Tetrahedron Letters 50 (2009) 2589-2592

Contents lists available at ScienceDirect

Tetrahedron Letters

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



Pd-catalyzed intramolecular amidation of 2-(buta-1,3-dienyl)phenylcarbamoyl chloride: a concise synthesis of spiro[indoline-3,3'-pyrrolidine]

Haruhi Kamisaki^a, Yoshizumi Yasui^b, Yoshiji Takemoto^{a,*}

^a Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan ^b World Premier International Research Center, Advanced Institute for Materials Research, Tohoku University, Aoba, Sendai 980-8578, Japan

ARTICLE INFO

Article history: Received 16 February 2009 Revised 12 March 2009 Accepted 13 March 2009 Available online 18 March 2009

ABSTRACT

A palladium-catalyzed intramolecular amidation of arylcarbamic acid derivatives bearing 1,3-diene moiety with or without external nucleophiles is described. The tandem cycloamidation and nucleophilic allylic substitution are successfully applied to the construction of the spiro[indoline-3,3'-pyrrolidine] skeleton as well as contiguous stereogenic centers with an aim of synthesizing spirocyclic oxindole alkaloids.

© 2009 Elsevier Ltd. All rights reserved.

The 3,3-disubstituted oxindoles are important synthetic targets for organic chemists due to their frequent occurrence as substructures or synthetic intermediates of natural products and biologically active molecules (Fig. 1).¹ With an aim of total synthesis of elacomine², spirotriprostatine B³, and alstonisine⁴, various synthetic methods have been intensively studied. However, most of these studies focused on the efficient construction of the spiroskeleton bearing quaternary and tertiary chiral centers at the C3 and C2' positions, starting from indole and oxindole derivatives.⁵

Although concurrent construction of two stereocenters along with the formation of oxindole skeleton would be desirable from the viewpoints of synthetic efficiency and economy, such concise synthetic approaches are quite limited.^{6,7} The elegant one-step synthesis of the spiro[indoline-3,3'-pyrrolidine] skeleton has been achieved by Murphy⁶ and Overman⁷ by using Radical-mediated or Pd-catalyzed tandem cyclization and intramolecular trapping reaction. In this Letter, we describe alternative synthetic strategy for spiro[indoline-3,3'-pyrrolidine] derivative bearing the stereogenic centers at the C3 and C2' positions, via the Pd-catalyzed intramolecular amidation to the 1,3-diene moiety (Fig. 2).

We recently developed the Pd(0)-catalyzed intramolecular cyanoamidation of 2-(alkenyl)phenylcarbamoyl cyanide to give the 3,3-disubstituted oxindoles (Eq. 1 in Fig. 2).^{8a-d} However, the reaction was limited to terminal olefins.^{8a} Then we planned to apply this reaction to 1,3-dienyl compound **A** expecting that the transformation of the intermediate **B** into **C** (X = CN) might be accelerated (Eq. 2). Furthermore, if the reaction is carried out in the presence of an external nucleophile, 1,4-functionalized adduct **D** may be obtained regioselectively via the nucleophilic allylic substitution with the π -allyl palladium complex **B**.^{9,10} Similarly, the intramolecular trapping by an appropriate nucleophile (R³ = CH₂CH₂NHR⁴) provides the desired spirocyclic product **E** predominantly (Eq. 3).¹¹ To the best of our knowledge, this is the first report on the double functionalization of 1,3-dienes by the Pd(0)-catalyzed amidation of carbamic acid derivatives.

We initially examined the intramolecular amidation of several carbamic acid derivatives **1a**–**c** under the reported conditions (Table 1).^{8b} In contrast to 2-(2-butenyl)phenyl carbamoyl cyanide, the reaction of 2-(2,4-pentadienyl) derivative **1a** with Pd(PPh₃)₄ at 130 °C proceeded slowly to afford the 1,4-adduct **2a** in 24% yield along with the recovery of the starting material (entry 1). Furthermore, the corresponding 1,2-adduct was not observed, but the unexpected cyclopropyl adduct **2a**'¹² was obtained in 13% yield. Further examination of the palladium source or the phosphine ligand did not improve the chemical yield of **2a** (entries 2 and 3). Although carbamoyl chloride **1b**^{8f,13} provided no cyclized product **2b**, the same treatment of carbamoyl sulfide **1c**¹⁴ furnished the corresponding 1,4-adduct **2c** in good yield (entries 4 and 5).

