ORGANIC LETTERS

2005
Vol. 7, No. 18
3937−3940

Palladium-Catalyzed Cyanation of Porphyrins Utilizing Cyanoethylzinc Bromide as an Efficient Cyanide Ion Source

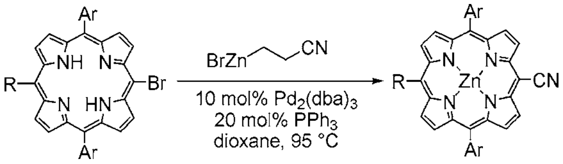
Toshikatsu Takanami, Mikiko Hayashi, Hiroshi Chijimatsu, Wakaba Inoue, and Kohji Suda*

Meiji Pharmaceutical University, 2-522-1, Noshio, Kiyose, Tokyo 204-8588, Japan

suda@my-pharm.ac.jp

Received June 20, 2005

ABSTRACT



Palladium-catalyzed cyanation of bromoporphyrins is now realized using cyanoethylzinc bromide as a specific cyanating agent. This new protocol provides an easy access to various cyanated Zn(II) porphyrins, including *meso*-mono-, *meso*-di-, and β-mono-cyano-substituted Zn(II) complexes.

Synthetic porphyrins and metalloporphyrins have found many important applications in various fields, including homogeneous catalysis, materials, and medicine.[1,2] Thus, new synthetic strategies and efficient intermediates for the preparation of porphyrin derivatives have been actively pursued.[1,2] Cyano-substituted porphyrins are accepted as being among the most useful precursors for subsequent transformations because the nitrile group is quite valuable in installation of other functionalities such as aldehydes, amines, amides, and acid derivatives.[2] Several useful procedures are available for monocyanation of porphyrins at the *meso*- and β-positions, but few existing methods provide facile and efficient preparation of porphyrins bearing more than one nitrile group.[4−8]

Palladium-catalyzed and related transition metal-catalyzed cyanation of aryl halides would offer an alternative access to cyanoporphyrins.[9−11] Among different palladium-catalyzed coupling reactions, however, the catalytic cyanation of aryl halides appears to be somewhat immature, still suffering from

---

(1) Kadish, K. M., Smith, K. M., Guilard, R., Eds. *The Porphyrin Handbook*; Academic Press: San Diego, 2003; Vols. 1−20.

(2) We have developed porphyrin-based Lewis acid catalysts that can promote regio- and stereoselective isomerization of epoxides to carbonyl compounds and Claisen rearrangement of allylvinyl ethers; see: (a) Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* **2002**, 2570−2571. (b) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554−9555. (c) Takanami, T.; Hayashi, M.; Suda, K. *Tetrahedron Lett.* **2005**, *46*, 2893−2896.

(3) (a) Rappoport, Z. *The Chemistry of the Cyano Group*; Interscience Publishers: London, 1970. (b) Larock, R. C. *Comprehensive Organic Transformations;* VCH: New York, 1988.

(4) The following four methods have been reported for the cyanation of porphyrins: (i) classic Rosemund−von Braun cyanation reactions with stoichiometric copper(I) cyanide at elevated temperatures (see ref 5); (ii) a multiple-step procedure involving Vilsmeier formylation, oxime formation, and dehydration (see ref 6); (iii) nucleophilic addition of cyanide ion to the π-cation radical of porphyrins (see ref 7); and (iv) Friedel−Crafts cyanation of porphyrins with cyanogen bromide/aluminum chloride (see ref 8). These reactions, other than Rosemund−von Braun cyanation, involve cationic porphyrin intermediates and, hence, can hardly be applied towards the preparation of porphyrins bearing more than one nitrile group: the introduction of a CN group deactivates the system toward further cyanation.

(5) (a) Callot, H. J. *Tetrahedron Lett.* **1973**, 4987−4990. (b) Callot, H. J. *Bull. Soc. Chim. Fr.* **1974**, 1492−1496. (c) Richeter, S.; Jeandon, C.; Kyritsakas, N.; Ruppert, R.; Callot, H. J. *J. Org. Chem.* **2003**, *68*, 9200−9208.

