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Tetrahedron Letters 48 (2007) 6518–6522
Tetrahedron Letters

Synthesis of new azido porphyrins and their reactivity in copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction with alkynes

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Received 23 May 2007; revised 5 July 2007; accepted 9 July 2007
Available online 13 July 2007

Abstract—We report herein the preparation of two novel porphyrins substituted with an azido group born either on the *para*-position of one phenyl *meso*-susbtituent of a tetraaryl zinc porphyrin (**1**) or directly on the *meso*-position of a trisaryl nickel porphyrin (**2**). We studied the scope and the limitation the Huisgen cycloaddition reaction of these two porphyrins using different catalytic conditions. We observed that the carbene (SIMes)CuBr in THF/H_2O 3:1 at 45 °C for 60 h gives almost quantitative yields for the reaction between **1** and different alkynes, but significantly lower yields with **2** probably due to its thermal instability.

Porphyrins are valuable compounds owing to their rich photochemical, electrochemical and catalytic properties that open the door to a wide range of applications in material science, medicine, catalysis and for solar energy conversion. The development of simple, efficient and versatile synthetic strategy to functionalize porphyrin is of a high interest for their broader utilizations in many areas. The copper(I)-catalyzed 1,3-dipolar cycloaddition of azides with alkynes has emerged as one of the most effective synthetic reaction, since it can be conducted in mild conditions, in various solvents, with generally high yields and independently of the steric hindrance and of the electronic properties of the reagents (with both electron-rich or electron-deficient substrates).[1] As a consequence, we were interested to develop the synthesis of azido substituted porphyrins, since these compounds could certainly represent valuable substrates to use in Huisgen reaction to easily connect various types of molecular units. During the course of this work, Chen and co-workers reported the synthesis and the dipolar cycloaddition reaction of β-azidotetraaryl porphyrins.[2] Herein, we report the synthesis and the reactivity of new azido porphyrins, whose azido group is born either directly on the *meso*-position or on the *para*-position of a *meso*-phenyl substituent (Fig. 1). The two new porphyrins **1** and **2** can advantageously complete the possibilities offered by the β-azidotetraarylporphyrins because the introduction of substituents on the *meso*-position will certainly change the magnitude of the electronic interactions with the porphyrin ring.

Besides, the position of the azido group in porphyrins **1** and **2** is more appropriate if one envisions to prepare linear arrays in the direction of the *meso*-axis of the porphyrin, because trans *meso*-disubstituted porphyrins are much more synthetically accessible than trans *beta* disubstituted porphyrins.[3] The synthesis of the porphyrin **1** is depicted in Scheme 1. Condensation of 3 equiv of *para*-*tert*-butylbenzaldehyde and 1 equiv of *para*-nitrobenzaldehyde with 4 equiv of pyrrole using Lindsey's conditions[4] afforded porphyrin **3** along with tetrakis(*tert*-butylphenyl)porphyrin and bis(nitrophenyl) bis(*tert*-butylphenyl) porphyrins.[5] The reaction mixture is best purified in the next step after the reduction of the nitro groups with tin chloride, because the desired amino porphyrin **4** is readily separated from the other porphyrins by column chromatography. The diazotation of the amine **4** with sodium nitrite in trifluoracetic acid followed by the addition of sodium azide at low temperature gives the expected azido porphyrin **5** with 95% yield after purification. The free base porphyrin **5** is then metallated with zinc acetate in a quantitative yield to afford **1**.[6]

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doi:10.1016/j.tetlet.2007.07.049

