Published in final edited form as:

Org Lett. 2020 April 17; 22(8): 3119–3122. doi:10.1021/acs.orglett.0c00879.

Enhanced Synthetic Access to Tris-CF₃-Substituted Corroles

Pinky Yadav^{[a],#}, Sally Khoury^{[a],#}, Atif Mohammed^[a], Maryann Morales^[b], Scott C. Virgil^{*,[b]}, Harry B. Gray^{*,[b]}, Zeev Gross^{*,[a]}

^[a]Schulich Faculty of Chemistry, Technion Israel Institute of Technology, Haifa, Israel 320000

^[b]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, USA 91125

Abstract

Separate focus on the oligomerization and oxidative cyclization steps required for the synthesis of 5,10,15-tris(trifluoromethyl)corrole revealed [bis(trifluoroacetoxy)iodo] benzene (PIFA) as a superior alternative oxidant. Under optimized conditions, the pure free-base corrole was obtained with a sixfold increase in chemical yield and an eleven-fold rise in isolated material per synthesis. The corresponding gallium(III) and manganese(III) complexes were isolated by adding the appropriate metal salt prior to corrole purification.

Graphical Abstract

*Corresponding Author: chr10zg@technion.ac.il, svirgil@caltech.edu; hbgray@caltech.edu.

#Authors who made equal contributions.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and spectroscopic data for synthesized compounds.

Following the 1999 discovery of a one-pot synthesis of tris-pentafluorophenyl-substituted corrole $H_3(tpfc)$ (Figure 1), numerous research groups have used it and its element chelated derivatives for multiple purposes.^{1–9} The reason is not just accessibility, considering the exceedingly large number of triarylcorroles that soon became available, but also because the powerfully electron-withdrawing *meso*-C₆F₅ groups enhance the stability of the electron-rich macrocycle. In addition, the F atoms facilitate structural assignment via the aid of ¹⁹F NMR, and the *para*-F atoms may be selectively substituted by nucleophiles, providing a straight forward route to corroles with tunable electronic and reactivity properties.^{10–19}

As many additional applications could readily be envisioned for tris(trifluoromethyl)-substituted corrole, $H_3(tfc)$, its synthesis has been attempted many times over the years. Notably, the corresponding (oxo)Re complex $(tfc)Re(O)$ was reported as early as 1998, but it

was obtained accidentally and did not open the way for further development.²⁰ Our earlier attempts have only been partially successful, leading to a corrole with three C₃F₇ groups and a corrole substituted by one C₆F₅ and two CF₃ groups.^{21–22} The Ghosh research group had better luck, being the first to report the synthesis of H₃(tfc); they have obtained the free base compound *via* a one-pot reaction of trifluoroacetaldehyde with pyrrole.²³ Although a step forward, only full characterization of the corresponding Co(PPh₃) complex was realized, due to the combination of a very expensive starting material (the aldehyde) and a very low (0.6%) chemical yield. Disappointingly, only very small amounts of isolated material could be obtained in a typical synthesis (6 mg). Some of these limitations were recently resolved by introducing halothane as a cheap CF₃ starting material (about 10% of the price of trifluoroacetaldehyde), raising the chemical yield to 1.5% and the amount of isolated product per synthesis to 78 mg.²⁴ This advance led to the full characterization of three new (tfc)M complexes, with M = Ga, Mn, and P. Importantly, comparison with analogous (tpfc)M complexes revealed that CF₃-substituted corroles are better oxidants than those with C₆F₅ moieties, as the formal potentials of the macrocycle-chelated metal complexes are shifted to more positive values. The higher potentials along with greater Lewis acidities of robust tfc complexes are properties that are often sought after by investigators in the rapidly growing field of oxidative electrocatalysis.

As it is likely that many applications will be found for CF₃-substituted corroles, we have ramped up research aimed at making H₃(tfc) available in quantity. We concentrated effort on each of the two steps of the one-pot synthesis: formation of the tetrapyrane (bilane) and its oxidative cyclization to corrole (Scheme 1). Reliable and reproducible protocols were developed for isolation of the desired product (bilane) from the mixture of oligomers (di, tri, tetra and pentapyrrane) in up to 30% yield, while the main breakthrough in work on the second step was the introduction of an alternative oxidant. Employing these procedures in a modified synthesis, we realized about a sixfold improvement in the accessible amounts of H₃(tfc).

