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Synthesis of *meso*-substituted dipyrromethanes using iodine-catalysis

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ABSTRACT

This Letter presents a non-conventional synthesis of *meso*-substituted dipyrromethanes, using molecular iodine as the catalyst. Various aromatic dipyrromethanes were obtained in good yields after a preliminary study using nitrobenzaldehyde. The reactants and reagents were used as such, without prior distillation.

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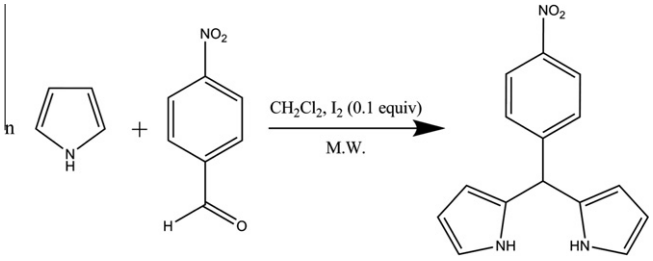
Dipyrromethanes are key chemical compounds, involved in numerous syntheses, such as porphyrin synthesis[1] or formation of polypyrrolic polymers.[2] Since the Woodward and Mac Donald works,[3] they have earned the status of building blocks in organic chemistry. The growing interest on these molecules led chemists to find new ways in order to increase yields and improve reaction conditions. We can notice the widely used synthesis, developed by Lindsey and co-worker,[4] using an acid catalyst, that is, trifluoroacetic acid or BF_3-etherate, and a large excess of pyrrole (100 equiv). During the past two decades, new syntheses of *meso*-substituted dipyrromethanes[5] have emerged to reduce this excess of pyrrole and/or to replace the inconvenient strong acid-catalyst.

In parallel, molecular iodine has recently emerged as an interesting and inexpensive catalyst. It has been used for its mild Lewis-acidity in numerous reactions such as electrophilic addition,[6] heterocycle synthesis,[7] or, more recently, porphyrin synthesis.[8] In line with our previous works, we have investigated the synthesis of several *meso*-substituted dipyrromethanes, using molecular iodine as the catalyst, under microwave irradiation.

First, we have proceeded to a preliminary study of the reaction conditions, using 4-nitrobenzaldehyde as the starting product. These reactions were conducted under microwave irradiation, with undistilled dichloromethane, undistilled pyrrole, and by using molecular iodine as the catalyst (Scheme 1).

The results, summarized in Table 1, show the great influence of the reactants ratio (pyrrole/aldehyde). Indeed, a great excess of pyrrole (entry 1) or a stoichiometric ratio (entry 4) led to moderate yields. The best yield (84%) was obtained with a 10:1 ratio (entry 2),



Scheme 1. Synthesis of 5-(4-nitrophenyl)dipyrromethane.

Table 1
Influence of the pyrrole/aldehyde ratio[a]

Entry	I_2 (equiv)	Pyrrole/aldehyde ratio	Isolated yield (%)
1	0.1	40:1	40
2	0.1	10:1	84
3	0.1	5:1	70
4	0.1	2:1	45
5	0	10:1	—[b]

[a] The reactions were performed with 1 mmol of 4-nitrobenzaldehyde and 0.1 mmol of molecular iodine, under microwave irradiation (1 min, 30 °C, 300 W) in 10 mL of dichloromethane.
[b] TLC did not show dipyrromethane formation.

which is safer than the most common methods (reactants ratio higher than 25:1).

This study also confirmed the role of molecular iodine as a Lewis-acid catalyst, because its absence did not conduce to the desired product (entry 5).

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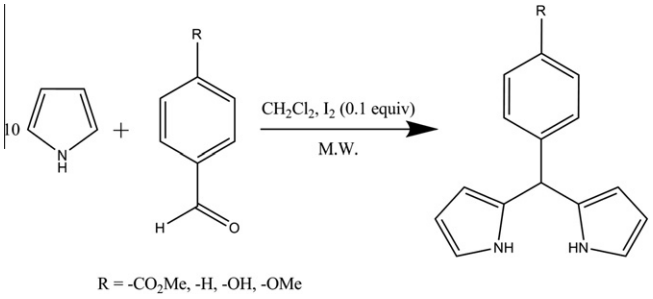
Considering these good results, and in order to generalize this method, we applied it to the synthesis of various *meso*-substituted aromatic dipyrromethanes (Scheme 2).

Different dipyrromethanes have been chosen for their interest in porphyrin synthesis[1] (Table 2) and the results were compared to the literature best yields. This method gave the products in good yields. In the case of the 5-(4-nitrophenyl)dipyrromethane and the 5-(4-methoxyphenyl)dipyrromethane, the iodine method led to the products in, respectively, 84% and 90% yields, which is higher than the Dan and Shu[9] synthesis (66% and 80%), consisting of the use of ceric ammonium nitrate.

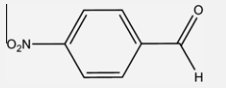
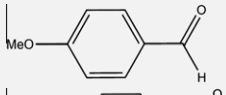
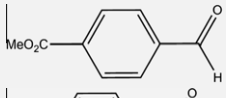
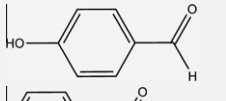
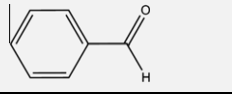
The synthesis of the 5-(4-carboxymethyl)dipyrromethane was significantly improved by the I_2/MW procedure (90%), compared to the more classical TFA-catalyzed synthesis,[10] which gives the product in 35% yield. The 5-(4-hydroxyphenyl)dipyrromethane, known as to be difficult to synthesize, was obtained by the simple Cozzi and co-worker method,[11] and conducted in water, catalyst-free, after 24 h, in 27% yield. The procedure developed here conduced to the final product in a twice higher yield, after one-minute irradiation. At last, the scalable synthesis of Laha et al.[12] afforded 5-phenyldipyrromethane in 82% yield, using $InCl_3$, with a large excess of pyrrole (100 equiv) and is solvent-free. Pyrrole is recovered after the reaction. In this case, the iodine method conduced to the product in a lesser yield of 60%.