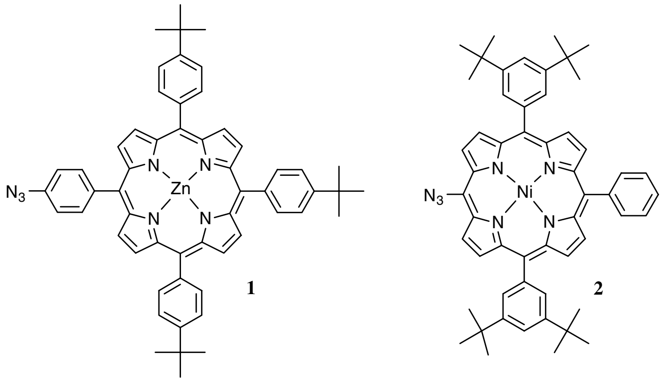
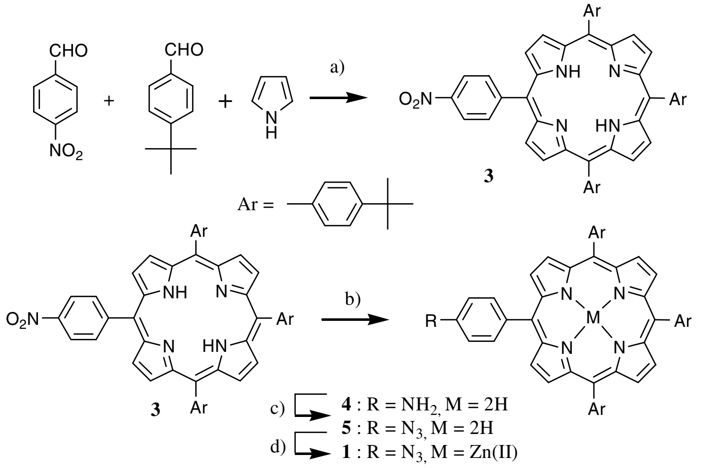
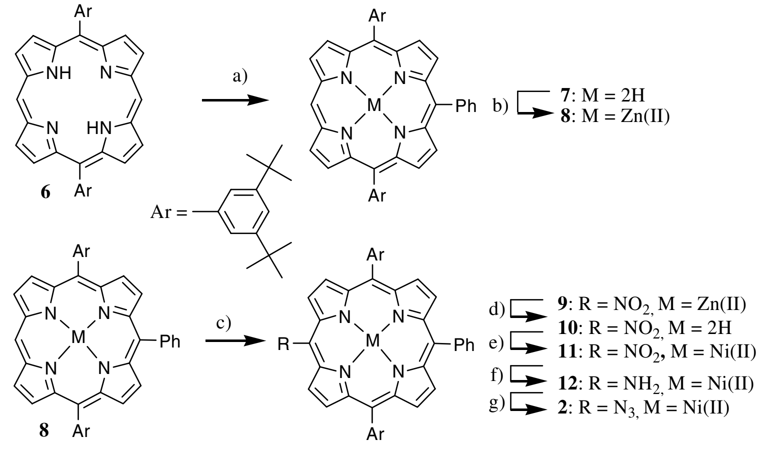


Figure 1. Structures of the two azido porphyrins **1** and **2** studied in this work.



Scheme 1. Synthetic route to prepare porphyrin **1**. Reagents and conditions: (a) $Et_2O{\cdot}BF_3$, CH_2Cl_2, 12 h, rt then DDQ, 1 h, rt (11%); (b) $SnCl_2$, HCl, $CHCl_3$, AcOH, reflux, 12 h (76%); (c) $NaNO_2$, NaN_3, TFA, H_2O, 0 °C (95%); (d) $Zn(OAc)_2$, CH_2Cl_2, MeOH, 60 °C, 2 h (100%).

The second porphyrin **2** was prepared in six steps from **6**[7] (Scheme 2). First, trisaryl porphyrin **7** was obtained in high yield according to Arnold's protocol[8] and using Senge's methodology[9] by reacting an excess of phenyl lithium with bisaryl porphyrin **6**. Zinc trisaryl porphyrin **8** was nitrated with silver nitrite in presence of iodine at 0 °C.[10] Then, the zinc nitro porphyrin **9** was demetalled with HCl and metalled with nickel(II). The nitro group of **11** was reduced with sodium tetrahydroborate at room temperature and the resulting amine **12** was



Scheme 2. Synthetic route to prepare porphyrin **2**. Reagents and conditions: (a) PhLi, THF, −78 °C, H_2O, DDQ (85%); (b) $Zn(OAc)_2$, CH_2Cl_2, MeOH, 60 °C, 2 h (100%); (c) I_2, $AgNO_2$, CH_3CN, CH_2Cl_2, 0 °C, 1 h (73%); (d) HCl, CH_2Cl_2 (100%); (e) $Ni(OAc)_2$, DMF, 110 °C, 2 h (97%); (f) Pd/C, $NaBH_4$, CH_2Cl_2, MeOH, rt, 1 h (95%); (g) $NaNO_2$, NaN_3, H_2SO_4, THF, H_2O, rt, 1 h (85%).

subsequently transformed into the diazonium salt that was finally reacted with sodium azide to give **2**.[11] The strong azide band could be detected by IR spectroscopy at 2120 cm^{-1} and 2105 cm^{-1}, respectively, for azido porphyrins **1** and **2**. It is worth noting that the amino porphyrin **12** is not very stable and should be used rapidly in the next step after its preparation. Similarly, but in a less extent, the azido porphyrin **2** is relatively prone to decomposition if not stored in the dark and at low temperature.

