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Microwave-assisted synthesis of metalloporphyrazines

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Abstract—The synthesis of metalloporphyrazines with enhanced yields directly from substituted maleonitriles is described. The one-step procedure involves tetramerization using hexamethyldisilazane, *p*-toluenesulfonic acid and DMF in a sealed tube under microwave irradiation. The reaction time has been drastically reduced from 24 h by classical oil-bath heating to just 15 min.

Porphyrinic macrocycles are the subject of great interest in areas such as catalysis,[1] photodynamic therapy[2] and in the fabrication of molecular electronic[3] or magnetic devices.[4] Porphyrazines have received significantly less attention compared to porphyrins and phthalocyanines. However they are now the subject of increasing research with respect to their synthesis, properties and applications.[4,5] Since its development in 1952, the Linstead macrocyclization[6] of acyclic maleonitriles is still the only widely used method for porphyrazine synthesis. Although it is hard to envisage a faster or more versatile route, the procedure is frequently plagued with poor yields and difficulties with purification. Barrett, Hoffman and co-workers have published extensively on the synthesis of porphyrazines bearing thiols, amines or alcohols as ring substituents, with the conversion of these polydentate ligands to a variety of coordination complexes.[5] Recently, Kadish and co-workers reported the synthesis of new Li^I, Na^I, Mn^{II} and Co^{II} porphyrazine complexes, which represents a convenient route for the preparation of several other metal complexes.[7] For our studies we were interested in various functionalized zinc porphyrazines and found that reported syntheses involved two to three steps, long reaction times, cumbersome work-up procedures and poor yields. Recently, we reported the one-pot synthesis of metalloporphyrazines from maleonitriles with hexamethyldisilazane (HMDS) and a catalytic amount of *p*-toluenesulfonic acid (PTSA) in a single step.[8]

However, this method required reaction temperatures as high as 100 °C, and long reaction times (10–24 h). There is a need to further reduce the reaction time such that decomposition of maleonitriles would be significantly reduced and hence should improve the yield of the products.

Microwave-assisted reactions have attracted much interest because of their simplicity in operation and milder reaction conditions.[9] The salient features of the microwave approach are enhanced reaction rates, formation of pure products in high yields and ease of isolation. We extended the microwave technology to synthesize porphyrazines efficiently, in short reaction times, and improved yields using a laboratory microwave oven. Our results are reported in this Letter.

1,2-Bis(dimethylamino)maleonitrile **1a** was subjected to tetracyclization with HMDS (4.0 equiv) and a catalytic amount of PTSA (0.2 equiv) in 4 mol/L DMF solution in the presence of $Zn(OAc)_2$ (0.25 equiv) under microwave irradiation for 11 min. The reaction, after work-up and column purification through neutral alumina, afforded the symmetrical porphyrazine **Zn-2a**[10] in 53% yield (Table 1, entry 1).[11] The reaction was run under similar conditions with $ZnCl_2$ and $ZnBr_2$ and gave **Zn-2a** in 42% and 44% yields, respectively (entries 2 and

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Keywords: Maleonitriles; Microwave irradiation; Substituted octaminoporphyrazines; Octakis(alkyl-thio)porphyrazines.

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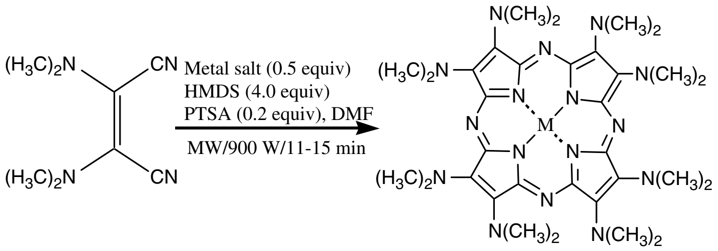
Table 1. Microwave-assisted synthesis of different metalloporphyrazines **M-2a** from maleonitrile **1a** using various metal salts

Entry	Metal salt	Irradiation time (min)	M	Product	Yield (%)
1	$Zn(OAc)_2$	11	Zn	**Zn-2a**	53
2	$ZnCl_2$	15	Zn	**Zn-2a**	42
3	$ZnBr_2$	15	Zn	**Zn-2a**	44
4	$CuCl_2$	15	Cu	**Cu-2a**	45
5	$Cu(OAc)_2$	15	Cu	**Cu-2a**	41
6	$MgCl_2$	15	Mg	**Mg-2a** **H_2-2a**	20 18
7	$Mg(OAc)_2$	15	Mg	**Mg-2a** **H_2-2a**	30 15
8	$NiCl_2$	15	Ni	**Ni-2a**	45
9	$CoCl_2$	15	Co	**Co-2a**	45
10	$InCl_3$	15	In	**InCl-2a**	42



1a **2a**

Scheme 1.

