ORGANIC LETTERS

2012
Vol. 14, No. 7
1776–1779

Base-Catalyzed Direct Conversion of Dipyrromethanes to 1,9-Dicarbinols: A [2 + 2] Approach for Porphyrins

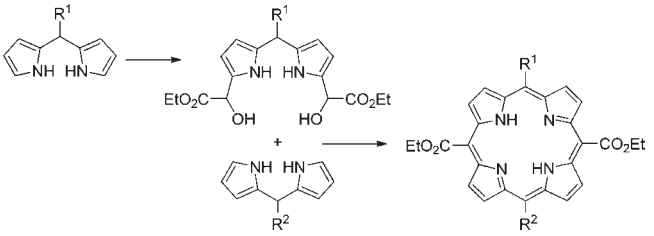
Yuichi Terazono, Emily J. North, Ana L. Moore,* Thomas A. Moore,* and Devens Gust*

Department of Chemistry and Biochemistry, Center for Bio-Inspired Solar Fuel Production, Arizona State University, Tempe, Arizona 85287-1604, United States

gust@asu.edu; amoore@asu.edu; tmoore@asu.edu

Received February 15, 2012

ABSTRACT



A variant of the MacDonald approach was devised for the synthesis of porphyrins. A new base-catalyzed one-step synthesis of 1,9-dipyrromethane−dicarbinols was achieved by Friedel−Crafts alkylation of dipyrromethanes using commercially available ethyl glyoxylate solution in toluene. This method avoids the use of acid chlorides, Grignard reagents, borohydride reductions, and acidic conditions. The [2 + 2] condensation of dipyrromethanedicarbinols and dipyrromethanes yielded 5,15-di(ethoxycarbonyl)porphyrins.

Porphyrins are key building blocks for photocatalytically active molecular assemblies.[1−10] Synthesis of such molecules requires manifold functionalization on the porphyrin for attachment of donor and acceptor moieties and for tuning the optical, redox, and other properties of the macrocycle.

In order to extend the scope of design and synthetic approaches to new, intriguing molecular structures, we have been exploring new synthetic methods for obtaining porphyrin building blocks with novel *meso* substituents. In *meso*-arylporphyrins, the planes of the *meso*-aryl groups lie at steep angles to the plane of the macrocycle due to steric hindrance. This is a great advantage for certain objectives such as mimicking the functional "pocket" of some proteins including hemoglobins[11] or cytochrome P-450s.[12] However, when such porphyrins are integrated into photochemically active molecules, the large torsional barriers to planarity reduce electronic coupling between the porphyrin core and redox or photoactive moieties linked to it via these aryl groups and can limit the approach of such moieties to the macrocycle. These structural constraints in turn can limit energy and electron transfer rates and reduce performance. Although halogenation at a porphyrin *meso* position followed by Pd-catalyzed coupling reactions can sometimes be used to attach nonaryl substituents to the macrocycle, halogen substitution usually lowers the

(1) Liddell, P. A.; Kuciauskas, D.; Sumida, J. P.; Nash, B.; Nguyen, D.; Moore, A. L.; Moore, T. A.; Gust, D. *J. Am. Chem. Soc.* **1997**, *119*, 1400–1405.

(2) Gust, D.; Moore, T. A. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 8, pp 153−190.

(3) Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **2009**, *42*, 1890–1898.

(4) Walter, M. G.; Rudine, A. B.; Wamser, C. C. *J. Porphyrins Phthalocyanines* **2010**, *14*, 759–792.

(5) El-Khouly, M. E.; Ju, D. K.; Kay, K. Y.; D'Souza, F.; Fukuzumi, S. *Chem.—Eur. J.* **2010**, *16*, 6193–6202.

(6) Aratani, N.; Kim, D.; Osuka, A. *Acc. Chem. Res.* **2009**, *42*, 1922–1934.

(7) Lee, S. H.; Larsen, A. G.; Ohkubo, K.; Cai, Z. L.; Reimers, J. R.; Fukuzumi, S.; Crossley, M. J. *Chem. Sci.* **2012**, *3*, 257–269.