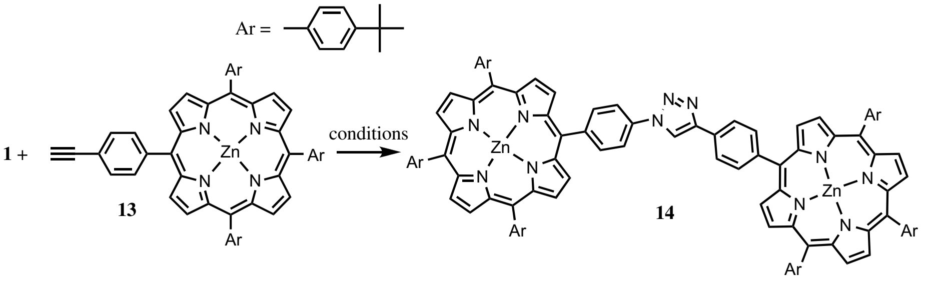
Attempts to prepare the azido free base porphyrin corresponding to **2** by the same route failed in the last step. Furthermore, the recently published coupling reaction of aryl halides with sodium azide using the catalytic mixture CuI-L-proline also failed to produce **2** when applied to zinc iodo porphyrin.[12] With reference to other works,[13] we reasoned that the metal complexed in the porphyrin controls the stability of the directly *meso*-substituted azido porphyrin such as **2**. The mass spectroscopy analyses clearly showed the facile fragmentation of the azido porphyrins **1** and **2** as well as the triazole derivatives resulting from the coupling of **1** or **2** with alkynes. During most mass analyses, the fragmentation of these compounds occurs readily with loss of nitrogen.

In a second stage, the successful preparation of the azido porphyrins **1** and **2** allowed us to study their reactivities with different alkynes using several copper-based catalysts. It is worthy of noticing that a free base porphyrin tends to be metallated by copper when subjected to most of the conditions listed in Table 1. Conversely, no transmetalation seems to occur using zinc porphyrin **1** or nickel porphyrin **2**. We started to investigate the coupling of zinc porphyrin **1** with ethynylphenyl zinc porphyrin **13** using different reaction conditions (Table 1). In a first experiment, we tried the classical conditions using copper sulfate with ascorbic acid in triethylamine and dichloromethane as solvent mixture, but the expected bisporphyrin **14** did not form at all (entry 1).[1] Highly polar solvents increase the solubility of the 'ligand free' copper catalyst and they were reported to facilitate the coordination of copper by alkyne.[14] The latter reaction is known to be a crucial step in the catalytic mechanism, but the utilization of the mixture DMSO/CH_2Cl_2/Et_3N 10:5:1 did not change the outcome of the reaction (entry 2). The low stability of the azido porphyrin **1** and **2** and their triazole derivatives as observed during the mass spectroscopy analyses prompted us to try the very recent conditions reported by Sharpless and co-workers which give good results when the C–N^3 bond of the triazole tends to brakes easily.[15] However, these conditions also failed to give detectable amount of **14** (entry 3).

The first success came when the organo-soluble copper catalysts $Cu(PPh_3)_3Br$ and $Cu[P(OEt)_3]I$ were used (entries 4–5). It is notable to observe the formation of porphyrin **15** with an appreciable yield (33%) as a side product when $Cu(PPh_3)_3Br$ was used (Fig. 2). The formation of this by-product can be certainly rationalized on the account of Staudinger reaction between the free triphenylphosphine and azide **1**.[16] The copper carbene complex with SIMes ligand, recently reported by Nolan and co-workers, proved to be the best catalyst for this reaction with the porphyrin azides **1** and **2** substrates.[17] These porphyrins being not soluble in water, we investigated other reaction mixture and found that the mixture THF/water 3:1 was satisfying to conduct the reaction with this catalyst and with water insoluble reagents. With these conditions, the isolated yield of **14** reaches 44% after 60 h of reaction at 45 °C (entry 7). Then, we turn our attention to other alkynes to investigate the origin of the modest yield obtained with porphyrin **1**.

Three different aryl–ethynyl substrates, spanning different electronic properties from neutral (**16**) to electron-rich (**17**) to electron-deficient (**18**), were reacted with the azido porphyrin **1** (Scheme 3).

