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Microwave-assisted synthesis of corroles

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Abstract—The recently developed Gross's method for the synthesis of corroles has been modified and successfully applied to the preparation of new free base tris-aryl- and tris-pyrimidyl-corroles using solvent-free conditions and microwave irradiation. Compared to conventional heating, the microwave technique afforded an increase in corrole yields of ca. 30% and led to noticeably cleaner reaction mixtures. It is demonstrated that short reaction times and high temperatures are required to afford optimum yields. © 2003 Elsevier Science Ltd. All rights reserved.

Corroles are porphyrin analogues which lack one *meso* carbon bridge. Recently several synthetic methods have been reported[1a–d,2a–c] which allow corroles to be obtained in reasonable quantities and to be used for a wide range of applications as catalysts.[3a–g] The solvent-free method developed by Gross on solid support is quite straightforward, it has been developed for electron-withdrawing aldehydes and in fact only tris-pentafluorophenylcorrole **4** was obtained in 8–11% yield after heating.[1a,b] We report here the application of this methodology to other electron-withdrawing benzylaldehydes as well as to one pyrimidyl-aldehyde. Furthermore, several reports have shown that using microwave irradiation (MW) instead of conventional heating (H) raises yields, enhances reaction rate, reduces thermal degradation by-products for a wide range of organic reactions[4] including cyclocondensation reactions leading to tetraarylporphyrins[5a,b] and phthalocyanines.[6a–d] In an effort to improve corrole yields, conventional heating was replaced by microwave irradiation. Indeed the microwave dielectric heating effect is an efficient heating source for thermally demanding organic reactions, such as corrole synthesis. Herein we report the first method to synthesize corroles under microwave irradiation, and the first application of Gross's method to other kinds of aldehydes.

New corroles **1**–**3** and **5**–**7** whose structures are depicted in Figure 1, and known ones like tris-pentafluorophenyl corrole **4**[1a,b] and tris-pyridyl-corrole **8**[1d] have been synthesized following two different heating procedures[7,8] and characterized by ^{1}H, ^{19}F NMR, HRMS and UV–vis.[9] In Table 1, yields of **1**–**8** are compared either when the reaction was carried on under the precise conditions described by Gross using conventional heating (entry H) or after using microwave irradiation (entry MW). Entry c gives the resulting increase of yield.

Previously Gross showed that **4** would be obtained in 8–11% yield after 1 min–4 h under conventional heating at 100°C;[1a,b] whereas we show here that 13–15% of isolated yield are obtained after only 2 min of microwave irradiation (ca. 47% increase). As pointed out by Gross, the reproducibility of this solvent-free synthesis on alumina in terms of isolated yields varies because of variation in the effectiveness of stirring. With a series of less reactive fluorinated benzaldehydes we showed that a similar range of yield increase is observed. Indeed, tetrafluorobenzaldehyde led to corrole **3** which went from 10.5% (H) to 13% (MW) (ca. 28% increase). However other aldehyde precursors did not react spontaneously with pyrrole at room temperature and require thermal or microwave activation. Thus trifluorobenzaldehyde led to corrole **2** in 6.7% (H) which increased to 8.9% (MW, ca. 33% increase). An experiment led to 12% which corresponds to 80% yield increase. Similarly *p*-fluorobenzaldehyde led to corrole **1** in 1.5% (H) and reached 2.0–2.5% (MW, 30% increase). We accounted for the observation Gross previously made on two precursors, 2,6-difluorobenzaldehyde and pentafluorobenzaldehyde,[1b] by examining a range of aldehydes of different degrees of fluorination here, that the yield of corroles **1**–**4** is dependent upon the percentage of electron-withdrawing F atoms of the aldehydes (Table 1).

Keywords: corrole synthesis; microwave irradiation.

