@mail.sysu.edu.cn (Y. Wan).

<sup>0926-860</sup>X/\$ - see front matter © 2012 Elsevier B.V. All rights reserved. http://dx.doi.org/10.1016/j.apcata.2012.12.008

solid was washed with water and dried in vacuo for 2 h at 50  $^\circ\text{C}$  to afford the desired products.

#### 2.2. General procedure B

KH<sub>2</sub>PO<sub>4</sub> (136 mg, 1.0 mmol), PEG-200 (1.5 g), H<sub>2</sub>O (1.5 mL), aldehyde (1.0 mmol), malononitrile (72.6 mg, 1.1 mmol), indole (128 mg, 1.1 mmol), and a magnetic stir bar were added to a 10 mL vial, which was then sealed. The reaction mixture was stirred at room temperature. The reaction mixture was extracted with water (20 mL) and ethyl acetate ( $3 \times 20$  mL). The combined organic phases was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuo. The crude product was purified by flash c.c. on silica gel using dichloromethane/petroleum ether (1:1; 2:1) as an eluent to afford the desired products.

# 3. Results and discussion

3-Indole derivatives have been efficiently obtained by Cu(II)sulfonato Salen catalyzed three-component reactions in water [5]. Moreover, PEGs, which are green and reusable solvents, have been widely used to establish green systems for MCRs [25,28,29,39]. Hence, as part of our ongoing research interest in aqueous organic reactions [40–43], we envisioned that our copper catalyst system for C–N coupling in water [40] might also be used in the three-component reaction. Initially, we examined the reaction of indole, benzaldehyde, and malononitrile in water in the

#### Table 1

Optimization of the model reaction.<sup>a</sup> .

H O t	CN + CN	N PEG, H <sub>2</sub> O Base, r.t.		NH
Entry	PEGs/H <sub>2</sub> O (g/g) <sup>b</sup>	Base (mol%) <sup>b</sup>	Time (h)	Yield (%) <sup>c</sup>
1	200 (1/2)	KH <sub>2</sub> PO <sub>4</sub> (100)	3	90 <sup>d,f</sup>
2	200 (1/2)	KH <sub>2</sub> PO <sub>4</sub> (100)	3	91 <sup>e,f</sup>
3	200 (1/2)	KH <sub>2</sub> PO <sub>4</sub> (100)	3	92 <sup>f</sup>
4	100(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	83
5	200(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	95
6	300(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	90
7	400(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	85
8	600(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	80
9	800(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	68
10	1000(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	60
11	200 (0/3)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	11
12	200(0.5/2.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	40
13	200 (1/2)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	75
14	200 (2/1)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	81
15	200 (3/0)	KH <sub>2</sub> PO <sub>4</sub> (100)	28	10
16	200(1.5/1.5)	KOH (100)	28	15
17	200(1.5/1.5)	$K_3PO_4(100)$	28	Trace
18	200(1.5/1.5)	K <sub>2</sub> CO <sub>3</sub> (100)	28	Trace
19	200(1.5/1.5)	KF(100)	28	70
20	200(1.5/1.5)	No addition	28	71
21	200(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (50)	28	86
22	200(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (200)	28	94
23	200(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	14	65
24	200(1.5/1.5)	KH <sub>2</sub> PO <sub>4</sub> (100)	24	86

 $^{\rm a}$  Reaction conditions: benzaldehyde (1.0 mmol), malononitrile (1.1 mmol), indole (1.1 mmol), base, PEG, H\_2O, r.t.

<sup>b</sup> Relative to benzaldehyde.

<sup>c</sup> Isolated yield.

 $^{\rm d}~$  Cu(OAc)\_2 (0.05 mmol), sucrose (0.5 mmol).

<sup>e</sup> Cu(OAc)<sub>2</sub> (0.05 mmol).

