

Pd-Mediated synthesis of 7*H*-benzo[3,4]azepino[1,2-*a*]indole-6-carboxylic acid derivatives from indole-containing Baylis–Hillman adducts

Hyun Seung Lee^a, Sung Hwan Kim^a, Taek Hyeon Kim^b, Jae Nyoung Kim^{a,*}

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

^b Department of Applied Chemistry and Center for Functional Nano Fine Chemicals, College of Engineering, Chonnam National University, Gwangju 500-757, Republic of Korea

Received 4 December 2007; revised 10 January 2008; accepted 11 January 2008

Available online 15 January 2008

Abstract

We synthesized novel tetracyclic fused indole derivatives via the intramolecular Heck reaction of indole-containing Baylis–Hillman adducts in good to moderate yields.

© 2008 Elsevier Ltd. All rights reserved.

Keywords: Baylis–Hillman adducts; Benzoazepino[1,2-*a*]indole; Heck reaction; Palladium

Due to the abundance of medium-sized heterocyclic compounds in many natural products, drugs, and preclinical leads, syntheses of these compounds by intramolecular Heck type reaction have received much attention.¹ Palladium-mediated direct aryl–aryl bond-forming protocols have also been studied extensively in this respect.² Among the approaches of aryl–aryl bond-forming reactions, the use of indole moiety as one of the aryl group received special interest due to the biological importance of indole moiety-containing heterocyclic compounds.^{1c,2a,b,3}

Although palladium-mediated synthesis of medium-sized heterocyclic compounds has been investigated,¹ studies involving the Baylis–Hillman adducts have not been reported much.^{4,5} Lamaty and co-workers reported the synthesis of benzazepines starting from the aza-Baylis–Hillman adducts.^{4a,b} Vasudevan and co-workers examined the cyclization of sulfonamide derivatives of Baylis–Hillman adducts and prepared seven-membered heterocyclic compounds.^{4c} Very recently, we reported the synthesis of pentacyclic benzoazepino[2,1-*a*]isoindole compounds via

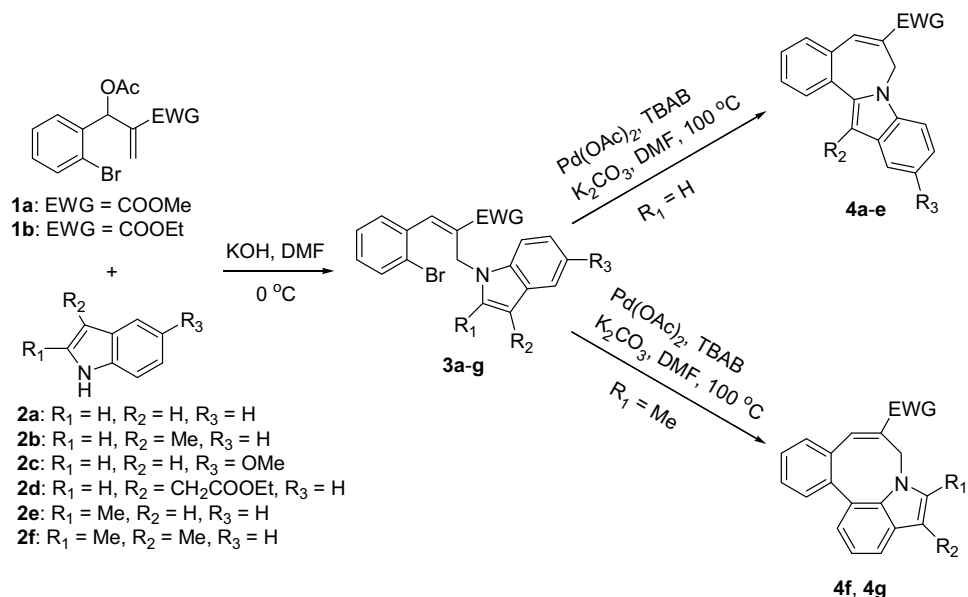
consecutive carbopalladation using enamides of Baylis–Hillman adducts.⁵

During the continuous studies we reasoned that indole-containing Baylis–Hillman adducts could be used efficiently for the synthesis of poly-fused heterocyclic compounds including benzo[3,4]azepino[1,2-*a*]indoles⁶ by applying intramolecular palladium-catalyzed arylation. Poly-fused heterocyclic compounds having indole moiety were known to possess many interesting biological activities^{6–8} including hepatitis C virus (HCV) NS5B polymerase inhibitory activity,⁶ thus we decided to examine the intramolecular Heck reaction with indole-containing Baylis–Hillman adducts as shown in Scheme 1.