Method development for separation of the various oligo-pyrromethanes - was addressed first, in work that identified reaction conditions that favored the formation of bilane, the corrole precursor (Scheme 1). The products were isolated by either preparative HPLC (Figure S1 – S5) or column chromatography, followed by identifying their structures by ¹H and ¹⁹F NMR spectroscopy (Figure S6 -S9). The full spectra of the di-, tri, tetra-, and pentapyrromethanes (the latter is the precursor to sapphyrin) are given in the supporting information (SI), while their ¹H and ¹⁹F NMR chemical shifts are summarized in Table S1.

Armed with the above information, reaction progress was followed by analytical HPLC in order to deduce which conditions would provide the desired bilane in highest yield (Table 1). This follow-up was highly rewarding, as the outcome was routine access to the bilane in respectable chemical yields (and amounts). The procedure consists of injecting a 4/3 molar ratio mixture of pyrrole and halothane (2.77 and 3.20 mL, respectively) into a suspension of 3 g sodium dithionite, 3.5 g sodium hydrogen carbonate, 20 mL acetonitrile and 10 mL water, preheated to 70–80 °C. Noticeable gas evolution (CO₂) occurred almost immediately; and the bilane appeared within 1 h, with the yellow suspension continually stirred and maintained at 70–80 °C for a total of 2h. Routine workup of the solution, which was almost

homogenous, was followed by column chromatography. Identification of the fractions of interest was achieved by adding tiny amounts of DDQ to each of them, as only those containing the bilane became fluorescent due to corrole formation. Up to 1.5 g of the desired product could be obtained, corresponding roughly to a 30% chemical yield (detailed analysis is given in the SI). The availability of rather large amounts of the bilane allowed investigation of the oxidative cyclization step. This was done by reacting bilane with DDQ, the most commonly used reagent for that purpose, and changing the following variables: a) solvent [dichloromethane, acetonitrile, ethyl acetate and THF]; b) temperature [−78, 5–7 and 35 – 40 °C]; and c) addition of metal salts for simultaneous insertion of [Ga, P, Mn and Co] into the corroles. These investigations uncovered one major reason for the overall low yields, namely, that this particular corrole is not stable in solutions containing DDQ. Accordingly, a search for alternative oxidants was carried out, which included *para*-chloranil, *ortho*-chloranil, KMnO₄, I₂/TFA, 2-iodoxybenzoic acid/CeCl₃, O₂, and tris (4-bromo- phenyl) ammoniumyl hexachloroantimonate. The major goal was to identify agents that are almost as oxidizing as DDQ for the overall process that includes oxidative aromatization, but not harmful to the corrole. We found that [bis(trifluoroacetoxy)iodo] benzene (PIFA) is the best alternative, since: a) it performs as good as DDQ; b) the product corrole is much more stable in its presence; and c) unlike DDQ, it does not form colored products that interfere with corrole isolation.

These benefits became apparent not only when applied with the isolated bilane, but even when the oligomers mixture from the first step was treated with PIFA (Table 2). The oxidation by PIFA was tested on both purified bilane and the mixture of oligomers, dissolved in either dichloromethane, acetonitrile or propionitrile under both aerobic and anaerobic conditions and at temperatures of 4–7, 25 and 40 °C. Performing the reactions under N₂ atmosphere gave fewer byproducts and the advantage of dichloromethane as solvent was easier purification of the desired product. Notably, the recommended reaction conditions for the preparation of H₃(tfc) are to treat the purified bilane with PIFA for 2 h at room temperature in acetonitrile under a N₂ or Ar atmosphere. Isolated yields were 12–20% relative to isolated bilane, which translates to 3.6–6% relative to pyrrole.²⁵ Under aerobic conditions, the *total* chemical yield dropped to 3% when the starting material was isolated tetrapyrane (Scheme 2) and to 1.1 % when PIFA was applied to the crude reaction mixture from the first step.

