Tetrahedron Letters 53 (2012) 1323–1327

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Palladium(II)-catalyzed oxidative homo-coupling of 1,3-dimethyluracil derivatives

Ko Hoon Kim, Hyun Seung Lee, Sung Hwan Kim, Jae Nyoung Kim *

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

ARTICLE INFO

Article history:
Received 2 December 2011
Revised 21 December 2011
Accepted 21 December 2011
Available online 20 January 2012

Keywords:
Palladium
1,3-Dimethyluracil
Oxidative homo-coupling
Uracil dimer
Uracil trimer

ABSTRACT

A palladium-catalyzed oxidative homo-coupling of 1,3-dimethyluracil was examined. Two types of uracil dimer, C5–C5′ linked dimer and C5–C6′ linked dimer were obtained in variable yields depending on the conditions along with a low yield of C5–C5′ and C6–C5′ linked uracil trimer.

© 2012 Elsevier Ltd. All rights reserved.

Transition metal-based drugs have received much attention since the finding of antitumor activity of cisplatin. Since then numerous efforts have been devoted to the development of drugs based on transition metals including platinum[1a–d] and palladium.[1c–f] Uracil dimers and its nucleoside analogs are not the natural nucleic acid component; thus, the formation of these compounds catalyzed by transition metal impurities or metal-containing drugs in vivo may cause severe problems. With this in mind, Lippert and co-workers have examined the preparation of C5–C5′ uracil dimers with the aid of a gold catalyst.[2] Daves and co-workers also examined the dimerization of pyrimidinylmercuric salts with an equivalent amount of palladium catalyst.[3]

In addition, various types covalently linked nucleic acids dimers have received much attention due to their potential biological activity, complexation properties, supramolecular self-assembly, Watson–Crick base pair bonding models, and protein binding.[4] Two types of dimers have been reported for uracil derivatives, those are C5–C5′ linked dimers[4a–h] and N^3–$N^{3'}$ linked dimers with a spacer.[4i–k] However, the synthesis of C5–C5′ directly-linked dimers without a spacer is much limited.[2,3] In these contexts, we decided to examine the synthesis of uracil dimers *in the presence of a catalytic amount of palladium catalyst*.

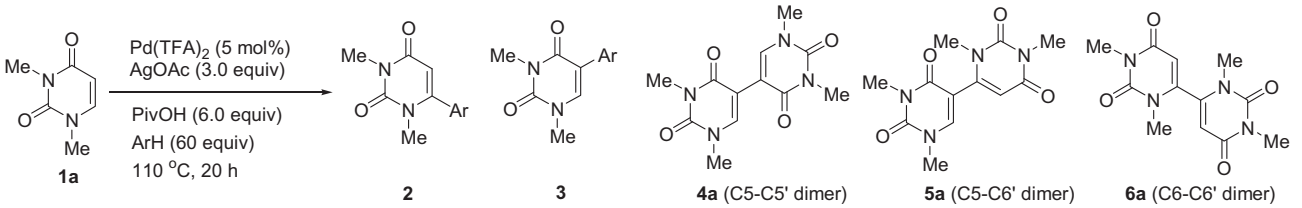
Recently, we reported a palladium-catalyzed regioselective 5-arylation of 1,3-dimethyluracil with bromoarenes.[5] In the same Letter, we also found a palladium-catalyzed regioselective 6-arylation with arenes via a concerted metalation–deprotonation (CMD) process.[5] During the 6-arylation reaction with *p*-xylene as an arylation partner, we observed the formations of a C5–C5′ linked uracil dimer **4a** (26%) and a C5–C6′ linked uracil dimer **5a** (11%), albeit in low yields,[6] while the reactions of **1a** and benzene, *m*-xylene or *o*-xylene produced only trace amounts of the homo-coupled products, **4a** and **5a**, as shown in Table 1 (entries 1–4). The amounts of uracil dimers **4a** and **5a** increased when the arene is sterically hindered as *p*-xylene or mesitylene. When we used mesitylene (entry 5), cross-coupled products (**2e** or **3e**) were not formed in any trace amount. Instead dimer **4a** was formed as a major product (52%) along with a low yield of dimer **5a** (20%).[7–9] The C6–C6′ linked uracil dimer **6a** was not formed in all entries.