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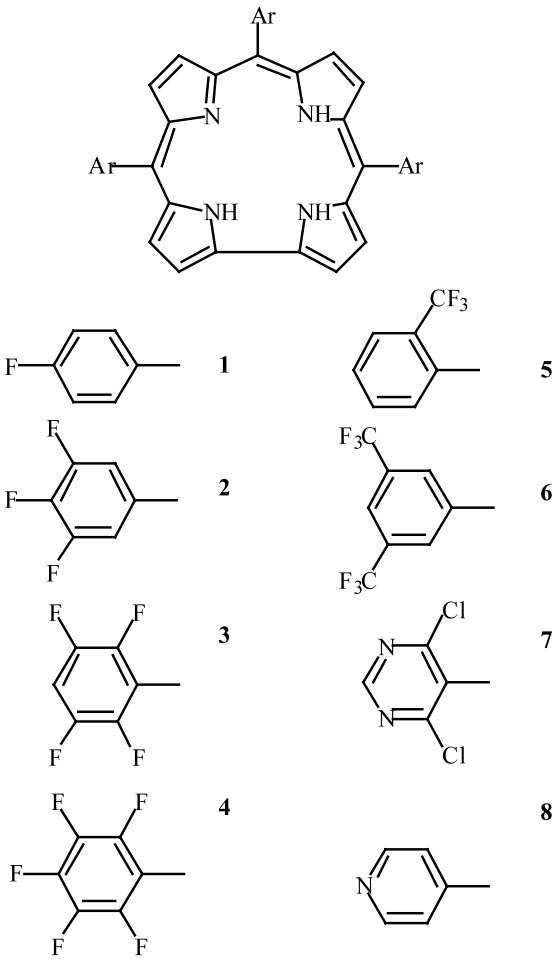

Figure 1.

Another series of aldehydes was examined comparing H versus MW wit h two trifluoromethyl-containing benzaldehydes. The *o*-monosubstituted derivatives afforded the corrole **5** in 9.1% yield (H) and 12% yield (MW, ca. 31% increase), while 3,5-bis-trifluoromethyl-benzaldehyde afforded corrole **6** in 8.5% yield (H) and 10.2–11% yield (MW, ca. 20–29% increase). Ghosh reported earlier 7–10% yield with the *para* analog of **5**.[10] This demonstrates that the trifluoromethyl moiety exerts a sufficient activating inductive effect to make the aldehyde reactive enough towards pyrrole to afford corroles **5**–**6** in reasonable yields. However these yields did not increase with the number of CF_3 groups, contrary to what is observed with F atoms.

Using 2,6-dimethyl-pyrimidyl-carbaldehyde, prepared as reported in the literature,[11a,b] corrole **7**, a close analogue of the 2,6-dichloropyrimidine-bis-(2,6-dichlorophenyl)-corrole reported by Asokan,[12] was obtained in 4.5% yield (H) and 6.2% yield (MW, ca. 37% increase). Unfortunately with 4-pyridyl-carbaldehyde, the yields of corrole **8** obtained remained very small 2.2% (H) versus 3.3% (MW) despite a greater increase in yield than with the other precursors (50% increase). Consequently the modified Rothemund method developed by Paolesse using a reflux in acetic acid appears to be the most appropriate method with a 9% reported yield.[1c,d] With trimesitaldehyde no trace of trimesityl-corrole was obtained (data not shown).

