FOUR COMPONENTS SYNTHESIS OF 1,2,3,4-TETRASUBSTITUTED PYRROLES USING IRON (III) PHOSPHATE AS A GREEN ACTIVATOR

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ABSTRACT

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A simple synthesis of 1,2,3,4-tetrasubstituted pyrrole derivatives is reported from the reaction of aromatic aldehydes, β–dicarbonyl compounds, amines and nitromethane in the presence of iron (III) phosphate under reflux conditions. The use of iron (III) phosphate as a green activator, mild reaction conditions and synthesis of some unprecedented tetrasubstituted pyrroles are the features of this protocol.

Keywords: $FePO_4$, tetrasubstituted pyrroles, four components synthesis.

INTRODUCTION

Pyrrole is one of the most important simple heterocyclic compound, which is found in a broad range of natural products and drug molecules. It was initially isolated in 1857 from the products of bone pyrolysis, and identified as biologically relevant when it was recognized as a structural fragment of heme and chlorophyll, two essential pigments for life (Estevez et al., 2010). In addition, pyrrole is one of the well-known heterocyclic compound that displays remarkable biological activities such as antibacterial (Fürstner, 2003; Bialer *et al*., 1979), antiviral (Starčević *et al*., 2007), antitumor (Stien *et al*., 1999; Fensome *et al*., 2005), antioxidative (Lehuédé *et al*., 1999), and anti-inflammatory properties (Lessigiarska *et al*., 2005; Harrak *et al*., 2007; Ushiyama *et al*., 2008). In particular, tetra- and pentasubstituted pyrroles have been identified as pharmacophores for the anti-inflammatory and anticancer drug: atorvastatin (Lipitor), a top-selling drug that is used as an antihyperlipidemic agent (Noble *et al*., 2004; Bergner *et al*., 2007). Therefore, highly substituted pyrroles have been one of the major targets in synthetic chemistry. Many methods for the efficient synthesis of pyrroles have been reported, which can be categorized as follows: the classical Paal-Knorr synthesis (Trost *et al*., 2000), the Hantzsch procedure (Palacios *et al*., 2001), cyclization (Kel'in *et al*., 2001), multicomponent reactions for the synthesis of pyrroles and four-component synthesis of highly substituted pyrroles in gluconic acid (Li *et al*., 2013).

Furthermore, multicomponent reactions (MCRs) are known to provide structurally complex molecules in a one-pot ensuring high atom economy, good overall yields and high selectivity, minimizing waste, labor and time consuming, and avoidance of costly purification processes (Singh *et al*., 2013). Recently, our research group reported some MCRs in the presence of green catalysts such as one-pot synthesis of 1,2,4,5-tetraarylated imidazoles (Behbahani and Yektanezhad, 2012), one-pot three components synthesis of 2,4,5-triarylated imidazoles (Behbahani, 2015) and *L*-proline-catalyzed synthesis of functionalized unsymmetrical dihydro-1H-indeno[1,2-b]pyridines (Behbahani and Alaei, 2013). Therefore in this paper, a one-pot four components synthesis of tetrasubstituted pyrroles via reaction of aromatic aldehydes, *β*–dicarbonyl compounds, amines and nitromethane in the presence of iron (III) phosphate under reflux conditions in good yields is reported (Figure 1).

