Expedient Syntheses of Unsymmetrical 4-Bromo-2-carboxyl-biaryls *via* Diels-Alder Cycloadditions of 3,5-Dibromo-2-pyrone with Vinyl Arenes, Followed by One Pot, Three Step Aromatization Reactions

Soo-Hyun Min, Yong-Woo Kim, Sunju Choi,† Kyung Bae Park,† and Cheon-Gyu Cho*

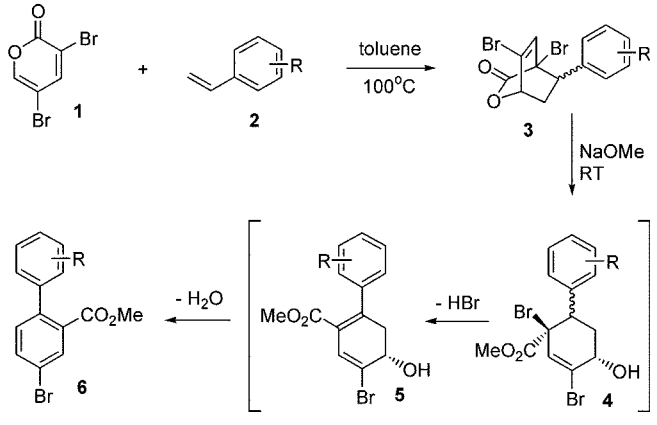
Department of Chemistry, Hanyang University, Seoul 133-791, Korea
†Radioisotope & Radiation Application Team, HANARO Center, KAERI, Daejeon 305-353, Korea
Received May 7, 2002

Keywords : Biaryls, Diels-Alder cycloaddition, 3,5-Dibromo-2-pyrone.

Biaryls are important structural cores, present in a number of naturally occurring compounds,[1] with a variety of applications in the areas of material and medicinal chemistry. As synthetic building blocks, they have been used for the production of liquid crystalline polymers, engineering plastics and polyester type fibres.[2] Also appeared in many therapeutic drugs, they play important roles in modulation of bindings with enzymes and receptors, due to their peculiar lipophilicity.[3]

Many efforts have been devoted in the synthesis of the structurally diverse biaryls for the aforementioned purposes.[1] They are prepared either from parent biaryls through relevant electrophilic aromatic substitutions or more commonly from aryl halides *via* various transition metal catalyzed coupling reactions. Although quite effective mostly, coupling approach has an intrinsic limitation; not tolerating presence of additional halogen atoms, in particular. We have recently found that 3,5-dibromo-2-pyrone undergo Diels-Alder cycloadditions with styrene derivatives to give rise to the corresponding bicyclolactones,[5] which can be readily manipulated into various 4-bromo-3-carboxyl-biaryls upon treatment with a base. Herein, we report its scope and limitation as an alternative to the conventional methods for the efficient synthesis of various functionaly distinct biaryls.

The reaction sequence comprises of Diel-Alder cycloadditions of 3,5-dibromo-2-pyrone with styrene derivatives, and one-pot, three-step sequential aromatization process (Scheme 1). The mixture of *endo*/*exo* cycloadducts can be treated directly with a base, without separation, for the subsequent one-pot, three step sequential reactions, wherein the initially formed products **4** undergo concomitant 1,2-eliminations of HBr and aromatizations to the corresponding biaryls.

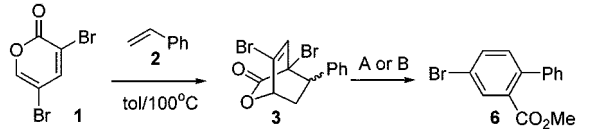


Scheme 1. Diels-Alder cycloadditions, followed by base-catalyzed aromatizations.

Table 1 summarizes the syntheses of various other 4-bromo-2-carboxyl-biaryls under this protocol. As shown, 3,5-dibromo-2-pyrone (**1**) underwent facile D-A cycloadditions with various substituted styrenes **2** to provide the corresponding cycloadducts **3** in 80 to 99% of isolated yields as readily separable mixtures of *endo*/*exo* isomers. Subsequent treatment with a base gave rise to the corresponding biaryls in good to excellent isolated yields.