To extend this cycloamidation to the synthesis of various oxindole derivatives, we next turned our attention to the intermolecular trapping of the π -allylpalladium intermediate by external nucleophiles (Table 2). The Pd(0)-catalyzed reaction of **1a–c** was carried out in the presence of HCO₂NH₄ (3 equiv) as a hydride



Figure 1. 3,3'-Pyrrolidinyl-spirooxindole-type natural products.

^{*} Corresponding author. Tel.: +81 75 753 4528; fax: +81 75 753 4569. *E-mail address:* takemoto@pharm.kyoto-u.ac.jp (Y. Takemoto).

^{0040-4039/\$ -} see front matter @ 2009 Elsevier Ltd. All rights reserved. doi:10.1016/j.tetlet.2009.03.100



Figure 2. Synthetic strategy for constructing the contiguous stereogenic centers of spirocyclic compounds.

Table 1 The Pd-catalyzed intramolecular amidation of dienes 1a-c



1	CN	$Pd(PPh_3)_4$ (10)	19	24 (13) ^a	29
2	CN	$Pd(dba)_2 (2)/t-Bu_3P (4)$	24	5	33
3	CN	Pd(dba) ₂ (2)/Me ₃ P (4)	24	0	89
4 ^b	Cl	$Pd(PPh_{3})_{4}$ (10)	24	0	81
5	SPh	Pd(PPh ₃) ₄ (10)	17	67	0

^a 13% of **2a**' was obtained.

^b 2 equiv of *n*-Bu₃N was used as an additive.

source. In all cases, the desired reductive product **3** was obtained in low to moderate yields with no contamination of 1,4-adducts **2a** and **2c** (entries 1–3). Further optimization of the reaction conditions revealed that the reaction of chlorocarbamate **1b** with $[Pd(\pi-allyl)Cl]_2/PPh_3$ in xylene at 100 °C gave the best results to afford 1,2-adduct **3** in 89% yield (entries 4–6).¹⁵ In contrast to these results, we discovered that the regioisomeric 1,4-adduct **4** was

Table 2

The Pd-catalyzed hydroamidation of dienes 1a-c

exclusively obtained by the treatment of **1b** with $Pd(OAc)_2/PPh_3$ in the presence of 5 equiv of BnOH (entry 7). Thus, we succeeded in the regioselective hydride reduction of the π -allylpalladium complex by switching the reducing agents.

Having established the reductive cycloamidation of **1b**, we next examined several external nucleophiles such as sulfonamide and phenol to introduce the functional group at C1' or C3' position. All reactions were carried out with the catalytic system composed of Pd(OAc)₂ and PPh₃ (Table 3). Treatment of **1b** with *p*-NsNH₂ in the presence of *n*-Bu₃N or BSA did not provide the desired product **5a** at all. However, when Cs₂CO₃ was used as a base, the 1,4-adduct 5a was obtained in 51% yield along with a 29% yield of the dialkylated product (entries 1-3). As expected, none of the 1,2-adducts was observed. In contrast to p-NsNH₂, both p-TsNH₂ and TfNH₂ were introduced regioselectively, giving the monoalkylated products **5b** and **5c** as the single products (entries 4 and 5). Furthermore, indole could be used as a nitrogen-nucleophile for the synthesis of 5d, while the reactions of 1b with morpholine and aniline afforded no cyclized products, leading to the exclusive production of the corresponding ureas which were obtained by the direct addition of the nucleophiles to carbamoyl chloride (entry 6). Similarly, less nucleophilic compounds such as phenol and benzoic acid also attacked the terminal carbon of the π -allylpalladium complex to give the corresponding ether 5e and ester 5f in good yields (entries 7 and 8). In addition, the arylated and alkenylated adducts were also synthesized in reasonable yields by the reaction



Entry	1 X	'Pd' reductant (equiv)	Temp (°C)	Time (h)	Product yield (%)
1	CN	$Pd(PPh_3)_4 HCO_2NH_4 (3)$	130	19	3 23 (49) ^a
2	Cl	$Pd(PPh_3)_4 HCO_2NH_4(3)$	130	6	3 42 (15) ^a
3	SPh	$Pd(PPh_3)_4$ (10) HCO_2NH_4 (3)	130	23	3 17 (65) ^a
4	Cl	$Pd(OAc)_2/Ph_3P^b HCO_2NH_4 (3)$	130	0.5	3 21
5	Cl	$Pd(OAc)_2/Ph_3P^b HCO_2NH_4 (3)$	100	19	3 58 (20) ^a
6	Cl	$[Pd(\pi-allyl)Cl]_2/Ph_3P^b HCO_2NH_4 (3)$	100	8	3 89
7	Cl	$Pd(OAc)_2/Ph_3P^b$ Cs ₂ CO ₃ , BnOH (5)	130	0.5	4 97

^a The values in parentheses are yields of the recovered starting material.