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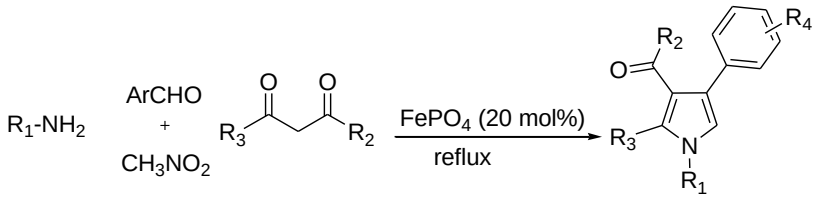
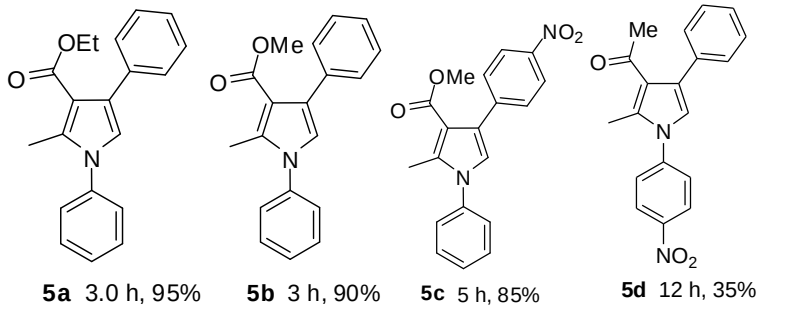
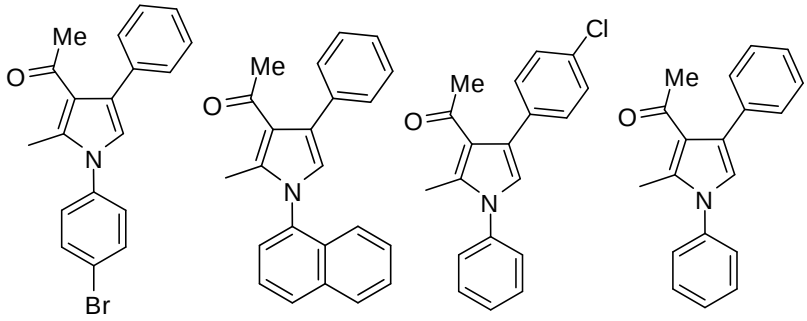


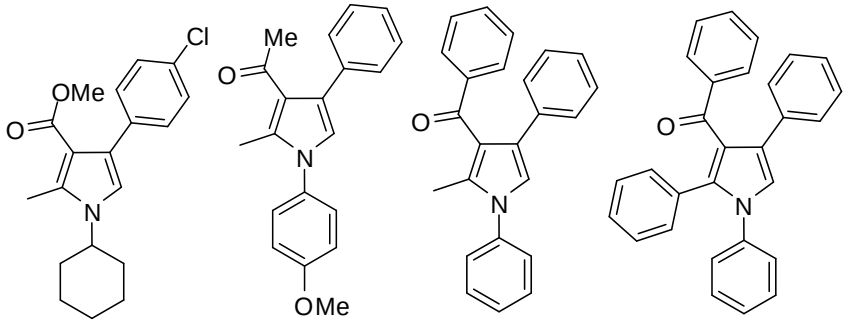
R_1= $C_5H_6^-$ R_2 = OEt R_3 = Me R_4 = H	**5a**
R_1= $C_5H_6^-$ R_2 = OMe R_3 = Me R_4 = H	**5b**
R_1= $C_5H_6^-$ R_2 = Me R_3 = Me R_4 = 4-NO_2	**5c**
R_1= 4-NO_2-$C_4H_6^-$ R_2 = Me R_3 = Me R_4 = H	**5d**
R_1= 4-Br-$C_4H_6^-$ R_2 = Me R_3 = Me R_4 = H	**5e**
R_1= 1-Naphtyl$^-$ R_2 = Me R_3 = Me R_4 = H	**5f**
R_1= $C_5H_6^-$ R_2 = Me R_3 = Me R_4 = 4-Cl	**5g**
R_1= $C_5H_6^-$ R_2 = Me R_3 = Me R_4 = H	**5h**
R_1= $C_6H_{11}^-$ R_2 = OMe R_3 = Me R_4 = 4-Cl	**5i**
R_1= 4-MeO-$C_4H_6^-$ R_2 = Me R_3 = Me R_4 = H	**5j**
R_1= $C_5H_6^-$ R_2 = Me R_3 = Me R_4 = H	**5k (new)**
R_1= $C_5H_6^-$ R_2 = $C_5H_6^-$ R_3 = $C_5H_6^-$ R_4 = H	**5l (new)**



5a 3.0 h, 95% **5b** 3 h, 90% **5c** 5 h, 85% **5d** 12 h, 35%



5e 10 h, 65% **5f** 5 h, 85% **5g** 4 h, 92% **5h** 4 h, 88%



5i 2 h, 95% **5j** 3 h, 89% **5k** 4 h, 90% **5l** 5 h, 90%

Figure 1. Synthesis of tetra-substituted pyrroles using anhydrous $FePO_4$.

