

# Three-Component Cascade Reactions with 2,3-Diketoesters: A Novel Metal-Free Synthesis of 5-Vinyl-pyrrole and 4-Hydroxy-indole Derivatives

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**Supporting Information** 



**ABSTRACT:** 5-Vinyl-pyrrole and 4-hydroxy-indole derivatives are synthesized by metal-free aldol/cyclization/aromatization cascade reactions of in situ generated enamines with 2,3-diketoesters. This convenient atom-economical process produces multifunctional pyrrole and indole products in moderate to good yields.

Dyrroles and indoles are two of the most abundant classes of heterocycles found in natural products and pharmaceuticals.<sup>1</sup> Extensive methods have been developed for their synthesis and further modification,<sup>2</sup> and those that employ enamines have played a prominent role. Three general routes involving enamine formation exemplify those that have been developed for their synthesis: (1) multicomponent enamine reactions with ketones and amines that form pyrroles via condensation reactions (Scheme 1, eq 1);  ${}^{3}(2)$  metal-catalyzed cycloaddition reactions of stable enamines with alkynes or vicinal diols (Scheme 1, eq 2);<sup>4</sup> and (3) the synthesis of pyrroles or indoles by intramolecular cyclization reactions in the presence of a catalyst and oxidant during which C-H activation occurs (Scheme 1, eq 3).<sup>5</sup> Individually, these methods have their unique advantages, and they complement each other to broaden applications for pyrrole and indole synthesis. However, their shortcomings, such as a narrow substrate scope and the use of heavy metal catalysts, are also obvious, and they suggest the need for new methods to prepare functionalized pyrroles.

Vicinal tricarbonyl (VTC) compounds are important intermediates for organic synthesis. The pioneering work by Wasserman and co-workers provided examples demonstrating wide applications of VTCs in the synthesis of natural products and synthetic intermediates.<sup>6</sup> Lash and co-workers have used them in the synthesis of pyrrole derivatives.<sup>7</sup> Our group has applied them to synthesize highly functionalized furans<sup>8</sup> and 3aminopyrroles.<sup>9</sup>

We also reported the first diastereoselective<sup>10</sup> and enantioselective<sup>11</sup> nucleophilic addition reactions that occur at the central

# Scheme 1. General Routes towards Pyrroles or Indoles Involving Enamine Formation

Multicomponent condensation reactions based on carbonyl compounds

$$R^{1,NH_{2}} + Q^{0} = R^{2} + R^{3} + R^{3}$$

Metal catalyzed intermolecular cycloaddition



Intramolecular cyclization via C-H activation



carbon of VTC compounds. The highly active nature of the middle carbonyl group makes them very receptive to participate in many kinds of nucleophilic addition reactions.<sup>12</sup> During our

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attempts to combine VTC chemistry with aldol chemistry by generating enamines in situ, we uncovered a novel threecomponent cascade methodology for the synthesis of 5-vinylpyrrole and 4-hydroxy-indole derivatives. This methodology includes tandem aldol condensation, cyclization, and dehydration/aromatization (Scheme 1, eq 4).

We have previously reported that 2,3-diketoesters are conveniently formed by oxidation of the corresponding  $\alpha$ diazo- $\beta$ -ketoesters,<sup>8–11</sup> and there are multiple methods that directly access these diazo compounds. 2,3-Diketoesters exist as monohydrates, the dehydration of which can be achieved by gentle warming under reduced pressure. However, although use of the hydrate of VTCs decreases the reaction rate of subsequent reactions, convenience in handling VTC hydrates makes them the primary target for investigation. Initially, we chose 2,2dihydroxy-3-oxobutanoate (1a), aniline (2a), and cyclohexanone (3a) as starting materials to examine pyrrole formation. The reaction was performed at 65 °C for 24 h using THF as the solvent, and 5-vinyl-pyrrole 4a was obtained, albeit in only 21% yield (Table 1, entry 1). Although these reaction conditions gave