(8) Song, H. e.; Taniguchi, M.; Diers, J. R.; Kirmaier, C.; Bocian, D. F.; Lindsey, J. S.; Holten, D. *J. Phys. Chem. B* **2009**, *113*, 16483–16493.

(9) Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435–461.

(10) Imahori, H. *Org. Biomol. Chem.* **2004**, *2*, 1425–1433.

(11) Collman, J. P.; Gagne, R. R.; Halbert, T. R.; Marchon, J. C.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 7868–7870.

(12) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032–1033.

10.1021/ol300267j
Published on Web 03/15/2012

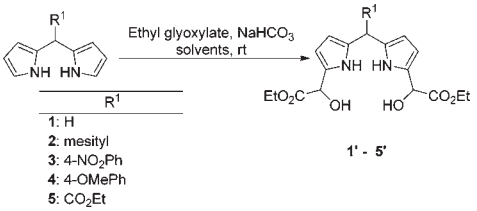
solubility of porphyrins significantly and can lead to problems with purification.

Although there are dozens of general methodologies for synthesizing porphyrins,[13−16] we focused on developing a variant of MacDonald synthesis,[17] i.e., the [2 + 2] approach, because it does not produce undesired porphyrin byproducts and a variety of symmetries such as A-, *trans*-A_2-, *trans*-AB-, *trans*-A_2B_2-, and *trans*-AB_2C-porphyrins (see refs 18 and 19 for nomenclature) can be prepared. For [2 + 2] approaches, modification of the 1- and 9-positions of dipyrromethane is required.[17,19−22] One of the useful precursors is a 1,9-dipyrromethane−dicarbinol which is obtained by two steps: acylation using acid chlorides followed by reduction[20,21] or Vilsmeier−Haack formylation followed by reduction.[23] Also, 1,9-imine substituted dipyrromethanes have been used as building blocks for a [2 + 2] porphyrin synthesis.[19,24] While we were searching for possibilities for one-step preparation of a dipyrromethane-dicarbinol from a dipyrromethane, we came across a report by Zhuang and Jørgensen[25] regarding Friedel−Crafts alkylation of indoles and pyrroles using ethyl glyoxylate under mild conditions, and we were prompted to investigate the reactivity of ethyl glyoxylate toward dipyrromethanes. Although one-step hydroxymethylation of 2,5-positions of pyrrole followed by a [3 + 1] condensation to yield porphin has been reported,[26,27] direct attachment of carbinols to pyrroles and dipyrromethanes for porphyrin synthesis is rare.

Here we report a facile one-step preparation of 1,9-dipyrromethane−dicarbinols from dipyrromethanes (Scheme 1) and [2 + 2] condensation of these products to yield porphyrins (Scheme 2).

Aqueous reaction conditions similar to those examined by Zhuang and Jørgensen[25] for small, water-soluble molecules were not appropriate for our studies; dipyrromethanes were not very soluble under aqueous conditions and reactions required excess ethyl glyoxylate.

Scheme 1. Synthesis of 1,9-Dipyrromethane−Dicarbinols[a]



[a] Reaction conditions: [dipyrromethane] = 0.1−0.33 M; ethyl glyoxylate, 1.05−1.1 equiv; $NaHCO_3$ or Na_2CO_3 or py or triethylamine, 3 equiv; solvent, CH_2Cl_2−toluene.

Surprisingly, Friedel−Crafts alkylation of the 1- and 9-positions of dipyrromethanes proceeds in dichloromethane using sodium bicarbonate as a catalyst. Although the base is not very soluble in this solvent, reactions occurred smoothly at ambient temperature using only 2 equiv of ethyl glyoxylate per dipyrromethane. It should be emphasized that we used the 50% wt/wt ethyl glyoxylate/toluene solution as purchased, which contains oligomers.[28,29]

Although we did not attempt to measure reaction rates, the concentration of the organic reactants seems to affect the rate significantly; the higher the concentrations of both reactants, the faster the reactions proceed. For dipyrromethanes **1**−**4**, formation of dicarbinols was complete in several hours. Dipyrromethane **5** required more time to react. The ethoxycarbonyl group of **5** may lower the electron densities in the pyrrole rings and slow the reaction. Reactions in dichloromethane also proceed with sodium carbonate, pyridine, or triethylamine as the base.