Table 1. Yield of isolated product **14** resulting from the reaction of the porphyrins **1** and **13** using the conditions listed below



Entry	Reaction conditions	Yield (%)
1	$CuSO_4$, $4H_2O$, ascorbic acid, CH_2Cl_2/Et_3N 5:1, 60 °C, 12 h	0
2	$CuSO_4$, $4H_2O$, ascorbic acid, 40 °C DMSO/CH_2Cl_2/Et_3N 10:5:1, 4 h	0
3	CuI, $4H_2O$, 1,6-dimethyl-pyridine, $CHCl_3$, 0 °C, 12 h, then rt 72 h	0
4	$Cu(PPh_3)_3Br$, DIEA/THF 1:5, 50 °C, 3 h	23
5	$Cu[P(OEt)_3]I$, DIEA/THF/H_2O 1:1:5, 50 °C, 12 h	29
6	(SIMes)CuBr, THF/H_2O 3:1, 45 °C, 12 h	32
7	(SIMes)CuBr, THF/H_2O 3:1, 45 °C, 60 h	44

DIEA = diisopropylethylamine. SIMes = *N*,*N*′-bis(2,4,6-trimethylphenyl)-4,5-dihydro-imidazol-2-ylidene.

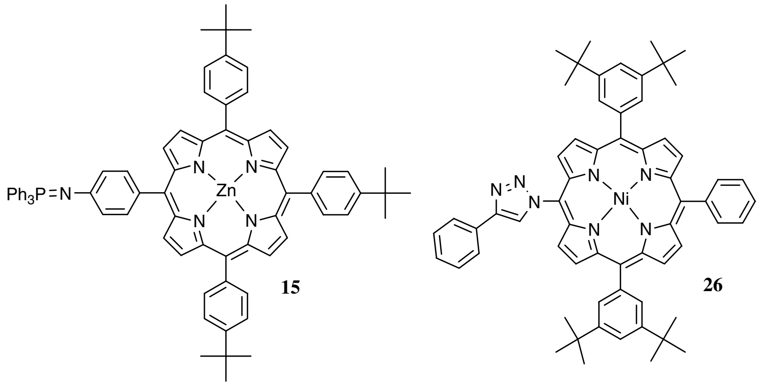
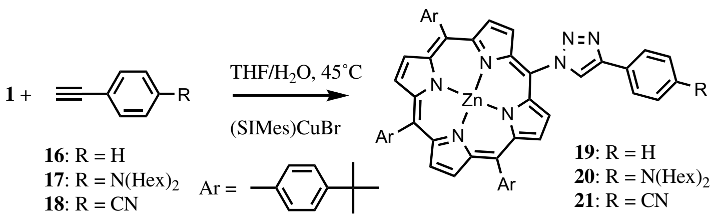


Figure 2. Structures of porphyrins **15** and **26**.

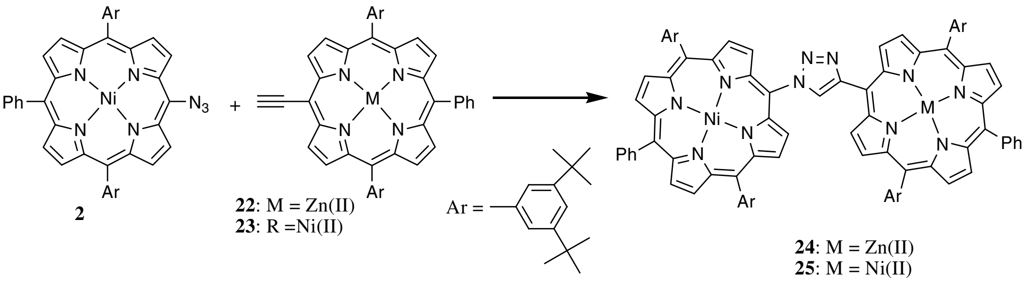


Scheme 3. Huisgen reaction of azido porphyrin **1** with the alkynes **16**–**18**.