The plausible reaction mechanism for the formations of **4a** and **5a** is suggested in Scheme 1.[5,10] An electrophilic metalation–deprotonation (EMD) of **1a** produced an uracilpalladium intermediate **II** via the iminium ion intermediate **I**. Heck-type carbopalladation of **II** to **1a** produced an intermediate **III**. A subsequent epimerization at the C5′-position of **III** via an *O*-palladium enol species and the following β-H elimination would produce a dimer **5a**. When the intermediate **II** reacted with **1a** in an EMD process, a diuracilpalladium intermediate **IV** could be formed. Final reductive elimination of Pd^0 from **IV** would produce a dimer **4a**. If the first palladation of **1a** occurs by a CMD process via the intermediate **V**, an uracilpalladium intermediate **VI** could be generated,[5] and a subsequent reaction of **VI** and **1a** in an EMD process would also produce compound **5a** via a diuracilpalladium intermediate **VIII**. However, the dimer **6a** was not formed at all presumably due to the involvement of a congested transition state **VII**. Similarly, we could not observe the formation of compound **2e**.

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
E-mail address: kimjn@chonnam.ac.kr (J.N. Kim).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.135

Table 1
Palladium-catalyzed homo-coupling reaction of 1,3-dimethyluracil (**1a**)

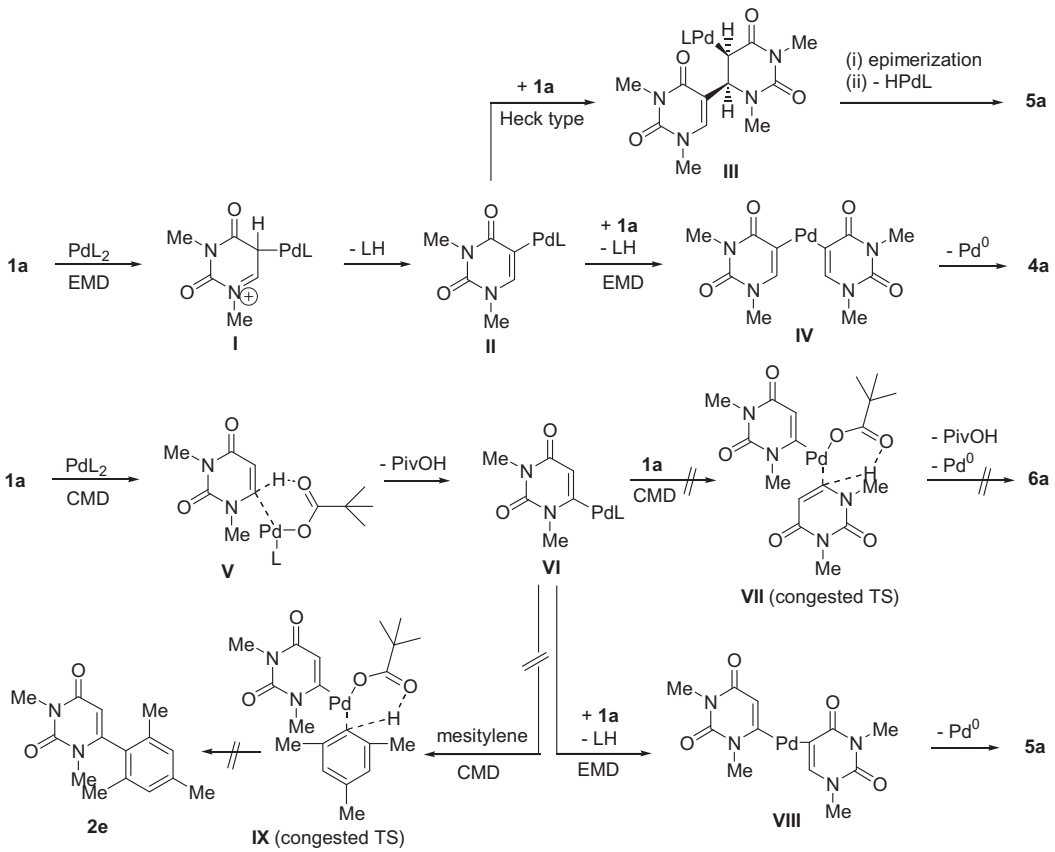


Entry	Arene	**2** (%)	**3** (%)	**4a** (%)	**5a** (%)
1	Benzene	**2a** (85)[a]	**3a** (6)[a]	—[b]	—[b]
2	*m*-Xylene	**2b** (80)[a]	**3b** (11)	—[b]	—[b]
3	*o*-Xylene	**2c** (66)[a]	**3c** (18)	—[b]	—[b]
4	*p*-Xylene	**2d** (52)[a]	**3d** (<5)	26	11
5	Mesitylene	**2e** (0)	**3e** (0)	52	20

[a] Reported data (Ref. 5).
[b] Trace amount (<5%).

In order to examine the dependence of yields and selectivity (**4a**/**5a**) on the reaction conditions, we carried out the reactions of **1a** under various conditions, and the results are summarized in Table 2. When we used PivOH as a solvent (entry 2), the result was similar to that in mesitylene solvent (entry 1). Increasing the amounts of PivOH decreased the yields of products (entry 3). The reaction in mesitylene without PivOH (entry 4) provided the highest combined yields of products (96%). In addition, a trimeric compound **7a** (vide infra) was isolated in a reasonable yield (18%).