	O OBn <sup>+</sup> OH	NH <sub>2</sub> + solver	Br ive (20 mol %) mperature M nt (0.5 mL), 24 h	
	_			4a
entry	solvent	additive <sup>a</sup>	temp	yield <sup>b</sup>
1	THF	-	65 °C	21
2	toluene	-	65 °C	35
3	methanol	-	65 °C	8
4	DCM	-	65 °C	20
5	DCE	-	65 °C	21
6	CHCl <sub>3</sub>	-	65 °C	32
7	MeCN	-	65 °C	12
8	Et <sub>2</sub> O	-	65 °C	36
9	toluene	TFA	65 °C	trace
10	toluene	$PTSA^d$	65 °C	16
11	toluene	$Zn(OTf)_2$	65 °C	trace
12	toluene	Et <sub>3</sub> N	65 °C	trace
13	toluene	benzoic acid	<b>65</b> °C	57(55 <sup>c</sup> )
14	toluene	4-isopropylbenzoic aci	d 65 °C	49
15	toluene	4-nitrobenzoic acid	65 °C	42
16	toluene	(CF <sub>3</sub> ) <sub>2</sub> CHOH	65 °C	41
17	toluene	benzoic acid	rt	trace
18	toluene	benzoic acid	110 °C	30

<sup>*a*</sup>Reaction conditions: **1a** (0.10 mmol), **2a** (0.11 mmol), **3a** (0.20 mmol), additive (0.02 mmol), at indicated temperature for 24 h. <sup>*b*</sup>Yield was determined by <sup>1</sup>H NMR spectroscopy of the reaction mixture using  $CH_2I_2$  as internal standard. <sup>*c*</sup>Isolated yield, average of two runs. <sup>*d*</sup>PTSA refers to *p*-toluenesulfonic acid.

a mixture of unidentified materials in addition to 4a, we were encouraged with the potential synthetic efficiency of this threecomponent reaction. Attempted optimization by changing the solvent (Table 1, entries 2-8) identified toluene as the best with 4a formed in 35% yield (Table 1, entry 2). Sensing that acid or base catalyst might increase the product yield, Bronsted acids, zinc triflate as a representative of a Lewis acid, and triethylamine were used as additives (Table 1, entries 9-16). Of these additives benzoic acid gave 4a in the highest yield (Table 1, entry 13). Performing this reaction under the optimized conditions at temperatures lower or higher than 65 °C significantly decreased the yield of 4a (Table 1, entries 17-18).

With the optimal reaction conditions in hand, we investigated the substrate scope with various 2,3-diketoesters and aliphatic monoketones (Scheme 2). Two representative 2,3-diketoesters





<sup>*a*</sup>Reaction conditions: **1** (0.20 mmol), **2a** (0.22 mmol), **3** (0.40 mmol), benzoic acid (0.04 mmol), toluene (1 mL), 65 °C, 36 or 60 h; yields refer to isolated yields. <sup>*b*</sup>110 °C for 16 h.

were investigated ( $\mathbb{R}^1 = \mathbb{M}e$ , Ph). Good yields were obtained by using different ester groups (Scheme 2, 4a-4c) and with cyclic monoketones having ring sizes of six or larger (Scheme 2, 4f-4j). However, when cyclopentanone was used, the desired product was obtained in only 10% yield; the sharp drop in yield may be due to ring tension of the five-membered ring which made the cyclization reaction less competitive (Scheme 2, 4e).<sup>4b,7b</sup> Also dihydro-2*H*-thiopyran-4(3*H*)-one gave 4i in 28% yield. Interestingly, 3-pentanone gave 4u in 53% yield, but a higher temperature (refluxing toluene) was required to make this reaction occur smoothly.

Various anilines were used for the formation of 4 to evaluate their electronic influences in the three-component process. Halide substituted anilines gave 5-vinyl-pyrroles in moderate to good yields (Scheme 3, 4k-4n), but strong electron-donating groups obviously favored the process. Anilines with electrondonating methoxy, methyl, or aryl groups either in the ortho or para positions gave 4 in good yields (Scheme 3, 4i-4l). However, anilines with electron-withdrawing groups on the phenyl ring gave the pyrrole derivatives in only moderate yield (Scheme 2, 4s-4t). The use of an aliphatic amine further demonstrates the generality of this methodology (Scheme 3, 4u). The structure of 5-vinyl-pyrrole product 4m was confirmed by Xray diffraction analysis.<sup>13</sup> In gram scale syntheses of 4m we obtained the same yield as in the small scale reaction, suggesting the potential of this process for large scale production.

To exemplify the ease with which these pyrrole products can be converted to indoles, we used one reported procedure to perform the indole formation reaction by using **4m** as starting material (Scheme 4). By using a Pd/C as catalyst and acetic acid as solvent,<sup>14</sup> **4m'** was obtained in 56% yield without optimization.

