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Nano Fe_3O_4-Catalyzed one-pot synthesis of dipyrromethanes under solvent-free condition

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ABSTRACT

A clean and efficient method for the synthesis of dipyrromethanes with nano Fe_3O_4 (MNP) as the catalyst under solvent-free conditions is described. This method provides several advantages, such as simple work-up procedure, neutral conditions using a cheap, non-toxic, environment friendly solvent, and high yields.

KEYWORDS

Dipyrromethanes;
Nano Fe_3O_4 (MNP);
Solvent-free conditions.

INTRODUCTION

In recent years, dipyrromethanes and its derivatives have aroused a strong interest due to their useful physiological properties and biological activities as important building blocks for the synthesis of porphyrins[1], Calixpyrrols[2] and Corroles[3]. Which have recent applications as chiral catalysts, chiral sensors, synthetic receptors for small molecular devices, potential sensitizers for photodynamic cancer therapy[4-6].

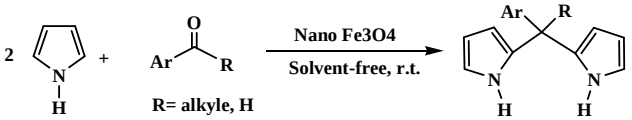
As a consequence, the synthesis and the applications of dipyrromethane derivatives still attract the attention of organic chemists. The most common strategy involved in the synthesis of dipyrromethanes is the mixture of pyrrole (2 mmol) and ketone (1 mmol) or aldehyde (1 mmol) compounds. Of the various other methods, syntheses involving transition-metal salts or lewis acid have recently been described for the preparation of substituted dipyrromethane derivatives[7-21].

However, all of the synthetic protocols reported so far suffer from disadvantages such as, use of metal and expensive reagent, prolonged reaction time, use of organic solvent, harsh reaction condition, use of excess pyrrole and low yield. Because of that the researcher still continuous to have a better methodology for the synthesis of dipyrromethanes in terms of simplicity, economic viability and high yielding at lowest pyrrole/aldehyde ratio.

RESULTS AND DISCUSSION

In connection with our ongoing studies, we wish, herein, to report on the use of nano Fe_3O_4 (MNP) as a more robust and efficient catalyst in the one-pot synthesis of dipyrromethane derivatives **3a-j** by the reaction of pyrrole **1** and ketone or aldehyde **(2a-j)** under solvent free conditions (Scheme 1).

During our investigation, at first, we chose



1 2a-j 3a-j

Scheme 1

benzaldehyde (1 mmol) and pyrrole (2 mmol) under solvent free condition as model reactants and examined the effect of the amount of nano Fe_3O_4 (MNP) (TABLE 1). According to this data, the optimum amount of catalyst was 0.01 g (0.04mmol) as shown in TABLE 1. Further increasing the amount of catalyst did not improve the yield and the reaction time.

A series of dipyrromethanes were prepared in high to excellent yields (TABLE 2).

TABLE 1 : The effect of amount of MNP on the reaction of pyrrole and benzaldehyde under solvent free conditions at room temperature

Entry	Catalyst (mmol)	Time (s)	Yield (%)
1	0.01	180	68
2	0.02	105	89
3	0.04	10	96
4	0.05	10	95
5	0	600	0

[a]**Yields refer to the pure isolated products**

TABLE 2 : Synthesis of dipyrromethanes by the reaction of pyrrole with aldehydes and Ketones.

