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An Efficient Synthesis of Meso-Substituted Dipyrromethane Derivatives Catalyzed By Ceric (IV) Ammonium Nitrate in Aqueous Media

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ABSTRACT

Meso-substituted dipyrromethanes were obtained in excellent yields by the one-pot condensation of aldehyde and pyrrole in the presence of catalytic amount of the inexpensive, readily available and non-toxic ceric (IV) ammonium nitrate (CAN) in aqueous media at room temperature. In this reaction the products were obtained in short reaction time and easy operation under mild conditions without using any strong acid and minimize the organic solvent.

Keywords: Dipyrromethanes, One-Pot, Ceric (IV) ammonium nitrate (CAN), Pyrrole, Aqueous media.

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INTRODUCTION

Meso-substituted dipyrromethanes are widely used as building blocks for the synthesis of porphyrins, corroles, and calixpyrroles; in particular, the strapped types that show enhanced anion binding abilities [1-3]. The synthesis of meso-substituted dipyrromethane basically involves the acid-catalyzed condensation of aldehyde/ketone with pyrrole or its derivatives. In addition, the meso-substituted dipyrromethane compounds are substantially used in ionic liquids [4] 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 [5]. Also sobral et al. proposed the synthesis of the dipyrromethane using water and hydrochloric acid [6-7].

Recently, there are several methods reported in the literature for the synthesis of meso-substituted dipyrromethanes using aqueous/ HCl [7], pyrrolidinium tetrafluoroborate [8], cation exchange resins [9], CF_3COOH [10], TFA/BF_3-etherat [11], $CF_3CHClBr$/ $Na_2S_2O_4$ [12]. 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.

Ceric (IV) ammonium nitrate catalyzed reactions are currently of great interest in organic chemistry. They have been used as water stable and reusable Lewis acids in several carbon–carbon bond forming reactions such as aldol, Michael, Diels-Alder and Friedel-Crafts acylation and alkylations [13].

In 1980, Breslow discovered that the Diels-Alder reaction performed in water could be subject to huge rate acceleration [14]. This observation leads to increased interest from synthetic organic chemists in organic reactions in water or aqueous media. To date, many more organic transformations have been carried out in water or aqueous media [6, 15].

In recent year, Ceric (IV) ammonium nitrate (CAN) has gained special attention as a catalyst in organic synthesis because many advantages such as excellent solubility in water, non-toxic, uncomplicated handling, inexpensiveness, eco-friendly nature, readily available and high reactivity. Recently, several synthetically useful organic transformations using CAN as a catalyst have been reported in the literature [16, 17, 19b]. Stirring has increasingly been used in organic synthesis in the last three decades. It has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. A large number of organic reactions can be carried out in higher yields, shorter reaction time or milder conditions under stirring [18].

EXPRRIMENT

The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc.

^{1}H NMR spectra were recorded on a Varian Gemini spectrometer at 400 MHz. Mass spectra was taken with a Varian Matt 312 operating in EI mode at 70 eV. The entire chemical were received from Aldrich and were used without further purification. Solvent (Merck, GR grade) were redistilled.

General procedure for the synthesis of meso-substituted dipyrromethane derivatives (**3a-k**)

A mixture of aldehyde (1 mmol), pyrrole (2 mmol) and CAN (5 mol%) in water-ethanol (5:5 mL) was stirred at room temperature. After completion of the reaction (TLC analysis). Then reaction mixture was extracted with ethyl acetate the organic layer was dried over Na_2SO_4 and ethyl acetate was removed using a rotary vaccum evaporator. The crude products, thus isolated, were pure (Single spot on TLC). They were subjected to further purification by chromatography through a column of silica-gel using 25% ethyl acetate in petroleum ether as eluent to yield the desired meso-substituted dipyrromethane in excellent yields of 86-95% and the products (**3a-k**) were confirmed by comparisons with authentic samples IR, ^{1}H NMR, mass spectra and melting points.

