Review

Current Advances in the Synthesis of Valuable Dipyrromethane Scaffolds: Classic and New Methods

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Abstract: This review presents the most recent developments on the synthesis of dipyrromethanes, covering classical synthetic strategies, using acid catalyzed condensation of pyrroles and aldehydes or ketones, and recent breakthroughs which allow the synthesis of these type of heterocycles with new substitution patterns.

Keywords: dipyrromethanes; dipyrromethenes; dipyrryl; BODIPY; pyrrolic macrocycles

1. Introduction

Dipyrromethanes are well known synthetic scaffolds for the synthesis of macrocycles and dipyrromethene metal complexes. Dipyrromethanes occupy a central place in porphyrin chemistry. The dipyrromethane structures employed in the synthesis of naturally occurring porphyrins typically bear substituents at the β-positions and lack any substituent at the meso-position. However, the dipyrromethanes with substituents at the meso-position have come to play a valuable role in the preparation of synthetic porphyrins [1,2], calixpyrroles [3], chlorins [4], corroles [5], and expanded porphyrins, namely saphyrins and smaragdyrins [6,7] (Figure 1).

The most representative example of dipyrromethene metal complexes are 4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes also known as BODIPYs, which have been successfully used as fluorescent probes in diverse applications [8–10]. Other metal complexes have also attracted researchers’ attention, for example, recently, aluminium complexes have been used as catalysts for polymerization reactions [11,12], iron complexes [13] have been used as catalysts for C-H bond amination [14,15], and ruthenium complexes of dipyrromethenes [16,17] were synthetized as precursors of bis(2,2′-bipyridyl)(dipyrrinato)ruthenium(II) complexes.

Beyond its use as synthetic scaffolds, the dipyrromethane framework used as ligand for the synthesis of organometallic complexes has attracted the interest of several research groups, mostly due to the ease of synthetic accessibility and versatility of substitution of this moiety. The electronic properties of this ligand can be modified by substitution at the beta-carbons and at the meso positions, while the steric properties can be tuned by substitution at the alpha-carbons. Zirconium complexes have been applied in olefin hydroamination [18] and ruthenium, rhodium and iridium complexes used as hydrogen transfer catalysts under aqueous and aerobic conditions [19]. The synthesis of dipyrromethene complexes has also been achieved with Mn, Co, Zn, Ni [20–22] or Sn [23]. Recently, a dipyrromethane-based diphosphane-germylene was synthetized and used as precursor of tetrahedral Cu(I) and T-shaped Ag(I) and Au(I) flexible pyrrole-derived Phosphorous-Germanium-Phosphorous (PGeP) germylene pincer complexes [24].
Anion recognition is an area of growing interest due to its important role in a wide range of environmental, clinical, chemical and biological applications. Interestingly, the acidic NH protons of dipyrromethanes can be used as anion sensors with good binding activity and selectivity [25–28]. Furthermore, polymers based on dipyrromethanes were developed for the molecular recognition of two homoserine lactone derivatives involved in bacterial quorum sensing [29].

Herein, bibliographic coverage of the developments on the synthesis of dipyrromethanes since the last reviews in this area [9,30–32] is provided (2014–2019). The synthetic strategies have been organized in two main approaches: classical synthetic strategies based on the first report on the synthesis of meso-substituted dipyrromethanes, disclosed in 1974 [33], using acid catalyzed condensation of pyrrole and aldehydes; and recent breakthroughs in dipyrromethane chemistry which allow the synthesis of dipyrromethanes with new substitution patterns.

2. Classic Synthetic Strategies

2.1. Hydrochloric Acid-Catalyzed Dipyrrromethane Synthesis

Receptor molecules grounded on guanidinium- and pyrrole-containing binding sites 3 were developed by Kataev and colleagues with the objective of selective recognizing orthophosphate anions in aqueous media (Scheme 1) [27].

Studies demonstrated that the pyrrole-containing binding site was of pronounced influence on the selectivity and that dipyrrromethane core structure 2, prepared from the HCl-catalyzed reaction of 4-heptanone 1 and pyrrole in boiling water in 13% isolated yield, demonstrated the highest selectivity for orthophosphate over other inorganic anions. A novel and readily available dipyrrromethane-based dual receptor 6 serving as colorimetric sensor for both F⁻ and Cu²⁺ ions was recently designed and prepared by Pandey and co-workers (Scheme 1) [28]. Treatment of pyrrole and acetophenone 4 in the presence of catalytic HCl in water was key in the formation of meso-methyl-meso-phenyl-dipyrrromethane 5 in 75% yield.
Balci et al. established a regioselective method for the preparation of dipyrrolo-diazepine derivatives [34]. This firstly involved the classic room temperature HCl-promoted synthesis of dipyrromethanes 7 (starting from excess pyrrole and suitable aldehydes), followed by reaction of propargyl bromide 8 in the presence of sodium hydride to append an alkyne functionality to the nitrogen atom at one of the pyrrole units. A final seven-exo-dig cyclization, between the alkyne group and the N-deprotonated pyrrole moiety, followed by prototropy produced the target compounds 10 in generally good overall yields (Scheme 2).