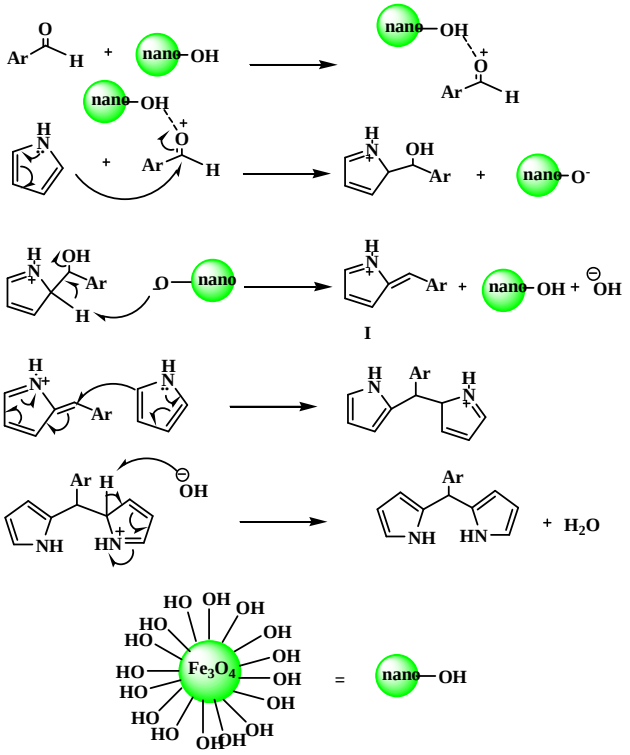
Entry	Product	Ar	R	Time(s)	Yelde(%)
1	3a	C_6H_5-	H	85	96
2	3b	4-MeC_6H_4-	H	90	95
3	3c	2-MeC_6H_4-	H	95	93
4	3d	4-MeOC_6H_4-	H	40	95
5	3e	2-MeOC_6H_4-	H	48	91
6	3f	4-$NO_2C_6H_4$-	H	10	97
7	3g	4-ClC_6H_4-	H	15	96
8	3h	4-BrC_6H_4-	H	30	95
9	3i	C_6H_5-	CH_3	97	93
10	3j	4-ClC_6H_4-	CH_3	42	91

a) All the products are known, characterized by IR, NMR spectral analysis and compared with the authentic samples b) Isolated yields. c) Melting points of compounds are consistent with reported values[15,28,29].

We propose a mechanism for these reactions in five steps as shown in Scheme 2.

Thus, the aldehydes derivatives acts as Michael acceptors and the pyrrole as the nucleophiles resulting in a Michael adduct which, under the influence of MNP, forms an intermediate **I** which undergoes nuclophilic reactions with pyrrole to afford dipyrromethane derivatives.

The electron withdrawing groups (EWD)



Scheme 2

substituted on benzaldehyde in *o*-QM intermediate increase the rate of 1,4-nucleophilic addition reaction because of alkene LUMO is at lower energy in the neighboring with-drawing groups than electron donating groups (EDG).

The advantages or the characteristic aspects of the method described herein, in comparison with those already reported are the following: The yields of products are better than the previously reported yields. In addition, the catalyst NMP is inexpensive and not moisture sensitive and sub-molar amounts of NMP are required. Longer reaction times are required when smaller amounts of NMP are employed. It is important to note that no dipyrromethane derivatives were formed when the reactions were carried out in the absence of NMP.

EXPERIMENTAL

Chemicals were obtained from Merck and Fluka chemical companies. The IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained in $CDCl_3$ using a 400 MHz JEOL FT NMR spectrometer. All melting points were determined on an Electro Thermal 9100

melting point apparatus

General procedure synthesis of dipyrromethanes

A mixture of pyrrole (2.0 mmol), aldehyde or ketone (1.0 mmol) and NMP (0.04 mmol) were added to a mortar and the mixture was pulverized with a pestle. A spontaneous reaction took place [< 1 min, Table 2, monitored by TLC (4:1, hexane/ acetone after completion of the reaction, Et_2O (2× 5 mL) was added and the catalyst was separated by an external magnet. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by column chromatography using silica gel with petroleum ether/ chloroform as the eluent. Pure products were obtained as solids.

All the products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy and have been identified by the comparison of the reported spectral data. The spectral and analytical data for the selected compounds are presented below.

5-Phenyldipyrromethane (3a)

Dark brown powder; mp 101-103 °C, IR (KBr) 3392, 2948, 1589, 1505, 1408, 1295, 1220, cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$); δ 5.46(s, 1H, C**H**), 5.89 (m, 2H, 2C$_{py.}$**H**), 6.11 (dd, *J*= 2.8, 5.9 Hz, 2H, 2 C$_{py.}$**H**), 6.61 (dd, *J*= 2.7, 4.3 Hz, 2H, 2 C$_{py.}$**H**), 7.19-7.33 (m, 5H, Ar**H**), 7.67 (br s,2H, 2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 44.05, 109.42, 109.79, 118.11, 127.05, 127.01, 128.63, 128.96, 132.35, 142.21; ESI-MS: m/z [M+1] 222.

