ORGANIC LETTERS

2002 Vol. 4, No. 19 3333–3336

Phenyliodonium Zwitterion as an Efficient Electrophile in the Palladium-Catalyzed Suzuki-Type Reaction: A Novel Method for the Synthesis of 3-Aryl-4-hydroxycoumarins

Qiang Zhu,*,[†] Jie Wu,[†] Reza Fathi,[‡] and Zhen Yang^{*,‡,§}

The Aaron Diamond AIDS Research Center (ADARC), The Rockefeller University, 455 First Avenue, New York, New York 10016, VivoQuest, Inc., 711 Executive Blvd., Valley Cottage, New York 10989, and College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P. R. China

z.yang@vivoquest.com

Received August 8, 2002

ABSTRACT



A palladium-catalyzed coupling reaction of phenyliodonium zwitterions with aryl boronic acids has been developed. The unique characteristics of the mild reaction conditions and convenient synthetic accessibility of phenyliodonium zwitterions make this method a valuable tool for generating diversified 3-aryl-4-hydroxycoumarins.

In recent years, we have witnessed a rapid growth in the field of organic hypervalent iodine chemistry, mainly due to its versatility in chemical transformations, lower-toxicity, and ease of preparation.¹ As an important branch of this family, zwitterionic iodonium compound (ZIC, or ylide) represents a molecule with a positive charge at iodine compensated by an internal negative charge that is localized formally at an α -carbon or nitrogen atom (1,2-dipole **2**, Scheme 1) or, in some instances, delocalized to a neighboring oxygen or nitrogen (1,4-zwitterionic structure **3**, Scheme 1).² The widely used ZIC can be simply prepared from 1,3-dicarbonyl compound **1** with DIB in aqueous or alcoholic alkali in high yield (Scheme 1).³ ZIC has been recognized



as a synthetic equivalent of the corresponding diazo compound as a precursor of carbene generated by photochemical or Rh, Cu salt-catalyzed decomposition.¹

The prototypical transformations are cyclopropanation,^{4a,b} carbon–hydrogen^{4c} or heteroatom–hydrogen^{4d} bond inser-

[†] The Rockefeller University.

[‡] VivoQuest, Inc.

[§] Peking University.

^{(1) (}a) Stang, P. J.; Zhdankin, V. V. Chem. Rev. 1996, 96, 1123–1178.
(b) Zhdankin, V. V.; Stang, P. J. Chem. Rev. 2002, 102, 2523–2584.

⁽²⁾ Margolis, A. Hypervalent Iodine In Organic Synthesis; Academic Press: San Diego, 1997.

⁽³⁾ For synthesis of β -dicarbonyl and β -disulfonyl iodonium ylides, see: (a) Schank, K.; Lick, C. Synthesis **1983**, 392. (b) Moriarty, R. M.; Prakash, I.; Prakash, O.; Freeman, W. A. J. Am. Chem. Soc. **1984**, 106, 6082. (c) Moriarty, R. M.; Bailey, B. R.; Prakash, O.; Prakash, I. J. Am. Chem. Soc. **1985**, 107, 1375.

tion, cycloaddition,^{4e-g} and miscellaneous reactions.^{4h,i} To our surprise, transition-metal-catalyzed cross-coupling using ZIC as an electrophile has not been reported, although 1,4-zwitterionic structure **3** has a structural similarity to the iodonium salt (iodonium cation is compensated by an external anion), which has been widely used in cross-coupling in recent years.⁵

As a privileged scaffold, coumarin is a ubiquitous subunit in many natural products with remarkable biological activities and unique physical properties.⁷ Methodology toward its synthesis has attracted considerable interest during the past decade.⁸ We report herein the utilization of coumarin-based zwitterionic iodonium compounds as effective electrophiles in the palladium-catalyzed Suzuki-type coupling with various aryl boronic acids to generate 3-substituted coumarins.