[3,9] It is interesting to note that the yield of **5a** increased to 46% when the reaction was performed at 80 °C (entry 5). However, the reaction at lower temperature (<65 °C) was so sluggish (entries 6 and 7). The results might imply that a Heck type reaction of **II** to form **5a** required relatively lower activation energy than the second EMD process of **II** to form **4a** (vide supra, Scheme 1). The use of $Cu(OAc)_2$ or $AgNO_3$ as an oxidant was not efficient (entries 8 and 9). The use of DMSO as a solvent was ineffective (entry 10). The reaction in the presence of $Pd(OAc)_2$ in CH_3CN was also ineffective (entry 11).[3]

As described above, it is interesting to note that a C5–C5′ and C6–C5′ linked uracil trimer **7a**[3,9] was isolated in some entries, albeit in low yield (see Fig. 1). The structure of **7a** could be easily deduced from its ^1H NMR spectrum by the presence of two singlets at δ = 7.12 and 7.63 ppm which correspond to the remaining H-6 protons of two uracil rings. The trimer **7a** could be formed either from

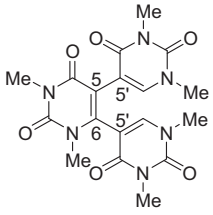


Scheme 1.

Table 2
Optimization of Pd-catalyzed homo-coupling of 1,3-dimethyluracil

Entry	Conditions	**1a** (%)[a]	**4a** (%)	**5a** (%)	**7a** (%)
1	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) PivOH (6.0 equiv), mesitylene (60 equiv), 110 °C, 20 h	10	52	20	—[b]
2	$Pd(TFA)_2$ (5 mol %), AgOAc (2.0 equiv) PivOH (20 equiv), O2 balloon, 120 °C, 14 h	9	54	18	—[b]
3	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) PivOH (60 equiv), 120 °C, 14 h	32	39	11	—[b]
4	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) mesitylene (60 equiv), 120 °C, 4 h	0	**52**	26	**18**
5	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) mesitylene (60 equiv), 80 °C, 16 h	0	38	**46**	14
6	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) mesitylene (60 equiv), 55 °C, 8 h	90	—[b]	—[b]	—[c]
7	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) mesitylene (60 equiv), 65 °C, 12 h	37	18	29	—[b]
8	$Pd(TFA)_2$ (5 mol %), Cu(OAc)2 (3.0 equiv) mesitylene (60 equiv), 120 °C, 14 h	75	—[b]	—[b]	—[c]
9	$Pd(TFA)_2$ (5 mol %), $AgNO_3$ (3.0 equiv) PivOH (60 equiv), 120 °C, 14 h	78	—[b]	—[b]	—[c]
10	$Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv) DMSO (60 equiv), 120 °C, 14 h	74	—[b]	—[b]	—[c]
11	$Pd(OAc)_2$ (10 mol %), AgOAc (3.0 equiv) CH_3CN, reflux, 12 h	52	—[b]	25	—[b]

