Highly Efficient Synthesis of Chloro- and Phenoxy-Substituted Subphthalocyanines

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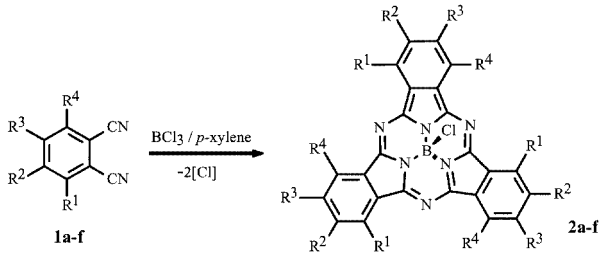
A highly efficient method for the synthesis of chloro-substituted subphthalocyanines employing a 1 M boron trichloride solution in *p*-xylene is described and compared to other previously described results. The substitution reaction of the axial chlorine atom by a phenoxy group has been optimized.

Subphthalocyanines[1] (SubPcs, Scheme 1) are cone-shaped, aromatic macrocycles made of three diiminoisoindoline units *N*-fused around a boron atom. Their 14 π-electron core and their peculiar geometry have made SubPcs of special interest in the fields of dyes,[2,3] optical recording,[4,5] supramolecular chemistry[6] and nonlinear optics.[7,8] Up to now, the physical properties of variously substituted SubPcs could not be fully exploited due to their difficult synthesis and purification.[1]

Among the different boron reagents employed so far in SubPc synthesis (BCl_3, BBr_3, BF_3, BPh_3, $BPhCl_2$), BCl_3 is the most commonly employed since it offers the best compromise between macrocyclization yields and stabilities of the chloroSubPcs formed. However, the handling of this hazardous gaseous reagent and its moisture sensitivity turn the cyclotrimerization reaction of phthalonitriles into a low-yielding and not fully reproducible method. The most recurrent synthetic procedure described so far in the literature requires the addition of an excess of BCl_3 to a solution of the phthalonitrile precursor in a high boiling solvent such as 1-chloronaphthalene.[1] The boron reagent is added as a previously condensed liquid or from solutions in low-boiling point solvents. The yields obtained usually range from 10% to 50% and, moreover, depend very much on the phthalonitrile employed and on the purity and dryness of the solvent. In this communication, we describe a new procedure for SubPc preparation that is easy to set up, quick, clean and high yielding.[2] Moreover, we have devised an optimized procedure for the axial substitution of chloro-SubPcs with phenol and phenol derivatives.



	1a / 2a	1b / 2b	1c / 2c	1d / 2d	1e / 2e	1f / 2f
R^1	H	F	H	H	H	H
R^2	H	F	SC_8H_{17}	$SO_2C_8H_{17}$	NO_2	I
R^3	H	F	SC_8H_{17}	$SO_2C_8H_{17}$	H	H
R^4	H	F	H	H	H	H

Scheme 1. Synthesis of chloroSubPcs **2a**−**f** from phthalonitriles **1a**−**f**

Results and Discussion

In the course of a research project aimed at scaling up the reaction and improving the yield of SubPc formation,

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it occurred to us that previously prepared solutions of BCl_3 in a moderately high-boiling aromatic solvent such as *p*-xylene may avoid the use of other, still higher-boiling solvents, while offering a simple and straightforward synthetic procedure. The use of a *p*-xylene solution presents several advantages: (i) it is easy to handle and allows the addition of exact quantities of boron trichloride; (ii) *p*-xylene is an excellent solvent for the starting benzodinitriles and its boiling point is sufficiently high (138 °C); (iii) the two equivalents of chlorine released during the formation of the SubPc (Scheme 1) can be efficiently reduced by this solvent, thus avoiding SubPc chlorinated by-products;[9,10] and (iv) the reaction is easy to set up. A standard version of this new method, applied to unsubstituted phthalonitrile **1a** (Scheme 1), consists of the addition of one equivalent of BCl_3 from a commercial 1 M solution in *p*-xylene to dry phthalonitrile under an argon atmosphere (Scheme 1). The reaction mixture is stirred at the reflux temperature of *p*-xylene for 20 min, then extracted with toluene. The solvents are evaporated from the filtrate and the remaining purple solid washed with methanol and hexane. Pure SubPc **2a** is obtained in 82% yield, noticeably higher than with previous methods.