Interesting work carried out by the research group of Swavey allowed the preparation of two new dipyrrolo-diazepine derivatives [24]. Scheme 1. Synthesis of meso-disubstituted dipyrromethanes 2 and 5 featured in ion receptor dipyrromethanes 3 and 6, respectively.

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Scheme 2. Synthesis of dipyrromethanes 7, alkyne-substituted dipyrromethanes 9 and dipyrrolo-diazepine derivatives 10.

2.2. Acetic/Propionic Acid-Catalyzed Dipyromethane Synthesis

Interesting work carried out by the research group of Swavey allowed the preparation of two new dipyrromethane bridging ligands [17], as well as their corresponding dimetallic ruthenium(II) [17] and osmium(II) [35] coordination complexes. Reaction of phenanthrolinepyrrole 11 (php) with the selected aryl aldehyde in acetic acid (AcOH) produced dipyrromethanes 12, comprising two php moieties linked by a meso-aryl group (Scheme 3). The use of benzaldehydes substituted with electron donating (vanillin) and electron withdrawing (cyano) groups did not greatly affect the efficiency of the reaction with php. However, the use of sterically hindered aldehydes, e.g., mesitylbenzaldehyde, 3,4,5-trimethoxybenzaldehyde and pentafluorobenzaldehyde, was completely unsuccessful. Coordination with Ru(II) or Os(II) bis(bipyridyl) chloride in refluxing ethanol, followed by saturation with aqueous ammonium hexafluorophosphate, created the novel dimetallic complexes 13 and 14 in good isolated yields (Scheme 3).
Scheme 3. Synthesis of diphenanthrolinepyrromethanes 12 and their corresponding dimetallic Ru(II) 13 and Os(II) 14 coordination complexes.

Access to C$_{2v}$ symmetric β-substituted porphyrins, e.g., protoporphyrin III 21, using the promptly accessible Knorr’s pyrrole 15, which is crucial in the preparation of the required dipyrromethane building blocks [36], was envisaged by Neya and colleagues in 2016 [37]. Two Knorr’s pyrrole units were coupled into symmetric dipyrromethane 16 in propionic acid (PrOH). Its 3,3′-dibenzyl groups were removed via hydrogenolysis affording the corresponding carboxilic acid substituents, which were removed by iodination giving dipyrromethane 17. This was further reduced to dipyrromethane 18 under a Pd/C-catalyzed hydrogen atmosphere. Reaction of 18 with acetyl chloride in the presence of aluminum chloride led to the formation of 3,3′-diacetyldipyrromethane dimethylester 19, which was then hydrolyzed using aqueous sodium hydroxide into the corresponding dipyrromethene-5,5′-dicarboxylic acid. Its terminal carboxylic residues were subsequently eliminated through iodinative decarboxylation, rendering 5,5′-diiododipyrromethane 20 in 10.2% overall yield after eight reaction steps (Scheme 4).

The multistep synthesis of 1,4,5,8-tetraethyl-2,3,6,7-tetravinylporphyrin 26 was reported by the same research team one year later, this time using closely related Knorr’s pyrrole analogue 22 as starting material [38]. The same experimental protocol was selected in order to produce 5,5′-diiododipyrromethane 23, which was then subjected to reduction to afford dipyrromethane 24, followed by formylation to dipyrromethane 25 (Scheme 5). These two new dipyrromethane derivatives, 24 and 25, were key in the subsequent preparation of the target symmetric porphyrin 26.
These were screened for antitubercular activity against Mycobacterium tuberculosis strains, interesting minimum inhibitory concentration (MIC) values being found (Scheme 6). The same research team one year later, this time using closely related Knorr’s pyrrole analogue starting material [38]. The same experimental protocol was selected in order to produce 5,5-diiododipyrromethane [39]. The same authors later described the preparation of some novel dipyrromethane-hydrazone derivatives, p-dichloromethane was refluxed for 8 h in the presence of a catalytic amount of £, SO2Cl2, PrOH i. POCl3, DMF ii. H2O/PrOH 100 ºC, 2 h iii. THF/MeOH H2, Pd/C, rt, 18 h iv. H2O, I2/KI 35 ºC, 2 h v. MeOH, H2, Pd/C reflux, 2 h vi. 1,2-DCE MeCOCl, AlCl3 vii. NaOH(aq) MeOH, 90 ºC, 3 h viii. H2O, I2/KI 45 ºC, 3 h

Scheme 4. Synthesis of dipyrromethanes 16–20 and protoporphyrin III 21 starting from Knorr’s pyrrole 15.