^b 20 mol % of PPh₃ was used.

Table 3

The Pd(0)-catalyzed cycloamidation of $\mathbf{1b}$ accompanied by the intermolecular allylic substitution



Entry	Nu-H, base (equiv)	Time (h)	Product yield (%)
1	$p-N_{s}NH_{2}$ (2), $n-Bu_{3}N$ (2)	20	5a 0 (36) ^a
2	p-NsNH ₂ (2), BSA (2)	21	5a 0 (59) ^a
3	p-NsNH ₂ (2), Cs ₂ CO ₃ (1.2)	2	5a 51 ^b
4	p-TsNH ₂ (2), Cs ₂ CO ₃ (1.2)	0.5	5b 73
5	TfNH ₂ (2), Cs ₂ CO ₃ (1.2)	3	5c 94
6	Indol (2), Cs ₂ CO ₃ (1.2)	8	5d 62
7	Phenol (2), Cs ₂ CO ₃ (1.2)	0.5	5e 81 ^c
8	Benzoic acid (2), Cs_2CO_3 (1.2)	0.5	5f 74
9	PhB(OH) ₂ (2), Cs ₂ CO ₃ (1.2)	0.5	5g 58
10	$PhCH = CHB(OH)_2$ (2), Cs_2CO_3 (1.2)	24	5h >37

^a The values in parentheses are yields of the recovered starting material.

^b 29% of double alkylation product was obtained.

^c 10% of carbamate was obtained.

of **1b** with the corresponding organoboronic acids under the same reaction conditions (entries 9 and 10).¹⁶

The plausible reaction mechanism is shown in Scheme 1. Similar to the intramolecular cyanoamidation of the alkenyl cyanoformamide, the cleavage of the C-Cl bond of the carbamoyl chloride **1b** initially took place via the oxidative addition with the Pd(0) catalyst to generate the intermediate F. The subsequent insertion of the diene moiety to the resulting C–Pd bond provides the π -allylpalladium complex G efficiently. When HCO₂NH₄ is used as a nucleophile, the intramolecular hydride shift occurs regioselectively via **H** to furnish the 1,2-addition product **3** exclusively.¹⁵ However, it is not yet clear why 1,4-adduct 4 was produced in the presence of BnOH and Cs₂CO₃. We presumed that the corresponding π -allylpalladium complex (X = H in **G**), generated from **G** by the hydride reduction, might be a promising precursor of **4** similar to the cases of **5g** and **5h** in Table 3 (X = Ph and Styryl in **G**). On the other hand, the 1,4-adducts **5a-f** would be obtained from the same complex \mathbf{G} by the backside attack of the soft nucleophiles.

Finally, we explored the synthesis of spiro[indoline-3,3'-pyrrolidine] derivative using the tandem Pd(0)-catalyzed cycloamidation and the intramolecular nucleophilic addition (Scheme 2). The carbamoyl chloride **11** was prepared from 2-iodoaniline derivative **7** and trimethylstannyl-1,3-hexadiene **8**¹⁷ in six steps. We chose



Scheme 1. Plausible reaction mechanism.



Scheme 2. Application of the tandem cycloamidation.

the Tf group as a protecting group of the amine. Expectedly, the treatment of **11** with 10 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 in the presence of Cs_2CO_3 (1.2 equiv) at 130 °C gave rise to the desired spirocyclic products **12** in 71% yield as a 63:37 mixture of two diastereomers. The relative configuration of these compounds was determined by the NOE study. It was revealed that the major product of **12** possessed the same configuration as spirotriprostatines.

In this Letter, we demonstrated that the cycloamidation reaction of the carbamoyl chlorides could be applied to 1,3-dienyl compounds as well as alkenes, and the subsequent intermolecular trapping of the resultant π -allylpalladium complex with various external nucleophiles proceeded regioselectively depending on the nucleophiles employed. Furthermore, the synthesis of spiro[indoline-3,3'-pyrrolidine] derivative was achieved from 2-(buta-1,3-dienyl)phenylcarbamoyl chloride **11** bearing triflic amide.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research (B) (Y.T.) and for Young Scientists (Start-up) (Y.Y.), and 'Targeted Proteins Research Program' from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and notes