With the observed generality of this methodology for 5-vinylpyrrole formation with aliphatic monoketones, the use of Scheme 3. Substrate Scope of Three-Component Reactions of Ethyl 2,2-Dihydroxy-3-oxo-3-phenylpropanoate 1d with Substituted Anilines and Cyclohexanone 3a<sup>a</sup>



<sup>*a*</sup>Reaction conditions: 1d (0.20 mmol), 2 (0.22 mmol), 3a (0.40 mmol), benzoic acid (0.04 mmol), toluene (1 mL), 65 °C, 36 h; yields refer to isolated yields. <sup>*b*</sup>4 mmol scale.

#### Scheme 4. Oxidative Aromatization of 4m



aliphatic 1,3-diketones was investigated. We envisioned that 1,3diketones could form 4-hydroxyindole derivatives following aromatization. We chose 2,2-dihydroxy-3-oxobutanoate (1a,  $R^1$ = Me), aniline (2a), and 1,3-cyclohexanedione (5a) as a model system to study this reaction. However, the desired indole product 6a was obtained in only 6% yield by using the optimized reaction conditions employed for the synthesis of 5-vinyl-pyrrole derivatives in Table 1 (Scheme 5, 6a). The reaction conditions for this transformation were optimized,<sup>14</sup> and after screening of various solvents and additives, we obtained 4-hydroxyindole 6a in 53% yield by using trifluoroacetic acid as an additive and 1,2dichloroethane as solvent. We then investigated other substrates to reveal the broad applications of this reaction (Scheme 5, 6b-6f). Similar to observations of reactivities of anilines in 5-vinylpyrrole forming reactions, anilines with electron-donating groups were favored in this transformation.

To better understand the mechanistic pathway of this complex transformation we focused on addressing the site at which imine formation first occurred. Reaction with either the 2,3-diketoester or the cyclohexanone is possible, and we examined each by (1) first combining 1a with aniline and then adding cyclohexanone (4a was formed in less than 10% yield) and (2) first combining cyclohexanone with aniline at 65 °C and then adding 2,3-diketoester 1a (4a was formed in 58% yield) (Scheme 6). These

Scheme 5. Substrate Scope of Three-Component Reactions of 2,3-Diketoesters with Anilines and 1,3-Cyclohexanediones<sup>*a*</sup>



<sup>a</sup>Reaction conditions: 1 (0.20 mmol), 2 (0.22 mmol), 5 (0.40 mmol), TFA (0.02 mmol), DCE (1 mL), 65 °C, 16 h; yields refer to isolated product yields.

#### Scheme 6. Studies on the Reaction Mechanism

(1) Form the imine of 2.3-diketoesters first NHbenzoic acid (20 mol %) 3a (0.40 mmol) ne, 65 °C, 3 h 65 °C, 36 h нΟ OH 0 20 mmol 0.22 mmo <10% vield<sup>e</sup> (2) Form the imine of cyclohexanone first BnO<sub>2</sub>C nzoic acid (20 mol %) 2a (0.20 mmol) toluene. 65 °C. 3 h 65 °C 36 h 0.40 mmo 3a 0.22 mmol 2a 4a 58% vield (3) Two steps reactions for the synthesis of 4a BnO<sub>2</sub>C 2a (0.11 mmol) L-proline (20 mol %) enzoic acid (20 mol %) ОН DCM, rt. 24 h toluene 65 °C 24 h н∩́ 0.10 mmol scale 1.5 mmol 3.0 mmol . 92% vield 1a 3a dr = 74:26 70% vield

<sup>*a*</sup>Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), benzoic acid (0.04 mmol), toluene (1 mL), 65 °C, 3 h; then **3a** (0.4 mmol), 65 °C, 36 h. <sup>*b*</sup>Reaction conditions: **3a** (0.40 mmol), **2a** (0.22 mmol), benzoic acid (0.04 mmol), toluene (1 mL), 65 °C, 3 h; then **2a** (0.20 mmol), 65°C, 36 h. <sup>*c*</sup>Reaction conditions: **1a** (1.50 mmol), **3a** (3.0 mmol), L-proline (0.30 mmol), DCM (10 mL), rt, 24 h; then 7 (0.10 mmol), **2a** (0.11 mmol), benzoic acid (0.02 mmol), toluene (0.5 mL), 65 °C, 24 h. <sup>*d*</sup>Isolated yield; dr was determined by <sup>1</sup>H NMR spectroscopy. <sup>e</sup>Yields were determined by <sup>1</sup>H NMR using  $CH_2I_2$  as the internal standard.

