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Molecular iodine- catalyzed convenient synthesis of meso substituted dipyrromethanes

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ABSTRACT

The reaction at room temperature of an aromatic aldehyde with pyrrole in the presence of Iodine, acetic acid catalyzed of meso-substituted dipyrromethane. The mixture was ground together in a mortar with a pestle at room temperature for short reaction time and easy operation under at room temperature. The meso substituted dipyrromethane is purified by crystallization and column chromatography on silica with eluants containing methanol: benzene. The reaction is compatible with aromatic aldehyedes. The meso substituted dipyrromethanes are stable in the purified from in the presence of atmospheric temperature. Meso-substituted dipyrromethane were obtained in excellent yield of the product.

Keywords: Meso-substituted dipyrromethane, pyrrole, Aromatic aldehyde, acetic acid, iodine.

INTRODUCTOIN

The development of pyrrole chemistry has largely been associated with the synthesis of natural products. Polypyrrolic compounds are of wide interest in several areas, namely in porphyrins and related macrocycles [1], Science materials [2], optics [3] and medicine [4]. Meso substituted dipyrromethane are important building blocks for the organic synthesis and pharmaceuticals [5, 6]. They were also widely used as ligands in organometallic synthesis and catalysis [7, 8]. In addition, the meso substituted dipyrromethane building blocks systems are convenient used in ionic liquids [9,10] that have been given a new approach to 'Green Chemistry'. Due to their great importance, many synthetic strategies have been developed. In 1994, Lindsay et al. reported the first synthesis of the meso-substituted dipyrromethane from pyrrole compound, various aldehydes and strong acid to obtain the meso-phenyl dipyrromethane [11]. Also sobral et al. proposed the synthesis of the dipyrromethane using water and hydrochloric acid [12-13]. Recently, there are several methods reported in the literature for the synthesis of meso-substituted dipyrromethanes using aqueous/ HCl [13], pyrrolidinium tetrafluoroborate [14], cation exchange resins [15], CF_3COOH [16], TFA/BF_3-etherat [17], $CF_3CHClBr$/ $Na_2S_2O_4$ [18]. However, these methods require prolonged reaction time and exotic reaction condition. Thus, the development of a new method, for the synthesis of meso-substituted dipyrromethane derivatives

would be highly desirable. In recent years, iodine has gained special attention as a catalyst in organic synthesis because many advantages such as excellent yield, uncomplicated handling, inexpensiveness, eco-friendly nature, readily available and high reactivity. Recently, several synthetically useful organic transformations using iodine as a catalyst have been reported in the literature [19, 20].

MATERIALS AND METHODS

Synthesis of meso substituted dipyrromethane (3a-m)

A solution of pyrrole (5 g) in acetic acid (1ml) was cooled in ice-bath at 0 ^{0}c. Take an appropriate aldehyde (0.5 molar equivalents), and add iodine (5 m mol%). After the addition, the mixture was ground together in a mortar with a pestle at room temperature for a several minutes, and then washed with $Na_2 S_2 O_3$ and finally dried in room temperature. A dark brown colored solid is obtained (90-98% yield). A purity check of this material by TLC in methanol- benzene (25: 75) shows spots of meso substituted dipyrromethane purification of the crude products was affected by column chromatography using silica gel with either pure methanol – benzene (25: 75) as the eluent. As the meso substituted dipyrromethanes undergo slow polymerization upon standing at room temperature.

5-Phenyldipyrromethane (3a). Dark brown powder; mp 100-101 ^{0}C, lit.:100-101 ^{0}C; yield 98%; IR (KBr) 3447, 2950, 1629, 1512, 1413, 1291, 1225, 1041, 760, 705, 609 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$); δ 5.47(s, 1H, *mesoH*), 5.99 (br s 2H, 2C3-H), 6.15 (dd, *J* 2.8, 5.9, 2H, 2C4-H), 6.64 (dd, *J* 2.7, 4.3, 2H, 2C5-H), 7.21-7.37 (m, 5H, Ar-H), 7.80 (br s,2H, 2N-H); ^{13}C NMR (100MHz, $CDCl_3$): δ 44.11, 109.47, 109.71, 118.09, 127.01, 127.00, 128.59, 128.64, 132.39, 142.20; MS (70 eV) m/z (%): 222 (M^+, 100).

5-(4-Methylphenyl)dipyrromethane (3b). Dark brown powder; mp 110-111 ^{0}C, lit.:110-111 ^{0}C; yield 90%; IR (KBr) 3415, 2354, 1632, 1504, 1422, 1253, 1085, 1023, 962, 902, 791 ,745, 502 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 5.45 (s, 1H, *mesoH*), 5.94 (br s, 2H, 2C3-H), 6.12 (dd, *J* 2.7, 5.7, 2H, 2C4-H) 6.60(dd, *J*2.6, 4.3, 2H, 2C5-H), 7.11-7.15 (m, 4H, Ar-H), 7.86 (br s, 2H, 2N-H); ^{13}C NMR (100MHz, $CDCl_3$): δ 21.11, 43.70, 107.36, 109.01, 117.03, 127.40, 129.03, 133.55, 136.44, 139.26; MS (70 eV) m/z (%): 236 (M^+, 100).