5-(4-Methylphenyl) dipyrromethane (3b)

Dark brown powder; mp 110-112 °C, IR (KBr) 3401, 2954, 1602, 1507, 1411, 1283, 1089, cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.33 (s, 3H, C**H**$_3$), 5.38 (s, 1H, C**H**), 5.97 (m, 2H, 2C$_{py.}$**H**), 6.24 (dd, *J*= 2.7, 5.7 Hz, 2H, 2 C$_{py.}$**H**) 6.64 (dd, *J*=2.6, 4.3 Hz, 2H, 2 C$_{py.}$**H**), 7.07-7.13 (m, 4H, Ar- H), 7.75 (br s, 2H, 2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 21.22, 43.73, 107.33, 108.91, 117.07, 127.56, 129.01, 133.68, 136.41, 139.32; ESI-MS: m/z [M+1] 236.

5-(2-Methylphenyl) dipyrromethane (3c)

Dark brown powder; mp 99-101 °C, IR (KBr) 3427, 2958, 1614, 1518, 1410, 1289, 1104, cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.30 (s, 3H, C**H**$_3$), 5.37 (s, 1H, C**H**), 5.85 (m, 2H, 2C$_{py.}$**H**), 6.21 (dd, *J*= 2.7, 5.7 Hz, 2H, 2 C$_{py.}$**H**) 6.69 (dd, *J*=2.6, 4.3 Hz, 2H, 2 C$_{py.}$**H**), 7.11-7.19 (m, 4H, Ar**H**), 7.81 (br s, 2H, 2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 21.09, 43.75, 107.31, 108.69, 117.12, 127.57, 129.13, 133.65, 136.36, 139.31; ESI-MS: m/z [M+1] 236.

5-(4-Methoxyphenyl) dipyrromethane (3d)

Dark brown powder; mp 107-109 °C, IR (KBr) 3383, 2965, 1604, 1515, 1452, 1290, 1238, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.82 (s, 3H, OC**H**$_3$), 5.61 (s, 1H, C**H**), 5.92-5.97 (m, 2H, 2 C$_{py.}$**H**), 6.14 (dd, *J*=2.9, 6.1 Hz, 2H, 2 C$_{py.}$**H**), 6.65 (m, 2H, 2 Ar**H**), 6.93 (d, *J*=8.6 Hz, 2H, Ar**H**),7.21 (d, *J*=8.7 Hz, 2H, Ar**H**), 7.86 (m, 2H, 2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 43.21, 55.15, 108.19, 108.58, 114.06, 117.05, 130.27, 132.54, 133.92, 159.08; ESI-MS: m/z [M+1] 252.

5-(2-Methoxyphenyl)dipyrromethane (3e)

Dark brown powder; mp 114-115 °C, IR (KBr) 3415, 2961, 1611, 1485, 1236, 1093, 1029, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.83 (s, 3H, OCH_3), 5.78 (s, 1H, C**H**), 5.91 (m, 2H, 2 C$_{py.}$**H**), 6.12 (d, *J*=2.5, 2H Hz, 2 C$_{py.}$**H**), 6.67 (d, *J*=1.4 Hz, Ar**H**), 7.31 (t, *J*=7.8 Hz, 1H, Ar**H**), 7.99 (br s, 2H, 2N**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.82, 55.38, 107.21, 108.75, 111.27, 115.87, 121.15, 128.12, 129.69, 131.12, 132.45, 156.78; ESI-MS: m/z [M+1] 252.

5-(4-Nitrophenyl) dipyrromethane (3f)

Dark yellow powder; mp 129-131 °C, IR (KBr) 3408, 2945, 1607, 1513, 1409, 1291, 1225, cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$); δ 5.61 (s, 1H, C**H**), 5.93 (m, 2H, 2C$_{py.}$**H**), 6.17 (dd, *J*= 2.8, 6.1 Hz, 2H, 2 C$_{py.}$**H**), 6.68 (dd, *J*= 2.7, 4.5 Hz, 2H, 2 C$_{py.}$**H**), 7.29-7.45 (m, 4H, Ar**H**), 7.75 (br s,2H, 2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 44.17, 109.78, 110.25, 118.16, 127.27, 128.05, 128.94, 129.16, 132.57, 143.05; ESI-MS: m/z [M+1] 267.

