

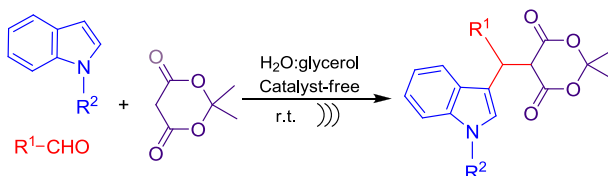
A combination of green solvent and ultrasonic irradiation promotes the catalyst-free reaction of aldehydes, indoles and Meldrum's acid

Cheng-Wei Lü¹ · Jia-Jing Wang¹ · Yan-Hang Liu¹ ·
Wen-Juan Shan¹ · Qi Sun¹ · Lei Shi¹

Received: 20 May 2016 / Accepted: 22 July 2016
© Springer Science+Business Media Dordrecht 2016

Abstract A facile and practical approach for the preparation of 3-indole derivatives was performed by the Yonemitsu condensation of indoles with Meldrum's acid and aldehydes in a mixture of solvent from glycerol and water under ultrasonic irradiation at room temperature without catalyst. A series of aromatic aldehydes representative of various electronic and steric conditions were employed to examine the scope of substrates for this protocol in moderate to good yields. No catalyst, clean reaction conditions, tolerating the substrates with diverse functional groups and an environmentally acceptable medium are the best features in this process.

Graphical Abstract



Keywords Yonemitsu condensation · 3-Indole derivatives · Catalyst-free · Ultrasonic irradiation · Aqueous glycerol

Electronic supplementary material The online version of this article (doi:10.1007/s11164-016-2675-8) contains supplementary material, which is available to authorized users.

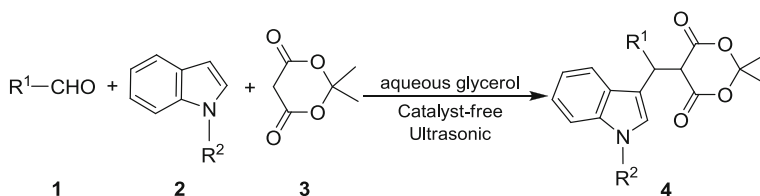
✉ Cheng-Wei Lü
chengweilv@126.com

¹ School of Chemistry and Chemical Engineering, Liaoning Normal University, Dalian 116029, People's Republic of China

Introduction

The efficient and high-throughput synthesis of complex organic molecules with a lower impact on the environment is one of the most important objectives in modern synthetic organic and green chemistry [1, 2]. As the pressure to produce the myriad of substances required by society in an environmentally benign fashion has continued to increase, it is now essential for chemists to develop new greener synthetic pathways under natural conditions as many as possible [3]. Green chemistry utilizes a set of principles that optimize the synthetic methodologies to reduce pollution, cost, and tedious work-ups [4–6]. One of the key areas of green chemistry is the reduction or elimination of expensive catalysts in chemical processes and the replacement of hazardous solvents with environment-friendly solvents [7–9]. Glycerol is the only green solvent like water that can combine at a low price with a low toxicity and has been recently proposed as an effective promoting medium for organic transformation [10, 11]. Many reactions can be performed under catalyst-free conditions in the presence of glycerol as a reaction medium [12, 13]. Despite these promising features, much effort has to be made in the future to extend the use of glycerol as a green solvent [10]. On the other hand, application of ultrasound in organic transformation has been proved to be a green-synthetic approach and a fantastic tool. Compared with conventional methods, this technique is more efficient, innocuous, convenient, and easily controlled. A large number of organic reactions can be efficiently carried out with high yields under ultrasonic irradiation [14–17].