Table 1. Reaction Times for **2′** Using Different Catalysts[a]

base	time (h)[b]
$NaHCO_3$	2.5
Na_2CO_3	7
pyridine	10
triethylamine	[c]
no base	21[d]

[a] Reaction conditions: [**2**] = 0.2 M, base = 3 equiv, dichloromethane = 500 μL, room temperature. [b] Time for complete conversion to the dicarbinol. [c] Decomposed. [d] Decomposed and not complete.

The results for **2** are summarized in Table 1. Dicarbinol **2′** was formed with all these bases, but sodium bicarbonate works most efficiently. With triethylamine, dipyrromethane **2** was consumed smoothly in the early stage of the reaction, but the color of the reaction mixture changed very quickly to dark orange. More gradual color changes to yellow or light orange were observed in all other reactions. In the case of triethylamine, a clear, bright orange

(13) Paine, J. B., III In *The Porphyrins, Part A: Structure and Synthesis*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 101−231.
(14) Smith, K. M. *J. Porphyrins Phthalocyanines* **2000**, *4*, 319–324.
(15) Kadish, K. M.; Smith, K. M.; Guilard, R. *The Porphyrin Handbook*; Academic Press: San Diego, 2000; Vol. 1.
(16) Lindsey, J. S. *Acc. Chem. Res.* **2010**, *43*, 300–311.
(17) Arsenault, G.; Bullock, E.; MacDonald, S. *J. Am. Chem. Soc.* **1960**, *82*, 4384–4389.
(18) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344.
(19) Fan, D.; Taniguchi, M.; Yao, Z.; Dhanalekshmi, S.; Lindsey, J. S. *Tetrahedron* **2005**, *61*, 10291–10302.
(20) Cho, W. S.; Kim, H. J.; Littler, B. J.; Miller, M. A.; Lee, C. H.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 7890–7901.
(21) Gryko, D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 2249–2252.
(22) Geier, G. R., III; Littler, B. J.; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 712–718.
(23) Lahaye, D.; Muthukumaran, K.; Hung, C. H.; Gryko, D.; Reboucas, J. S.; Spasojevic, I.; Batinic-Haberle, I.; Lindsey, J. S. *Bioorg. Med. Chem.* **2007**, *15*, 7066–7086.
(24) Taniguchi, M.; Balakumar, A.; Fan, D.; McDowell, B. E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2005**, *9*, 554–574.
(25) Zhuang, W.; Jorgensen, K. A. *Chem. Commun.* **2002**, 1336–1337.
(26) Taniguchi, S.; Hasegawa, H.; Nishimura, M.; Takahashi, M. *Synlett* **1999**, 73–74.
(27) Taniguchi, S.; Hasegawa, H.; Yanagiya, S.; Tabeta, Y.; Nakano, Y.; Takahashi, M. *Tetrahedron* **2001**, *57*, 2103–2108.
(28) Burel, F.; Rossignol, L.; Pontvianne, P.; Hartman, J.; Couesnon, N.; Bunel, C. *e-Polym.* **2003**, *31*, 1–12.
(29) Belloncle, B.; Burel, F.; Oulyadi, H.; Bunel, C. *Polym. Degrad. Stab.* **2008**, *93*, 1151–1157.