MATERIALS AND METHODS

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer scanning between 4000–400 cm^{-1}. ^{1}HNMR and ^{13}C NMR spectra were obtained on Bruker DRX- 300 MHZ NMR instrument. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60 F-254 on aluminium). Mass spectra were taken on an Agilent 5973 Network Mass Selective Detector instrument. Elemental analyses of the new products were done using a Vario EL III apparatus.

Typical procedure for one-pot synthesis of functionalized pyrroles

The mixture of amine (1 mmol), aldehyde (1 mmol), 1,3-dicarbonyl compound (1 mmol), and CH_3NO_2 (1 ml) in the presence of $FePO_4$ (20 mol %) were stirred under reflux conditions. Progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the reaction mixture was cooled to room temperature and dichloromethane was added and the $FePO_4$ was filtered off. The organic layer obtained was washed with 20 ml of 5% HCl, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified using the mixture of petroleum ether and ethyl acetate to produce the pure product.

Our attention was then turned to recycle the $FePO_4$ since the recovery and reuse of the medium are highly preferable for a greener process. Therefore, the filtered $FePO_4$ was washed with dichloromethane and dried in 50 °C. Then it was employed for the next three runs in the model reaction. After three recycles, $FePO_4$ still showed a high activity and gave the corresponding product in high yields (**5a:** 95, 93, 93 %, Figure 1).

Physical and spectral data for the new compounds

(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)(phenyl) methanone (5k). [yield: 0.31 g 90%] m.p 154-156 °C. Analysis: Calculated for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; Cl, 10.68; N, 4.22. Found: C, 68.69; H, 6.61; N, 4.13. MS *m/z*: 337.15 $[M]^+$. IR (KBr, cm^{-1}): 3100, 2923, 1688, 1588, 1548, 1031; ^{1}H NMR ($CDCl_3$, 300MHz, ppm): 2.15(s, 3H), 5.91 (s, 1H), 7-23-7018 (m, 3H), 7.50-7.35 (m, 8H), 7.91 (d, 2H, ArH), 8.13 (d, 2H, ArH). ^{13}C NMR ($CDCl_3$, 300MHz, ppm):191.0, 141.0, 140.0, 136.5, 134.5, 130.4, 129.4, 127.5, 125.7, 121.6, 118.5, 5.0.

Phenyl (1,2,4-triphenyl-1H-pyrrol-3-yl) methanone (5l). [yield: 0.48 g 90%] m.p 160-161 °C. Analysis: Calculated for $C_{29}H_{21}NO$: C, 87.19; H, 5.30; N, 3.51. Found: C, 87.15; H, 5.23; N, 3.42. MS *m/z*: 399.16 $[M]^+$. IR (KBr, cm^{-1}): 3026, 2923, 16883, 1590, 1566, 1053; ^{1}H NMR ($CDCl_3$, 300MHz, ppm): 6.11 (s, 1H), 6.57 (s, 2H), 7.76-671 (m, 15H, ArH), 8.00 (s, 2H, ArH), 8.15 (d, 2H, ArH). ^{13}C NMR ($CDCl_3$, 300MHz, ppm):191.0, 141.0, 136.5, 135.5, 133.1, 129.3, 125.5, 121.6, 120, 118.5, 108.

RESULTS AND DISCUSSION

As depicted in Table 1, the investigations were initiated with aniline, benzaldehyde, ethyl acetoacetate, and nitromethane as model substrates to find the optimal conditions. The blank experiment did not show any product under additive-free conditions (Table 2, entry 1). In the presence of Lewis acids such as $AlCl_3$, $Fe_2(SO_4)_3$, $Fe(acac)_3$ and $FePO_4$, the desired compound was obtained in low-to-high yields (Table 1). Increasing of the $FePO_4$ amount from 10 to 20 mol %, further improved product yields.

