Pergamon

Tetrahedron Letters 39 (1998) 8935–8938

TETRAHEDRON LETTERS

Palladium Catalyzed Carbonylation of Br-substituted Porphyrins

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Received 25 June 1998; revised 24 July 1998; accepted 7 August 1998

Abstract: The Pd-catalyzed carbonylation of Br-substituted porphyrins is reported. Several new alkoxycarbonylporphyrins are synthesized in good yields. The reaction is found particularly useful for derivatization of the tetrabenzoporphyrin system.

The development of synthetic methods for the construction of porphyrins bearing simple functional groups on the periphery is a key step on the path to many porphyrin-based materials. Such substituents serve as anchor points to which additional fragments, required by a specific application, can be linked. In the majority of cases, functionalized porphyrins are built from already modified starting materials. For example, a large variety of tetra-*meso*-arylsubstituted porphyrins can be synthesized *via* either Alder-Longo [1] or Lindsey [2] route, by employing a broad range of substituted benzaldehydes and/or pyrroles. There are some instances, however, when only relatively inert substituents can be added to a porphyrin macrocycle, such as, for example, in the case of tetrabenzoporphyrins (TBP). TBP's are used as near infra-red phosphors for optical assessment of oxygen *in vivo*,[3] and also considered promising PDT agents [4]. The synthesis of TBP's normally involves high temperature condensation,[5] which very few inert functional groups can survive [6]. Recently we reported the synthesis of *meso*-tetraphenyl-TBP's, symmetrically substituted with four bromines in either benzo- or phenyl rings [7]. To allow further derivatization, bromine substituents must be converted into more reactive, preferably hydrophilic, functional groups, such as carboxyls. Since Pd-catalysis has been already proven successful for various transformations of haloporphyrins,[8] we decided to explore the direct route to the carboxyl-substituted TBP's using another popular Pd-catalyzed reaction, namely catalytic carbonylation [9].

Taking into account the high cost of the brominated TBP's, we chose to use Zn-*meso*-(4-BrC_6H_4)$_4$-porphyrin (**1**) as a model substrate to optimize the reaction conditions. Being on one hand a close analog of the corresponding TBP (Zn-*meso*-(4-BrC_6H_4)$_4$-tetrabenzoporphyrin), **1** can be easily prepared in any necessary amount [10]. Our goal was to find the optimal conditions for the complete conversion of **1** into the corresponding tetracarbonylated derivative (Scheme 1, Table 1).

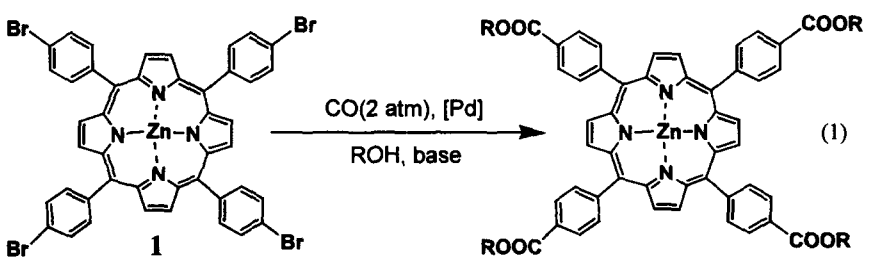

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Table 1. Carbonylation of **1** under Various Conditions [11].

#	R	Base	Solvent	[Pd] [a]	Reaction Conditions	Conv. ratio (%) [12]	Yield [b] (%)
1	H	Na_2CO_3	DMF	$PdCl_2$ (10%)/PPh_3	90°C, 48 h.	<5	-
2	H	NaOH	p-xylene/H_2O, Bu_4NBr	$PdCl_2$ (10%)/PPh_3	90°C, 48 h.	0	-
3	Et	Bu_3N	EtOH/THF	$Pd(PPh_3)_4$ (10%)	70°C, 48 h.	50	-
4	Et	Bu_3N	EtOH/THF	$Pd(PPh_3)_4$ (10%)	70°C, 80 h.	70	-
5	*n*-Bu	Bu_3N	BuOH	$Pd(PPh_3)_4$ (10%)	90°C, 48 h.	100	79
6	***n*-Bu**	**Et_3N**	**BuOH**	**$Pd(PPh_3)_4$ (10%)**	**90°C, 48 h.**	**100**	**83**
7	*n*-Bu	Et_3N	BuOH	$Pd(PPh_3)_4$ (10%)	90°C, 20 h.	85	-
8	*n*-Bu	Et_3N	BuOH	$Pd(PPh_3)_4$ (1%)	90°C, 48 h.	50	-
9	*n*-Bu	Et_3N	BuOH	$Pd(PPh_3)_4$ (1%)	90°C, 110 h.	60	-
10	*n*-Bu	Et_3N	BuOH	$Pd(OAc)_2$ (10%)/PPh_3	90°C, 48 h.	60	-
11	*n*-Bu	Et_3N	BuOH	$PdCl_2$ (10%)/PPh_3	90°C, 48 h.	40	-
12	*n*-Bu	Et_3N	BuOH	$PdCl_2$ (50%)/PPh_3	90°C, 48 h.	100	42
14	All	Et_3N	AllOH	$Pd(PPh_3)_4$ (10%)	90°C, 100 h.	0	-
13	*n*-Hex	Et_3N	HexOH	$PdCl_2$ (25%)/PPh_3	90°C, 48 h.	40	-
15	Bz	Et_3N	BzOH	$PdCl_2$ (25%)/PPh_3	90°C, 48 h.	100	61