(6) (a) Inhoffen, H. H.; Fuhrhop, J.-H.; Voigt, H.; Brockmann, H., Jr. *Liebigs Ann. Chem.* **1966**, *695*, 133−143. (b) Johnson, A. W.; Oldfield, D. *J. Chem. Soc. C* **1966**, 794−798.

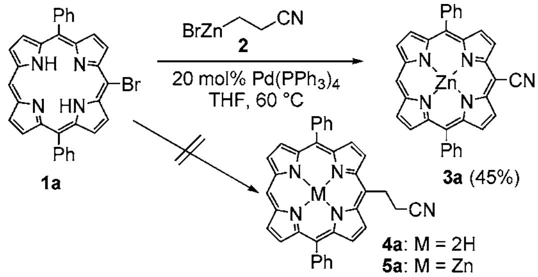
(7) (a) Smith, K. M.; Barnett, G. H.; Evans, B.; Martynenko, Z. *J. Am. Chem. Soc.* **1979**, *101*, 5953−5961. (b) Callot, H. J.; Louati, A.; Gross, M. *Tetrahedron Lett.* **1980**, *21*, 3281−3284. (c) Wu, G.-Z.; Leung, H.-K.; Gan, W.-X. *Tetrahedron* **1990**, *46*, 3233−3244.

(8) Smith, K. M.; Goff, D. A.; Simpson, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 4946−4954.

10.1021/ol0514294 CCC: $30.25

low turnover numbers and frequencies and applicability to a limited range of substrates: the major problem of palladium- and nickel-catalyzed cyanation is catalyst deactivation by an excess of dissolved cyanide ions in the reaction mixture.[12,13] As a result, application of the palladium-based cyanation to porphyrins has, to the best of our knowledge, never been described. We report herein an unprecedented cyanation of porphyrins via a palladium-catalyzed reaction of bromoporphyrins with 2-cyanoethylzinc bromide that works as an effective and convenient cyanide ion source in the reaction. This new protocol provides a facile and efficient access to a variety of cyano-substituted porphyrins, including *meso*-mono-, *meso*-di-, and β-mono-cyanated porphyrins.

Scheme 1



In an initial study, we explored the reaction of 5-bromo-10,20-diphenylporphyrin **1a** with 2-cyanoethylzinc bromide **2** (5 equiv) in the presence of 20 mol % $Pd(PPh_3)_4$ in THF at 60 °C. As shown in Scheme 1, we unexpectedly obtained neither the corresponding *meso*-alkylated porphyrin **4a** nor its zinc complex **5a** but *meso*-cyano-substituted Zn(II) porphyrin **3a** as the major product in 45% isolated yield.[14] This result indicates that the organozinc reagent **2** works as a cyanide ion source in the reaction and was very surprising compared with the known palladium and related transition metal-mediated coupling reactions of aryl halides with the reagent **2**, which usually affords the corresponding cyanoethyl-substituted products.[15] Thus, we further investigated the reaction of porphyrin **1a** with the reagent **2** (5 equiv) using different combinations of palladium catalysts, phosphine ligands, and solvents. As shown in Table 1, $Pd_2(dba)_3$ was found to be superior to $Pd(OAc)_2$ as the Pd source, and the combination of a monodentate phosphine ligand, especially PPh_3, and 1,4-dioxane as the solvent proved to be effective for the catalytic cyanation of **1a**, giving the desired cyanoporphyrin **3a** in 94% isolated yield (entry 9). On the basis of these preliminary outcomes, subsequent cyanation reactions were generally conducted with 5−10 equiv of cyanoethylzinc reagent **2** and the catalyst system consisting of 10 mol % $Pd_2(dba)_3$ and 20 mol % PPh_3 in dioxane at 95 °C under an inert atmosphere.