Spectral data of principal compounds Compound (**3a**) IR (KBr): 3444, 2955, 1634, 1508, 1420, 1283, 1231, 1052, 763, 700, 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):d 5.47 (s, 1H, mesoH), 5.88 (brs, 2H, 2C3-H), 6.00 (dd, *J* 2.7, 5.10, 2H, 2C4-H), 6.78 (dd, *J* 2.5, 4.2, 2H, 2C5-H), 7.20–7.41 (m, 5H, Ar-H), 7.70 (brs, 2H, 2N-H); EIMS (*m /z*, %): 211 (M + 1). **Compound** (**3b**) IR (KBr): 3370, 2950, 2930, 2860, 1649, 1480, 1400, 1249, 1097, 1032, 766, 720, 550, 507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d 5.57 (s, 1H, meso H), 5.92 (brs, 2H, 2C3-H), 6.19 (dd, *J* 2.7, 5.9, 2H, 2C4-H), 6.46 (dd, *J* 2.7, 4.2, 2H, 2C5-H), 7.15 (d, *J* 8.4, 2H, Ar-H), 7.40 (d, *J* 8.4, 2H, Ar-H), 7.67 brs, 2H, 2N-H); EIMS (*m / z*, %): 247 (M + 1). **Compound** (**3c**) IR (KBr): 3365, 3080, 2967, 2924, 2857, 1707, 1477, 1400, 1088, 1019, 765, 720, 643, 544, 503 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d 5.41 (s, 1H, mesoH), 5.86 (br s, 2H, 2C3-H), 6.10 (dd, *J* 2.8, 5.9,2H, 2C4-H), 6.70 (dd,*J*2.6, 4.2, 2H, 2C5-H), 7.11 (d, *J* 8.4, 2H, Ar-H), 7.60 (d, *J* 8.4, 2H, Ar-H), 7.87 (brs, 2H, 2N-H); EIMS (*m/z*, %): 290 (M + 1). **Compound** (**3d**) IR (KBr): 3400, 2933, 1611, 1488, 1461,1280, 1175, 1103, 970, 764, 554 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$):d 5.50 (s, 1H, mesoH), 5.90 (brs, 2H, 2C3-H), 6.09 (dd, *J* 2.8, 5.8, 2H, 2C4-H), 6.64 (brs, 2H, 2C5-H), 7.01–7.07 (m, 2H, Ar-H), 7.16–7.20 (m, 2H, Ar-H), 7.74 (brs, 2H, 2N-H); EIMS (*m/z*, %): 229 (M + 1). **Compound** (**3e**) IR (KBr): 3390, 3350, 3111, 1585, 1514, 1348, 1114, 1027, 804, 735, 661, 568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): d 5.55 (s, 1H, meso H), 5.89 (brs, 2H, 2C3-H), 6.11 (dd, *J* 2.8, 6.0, 2H, 2C4-H), 6.77 (dd, *J* 2.6, 4.2, 2H, 2C5-H), 7.35 (d, *J* 8.6, 2H, Ar-H), 7.91 (br s, 2H, 2N-H), 8.11 (d, *J* 8.8, 2H, Ar-H); EIMS (*m/z*, %): 246 (M +1).

RESULTS AND DISCUSSION

As a part of our ongoing investigation in developing a versatile and efficient method for synthesis of heterocyclic compounds [20], we report here an efficient synthetic method for the synthesis of meso-substituted dipyrromethanes from pyrrole and aldehydes in the presence of CAN (**Scheme 1**).

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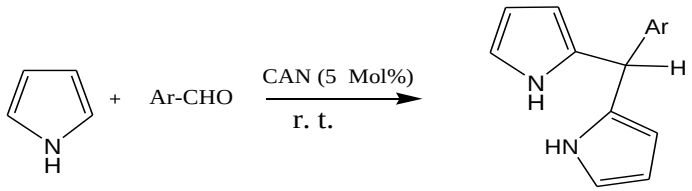

Scheme 1. Synthesis of meso-substituted dipyrromethanes using pyrrole (1), aldehydes (2) and CAN as a catalyst under stirring at room temperature.

Entry	Solvent (mL)	Mol % of CAN	Yield (%)*
			Dipyrromethane (3b)
1	Pure H_2O (10)	10	60
2	Pure EtOH (10)	10	66
3	H_2O/THF (5:5)	10	79
4	H_2O/ CH_3CN (5:5)	10	75
5	H_2O/ EtOH (5:5)	10	95
6	H_2O/ EtOH (5:5)	5	95
7	H_2O/ EtOH (5:5)	2.5	79
8	H_2O/ EtOH (2:8)	5	68
9	H_2O/ EtOH (3:7)	5	72

*Isolated yields.