[a] [Pd] denotes Pd(II) salt or Pd(0) complex added initially to the reaction mixture. The actual catalyst, in some cases, was formed from this salt *in situ* during the reaction.

[b] Yields are reported for the isolated compounds.

Attempts to carry out carbonylation in the presence of the inorganic base, Na_2CO_3, which would directly lead to the tetracarboxylated porphyrin, proved unsuccessful. When the reaction was carried in DMF (Entry 1) or in biphasic system (Entry 2) with $PdCl_2/PPh_3$ as a catalyst, practically no conversion of **1** was detected, while Pd was found mostly reduced to Pd-black. Addition of a 10-fold molar excess of PPh_3 to stabilize Pd(0) in solution did not prevent the loss of the catalyst.

It is known that alcohols, when used as nucleophiles, generally improve the performance of carbonylation [9]. Indeed, when the reaction was carried in a mixture of EtOH/THF [13] at 70°C in the presence of Bu_3N and $Pd(PPh_3)_4$ it resulted in an almost 50% conversion of **1** (Entry 3), while the extension of the reaction time improved the conversion ratio up to 70%.

The largest yield was achieved, however, when BuOH was used as both a nucleophile and a solvent. The initial butoxycarbonylation (Entry 5) gave quantitative conversion of **1**, and Zn *meso*-(4-$BuOOCC_6H_4$)$_4$Porph (**2**) was isolated in 79% yield. Such significant improvement is probably due to the solubilizing effect of BuOH, which happens to be a reasonably good solvent for **1** already at room temperature, and, on the other hand, it probably stabilizes Pd(0) catalytic species in solution. An even higher yield (83%) was achieved with Et_3N used as a base (Entry 6) instead of Bu_3N. In general, the use of low boiling Et_3N was found preferable, as it can be completely removed from the reaction mixture by simply drying in vacuum at r.t. On the contrary, traces of Bu_3N always remained in the samples even after prolonged heating in vacuum. This complicated the chromatography of the resulting alkoxycarboxylated porphyrins.

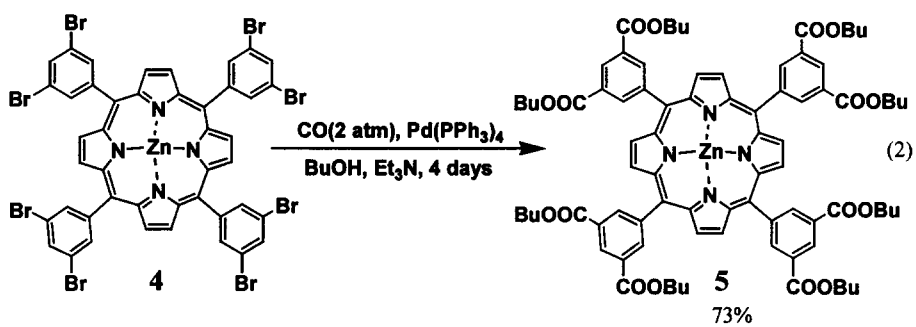
Decrease in the reaction time and/or in the amount of catalyst diminished the conversion ratio. For example, carrying out the reaction over 20 h. (Entry 7) led to only 85% conversion, while when the amount of the catalyst was reduced 10 times (to 1 mol. %) only about 50% of **1** reacted even after the standard 48 h. period (Entry 8).

