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Pd-Catalyzed Tandem Cyclization of Ethyl Glyoxalate and Amines: Rapid Assembly of Highly Substituted Cyclic Dehydro-α-Amino Acid Derivatives

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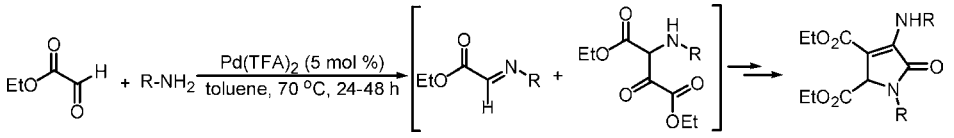
ABSTRACT



A novel cascade cyclization of ethyl glyoxalate and amines proceeds in the presence of $Pd(TFA)_2$ (5 mol %) to give the cyclic dehydro-α-amino acid derivatives. This method provides a fast and simple access to highly substituted dihydro-pyrrol-2-ones in good yields.

Dihydro-pyrrol-2-one (DPO) derivatives are widely utilized as key building blocks for the construction of various biologically active natural products and pharmaceutical molecules,[1] and their importance has already triggered many efficient synthetic strategies to access such a lactam family.[2] Among these versatile synthetic methods, transition-metal catalyzed multicomponent reactions (MCRs) involved in aldehydes and amines have attracted particular attention, as they can provide expedient synthesis of multisubstituted pyrrol-2-one compounds.[2g−i] In all of these transformations, imines derived from aldehydes and amines were proposed as intermediates which then further reacted with the third reactive partner such as an alkene, alkyne, etc. to furnish the target DPO analogs (Scheme 1a).[2g−i] However, despite much progress in this field, studies on transition-metal catalyzed rapid assembly of DPO molecules only from an aldehyde and an amine were unprecedented. Nevertheless, given that ethyl glyoxalate (**1a**) and

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(1) For selected examples, see: (a) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329. (b) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834. (c) Celmer, W. D.; Salomons, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 2861. (d) Mandal, A. K.; Hines, J.; Kuramochi, K.; Crews., C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4043.

(2) For selected examples, see: (a) Montforts, V. F. P.; Schwartz, U. M. *Angew. Chem.* **1985**, *97*, 767. (b) Albrecht, D.; Basler, B.; Bach, T. *J. Org. Chem.* **2008**, *73*, 2345. (c) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (d) Li, W. R.; Lin, S. T.; Hsu, N. M.; Chern, M. S. *J. Org. Chem.* **2002**, *67*, 4702. (e) Tekkam, S.; Alam, M. A.; Jonnalagadda, S. C.; Mereddy, V. R. *Chem. Commun.* **2011**, *47*, 3219. (f) Anders, J. T.; Görls, H.; Langer, P. *Eur. J. Org. Chem.* **2004**, 1897. (g) Zhu, Q.; Jiang, H.; Li, J.; Liu, S.; Xia, C.; Zhang, M. *J. Comb. Chem.* **2009**, *11*, 685. (h) Sun, J.; Wu, Q.; Xia, E. Y.; Yan, C. G. *Eur. J. Org. Chem.* **2011**, 2981. (i) Roy, S.; Reiser, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 4722.

(3) (a) Olmos, A.; Louis, B.; Pale, P. *Chem.—Eur. J.* **2012**, *18*, 4894. (b) Li, X.; Mao, Z.; Dai, X.; Lu, P.; Wang, Y. *Chem. Commun.* **2011**, *47*, 6620. (c) Olmos, A.; Sommer, J.; Pale, P. *Chem.—Eur. J.* **2011**, *17*, 1907. (d) Saupe, J.; Roske, Y.; Schillinger, C.; Kamdem, N.; Radetzki, S.; Diehl, A.; Oschkinat, H.; Krause, G.; Heinemann, U.; Rademann, J. *ChemMedChem* **2011**, *6*, 1411. (e) Borrione, E.; Prato, M.; Scorrano, G.; Stivanello, M.; Lucchini, V. *J. Heterocycl. Chem.* **1988**, *25*, 1831.

