R. Kaur and K. Kumar | Journal of Medicinal and Chemical Sciences | Review Article

J. Med. Chem. Sci. 2 (2019) 110-117

http://jmchemsci.com

A Journey Towards $FeCl_3$ Catalysed Synthesis of Multisubstituted Pyrrole

Ramandeep Kaur [a], Kapil Kumar [b,c]*

[a] *Department of Pharmaceutical Chemistry, Indo-Soviet Friendship College of Pharmacy (ISFCP), Moga,Punjab-142001, India*
[b] *School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurgaon, Haryana-122103, India*
[c] *National Institute of Phramaceutical Education and Research, Sector-67, S.A.S. Nagar, Mohali, Punjab-160062, India*

ARTICLE INFO

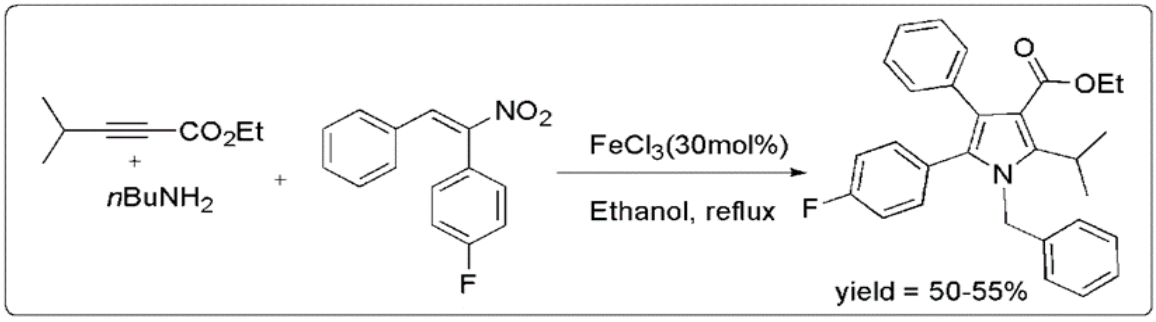
Article history:
Received
Revised
Accepted
Available online

Keywords:
Pyrrole
TosMIC
$FeCl_3$
Cyclization
Lewis acid
Ethanol

ABSTRACT

An efficient procedure was developed for the synthesis of different derivatives of 3,4-disubstituted pyrrole using TosMIC with ethyl cinnamate in DMF and lithium hydroxide monohydrate as a base. Moreover, trisubstituted pyrrole was synthesized using nitrostyrene, ethyl-propiolate and benzylamine in toluene as a reaction medium. This reaction was catalysed by $FeCl_3$. This strategy was further modified to synthesized tetra and penta substituted pyrrole using ethanol as a reaction medium keeping other conditions intact. This method is very economical and successfully utilized for the synthesis of its derivatives with moderate to good yields.

GRAPHICAL ABSTRACT



1. Introduction

Pyrrole has been found to be the most explored heterocycle because of its significant therapeutic importance which includes antibacterial, [1] antifungal, [2] antiviral, [3] anti-inflammatory, [4] and anticancer properties[5]. The pyrrole skeleton is an imperative structural framework found in a wide range of biologically active natural products and pharmaceutically active agents. [6, 7] It is one of the most important components of complex macrocycles, including the porphyrins of heme, chlorins,bacteriochlorins, chlorophyll , porphyrinogens. [8-11] Pyrrole and its derivatives are widely used as intermediates in synthesis of pharmaceuticals, medicines, agrochemicals, dyes, photographic chemicals, perfumes, and other organic compounds.