The indole nucleus is an important structural unit that is present in many drugs currently on the market [18]. Most of these belong to the 3-substituted indole family, which is an important intermediate for chemical synthesis and widely distributed in many important natural products [19–21]. Consequently, several research groups have turned their attention to access those 3-substituted indoles by simple synthetic methods [22–24]. The Yonemitsu trimolecular reaction of indole with Meldrum's acid and aldehyde for the construction of 3-substituted indole frameworks has recently been the subject of numerous investigations [25, 26]. A plethora of improved Yonemitsu condensations involving the solid phase reaction without catalyst [27], the reaction in ethanol without catalyst [28], and the reaction in deep eutectic solvent [29] has been elaborated in order to develop green technology for this reaction. However, the development of simple, efficient, and environmentally benign synthetic approaches for 3-substituted indole derivatives via a Yonemitsu type reaction still remains an active research area [30–36]. Thus, the synthetic utility of such protocols is further made more attractive when the reactions are promoted by glycerol under catalyst-free and ultrasonic irradiation conditions. In continuation of our efforts to develop green chemistry methods as well as our interest in the application of Meldrum's acid to synthesis of useful organic molecules [37–40], in this manuscript the Yonemitsu condensation using glycerol as green medium without catalyst under ultrasonic irradiation at room temperature is described (Scheme 1). Compared to the catalyst-free methods



Scheme 1 The approach for the preparation of 3-indole derivatives

reported in the literature [27, 28], various aromatic aldehydes have been applied for this reaction, and moderate to good yields have been obtained.

Experimental

General

Unless otherwise stated, all reagents were obtained from commercial sources and were used without further purification. Melting points were determined on a Beijing Tech X-5 melting point detector and were uncorrected. The IR spectra were measured with a Bruker Shimadzu IR-460 spectrometer. ^1H NMR spectra were recorded on a Bruker Avance III 400 MHz or a Bruker Avance III 500 MHz. The chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) in Hertz. A commercially available Kunshan KQ 2200DB, 80 W ultrasonic cleaner (220 V, 40 kHz, 3 L capacity) was utilized for reactions.

Typical experimental procedure for synthesis of 4

A mixture of indole (0.5 mmol), Meldrum's acid (0.55 mmol), and 2 mL glycerol:H₂O (1.3:0.7 v/v) was added in a 10 mL Schlenk tube, then aldehyde (0.5 mmol) was added, and the mixture was placed in an ultrasonic bath at r.t. 40 kHz for 20 min three times (with a 5 min rest). The temperature of the process was maintained at 25 ± 3 °C by means of supply of water to the reactor used for the synthesis. After completion of reaction, the product stood for 4 h at room temperature. The precipitate was separated by filtration and washed with aqueous ethanol. The crude products were recrystallized from an appropriate solvent to obtain the corresponding adducts.

Results and discussion

As a starting point for the development of our methodology, we commenced our work to optimize the reaction condition by carrying out the three-component condensation of indole, Meldrum's acid, and benzaldehyde in equimolecular amounts of 0.5 mmol. The effects of reaction parameters were studied. Initially,

3 mL glycerol was used as the solvent without catalyst. After ultrasonic 20 min for three times at room temperature, the product was collected in 81 % yield (Table 1, entry 1). As we know, water could promote the condensation of Meldrum's acid with aldehydes avoiding the addition of any catalyst [41, 42] and also exhibits unique reactivity in this multicomponent reaction [30, 38]. In another attempt, we employed 2 mL glycerol and 1 mL H₂O as solvent. To our delight, the required product was formed in 89 % yield (Table 1, entry 2). In order to improve the yield, various volumes and ratios of the water and glycerol were screened (Table 1, entries 2–6). The reaction showed a surprising dependence on the solvent, with 1.3 mL glycerol and 0.7 mL water giving the best yield and purity of the desired product (Table 1, entry 6). The reaction in water was also investigated and afforded the corresponding adduct in moderate yield due to the formation of homodimeric by-products (Table 1, entry 7). On the basis of the above results, we examined the effects of the reaction temperature and time. As shown in Table 1, the reaction at r.t. was a feasible option. Further elevating or lowering the temperature failed to improve the yield (Table 1, entries 8, 9). The effect of the reaction time was also surveyed, and a similar result as for entry 6 was achieved as the time was prolonged to 80 min (Table 1, entry 11). Decreasing the reaction time to 40 min was detrimental to the result (Table 1, entry 10).