(4) For selected examples about insertion of Co(I), Rh(I), and Ru(0) into aldehyde C_{sp^2}–H bond, see: (a) Garralda, M. A. *Dalton Trans.* **2009**, 3635. (b) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674. (c) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965. (d) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (e) Kwong, F. Y.; Li, Y. M.; Lam, W. H.; Qiu, L. Q.; Lee, H. W.; Yeung, C. H.; Chang, K. S.; Chan, A. S. C. *Chem.—Eur. J.* **2005**, *11*, 3872. For examples about insertion of Pd(II) into aldehyde C_{sp^2}–H bond, see: (f) Wu, Y.; Li, B.; Mao, F.; Li, X.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 3258. (g) Álvarez-Bercedo, P.; Flores-Gaspar, A.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 466. (h) Waldo, J. P.; Zhang, X.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 6679. (i) Wei, L.; Wei, L.; Pan, W.; Wu, M. *Synlett* **2004**, 1497. (j) Sakakibara, K.; Yamashita, M.; Nozaki, K. *Tetrahedron Lett.* **2005**, *46*, 959. (k) Flores-Gaspar, A.; Marin, R. *Adv. Synth. Catal.* **2011**, *353*, 1223. (l) Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004**, *6*, 2437. (m) Pan, C.; Jia, X.; Cheng, J. *Synthesis* **2012**, *5*, 677.

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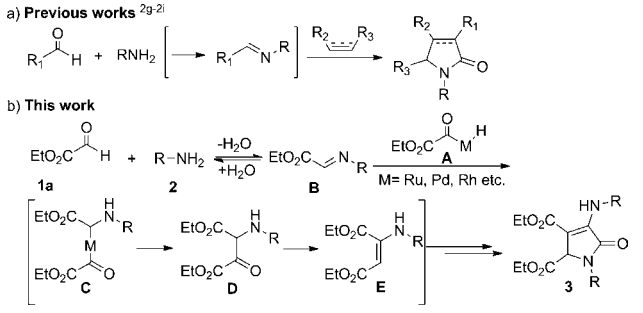
amines (**2**) were often employed in most MCRs to construct multifunctionalized heterocycles,[3] we envisioned that the oxidative addition of aldehyde C_{sp^2}–H to transition metal salts (M) could provide the M–H species **A**[4] and the subsequent imine (**B**) insertion to **A**,[5] reductive elimination, carbonyl reduction and dehydration would possibly lead to the formation of enamine **E**, which could be further cross-coupled or cyclized with α-imino ester **B** to furnish DPO derivatives **3** (Scheme 1b). To test this hypothesis, herein we describe a convenient synthesis of highly substituted 1,5-dihydro-2*H*-pyrrol-2-ones through Pd(II)-catalyzed cascade cyclization of ethyl glyoxalate and amine.

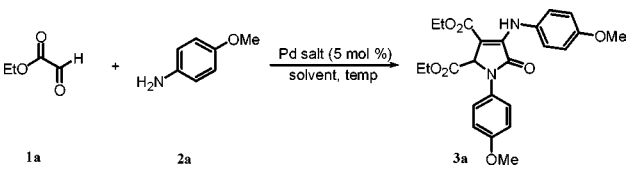
Scheme 1. Synthetic Strategies of the Pyrrol-2-ones Derivatives



At the outset of our study, we conducted the Pd(II)-catalyzed tandem assembly of 1, 5-dihydro-2*H*-pyrrol-2-one using ethyl glyoxalate (**1a**) and *p*-anisidine (**2a**) as model substrates to screen the reaction conditions for the optimization of the catalyst, solvent, and temperature under an Ar atmosphere. First, ethyl glyoxalate **1a** (0.30 mmol) was treated with $Pd(OAc)_2$ (5 mol %) and *p*-anisidine **2a** (0.30 mmol) in toluene (2.0 mL) at 25 °C for 24 h. As expected, we obtained a 10% yield of pyrrol-2-one **3a** (Table 1, entry 1), and this positive result encouraged us to further screen various palladium salts such as $PdCl_2$, $PdCl_2(PhCN)_2$, etc. to achieve satisfying yields (entries 1–7). To our delight, $Pd(TFA)_2$ gave a 37% yield of target compound **3a** (entry 7). It is noteworthy that no **3a** formation was observed in the absence of palladium salts (entry 8). We then switched to using 2.0 equiv of **2a** to increase the yield of this trasnformation. Again, no reaction was noted (entry 9). Subsequently, the increased yield (68%) was obtained by using 2.0 equiv of **1a** at 70 °C for 48 h (compare entries 10–11 with 16). A further increase in reaction temperature (90 °C) or use of other polar solvents such as ethyl acetate, acetonitrile, etc. resulted in poorer yields (entries 12–15) (see Supporting Information (SI) for more details).

(5) For selected examples about insertion of Pd species into imine C=N bond, see: (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412. (b) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (c) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650. (d) Ma, G. N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875.