Required starting materials **3a–g** were synthesized by the reaction of Baylis–Hillman acetates **1**^{4d} and indole derivatives **2** (KOH, DMF, 0 °C)⁹ in 45–95% yields. In all cases, *E*-forms of **3a–g** were formed as the majors and we separated them easily from the minor *Z*-isomers (5–10%).^{4,5} We examined the optimum reaction conditions for the intramolecular palladium-catalyzed arylation with compound **3a**, and the results are summarized in Table 1. Although all the conditions examined afforded desired product **4a** in variable yields (24–65%), the conditions

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.

E-mail address: kimjn@chonnam.ac.kr (J. N. Kim).



Scheme 1.

Table 1
Optimization of the reaction conditions for the synthesis of **4a**

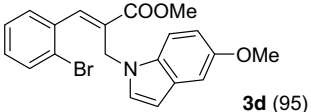
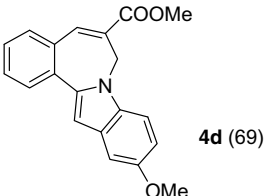
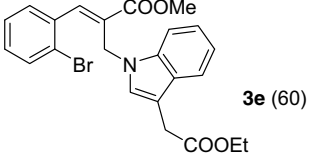
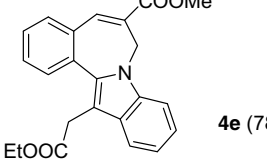
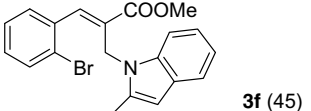
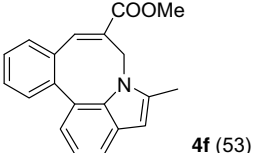
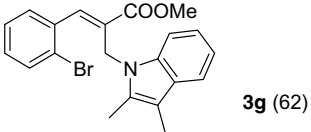
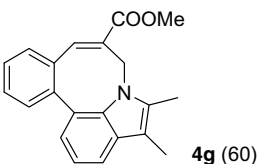
Entry	Conditions	Time (h)	4a ^a (%)	3a ^a (%)
1	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), K_2CO_3 (2.0 equiv), DMF, 100 °C	1	65	0
2	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), K_2CO_3 (2.0 equiv), DMF, 100 °C	1	61	0
3	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), KOAc (2.0 equiv), DMF, 100 °C	1	58	0
4	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN , reflux	1	54	8
5	$Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), $NaHCO_3$ (2.0 equiv), DMF, 100 °C	8	45	5
6	$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2.0 equiv), DMF, 100 °C	18	24	32

^a Isolated yield.

Table 2
Pd-mediated cyclizations of indole moiety-containing Baylis–Hillman adducts

Entry	Substrate ^a (%)	Time (min)	Product ^b (%)
1	 3a (73)	60	 4a (65)
2	 3b (50)	60	 4b (82)
3	 3c (51)	30	 4c (66)

Table 2 (continued)

Entry	Substrate ^a (%)	Time (min)	Product ^b (%)
4	 3d (95)	120	 4d (69)
5	 3e (60)	30	 4e (78)
6	 3f (45)	60	 4f (53)
7	 3g (62)	300	 4g (60)

^a Conditions: **1** (1.2 equiv), **2** (1.0 equiv), KOH (1.2 equiv), DMF, 0 °C, 30 min to 4 h. The stereochemistry of **3a–g** was confirmed as *E* by their chemical shifts of vinyl protons (δ = 7.83–7.98 ppm).

^b Conditions: **3** (1.0 equiv), Pd(OAc)₂ (10 mol %), TBAB (1.0 equiv), K₂CO₃ (2.0 equiv), DMF, 100 °C, 30 min to 5 h.

using Pd(OAc)₂/TBAB (tetrabutylammonium bromide)/K₂CO₃ in DMF (entry 1) was the best (65%). Under the optimized conditions we examined the reactions of **3b–g** and the results are summarized in Table 2.¹⁰ For the indole derivatives **3a–e**, the reactions produced seven-membered benzoazepino[1,2-*a*]indole derivatives **4a–e** in good yields (65–82%). However, 2-methyl group in compounds **3f** and **3g** rendered the formation of seven-membered ring impossible, and aryl–aryl bond-formation occurred to form the eight-membered compounds **4f** and **4g** in moderate yields (53–60%).¹⁰ The extreme selectivity between seven- and eight-membered ring-formation could be used for further elaboration of this strategy.

In summary, we synthesized tetracyclic indole derivatives via the palladium-mediated intramolecular Heck reaction from indole-containing Baylis–Hillman adducts.