<sup>f</sup> 60 °C.

presence of our previously reported  $Cu(OAc)_2$ -sucrose-PEG200 system. As expected, 2-((1H-indol-3-yl)(phenyl) methyl)malononitrile, as a desired product, was isolated in 90% yield (Table 1, entry 1). However, further control experiments (Table 1, entries 2, 3) indicated that either the copper catalyst or sucrose were not needed for the reaction. We then logically optimized the conditions by exploring the effects of the base, time, and temperature on the model reaction. As shown in Table 1, the reaction proceeded smoothly at room temperature, although it could be accelerated at higher temperature (Table 1, entries 3, 13). The weak acid  $KH_2PO_4$  was beneficial to the reaction, whereas stronger bases were obstructive (Table 1, entries 16, 17, 18). It was found that PEGs were essential to promoting the model reaction, of which PEC-200 was the most effective as a co-solvent and a phase transfer catalyst. The influence of the ratio

PEG-200 (1.5 a) H<sub>2</sub>O (1.5 g) KH<sub>2</sub>PO<sub>4</sub> (1 mmol) r.t. 1 mmol 1.1 mmol 1.1 mmol NC W12, R=OCH<sub>3</sub>, 89%<sup>b</sup> W1, R=OCH<sub>3</sub>, 55%<sup>d</sup> W2, R=CH<sub>3</sub>, 92%<sup>d</sup> W13, R=CH<sub>3</sub>, 83%<sup>b</sup> W3, R=CH(CH<sub>3</sub>)<sub>2</sub>, 93%<sup>d</sup> W14, R=Cl, 94%b W4. R=Cl. 93%<sup>c</sup> W15, R=NO<sub>2</sub>, 95%<sup>b</sup> W5, R=Br, 91%<sup>c</sup> W6, R=H, 95%<sup>b</sup> W7, R=F, 83%<sup>b</sup> W8, R=CN, 88%<sup>b</sup> W9, R=COCH<sub>3</sub>, 82%<sup>b</sup> W10, R=CF<sub>3</sub>, 87%<sup>b</sup> H W11, R=NO2, 98%b W21, 93% CN NC N W22, 80%° W16, R=OCH<sub>3</sub>, 93%<sup>c</sup> W23, 75%° W17, R=CH<sub>3</sub>, 86%<sup>c</sup> W18, R=Cl, 94%<sup>b</sup> W19, R=F, 93%<sup>b</sup> W20, R=NO2, 60%b CN NC W25, 90%<sup>b</sup>



W24, 90%<sup>b</sup>

between PEG-200 and water on the reaction was then further studied (Table 1, Entries 5, 11–15). Notably, only approximately 10% isolated yield of the desired product was obtained in pure PEG-200 or pure water (Table 1, Entries 11, 15). However, when the mass ratio between water and PEG-200 was 1:1, the isolated yield increased dramatically to 95% (Table 1, Entry 5). Overall, the use of equivalent amounts (in mass ratio) of water and PEG-200 with KH<sub>2</sub>PO<sub>4</sub> as an additive at room temperature was identified as the optimum conditions for the present MCR (Table 1, entry 5).

To assess the application scope of this simple system, a variety of aldehydes were tested under the optimized conditions. As shown in Scheme 1, most of the electron-rich, electron-neutral, and electronpoor aromatic aldehydes reacted with indole and malononitrile to afford the desired 2-((1H-indol-3-yl)(aryl)methyl)malononitriles in high yields. In contrast, slightly lower yields were obtained from 4-methoxybenzaldehyde due to the strong electron-donating nature of the methoxy group and 2-nitrobenzaldehyde due to side reactions [44]. Notably, the steric hindrance of aldehydes seemed to have very intriguing effects on the reaction outcomes: all the ortho-para directors (such as methyl, methoxyl, chloro, and fluoro) in the ortho-position of benzaldehydes promoted the reactions better than those on the para-position (Scheme 1, W1, W2, W4, W16-W18). In terms of product purification, in most cases, the operation was very simple and easy, without requiring special purification techniques, such as column chromatography. The filtration of the reaction mixture very straightforwardly afforded the solid product (Scheme 1, W2-7, W11-19, W21, W24, W25). In addition, aliphatic aldehydes, such as pivalaldehyde and formaldehyde, also provided the desired product in high yield (Scheme 1, W22, W23).