5-(4-Methoxyphenyl)dipyrromethane (3c). Dark brown powder; mp 98-99 ^{0}C, lit.:99 ^{0}C; yield 92 %; IR (KBr) 3403, 2961, 2935, 1614, 1502, 1454, 1297, 1242, 1174, 1101, 1025, 962, 835, 773, 725, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.88 (s, 3H, OCH_3), 5.44 (s, 1H, *mesoH*), 5.90-5.95 (m, 2H, 2C3-H), 6.12 (dd, *J* 2.9, 6.1, 2H, 2C4-H), 6.62-6.65 (m, 2H, 2C5-H), 6.85 (d, *J* 8.6, 2H, Ar-H),7.17 (d, *J* 8.7, 2H, Ar-H), 7.80 (br s, 2H, 2N-H); ^{13}C NMR (100MHz): δ 43.22, 55.11, 108.27, 108.62, 114.00, 117.04, 130.46, 132.79, 133.90, 159.01; MS (70 eV) m/z (%): 252 (M^+ 100)

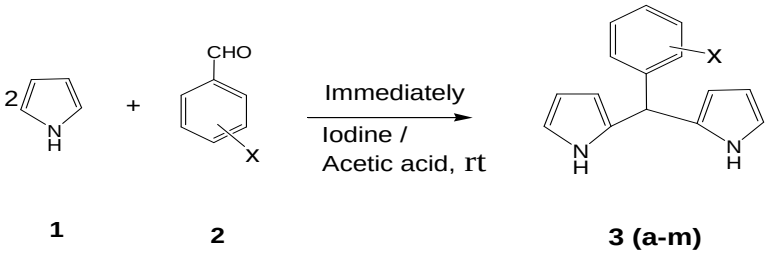
5-(2-Methoxyphenyl)dipyrromethane (3d). Dark brown powder; mp 114-115 ^{0}C, lit.: 115 ^{0}C; yield 90% ; IR (KBr) 3421, 1635, 1484, 1245, 1091, 1025, 962, 717, 556 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$); δ 3.88 (s, 3H, OCH_3), 5.80 (s, 1H, *mesoH*), 5.94 (br s, 2H, 2C3-H), 6.16 (d, *J* 2.5, 2H, 2C4-H), 6.68 (d, *J* 1.4, Ar-H), 7.29 (t, *J* 7.8, 1H, Ar-H), 7.98 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.65, 55.78, 107.15, 108.74, 111.25, 116.69, 121.05, 128.06, 129.64, 131.10, 132.46, 156.75; MS (70 eV) m/z (%): 252 (M^+ 100).

5-(2-Hydroxyphenyl)dipyrromethane (3e). Dark brown powder; mp 90 ^{0}C; yield 93 % ; IR (KBr) 3425, 2056, 16354, 1497, 1449, 1335, 1250, 1082, 1020, 907, 791, 742, 525 cm-1; ^{1}H

NMR (400MHz $CDCl_3$): δ 5.14 (br s, 1H, OH), 5.50 (s, 1H, *mesoH*), 6.00 (br s, 2H, 2C3-H), 6.10 (dd, *J*2.8, 5.7, 2H, 2C4-H), 6.71 (br s, 2H, 2C3-H), 6.16 (dd, *J* 2.7, 5.5, 2H, 2C3-H), 6.74 (dd, *J* 2.5, 4.8, 2H, 2C5-H), 6.80-6.99 (m, 2H, Ar-H), 7.05-7.18 (m, 1H, Ar-H), 7.17-7.25 (m, 1H, Ar-H), 8.17 (br s, 2H, 2N-H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 40.51, 106.20, 107.90, 118.02, 118.00, 122.09,129.05, 128.80, 130.15, 130.78, 153.86; MS (70 eV) m/z (%): 238 (M^+ 100); Anal.Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.48; H, 6.03; N, 11.58.

RESULTS AND DISCUSSION

Taking into account the pharmacological importance of meso substituted dipyrromethanes, and as part of our continuing efforts on the development of new routes for the preparation of heterocyclic compounds, [19,20] we have recently focused on improving the synthesis of this nucleus. Herein we report a convenient synthesis of meso substituted dipyrromethanes, via a one-pot reaction. Thus, a mixture of a pyrrole with various aromatic aldehydes using molecular iodine under acetic acid and in the presence of atmospheric temperature to produce meso substituted dipyrromethanes (**3a-m)** in 90-98% yields (Scheme1).