Extending the duration up to 110 h., but still using 1 mol. % of $Pd(PPh_3)_4$ (Entry 9), only slightly increased the conversion ratio. Attempts to carry out carbonylation in *n*-butanol with Pd(0) produced *in situ* from Pd(II) precursors, did not improve the reaction yield. Thus, with Pd acetate (Entry 10) about 60% of **1** was converted after 48 h. and even lower conversion, 40%, was observed in the case of $PdCl_2$ (Entry 11). In general, it seems that the most critical parameter for successful carbonylation is the actual amount of Pd(0) present in solution. Given highly reducing conditions and generally low rates of oxidative insertion, Pd always tends to precipitate as Pd-black, in spite of the fact that supporting PPh_3 is always present in a large (5-10 fold) excess. Thus it is quite possible that other ligands, particularly chelating ones, such as dipp (bis(diisopropylphosphino)propane), would improve the catalytic performance by providing a better support to Pd(0) in solution. Nevertheless, in our case the cost of substrate is almost always much higher than the cost of Pd-catalyst and so carrying out the carbonylation even under semi-catalytic conditions (e.g. 50% mol. of $PdCl_2$, Entry 12) might be well justified.

Next, we examined carbonylation with other alcohols as nucleophiles. The allyloxycarbonylation in the presence of $Pd(PPh_3)_4$ was completely unsuccessful even after 100 h. (Entry 13). The use of *n*-hexyl alcohol led to about 40% conversion of the substrate with $PdCl_2$ (25 mol. %)/PPh_3 (Entry 14), while with benzyl alcohol complete conversion of **1** was obtained already after 48 h. and Zn *meso*-(4-$C_6H_5CH_2OOCC_6H_4$)$_4$Porph (**3**) [14] was isolated in 61% yield.

After optimal conditions for alkoxycarbonylation were established (Entry 6, shown in bold) we tested the effectiveness of the approach on the porphyrin containing more than four bromine substituents, namely Zn *meso*-(3,5-$Br_2C_6H_3$)$_4$Porph (**4**). The corresponding octaalkoxycarbonylporphyrins cannot be obtained through the direct condensation because of the limited availability of starting 3,5-alkoxycarbonylbenzaldehydes. On the other hand, 3,5-dibromobenzaldehyde is sold commercially and the corresponding porphyrin, metal-free precursor of **4**, could be conveniently synthesized in 32% yield [14] using Lindsey's method [2].

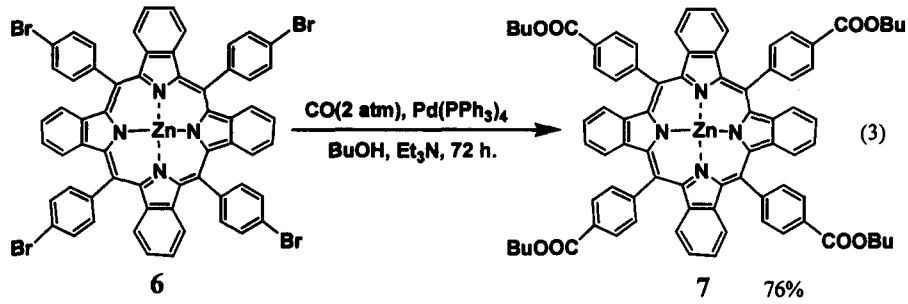
The carbonylation of **4** (Scheme 2) required longer time (about 4 days) to reach completion, but gave Zn *meso*-(3,5-(BuOOC)$_2$$C_6H_3$)$_4$Porph (**5**) [14] in 73 % yield.



(2)

The new porphyrin **5**, after exchange of Zn for Pd and hydrolysis of butyl ester groups, gave Pd *meso*-tetra-3,5-dicarboxyphenylporphyrin, a useful core element for building dendritic phosphorescent oxygen probes [15].

Finally, the method was applied to the modification of Zn *meso*-(4-BrC_6H_4)-tetrabenzoporphyrin (**6**). Using the conditions described above **6** was transformed into the corresponding Zn tetrabutoxycarbonyl-TBP (**7**) (Scheme 3) in 76% yield [16]. After conversion into the corresponding Pd-complex, the latter porphyrin **7** could be quantitatively deesterified, giving tetracarboxylated derivative, a novel and highly useful near-IR phosphorescent dye.



6 7 76%

To summarize, Pd(0)-catalyzed carbonylation was found to be an effective method for the modification of the brominated porphyrins.

Acknowledgment

This work was supported by grants HL-60100 and NS-31465 from The National Institutes of Health (USA).