Table 1. Optimization Results for the Palladium-Catalyzed Cascade Cyclization of Ethyl Glyoxalate with *p*-Anisidine[a]



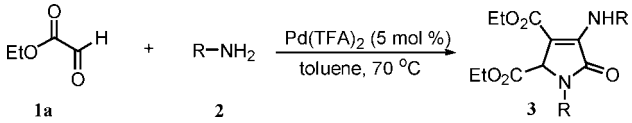
entry	catalyst	**1a**/**2a** (equiv)	temp (°C)	solvent	yield (%)[b]
1	$Pd(OAc)_2$	1/1	25	toluene	10
2	$PdCl_2(CH_3CN)_2$	1/1	25	toluene	18
3	$PdCl_2$	1/1	25	toluene	15
4	$PdCl_2(Ph_2PCH_2)_2$	1/1	25	toluene	8
5	$PdCl_2(PhCN)_2$	1/1	25	toluene	trace
6	$PdCl_2(PPh_3)_2$	1/1	25	toluene	10
7	$Pd(TFA)_2$	1/1	25	toluene	37
8	–	1/1	25	toluene	0
9	$Pd(TFA)_2$	1/2	25	toluene	trace
10	$Pd(TFA)_2$	2/1	25	toluene	61
11	$Pd(TFA)_2$	2/1	70	toluene	63
12	$Pd(TFA)_2$	2/1	90	toluene	42
13	$Pd(TFA)_2$	2/1	70	CH_2Cl_2	42
14	$Pd(TFA)_2$	2/1	70	EtOAc	43
15	$Pd(TFA)_2$	2/1	70	CH_3CN	11
16	$Pd(TFA)_2$	2/1	70	toluene	68[c]

[a] Reactions were run with **1a** (0.15–0.60 mmol), **2a** (0.30 mmol), Pd(II) salt (5 mol %), and solvent (2.0 mL) under Ar in a sealed pressure tube at the given temperature for 24 h unless otherwise noted. [b] Isolated yield. [c] Reaction time: 48 h.

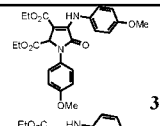
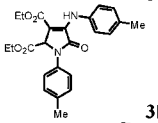
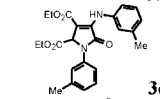
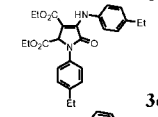
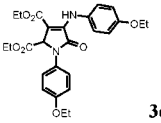
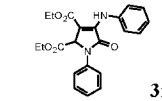
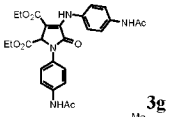
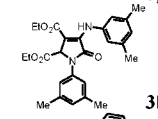
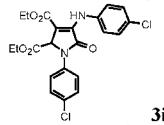
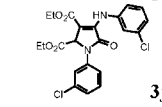
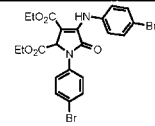
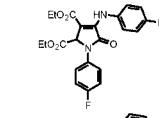
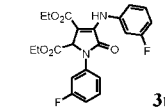
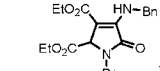
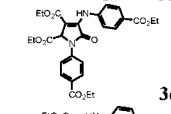
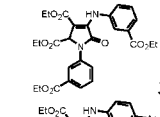
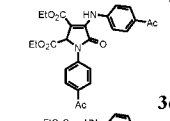
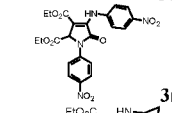
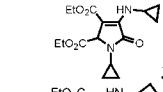
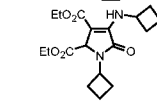
Having established an efficient reaction protocol that enables the rapid assembly of DPO, we next applied this method to the synthesis of a focused DPO library. As shown in Table 2, common functional groups on the benzene rings attached to the amine nitrogen, including alkoxyl (entries 1 and 5), alkyl (entries 2–4 and 8), amide (entry 7), halogen (entries 9–13), ester (entries 15 and 16), and ketone (entry 17), were all compatible with this cascade cyclization and gave moderate-to-good yields of DPO derivatives. Meso-substituted arylamines led to a substantial decrease in product yield presumably due to the increased steric hindrance around the amine nitrogen (compare entries 2, 3, and 8; 9 and 10; 12 and 13). Unfortunately, no reaction occurred for the 4-nitrobenzenamine, possibly due to the strong electron-withdrawing inductive effect from the nitro group (entry 18). Alkyl amines such as benzylamine, cyclopropylamine, and cyclobutylamine underwent slightly worse conversion and provided a lower yield of target products (34–56%, entries 14, 19–20). The structure of **3a** was unambiguously assigned by its single crystal X-ray analysis (see Figure 1 and SI for more details).