[a] Recovered starting material.
[b] Trace amount (<5%).
[c] Not observed.



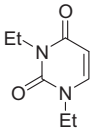
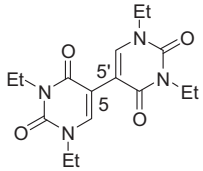
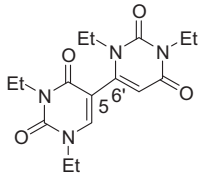
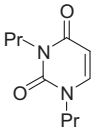
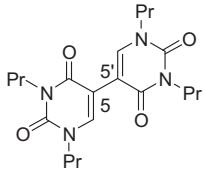
7a (C5-C5' and C6-C5' trimer)

Figure 1.

4a or **5a** by many possible routes, including the reaction between **4a** and **II** in a Heck manner or **5a** and **II** in an EMD process.

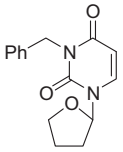
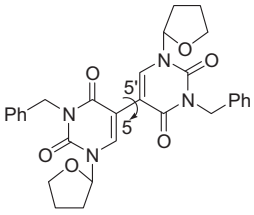
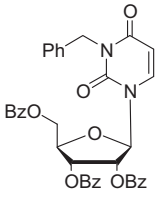
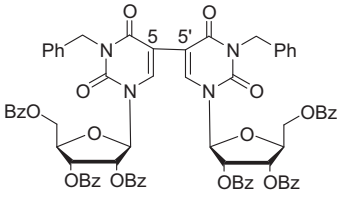
The reaction of 1,3-diethyluracil (**1b**) was examined under the conditions of entry 4 in Table 2, and the results are summarized in Table 3 (entry 1). As expected, a C5–C5′dimer **4b** was isolated in a good yield (67%) along with a low yield (10%) of C5–C6′ dimer **5b**.[9,11] We observed the formation of the corresponding trimer in a right position on TLC; however, we failed to isolate the component in pure state in appreciable amounts. As in the case of **1a**, we carried out the reaction of **1b** at low temperature (see entry 5 in Table 2). Although the yield of **5b** increased a little (up to 18%); however, the ratio of **4b**/**5b** was not reversed. The reaction of 1,3-dipropyluracil (**1c**) showed a similar result (entry 2). A C5–C5′ dimer **4c** was obtained as a major product in a good yield (72%). Although we observed the formation of a C5–C6′ dimer in a right position on TLC; however, we failed to isolate the component in appreciable amounts. The reaction of N^1-tetrahydrofuranyl derivative **1d** (entry 3) produced the corresponding C5–C5′ dimer **4d** in moderate yield (52%) along with the appreciable amounts of recovered **1d** (28%). It is interesting to note that the two H-6 protons of **4d** appeared as two singlets (1:1) at δ = 8.26 and 8.36 ppm in its ^{1}H NMR spectrum

Table 3
Synthesis of uracil dimers **4b**–**e** and **5b**[a]

Entry	Substrate	Product (%)
1	 **1b**	 **4b** (67%, C5-C5' dimer)  **5b** (10%, C5-C6' dimer) (80 °C, 24 h: **4b**, 60% and **5b**, 18%)
2	 **1c**	 **4c** (72%, C5-C5' dimer)