Scheme 5. Synthesis of dipyrromethanes 23–25 and 1,4,5,8-tetraethyl-2,3,6,7-tetravinylporphyrin 26 starting from Knorr’s pyrrole analogue 22.
2.3. p-Toluenesulphonic Acid-Catalyzed Dipyrromethane Synthesis

A solution of furan-2-carboxaldehyde 27 and ethyl 2-cyano-3-(1H-pyrrol-2-yl)-acrylate 28 in dichloromethane was refluxed for 8 h in the presence of a catalytic amount of p-toluenesulphonic acid (p-TSA) to afford 1,9-bis(2-cyano-2-ethoxy carbonylvinyl)-5-(2-furanyl)-dipyrromethane 30 in 32% yield (Scheme 6). This new dipyrromethane was extensively characterized through experimental spectroscopic measurements and theoretical quantum chemical calculations by Singh and co-workers [39]. The same authors later described the synthesis of some novel dipyrromethane-hydrazone derivatives 31, by condensing previously synthesized 2-[(4-isonicotinoyl)-hydrazonomethyl]-1H-pyrrole 29 with suitable aldehydes, also under classic p-TSA catalyzed reactional conditions, high yields being attained [40]. These were screened for antitubercular activity against *Mycobacterium tuberculosis* H37Rv strains, interesting minimum inhibitory concentration (MIC) values being found (Scheme 6).

![Scheme 6. Meso-Dipyrromethanes 30 and 31 synthesized under standard p-TSA-catalyzed conditions.](image)

2.4. Trifluoroacetic Acid-Catalyzed Dipyrromethane Synthesis

Aiming to synthesize a 5,10-diacyltripyrrane, an essential intermediary synthon for the preparation of a 5,10-diacylcalix[4]pyrrole, Mahanta and Panda were able to unexpectedly isolate acyldipyrromethane 32 with a yield up to 31% (Figure 2), following the trifluoroacetic acid (TFA)-catalyzed reaction of 2,3-butanedione and excess pyrrole [41]. Yildiz et al. have described the synthesis, characterization, crystal structure and theoretical calculations of two new meso-borondipyrromethene (BODIPY) incorporating a phthalonitrile moiety [42,43]. Crucial for their detailed report was the preparation of meso-phenoxypthalonitrile dipyrromethanes 33 and 34 (Figure 2), which were attained in 53% and 61% yields, respectively, after typical room temperature condensation of suitable and previously obtained aldehydes with excess pyrrole in the presence of TFA. A very similar experimental setup was applied to the synthesis of unsubstituted dipyrromethane [44], meso-2-pyryloyldipyrromethane 37c (see Scheme 2) in 90% yield [45], as well as to the preparation of dipyrromethane 35, in 43% yield [46]. Three meso-(trimethylsilyl)phenyl-dipyrromethane structures 36 were obtained in good yields, ranging from 60% to 66% (Figure 2), after solventless condensation catalyzed by TFA of the corresponding silylated aldehydes with pyrrole [47]. Extensive work on the synthesis of novel pentfluorosulfonyl-substituted A4-type porphyrins (and their respective Zn(II) and Pd(II) complexes), A3-, ABy- and A3B-type corroles, trans-A2B2-type porphyrins and BODIPYs has been reported [48]. Regarding the three latter molecular targets, *meta*-SF5-phenyl-substituted dipyrromethanes 37a–c, prepared in high yields (62%–80%) under standard TFA-catalyzed reaction conditions using appropriate pentfluorosulfonyl-bearing aryl aldehydes and surplus pyrrole, were the strategic intermediates (Figure 2). More recently, the same authors reported the efficient preparation, under similar standard conditions, of useful meso-aryldipyrromethane scaffolds 37d [49] and 37e [50] (in 92% and 87% yields,
correspondingly), which were further functionalized and/or used as building blocks for the formation of other interesting BODIPY or porphyrinoid molecular species.

![Chemical structures](image)

**Figure 2.** Dipyrrmethanes 32–37 synthesized under standard TFA-catalyzed conditions.

Bis-dipyrromethanes 38a–d and 39a–d, as well as tris-dipyrromethane 38e and 39e, were prepared from commercially accessible starting materials by Sessler’s research team [51,52], following the strategy summarized in Scheme 7. Their anion binding properties were then evaluated in both organic media and in the solid state, compounds 39 displaying a good affinity for dihydrogenphosphate and pyrophosphate anions (as tetrabutylammonium salts) in chloroform solutions, acting as conformationally switchable receptors.

![Reaction scheme](image)

**Scheme 7.** Dipyrrmethane derivatives 38 synthesized under typical TFA-catalyzed conditions and subsequent formylation to dipyrrmethane products 39.

Acyclic and macrocyclic dipyrrmethanes were synthesized by Love et al. by applying common Schiff-base condensation chemistry to *meso*-pentafluorophenyldipyrromethane dialdehyde
40, diiminodipyrromethane derivative 41 being obtained in 74% yield (Scheme 8) [53]. Bridged macrocyclic dipyrromethanes 43 were prepared by condensation of 40 with either ortho-phenylene 42a or 1,5-anthracene-diamine 42b, again using TFA as catalyst. After neutralization with triethylamine, the target molecules precipitated neatly from the reaction medium (Scheme 8).