Finally, we also ran the Pd(II)-catalyzed cascade cross-cyclization of **1a** (3.0 equiv) with **2a** (1.0 equiv) and 4-chloroaniline (**2i**) (1.0 equiv) under standard conditions. As expected, we obtained the corresponding cross-cyclization

Table 2. Pd(II)-Catalyzed Cascade Cyclization of Ethyl Glyoxalate with Amines to 2,5-Dihydropyrro-2-one Derivatives[a]



1a 2 3

entry	R	time (h)	product	yield (%)[b]
1	4-MeO-C_6H_4	48	 **3a**	68
2	4-Me-C_6H_4	24	 **3b**	62
3	3-Me-C_6H_4	24	 **3c**	36
4	4-Et-C_6H_4	12	 **3d**	71
5	4-EtO-C_6H_4	24	 **3e**	63
6	C_6H_5	24	 **3f**	56
7	4-AcNH-C_6H_4	24	 **3g**	38[c]
8	3, 5-bis(Me)-C_6H_3	24	 **3h**	35
9	4-Cl-C_6H_4	40	 **3i**	76
10	3-Cl-C_6H_4	12	 **3j**	65
11	4-Br-C_6H_4	40	 **3k**	74
12	4-F-C_6H_4	12	 **3l**	71
13	3-F-C_6H_4	16	 **3m**	37
14	Bn	48	 **3n**	40
15	4-EtO_2C-C_6H_4	36	 **3o**	57
16	3-EtO_2C-C_6H_4	24	 **3p**	69
17	4-Ac-C_6H_4	24	 **3q**	52
18	4-NO_2-C_6H_4	49	 **3r**	0
19	Cyclopropyl	56	 **3s**	56
20	Cyclobutyl	48	 **3t**	34

[a] Reactions were run with ethyl glyoxalate **1a** (0.60 mmol), aimines **2** (0.30 mmol), Pd(TFA)2 (5 mol %), and toluene (2.0 mL) under Ar in a sealed pressure tube at 70 °C for the given time unless otherwise noted. [b] Isolated yield. [c] Using ethyl acetate as solvent.

products **3u** (22% yield) and **3v** (18% yield) besides **3a** (9% yield) and **3i** (16% yield) (see Scheme 2).[6]

To further probe the reaction mechanism, we conducted the Pd(II)-catalyzed cascade cyclization of ethyl glyoxalate (**1a**) and *p*-anisidine (**2a**) and monitored the reaction progress using GC-MS spectra to detect some possible byproducts and intermediates.[7] After the reaction was carried out for 24 h, we could observe the formation of 2-(4-methoxy-phenylamino)-3-oxo-succinic acid diethyl ester (**D-a**)[8] (< 5% isolated yield) and *N*-(4-methoxy-phenyl)-oxalamic acid ethyl ester (**I-a**)[8] (< 10% isolated

(6) We also ran the cascade cross-cyclization of *p*-anisidine (0.6 mmol, 2.0 equiv) with ethyl glyoxalate (0.3 mmol, 1.0 equiv) and benzaldehyde (0.3 mmol, 1.0 equiv) under standard conditions; unfortunately, only a 25% yield of **3a** was obtained, and no other cross-cyclization produts were observed.

(7) See SI for the detailed GC-MS spectra.

(8) We have already separated and characterized the byproduct **D-a** and **I-a** by ^{1}H NMR, ^{13}C NMR, and HR-MS spectra (see SI for more detail).

(9) Palacious, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, 2843.

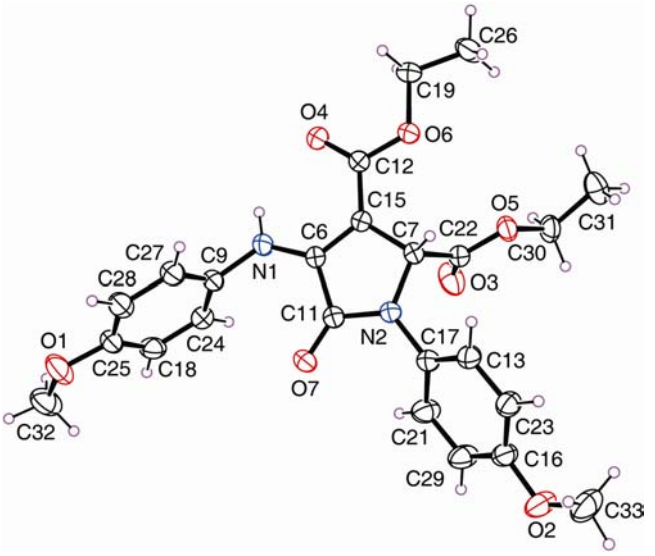
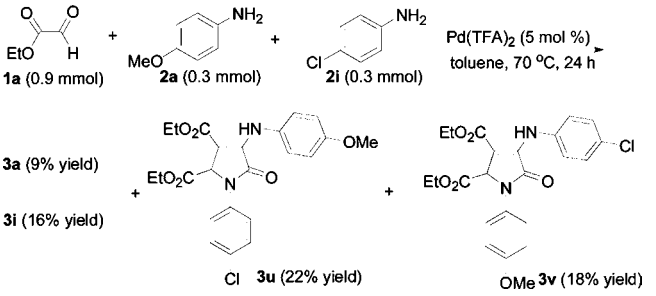