Although there was remarkable improvement from 1.5% to 6% chemical yield, a substantial loss of desired material became apparent upon product separation via column chromatography. Since all corroles are much more stable once metallated, the oxidized mixture was treated with gallium(III) chloride prior to purification. The selection was made because (tfc)Ga is fluorescent, which greatly assists in product identification and isolation. The final procedure was as follows: oxidation by PIFA in dichloromethane under N₂, treatment with GaCl₃, and separation of (tfc)Ga by column chromatography both with and without prior separation of the oligomer mixture. In the latter case, the total chemical yield from pyrrole and halothane was 1.7%, as compared to 5–6% in the former case. Taken together, the total amount and chemical yield for the in situ preparation of (tfc)Ga via the metalation/chromatography method was five times higher than by isolation of H₃(tfc) followed by gallium insertion (Scheme 2). Similar approaches but with prior metalation by

Cu(II) and Co(III) salts have not been successful to date, but prior metalation by manganese(II) acetate provided a 12–14% yield of (tfc)Mn).

In summary, we achieved an almost sixfold increase in the accessibility of tris-CF₃-substituted corrole H₃(tfc), by optimizing the first of the two-step synthesis to about 30% yield and by identifying PIFA as a superior alternative to the commonly used DDQ for the second step. The best overall yields were obtained when oxidative cyclization was performed under an inert atmosphere, and when gallium insertion was performed prior to purification of the free-base corrole. Our improved synthesis of the CF₃-substituted corrole, in up to 870 mg in two steps without purification in between, paves the way for greatly increased use of the corresponding metal complexes in multiple applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This research was supported by the Israel Science Foundation (to ZG) and the United States National Institutes of Health (R01 DK019038 to HBG).

REFERENCES

- (1). Zhang W; Lai W; Cao R Chem. Rev 2017, 117, 3717. [PubMed: 28222601]
- (2). Paolesse R; Nardis S; Monti D; Stefanelli M; Di Natale C Chem. Rev 2017, 117, 2517. [PubMed: 28222604]
- (3). Teo RD; Hwang JY; Termini J; Gross Z; Gray HB Chem. Rev 2017, 117, 2711. [PubMed: 27759377]
- (4). Barata JFB; Neves MGPMS; Faustino MAF; Tome AC; Cavaleiro JA S. Chem. Rev 2017, 117, 3192.
- (5). Sinha W; Mahammed A; Fridman N; Diskin-Posner Y; Shimon LJW; Gross Z Chem. Commun 2019, 55, 11912.
- (6). Shpilman JS; Friedman A; Zion N; Levy N; Major DT; Elbaz LJ Phys. Chem. C 2019, 123, 30129.
- (7). Kwak W-J; Mahammed A; Kim H; Nguyen TT; Gross Z; Aurbach D; Sun Y-K Mater. Horiz 2019, DOI: 10.1039/c9mh01043b.
- (8). Gonglach S; Paul S; Haas M; Pillwein F; Sreejith SS; Barman S; De R; Müllegger S; Gerschel P; Apfel U-P; Coskun H; Aljabour A; Stadler P; Schöffberger W; Roy S Nat. Commun 2019, 10, 3864. [PubMed: 31455766]
- (9). Oppenheim J; Gray MHB; Di Bilio AJ; Brennan BJ; Henling LM; Lim P; Soll M; Termini J; Virgil SC; Gross Z; Gray HB Inorg. Chem 2019, 58, 10287. [PubMed: 31335126]
- (10). Osterloh WR; Quesneau V; Desbois N; Brande S; Shan W; Blondeau-Patissier V; Paolesse R; Gros CP; Kadish KM Inorg. Chem 2019, DOI: 10.1021/acs.inorgchem.9b02855.
- (11). Pomarico G; Monti D; Bischetti M; Savoldelli A; Fronczek FR; Smith KM; Genovese D; Prodi L; Paolesse R Chem. Eur. J 2018, 24, 8438. [PubMed: 29637630]
- (12). Basumatary B; Reddy RVR; Rahul, Sankar J Angew. Chem. Int. Ed 2018, 57, 5052.
- (13). Gomes LMF; Mahammed A; Prosser KE; Smith JR; Silverman MA; Walsby CJ; Gross Z; Storr T Chem. Sci 2019, 10, 1634. [PubMed: 30842826]
- (14). Soll M; Goswami TK; Chen Q-C; Saltsman I; Teo RD; Shahgholi M; Lim P; Di Bilio AJ; Cohen S; Termini J; Gray HB; Gross Z Sci. Rep 2019, 9, 2294. [PubMed: 30783138]
- (15). Sharma VK; Mahammed A; Soll M; Tumanskii B; Gross Z Chem. Commun 2019, 55, 12789.
- (16). Mahammed A; Gross Z Coord. Chem. Rev 2019, 379, 121.