Table 1. Four component coupling reactions under various Lewis acid conditions.

Entry	Lewis acid	Yield%
1	$AlCl_3$	10
2	$Fe_2(SO_4)_3$	65
3	$Fe(acac)_3$	45
4	$FePO_4$	95

Reaction conditions: Aniline (1 mmol), benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), nitromethane (1 mL) and Lewis acid (20 mol %) under reflux conditions for 3 h.

Table2. Optimization of the $FePO_4$ amount in the synthesis of ethyl 2-methyl-1,4-diphenyl-1H-pyrrole-3-carboxylate.

Entry	Catalyst (mol %)	Yield%
1	free	-
2	10	70
3	15	80
4	20	95

Reaction conditions: Aniline (1 mmol), benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), nitromethane (1 mL) and $FePO_4$ (20 mol %) under reflux conditions for 3 h.

To evaluate model reaction, the authors investigated the scope and limitation of this multicomponent protocol and the typical results are compiled in Figure 1. The authors examined the reaction of aryl amines, β-dicarbonyl compounds and nitromethane with a variety of aldehydes. Benzaldehydes possessing electron withdrawing groups, such as 4-chloro, and 4-nitro were smoothly converted to the corresponding pyrroles in good yields. The electronic effect of the substitutions had little impact on the reaction times and the products yields. The reactions were also proceeded in the presence of amines under the optimal conditions. As shown in Figure 1, the anilines bearing electron-releasing groups required shorter reaction times than electron-withdrawing groups and gave higher yields. 4-Nitroaniline containing a strongly electron-withdrawing group worked effectively in the present system to obtain the product with 35% yield. This indicated that 4-nitroaniline can be a substrate under this mild system in spite of the lower yield. The same procedure was further reported with 1-naphthalen amine and the desired product was isolated with 65% yield. These results led to expanding the scope of this reaction with respect to 1,3-dicarbonyl compounds. Various β-ketoesters, such as methyl acetoacetate, ethyl acetoacetate, and acetyl acetone were exposed to this reaction. These successful results clearly indicated that this procedure is extendable to a variety of reactions.

Plausible mechanism for the synthesis of tetrasubstituted pyrroles is shown in Figure 2. Both aryl aldehydes **4** and dicarbonyl compounds **7** were activated by $FePO_4$. Nucleophilic attack of nitromethane anion **2** to activated aldehydes **4** produced β-hydroxy nitrocompound **5, and** following dehydration gave 2-nitrovinylbenzene derivatives **6**. β-iminoketone **10** was produced by condensation reaction of $FePO_4$-activated β-dicarbonyl compound **7** and amine **8** following tuatomerization imine-enamine produced β-aminoketone **11**. The intermediates **11** and **12** reacted via Michael addition to afford intermediate **13** and followed by tuatomerization to give intermediate **14**. The cyclization was taken place via intramolecular Michael addition-like reaction of intermediate **14.** The elimination of H_2O and nitroxyl of cyclic intermediate **15** provided the desired product **16**.