Table 1. Selected Optimization Studies for Cyanation of Porphyrin **1a** with Cyanoethylzinc Bromide **2**[a]

entry	catalyst	ligand	solvent	T (°C)	t (h)	**3a** (%)[b]
1	$Pd(PPh_3)_4$		THF	60	3.5	45
2	$Pd(OAc)_2$	dpph[c]	THF	60	2	17
3	$Pd(OAc)_2$	$^tBu_3P$	THF	60	7	18
4	$Pd(OAc)_2$	PPh_3	THF	60	3.5	10
5	$Pd_2(dba)_3$	dpph[c]	THF	60	2.5	16
6	$Pd_2(dba)_3$	$^tBu_3P$	THF	60	2	82
7	$Pd_2(dba)_3$	PCy_3	THF	60	2.5	65
8	$Pd_2(dba)_3$	PPh_3	THF	60	1.5	87
9	$Pd_2(dba)_3$	PPh_3	dioxane	95	0.5	94
10	$Pd_2(dba)_3$	PPh_3	toluene	100	0.5	69

[a] Conditions: 10 mol % catalyst, 20 mol % ligand, 5 equiv of **2**. [b] Isolated yield. [c] dpph = $Ph_2P(CH_2)_6PPh_2$.

The present catalytic cyanation is easily applicable to a wide range of mono- and dibromoporphyrins (Figure 1), and these results are summarized in Table 2. Under the general conditions, *meso*-monobrominated diarylporphyrins such as those having aliphatic, vinyl, and alkoxy moieties on their phenyl group, **1b−d**, were converted to the corresponding *meso*-cyano Zn(II) complexes, **3b−d**, in good to high yields.

---

(9) For a review on the transition metal-catalyzed carbon−carbon bond formation of porphyrins at the *meso*- and β-positions, see: Sharman, W. M.; Van Lier, J. E. *J. Porphyrins Phthalocyanines* **2000**, *4*, 441−453.

(10) For some examples of leading works on fabrication of alkyl- and aryl-substituted porphyrins via Suzuki, Stille, and Sonogashira cross-coupling reactions, see: (a) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 2513−2515. (b) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Org. Chem.* **1993**, *58*, 5983−5993. (c) Chan, K. S.; Zhou, X.; Au, M. T.; Tam, C. Y. *Tetrahedron* **1995**, *51*, 3129−3136. (d) Boyle, R. W.; Johnson, C. K.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1995**, 527−528. (e) Hyslop, A. G.; Kellett, M. A.; Iovine, P. M.; Therien, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 12676−12677. (f) Shanmugathasan, S.; Johnson, C. K.; Edwards, C.; Matthews, E. K.; Dolphin, D.; Boyle, R. W. *J. Porphyrins Phthalocyanines* **2000**, *4*, 228−232. (g) Deng, Y.; Chang, C. K.; Nocera, D. G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1066−1068. (h) Vas, B.; Alvarez, R.; Nieto, M.; Paniello, A. I.; de Lera, A. R. *Tetrahedron Lett.* **2001**, *42*, 7409−7412. (i) Chng, L. L.; Chang, C. J.; Nocera, D. G. *J. Org. Chem.* **2003**, *68*, 4075−4078. (j) Chen, Y.-J.; Lee, G.-H.; Peng, S.-M.; Yeh, C.-Y. *Tetrahedron Lett.* **2005**, *46*, 1541−1544. (k) Kurotobi, K.; Osuka, A. *Org. Lett.* **2005**, *7*, 1055−1058. (l) Hata, H.; Shinokubo, H.; Osuka, A. *J. Am. Chem. Soc.* **2005**, *127*, 8264−8265.

(11) We and Zhang et al. reported metal-catalyzed carbon−heteroatom bond formation reactions for porphyrin synthesis: (a) Takanami, T.; Hayashi, M.; Hino, F.; Suda, K. *Tetrahedron Lett.* **2003**, *44*, 7353−7357. (b) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 4432−4438. (c) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 3261−3264. (d) Gao, G. Y.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2004**, *6*, 1837−1840. (e) Gao, G. Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2004**, *69*, 8886−8892.