In addition, we have also investigated the fate of varying the molar ratio of each substrate (Table 2, entries 1–3). It is clear that, when increased the reagent's loading of Meldrum's acid to 0.55 mmol, a better outcome to afford the desired product in 96 % yield was observed. To show the role of ultrasound, the control experiment was investigated without ultrasonic irradiation at the same temperature under traditional stirring conditions. It was observed that the use of ultrasound leads to the faster reaction and higher yields (Table 2, entries 3, 4).

Table 1 The screening of reaction conditions

Entry ^a	Solvent	Volume (mL)	Temp. (°C)	Time (min)	Yield ^b (%)
1	Glycerol	3.0	rt	60	81
2	Glycerol/H ₂ O	2.0/1.0	rt	60	89
3	Glycerol/H ₂ O	2.5/0.5	rt	60	78
4	Glycerol/H ₂ O	1.5/1.5	rt	60	69
5	Glycerol/H ₂ O	2.7/1.3	rt	60	78
6	Glycerol/H ₂ O	1.3/0.7	rt	60	93
7	H ₂ O	3.0	rt	60	66
8	Glycerol/H ₂ O	1.3/0.7	35	60	90
9	Glycerol/H ₂ O	1.3/0.7	20	60	89
10	Glycerol/H ₂ O	1.3/0.7	rt	40	86
11	Glycerol/H ₂ O	1.3/0.7	rt	80	92

^a The reactions were carried out with benzaldehyde, indole, and Meldrum's acid in equimolecular amounts of 0.5 mmol without catalyst under ultrasound conditions

^b Isolated yield

Table 2 The screening of reaction conditions

Entry ^a	Condition	Benzaldehyde/indole/Meldrum's acid	Time (min)	Yield ^b (%)
1	US	0.5 mmol/0.55 mmol/0.5 mmol	60	87
2	US	0.55 mmol/0.5 mmol/0.5 mmol	60	85
3	US	0.5 mmol/0.5 mmol/0.55 mmol	60	96
4	Vigorously stirred	0.5 mmol/0.5 mmol/0.55 mmol	480	90

^a The reactions were carried out at rt^b Isolated yield

The optimal result was achieved when the transformation was sonicated in a mixture solvent from 1.3 mL glycerol and 0.7 mL water at r.t. for twenty minutes and for three times under catalyst-free conditions. A substrate scope evaluation showed that the method is compatible with many substituted benzaldehydes, and all the substrates that were tested (see Table 3) afforded moderate to good yields. As shown in Table 3, the presence of electron withdrawing or electron donating substituents in the same position on the ring of various aromatic aldehydes had different influences on the procedure to furnish the desired products. When introducing methoxy group in the para- or meta-position on the benzene ring, the

Table 3 Substrate scope for the synthesis of product **4**

Entry ^a	R ¹	R ²	Product	Yield ^b (%)	M.p. (°C)
1	C ₆ H ₅	H	4a	96	140–142 (140–142 [27])
2	4-MeC ₆ H ₄	H	4b	82	130–132 (137–139 [38])
3 ^c	3-MeC ₆ H ₄	H	4c	65	120–122 (115–117 [38])
4	2-MeC ₆ H ₄	H	4d	78	139–141 (136–138 [39])
5	4-MeOC ₆ H ₄	H	4e	37	122–124 (125–127 [38])
6 ^c	3-MeOC ₆ H ₄	H	4f	59	130–132 (139–141 [38])
7	2-MeOC ₆ H ₄	H	4g	92	155–157 (160–162 [38])
8	4-ClC ₆ H ₄	H	4h	70	133–135 (131–133 [38])
9 ^c	3-ClC ₆ H ₄	H	4i	76	138–140 (138–139 [38])
10	2-ClC ₆ H ₄	H	4j	66	140–142 (134–136 [38])
11	4-BrC ₆ H ₄	H	4k	61	136–138 (142–144 [38])
12	3-BrC ₆ H ₄	H	4l	92	139–141 (138–141 [38])
13	4-NO ₂ C ₆ H ₄	H	4m	91	145–147 (142–144 [27])
14	3-NO ₂ C ₆ H ₄	H	4n	93	157–159 (157–159 [27])
15	(CH ₃) ₂ CH	H	4o	Trace	–
16	C ₆ H ₅	CH ₃	4p	36	148–150 (152–153 [38])
17	4-NO ₂ C ₆ H ₄	CH ₃	4q	80	143–145 (143–145 [38])