However, until this day, it is important to notice that none of the numerous dipyrromethane syntheses affords the desired compound with all of these parameters: high yields, use of a green solvent or being solvent-free, without any catalyst or any excess of pyrrole, in a large scale, and avoiding inconvenient purification.



Scheme 2. Synthesis of various *meso*-substituted dipyrromethanes.

Table 2
Comparison of the yields with best methods found in the literature

Aldehyde	Isolated yield[a] (%)	Literature best yield (%)
	84	66[9]
	90	80[9]
	90	35[10]
	55	27[11]
	60	82[12]

[a] Conditions: aldehyde (1 mmol), pyrrole (10 mmol), molecular iodine (0.1 mmol), under microwave irradiation (1 min, 30 °C, 300 W), in 10 mL of dichloromethane. [13]

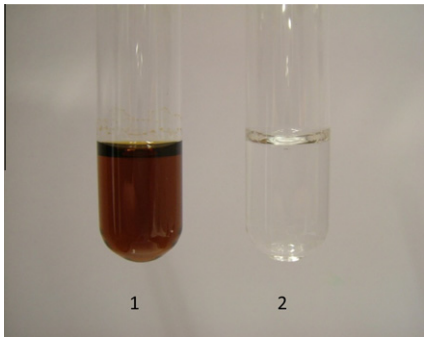


Figure 1. (1) Pyrrole used in this work (undistilled), (2) distilled pyrrole.

Taking advantage of its inexpensive and powerful catalyst and its use of undistilled reagents (Fig. 1), this new and rapid method of dipyrromethane synthesis afforded various products in good yields. In addition, we have obtained promising results with this method, in a larger scale, for the synthesis of the 5-(4-nitrophenyl)dipyrromethane. Its interest relies on the further use in porphyrin conjugate synthesis.

The strength of this pathway is the use of a limited excess of pyrrole and a very short reaction time that limits the polymerization of pyrrole and makes the further separation easier.

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13. *General procedure*: aldehyde (1 mmol), iodine (25 mg, 0.1 mmol) and then pyrrole (694 μL, 10 mmol) were added successively to 10 mL dichloromethane, without particular precautions. Benzaldehyde, pyrrole and dichloromethane are used as such, without prior distillation. After microwave irradiation (1 min, 30 °C, 300 W), TLC showed total conversion of aldehyde. The mixture was evaporated on florisil and purified by automated flash chromatography using a gradient of petroleum ether/chloroform as the eluent. Pure products were obtained as solids. All physicochemical and spectroscopic properties coincided with literature data.
5-(4-Nitrophenyl)dipyrromethane: mp = 159 °C, lit.: 159–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (s, 1H, *meso*H), 5.87 (d, 2H, J = 5.7 Hz, $2C_3$–H), 6.17 (dd, 2H, J = 2.8, 5.7, $2C_4$–H), 6.74 (dd, 2H, J = 2.8, 1.2, $2C_5$–H), 7.36 (d, 2H, J = 8.6, H-Ar), 7.98 (br s, 2H, N–H), 8.16 (d, 2H, J = 8.6, Ar-H). 5-(4-Methoxyphenyl)dipyrromethane: mp = 99 °C, lit.: 99 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H, CH_3), 5.40 (s, 1H, *meso*H), 5.90 (m, 2H, $2C_3$–H), 6.14 (dd, 2H, J = 2.8, 5.9, $2C_4$–H), 6.67 (m, 2H, $2C_5$–H), 6.84 (d, 2H, J = 8.7, H-Ar), 7.12 (d, 2H, J = 8.7, Ar-H), 7.92 (br s, 2H, N–H). 5-(4-Methoxycarbonylphenyl)dipyrromethane: mp = 164 °C, lit.: 162–163 °C. ^{1}H NMR (400 MHz, DMSO): δ 3.82 (s, 3H, CH_3), 5.44 (br s, 1H, *meso*H), 5.66 (br d, 2H, J = 5.3 Hz, $2C_3$–H), 5.90 (dd, 2H, J = 2.6, 5.3, $2C_4$–H), 6.62 (br d, 2H, J = 2.6, $2C_5$–H), 7.29 (d, 2H, J = 8.2, H-Ar), 7.88 (d, 2H,

J = 8.2, Ar-H), 10.61 (br s, 2H, N–H). 5-(4-hydroxyphenyl)dipyrromethane: mp = 158 °C, lit.: 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (s, 1H, *meso*H), 5.90 (m, 2H, $2C_3$–H), 6.14 (dd, 2H, J = 2.8, 5.8, $2C_4$–H), 6.67 (m, 2H, $2C_5$–H), 6.75 (d, 2H, J = 8.5, H-Ar), 7.05 (d, 2H, J = 8.5, Ar-H), 7.96 (br s, 2H, N–H). 5-Phenyldipyrromethane: mp = 100 °C, lit.: 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (br s, 1H, *meso*H), 5.90 (m, 2H, $2C_3$–H), 6.14 (dd, 2H, J = 2.8, 5.8, $2C_4$–H), 6.67 (br d, 2H, J = 2.8, $2C_5$–H), 7.20 (m, 2H, H-Ar), 7.25 (m, 2H, Ar-H), 7.88 (br s, 2H, N–H).