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate	Product (%)
3	 **1d**	 **4d** (52%, C5-C5′ dimer)
4[b]	 **1e**	 **4e** (43%, C5-C5′ dimer)

[a] Conditions: $Pd(TFA)_2$ (5 mol %), AgOAc (3.0 equiv), mesitylene (60 equiv), 120 °C, 4 h.
[b] Reaction time is 12 h.

in $CDCl_3$.[9] The observation revealed the existence of a pair of rotational isomers in a solution at room temperature presumably due to hindered rotation around the C5–C5′ single bond. When we took the ^1H NMR in DMSO-d_6, the two singlets were coalesced to a broad singlet which appeared at $\delta = 8.24$ ppm even at room temperature.[9] As a last entry, the reaction of N^3-benzyl-2′,3′,5′-tri-*O*-benzoyluridine (**1e**) afforded the corresponding C5–C5′ dimer **4e** in a reasonable yield (43%, entry 4). The compound **4e** appeared as a single isomer in its ^1H NMR spectrum (singlet of H-6 proton at $\delta = 8.42$ ppm). This implied that compound **4e** favors only one rotational isomer state presumably due to the presence of extremely bulky sugar moieties, as compared to **4d** that existed as two restricted rotational isomers.

However, the reactions of 1,3,5-trimethyluracil (**1f**) or 1,3,6-trimethyluracil (**1g**) failed completely. The only possible C6–C6′ coupling reaction of **1f** was not observed as in the case of 1,3-dimethylurcil. Actually, we expected the formation of a C5–C5′ coupling product in the reaction of **1g** via a double EMD and/or an EMD-Heck process; however, we did not observe the formation and the reason might be the steric hindrance between the two 6-methyl groups.

In summary, we examined a Pd (II)-catalyzed oxidative homocoupling reaction of 1,3-dimethyluracil and related derivatives. Based on the experimental results we proposed a mechanistic scenario in detail. Further studies on the synthesis of un-protected nucleoside dimers and the conformational characteristics are currently underway.

Acknowledgments

This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (2011-0002570). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