spot appeared between the starting material (**2**) and monocarbinol on the TLC plate (F254 basic alumina, 4% methanol–dichloromethane). We could isolate the orange compound by chromatography using basic alumina and dichloromethane as an eluent. MALDI-TOF-MS of the orange compound showed a major peak at 451.1893 (with 5,10,15,20-tetratolylporphyrin: 670.3091 as a reference), which is 17 less than the mass of **2′** (468.2260), and a peak with ca. 20% relative intensity at 450.1785, which corresponds to the mass of compound **2″** (Figure 1). It is likely that the major peak in the mass spectrum represents protonation of the minor peak species (**2″**) in the MALDI-TOF vacuum chamber. As shown in Figure 1, we speculate that triethylamine can catalyze dehydration of dicarbinol **2′**, leading to the formation of **2″**. Compound **2″** was also formed in the reaction without base, which initially produced dicarbinol **2′** in a significant amount. However the reaction was incomplete even after 21 h. All dicarbinol formation reaction mixtures darkened when allowed to stand for longer times. These results suggest that dehydration of dipyrromethane–dicarbinols occurs eventually and is accelerated in the presence of a strong base. The ^{1}H NMR spectrum of **2″** could not be obtained because of the instability of the molecule. A mechanism similar to that suggested in Figure 1 but featuring acid rather than base catalysis has been proposed in other dipyrromethane–dicarbinol systems.[30]

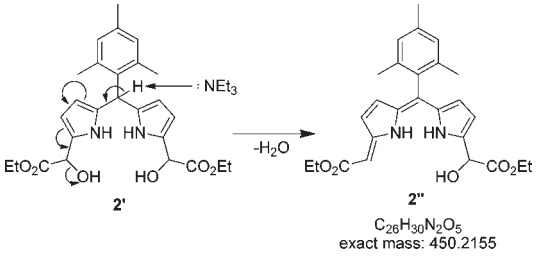


Figure 1. A possible decomposition mechanism.

For both aqueous and nonaqueous conditions, column chromatographic purification of the product was unnecessary. In fact, the dicarbinols are acid-sensitive and can decompose on silica gel. Dipyrromethane–dicarbinols are relatively stable on basic alumina, although dehydration is also possible under these conditions. Thus the workup process after reactions in dichloromethane was simple; filtration of the reaction mixture to remove sodium bicarbonate was followed by evaporation of dichloromethane and toluene by a rotary evaporator under vacuum. The ^{1}H and ^{13}C NMR spectra, MALDI-TOF-MS, as well as F254 basic alumina TLC of dicarbinols after this simple workup showed that dicarbinols were formed quantitatively and clean enough to proceed to porphyrin synthesis. The filtered dicarbinol solution can also be used directly, without vacuum-drying, for the [2 + 2] condensation with dipyrromethanes to obtain porphyrins. Solid dipyrromethane–dicarbinols were stored at −20 °C for weeks without noticeable degradation.

Stirring dipyrromethane **2** with 2 equiv of benzaldehyde and 3 equiv of sodium bicarbonate in dichloromethane at room temperature overnight yielded a bluish green solution, but no carbinols were formed.

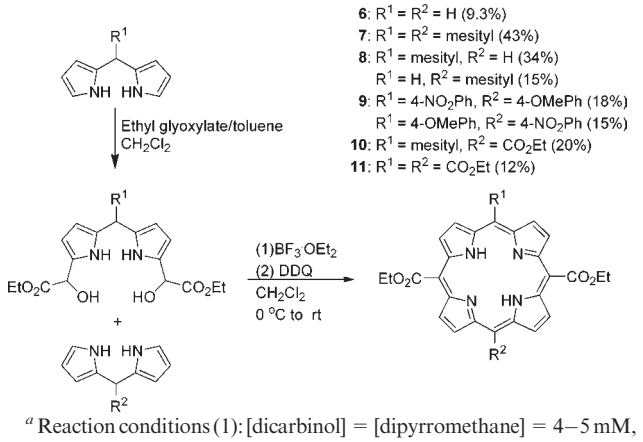
Porphyrin synthesis was performed in dichloromethane using boron trifluoride etherate as a Lewis acid (Scheme 2). Dipyrromethane **5** and some porphyrins having alkoxycarbonyl groups at *meso*-positions have been synthesized previously using other methods.[31–33] Our approach gives dipyrromethane **5** and then *meso*-ethoxycarbonyl porphyrins in moderate yields (Scheme 2). The porphyrin synthesis using dicarbinol **1′** resulted in lower yields (for **6** and **8** (R^1 = H, R^2 = mesityl)). On the other hand, use of dicarbinol **2′** gave porphyrins in good yields (for **7** and **8** (R^1 = mesityl, R^2 = H)). We examined this [2 + 2] approach under one set of conditions (except for synthesis of **11**, in which reactants were more diluted), and improved yields might be obtained by changing the solvents, concentration of reactants, catalysts, temperature, etc.