Replacing thermal heating by microwave irradiation led to a noticeable increase in yield of at least 30% in most cases. Similarly we noticed that after MW use, the amount of impurities whose R_f values are close to corrole's dropped significantly. For example, the pentapyrrotetramethene side product previously reported in the synthesis of **4**[1b] was isolated from the synthesis of **6** in smaller yield after MW heating (4%) than after conventional heating (8%).[13] The same observation was made for the syntheses of corroles **1**–**4**, and **5**. In terms of reaction time, Gross showed that using pentafluorobenzaldehyde, corrole **4** was obtained within 1 min.[1b] We show here that such short reaction times are feasible using the tetrafluorinated and pyrimydyl precursors which underwent an exothermic reaction with pyrrole at room temperature affording corroles **3** and **7**. But in any case heating is required to afford the optimum yields of corroles **3**, **4** and **7**. On the other hand, less reactive aldehydes leading to corroles **1**–**2**, **5**–**6** and **8** required either thermal or microwave assistance to react with pyrrole. It is interesting to point out that the reaction of 2,6-dichloro-pyrimidine carbaldehyde with pyrrole is very exothermic and afforded compound **7** in reasonable yields (4.5% (H) versus 6.2% (MW)) while an earlier work reported that no corrole was formed with 2,6-dichlorobenzaldehyde even after heating.[1a]

The temperature and reaction time were checked on the synthesis of corrole **6** (Table 2). When the temperature was raised to 200°C at a reaction time of 2 min, the yields increased to 12.8% (ca. 45% increase), while higher temperature (250°C) led to 7.5% of **6** only. When the reaction time was prolonged to 20 min a loss of 20% of the overall yield was observed at 120°C. This

Table 1. Yields of corroles **1**–**8** after conventional (H) or microwave (MW) heating at 120°C. Entry (c) corresponding yield increase (MW versus H)

Entry	C	O	R	R	O	L	E	S
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
H	1–1.5	6.7	10.5	8–11	9.1	5.7–9.5	4.5	2
MW	2.5	8.9 (12)	14	13–15	12	10.2–11.2	6.2	3.3
c	40	33 (80)	28	36	31	23	37	25–50

Table 2. Effects of temperature and reaction times on the yields of corrole **6** (MW heating)

			Temperature (°C)	
Time (min)	120	160	200	250
2	10.2	10.3	**12.8**	7.5
10	9.0	8.3	–	–
20	8.0	–	4.2	1.5

Table 3. Yields of corrole **6** under conventional (H) or microwave (MW) heating at 120°C, after some modifications in the general procedure. Entry (a) as reported in Table 1. (b) NaCl introduction. (c) 3 equiv. acetic acid

Entry	A	B	c
H	5.7/9.5	8.5	7.4
MW	10.2–11.2	10.5	6.7

drop is even more spectacular at 200°C (67% loss of the overall yield) (a control experiment using a mixture of corrole **6** and pyrrole over alumina did not show any decomposition of **6** when heated (H or MW) for 20 min at 200°C). We conclude that a short reaction time and a high temperature are required to afford this corrole in good yield.

Other modifications in the procedure were developed for the synthesis of corrole **6** by introducing charges which would likely make the system more prone to activation by microwave radiation (Table 3). Neither the addition of inorganic additives (entry b), known to raise the corrole yield during the coupling of tetrapyrromethanes,[14] nor the introduction of acid (entry c), improved the yields. In the former case they remained unchanged (8% (H), 10.5% (MW)) while in the later they dramatically dropped to 6.7–7.4% when 3 equiv. of acetic acid was added (entry c).

As a result, microwave irradiation used in the synthesis of corrole constitutes an improvement in terms of yield, and by-product formation, to the straightforward method previously described by Gross for the corrole synthesis.