- For a review, see: (a) Galliford, C. V.; Sheidt, K. A. Angew. Chem., Int. Ed. 2007, 46, 8748; For recent examples, see: (b) Kolackowski, M.; Nowak, M.; Pawlowski, M.; Bojarski, A. J. J. Med. Chem. 2006, 49, 6732; (c) Kato, H.; Yoshida, T.; Tokue, T.; Nojiri, Y.; Hirota, H.; Ohta, T.; Williams, R. M.; Tsukamoto, S. Angew. Chem., Int. Ed. 2007, 46, 2254; (d) Uddin, M. K.; Reignier, S. G.; Coulter, T.; Montalbetti, C.; Gränäs, C.; Butcher, S.; Krog-Jensen, C.; Felding, J. Bioorg. Med. Chem. Lett. 2007, 17, 2854; (e) Stevens, F. C.; Bloomquist, W. E.; Borel, A. G.; Cohen, M. L.; Droste, C. A.; Heiman, M. L.; Kriauciunas, A.; Shall, D. J.; Tinsley, F. C.; Jesudason, C. D. Bioorg. Med. Chem. Lett. 2007, 17, 6270.
- Syntheses: (a) Pellegrim, C.; eber, M.; Borschberg, H.-J. Helv. Chim. Acta. 1996, 79, 151; (b) Miyake, F. Y.; Yakushijin, K.; Home, D. A. Org. Lett. 2004, 6, 711.
- Isolation: (a) Cui, C. B.; Kakeya, H.; Osada, H. J. Antibiot. 1996, 49, 832; (b) Cui, C. B.; Kakeya, H.; Osada, H. *Tetrahedron* 1996, 52, 12651; Syntheses: (c) Trost, B. M.; Stiles, D. T. Org. Lett. 2007, 9, 2763, and references sited therein.
- Isolation (a) Elderfield, R. C.; Gilman, R. E. Phytochemistry 1972, 11, 339; (b) Ghedira, K.; Hanrot, M. Z.; Richard, B.; Massiot, G.; Oliver, L. L. M.; Sevener, T.; Goh, S. H. Phytochemistry 1988, 27, 3955; (c) Wong, W. H.; Lim, P. B.; Chuah, C. H. Phytochemistry 1996, 41, 313; Biomimetic transformations: (d) Garnick, R. L.; LeQuensne, P. W. J. Am. Chem. Soc. 1978, 100, 4213; Syntheses (e) Yang, J.; Wearing, X. Z.; Quesne, P. W. L.; Deschamps, J. R.; Cook, J. M. J. Nat. Prod. 2008,

71, 1431; (f) Wearing, X. Z.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4237, and references sited therein.

- For a review, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209; Recent example, see: (b) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006**, *8*, 2027. and Refs. 3(c), 4(f).
- 6. Lizos, D.; Tripoli, R.; Murphy, J. A. Chem. Commun. 2001, 2732.
- Synthesis of spirotriprostatin: (a) Overman, L. E.; Rosen, M. D. Angew. Chem., Int. Ed. 2000, 39, 4596; Synthesis of gelsemines: (b) Earley, W. G.; Oh, T.; Overman, L. E. Tetrahedron Lett. 1988, 29, 3785; (c) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. Angew. Chem., Int. Ed. 1999, 38, 2934; (d) Beyersbergen van Henegouwen, W. G. B.; Fieseler, R. M.; Rutjes, F.; Hiemstra, H. Angew. Chem., Int. Ed. 1999, 38, 2214; (e) Beyersbergen van Henegouwen, W. G. B.; Fieseler, R. M.; Rutjes, F.; Hiemstra, H. J. Org. Chem. 2000, 65, 8317.
- For a review, see: (a) Yasui, Y.; Takemoto, Y. Chem. Rec. 2008, 8, 386; Pd-catalyzed cyanoamidation: (b) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. Org. Lett. 2006, 8, 2711; (c) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. Tetrahedron 2007, 63, 2978; (d) Yasui, Y.; Kamisaki, H.; Takemoto, Y. Org. Lett. 2008, 10, 3303; Rh-catalyzed Intramolecular hydroamidation of alkynes: (e) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. Tetrahedron Lett. 2005, 46, 7549; Pd-catalyzed Heck-type reaction of chloroformamides: (f) Yasui, Y.; Takeda, H.; Takemoto, Y. Chem. Pharm. Bull. 2008, 56, 1567.
- (a) Heck, R. F. J. Am. Chem. Soc. 1963, 85, 3381; (b) Robinson, S. D.; Shaw, B. L. J. Chem. Soc. 1963, 4806; (c) Rowe, R. M.; White, D. A. J. Chem. Soc. 1967, 1451.
- For a review, see: (a) Andersson, P. G.; Backvall, J.-E. In Handbook of Organopalladium Chemsitry for Organic Synthesis; Negishi, E., Ed.; John Wiley & Sons, 2002; pp 1859-1874; (b) Vackvall, J.-E. In Metal-catalyzed Crosscoupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 339-385; (c) Balme, G.; Bossharth, E.; Monterio, N. Eur. J. Org. Chem. 2003, 4101.
- Addition of *N*-nucleophles to conjugated dienes catalyzed by palladium(0), see:

 (a) Patel, B. A.; Dickerson, J. E.; Heck, R. F. J. Org. Chem. **1978**, 43, 5018;
 (b) Stakem, F. G.; Heck, R. F. J. Org. Chem. **1980**, 45, 3584;
 (c) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E. J. Org. Chem. **1983**, 48, 807;
 (d) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. J. Org. Chem. **1983**, 48, 3894;
 (e) Mitsudo, T.; Fischetti, W.; Heck, R. F. J. Org. Chem. **1984**, 49, 1640;

(f) Larock, R. C.; Berrios-Pena, N.; Narayanan, K. J. Org. Chem. **1990**, 55, 3447; (g) Back, T. G.; Bethell, R. J. Tetrahedron Lett. **1998**, 39, 5463; (h) Flubacher, D.; Helmchen, G. Tetrahedron Lett. **1999**, 40, 3867; (i) Xie, X.; Lu, X. Tetrahedron Lett. **1999**, 40, 8415.

- 12. Currently, the mechanism of the generation of **2a**' is not clear.
- 13. Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. J. Org. Chem. 2007, 72, 5898.
- 14. For a review, see: (a) Kuniyasu, H.; Kambe, N. Chem. Lett. 2006, 35, 1320; Recently, various acylation reactions of unsaturated bonds were investigated, see: thioacylation, (b) Minami, Y.; Kuniyasu, H.; Kambe, N. Org. Lett. 2008, 10, 2469; (c) Kuniyasu, H.; Kato, T.; Asano, S.; Ye, J.-H.; Ohmori, T.; Morita, M.; Hiraike, H.; Fujiwara, S.; Terao, J.; Kurosawa, H.; Kambe, N. Tertahedron Lett. 2006, 47, 1141; Selenoacylation: (d) Toyofuku, M.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. J. Am. Chem. Soc. 2005, 127, 9706; (e) Toyofuku, M.; Murase, E.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. Org. Lett. 2008, 10, 3957; Recently, interesting vinylchalcogenation was investigated, see: (f) Toyofuku, M.; Fujiwara, S.; Shin-ike, T.; Kuniyasu, H.; Kambe, N. J. Am. Chem. Soc. 2008, 130, 10504; Cyanocarbonylation: (g) Nozaki, K.; Sato, N.; Takaya, H. J. Org. Chem. 1994, 59, 2679; (h) Nozaki, K.; Sato, N.; Takaya, H. Bull. Chem. Soc. Jpn. 1996, 69, 1629; (i) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. Org. Lett. 2005, 7, 2639; (j) Nishihara, Y.; Inoue, Y.; Izawa, S.; Miyasaka, M.; Tanemura, K.; Nakajima, K.; Takagi, K. Tetrahedron 2006, 62, 9872; (k) Nakao, Y.; Hirata, Y.; Hiyama, T. J. Am. Chem. Soc. 2006, 128, 7420. and our examples, see ref.8.
- (a) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. J. Org. Chem. 1992, 57, 1326; Hydrogenation of π-allyl Pd complexes, see: (b) Tsuji, M.; Mandai, T. Synthesis 1996, 1; Pd(II)-catalyzed oxidation of alcohols, see: (c) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. J. Org. Chem. 1999, 64, 6750; Pd(0)-catalyzed allylic reduction with polymethylhydrosiloxane (PMHS), see: (d) Greenspoon, N.; Keinan, E. J. Org. Chem. 1988, 53, 3723; (e) Keinan, E.; Greenspoon, N. J. Org. Chem. 1983, 48, 3545.
- Pd-catalyzed cyclization of carbamoyl chlorides via anion capture processes using organostannanes and organoboranes, see: Anwar, J.; Fielding, M. R.; Grigg, R.; Sridharan, V.; Urch, C. J. J. Organomet. Chem. 2006, 691, 1476.
- Synthesis of (Z)-6-tert-butyldimethylsilyloxy-4-trimethylstannyl-1,3-hexadiene, see: Piers, E.; Tillyer, R. D. Can. J. Chem. 1996, 74, 2048.