The facile attachment of carboxylic functionality at the *meso*-positions described here will allow an expansion of the use of porphyrins not only for the preparation of new molecules for bioconjugation chemistry but also for applications in surface attachment, such as linking to metal oxides or to amine-containing surface bound groups. In addition, since *meso*-alkoxycarbonyl groups on the porphyrin can be removed by hydrolysis and decarboxylation,[34] our approach opens a path to *trans*-AB-porphyrins or A-porphyrins from 5,15-di(ethoxycarbonyl)-10-A-20-B-pophyrins and 5,10,15-tri(ethoxycarbonyl)-20-A-porphyrins. These precursor porphyrins are formed as sole porphyrin reaction products. Thus, this approach avoids the separation of mixtures of porphyrin products.

The synthetic method reported here permits much more facile preparation of some porphyrins than previously reported methods. For example, a compound similar to porphyrin **7**, 5,15-dicarboxy-10,20-bis(3,5-di-*tert*-butylphenyl)porphyrin, was previously prepared from hydrolysis of (5,15-dicyano-10,20-bis(3,5-di-*tert*-butylphenyl)-porphyrinato)zinc(II). This material in turn was synthesized from 5,15-bis(3,5-di-*tert*-butylphenyl)porphyrin, which was first dibrominated and then subjected to Pd-catalyzed cyanation.[35] The zinc was introduced into the porphyrin during the cyanation reaction.

(30) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828–836.
(31) Trova, M. P.; Gauuan, P. J.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695–2707.
(32) Yao, Z.; Bhaumik, J.; Dhanalekshmi, S.; Ptaszek, M.; Rodriguez, P. A.; Lindsey, J. S. *Tetrahedron* **2007**, *63*, 10657–10670.
(33) Lindsey, J. S.; Taniguchi, M.; Fan, D. U.S. Patent 20070027311, 2007.
(34) Neya, S.; Quan, J.; Hata, M.; Hoshino, T.; Funasaki, N. *Tetrahedron Lett.* **2006**, *47*, 8731–8732.
(35) Balaban, M. C.; Eichhoefer, A.; Buth, G.; Hauschild, R.; Szmytkowski, J.; Kalt, H.; Balaban, T. S. *J. Phys. Chem. B* **2008**, *112*, 5512–5521.

Scheme 2. [2 + 2] Porphyrin Synthesis[a]



[a] Reaction conditions (1): [dicarbinol] = [dipyrromethane] = 4–5 mM, $[BF_3 \cdot OEt_2]$ = 0.4–0.5 mM.

The synthesis of 1,9-dipyrromethane–dicarbinols from the corresponding dipyrromethanes using commercially available ethyl glyoxylate in toluene solution reported here is simple and chromatography-free. It is carried out in basic solution and avoids the use of acid chlorides, organomagnesium compounds, and borohydride reductions required by some other methods. The dicarbinols can be used immediately for [2 + 2] porphyrin synthesis. This new approach opens synthetic pathways to a wide variety of porphyrins by using combinations of different dicarbinols and dipyrromethanes.

Acknowledgment. This research was supported as part of the Center for Bio-Inspired Solar Fuel Production, an Energy Frontier Research Center funded by the U.S. Department of Energy, Office of Science, Office of Basic Energy Sciences under Award Number DE-SC0001016.

Supporting Information Available. Details of compound synthesis and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.