Encouraged by these results, *N*-methyl indole and 2-methyl indole were tested to extend the scope of the methodology. As expected, 2-methyl indole readily reacted with various aldehydes and malononitrile to produce the corresponding products in excellent yields due to the electron-donating effect of 2-methyl group (Scheme 2). In contrast, *N*-methyl indole did not afford the desired product. In this regard, the presence of the acidic *N*–*H* proton seemed to be mandatory and we assumed that an acidic *N*–*H* 



W39, R=CH<sub>3</sub>, 93%<sup>a</sup>

**Scheme 2.** The products of the three-component reaction of aldehydes, 2-methylindole and malononitrile. <sup>a</sup> 12 h, <sup>b</sup> 28 h.

proton of indole activates the nitrile moiety through hydrogen bonding [45] to dramatically enhance the rates and yields of the reactions.

It should be noted that the protocol easily and rapidly afforded chromene when salicylaldehyde was used instead of benzaldehyde (Scheme 1, W25; Scheme 2, W39).

Finally, the heterogeneous characteristic of the model reaction encouraged us to further test the recyclability of the system. After filtration and washing the solid products with cold water, the filtrate was combined and concentrated in vacuo to the original size (3 mL). The model reaction was then run again to afford the desired product with excellent yield. The reaction was run an additional three times to afford the desired product with the same yields as that (95%) in the first run.

# 4. Conclusions

In conclusion, we have established a recyclable, environmentally benign synthesis of 3-indole derivatives by the threecomponent reaction of indoles, malononitrile and aldehydes in water, which was dramatically promoted by PEG-200. The simplicity of the protocol will be beneficial to the sustainable synthesis of 3-indole derivatives in the laboratory and in industry.

#### Acknowledgments

This work was supported financially by grants from the National Natural Science Foundation of China (20872182, 20802095).

### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j. apcata.2012.12.008.

#### References

- [1] M. Shiri, Chem. Rev. 112 (2012) 3508-3549.
- [2] I.V. Magedov, A. Kornienko, Chem. Heterocycl. Compd. 48 (2012) 33-38.
- [3] B. Jiang, M.-S. Yi, F. Shi, S.-J. Tu, S. Pindi, P. McDowell, Chem. Commun. 48 (2012) 808–810.
- [4] J. Sapi, J.-Y. Laronze, ARKIVOC 8 (2004) 208–222.
  [5] Y. Qu, F. Ke, L. Zhou, Z. Li, H. Xiang, D. Wu, X. Zhou, Chem. Commun. 47 (2011) 3912–3914.
- [6] F. Zhang, Y. Zhao, L. Sun, L. Ding, Y. Gu, P. Gong, Eur. J. Med. Chem. 46 (2011) 3149–3157.
- [7] Z.-J. Quan, R.-G. Ren, Y.-X. Da, Z. Zhang, X.-C. Wang, Synth. Commun. 41 (2011) 3106–3116.
- [8] M. Kidwai, N.K. Mishra, D. Bhatnagar, A. Jahan, Green Chem. Lett. Rev. 4 (2011) 109–115.
- [9] G. Shanthi, P.T. Perumal, U. Rao, P.K. Sehgal, Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem. 48B (2009) 1319–1323.
- [10] G. Shanthi, P.T. Perumal, Tetrahedron Lett. 48 (2007) 6785-6789.
- [11] W. Kemnitzer, J. Drewe, S. Jiang, H. Zhang, J. Zhao, C. Crogan-Grundy, L. Xu, S. Lamothe, H. Gourdeau, R. Denis, B. Tseng, S. Kasibhatla, S.X. Cai, J. Med. Chem. 50 (2007) 2858–2864.
- [12] J. Zhu, H. Bienaymé, Multicomponent Reactions, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2005.
- [13] A. Domling, W. Wang, K. Wang, Chem. Rev. 112 (2012) 3083-3135.
- [14] B.M. Shaikh, S.G. Konda, A.V. Mehare, G.G. Mandawad, S.S. Chobe, B.S. Dawane,
- Pharma. Chem. 2 (2010) 25–29. [15] V. Estevez, M. Villacampa, J.C. Menendez, Chem. Soc. Rev. 39 (2010) 4402–4421.
- [16] M. Colombo, I. Peretto, Drug Discov. Today 13 (2008) 677–684.
- [17] I. Akritopoulou-Zanze, Curr. Opin. Chem. Biol. 12 (2008) 324-331.
- [18] M.A. Mironov, QSAR Comb. Sci. 25 (2006) 423-431.
- [19] A. Domling, Chem. Rev. 106 (2006) 17-89.
- [20] L. Weber, Drug Discov. Today 7 (2002) 143-147.
- [21] C.D. Graaff, E. Ruijter, R.V.A. Orru, Chem. Soc. Rev. 41 (2012) 3969-4009.
- [22] B.B. Toure, D.G. Hall, Chem. Rev. 109 (2009) 4439-4486.
- [23] G.R. Reddy, T.R. Reddy, S.C. Joseph, K.S. Reddy, C.L.T. Meda, A. Kandale, D. Rambabu, G.R. Krishna, C.M. Reddy, K.V.L. Parsa, K.S. Kumar, M. Pal, RSC Adv. 2 (2012) 9142–9150.
- [24] K.C. Majumdar, S. Ponra, T. Ghosh, RSC Adv. 2 (2012) 1144-1152.