Table 1. Influence of the temperature on the yield of chloroSubPc formation in *p*-xylene

Temperature [°C]	Yield [%]
0	0
45	19
100	57
138	82
145[a]	78

[a] Using cumene as cosolvent.

In order to reach the most suitable experimental conditions we tested the influence of a number of reaction parameters on the yield of isolated SubPc **2a**, namely the reaction temperature (Table 1), the amount of boron trichloride (Table 2), the use of additional solvent (Table 3) and the concentration of starting phthalonitrile (Table 3).

Table 2. Influence of the number of BCl_3 equivalents on the yield of chloroSubPc formation in *p*-xylene at reflux temperature (138 °C)

BCl_3 equivalent [mol/mol intended SubPc]	Yield [%]
1	19
2	32
3	82
4	72
5	68

When the reaction is carried out entirely in an ice bath, the white slurry formed after addition of BCl_3 stays white even after 6 hours at 0 °C and no SubPc material could be isolated (Table 1). The reaction does take place at 45 °C, but the isolated yield is only 19% after 2 h. The condensation of phthalonitrile **1a** is more efficient when the reaction is carried out at higher temperatures. Thus, the isolated yield increased from 57% at 100 °C to 82% in refluxing *p*-xylene. Higher reflux temperatures were attained by adding 2 mL of dry cumene, another reducing aromatic solvent [purified following method (iv), see below], but the yield was not further improved (78%). It may be concluded that the reactivity of cumene towards the chlorine liberated is not materially different from that of xylene. This would suggest that chlorine is expelled in its atomic form, as Cl atoms are known to react at diffusion-controlled rates with benzylic compounds.[11]

Table 3. Influence of the cumene cosolvent volume and purification method on the yield of chloroSubPc formation at reflux using three equivalents of BCl_3 (1 M in *p*-xylene) with respect to the formed SubPc

	Purification Method[a]			
Cumene Volume [mL]	(i)	(ii)	(iii)	(iv)
0	82	82	82	82
2	23	34	46	77
4	10	16	21	71

[a] See text.

To the best of our knowledge, no experimental correlation between the phenomenological stoichiometry of BCl_3 with respect to the starting phthalonitrile has been reported. Nevertheless, all the synthetic procedures described so far in the literature employ a large excess of BCl_3. Our experiments (Table 2) have shown that an excess of BCl_3 is required and that a maximum yield (82%) was reached upon addition of three equivalents of BCl_3 per SubPc formed (one equivalent per starting phthalonitrile), higher excesses resulting in slightly lower yields. On the other hand, the addition of sub-stoichiometric amounts of BCl_3 resulted in much lower yields (from 19 to 32%, Table 2).

Many different aromatic solvents (1-chloronaphthalene, 1-methylnaphthalene, naphthalene, 1,2,4-trichlorobenzene, chlorobenzene...)[1] have been employed in SubPc synthesis. From our own experience, their purity and dryness are critical factors. This became apparent when a series of experiments were carried out employing cumene as co-solvent (cumene was used because it was hoped that this highly H-donating compound might further increase the yield). Prior to the reaction, cumene was treated using four different methods: (i) cumene was introduced without treatment, (ii) cumene was dried through an Alumina column, (iii) cumene was purified by distillation, and (iv) cumene was thoroughly purified and dried by first washing it with concentrated sulfuric acid until the acid layer became transparent, then it was washed with water and with a 10% $NaHCO_3$ solution, dried over $MgSO_4$ and distilled from over Na.[12] The cumene obtained after each of these treatments was added to the phthalonitrile before the addition of the solution of BCl_3 in *p*-xylene. Table 3 shows the isolated SubPc yields obtained when adding different volumes of each kind of treated cumene. These data outline the significance of purity and dryness of the solvent in this reaction. When the

cumene was treated using method (iv), the yield decreased only slightly as the volume added increases; with cumene treated by procedures (i) to (iii), the decrease was much larger. This decrease could be due to an incomplete purification/drying but also, in case (iv), it may indicate that higher dilution of the reactants has a negative effect on the outcome of the condensation.