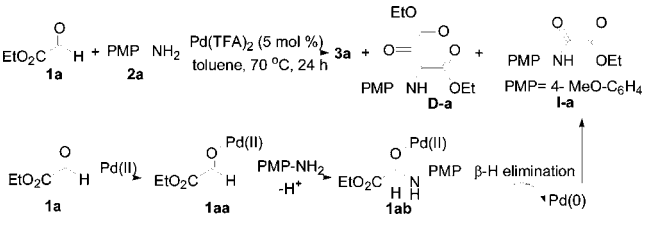
Figure 1. Single crystal structure of pyrrol 2-one **3a**.

Scheme 2. Pd(II)-Catalyzed Cascade Cross-Cyclization of Ethyl Glyoxalate (**1a**) with *p*-Anisidine (**2a**) and 4-Chloroaniline (**2i**)



yield) which have already been identified by ^{1}H NMR, ^{13}C NMR, and MS spectra. The byproduct **I-a** was possibly derived from a cross-coupling reaction of ethyl glyoxalate and *p*-anisidine via a nucleophilic reaction and subsequent *β*-hydride elimination (Scheme 3).

Scheme 3. Byproducts from the Pd(II)-Catalyzed Cascade Reaction of Ethyl Glyoxalate (**1a**) and *p*-Anisidine (**2a**)



On the basis of the above-mentioned experimental results, a possible mechanism for this reaction is outlined in Figure 2. For the first step, $Pd(TFA)_2$ activated the aldehyde carbonyl group of **1a** and facilitated the addition of amines. After *β*-hydride elimination, **I** was formed with the formation of the Pd(0) species, the subsequent oxidative addition of Pd(0) to the aldehyde C_{sp^2}−H bond of **1a** afforded the hydrogen−palladium species H−Pd(II)−$COCO_2Et$ (**A**),[4] and then the following iminoester **B** insertion into **A**[5] and reductive elimination provided intermediate **D**[8] which could be reduced to alcohol **E** by H−Pd species **A**. On the other hand, species **A** also could lead to the formation of byproduct **I**[8] via ligand exchange with amines **2** and reductive elimination. Further dehydration of **E** gave enamine **F**, and the subsequent cross-coupling and cyclization of **F** with iminoester **B** produced the cyclic dehydro-α-amino acid derivatives **3**.[2g,9]

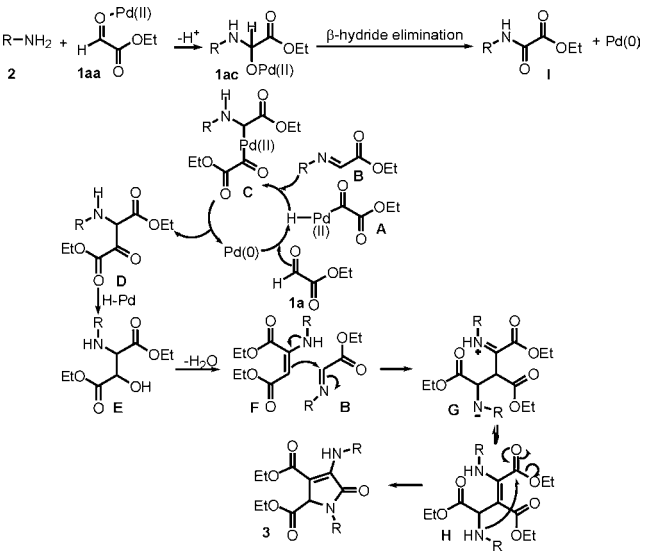


Figure 2. Proposed the possible reaction mechanism.

In summary, we have developed a novel method of synthesizing highly substituted 1,5-dihydro-2*H*-pyrrol-2-one derivatives from the palladium-catalyzed cascade cyclization of ethyl glyoxalate and amines. Further investigations of their possible biological activities will make these compounds even more valuable and are also currently underway in our laboratory.

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Supporting Information Available. Detailed experimental procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.