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References

1. (a) Gross, Z.; Galili, N.; Saltsman, I. *Angew. Chem., Int. Ed.* **1999**, *38*, 1427–1429; (b) Gross, Z.; Galili, N.; Saltsman, I.; Simkhovich, L.; Saltsman, I.; Botoshansky, M.; Blaser, D.; Boese, R.; Goldberg, I. *Org. Lett.* **1999**, *1*, 599–602; (c) Paolesse, R.; Jaquinod, L.; Nurco, D. J.; Mini, S.; Sagone, F. *Chem. Commun.* **1999**, 1307–1308; (d) Paolesse, R.; Nardis, S.; Sagone, F.; Khoury, R. G. *J. Org. Chem.* **2001**, *66*, 550–556.
2. (a) Gryco, D. T. *Eur. J. Org. Chem.* **2002**, *11*, 1735–1743; (b) Gryko, D. T. *Chem. Commun.* **2000**, *22*, 2243–2244; (c) Gryko, D. T.; Jadach, K. *J. Org. Chem.* **2001**, *66*, 4267–4275.
3. (a) Gross, Z.; Golubkov, G.; Simkhovich, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 4045–4047; (b) Gross, Z.; Simkhovich, L.; Galili, N. *Chem. Commun.* **1999**, *39*, 599–600; (c) Simkhovich, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089–8092; (d) Simkhovich, L.; Mahammed, A.; Goldberg, I.; Gross, Z. *Chem. Eur. J.* **2001**, *7*, 1041–1055; (e) Jerome, F.; Gros, C. P.; Tardieux, C.; Barbe, J.-M.; Guilard, R. *New J. Chem.* **1998**, 1327–1329; (f) Kadish, K. M.; Ou, Z.; Shao, J.; Gros, C. P.; Barbe, J.-M.; Jerome, F.; Bolze, F.; Burdet, F.; Guilard, F. *Inorg. Chem.* **2002**, *41*, 3990–4005; (g) Aviezer, D.; Cotton, S.; David, M.; Segev, A.; Khaselev, N.; Galili, N.; Gross, Z.; Yayon, A. *Cancer Res.* **2000**, *60*, 2973–2980.
4. (a) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283; (b) Caddick, S. *Tetrahedron* **1995**, *38*, 10403–10432; (c) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692.
5. (a) Petit, A.; Loupy, A.; Maillard, Ph.; Momenteau, M. *Synth. Commun.* **1992**, *22*, 1137–1142; (b) Chauhan, S. M. S.; Sahoo, B. B.; Srinivas, K. A. *Synth. Commun.* **2001**, *31*, 33–37.
6. (a) Unguranesu, C. *Synthesis* **1999**, *10*, 1729–1730; (b) Shaabani, A. *J. Chem. Res. (S)* **1998**, 672–673; (c) Jung, K. S.; Ro, J. Y.; Lee, J. Y.; Park, S. S. *J. Materials Sci. Lett.* **2001**, *20*, 2203–2205; (d) Villemin, D.; Hammadi, M.; Hachemi, M.; Bar, N. *Molecules* **2001**, *6*, 831–844.
7. General Procedures for compounds **1**–**8**. **Conventional procedure**: (H) described by Gross[1a,b] and modified as follows: Aldehyde (1.871 mmol) was mixed with oven-activated basic alumina (50 mg) in a one-neck-conical flask, then fast introduction of pyrrole (3 equiv., 0.366 ul) was carried out while the mixture was under violent agitation. With reactive aldehydes the reaction mixture turned brown within 30 s, and only then was the vessel plunged into a preheated bath (120°C) and heated under agitation for 20 min. **Microwave procedure**: (MW) the reagents were mixed the same way as above in a Teflon vessel (8.0×1.5 cm) sealed with a cap and microwave-heated for 2–20 min at 120–200°C. The microwave apparatus used was a Smith-Synthesizer (Single-mode microwave heating; Power 300 W). The reaction mixture was inserted in a conical Teflon vessel (50×15 mm; 5 mm thick walls) screw-capped by a stopper tightly sealed with a schrimper. The agitation was performed with special stir-bars provided by Smith-Synthesizer Ltd. **Workup**: After the dark oily mixture had cooled down to room temperature and solidified; it was digested with portions of dichloromethane (total volume ca. 200 ml) under sonication. Powdered DDQ (0.5–0.6 equiv.) was then added and the reaction mixture was stirred at room temperature for an additional 15 min. Unless otherwise stated, the solution was filtered through an alumina pad (5×3 cm), then the solvent was evaporated and the residue submitted to chromatography on basic alumina (10×3 cm) of low activity[8] using a hexane/

dichloromethane mixture (gradient elution) whose ratio was varied for each corrole. A second chromatography afforded the desired corrole in high purity. For corroles **1**–**8** traces of porphyrins were sometimes detected and were neglected. This did not vary with the mode of heating (H or MW).