- (17). Zhan X; Teplitzky P; Diskin-Posner Y; Sundararajan M; Ullah Z; Chen Q-C; Shimon LJW; Saltsman I; Mahammed A; Kosa M; Baik M-H; Churchill DG; Gross Z *Inorg. Chem* 2019, 58, 6184. [PubMed: 31002247]
- (18). Mahammed A; Chen K; Vestfrid J; Zhao J; Gross Z *Chem. Sci* 2019, 10, 7091. [PubMed: 31588277]
- (19). Zhan X; Yadav P; Diskin-Posner Y; Fridman N; Sundararajan M; Ullah Z; Chen Q-C; Shimon LJW; Mahammed A; Churchill DG; Baik M-H; Gross Z *Dalton Trans* 2019, 48, 12279. [PubMed: 31342035]
- (20). Tse MK; Zhang Z; Chan KS *Chem. Commun* 1998, 1199.
- (21). Simkhovich L; Goldberg I; Gross ZJ *Inorg. Bio-chem* 2000, 80, 235.
- (22). Goldschmidt R; Goldberg I; Balazs Y; Gross ZJ *Porphyrins Phthalocyanines* 2006, 10, 76.
- (23). Thomas KE; Conradie J; Hansen LK; Ghosh A *Inorg. Chem* 2011, 50, 3247. [PubMed: 21366225]
- (24). Chen Q-C; Soll M; Mizrahi A; Saltsman I; Fridman N; Saphier M; Gross Z *Angew. Chem* 2018, 130, 1018.
- (25). A solution of the crude mixture (23.4 g, obtained from the reaction of 14 g pyrrole (0.209 mol) and 38.5 halo-thane) in acetonitrile (4L) was deaerated at room temperature by bubbling with argon for 5 min, after which solid PIFA (46 g, 0.107 mol) was added with stirring. After 16 h, the reaction mixture was evaporated and the residue was dissolved in warm ethyl acetate (160 mL), then diluted with 240 mL hexane and purified by column chromatography (200 g silica, 65 mm column dia., 40% ethyl acetate/hexane). The corrole-containing fractions were combined and further purified by column chromatography on silica with 25% ethyl acetate/hexane. Recrystallization of the product in two crops from 10% ethyl acetate/hexane afforded H₃(tfc) (0.87 g, 1.7 mmol, 3.3% relative to pyrrole) as dark purple crystals (see the SI for more details).

Figure 1.
Previously reported corroles substituted by fully fluorinated aryl or alkyl groups.

Scheme 1.

Synthesis of H₃(tfc) according to the published route.

Scheme 2.

Optimized routes for the syntheses of H₃(tfc) and (tfc)Ga.

Table 1.

Variation of reaction conditions favoring particular oligo-pyrromethanes.

	Reaction time (h)	Temperature °C	% Yield
Di	1	40–50	40–50
Tri	1	70–80	35–40
Tetra (bilane)	2	70–80	30
Penta	4	70–80	8–10

Table 2.

Chemical yields obtained via variations in reaction conditions (PIFA, solvent, 2 h, air vs. N₂) for the oxidative cyclization step by using either a mixture of oligomers or isolated tetrapyrromethane with/without gallium insertion prior to isolation of the free-base corrole.

Solvent/ atmos- phere	Starting material	<i>In situ</i> Ga(III) metalla- tion	Product	Yield (%)
CH ₂ Cl ₂ , under air	Oligomeric mixture	no	H ₃ (tfc)	1.1 ^b
	Oligomeric mixture	yes	(tfc)Ga	1.2 ^b
	bilane	no	H ₃ (tfc)	10 ^a
	bilane	yes	(tfc)Ga	14 ^a
CH ₂ Cl ₂ / CH ₃ CN/	Oligomeric mixture	no	H ₃ (tfc)	3.3 ^{b,c}
C ₃ H ₇ CN, under N ₂	Oligomeric mixture	yes	(tfc)Ga	1.7 ^b
	bilane	no	H ₃ (tfc)	12–20 ^a
	bilane	yes	(tfc)Ga	17–20 ^a

^a yield relative to bilane,

^b yield relative to pyrrole,

^c 16 h re- action time.