Scheme 8. Acyclic and macrocyclic dipyrromethane derivatives 41 and 43 synthesized under standard TFA-catalyzed Schiff-base conditions.

Novel bis-dipyrromethane derivatives 45 were synthesized in moderate yields by reacting previously prepared dialdehydes 44 with surplus pyrrole in the presence of TFA as catalyst (Scheme 9). These bis-dipyrromethanes 45, as well as 38c (see Scheme 7) and dipyrromethane 35 (see Figure 2), undergo electropolymerization on the electrode surface occurring upon multiple oxidation cycles [46]. The authors uncovered that quicker electropolymerization rates arise when the monomeric species contains more than one dipyrromethene component, and that the resulting polymers exhibit greater stability, while also showing low roughness and a very uniform and homogenous morphology.

Scheme 9. Bis-dipyrromethanes 45 synthesized under normal TFA-catalyzed conditions.
β-Formyl-tetapyrrole macrocycles have been used for the synthesis of dipyrrromethene derivatives through condensation with pyrroles (Scheme 10). Temelli and Kalkan recently described the synthesis of meso-porphyrinyl-dipyrrromethene 47 in high yield, by reacting 2-formyl-meso-tetraphenylporphyrin 46 prepared beforehand and excess pyrrole under classic TFA catalysis conditions. The unforeseen construction of β/meso-directly connected diporphyrinic molecules in reactions of β-formylated porphyrins with pyrrole under ordinary Adler-Longo conditions was also established, early mechanistic studies showing that dipyrrromethane 47-type intermediates are fundamental in the process [54]. On the other hand, Galium(III) corrole-BODIPY hybrid 49 was obtained from the TFA-catalyzed reaction of formyl-corrole 48 with 2,4-dimethylpyrrole followed by oxidation and complexation with boron trifluoride [55].

![Scheme 10. Synthesis of dipyrrromethane derivatives with tetrapyrrrole macrocycle substituents.](image)

New meso/meso-straightly linked Ni(II) porphyrin hybrids were designed and prepared by Kong and co-workers, the metalloporphyrinic units being connected with dipyrrromethene, bis-dipyrrromethene or thiacorrole units [56]. Instrumental in the synthetic strategy of the authors was meso-dipyrrromethane-subsstituted Ni(II) porphyrin 51, which was effortlessly obtained in good yield via TFA-catalyzed room temperature condensation of Ni(II) 10,20-di(3,5-di-t-butylphenyl)-5-formyl porphyrin 50 and pyrrole (Scheme 11).

The synthesis and characterization (structural, spectral and electrochemical) of Pd(II), Re(I) and Ru(II) 3-pyrrrolyl-BODIPY/porphyrinmes complexes 55a–c was reported by Ravikanth’s research team in 2014 [57]. The pertinent and necessary dipyrrromethane-substituted 3-pyrrrolyl BODIPY intermediate 53a was prepared in 85% yield by mixing a dichloromethane solution of formylated 3-pyrrrolyl BODIPY 52a, produced and isolated beforehand, and excess pyrrole under TFA-catalyzed and inert atmosphere conditions (Scheme 12). Related α-dipyrrromethanyl 3-pyrrrolyl BODIPY 53b was synthesized in a similar fashion by the same research group a few years later (Scheme 12) [58]. This was further transformed into 3-pyrrrolyl BODIPY/BODIPY dimer 54, comprising an ethynyl functionality at the meso-aryl location, which was then coupled to selected monomeric BODIPYs in order to create the authors’ target near-infrared emitting BODIPY oligomers.
Scheme 11. Synthesis of meso/meso-linked porphyrin-dipyrromethane 51 catalyzed by TFA.

Scheme 12. TFA-catalyzed synthesis of α-dipyrromethanyl 3-pyrolyl BODIPY 53 required for the preparation of Pd(II), Re(I) and Ru(II) 3-pyrolyl-BODIPY/dipyrromethenes complexes 55a-c, and 3-pyrolyl BODIPY/BODIPY 54.

2.5. Boron Trifluoride Diethyl Etherate-Catalyzed Dipyrrmethane Synthesis

New meso-phenothiazinylpyrromethanes 56, having alkyl groups of growing bulkiness linked to the heterocyclic nitrogen of the phenothiazine core were synthesized in high yields (81%–89%) by condensing proper N-alkyl-phenothiazin-3-carbaldehydes with pyrrole at room temperature, in the dark, and in the presence of boron trifluoride diethyl etherate (BF3.Et2O) as catalyst (Figure 3) [59]. A BODIPY dye [59], a trans-A2B2-type porphyrin [59], and some Sn(IV) coordination complexes [60] bearing an N-methyl-phenothiazinyl motif were later prepared utilizing dipyrrmethane 56a as the building block. Thilagar and colleagues conveyed the simple preparation, under typical
BF₃·Et₂O-catalyzed reaction conditions of four novel triarylborane-dipyrromethane derivatives 57a–d (Figure 3) that encompassed dual receptor sites (Lewis acidic boron and hydrogen bond donor NH) and displayed a discriminating fluorogenic response towards the fluoride anion in dichloromethane solution [61]. Broadly acknowledged meso-substituted dipyrromethanes 7c (Scheme 2) and 58 were recently obtained by Bagherzadeh and co-workers via the dropwise addition of pyrrole to a dilute aqueous solution of the aryl aldehydes, using boron trifluoride diethyl etherate as catalyst (Figure 3) [62]. This methodology was adapted from an earlier report that used aqueous HCl at 90 °C [63], tripyrromethane and other oligomers being obtained as byproducts when large and sterically hindered aryl aldehydes are employed. The reaction occurred smoothly in mild conditions, 30–70 min at 70–80 °C under an argon atmosphere, moderate to high yields (60%–85%) being obtained, even when employing bulky electron donating (mesityl) or electron withdrawing (2,6-dichlorophenyl) aldehydes, and no decomposition or scrambling being noticed.

