HETEROCYCLES, Vol. 84, No. 1, 2012, pp. 323 - 326. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 10th June, 2011, Accepted, 1st August, 2011, Published online, 10th August, 2011
DOI: 10.3987/COM-11-S(P)34

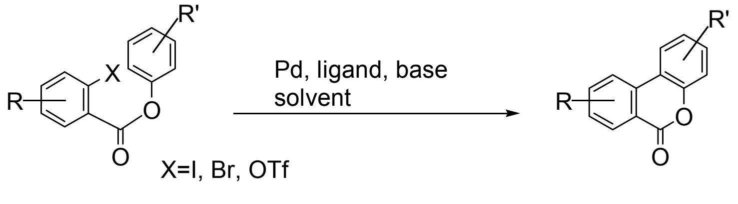
HIGHLY REGIOSELECTIVE INTRAMOLECULAR BIARYL COUPLING REACTION OF A PHENYL BENZOATE DERIVATIVE FOR THE SYNTHESIS OF GRAPHISLACTONE G

Hitoshi Abe,[a]* Takuya Matsukihira,[a] Tomoko Fukumoto,[b]
Yoshikazu Horino,[a] Yasuo Takeuchi,[b]* and Takashi Harayama[b]

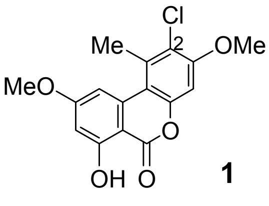
a) Graduate School of Science and Engineering, University of Toyama, Gofuku, Toyama 930-8555, Japan b) Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama University, Okayama 700-8530, Japan
abeh@eng.u-toyama.ac.jp; take@pharm.okayama-u.ac.jp

Abstract – The 6*H*-dibenzo[*b,d*]pyran-6-one type natural product graphislactone G was synthesized using a palladium-mediated aryl-aryl coupling reaction of the phenyl benzoate derivative. The regioselectivity in the coupling step was also investigated.

A palladium-catalyzed intramolecular aryl-aryl coupling reaction is a useful technique for preparing heterocyclic compounds.[1] For example, phenyl benzoates are good precursors for constructing a 6*H*-dibenzo[*b*,*d*]pyran-6-one ring system (Scheme 1).[2] Using this strategy, we synthesized several natural products possessing a 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton,[3] such as graphislactones A-D[4] and H,[5] and alternariol.[6, 7]



Scheme 1. Intramolecular biaryl coupling reaction of phenyl benzoate

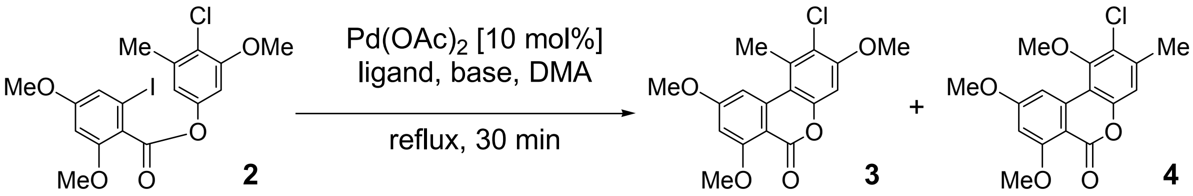


1

Recently, the total synthesis of graphislactone G (**1**), which is a phenolic constituent isolated from *Cepharosporium acremonium* IFB-E007 in 2005,[8] was reported by Cudaj and Podlech.[9] Structually, compound **1** possesses a highly functionalized 6*H*-dibenzo[*b*,*d*]pyran-6-one ring system and has a chlorine atom at the 2-position. Biologically, **1** is cytotoxic to the SW1116 cell line.[8] In the Podlech's synthesis, they employed the Suzuki-Miyaura coupling reaction as the key step.[9]

In this study, we planned the synthesis of **1**, using the intramolecular aryl-aryl coupling reaction of a phenyl benzoate derivative. Initially, we prepared the ester (**2**) by simple condensation between the corresponding phenol and benzoic acid derivative as a precursor for the intramolecular biaryl coupling reaction. Several reaction conditions were examined for the palladium-mediated biaryl coupling of **2** in order to construct the 6*H*-dibenzo[*b*,*d*]pyran-6-one skeleton (Table 1).

Table 1. Reactivity and regioselectivity in the palladium-mediated biaryl coupling



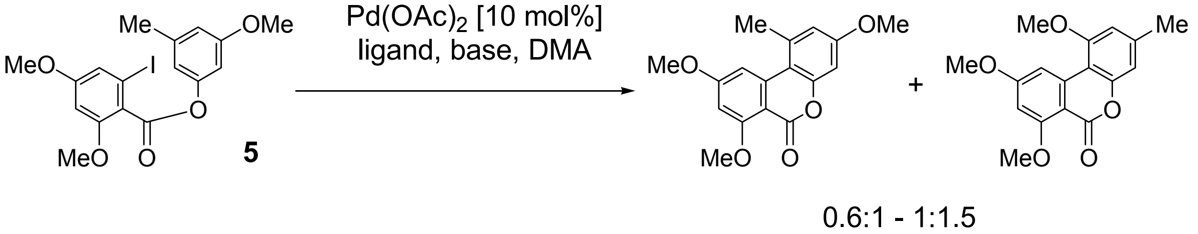
Run	Ligand [mol%]	Base	Yield (%) $3 + 4$	Ratio[a)] $3 : 4$
1	P(*o*-tolyl)$_3$ [20]	K_2CO_3	63	>20 : 1
2	PPh_3 [20]	K_2CO_3	68	11 : 1
3	^{n}Bu$_3$P [20]	K_2CO_3	57	7.7 : 1
4	DPPP [10], ^{n}Bu$_3$P [10]	Ag_2CO_3	80	1.4 : 1