In order to demonstrate the relevance of this procedure for the production of larger SubPc quantities, the reaction was scaled up to gram amounts of starting phthalonitrile. Thus, starting with 2 and 20 grams of phthalonitrile, SubPc **2a** was obtained in 77% and 73% yields, respectively.

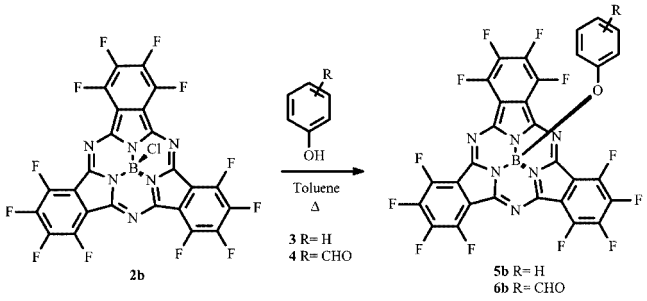
This method would not be of much interest if its scope was limited to the synthesis of unsubstituted chloroSubPc. Thus, the reaction was carried out with a representative range of substituted phthalonitriles **1b**−**f** employing the standard procedure described above. Table 4 shows the yields of isolated SubPcs and compares them with the best yields reported in the literature so far. It is clear from these results that this new method, besides being very straightforward, surpasses any other from all points of view.

Table 4. Comparison between the yields obtained with the present method and the best reported yields for the same chloro-subphthalocyanines

Starting phthalonitrile	Reported yield [%]	Obtained yield [%]
Phthalonitrile (**1a**)	64[18]	82
Tetrafluorophthalonitrile (**1b**)	not reported[19,20]	74
4,5-Bis(octylthio)phthalonitrile (**1c**)	26[7]	51[a]
4,5-Bis(octylsulfonyl)phthalonitrile (**1d**)	11[7]	64
4-Nitrophthalonitrile (**1e**)	80[21]	88
4-Iodophthalonitrile (**1f**)	45[21]	70

[a] Hydroxysubphthalocyanine was isolated from this reaction in 11% yield.

It is a well-known fact that chloro-SubPcs tend to decompose over a few weeks in solution in the presence of light.[1,19] With the prototype **2a**, we have observed a quantum yield of bleaching of about 2×10^{-4} in the UV at a wavelength of 313 nm based on ferrioxalate actinometry.[13] Probably, the weak boron-chlorine bond together with the long-lived triplet state[7,14] are responsible for this light-driven instability. One way of partially overcoming this instability might be to shorten the triplet lifetime by appropriate substitution, and, in particular, replacing the chlorine atom by other axial substituents. Also, the variation of axial substitution is of more general interest beyond the question of photostability. Among the many possible substituting groups, we found that phenol derivatives, for experimental reasons, offer many advantages: (i) phenol derivatives are available in large quantities, (ii) they may be useful for introducing new functional groups in the axial position of SubPcs, and (iii) it is possible to alter their substitution pattern in order to control the geometry of their adducts with SubPcs.[15] Since this substitution reaction is of great relevance for expanding the chemistry of SubPcs, we devised an optimized procedure that ultimately led to the formation of phenoxy-SubPc **5b**[20] (Scheme 2) in 91% yield.