(12) To avoid this problem, less soluble metal cyanides such as NaCN, KCN, CuCN, $Zn(CN)_2$, and $K_4[Fe(CN)_6]$ are typically used as a cyanide ion source in the catalytic cyanation of aryl halides: (a) Yang, C.; Williams, M. *Org. Lett.* **2004**, *6*, 2837−2840. (b) Stazi, F.; Palmisano, G.; Turconi, M.; Santagostino, M. *Tetrahedron Lett.* **2005**, *46*, 1815−1818. (c) Weissmann, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508−1510. (d) Hatsuda, M.; Seki, M. *Tetrahedron Lett.* **2005**, *46*, 1849−1853.

(13) Beller et al. reported palladium-catalyzed cyanation reactions of aryl halides utilizing acetone cyanohydrin and trimethylsilyl cyanide as a cyanide ion source. In this case, a continuous slow addition of the cyanating reagents via a syringe pump to the reaction mixture is a prerequisite for preventing catalyst deactivation by an excess of cyanide ions in the solution: (a) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661−1664. (b) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50−55.

(14) Only the debrominated product [5,15-diphenylporphinato]zinc(II) was isolated as a byproduct.

(15) For examples, see: (a) Kasák, P.; Putala, M. *Tetrahedron Lett.* **2004**, *45*, 5279−5282. (b) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163−6166.

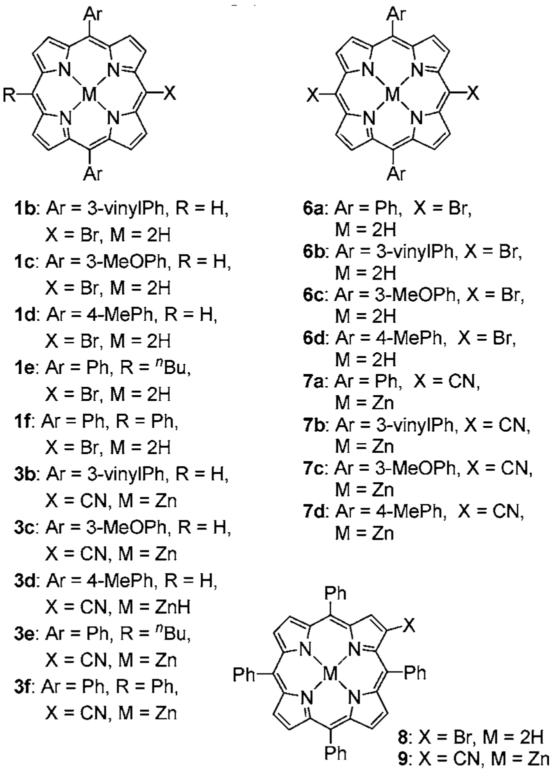


Figure 1. Structures of porphyrins.

Similarly, bromoporphyrins, **1e** and **1f**, bearing alkyl or phenyl groups at the *meso*-position[16] underwent the catalytic cyanation to furnish the corresponding *meso*-cyano-substituted Zn(II) porphyrins, **3e** and **3f**, in appreciable yields. Although the introduction of two nitrile groups to the porphyrin core represents a challenging problem that thus far could not be generally solved using reported methods,[4−8] subjecting dibromoporphyrins, **6a**−**d**, to the catalyst system led to formation of the corresponding dicyano-substituted Zn(II) complexes, **7a**−**d**, in good to excellent yields. Cyanation at the β-position of the porphyrin core was also achievable under the same conditions, β-cyanated Zn(II) porphyrin **9** being obtained in 61% isolated yield from the corresponding base porphyrin **8**.