![Figure 3](image-url)  
**Figure 3.** Dipyrromethanes 56-58 synthesized under standard BF₃·Et₂O-catalyzed conditions.

Sessler and co-workers synthesized pyrene-bridged bis-dipyrromethane 60 in 41% yield by reacting previously prepared pyrene dialdehyde 59 with excess pyrrole in ethanol at room temperature for three days and using BF₃·Et₂O as catalyst (Scheme 13) [64]. After formylation under standard reaction conditions, pyrene-linked tetraformylated bis-dipyrromethane 61 was obtained in moderate yield. Anion recognition studies revealed that the latter performs as a selective fluorescent probe in chloroform solution for dihydrogen phosphate over other tested anions.

Ravikanth’s research group reported the preparation and characterization (structural, photophysical and electrochemical) of β-meso covalently linked azabODIPY/BODIPY dyad 64 [65] and Pd(II) azabODIPY/dipyrromethene complex 65 [66,67]. The unconditionally required dipyrromethane-substituted azabODIPY intermediary 63 was synthesized in reasonable yield by stirring a dichloromethane solution of 2-formyl azabODIPY 62, and surplus pyrrole, at room temperature, under boron trifluoride diethyl etherate catalysis and inert atmosphere conditions (Scheme 14). A similar synthetic strategy, condensation of 3-formyl-BODIPY with pyrrole catalyzed by BF₃·OEt₂ was used for the synthesis of BODIPY/BODIPY dimers [68].
Scheme 13. Bis-dipyrrromethane derivative 60 synthesized under typical BF$_3$.Et$_2$O-catalyzed conditions and subsequent formylation.

Scheme 14. BF$_3$.Et$_2$O-catalyzed synthesis of dipyrrromethane-substituted azaBODIPY 63 required for the preparation of azaBODIPY/BODIPY 64 and Pd(II) azaBODIPY/dipyrrromethene complex 65.
2.6. Indium(III) Chloride-Catalyzed Dipyrrromethane Synthesis

meso-Substituted dipyrrromethanes 66a,b were prepared by simple solvent-free condensation of the appropriate aryl aldehydes with excess pyrrole, under a saturated argon atmosphere and indium chloride (InCl₃)-catalyzed conditions, (Figure 4) moderate yields being attained [69]. Lindsey’s research team designed and synthesized a series of interesting trans-AB-kind porphyrins and metalloporphyrins comprising one water-solubilization moiety and one bioconjugatable functionality [70]. Key for their strategy was the previous preparation of suitable dipyrrromethane building blocks, including novel compound 66c, which was obtained in 33% yield using the same catalytic conditions (Figure 4). A related setting was also applied for the synthesis of meso-nonyldipyrrromethane 67 in 78% yield and meso-methoxycarbonyldipyrrromethane 68 in 52% yield [71]. In addition to the latter, the synthetic process also provided regioisomer 69 and cyclic derivative 70, a by-product resulting from intramolecular aminolysis of ester 68, in 32% and 10% isolated yields, respectively (Figure 4). Moreover, the same authors prepared dipyrrromethane derivatives 71 and 72 in moderate to reasonable yields, 47%–62% by simply mixing the adequate aldehydes or acetals with excess pyrrole in an inert atmosphere using indium chloride as catalyst. Dipyrrromethanes 67–69 and 71–72 were later crucial for the preparation of several trans-AB-type porphyrins and metalloporphyrins (Figure 4) [71].

![Figure 4. Dipyrrromethanes 66-72 synthesized under standard InCl₃-catalyzed conditions.](image)

Aiming to combine porphyrin, BODIPY and triptycene chemistry, Senge et al. recently presented meso-triptycenyldipyrrromethane synthon 74, synthesized in 60% yield from the condensation of 2-formyltriptycene 73 and surplus pyrrole under standard InCl₃-catalyzed conditions (Scheme 15) [72]. The extreme utility of dipyrrromethane 74 was noticeably demonstrated by its application in the preparation of triptycene-substituted BODIPY 75a, triptycene-substituted 3-pyrrrolyl-BODIPY 75b, trans-Å₂B₂ triptycenylporphyrins 76a,b and Å3B-type triptycenylporphyrins 76c,d.