1. For the leading references on transition metal-containing drugs including Pt and Pd, see: (a) Klein, A. V.; Hambley, T. W. *Chem. Rev.* **2009**, *109*, 4911–4920; (b) Wheate, N. J.; Walker, S.; Craig, G. E.; Oun, R. *Dalton Trans.* **2010**, *39*, 8113–8127; (c) Ali, M. A.; Mirza, A. H.; Butcher, R. J.; Tarafder, M. T. H.; Keat, T. B.; Ali, A. M. *J. Inorg. Biochem.* **2002**, *92*, 141–148; (d) Castan, P.; Colacio-Rodriguez, E.; Beauchamp, A. L.; Cros, S.; Wimmer, S. *J. Inorg. Biochem.* **1990**, *38*, 225–239; (e) Padhye, S.; Afrasiabi, Z.; Sinn, E.; Fok, J.; Mehta, K.; Rath, N. *Inorg. Chem.* **2005**, *44*, 1154–1156; (f) Butour, J. L.; Wimmer, S.; Wimmer, F.; Castan, P. *Chem. Biol. Interact.* **1997**, *104*, 165–178.
2. Zamora, F.; Amo-Ochoa, P.; Fischer, B.; Schimanski, A.; Lippert, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 2274–2275.
3. Arai, I.; Hanna, R.; Daves, G. D., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 7684–7685.
4. For the leading references on nucleic acids dimers, see: (a) Sniady, A.; Sevilla, M. D.; Meneni, S.; Lis, T.; Szafert, S.; Khanduri, D.; Finke, J. M. Dembinski *Chem. Eur. J.* **2009**, *15*, 7569–7577. and further references cited therein; (b) Murata, S.; Mizumura, Y.; Hino, K.; Ueno, Y.; Ichikawa, S.; Matsuda, A. *J. Am. Chem. Soc.* **2007**, *129*, 10300–10301; (c) Semenov, V. E.; Galiullina, L. F.; Lodochnikova, O. A.; Kataeva, O. N.; Gubaidullin, A. T.; Chernova, A. V.; Efremov, Y. Y.; Latypov, S. K.; Reznik, V. S. *Eur. J. Org. Chem.* **2007**, 4578–4593; (d) Accetta, A.; Corradini, R.; Sforza, S.; Tedeschi, T.; Brognara, E.; Borgatti, M.; Gambari, R.; Marchelli, R. *J. Med. Chem.* **2009**, *52*, 87–94; (e) Semenov, V. E.; Akamsin, V. D.; Reznik, V. S.; Chernova, A. V.; Dorozhkina, G. M.; Efremov, Y. Y.; Nafikova, A. A. *Tetrahedron Lett.* **2002**, *43*, 9683–9686; (f) Kumar, S.; Malik, V.; Kaur, N.; Kaur, K. *Tetrahedron Lett.* **2006**, *47*, 8483–8487; (g) Das, S.; Thakur, A. J. *Eur. J. Org. Chem.* **2011**, 2301–2308; (h) Spacilova, L.; Dzubak, P.; Hajduch, M.; Krupkova, S.; Hradil, P.; Hlavac, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6647–6650; (i) Ono, T.; Yoshida, K.; Saotome, Y.; Sakabe, R.; Okamoto, I.; Ono, A. *Chem. Commun.* **2011**, *47*, 1542–1544; (j) Li, G.-R.; Liu, J.; Pan, Q.; Song, Z.-B.; Luo, F.-L.; Wang, S.-R.; Zhang, X.-L.; Zhou, X. *Chem. Biodiversity* **2009**, *6*, 2200–2208; (k) Nakane, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 1842–1851.
5. Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2011**, *52*, 6228–6233. and further references cited therein.
6. Unreported results.
7. For the synthesis of a C5–C5′ uracil dimer, see: (a) Park, B. R.; Kim, K. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2011**, *52*, 4405–4407; (b) Senga, K.; Ichiba, M.; Nishigaki, S. *J. Org. Chem.* **1978**, *43*, 1677–1683; (c) Kruger, O.; Wille, U. *Org. Lett.* **2001**, *3*, 1455–1458.
8. For the C5–C6′ uracil dimer, see: (a) Brown, D. J.; Strekowski, L. *Aust. J. Chem.* **1981**, *34*, 1157–1160; (b) Arai, I.; Lee, T. D.; Hanna, R.; Daves, G. D., Jr. *Organometallics* **1982**, *1*, 742–747.
9. *Typical procedure for the synthesis of **4a**, **5a** and **7a**:* A stirred mixture of 1,3-dimethyluracil (**1a**, 140 mg, 1.0 mmol), $Pd(TFA)_2$ (17 mg, 5 mol %), and AgOAc (501 mg, 3.0 mmol) in mesitylene (8.3 mL, 60 equiv) was heated to 120 °C for 4 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The solvent was removed and the residue was purified by column chromatography (hexanes/EA, 1:1) to afford **4a** (73 mg, 52%), **5a** (36 mg, 26%), and **7a** (25 mg, 18%) as white solids. Other compounds were prepared similarly, and the selected spectroscopic data of compounds **4a**,[2,3,7] **5a**,[3,8] **7a**,[3] **4b**, **5b**, and **4c–e** are as follows.
*Dimer **4a**:*[2,3,7] 52%; white solid, mp 278–279 °C (lit.[7b] 286 °C); IR (KBr) 1702, 1661, 1482, 1452, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.41 (s, 6H), 3.48 (s, 6H), 8.41 (s, 2H); ESIMS *m/z* 301 [M^++Na]. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.93; H, 5.12; N, 20.02.
*Dimer **5a**:*[3,8] 26%; white solid, mp 291–292 °C (lit.[3] 295 °C); IR (KBr) 1707, 1650, 1483, 1443, 1347 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.29 (s, 3H), 3.37 (s, 3H), 3.41 (s, 3H), 3.51 (s, 3H), 5.65 (s, 1H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.07, 28.38, 33.56, 37.58, 103.69, 108.28, 143.13, 147.59, 151.00, 152.13, 160.34, 162.31; ESIMS *m/z* 301 [M^++Na]. Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.56; H, 5.34; N, 19.94.
*Trimer **7a**:*[3] 18%; white solid, mp >290 °C (lit.[3] >350 °C); IR (KBr) 2956, 1701,