Acknowledgments

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2006-311-C00384). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

- For the synthesis of medium-sized ring by Heck type cyclization, see: (a) Arnold, L. A.; Luo, W.; Guy, R. K. *Org. Lett.* **2004**, *6*, 3005–3007; (b) Gibson, S. E.; Guillo, N.; Tozer, M. J. *Chem. Commun.* **1997**, 637–638; (c) Avila-Zarraga, J. G.; Lujan-Montelongo, A.; Covarrubias-Zuniga, A.; Romero-Ortega, M. *Tetrahedron Lett.* **2006**, *47*, 7987–7989; (d) Soderberg, B. C. G.; Hubbard, J. W.; Rector, S. R.; O'Neil, S. N. *Tetrahedron* **2005**, *61*, 3637–3649; (e) Donets, P. A.; Van der Eycken, E. V. *Org. Lett.* **2007**, *9*, 3017–3020; (f) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835; (g) Joucla, L.; Popowycz, F.; Lozach, O.; Meijer, L.; Joseph, B. *Helv. Chim. Acta* **2007**, *90*, 753–763.
- For the examples of palladium-mediated intramolecular aryl–aryl couplings, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238 and further references cited therein; (b) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900; (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581–590; (d) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187; (e) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857–1860; (f) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578–7584; (g) Gomez-Lor, B.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 2993–2996; (h) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193.
- For the examples of Heck type cyclization involving indole moiety, see: (a) Routier, S.; Merour, J.-Y.; Dias, N.; Lansiaux, A.; Bailly, C.; Lozach, O.; Meijer, L. *J. Med. Chem.* **2006**, *49*, 789–799; (b) Putey, A.; Joucla, L.; Picot, L.; Besson, T.; Joseph, B. *Tetrahedron* **2007**, *63*, 867–879; (c) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, 32,