References and Notes

1. Adler, A. D.; Longo, F. R.; Shergalis, W. D. *J. Am. Chem. Soc.* **1964,** *86,* 3145-3149; Adler, A. D.; Sklar, L.; Longo, F. R.; Finarelli, J. D.; Finarelli, M. G. *Heterocycl. Chem.* **1968,** *5,* 669-678.
2. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987,** *52,* 827-836; Lindsey, J. S.; Maccrum, K. A.; Tyhonas, J. S.; Chuang, Y. Y. *J. Org. Chem.* **1994,** *59,* 579-587.
3. Vinogradov, S. A.; Wilson, D. F. *J. Chem. Soc., Perkin Trans.II* **1994,** 103-111; Vinogradov, S. A.; Lo, L.-W.; Jenkins, W. T.; Evans, S. M.; Koch, C.; Wilson, D. F. *Biophys. J.* **1996,** *70,* 1609-1617.
4. Lavi, A.; Johnson, F. M.; Ehrenberg, B. *Chem. Phys. Lett.* **1994,** *231,* 144-150.
5. For review see: Kobayashi, N. *in Phthalocyanines. Properties and Applications*; ed. Leznoff, C. C.; Lever, A. B. P., VCH: New York, 1993; Vol. 2, p.97.
6. The recent work of Cavaleiro et al. [Vicente, M. G. H.; Tome, A. C.; Walter, A.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **1997,** *38,* 3639-3642] presents an alternative and promising route to the TBP system, however to date only the synthesis of basic non-substituted tetrabenzoporphyrin has been reported.
7. Khoroshutin, A.V., Vinogradov, S.A., Wilson, D.F, *Abstr. Pap. ACS,* **215**: 49-ORGN, U16-U16 Part 2, Apr 2, 1998.
8. Arnold, D. P.; Nitschinsk, L. J. *Tetrahedron* **1993,** *34,* 693-696; DiMagno, S. G.; Lin, V. S. Y.; Therien, M. J. *J. Org. Chem.* **1993,** *58,* 5983-5993; Chan, K. S.; Zhou, X.; Luo, B. S.; Mak, T. C. W. *J. Chem. Soc. Chem. Comm.* **1994,** 271-272; Ali, H.; Vanlier, J. E. *Tetrahedron* **1994,** *50,* 11933-11944.
9. Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, Ch.8, p.341-451.
10. 1 was synthesized by refluxing free base *meso*-(4-BrC_6H_4)$_4$-porphyrin with Zn acetate in DMF. The porphyrin itself was prepared from 4-bromobenzaldehyde (Aldrich) and pyrrole (Aldrich) by Lindsey method [2] in 31% yield.
11. In a typical procedure, a 50-100 mg of substrate, Pd-catalyst, excess of PPh_3 (5-10 fold), 1-2 ml of base (Et_3N or Bu_3N) and 20-30 ml of solvent were placed in a pressure resistant glass vial (Ace Glass Inc.), connected to a CO tank by a copper tubing. The vial was immersed in the oil bath and temperature was brought up to the desired value (normally 90-95°C) under continuous stirring and slow flow of CO. The lid of the vial was then tightened and the pressure was raised to 2 atm. The reaction mixture workup involved filtration, removal of the solvent in vacuum and chromatography of the product.
12. The conversion ratio was determined spectroscopically. A sample of the reaction mixture was chromatographed on a TLC plate (Silicagel), the colored zones were separated and extracted with DMF. The volumes of all extracts were made equal (2-5 ml) and the relative amounts of Zn-porphyrins in each fraction were assigned by comparing absorption intensities at Soret band maxima (λ_{max} = 425 nm).
13. THF was added to improve the solubility of the substrate.
14. The description of synthesis of Zn *meso*-(3,5-$Br_2C_6H_3$)$_4$Porph (4) as well as analytical and spectroscopic data on all newly synthesized porphyrins are available on request and will be published elsewhere.
15. Vinogradov, S.A., Wilson, D.F. *Adv. Exptl. Med. Biol.,* **1997,** *428,* 657-662; Vinogradov, S.A., Wilson, D.F. *Abstr. Pap. ACS,* **215**: 50-ORGN, U16-U16 Part 2, Apr 2, 1998.
16. The yield was determined after conversion of **6** into the corresponding Pd complex. This was done by the treatment of **6** with CF_3COOH in CH_2Cl_2, followed by refluxing of the resulting free-base TBP with $PdCl_2$ in DMF.