1 **2** **3 (a-m)**

Scheme 1

Reaction were carried out simply by mixing pyrrole with an aromatic aldehyde and acetic acid in the presence of a catalytic amount (5 mol %) of iodine under reaction condition summarized in Table 3. The mixture was ground together in a mortar with a pestle at room temperature for short reaction time, and then purified by column chromatography, meso substituted dipyrromethane derivatives were obtained in excellent yields. Accordingly, (5 mol%) was sufficient to catalyze the reaction. A rate enhancement with high yield was observed when higher molar ratios of iodine and acetic acid were used. However, no product formation was observed in absence of iodine and acetic acid. By getting this result, we have extended this protocol to a variety of aromatic aldehydes summarized in Table 1. Meso substituted dipyrromethane are formed in almost quantitative yields when pyrrole was treated with various aromatic aldehydes in the presence of a catalytic amount (5 mol%) of I_2 in acetic acid. The electrophilic substitution reaction of pyrrole with aldehyde proceeded smoothly at room temperature, clearly indicate the scope and generality of the reaction as the reactions of aromatic aldehydes (entry **3a-3m**). A variety of substituted aromatic aldehydes with pyrrole in the presence of I_2 (5 mol%) in acetic acid gave the corresponding meso substituted dipyrromethanes in excellent yields. It is reported that aromatic aldehydes with strong electron withdrawing substituent on the ring and aromatic aldehyde require longer reaction time giving low to excellent yields of the corresponding meso substituted dipyrromethane. In this context the present protocol is note worthy because even nitro substituted aromatic aldehydes underwent smooth reactions with pyrrole giving excellent yield of products in a very short reaction time. However, the reported catalysts require longer reaction time giving moderate yields of products for this conversion. The present procedure is superior comparison with authentic sample.

Table 1. I_2 catalyzed synthesis of meso substituted dipyrromethane

Compound	Ar-CHO	Yield(%)[a,b]	Melting Point ^{0}C
3a	X-H	98	100
3b	X- 4-Me	90	110
3c	X- 4-OMe	92	98
3d	X- 2-OMe	90	114
3e	X- 2-OH	93	90
3f	X- 4-NO_2	97	160
3g	X- 2-NO_2	97	160
3h	X- 4-NMe_2	97	124
3i	X- 4-CN	93	161
3j	X- 4-Cl	96	112
3k	X- 4-CF_3	40	Liquid
3l	X- 4-F	92	80
3m	X- 4-Br	95	122

a. Yield of isolated pure products b. Products was characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass elemental analysis and comparison with authentic sample.

For acid initially, a systematic study was carried out for catalytic evolution of acetic acid for meso substituted dipyrromethane, 4 – chlorobenzaldehyde and iodine (**Table 2**) the enhancement of 1 m ml of acetic acid, enhance the yield of the product and reduce the reaction time (**entry 1-6**).The reaction went to completion in a very short reaction time with different m ml of acetic acid. Accordingly, 1 m ml was sufficient to catalyze the reaction. A rate enhancement with high yield was observed when higher m ml ratios of acetic acid were used. However, no product formation was observed in absence of acetic acid.

Table 2. Catalytic evolution for synthesis of 3j in an Acetic acid at room temperature

Entry	Time (min)	Yield(%)*	Acetic acid (m ml)/I_2 (5 mol%)
1	180	00	0.00/00
2	100	15	0.10
3	90	33	0.20
4	70	70	0.40
5	30	85	0.50
6	01	96	1.00

** Isolated yield after column chromatography.*

Table 3. Catalytic evolutions for synthesis of 3j in Iodine at room temperature

Entry	Time (min)	Yield (%)*	I_2 (mol%)/ Acetic acid (1ml)
1	180	00	No iodine / No Acetic acid
2	90	50	1
3	45	65	2
4	30	85	3
5	01	96	5

** Isolated yield after column chromatography.*

We now, characterized freshly prepared samples by low/high resolution mass spectrometry and NMR, IR. Confirmed that the desired products were obtained and indicated no discernable impurities. For all the products except **3g**, the base peak in the mass spectra arises from the molecular ion (electron impact source used) with **3g**. There is still a significant molecular ion peak (33%) but due to the ortho-nitro substituent, the base peak originates from the ion after loss of water and NO.

CONCLUSION

we have developed a convenient and one-pot reaction of pyrrole, aromatic aldehydes, iodine and acetic acids for the preparation of meso substituted dipyrromethanes of potential synthetic and pharmacological interest. The simplicity of the starting materials, excellent yields of the products. The reaction procedure is simple and short reaction time, cleaner reaction, and easy workup makes this protocol practical and economically attractive. We believe this experimentally simple approach could be a useful addition to reported methods.

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