Scheme 2. Axial substitution of chloroSubPc **2b** with phenols **3** and **4** that yield phenoxySubPcs **5b** and **6b**

The most commonly reported substitution methods make use of the crude product from chloro- and bromo-SubPc formation reactions that are quenched with the desired alcohol to yield the corresponding alkoxy-SubPc.[1,16] This method proved to be rather low-yielding and the resulting alkoxy-SubPcs are difficult to purify as a consequence of the low purity of the starting chloro- or bromo-SubPcs. We found that the reaction between pure chloro-SubPc **2b** and a fivefold excess of phenol in toluene at reflux gave very good yields of phenoxy SubPc **5b**. A standard version of this procedure is the following: SubPc (**2b**; 325 mg, 0.5 mmol) and phenol (**3**; 235 mg, 2.5 mmol) were heated to reflux in 2 mL of toluene (Scheme 2) until complete consumption of the starting material (typically 16−20 hours checked by TLC). The solvent was evaporated and the resulting crude solid was washed with a 4:1 mixture of methanol and water to remove the unreacted phenol. SubPc **5b** was further purified by silica gel column chromatography (CH_2Cl_2/hexane, 2:1) and obtained in 91% yield.

In a similar way as described in the previous section, the influence of the solvent, the temperature and the concentration of the starting materials on the outcome of the reaction were studied.

In a polar solvent such as acetonitrile the reaction is faster but the yield is moderate (63% after 3 hours at reflux) as a consequence of SubPc decomposition in polar media.[19] When the reaction is carried out at reflux in less-polar solvents such as THF, toluene or *o*-xylene the reaction is slower but the decomposition is much less significant. In this case, higher-boiling solvents like toluene or *o*-xylene provide better yields (91% and 90%, respectively, after 20 hours) than lower-boiling ones such as THF (68% after 50 hours). Increasing the reaction temperature resulted in better yields and also in a notable shortening of the reaction times (Table 5). The same reaction performed without solvent in molten phenol (melting point: 40−42 °C) gave lower yields (ca. 70−80%) at 50, 70 and 110 °C but proceeded with much shorter reaction times (Table 5). The use of equimolar quantities of sodium phenolate, instead of phenol, or the addition of stoichiometric amounts of strong bases such as NaH or DBU to the reaction medium resulted in very fast decomposition of the SubPc macrocycle and

yielded only very small amounts (<5%) of isolated phenoxy-SubPc even at low temperature (−10 °C).

Table 5. Influence of the temperature on the yield and the time necessary for the completion of the substitution reaction of SubPc (**2b**) with phenol in toluene or without solvent

	In toluene		Without solvent	
Temperature [°C]	Time [h]	Yield [%]	Time [h]	Yield [%]
50	100[a]	51	16	82
70	54	70	10	71
110	20	91	1	78

[a] The reaction was stopped before completion.

During the course of our experiments, we also noticed a significant increase of the axial substitution rate at increasing reactant concentrations. Table 6 shows the time required for completing the reaction at different SubPc (**2b**) concentrations in toluene. When the reaction was carried out using phenol itself as solvent,[17] the substitution was rapidly completed but the yield was lower than in toluene (Table 5). In addition, decreasing the SubPc concentration resulted in lower yields as a consequence of the decomposition of SubPc during such long periods of time.

Table 6. Influence of the starting SubPc concentration on the yield of the substitution reaction of **2b** with phenol in toluene at reflux temperature

SubPc concentration [M]	Time [h]	Yield [%]
0.01	100[a]	54
0.05	89	70
0.1	46	83
0.25	20	91

[a] The reaction was stopped before completion.

We also found that when trying to incorporate some substituted phenols, such as 3-hydroxybenzaldehyde (**4**), the reaction in toluene was very slow (39% after 3 days at reflux in standard conditions) while carrying out the reaction in molten hydroxybenzaldehyde (melting point: 103−105 °C) resulted in much better yields of SubPc **6b** (76% after 1 h at 120 °C).

Conclusion

SubPc chemistry is a rapidly expanding field that needs to be able to rely on a strong synthetic base in order to receive the attention it deserves. In this communication, we have demonstrated that SubPcs are versatile compounds which can be synthesized in good yields and which can be readily functionalized with phenol derivatives.