Following a similar synthetic approach, the same authors also devised the synthesis of a more complex tris-dipyrrromethane-substituted triptycene 78 in 37% yield [72], starting from 2,6,14-tri(4-formylphenyl)triptycene derivative 77, which was prepared and isolated beforehand (Scheme 16). Tris-dipyrrromethane 78 was later successfully utilized as a valuable intermediate in the synthesis of tris-BODIPY-substituted triptycene 79.
Scheme 15. InCl₃-catalyzed synthesis of triptycenyldipyrromethane 74 for the preparation of triptycene-substituted BODIPY, triptycene-substituted 3-pyrrolyl-BODIPY, trans-Å₂B₂ triptycenylporphyrins and Å₃B triptycenylporphyrins.

Scheme 16. InCl₃-catalyzed synthesis of tris-dipyrromethane-substituted triptycene 78 required for the preparation of tris-BODIPY-substituted triptycene.
2.7. Other Strategies

The synthetic route that Trofimov’s research group developed in order to obtain new meso-trifluoromethyldipyrromethanes 85 and 86 using 2-aminophenyl-1H-pyrroles 80 as starting material is depicted in Scheme 17 [73]. Briefly, the protection of the amino functionality of pyrroles 80 with acetic anhydride, followed by a reaction with trifluoroacetic anhydride (TFAA), rendered 2-trifluoroacetylpyrroles 82 in high yields. Sodium borohydride-promoted reduction of pyrroles 82 and ensuing reaction of pyrrole carbinols 83 with 2-phenylpyrrole 84, in the presence of dehydration agent phosphorous pentoxide (P2O5), gave dipyrromethanes 85 in good yields. Finally, conversion of the acetamide substituents into amino groups in refluxing acidic media originated dipyrromethanes 86 (Scheme 17). Both dipyrromethane derivatives 85 and 86 were later used in the preparation of their corresponding meso-CF3-BODIPY dyes, a big influence of the coexistence of the strong electron donor NH2 and electron acceptor CF3 groups, along with the location of the amine at the aryl ring, being determined on the optical properties of chromophores 86 [73].

Scheme 17. Synthesis of meso-trifluoromethyldipyrromethanes 85 and 86 from 2-aminophenyl-1H-pyrroles.

The preparation of novel meso-trifluoromethyldipyrromethanes 92 and 93, comprising isoxazole substituents in their molecular structure, starting from ethynylpyrrole 87 was also recently described by the same authors (Scheme 18) [74]. Initial cyclization of 87 with hydroxylamine hydrochloride and subsequent condensation of the obtained isoxazoles 89 or 90 with previously prepared pyrrole carbinols 91 in the presence of dehydration agent P2O5 leads to the desired and unreported dipyrromethane derivatives 92 and 93 (Scheme 18). The latter were again further explored in the synthesis of their respective meso-CF3-BODIPY dyes, some photophysical studies and quantum chemical calculations having been carried out [74].

Aiming to synthesize the illusive and highly sought 2,3,7,8,12,13,17,18-octafluoroporphyrin with a reasonable yield, Chang and colleagues choose the approach summarized in Scheme 19 [75], ensuing an older account by Clezy and Smythe [76]. In brief, tetrafluorinated dipyrromethane 97 was obtained in three steps starting from 3,4-difluoropyrrole 94. Reaction with thiophosgene under an inert atmosphere rendered dipyrrothioketone 95 in high yield. Subsequent hydrogen peroxide-promoted oxidation to dipyrroketone 96, followed by sodium borohydride-mediated reduction, originated dipyrromethane derivative 97. Having this valuable scaffold in hands, the authors were thus able to prepare trans-A2B2-type porphyrins 98, as well as β-octafluoroporphyrins 99.
3. Novel Synthetic Strategies

3.1. Dipyrromethane Synthesis from Aldehydes and Pyrroles

Despite the wide variety of standard available methods, there is still an open door for the development of new synthetic approaches for dipyrromethanes. For instance, there is a growing interest in the use of catalysts that can be easily removed from the reaction medium and reused, while also having an economically and ecologically friendly access. Konar and co-workers described the synthesis of a wide range of meso-thienyl dipyrromethanes 101 using an amine functionalized MOF (Metal-Organic Framework) for the controlled release of the catalyst, iodine (Scheme 20) [77]. Dipyrromethanes 101 were obtained in high yields (50%–69%) with the ratio aldehyde/pyrrole (1:5) in the presence of 20 mol% of NH₂-MOF(I₂), without organic solvents and under mild conditions. The catalyst was reused for three cycles, although with a slight yield decrease. After immersion in an iodine solution, the catalytic performance was comparable with the freshly prepared NH₂-MOF(I₂).
The authors tested other catalysts, such as unfunctionalized MOFs (H-MOF(I2)), conventional TFA and molecular iodine; however, dipyrromethanes 101 were obtained with lower yields.