- [25] K. Karnakar, N.S. Murthy, K. Ramesh, G. Satish, J.B. Nanubolu, Y.V.D. Nageswar, Tetrahedron Lett. 53 (2012) 2897–2903.
- [26] X. Hu, Y. Ma, Z. Li, J. Organomet. Chem. 705 (2012) 70-74.
- [27] Y. Gu, Green Chem. 14 (2012) 2091–2128.
- [28] L. Nagarapu, R. Mallepalli, L. Yeramanchi, R. Bantu, Tetrahedron Lett. 52 (2011) 3401-3404.
- [29] R. Mallepalli, L. Yeramanchi, R. Bantu, L. Nagarapu, Synlett (2011) 2730-2732.
- [30] B.V.S. Reddy, D. Somashekar, A.M. Reddy, J.S. Yadav, B. Sridhar, Synthesis (2010) 2069–2074.
- [31] N.R. Candeias, P.M.S.D. Cal, V. André, M.T. Duarte, L.F. Veiros, P.M.P. Gois, Tetrahedron 66 (2010) 2736–2745.
- [32] K. Kumaravel, G. Vasuki, Curr. Org. Chem. 13 (2009) 1820–1841.
- [33] P. Srihari, V.K. Singh, D.C. Bhunia, J.S. Yadav, Tetrahedron Lett. 50 (2009) 3763-3766.
- [34] P.A. Wender, B.L. Miller, Nature 460 (2009) 197-201.
- [35] P. Tundo, P. Anastas, D.S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff, W. Tumas, Pure Appl. Chem. 72 (2000) 1207–1228.
- [36] P.T. Anastas, T.C. Williamson, Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes, Oxford University Press, Oxford, UK, 1998.

- [37] P.T. Anastas, J.C. Warner, Green Chemistry: Theory and Practice, Oxford University Press, Oxford, UK, 1998.
- [38] W.-L. Chen, Y.-F. Cai, X. Fu, X.-H. Liu, L.-L. Lin, X.-M. Feng, Org. Lett. 13 (2011) 4910–4913.
- [39] V.V. Kouznetsov, D.R.M. Arenas, A.R.R. Bohórquez, Tetrahedron Lett. 49 (2008) 3097–3100.
- [40] M. Huang, L. Wang, X. Zhu, Z. Mao, D. Kuang, Y. Wan, Eur. J. Org. Chem. (2012) 4897–4901.
- [41] M. Huang, X. Lin, X. Zhu, W. Peng, J. Xie, Y. Wan, Eur. J. Org. Chem. (2011) 4523–4527.
- [42] G. Chen, J. Weng, Z. Zheng, X. Zhu, Y. Cai, J. Cai, Y. Wan, Eur. J. Org. Chem. (2008) 3524–3528.
- [43] X. Zhu, Y. Ma, L. Su, H. Song, G. Chen, D. Liang, Y. Wan, Synthesis (2006) 3955–3962.
- [44] B.S. Rane, M.A. Kazi, S.M. Bagul, D.P. Shelar, R.B. Toche, M.N. Jachak, J. Fluoresc. 20 (2010) 415–420.
- [45] Z.-T. Zhang, Y.-Q. Ma, Y. Liang, D. Xue, Q. He, J. Heterocycl. Chem. 48 (2011) 279–285.