results show that condensation of cyclohexanone with aniline occurs initially after which aldol condensation and subsequent reactions occurred to form the pyrrole product. Independently, the aldol condensation product formed between 2,3-diketoester **1a** and cyclohexanone formed **4a** in 70% yield when treated with aniline under optimized conditions employed in Table 1 (see (3) in Scheme 6).

Based on these observations, we propose that enamine formation from cyclohexanone preceeds aldol condensation with the dehydrated 2,3-diketoester to form enamine A (Scheme 7). Cyclization by condensation of A with the keto group at the 3position forms B. Acid promoted loss of water (B to C) and dehydration by 1,4-elimination (C to D) result in aromatization that with proton transfer forms 5-vinyl-pyrrole products (E).

In summary, we have reported a new, efficient, and straightforward methodology for the synthesis of 5-vinyl-

#### Scheme 7. Proposed Mechanism



substituted pyrrole derivatives via the metal-free threecomponent reactions of 2,3-diketoesters with anilines and cyclic ketones. Moreover, 4-hydroxyl-indole analogues are prepared by using 1,3-cyclohexanedione. This methodology has synthetic advantages as a multicomponent reaction that is consistent with green chemistry principles and is suitable to scale up.

#### ASSOCIATED CONTENT

#### Supporting Information

General experimental procedures, the X-ray structure of **4m**, and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01855.

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#### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) For pyrroles, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J. F. Chem. Rev. 2008, 108, 264-287. (b) Dipakranjan, M.; Brateen, S.; Bidyut, K. D. Pyrrole and Its Derivatives. In Heterocycles in Natural Product Synthesis; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 187-220. (c) Wang, M.; Xu, H.; Liu, T.; Feng, Q.; Yu, S.; Wang, S.; Li, Z. Eur. J. Med. Chem. 2011, 46, 1463-1472. (d) Amara, Z.; Caron, J.; Joseph, D. Nat. Prod. Rep. 2013, 30, 1211-1225. For indoles, see: (e) Somei, M.; Yamada, F. Nat. Prod. Rep. 2004, 21, 278-311. (f) Kawasaki, T.; Higuchi, K. Nat. Prod. Rep. 2005, 22, 761-793. (g) Somei, M.; Yamada, F. Nat. Prod. Rep. 2005, 22, 73-103. (h) Dandia, A.; Singh, R.; Khaturia, S.; Merienne, C.; Morgant, G.; Loupy, A. Bioorg. Med. Chem. 2006, 14, 2409-2417. (i) Smart, B. P.; Oslund, R. C.; Walsh, L. A.; Gelb, M. H. J. Med. Chem. 2006, 49, 2858-2860. For a general overview, see: (j) d'Ischia, M.; Napolitano, A.; Pezzella, A. In Comprehensive Heterocyclic Chemistry III; Elsevier: Oxford, 2008; Vol. 3, pp 353-388.

(2) For pyrroles, see: (a) Balme, G. Angew. Chem., Int. Ed. 2004, 43, 6238-6241. (b) Nakamura, I.; Yamamoto, Y. Chem. Rev. 2004, 104, 2127-2198. (c) Wang, J. Y.; Wang, X. P.; Yu, Z. S.; Yu, W. Adv. Synth. Catal. 2009, 351, 2063-2066. (d) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Chem. Rev. 2013, 113, 3084-3213. (e) Schranck, J.; Tlili, A.; Beller, M. Angew. Chem., Int. Ed. 2013, 52, 7642-7644. (f) Ackermann, L. Acc. Chem. Res. 2014, 47, 281-295. For indoles, see: (g) Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem. Rev.

**2003**, *103*, 893–930. (h) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (i) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (j) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (k) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.

(3) (a) Roomi, M. W.; MacDonald, S. F. *Can. J. Chem.* **1970**, *48*, 1689–1697. (b) Kameswaran, V.; Jiang, B. *Synthesis* **1997**, *1997*, 530–532. (c) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2896–2899. (d) Palacios, F.; Aparicio, D.; de los Santos, J. M.; Vicario, J. *Tetrahedron* **2001**, *57*, 1961–1972. (e) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. J. Org. Chem. **2008**, *73*, 2090–2095. (f) Dou, G.; Shi, C.; Shi, D. J. Comb. Chem. **2008**, *10*, 810–813.