Strategically, we would like to generate our coumarin library by introducing diversities at C-3 and C-4 positions-(Figure 1), which would be more efficient than the construc-



Figure 1. Retrosynthetic analysis of coumarin library.

tion of the diversified lactone moiety by condensation of the preassembled acyclic precursors.⁹

We have previously developed the chemistry for diversification of coumarin at the C-4 position from its correspond-

(5) (a) Radhakrishnan, U.; Stang, P. J. Org. Lett. 2001, 6, 859. (b) Kang
S.-K.; Yoon, S.-K.; Kim, Y.-M. Org. Lett. 2001, 3 (17), 2697. (c) Kang,
S.-K.; Ryu, H.-C.; Lee, S.-W. J. Chem. Soc., Perkin Trans. 1 1999, 2661.
(d) Kang, S.-K.; Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S. J. Org.
Chem. 1996, 61, 9082. (e) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Ho, P.-S.
J. Org. Chem. 1996, 61, 4720. (f) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. J. Org. Chem. 1996, 61, 2604.

(6) (a) Schreiber, S. L. *Science* **2000**, 287, 1964. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968.

(8) (a) Clerici, A.; Porta, O. Synthesis 1993, 99. (b) Trost, B. M.; Toste,
F. D. J. Am. Chem. Soc. 1996, 118, 6305. (c) Kalinin, A. V.; da Silva, A.
J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. Tetrahedron Lett. 1998, 39, 4995. (d) Kalinin, A. V.; Snieckus, V. Tetrahedron Lett. 1998, 39, 4999.
(e) Ochiai, M.; Kitagawa, Y. J. Org. Chem. 1999, 64, 3181. (f) Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. J. Org. Chem. 1999, 64, 1033. (g) Kadnikov, D. V.; Larock, R. C. Org. Lett. 2000, 2, 3643. (h) Potdar, M.
K.; Mohile, S. S.; Salunkhe, M. M. Tetrahedron Lett. 2001, 42, 9285.

ing 4-hydroxycoumarin derivatives.^{9e,f} However, methods for the synthesis of 3-substituted coumarins from coumarin scaffolds are limited to a few examples, such as ligand coupling reaction¹⁰ and transition-metal-catalyzed crosscoupling reaction of 3-bromocoumarins with some organometallics.^{9a} Neverheless, the above-mentioned methods are either less efficient or associated with toxic reagents.¹¹

Although compound **4** was prepared more than twenty years ago, its synthetic application was limited to a few examples of diversified coumarin scaffolds.¹⁰ Since the vinyl or diaryl iodonium salts are remarkable substituents for vinyl or aryl halides or triflates in the transition-metal-catalyzed cross-coupling,⁵ we anticipated that the coumarin-based phenyl iodonium zwitterion **4** (Scheme 2) may have a similar



property. Considering its pronounced thermoinstability,¹² we preferred to select the palladium-catalyzed Suzuki-type coupling reaction to test our hypothesis, since this reaction can be carried out at room temperature.

Initially, we evaluated the Suzuki reaction by coupling of compound **4** with 4-methoxyphenylboronic acid using 10 mol % of Pd(PPh₃)₄ as a catalyst (Scheme 2).⁵ Gratifyingly, this reaction indeed proceeded to give compound **5**, albeit in a low yield (10%), concurrent with the starting material recovered.

We then focused on improving the reaction yield. Prolonging the reaction time gave no improvement of the yield at all. Increasing the loading level of $Pd(PPh_3)_4$ resulted in an even poorer yield of desired compound **5**. On the contrary, increased concentration of $Pd(PPh_3)_4$ led to a significant amount of a side product, which was finally identified as the phosphonium ylide **6** (Scheme 2), derived from transylidation of triphenylphosphine from catalysts $Pd(PPh_3)_4$ with iodonium ylide **4**.¹³

^{(4) (}a) Gallos, J. K.; Koftis, T. V.; Koumbis, A. E. J. Chem. Soc., Perkin Trans. 1 1994, 611. (b) Hatjiarapoglou, L.; Schank, K. Tetrahedron Lett. 1989, 30, 6673. (c) Hatjiarapoglou, L.; Varvoglis, A. J. Heterocycl. Chem. 1988, 25, 1599. (d) Kume, M.; Kubota, T.; Iso, Y. Tetrahedron Lett. 1995, 36, 8043. (e) Spyroudis, S.; Tarantili, P. J. Org. Chem. 1993, 58, 4885. (f) Papoutsis, I.; Spyroudis, S.; Varvoglis, A. Tetrahedron Lett. 1994, 35, 8449. (g) Spyroudis, S.; Tarantili, P. Tetrahedron 1994, 50, 11541. (h) Nikas, S.; Rodios, A.; Terzis, A.; Varvoglis, A. Phosphorus, Sulfur Silicon Relat. Elem. 1994, 90, 285. (i) Ochial, M.; Kitagawa, Y. J. Org. Chem. 1999, 64, 3181.