1647, 1452, 1349 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.29 (s, 3H), 3.33 (s, 3H), 3.35 (s, 3H), 3.36 (s, 3H), 3.39 (s, 3H), 3.40 (s, 3H), 7.12 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 28.33, 28.34, 28.66, 33.44, 37.29, 37.37, 105.77, 105.93, 108.06, 143.31, 144.22, 146.86, 150.93, 151.36, 151.60, 160.63, 162.32, 163.22; ESIMS *m/z* 439 [M^++Na]. Anal. Calcd for $C_{18}H_{20}N_6O_6$: C, 51.92; H, 4.84; N, 20.18. Found: C, 52.06; H, 4.71; N, 20.11.

Dimer ***4b****:* 67%; white solid, mp 174–176 °C; IR (KBr) 2975, 1690, 1639, 1445, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (t, *J* = 7.2 Hz, 6H), 1.37 (t, *J* = 7.2 Hz, 6H), 3.90 (q, *J* = 7.2 Hz, 4H), 4.07 (q, *J* = 7.2 Hz, 4H), 8.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.74, 14.04, 36.92, 45.27, 104.36, 141.99, 149.79, 162.18; ESIMS *m/z* 357 [M^++Na]. Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.76; H, 6.86; N, 16.49.

Dimer ***5b****:* 10%; pale yellow solid, mp 120–122 °C; IR (KBr) 2980, 1700, 1658, 1449, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 3.48 (br s, 1H), 3.89 (q, *J* = 7.2 Hz, 2H), 4.01 (br s, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 4.06 (q, *J* = 7.2 Hz, 2H), 5.61 (s, 1H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.70, 12.72, 14.24, 14.41, 36.53, 37.14, 42.11, 45.40, 104.65, 108.45, 141.97, 147.07, 150.17, 151.22, 160.19, 162.01; ESIMS *m/z* 357 [M^++Na]. Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.61; H, 6.67; N, 16.52.

Dimer ***4c****:* 72%; white solid, mp 154–155 °C; IR (KBr) 2961, 1687, 1649, 1446, 1350, 1240 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, *J* = 7.5 Hz, 6H), 0.98 (t, *J* = 7.5 Hz, 6H), 1.61–1.72 (m, 4H), 1.73–1.84 (m, 4H), 3.79 (t, *J* = 7.5 Hz, 4H), 3.96 (t, *J* = 7.5 Hz, 4H), 8.40 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.89, 11.31, 20.81, 22.41, 43.34, 51.72, 104.06, 142.44, 150.18, 162.34; ESIMS *m/z* 413 [M^++Na]. Anal. Calcd for $C_{20}H_{30}N_4O_4$: C, 61.52; H, 7.74; N, 14.35. Found: C, 61.39; H, 7.92; N, 14.21.