^a The reactions were carried out with benzaldehyde/indole/Meldrum's acid (0.5 mmol/0.5 mmol/0.55 mmol) at rt without catalyst under ultrasound conditions^b Isolated yield^c Reacted at 40 °C

lowest yield was observed (Table 3, entries 5, 6). High yields were obtained when the strong electron withdrawing substituents were present in the meta- and para-positions on the ring of aromatic aldehydes. For example, 3-nitrobenzaldehyde and 4-nitrobenzaldehyde gave the best results (Table 3, entries 13, 14). On the other hand, when employing ortho-substituted aromatic aldehyde as substrate, the steric hindrance was dominant than other factors in the product formation. Poor yields or no products were obtained for the ortho-substituted benzaldehydes, such as 2-chlorobenzaldehyde, 2-bromobenzaldehyde, and 2-nitrobenzaldehyde. Unexpectedly, 2-tolualdehyde and 2-methoxybenzaldehyde gave 78 and 92 % yields in this three-component reaction (Table 3, entries 4, 7). Unfortunately, aliphatic aldehyde had a low reactivity in this reaction (Table 3, entry 15). Finally, when 1-methylindole was used as starting material, a lower yield than indole was obtained (Table 3, entries 16, 17).

Conclusions

A glycerol and water-mediated procedure for the synthesis of 5-[(indol-3-yl)-arylmethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione derivatives from the condensation of indole with Meldrum's acid and aldehyde under ultrasonic irradiation has been developed. This green synthetic pathway has many advantages, such as using inexpensive green solvents, catalyst-free, mild reaction conditions and tolerant the substrates with diverse functional groups.

Acknowledgments We are grateful for financial support from the National Natural Science Foundation of China (21403100, 21576128) and Liaoning Province, and the Doctoral Scientific Research Foundation (201411100).

References

1. E. Mosaddegh, A. Hassankhani, *Catal. Commun.* **33**, 70 (2013)
2. H. Singh, S. Kumari, J.M. Khurana, *Chin. Chem. Lett.* **25**, 1336 (2014)
3. V. Polshettiwar, R.S. Varma, *Acc. Chem. Res.* **41**, 629 (2008)
4. R.S. Varma, *Green Chem.* **16**, 2027 (2014)
5. K. Schröder, K. Matyjaszewski, K.J.T. Noonan, R.T. Mathers, *Green Chem.* **16**, 1673 (2014)
6. M.D. Rosa, A. Soriente, *Tetrahedron* **66**, 2981 (2010)
7. T.M. Potewar, S.A. Ingale, K.V. Srinivasan, *Tetrahedron* **64**, 5019 (2008)
8. L. Nagarapu, R. Mallepalli, U.N. Kumar, P. Venkateswarlu, R. Bantu, L. Yeramanchi, *Tetrahedron Lett.* **53**, 1699 (2012)
9. M.V. Reddy, J.S. Kim, K.T. Lim, Y.T. Jeong, *Tetrahedron Lett.* **55**, 6459 (2014)
10. Y. Gu, F. Jérôme, *Green Chem.* **12**, 1127 (2010)
11. J.I. García, H. García-Marín, E. Pires, *Green Chem.* **16**, 1007 (2014)
12. F. Hei, P. Li, Y. Gu, G. Li, *Green Chem.* **11**, 1767 (2009)
13. M. Shekouhy, A.M. Sarvestani, S. Khajeh, A. Khalafi-Nezhad, *RSC Adv.* **5**, 63705 (2015)
14. B.S. Singh, H.R. Lobo, D.V. Pinjari, K.J. Jarag, A.B. Pandit, G.S. Shankarling, *Ultrason. Sonochem.* **20**, 287 (2013)
15. H. Naeimi, F. Kiani, *Ultrason. Sonochem.* **27**, 408 (2015)
16. F. Nemati, S.H. Nikkhah, A. Elhampour, *Chin. Chem. Lett.* **26**, 1397 (2015)
17. J. Safaei-Ghomi, F. Eshteghal, H. Shahbazi-Alavi, *Ultrason. Sonochem.* **33**, 99 (2016)