As shown in the table, in the cases where the cycloadducts **3** have substituents at *ortho* positions (entries 2, 4, 6, 7, 9 and 10), the 1,2-eliminations of HBr (**4** → **5** in Scheme 1) were quite slow with NaOMe. Lactone ring openings with NaOMe, followed by treatment with DBU in boiling CH_2Cl_2 (condition B) facilitated the reactions to provide the corresponding

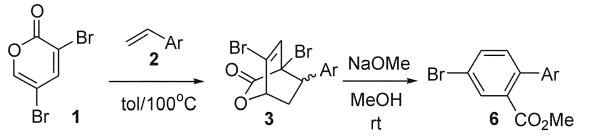
Table 1. Synthesis of 4-bromo-2-carboxyl-biphenyls



Entry	2	3	Time	Yield	6	Time	Yield
1	**2a** (H)	**3a**	5h	90%	**6a**	1h (A)	77%
2	**2b** (2-Br-)	**3b**	15h	96%	**6b**	1h (A)	56%
3	**2c** (4-Br-)	**3c**	12h	79%	**6c**	1h (A)	89%
4	**2d** (2-OMe-)	**3d**	6h	87%	**6d**	5h (B)	70%
5	**2e** (4-OMe-)	**3e**	5h	86%	**6e**	2h (A)	60%
6	**2f** [2,3-$(OMe)_2$-]	**3f**	12h	99%	**6f**	7h (B)	62%
7	**2g** [2,4-$(OMe)_2$-]	**3g**	3h	90%	**6g**	12h (B)	40%
8	**2h** [3,4-$(OMe)_2$-]	**3h**	10h	94%	**6h**	1h (A)	85%
9	**2i** [1,4-$(OMe)_2$-]	**3i**	5h	85%	**6i**	7h (A)	62%
10	**2j** [1,3,4-$(OMe)_3$-]	**3j**	8h	80%	**6j**	8h (A)	60%
11	**2k** [4-Me_2N-]	**3k**	6h	98%	**6k**	7h (A)	87%
12	**2l** [4-MeCONH-]	**3l**	9h	99%	**6l**	1h (A)	65%

(A) NaOMe MeOH/rt, (B) NaOMe/MeOH/rt, then DBU/CH_2Cl_2/reflux.

Table 2. Synthesis of 4-bromo-2-carboxyl-hetero-biaryls



Entry	Ar	3	Time	Yield	6	Time	Yield
13		**3m**	13h	60%	**6m**	3h	80%
14		**3n**	7h	93%	**6n**	2h	84%
15		**3o**	9h	82%	**6o**	6h	83%
16		**3p**	5h	94%	**6p**	1h	79%

biaryls in reasonable isolated yields. Noteworthy is that the whole sequence can be carried out in single flask, by treating the cycloaddition reaction mixtures with relevant bases, omitting the isolation of the bicyclolactones **3**.

Cycloadditions of 3,5-dibromo-2-pyrone with hetero-arenes bearing vinyl groups provided various bicyclolactones **3m** through **3p**. Subsequent treatments with NaOMe in MeOH at rt afforded a variety of hetero-biaryls as shown below (Table 2).

In summary, we have demonstrated that the cycloadducts from the Diels-Alder cycloadditions of 3,5-dibromo-2-pyrone with various styrenes or vinyl heteroarenes can be readily converted into a variety of biaryls, in one-pot, three step sequential reactions. The resulting 4-bromo-2-carboxyl-biaryls may find further usages as key scaffolds with various interests.

Acknowledgment. This work was supported by Nuclear R&D Program of the Ministry of Science and Technology (MOST).

References

1. (a) Bringmann, G.; Tasler, S. *Tetrahedron* **2001**, *57*, 331. (b) Cortez, D. A. G.; Young, M. C. M.; Marston, A.; Wolfender, J.-L.; Hostettmann, K. *Phytochemistry* **1998**, *47*, 1367. (c) Pascal, C.; Dubois, J.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **1998**, *63*, 6414. (d) Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248.
2. Setayesh, S.; Grimsdal, A. C.; Weil, T.; Enkelmann, V.; Mullen, K.; Meghdadi, F.; List, E. J. W.; Leising, G. *J. Am. Chem. Soc.* **2001**, *123*, 946.
3. (a) Yu, S.; Saenz, J.; Srirangam, J. K. *J. Org. Chem.* **2002**, *67*, 1699. (b) Shen, W.; Fakhoury, S.; Donner, G.; Henry, K.; Lee, J.; Zhang, H.; Cohen, J.; Warner, R.; Saeed, B.; Cherian, S.; Tahir, S.; Kovar, P.; Bauch, J.; Ng, S.-C.; Marsh, K.; Sham, H.; Rosenberg, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 703. (c) Chen, M.-H.; Pollard, P. P.; Patchett, A. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1261.
4. (a) Yin, Y.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (b) Neustadt, B. R.; Smith, E. M.; Lindo, N.; Nechuta, T.; Bronnenkant, A.; Wu, A.; Armstrong, L.; Kumar, C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2395.
5. (a) Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, *4*, 1171. (b) Cho, C.-G.; Kim, Y.-W.; Lim, Y.-K.; Park, J.-S.; Lee, H. *J. Org. Chem.* **2001**, *67*, 290. (c) Cho, C.-G.; Park, J.-S.; Jung, I.-H.; Lee, H. *Tetrahedron Lett.* **2001**, *42*, 1065. (d) Cho, C.-G.; Kim, Y.-W.; Kim, W.-K. *Tetrahedron Lett.* **2001**, *42*, 8193.