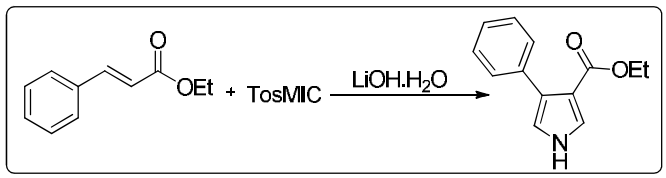
Synthesis of substituted pyrrole is a major challenge due to functional group complexity and stability issues. Thus, among various synthetic strategies, two types of strategies are most commonly employed: (a) condensation reactions [12-14] and (b) functionalization of pyrrole by substitution reactions. Recently, new advancement in the synthesis of pyrrole involves reaction between enamines and nitroalkenes. [15] Polysubstituted pyrroles were synthesized from ketones using *N*-iodosuccinimide, amines, *β*-dicarbonyl compounds on a high-speed vibration mill in the presence of cerium (IV) ammonium nitrate and silver nitrate. [16] Meshram *et al*. developed a greener method by utilizing four-component reaction of amines, aldehydes, nitromethane, and *β*-diketones employing an ionic liquid. [17] Another four-component one-pot reaction involving aryl aldehydes, benzyl amines, *β* -ketoesters, and nitroalkanes was reported using $NiCl_2.6H_2O$ as a catalyst. [18] Various substituted pyrroles were synthesized using *β*-nitrostyrene, *β*-diketones, and aryl amines employing $CeCl_3.7H_2O$ as catalyst under microwave irradiation. [19] A one-pot coupling reaction of amines, 1, 3-diketones, and phenacyl bromide was reported recently for the synthesis of pyrroles using $Yb(OTf)_3$. [20] In spite of the vast amount of literature available, several drawbacks have been encountered during

the synthesis of substituted pyrroles such as incompatibility of functional groups, lack of regioselectivity, non-availability of suitable starting materials for desired reactions, harsh reaction conditions, and use of costly reagents as well as involvement of tedious purification procedures with poor yields. [21]

p-Tosylmethylisocyanide (TosMIC) has atypical structure and reactivity. It is considered to be the most versatile synthon derived from methyl isocyanide and exhibits a multifaceted chemistry that is of great utility in organic synthesis. It constitutes a densely functionalized building block with three crucial groups contributing to a multitude of reactions: the isocyano function undergoes typical *α*-addition reactions, the acidic α-carbon atom, and the sulphonyl group in the *α*-position that serves two functions, acting both as a sulphinyl leaving group and further enhancing the acidity of the α-carbon. [22-24]

Result & Discussions

Based on our interest on method development and heterocyclic synthesis, [25-27] we commenced a reaction for the synthesis of the desired pyrrole using TosMIC and ethyl cinnamate in ethanol (**Scheme 1**). But, the obtained yield was very low.



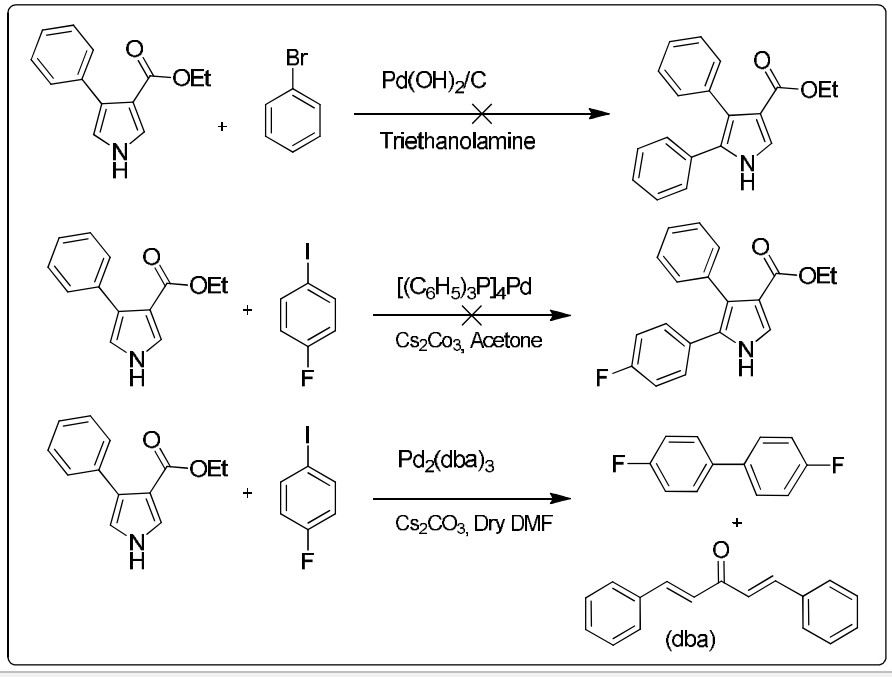
Scheme 1: Synthesis of ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate

So, we tried to optimize the reaction by carrying out the reaction with different solvents and finally, appreciable yield was obtained using DMF as a solvent (**Table 1**).

Table 1: Solvent screening for synthesis of pyrrole derivatives.