3). The reaction was also carried out in the presence of several different metal salts. $CuCl_2$ and $Cu(OAc)_2$ afforded **Cu-2a** in 45% and 41% yields (entries 4 and 5). In the cases of $MgCl_2$ and $Mg(OAc)_2$, the formation of metal-free porphyrazine **H_2-2a** was also observed along with the metallated product **Mg-2a** in 38% and 45% total yields (entries 6 and 7). Under conventional heating, **Mg-2a** was the minor product and **H_2-2a** the major.[8] We assumed that a long reaction time at high temperature results in demetallation by PTSA present in the reaction medium to give metal-free porphyrazine, whereas a short reaction time (microwave) supresses demetallation. Products **Ni-2a**, **Co-2a** and **InCl-2a** were formed in moderate yields (entries 8–10) (Scheme 1).

Table 2 depicts the results of the tetracyclization reaction of various 1,2-disubstituted maleonitriles **1a**–**g** to the corresponding Zn porphyrazines. The differences in the reaction times and yields obtained under microwave irradiation compared to those from oil-bath heating is noteworthy. Invariably, all the substrates reacted within 11–15 min improving the yields by 8–15%. Thus, porphyrazinoctaamine derivatives **2a**,**b** were synthesized from 1,2-bis(dimethylamino)maleonitrile **1a** and 1,2-

Table 2. Microwave-assisted synthesis of Zn-porphyrazines (**2a**–**g**), a comparative study of reaction time and yield with MW verses oil-bath heating

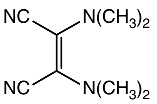
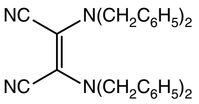
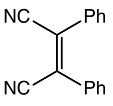
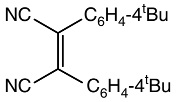
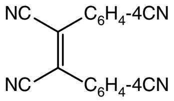
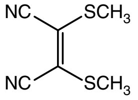
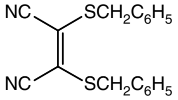
Entry	Substrate	Product	MW		Oil-bath heating[a]	
			Time (min)	Yield (%)	Time (h)	Yield (%)
1	 **1a**	**2a**	11	53	24	43
2	 **1b**	**2b**	15	50	24	38
3	 **1c**	**2c**	15	48	24	40

Table 2 (*continued*)

Entry	Substrate	Product	MW		Oil-bath heating[a]	
			Time (min)	Yield (%)	Time (h)	Yield (%)
4	 **1d**	**2d**	12	45	24	29
5	 **1e**	**2e**	15	42	24	31
6	 **1f**	**2f**	15	43	24	35
7	 **1g**	**2g**	15	40	24	28

[a] Results cited from Ref. 8.

bis(dibenzylamino)maleonitrile **1b** under microwave irradiation in 53% and 50% yields, respectively, where the improvement in yield was 10–12% and the reaction time was reduced from hours to minutes (Table 2, entries 1 and 2). Aryl-substituted maleonitriles **1c**–**e** afforded **2c**, **2d** and **2e** also in improved yields. In other reported methods, diarylmaleonitriles were first converted to five-membered heterocyclic intermediate pyrrolinediimines which were then tetramerized to the octaaryl-substituted porphyrazines. The increased number of steps led to reduction of the overall yields.[12] 1,2-Bis(methylthio and benzylthio)maleonitriles **1f**–**g** gave, after microwave irradiation for 15 min, octakis(alkylthio)porphyrazines **2f**,**g** in 43% and 40% yields, respectively, whereas under thermal heating the yields were only 35% and 28%. The structures of all the products were confirmed by mass (MALDI-TOF), IR and/or ^{1}H NMR spectroscopy as well as elemental analyses.

In conclusion, we have developed a very convenient and fast synthesis of metalloporphyrazines in improved yields directly from various maleonitriles under microwave irradiation conditions. Extension of the technique for the synthesis of unsymmetrical, hybrid and binuclear porphyrazines is in progress.

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11. *Representative procedure*: A Teflon vial was charged with 1,2-bis(dimethylamino)maleonitrile (328 mg, 2 mmol),

HMDS (1.68 mL, 8 mmol), $Zn(OAc)_2$ (220 mg, 1 mmol), PTSA (76 mg, 0.4 mmol) and DMF (1 mL) and sealed under nitrogen. The contents were mixed thoroughly and irradiated in a commercial laboratory microwave oven (Ethos 1600 Advanced Microwave Labstation) at 900 W for 11 min. The colour changed to dark blue during the reaction. After cooling, the reaction mixture was evaporated to dryness under reduced pressure and the residue was subjected to neutral alumina column chromatography eluting with hexane–EtOAc (9:1). The blue coloured band was collected and evaporated to dryness to give [2,3,7,8,12,13,17,18-octakis(dimethylamino)porphynazinato]-zinc(II) **2a** (198 mg, 55% yield) as a dark blue crystalline solid (mp >350 °C).

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