5-(4-Chlorophenyl) dipyrromethane (3g)

Dark brown powder; mp 115-117 °C, IR (KBr) 3394, 2961, 1598, 1517, 1439, 1292, 1244, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ 5.65 (s, 1H, C**H**), 5.87 (m, 2H, 2 C$_{py.}$**H**), 6.18 (dd, *J*=2.9, 5.9 Hz, 2H, 2 C$_{py.}$**H**), 6.71 (m, 2H, 2 Ar**H**), 6.85 (d, *J*=7.2 Hz, 2H, Ar**H**),7.13 (d, *J*=8.5 Hz, 2H, Ar**H**), 7.79 (m, 2H,

2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 55.28, 107.59, 108.14, 113.27, 116.89, 130.08, 132.15, 132.94, 159.11; ESI-MS: m/z [M+1] 256.

5-(4-Bromophenyl) dipyrromethane (3h)

Dark brown powder; mp 114-116 °C, IR (KBr) 3386, 2957, 1613, 1519, 1405, 1287, 1116, cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 5.35 (s, 1H, C**H**), 5.86 (m, 2H, 2$C_{py.}$**H**), 6.18 (dd, *J*= 2.7, 8.2 Hz, 2H, 2 $C_{py.}$**H**) 6.65 (dd, *J*=2.6, 4.3 Hz, 2H, 2 $C_{py.}$**H**), 7.07-7.16 (m, 4H, Ar**H**), 7.82 (br s, 2H, 2N**H**); ^{13}C NMR (100MHz, $CDCl_3$): δ 43.61, 107.35, 108.67, 117.09, 127.62, 129.11, 133.73, 136.35, 139.24; ESI-MS: m/z [M+1] 301.

***meso*-Methyl-*meso*-phenyl-2,2-pyrromethane (3i)**

Dark brown powder; mp 102–104°C, IR (KBr) 3392, 2952, 1589, 1506, 1398, 1290, 1218, cm^{-1}; ^{1}H NMR (400MHz: $CDCl_3$): δ 2.14 (s, 3H, C$\mathbf{H}_3$), 5.86 (m, 2H, C_{py}**H**), 6.17 (m, 2H, $C_{py.}$**H**), 6.65 (m, 2H, $C_{py.}$**H**), 7.24 (m, Ar**H**, 2H), 7.31 (m, 3H, Ar**H**), 7.44, (br s, 2H, ls, N**H**). ^{13}C NMR (100MHz, $CDCl_3$): δ 43.38, 107.39, 108.29, 117.11, 127.65, 129.14, 133.61, 136.38, 140.09; ESI-MS: m/z [M+1] 236.

***meso*-Methyl-*meso*-4-chlorophenyl-2,2-pyrromethane (3j)**

Dark brown powder; mp 112–114°C, IR (KBr) 3407, 2961, 1595, 1523, 1405, 1296, 1223, cm^{-1}; ^{1}H NMR (400MHz: $CDCl_3$): δ 2.17 (s, 3H, C$\mathbf{H}_3$), 5.85 (m, 2H, C_{py}**H**), 6.19 (m, 2H, $C_{py.}$**H**), 6.68 (m, 2H, $C_{py.}$**H**), 7.11-7.28 (m, 4H, Ar**H**), 7.46, (br s, 2H, ls, N**H**). ^{13}C NMR (100MHz, $CDCl_3$): δ 43.41, 107.38, 108.37, 117.08, 127.64, 129.09, 133.62, 136.39, 139.87; ESI-MS: m/z [M+1] 270.

CONCLUSION

The present methodology shows that 1,3-dibromo-5,5- dimethylhydantoin (DBH) is an efficient catalyst in the one pot synthesis of dipyrromethane derivatives under solvent-free in room temperature. The main advantages of the presented protocol are mild, clean and environmentally benign reaction conditions, as well as the high yields. Furthermore, this method is also expected to find application in organic synthesis due to the low cost of the reagent. It is believed that this method will be a useful addition to modern synthetic methodologies.

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