Dipyrromethanes 104e underwent oxidation and chelation by copper producing a red bis(dipyrinato)copper(II) complex 105 (Scheme 22). This characteristic makes it an efficient naked eye colorimetric chemosensor for copper ions, even in the presence of several other metal ions [79,80].

Dipyrromethanes 7c, 103b and 106 were synthesized in good yields by the iodine-catalyzed double Friedel-Crafts reaction, using toluene or water as solvent (Scheme 23) [81]. The reaction of pyrrole derivatives with aldehydes, (2:1) ratio, in presence of 10 mol% of molecular iodine in water gave dipyrromethanes in better yields (60%–87%) than the reaction carried out in toluene (42%–62%).
Sirion and co-workers described the synthesis of dipyrromethanes through the reaction of aldehydes with pyrrole catalyzed by SO$_3$H-functionalized ionic liquids (SO$_3$H-ILs) in aqueous media [82]. The authors tested a few SO$_3$H-ILs containing imidazolium or pyridinium cations and different anions, and found that [bmmim][HSO$_4$] (i.e., 1-butylsulfonic-3-methylimidazolium hydrogen sulfate) was the ideal catalyst for the synthesis of dipyrromethanes (Scheme 24). Dipyrromethanes 107 were obtained in moderate to good yields from the reaction of pyrrole with aliphatic or aromatic aldehydes, in the presence of 10 mol% of catalyst in water under mild conditions. The described method comprised a large variety of aromatic aldehydes with both electron withdrawing and electron donating substituents, heteroaromatic aldehydes as well as alky aldehydes. Moreover, the catalyst was easily removed from the reaction media through a simple extraction and recycling [82]. Later, the synthesis of meso-aryl-dipyrromethanes using 1-propylsulfonic-3-methylimidazolium trifluoromethylacetate as a catalyst was described, however, organic solvents were used [83].

The research group of Majee explored the use of imidazolium zwitterionic molten salt as organocatalyst in the synthesis of meso-substituted dipyrromethanes under solvent-free conditions (Scheme 25) [84]. This catalytic system acts as an electrophilic activator of the aldehyde by the hydrogen bond with imidazolium C-2 hydrogen, emphasizing the importance of this cationic moiety. The reaction of pyrrole or N-methylpyrrole with aromatic or aliphatic aldehydes (ratio 2:1), in the presence of 10 mol% of the catalyst at room temperature and without solvent, gave access to a wide range of dipyrromethanes in very high yields. Aromatic aldehydes containing electron withdrawing or donating groups react with pyrrole or N-methylpyrrole to give dipyrromethanes 108a in yields from 72% to 87%. Dipyrromethanes with a naphthyl 108b, pyrrole or indole 108c, and propyl 108d substituents were also synthesized in high yields, using the same imidazolium zwitterionic molten salt as catalyst. The methodology developed was seen by the authors as being a green synthetic protocol, because it was metal- and solvent-free, and environmentally friendly with a good atom economy [84].

meso-Acetyldipyrromethane 110 was synthesized in 70% yield by the reaction of methylglyoxal 109 with pyrrole, in a 1:2.5 ratio, using boric acid as catalyst in aqueous media (Scheme 26) [85]. In addition to dipyrromethane 110, other dipyrromethanes were synthesized using aromatic aldehydes and similar reaction conditions. Boric acid is weakly acidic and reacts with water decreasing the pH of

**Scheme 22.** Formation of bis(dipyrromethane)copper(II) complex 105.

**Scheme 23.** Synthesis of dipyrromethanes 7c, 103b and 106 catalyzed by iodine.
the aqueous layer; given that the reaction of pyrrole with aldehydes occurs in the interface with the organic layer, the formation of side products is thus prevented.

Scheme 24. Synthesis of dipyrrmethanes 7f and 107 catalyzed by a SO₃H-functionalized ionic liquid.

Scheme 25. Synthesis of dipyrrmethanes 108 catalyzed by an imidazolium zwitterionic molten salt.

Scheme 26. Synthesis of meso-acetyl-dipyrrmethane catalyzed by boric acid.

3.2. Dipyrrmethane Synthesis via Alternative Methods

Pinho e Melo and co-workers developed an on-water one-pot synthetic approach to meso-substituted dipyrrmethanes via hetero-Diels-Alder reaction (or conjugated addition) of nitrosoalkenes and azoalkenes with pyrrole (Scheme 27) [86,87]. Dehydrohalogenation of α,α-dihalooximes or α,α-dihalohydrazones, in the presence of base, produces transient nitrosoalkenes or azoalkenes I. These reactive species react with pyrrole to give pyrroles II functionalized at C-2 with a side chain, which undergo dehydrohalogenation to form the second transient nitrosoalkenes or azoalkenes III. The reaction with another molecule of pyrrole gives the dipyrrmethanes 112 or 113, in moderate
to high yields (21%–82%). The formation of dipyromethanes 112 and 113 are accelerated and more efficient using water as solvents allowing easier purification procedures than the reaction performed in dichloromethane or in the absence of solvent. Dipyromethanes synthesized by this approach have the unique feature of being meso-substituted with oxime and hydrazone moieties [86]. The same research group described the functionalization of dipyromethanes at positions 1 and/or 9 through hetero-Diels-Alder reaction or conjugated addition of nitrosoalkenes and azoalkenes [88–90].