Experimental Section

UV/Vis spectra were recorded with a Hewlett−Packard 8453 instrument. IR spectra were recorded on a Bruker Vector 22 spectrophotometer. LSI-MS and HRMS spectra were determined on a VG AutoSpec instrument. NMR spectra were recorded with a BRUKER AC-300 instrument. Elemental analyses were performed with a Perkin−Elmer 2400 apparatus. Column chromatography was carried out on silica gel Merck-60 (230−400 mesh, 60 Å), and TLC on aluminum sheets precoated with silica gel 60 F_{254} (E. Merck). Chemicals were purchased from Aldrich and used as received without further purification.

Standard Procedure for the Synthesis of SubPcs 2a−f: BCl_3 (2 mL, 1 M solution in *p*-xylene) was added to dry phthalonitrile (2 mmol) under an argon atmosphere. The reaction mixture was stirred under reflux for 20 min. The purple solution was then flushed with argon. **2a:** The solvent was evaporated and the solid was extracted with toluene (100 mL). The solution was evaporated and the resultant purple solid was thoroughly washed with methanol (50 mL) and hexane (50 mL) to yield pure SubPc (**2a**), 235 mg (82%) with physical characteristics identical to the ones already described.[18] **2b−f:** The solvent was evaporated and the resulting purple solid was subjected to silica gel column chromatography [eluent: **2b** hexane/ethyl acetate (3:1, v:v), **2c** hexane/ethyl acetate (20:1, v:v), **2d** dichloromethane, **2e** toluene/ethyl acetate (10:1, v:v), **2f** toluene] to yield **2b** (319 mg, 74%), **2c** (441 mg, 51%), **2d** (635 mg, 64%), **2e** (332 mg, 88%), **2f** (377 mg, 70%) with physical characteristics identical to the ones already described.[7,20,21]

Standard Procedure for the Axial Substitution Reaction of SubPc 2b: SubPc (**2b**; 325 mg, 0.5 mmol) and phenol (235 mg, 2.5 mmol) were refluxed in toluene (2 mL) for 16 h. The reaction mixture was cooled down to room temperature, the solvents evaporated and the resulting purple solid was washed with a 4:1 mixture of methanol/water before being subjected to column chromatography on silica gel using dichloromethane/hexane (1:2, v:v) as eluent. SubPc (**5b**) was isolated as a purple solid in 91% yield with physical characteristics identical to the ones already described.[20]

Subphthalocyanine 6b: A mixture of SubPc (**2b**; 325 mg, 0.5 mmol) and 3-hydroxybenzaldehyde (305 mg, 2.5 mmol) was stirred at 120 °C for 1 h, cooled down to room temperature, the solvents evaporated and the resulting purple solid was washed with a 4:1 mixture of methanol and water before being subjected to column chromatography on silica gel using dichloromethane/hexane (2:1, v:v) as eluent. SubPc (**6b**) was isolated as a purple solid in 76% yield (278 mg). m.p. > 250 °C. R_f (dichloromethane/hexane, 2:1) = 0.39. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.58 (s, 1 H, CHO), 7.20 (d, J_o = 7.6 Hz, 1 H), 6.98 (dd, J_o = 7.6, $J_{o'}$ = 8.2 Hz, 1 H), 5.90 (m, 1 H), 5.55 (dd, J_o = 8.2, J_m = 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 191.1 (CHO), 152.0, 148.4, 144.3 (m, C-F), 140.7 (m, C-F), 137.6, 130.1, 124.8, 124.7, 118.9, 114.9 (m, C-O) ppm. FAB-MS: *m/z* = 731.9 $[M]^+$. HRMS calcd. for $C_{31}H_5F_{12}BO_2N_6$: 732.0375; found 732.0406. UV/Vis ($CHCl_3$): λ_{max} (log ε) = 571 (4.5), 531 (1.3), 307 (2.0), 268 (1.4), 241 (1.4). IR (KBr): $\tilde{\nu}$ = 1682 (C=O), 1533, 1483, 1266, 1112, 1091, 1054 (B-O), 966 cm^{-1}.

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