8. Basic alumina of low activity was prepared by leaving activated basic alumina for 1 week in a beaker covered with alumina foil. Indeed we observed that activated basic alumina was responsible for a significant loss of corrole which remained stuck to the gel (ca. 0.5–1.2% of the overall yield).
9. Characterization of compounds:
(a) 5,10,15-Tris(4-fluorophenyl) corrole (**1**): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.87 (d, $J=3.53$ Hz, 2H), 8.80 (d, $J=4.02$ Hz, 2H), 8.58 (m, 4H), 8.29 (m, 4H), 8.10 (d, $J=3.02$ Hz, 2H), 7.50 (m, 6H), −2.30 (brs, 3H). ^{19}F NMR (500 MHz, $CFCl_3$) δ (ppm): −119.40 (s, 2F), −119.62 (s, 1F). UV–vis: (CH_2Cl_2) λ ($\varepsilon\times10^{-3}$): 414 (68.1), 572 (11.0), 613 (8.6), 623 (8.1), 630 (8.1), 648 (7.2) nm. HR-MS (EI, m/z) = 580.1875 (calcd for $C_{37}H_{23}F_3N_4$: 580.1895). TLC (alumina, hexane/dichloromethane, 6:2.5) R_f 0.24.
(b) 5,10,15-Tris(3,4,6-trifluorophenyl) corrole (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.03 (d, $J=3.53$ Hz, 2H), 8.80 (d, $J=4.02$ Hz, 2H), 8.58 (m, 4H), 7.94 (m, 4H), 7.77 (m, 2H), −2.30 (brs, 3H). ^{19}F NMR (500 MHz, $CFCl_3$) δ (ppm): −141.20 (t, 2F), −140.20 (t, 1F), −166.00 (m, 6F). UV–vis: (CH_2Cl_2) λ ($\varepsilon\times10^{-3}$): 414 (99.7), 573 (13.9), 612 (7.4), 647 (4.2) nm. HR-MS (EI, m/z) = 688.1311 (calcd for $C_{37}H_{17}F_9N_4$: 688.1309). TLC (alumina, hexane/dichloromethane, 6:2.5) R_f 0.41.
(c) 5,10,15-Tris(2,3,5,6-tetrafluorophenyl) corrole (**3**): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.07 (d, $J=4.02$ Hz, 2H), 8.78 (d, $J=4.77$ Hz, 2H), 8.59 (d, $J=4.78$ Hz, 2H), 8.56 (d, $J=3.90$ Hz, 2H), 7.53 (m, 3H), −2.10 (brs, 3H). ^{19}F NMR (500 MHz, $CFCl_3$) δ (ppm): −142.12 (m, 2F), −142.75 (m, 8F), −143.22 (m, 2F). UV–vis: (CH_2Cl_2) λ ($\varepsilon\times10^{-3}$): 408 (118.6), 418 sh (104.9), 562 (19.7), 605 (9.8) nm. HR-MS (EI m/z) = 742.2176 (calcd for $C_{37}H_{14}F_{12}N_4$: 742.1027). TLC (alumina, hexane/dichloromethane, 6:2.5) R_f 0.30.
(d) 5,10,15-Tris(2-trifluoromethyl-phenyl) corrole (**5**): Three atropisomers: TLC (alumina, hexane/dichloromethane, 6:2.5) R_f 0.72, 0.61, 0.55, respectively. Spectroscopic data of the major fraction (R_f 0.61). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.90 (m, 2H), 8.37 (m, 2H), 8.26 (m, 2H), 8.18 (m, 2H), 8.05 (m, 5H), 7.81 (m, 7H), −2.01 (brs, 3H). ^{19}F NMR (500 MHz, $CFCl_3$) δ (ppm): −61.67 (m, F), −62.31 (m, F). UV–vis: (CH_2Cl_2) λ ($\varepsilon\times10^{-3}$): 405 (91.6), 420 (68.6), 561 (11.5), 601 (5.9), 624 (1.07) nm. HR-MS (EI, m/z) = 730.1765 (calcd for $C_{40}H_{23}F_9N_4$: 730.1779).