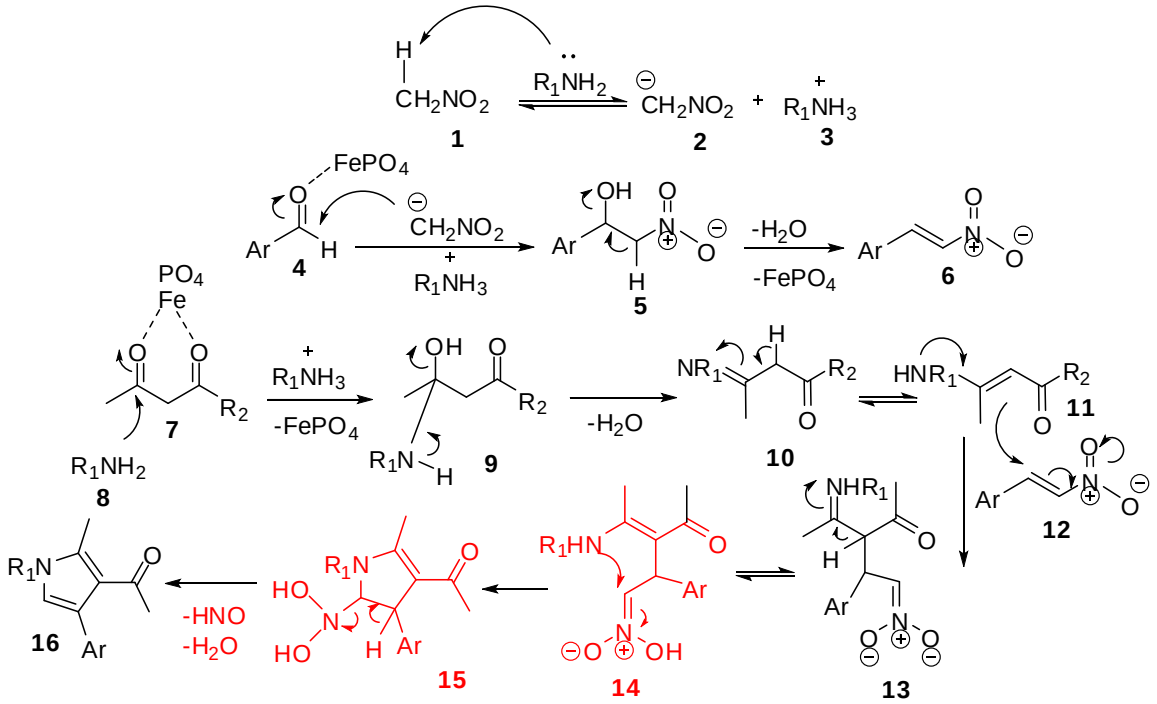
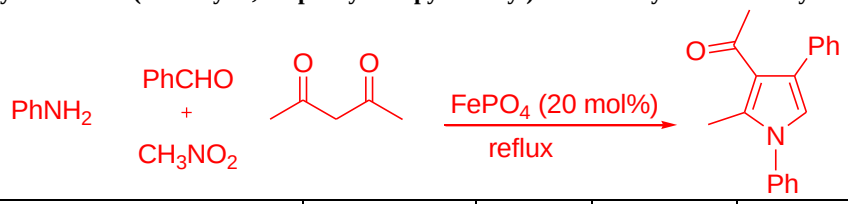


Figure 2. Proposed mechanism for the synthesis of tetrasubstituted pyrroles.

To show the fairly advantages of utilizing iron (III) phosphate as a green activator in the preparation of 1-(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl) ethanone, this procedure was compared with previously reported methods (Table 3). As shown in table 3, the advantages of this work are improvements in yield and time of the reactions which are very important factors for the chemical industry, in addition to easiness of separation and reusability of the activator.

Table 3. **The synthesis of 1-(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl) ethanone by various catalysts and activators.**



Entry	Catalyst or activator/mol %	*Temp.* (°C)	Time(h)	Yield (%)	Ref.
1	$FeCl_3$ / 10	reflux	14	54	(Maiti, 2010)
2	[a][bmim]HSO_4 / 20	90-95	3.0	90	(Gupta, 2014)
3	Gluconic acid aqueous solution/ 15	100	7.0	87	(Bao-Le Li, 2013)
4	Nano-$CoFe_2O_4$ supported molybdenum/ 1	90	4.0	90	(Bao-Le Li, 2014)
5	nickel(II) chloride hexahydrate / 10	reflux	10	52	(Khan and Patra, 2012)
6	$FePO_4$ / 20	reflux	4.0	88	This work

[a] 1-butyl- 3-methylimidazolium hydrogen sulfate

In summary, $FePO_4$ proved to be an effective activator for the synthesis of tetrasubstituted pyrroles through one-pot, four-components coupling reaction of amines, aldehydes, 1,3-dicarbonyl compounds, and nitro methane. Mild reaction conditions, wide variety of substrate and functional groups, good yields, cheap and environmentally benign activator are the key advantages of this procedure.

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