a) Determined by NMR analysis

In each case, the coupling reaction proceeded smoothly, producing the lactone compounds **3** and **4** in moderate to good yield. The product ratio of **3** and **4** changed dramatically with the reaction conditions. When P(*o*-tolyl)$_3$ was used as the ligand, extremely high regioselectivity was observed (run 1), generating the product **3**, which was reacted at the position *ortho* to the methyl group. By contrast, the DPPP-^{n}Bu$_3$P combination system[10] was not effective for regioselectivity (run 4).

These results are very different from our previous report on the synthesis of alternariol, in which the similar coupling reaction of **5** proceeded with the regioselectivity of 0.6:1 to 1.5:1 ratio (Scheme 2).[6] This difference of selectivity indicates that the chlorine atom on the phenoxy group exhibits a powerful directing property in the coupling reaction. The mechanistic aspect of this selectivity is being studied intensively in our laboratory.

Using the major cyclized product **3**, selective demethylation was achieved with Node's protocol ($AlCl_3$-NaI/MeCN-CH_2Cl_2, 0 °C to rt, 84%),[11] to complete the synthesis of graphislactone G (**1**). The ^{1}H- and ^{13}C-NMR data of the product were identical to those reported by Podlech *et al.*[9]



Scheme 2. Intramolecular biaryl coupling reaction of **5**

ACKNOWLEDGEMENTS

A part of this research was financially supported by the Japan Society for the Promotion of Science to H. A. (22590003). The authors thank the SC-NMR Laboratory of Okayama University for the NMR experiments.

REFERENCES AND NOTES

1. a) For a recent review, see: M. Livendahl and A. M. Echavarren, *Isr. J. Chem.*, 2010, **50**, 630; b) D. Alberico, M. E. Scott, and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359.
2. a) For a pioneering work on the synthesis of 6*H*-dibenzo[*b,d*]pyran-6-one, see: B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, V. Snieckus, and P. D. Josephy, *J. Org. Chem.*, 1991, **56**, 3763; b) C.-L. Sun, J. Liu, Y. Wang, X. Zhou, B.-J. Li, and Z.-J. Shi, *Synlett*, 2011, 883 and references cited therein.
3. a) K. Shioe, Y. Sahara, Y. Horino, T. Harayama, Y. Takeuchi, and H. Abe, *Tetrahedron*, 2011, **67**, 1960; b) K. Shioe, Y. Takeuchi, T. Harayama, and H. Abe, *Chem. Pharm. Bull.*, 2010, **58**, 435; c) H. Abe, M. Arai, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2009, **77**, 1409; d) H. Abe, M. Arai, K. Nishioka, T. Kida, K. Shioe, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2008, **76**, 291; e) H. Abe and T. Harayama, *Heterocycles*, 2008, **75**, 1305; f) H. Abe, Y. Sahara, Y. Matsuzaki, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2008, **49**, 605; g) S. Takeda, H. Abe, Y. Takeuchi, and T. Harayama, *Tetrahedron*, 2007, **63**, 396; h) H. Abe, S Takeda, T. Fujita, K. Nishioka, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2004, **45**, 2327.
4. H. Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2005, **46**, 3197.
5. H. Abe, T. Fukumoto, Y. Horino, T. Harayama, and Y. Takeuchi, *Heterocycles*, 2010, **82**, 851.
6. H. Abe, T. Fukumoto, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2007, **74**, 265.
7. Podlech and co-workers have reported the synthesis of graphislactones and alternariol using

Suzuki-Miyaura coupling: a) M. Altemöller, T. Gehring, J. Cudaj, J. Podlech, H. Goesmann, C. Feldmann, and A. Rothenberger, *Eur. J. Org. Chem.*, 2009, 2130; b) K. Koch, J. Podlech, E. Pfeiffer, and M. Metzler, *J. Org. Chem.*, 2005, **70**, 3275.

8. H.-W. Zhang, W.-Y. Huang, Y.-C. Song, J.-R. Chen, and R.-X. Tan, *Helv. Chim. Acta*, 2005, **88**, 2861.
9. J. Cudaj and J. Podlech, *Tetrahedron Lett.*, 2010, **51**, 3092.
10. a) T. Harayama, T. Akiyama, Y. Nakano, H. Nishioka, H. Abe, and Y. Takeuchi, *Chem. Pharm. Bull.*, 2002, **50**, 519; b) T. Harayama, T. Akiyama, and Y. Nakano, *Chem. Pharm. Bull.*, 1997, **45**, 1723.
11. M. Node, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, *Bull. Inst. Chem. Res., Kyoto Univ.*, 1992, **70**, 308.