^{(7) (}a) O'Kennedy, R.; Thornes, R. D. Coumarins: Biology, Applications and Mode of Action; Wiley & Sons: Chichester, UK, 1997. (b) Zahradnik, M. The Production and Application of Fluorescent Brightening Agents; Wiley & Sons: Chichester, UK, 1992. (c) Murray, R. D. H.; Mendez, J.; Brown, S. A. The Natural Coumarins: Occurrence, Chemistry and Biochemistry; Wiley & Sons: New York, 1982.

^{(9) (}a) Schiedel, M.-S.; Briehn, C. A.; Bauerle, P. Angew. Chem., Int. Ed. 2001, 40, 4677. (b) Mitra, A. K.; De, A.; Karchaudhuri, N.; Mitra, J. J. Chem. Res., Synop. 1998, 766. (c) Boland, G. M.; Donnelly, D. M. X.; Finet, J.-P.; Rea, M. D. J. Chem. Soc., Perkin Trans. 1 1996, 2591. (d) Yao, M.-L.; Deng, M.-Z. Heteroat. Chem. 2000, 11, 380. (e) Wu, J.; Liao, Y.; Yang, Z. J. Org. Chem. 2001, 66, 3642. (f) Wu, J.; Yang, Z. J. Org. Chem. 2001, 66, 3642.

⁽¹⁰⁾ Finet, J.-P. Ligand Coupling Reactions with Heteroatomic Compounds; Elsevier Science. Ltd.: Oxford, 1998.

^{(11) (}a) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Stenson, P. H. *Tetrahedron Lett.* **1988**, 44, 6387; (b) *J. Chem. Soc., Perkin Trans. 1* **1995**, 2531. (c) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, 47, 5088. (d) Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1988**, 61, 449. (e) Ley, S. V.; Whittle, A. J. *Tetrahedron Lett.* **1981**, 22, 3301. (f) Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron Lett.* **1999**, 40, 5889.

^{(12) (}a) Thomas, K.; Gertraud, K.; Wolfgang, S. *Chem. Ber.* **1978**, *111*, 3857. (b) Erik, P.; Thomas, K. *Monatsh. Chem.* **1984**, *115*, 231. (c) Rita, L.; Thomas, K. *Synthesis* **1990**, 387.

⁽¹³⁾ Hadjiarapoglou, L.; Varvoglis, A. Synthesis 1988, 913.





Entry	Boronic acid	Product	Yield (%)
1	MeO- B(OH)2	OH COMe	92
2	B(OH)2		72
3	OMe		82
4	FB(OH)2		80
5	CIB(OH)2		68
6	F ₃ C-		56
7	B(OH)2		82
8	B(OH)2		80
9	B(OH)2		80
10	B(OH)2		88
11	9-BBN		46

 a Conditions: phenyliodonium zwitterion **4** (0.55 mol), boronic acid (1.21 mmol), Pd(OAc)₂ (6.2 mg, 0.06 mmol), P(*t*-Bu)₃ (27 μ L, 0.24 mmol), and LiOH (69.0 mg, 2.9 mmol) in DME (10 mL) and H₂O (2.5 mL) at 25 °C for 20 h under Ar.