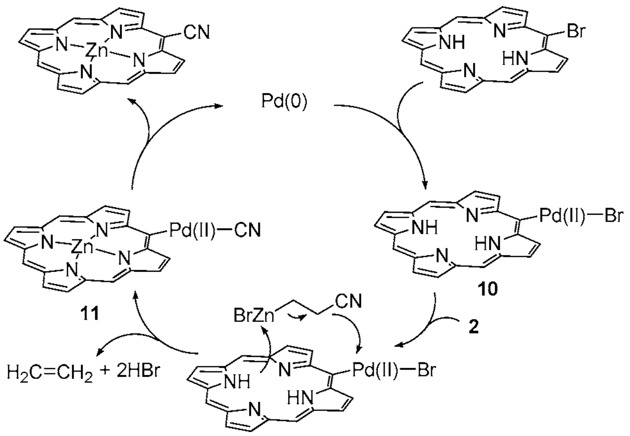
Table 2. Catalytic Cyanation of Porphyrins with Cyanoethylzinc Bromide **2**[a]

entry	substrate	product	*t* (h)	yield (%)[b]
1	**1a**	**3a**	0.5	94
2	**1b**	**3b**	2.5	62
3	**1c**	**3c**	0.5	60
4	**1d**	**3d**	0.5	65
5	**1e**	**3e**	0.5	70
6	**1f**	**3f**	0.5	72
7	**6a**	**7a**	1.5	91[c]
8	**6b**	**7b**	0.5	57[c]
9	**6c**	**7c**	0.5	74[c]
10	**6d**	**7d**	0.5	50[c]
11	**8**	**9**	1	61

[a] Reaction conditions: 10 mol % $Pd_2(dba)_3$, 20 mol % PPh_3, 5 equiv of the zinc reagent **2**, dioxane, 95 °C. [b] Isolated yield. [c] Performed with 10 equiv of **2**.

Although details of the present catalytic process are not clear as yet, we tentatively assume the mechanism as depicted in Scheme 2. The reaction is initiated by the oxidative addition of Pd(0) to the C−Br bond of the substrate. Subsequent metal ion insertion from the zinc reagent **2** to the porphyrin core synchronously generates the cyanide ion along with evolution of ethylene.[17] Finally, reductive elimination of the resulting Pd(II) cyanide intermediate **11** gives the product. It should be noted that, in this process, the requisite amount of the cyanide ion in a 1:1 molecular ratio to the catalyst can be supplied into the reaction mixture, thereby effectively preventing catalyst deactivation.[12,13] Further experiments are currently underway to elucidate the mechanism in more detail.

Scheme 2. Reaction Pathways for the Catalytic Cyanation of Porphyrins[a]



[a] Peripheral substituents have been omitted.

In conclusion, we have developed the first method that achieves catalytic mono- and dicyanation of porphyrins. These palladium-catalyzed cyanation reactions utilizing cyanoethyl zinc bromide as an efficient cyanide ion source are compatible with an array of *meso*-mono-, *meso*-di-, and β-bromo-substituted porphyrins and generally proceed in good yields. This new protocol should be a valuable addition to the porphyrin chemist's toolkits for development of porphyrin-based functional materials. Further studies of this

---

(16) (a) Kalisch, W. W.; Senge, M. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 1107−1109. (b) Feng, X.; Bischoff, I.; Senge, M. O. *J. Org. Chem.* **2001**, *66*, 8693−8700.

(17) Catalytic cyanation of porphyrins could be achieved at a lower reaction temperature: e.g., the reaction of **1a** with the cyanoethylzinc reagent **2** took place smoothly in the presence of 20 mol % $Pd(PPh_3)_4$ in THF at 40 °C, giving essentially the same result as that obtained from the reaction performed at 60 °C (cf. entry 1 in Table 1), affording the corresponding cyanated product **3a** (41%), though a longer reaction time (12 h) was necessary to complete the reaction. Thus, another reactive metallic-cyano species seems not to be formed from degradation of cyanoethylzinc bromide **2** in the catalytic process under the present reaction conditions.

and related functionalization reactions of porphyrin are in progress.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research (C) (KAKENHI 16590020) from JSPS and a Special Grant (GAKUCHO-GRANT) from Meiji Pharmaceutical University.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0514294