18. T.R. Garbe, M. Kobayashi, N. Shimizu, N. Takesue, M. Ozawa, H. Yukawa, *J. Nat. Prod.* **63**, 596 (2000)
19. D.J. Faulkner, *Nat. Prod. Rep.* **16**, 155 (1999)
20. A. Kumar, M.K. Gupta, M. Kumar, D. Saxena, *RSC Adv.* **3**, 1673 (2013)
21. U.C. Rajesh, J. Wang, S. Prescott, T. Tsuzuki, D.S. Rawat, A.C.S. Sus. Chem. Eng. **3**, 9 (2015)
22. L. Jing, J. Wei, Z. Huang, Z. Li, D. Wu, H. Xiang, X. Zhou, *Chem. Eur. J.* **16**, 10955 (2010)
23. M. Terada, K. Moriya, K. Kanomata, K. Sorimachi, *Angew. Chem. Int. Ed.* **50**, 12586 (2011)
24. Y.C. Chen, Z.F. Xie, *Chin. J. Org. Chem.* **32**, 462 (2012)
25. A. Renzetti, E. Dardennes, A. Fontana, P.D. Maria, J. Sapi, S. Gérard, *J. Org. Chem.* **73**, 6824 (2008)
26. S. Gérard, A. Renzetti, B. Lefevre, A. Fontana, P.D. Maria, J. Sapi, *Tetrahedron* **66**, 3065 (2010)
27. C. Wang, Y.Q. Zhang, G.S. Li, J.C. Li, X.L. Li, *Chin. J. Org. Chem.* **23**, 1416 (2003)
28. C. Wang, G.S. Li, J.C. Li, Y.Q. Zhang, *Chem. Reag.* **25**, 369 (2003)
29. N. Yan, Y.K. Xiong, J.H. Xia, P.X. Rui, Z.W. Lei, W.L. Liao, B. Xiong, *Chin. J. Org. Chem.* **35**, 384 (2015)
30. Y. Qu, F. Ke, L. Zhou, Z. Li, H. Xiang, D. Wu, X. Zhou, *Chem. Commun.* **47**, 3912 (2011)
31. S. Chandrasekhar, V. Patro, G.P.K. Reddy, R. Grée, *Tetrahedron Lett.* **53**, 6223 (2012)
32. Z.H. Xu, C.H. Lin, W.L. Liao, *Chin. J. Appl. Chem.* **32**, 278 (2015)
33. Z.H. Xu, *Chin. J. Org. Chem.* **34**, 1687 (2014)
34. M. Li, A. Taheri, M. Liu, S. Sun, Y. Gu, *Adv. Synth. Catal.* **356**, 537 (2014)
35. U.C. Rajesh, V.S. Pavan, D.S. Rawat, *ACS Sus. Chem. Eng.* **3**, 1536 (2015)
36. Y.H. He, J.F. Cao, R. Li, Y. Xiang, D.C. Yang, Z. Guan, *Tetrahedron* **71**, 9299 (2015)
37. C.W. Lü, Y.H. Liu, X.X. Zhou, J.J. Wang, *Chem. Res. Chin. Univ.* **31**, 208 (2015)
38. C.W. Lü, Y.H. Liu, J.J. Wang, X.X. Zhou, *Chin. J. Appl. Chem.* **32**, 1371 (2015)
39. C.W. Lü, Y.H. Liu, J.J. Wang, X.X. Zhou, *Chin. J. Org. Chem.* **36**, 1407 (2016)
40. W.Y. Pan, Y.M. Xiao, H.Q. Xiong, C.W. Lü, *Res. Chem. Intermed.* (2016). doi:[10.1007/s11164-016-2517-8](https://doi.org/10.1007/s11164-016-2517-8)
41. F. Bigi, S. Carloni, L. Ferrari, R. Maggi, A. Mazzacani, G. Sartori, *Tetrahedron Lett.* **42**, 5203 (2001)
42. R. Maggi, F. Bigi, S. Carloni, A. Mazzacani, G. Sartori, *Green Chem.* **3**, 173 (2001)