This rather intriguing observation eventually led us to use $P(t-Bu)_3^{14}$ as a ligand by taking advantage of its bulkiness to prevent the observed transylidation. Accordingly, we set up the reaction by using $Pd(OAc)_2$ and $P(t-Bu)_3$ as a catalyst, and the coupling yield was indeed improved dramatically. We next optimized the reaction conditions by a survey of solvents (CH₂Cl₂, DMF, THF, CH₃CN, and DME) and bases (Et₃N, K₃PO₄, K₂HPO₄, Ba(OH)₂, CsHCO₃, CsOAc, LiOH, KF, NaOAc, and NaHCO₃), which established DME with



 a Conditions: phenyliodonium zwitterion (0.55 mol), boronic acid (1.21 mmol), Pd(OAc)_2 (6.2 mg, 0.06 mmol), P(t-Bu)_3 (27 μ L, 0.24 mmol), and LiOH (69.0 mg, 2.9 mmol) in DME (10 mL) and H₂O (2.5 mL) at 25 °C for 20 h under Ar.

20% of H_2O and LiOH as ideal solvents and base. An excellent result was eventually obtained (See entry 1, Table 1).

The above results indicate that the present reaction is rather general and high yielding for the aromatic-based boronic acids (entries 1–10), while the benzyl-based borane (entry 11) provides a rather low yield (Table 1). It is noteworthy that all the bicyclic-based boronic acids (entries 7–10) generate their corresponding products 7g-j in high yields, including the thianaphthene-2-boronic acid (entry 10), which results in a satisfactory yield.

To evaluate the substitution effect on the aromatic ring of the coumarin-based phenyliodonium zwitterions, five different substituted coumarin phenyl-iodonium zwitterions (8a-e) were synthesized accordingly¹⁵ and coupled with 4-methoxyphenyl boronic acid,¹⁶ under the identical conditions described in Table 1. The results are shown in Table

⁽¹⁴⁾ Littke, A. F.; Schwarz, L.; Fu, G. C. J. Am. Chem. Soc. 2002, 124, 6343.

⁽¹⁵⁾ Detailed procedure for the synthesis of compounds 4 and 8a-e: Iodobenzene diacetate (10 mmol) was suspended in a solution of Na₂CO₃ (10 mmol) in water (100 mL) and stirred for 30 min at room temperature. To this solution was added a mixture of 4-hydroxycoumarin (10 mmol) and Na₂CO₃ (10 mmol) in water (100 mL). After the mixture was stirred at room temperature for 2 h, the precipitate was collected by filtration, washed with water (20 mL × 5), and dried under vacuum. The resulting white solid was used without further purification. Detailed spectra data for these compounds are provided in the Supporting Information.

2. These monosubstituted coumarin zwitterions **8a**-d afford their corresponding products **9a**-d in acceptable yields, except the dichlorocoumarin zwitterion **8e**, which provides **9e** in only 47% yield (entry 5, Table 2).

In summary, we have developed a successful palladiumcatalyzed Suzuki-type reaction using phenyliodonium zwitterions as effective electrophiles to generate 3-arylcoumarins that would not be otherwise easily synthesized via alternative methods. The mild reaction conditions and the commercial availability of both 4-hydroxycoumarins and boronic acids make this method a valuable tool for generating diversified 3-aryl-4-hydroxy-coumarins. Together with the well-established methods for diversifying the C-4 position of coumarin, the present method will benefit 3,4-disubstituted coumarin library construction. Further studies to address this reaction mechanism and to expand the scope of both iodonium zwitterions and the type of transition-metal-mediated crosscoupling reactions are underway in our laboratories.

Acknowledgment. We thank Professor David Ho for his encouragements during the course of this research. Financial support from VivoQuest, Inc., is gratefully acknowledged.

Supporting Information Available: Experimental procedures and NMR and LC-MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020159B

⁽¹⁶⁾ General procedure for the cross-coupling: A degassed solution of boronic acid (1.209 mmol, 2.2 equiv) and $P(t-Bu)_3$ (27 μ L) in DME and water (4:1, 12.5 mL) was added to a mixture of iodonium ylide (200 mg, 0.55 mmol), LiOH·H₂O (69 mg, 3.0 equiv), and Pd(OAc)₂ (6.2 mg, 5 mol %) under argon at room temperature. After being stirred overnight (14 h), silica gel (3–5 g) was added to the reaction mixture. The mixture was dried completely under vacuum, and the residue was then purified by flash silica gel chromatography.