Dimer ***4d****:* 52%; white solid, mp 212–214 °C; IR (KBr) 2957, 1690, 1650, 1442, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.95–2.20 (m, 6H), 2.28–2.49 (m, 2H), 4.01 (dd, *J* = 14.7 and 7.5 Hz, 2H), 4.26–4.35 (m, 2H), 5.13 (d, *J* = 15.6 Hz, 2H), 5.18 (d, *J* = 15.6 Hz, 2H), 6.08–6.12 (m, 2H), 7.20–7.35 (m, 6H), 7.40–7.51 (m, 4H), 8.26 (s, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (23.74, 23.79), (32.97, 33.07), 44.46, (70.33, 70.38), (88.14, 88.23), (104.31, 104.33), 127.56, (128.36, 128.37), (128.91, 128.97), (136.66, 136.67), (137.58, 137.60), 149.82, (161.94, 161.97); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.84–2.20 (m, 6H), 2.25–2.48 (m, 2H), 3.85–4.05 (m, 2H), 4.10–4.30 (m, 2H), 5.07 (d, *J* = 16.2 Hz, 2H), 5.13 (d, *J* = 16.2 Hz, 2H), 6.01–6.18 (m, 2H), 7.18–7.49 (m, 10H), 8.24 (br s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (23.51, 23.53), (31.95, 31.98), 43.85, 69.67, (87.60, 87.62), (104.38, 104.47), 127.20, 127.64, 128.35, 136.94 (138.01, 138.03), 149.56, (161.31, 161.32); ESIMS *m/z* 565 [M^++Na]. Anal. Calcd for $C_{30}H_{30}N_4O_6$: C, 66.41; H, 5.57; N, 10.33. Found: C, 66.54; H, 5.72; N, 10.14.

Dimer ***4e****:* 43%; white solid, mp 174–176 °C; IR (KBr) 1730, 1659, 1447, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.60 (dd, *J* = 12.6 and 3.3 Hz, 2H), 4.73 (d, *J* = 13.8 Hz, 2H), 4.75–4.82 (m, 2H), 4.93 (d, *J* = 13.8 Hz, 2H), 4.90–4.98 (m, 2H), 5.87 (dd, *J* = 5.1 and 5.1 Hz, 2H), 5.98 (dd, *J* = 5.1 and 5.1 Hz, 2H), 6.39 (d, *J* = 5.1 Hz, 2H), 7.16–7.23 (m, 6H), 7.28–7.47 (m, 18H), 7.52–7.64 (m, 4H), 7.92–7.97 (m, 4H), 7.98–8.06 (m, 8H), 8.42 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.71, 63.96, 70.90, 74.60, 80.45, 88.64, 105.57, 127.64, 128.33, 128.37, 128.50, 128.59, 129.07, 129.27, 129.48, 129.81, 129.97, 133.38, 133.72, 133.81, 136.04, 136.92, 149.56, 160.88, 165.18, 165.26, 165.76 (two carbons were overlapped); HRMS (ESI$^+$) *m/z* Calcd for $C_{74}H_{59}N_4O_{18}$ [M^++H]: 1291.3825, Found: 1291.3839. Anal. Calcd for $C_{74}H_{58}N_4O_{18}$: C, 68.83; H, 4.53; N, 4.34. Found: C, 68.67; H, 4.71; N, 4.18.

10. For the transition metal-catalyzed oxidative coupling of heteroaromatic compounds and their proposed reaction mechanisms, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068–5083. and further references cited therein; (b) Li, Y.; Wang, W.-H.; Yang, S.-D.; Li, B.-J.; Feng, C.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 4553–4555; (c) Li, Y.; Jin, J.; Qian, W.; Bao, W. *Org. Biomol. Chem.* **2010**, *8*, 326–330; (d) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822–1824; (e) Li, Z.; Wang, Y.; Huang, Y.; Tang, C.; Xu, J.; Wu, X.; Yao, H. *Tetrahedron* **2011**, *67*, 5550–5555; (f) Liang, Z.; Zhao, J.; Zhang, Y. *J. Org. Chem.* **2010**, *75*, 170–177; (g) Xia, J.-B.; Wang, X.-Q.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 456–458; (h) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200–1203; (i) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052–17053; (j) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Somete, T.; Mori, A. *Tetrahedron Lett.* **2010**, *51*, 850–852; (k) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930–10933; (l) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074–5075.

11. One of the methylene (–CH_2–) moiety among the four ethyl groups of **5b** appeared in ^1H NMR as two broad singlets presumably due to a restricted rotation.[9]