\[
\begin{align*}
\text{Scheme 27. Synthesis of dipyromethanes 112 and 113 based on the chemistry of nitrosoalkenes and azoalkenes.}
\end{align*}
\]

The one-pot synthesis of ortho-hydroxymethyl 8-C-aryl BODIPY derivatives 117 was achieved through the key intermediate dipyromethanes 116 (Scheme 28) [91]. Ethyl phthalidinium salts 115, obtained by O-ethylation of phthalides 114 using Meerweins reagent, reacted with pyrrole to form intermediate ketal I. Elimination of the ethoxy group from intermediate I gave the oxonium ion II, which reacted with a second pyrrole unit to produce dipyromethane 116. Reaction of dipyromethanes 116 with BF\(_3\).OEt\(_2\) gave the BODIPY derivatives 117 in moderate yields (26%–45%). The masked 5-alkoxy-5-phenyldipyrromethane 116 with \(R^1 = H\), was isolated and treated with BF\(_3\).OEt\(_2\) in order to confirm that this is a key intermediate in the synthesis of the corresponding borondipyrromethenes 117.

\[
\begin{align*}
\text{Scheme 28. One-pot synthesis of ortho-hydroxymethyl 8-C-aryl BODIPY derivatives.}
\end{align*}
\]
Borbás and Xiong developed a strategy to synthesize unsymmetrical dipyrromethanes 120 through the Mannich reaction between pyrroles and Eschenmoser’s salt (Scheme 29) [92]. Initially, pyrroles 118 reacted with Eschenmoser’s salt to give the Mannich product 119, which undergo substitution of the N,N-dimethylamino group under microwave irradiation using pyrrole as reactant and solvent. This method encompasses acid-sensitive and formyl groups and does not require the use of acid to activate the pyrrole unit.

\[
\text{Eschenmoser’s salt} \xrightarrow{\text{MeCN, rt, 40-99\%}} 118a \quad R^1 = R^2 = R^3 = H \\
\text{118b} \quad R^1 = \text{Bn}, R^2 = R^3 = H \\
\text{118c} \quad R^1 = R^3 = H, R^2 = \text{Me} \\
\text{118d} \quad R^1 = R^2 = H, R^3 = \text{p-IC$_3$H$_4$} \\
\text{118e} \quad R^1 = R^2 = H, R^3 = \text{CHO}
\]

\[\text{Scheme 29. Synthesis of unsymmetrical dipyrromethanes 120.}\]

meso- and α-Unsubstituted dipyrromethanes 124 were formed by the decarboxylation of 1,9-diehoxycarbonyldiyrromethanes 123 with KOH in ethylene glycol (Scheme 30) [93]. Bromination of the α-methyl group of pyrrole 121, followed by nucleophilic substitution generated α-acethoxymethyl pyrroles 122, which underwent self-condensation in the presence of HCl to give meso-unsubstituted dipyrromethanes 123 in good yields. Dipyrromethanes 124 are key intermediates in the synthesis of porphyrins 125, that are meso-unsubstituted and β-substituted.

\[\text{Scheme 30. Synthesis and reactivity of meso- and α-unsubstituted dipyrromethanes.}\]

Thompson and co-workers developed a methodology to generate dipyrromethanes through the microwave-assisted reduction of F-BODIPYs and dipyrromethenes (Scheme 31) [94]. meso-Aryl BODIPYs 126 or dipyrromethenes 127 are reduced to the corresponding dipyrromethanes 128 in ethylene glycol and an excess of sodium methoxide under microwave irradiation at 215 °C for 10 minutes. This methodology is useful when BODIPYs or dipyrromethenes are formed in one-pot procedures and it is necessary to regenerate the dipyrromethane.

Neo-confused porphyrins 133 have been synthesized from the reaction of neo-confused dipyrromethanes 131 with dipyrromethane 132 (Scheme 32) [95]. The treatment of pyrrole-3-carboxaldehyde 129 with NaH in DMF at room temperature, followed by addition of methyl 4-formylpyrrole-2-carboxylate (130) gave the corresponding neo-confused dipyrromethanes 131 in good yields (45%-75%).
Given the continual relevance of the dipyrromethane scaffold, either by its own merits and applications or because of its extreme usefulness as a synthetic intermediate for other high value molecules, e.g., calix[4]pyrroles, (hydro)porphyrins, expanded porphyrins, corroles, BODIPY dyes, and metal coordination compounds, classical synthetic methods employing effective tried-and-tested catalysts still find their place on laboratory benches across the world. Nonetheless, as can be realized from this literature review covering the past six years, it is highly expected that organic and medicinal chemists, as well as material scientists, will keep pursuing innovative technologies and/or novel synthetic approaches with the aim of obtaining original, interesting, and much needed dipyrromethane structures.

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