(e) 5,10,15-Tris(3,5-Bis(trifluoromethyl)phenyl) corrole (**6**): Purified on silica gel 15×6 cm, gradient eluent hexane/dichloromethane, 8.5:1.5 vol. Then recrystallized in hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.03 (d, $J=4.01$ Hz, 2H), 8.81 (d, $J=4.72$ Hz, 2H), 8.76 (s, 4H), 8.64 (s, 2H), 8.53 (d, $J=4.29$ Hz, 2H), 8.50 (d, $J=4.72$ Hz, 2H), 8.30 (s, 1H), 8.25 (s, 2H), −2.30 (brs, 3H). ^{19}F NMR (500 MHz, $CFCl_3$) δ (ppm): −66.56 (s, 6F), −66.65 (s, 12F). UV–vis: (CH_2Cl_2) λ ($\varepsilon\times10^{-3}$): 418 (140.8), 575 (22.7), 614 (13.0), 648 (8.3) nm. HR-MS (EI, m/z) = 935.7621 (calcd for M+1 $C_{43}H_{21}F_{18}N_4$: 935.6401). TLC (alumina, hexane/dichloromethane, 3:1) R_f 0.74.
(f) 5,10,15-Tris(2,6-dichloropyrimidyl) corrole (**7**): purified on alumina gel (17×3 cm) using dichloromethane as eluent. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.20 (m, 3H), 9.06 (d, $J=4.39$ Hz, 2H), 8.58 (d, $J=4.78$ Hz, 2H), 8.43 (d, $J=4.29$ Hz, 2H), 8.41 (d, $J=4.83$ Hz, 2H), −2.40 (brs, 3H). UV–vis: (CH_2Cl_2) λ ($\varepsilon\times10^{-3}$): 414 (31.0), 426 (28.6), 562 sh (5.5), 569 (5.8), 609 (3.5) nm. HR-MS (EI$^+$, m/z) = 737.9514 (calcd for M+2H $C_{31}H_{14}N_{10}$:Cl_6: 737.9691). TLC (alumina, dichloromethane) R_f 0.32.
(g) Compounds **4** and **8** were characterized by ^{1}H, ^{19}F NMR (compound **4**) HRMS and UV–vis and were as previously described.[1a,d]
10. Wasbotten, I. H.; Wondimagegn, T.; Ghosh, A. *J. Am. Chem. Soc.* **2002**, *124*, 8104–8116.
11. (a) Klotzer, W.; Herberz, M. *Monatsch. Chem.* **1965**, *96*, 1567–1572; (b) Bredereck, H.; Simchen, G.; Santo, A. A. *Chem. Ber.* **1967**, *100*, 1344–1352.
12. Asokan, C. V.; Smeets, S.; Dehaen, W. *Tetrahedron Lett.* **2001**, *42*, 4483–4485.
13. Pentapyrrotetramethene isolated from the synthesis of **6**. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)12.52 (brs, 3H), 7.91 (m, 8H), 7.71 (brs, 4H), 6.76 (s, 2H), 6.52 (s, H), 6.49 (m, 2H), 6.39 (m, 2H), 6.06 (m, 2H), 6.00 (m, 2H). MS (ESI$^+$, m/z) 1226.3, (ESI$^-$, m/z) 1224.3 (calcd for $C_{56}H_{27}N_5F_{24}$: 1225.1).
14. Ka, J.-W.; Cho, W.-S.; Lee, C.-H. *Tetrahedron Lett.* **2000**, *41*, 8121–8125.