- 3317–3320; (d) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003–4018.
4. For the Pd-mediated reactions involving Baylis–Hillman adducts, see: (a) Ribiere, P.; Declerck, V.; Nedellec, Y.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *Tetrahedron* **2006**, *62*, 10456–10466; (b) Declerck, V.; Ribiere, P.; Nedellec, Y.; Allouchi, H.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2007**, 201–208; (c) Vasudevan, A.; Tseng, P.-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591–8593; (d) Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I.; Buffon, R. *Tetrahedron* **2006**, *62*, 4563–4572.
5. Gowrisankar, S.; Lee, H. S.; Lee, K. Y.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 8619–8622 and further references cited therein on the synthesis and biological activities of benzoazepino[2,1-*a*] isoindole moiety-containing compounds. For the general review on Baylis–Hillman reaction, please see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201–350; (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (d) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490 and further references cited therein.
6. (a) For the preparation of benzoazepino[1,2-*a*]indole derivatives as inhibitors of hepatitis C virus (HCV) replication, see: Hudyma, T. W.; Zheng, X.; He, F.; Ding, M.; Bergstrom, C. P.; Hewawasam, P.; Martin, S. W.; Gentles, R. G. WO 2007092000, 2007; *Chem. Abstr.* **2007**, *147*, 277782; (b) Meanwell, N. A.; Gentles, R. G.; Ding, M.; Bender, J. A.; Kadow, J. F.; Hewawasam, P.; Hudyma, T. W.; Zheng, X. U.S. Patent 2,007,184,024, 2007; *Chem. Abstr.* **2007**, *147*, 257667.
7. For the synthesis and biological importance of 1,7-annulated indole derivatives, see: (a) Al-awar, R. S.; Ray, J. E.; Hecker, K. A.; Huang, J.; Waid, P. P.; Shih, C.; Brooks, H. B.; Spencer, C. D.; Watkins, S. A.; Patel, B. R.; Stamm, N. B.; Ogg, C. A.; Schultz, R. M.; Considine, E. L.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Grutsch, J. L.; Joseph, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3217–3220; (b) Zhu, G.; Conner, S. E.; Zhou, X.; Chan, H.-K.; Shih, C.; Engler, T. A.; Al-awar, R. S.; Brooks, H. B.; Watkins, S. A.; Spencer, C. D.; Schultz, R. M.; Dempsey, J. A.; Considine, E. L.; Patel, B. R.; Ogg, C. A.; Vasudevan, V.; Lytle, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3057–3061; (c) Van Wijngaarden, I.; Hamminga, D.; van Hes, R.; Standaar, P. J.; Tipker, J.; Tulp, M. Th. M.; Mol, F.; Olivier, B.; de Jonge, A. *J. Med. Chem.* **1993**, *36*, 3693–3699; (d) Toscano, L.; Grisanti, G.; Fioriello, G.; Seghetti, E.; Bianchetti, A.; Bossoni, G.; Riva, M. *J. Med. Chem.* **1976**, *19*, 208–213.
8. For the synthesis and biological importance of tetracyclic indole derivatives, see: (a) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149 and further references cited therein; (b) Ikegashira, K.; Oka, T.; Hirashima, S.; Noji, S.; Yamanaka, H.; Hara, Y.; Adachi, T.; Tsuruha, J.-I.; Doi, S.; Hase, Y.; Noguchi, T.; Ando, I.; Ogura, N.; Ikeda, S.; Hashimoto, H. *J. Med. Chem.* **2006**, *49*, 6950–6953; (c) Faust, R.; Garratt, P. J.; Jones, R.; Yeh, L.-K.; Tsotinis, A.; Panoussopoulou, M.; Calogeropoulou, T.; Teh, M.-T.; Sugden, D. *J. Med. Chem.* **2000**, *43*, 1050–1061; (d) Rivara, S.; Mor, M.; Silva, C.; Zuliani, V.; Vacondio, F.; Spadoni, G.; Bedini, A.; Tarzia, G.; Lucini, V.; Pannacci, M.; Frascini, F.; Plazzi, P. V. *J. Med. Chem.* **2003**, *46*, 1429–1439.
9. (a) Bodwell, G. J.; Li, J. *Org. Lett.* **2002**, *4*, 127–130; (b) Caddick, S.; Shering, C. L.; Wadman, S. N. *Tetrahedron* **2000**, *56*, 465–473.
10. *Typical procedure for the synthesis of 3a and 4a*: To a stirred solution of indole (**2a**, 117 mg, 1.0 mmol) and KOH (79 mg, 1.2 mmol) in DMF (1.5 mL) was added a solution of Baylis–Hillman acetate **1a** (376 mg, 1.2 mmol) in DMF (0.5 mL) at 0 °C, and maintained at 0 °C for 4 h with stirring. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 10:1), we obtained **3a** (271 mg, 73%) as a white solid. A stirred mixture of **3a** (185 mg, 0.5 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), TBAB (161 mg, 0.5 mmol), and K₂CO₃ (138 mg, 1.0 mmol) in DMF (2 mL) was heated to 100 °C for 1 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 10:1), we obtained **4a** (95 mg, 65%) as a pale yellow solid. Other compounds **3b–g** and **4b–g** were synthesized similarly and the representative spectroscopic data of compounds **3a**, **4a**, and **4f** are as follows: Compound **3a**: 73%; white solid, mp 95–97 °C; IR (film) 1717, 1463, 1435, 1248 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.74 (s, 3H), 5.03 (s, 2H), 6.43 (d, *J* = 3.3 Hz, 1H), 6.99–7.30 (m, 7H), 7.56 (d, *J* = 6.9 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.98 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 42.26, 52.36, 101.54, 109.52, 119.36, 120.72, 121.41, 123.87, 127.47, 127.48, 128.50, 129.51, 130.14, 130.53, 133.10, 134.90, 136.04, 142.48, 166.81; ESIMS *m/z* 370.09 (M⁺+H). Compound **4a**: 65%; yellow solid, mp 142–144 °C; IR (film) 1705, 1457, 1242 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 3.84 (s, 3H), 4.97 (s, 2H), 6.74 (s, 1H), 7.08–7.13 (m, 1H), 7.20–7.28 (m, 1H), 7.35–7.48 (m, 3H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.86 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 39.19, 52.41, 101.23, 109.27, 119.78, 120.71, 122.00, 127.58, 128.16, 129.66, 129.98, 130.22, 131.82 (2C), 133.15, 136.33, 139.21, 142.71, 166.03; ESIMS *m/z* 290.19 (M⁺+H). Anal. Calcd for C₁₉H₁₅NO₂: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.67; H, 5.47; N, 4.76. Compound **4f**: 53%; white solid, mp 179–181 °C; IR (film) 1714, 1438, 1225 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.57 (d, *J* = 0.6 Hz, 3H), 3.73 (s, 3H), 4.82 (d, *J* = 14.1 Hz, 1H), 5.01 (d, *J* = 14.1 Hz, 1H), 6.21 (d, *J* = 0.6 Hz, 1H), 6.77 (dd, *J* = 7.2 and 0.6 Hz, 1H), 7.05–7.10 (m, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.35–7.52 (m, 4H), 8.10 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 12.65, 40.91, 52.03, 100.52, 119.47, 119.98, 125.76, 125.78, 126.74, 127.39, 129.47, 130.08, 131.65, 133.48, 134.62, 135.23, 137.72, 140.25, 145.46, 166.62; ESIMS *m/z* 304.18 (M⁺+H). Anal. Calcd for C₂₀H₁₇NO₂: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.05; H, 5.78; N, 4.53.