The coupled products **19**–**21** were isolated with a yield above of 95% after 60 h of reaction. Therefore, the lower yield of **14** is certainly not ascribed to a steric factor, because Huisgen reaction is known to be relatively insensitive to sterically hindered substrates and the substitution in *para*-position of the phenyl leaves a large free space around the azido or ethynyl group.[1] Second, the high yields of formation of **19**–**21** clearly show that electronic factor can be also excluded. More certainly, the low yield of **14** is due to the presence of zinc porphyrin that partly degrades during the silica gel column chromatography. This phenomenon is particularly accentuated with the zinc porphyrin dimer **14** compared to mono zinc porphyrin **19**–**21**. A good support of this assumption is that the purification of the crude after demetalation of the porphyrins by HCl permitted us to obtain the expected bis(free base porphyrin) analagous of **14** with a 70% yield.

Finally, we investigated the reaction of the *meso*-azido porphyrin **2** with phenyl acetylene **16** and *meso*-ethynyl zinc porphyrin **22** using (SIMes)CuBr as catalyst in the above conditions. The coupled products **26** and **24** were formed with 41% and 18% yield, respectively, (Fig. 2 and Scheme 4). The lower yield for the zinc porphyrin containing compound **24** compared to that of **26** and **25** is also explained by the degradation of the ZnP unit during silica gel column chromatography. Unlike porphyrins **1** and **13** which are strictly insoluble in DMF, the significant solubility of the porphyrins **2**, **22** and **23** in this latter solvent allowed us to test the conditions reported by Chen and co-workers for β-azidotetraaryl porphyrins ($CuSO_4$, $4H_2O$, ascorbic acid, 50 °C, DMF, 50 h).[2] In these conditions, **24** and **25** were effectively formed with 18% and 41% yields, respectively. These latter experiments, firstly show that the conditions reported here with (SIMes)CuBr are at least as efficient and probably superior than those using $CuSO_4$, $4H_2O$ in DMF and secondly they confirm that the presence of zinc porphyrin reduces the isolated yield, since **25** is formed with more than a fold yield relative to that of **24**.

Overall, the general lower yields of the Huisgen reaction with porphyrin **2** relative to those obtained with porphy-



Scheme 4. Huisgen reaction of the azido porphyrin **2** with the ethynylporphyrins **22** and **23**.

rin **1** are most probably correlated with the thermal instability of the azido porphyrin **2**, which may partly decompose during the reaction with the alkyne.

In summary, we report the successful preparation of new azido porphyrins **1** and **2** with relatively good yields. When the azido group is directly connected to the porphyrin core (compound **2**), we observed that its stability is highly dependent of the metal inside the porphyrin. The reactions of these azido porphyrins **1** and **2** with several terminal alkynes were investigated using different catalytic systems. We found that the recently reported copper carbene (SIMes)CuBr[17] was a better catalyst than most of the usual copper complexes used for this transformation. The former proved to be particularly efficient with azido phenyl porphyrin **1**, but the yields obtained with *meso*-substituted azido porphyrin **2** were much lower probably due to its thermal decomposition during the course of the reaction. However, using (SIMes)CuBr catalyst in the solvent mixture THF/water 3:1, several adducts with porphyrins **1** and **2** were formed, opening thus the possibility to click probably numerous terminal alkynes on azido porphyrins **1** and **2** in very mild conditions. We believe that these latter synthons could be useful to prepare new porphyrin-based systems in view of various applications.

General Procedure for Huisgen reaction: Azido porphyrin (0.03 mmol, 1 equiv) and alkyne (1 equiv) were solubilized in 3 mL of THF. SIMesCuBr (15 μmol) and 1 mL of water were added. The mixture was stirred at 45 °C for 72 h. After cooling to room temperature, the crude mixture was evaporated to dryness and the residue was purified by silica gel flash column chromatography to give the coupled product.

Acknowledgements

The French Research Ministry is gratefully acknowledged for the financial support of these researches through the ANR program entitled ‘PhotoCumElec’ and Region Pays de la Loire for CER program. FO thanks Benoit Colasson (Univ. Paris 5) for fruitful discussion about the preparation of azido derivatives.

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6. *Analytical data of* **1**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.62 (s, 27H, ^{t}Bu), 7.39 (d, 2H, H-*m*-aryl-N$_3$), 7.76 (d, 6H, H-*m*-aryl-^{t}Bu), 8.15 (d, 6H, H-*o*-aryl-^{t}Bu), 8.21 (d, 2H, H-*o*-aryl-N$_3$), 8.89 (d, 2H, H$_\beta$), 9.00 (m, 6H, H$_\beta$), MS MALDI-TOF, *m*/*z* calculated for $C_{56}H_{51}N_7Zn - N_2 + 2H$: 859.3; found, 859.2.
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