Table 1. Optimization of reaction condition and mol% of CAN using pyrrole, 4- chlorobenzaldeyde under stirring at room temperature (Table 2 Compound 3b).

Entry	Ar-CHO	Reaction time (min)	Yield (%)* (**3a-k**)	M.P (^oC)	
				Found	Lit.
3a	C_6H_5	30	95	99	100[19a]
3b	4-ClC_6H_4	30	95	110	112[19a]
3c	4-BrC_6H_4	45	94	122	125[19a]
3d	4-FC_6H_4	50	90	80	81[19a]
3e	4-NO_2 C_6H_4	70	86	160	159[19a]
3f	4-$N(Me)_2C_6H_4$	60	90	125	124[21]
3g	4-MeO C_6H_4	60	92	111	110[19a]
3 h	4-Me C_6H_4	45	89	110	110[19a]
3i	2,6-ClC_6H_3	50	88	101	102[9]
3j	4-CNC_6H_4	45	90	160	161[21]
3k	2-MeO C_6H_4	63	89	113	115[19a]

*Isolated yields.

Table 2. Synthesis of dipyrromethanes using CAN as catalyst under stirring at room temperature.

We initially studied the catalytic efficiency of CAN for the synthesis of 5- (4-Chlorophenyl) dipyrromethane (Table 2, compound **3b**) using pyrrole, 4-chlorobenzaldehyde in different solvents and various mol% of CAN (Table 1). From Table 1, the reaction in pure water and ethanol afforded 5-(4-chlorophenyl) dipyrromethane in a low yields after 160 and 180 min, respectively (Table 1, compounds **1** and **2**). The use of THF and CH_3CN as co-solvent delivers low yields (Table 1, compounds **3** and **4**) as compared to optimized reaction condition (Table 1, compounds **6**). A quantitative yield of desired product was obtained in

the presence of 5 mol% CAN for 30 min; indicating that the CAN (5 mol %) H_2O/EtOH (5:5mL) catalytic system is highly active for this reaction. We even changed the ratio of water and ethanol, but we observed that when ratio of water and ethanol was less than (5:5 mL) then yield was nearly 68-72% (Table 1, compounds **8** and **9**). These results suggest that 5:5 mL ratio of water and ethanol is the best solvent for this condensation reaction. From the results obtained Table 2, the aldehydes with electron-donating substituents favor the reaction and it was completed within the shorter reaction time with excellent yields (compounds **3a** and **3b**) than the aldehydes with electron-withdrawing substituents (compound **3e**). Also, the present method was found to be effective for all aromatic aldehydes for the synthesis of meso-substituted dipyrromethane with excellent yields.

Table 3. Comparisons of some other reported procedures with the present method for the synthesis 5- (4-Methoxy-Phenyl) dipyrromethane. (Table 2 entry 3g)

Entry*	[Lit.]	Catalyst	Solvent	Reaction condition	Time	Yield (%)#
1	[7.]	HCl	H_2O/ HCl	r.t. Stirring	Over night	69
2	[Present]	CAN	H_2O/ EtOH	r.t. Stirring	60 min	92

*All reaction were carried out in pyrrole: 4- methoxybenzaldehyde: CAN (2:1:5) under different reaction conditions. #Isolated yields.

To determine the role of CAN, the same reaction was carried out in the absence of catalyst at the same condition, which resulted in no product formation, after 180 min. This result indicates that CAN exhibits a high catalytic activity in this transformation. The aryl groups substituted with different groups did not show any effect on the formation of meso-substituted dipyrromethanes. The *ortho* and *para* substituent activate the aromatic ring of aldehydes and increase the rate of the reaction. While *meta* substitution requires some what greater time as compared to the *o/p* substitutents. Therefore, we chose this method to perform the synthesis of all derivatives of meso-substituted dipyrromethanes under stirring at room temperature.

In Table 3, we compared our result with result obtained by a reported procedure [7] for the synthesis of 5-(4- Methoxyphenyl) dipyrromethane (compound **3g**). The data presented in this table show the promising feature of this method in term of reaction rate and the yield of product compared with that reported in the literature.

CONCLUSIONS

We have optimized a convenient and mild methodology for the synthesis of meso-substituted dipyrromethanes derivatives using cheap and readily available CAN as a catalyst. The notable merits offered by this methodology are mild reaction conditions, simple procedure, cleaner reactions, short reaction time and excellent yield of products.

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