(4) (a) Rakshit, S.; Patureau, F. W.; Glorius, F. J. Am. Chem. Soc. 2010, 132, 9585–9587. (b) Zhang, M.; Fang, X. J.; Neumann, H.; Beller, M. J. Am. Chem. Soc. 2013, 135, 11384–11388. (c) Zhao, M. N.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. Org. Lett. 2014, 16, 608–611. (d) Xie, Y.; Chen, T. F.; Fu, S. M.; Li, X. S.; Deng, Y. F.; Jiang, H. F.; Zeng, W. Chem. Commun. 2014, 50, 10699–10702.

(5) (a) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. Angew. Chem., Int. Ed. 2008, 47, 7230–7233. (b) Yu, W. Q.; Du, Y. F.; Zhao, K. Org. Lett. 2009, 11, 2417–2420. (c) Saito, A.; Konishi, T.; Hanzawa, Y. Org. Lett. 2010, 12, 372–374. (d) Guan, Z. H.; Yan, Z. Y.; Ren, Z. H.; Liu, X. Y.; Liang, Y. M. Chem. Commun. 2010, 46, 2823–2825. (e) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. Chem. - Eur. J. 2011, 17, 7298–7303. (f) Toh, K. K.; Wang, Y. F.; Ng, E. P. J.; Chiba, S. J. Am. Chem. Soc. 2011, 133, 13942–13945. (g) Wei, Y.; Deb, I.; Yoshikai, N. J. Am. Chem. Soc. 2012, 134, 9098–9101.

(6) Wasserman, H. H.; Parr, H. Acc. Chem. Res. 2004, 37, 687-701.

(7) (a) Lash, T. D.; Bladel, K. A.; Shiner, C. M.; Zajeski, D. L.; Balasubramaniam, R. P. J. Org. Chem. 1992, 57, 4809–4820.
(b) Quizon-Colquitt, D. M.; Lash, T. D. J. Heterocycl. Chem. 1993, 30, 477–482.

(8) Truong, P.; Xu, X. F.; Doyle, M. P. Tetrahedron Lett. 2011, 52, 2093–2096.

(9) Truong, P.; Mandler, M. D.; Doyle, M. P. Tetrahedron Lett. 2015, 56, 3042–3045.

(10) Truong, P.; Shanahan, C. S.; Doyle, M. P. Org. Lett. 2012, 14, 3608-3611.

(11) Truong, P.; Zavalij, P. Y.; Doyle, M. P. Angew. Chem. 2014, 126, 6586-6590.

(12) (a) Wasserman, H. H.; Kuo, G. H. Tetrahedron Lett. **1989**, 30, 873–876. (b) Beak, P.; Song, Z.; Resek, J. E. J. Org. Chem. **1992**, 57, 944–947. (c) Gill, G. B.; Idris, M. S. H.; Kirollos, K. S. J. Chem. Soc., Perkin Trans. 1 **1992**, 2355–2365. (d) Gill, G. B.; Idris, M. S. H. Tetrahedron **1993**, 49, 219–234. (e) Wasserman, H. H.; Lee, G. M. Tetrahedron Lett. **1994**, 35, 9783–9786. (f) Black, D. St. C.; Bowyer, M. C.; Condie, G. C.; Craig, D. C.; Kumar, N. Tetrahedron **1994**, 50, 10983–10994. (g) Kneubühler, S.; Thull, U.; Altomare, C.; Carta, V.; Gaillard, P.; Carrupt, P. A.; Carotti, A.; Testa, B. J. Med. Chem. **1995**, 38, 3874–3883.

(13) The crystal data for compound **4m** have been deposited with the Cambridge Crystallographic Data Centre (no. CCDC1404003). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)336033; Email: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data\_request/cif].

(14) Nakamichi, N.; Kawashita, Y.; Hayashi, M. Org. Lett. 2002, 4, 3955–3957.

(15) For details, see Supporting Information.

(16) List, B.; Lerner, R. A.; Barbas, C. F., III J. Am. Chem. Soc. 2000, 122, 2395–2396.