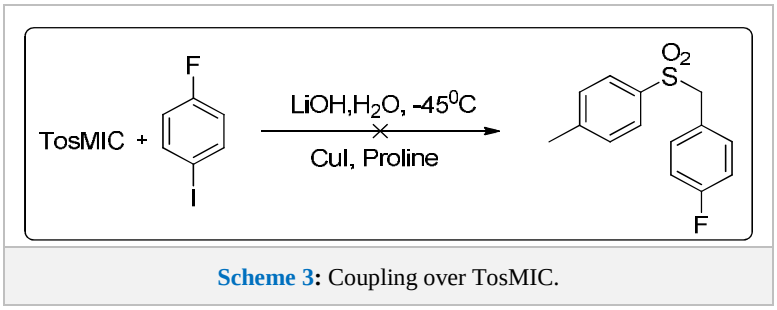
Entry No.	Solvent	Yield (%)
1.	ethanol	10
2.	dmso	50
3.	dmf	75

further we tried to carry out different conditions of C-2 arylation of ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate using Pd- catalyst with ligand and strong base (**Scheme 2**) but fruitful results were not obtained.



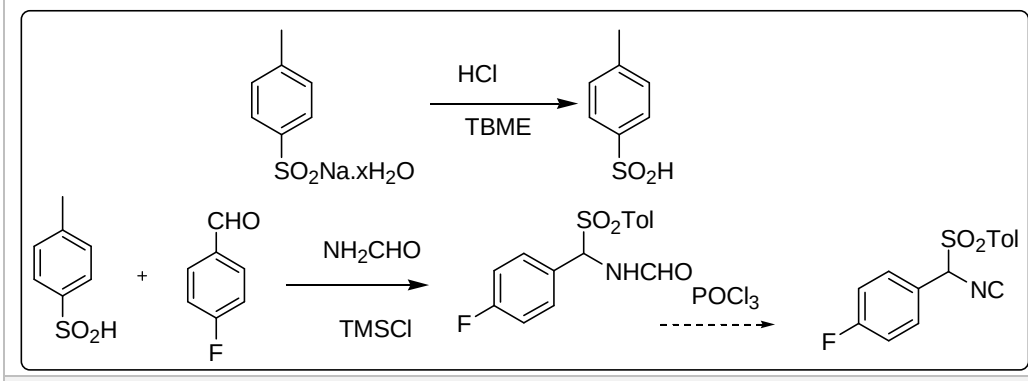
Scheme 2: C-2 arylation of ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate using Pd- catalyst.

We failed to get C-2 arylation of ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate so we tried an alternate the strategy by coupling 4-fluoro iodobenzene over TosMIC and CuI as catalyst and $LiOH.H_2O$ as a base at -45°C temperature, but reaction was failed (**Scheme 3**).



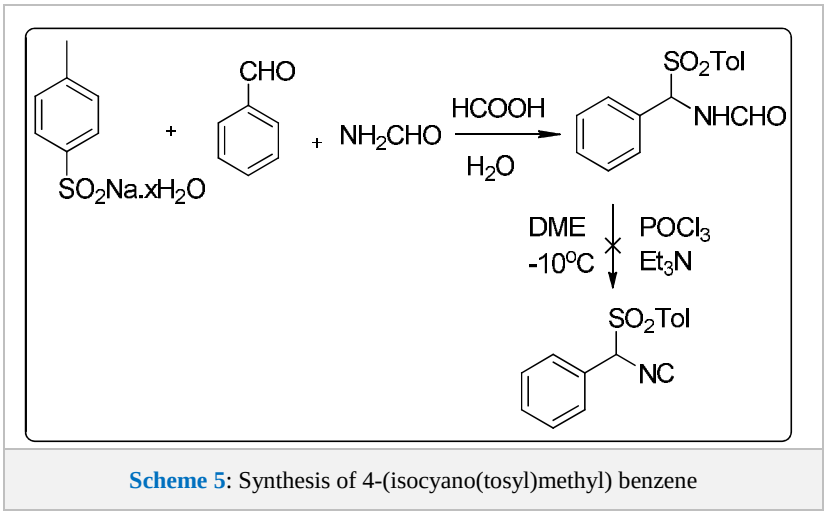
Scheme 3: Coupling over TosMIC.

An alternative method for the synthesis of 1-fluoro-4-(isocyano(tosyl)methyl)benzene was developed as shown in **Scheme 4.**



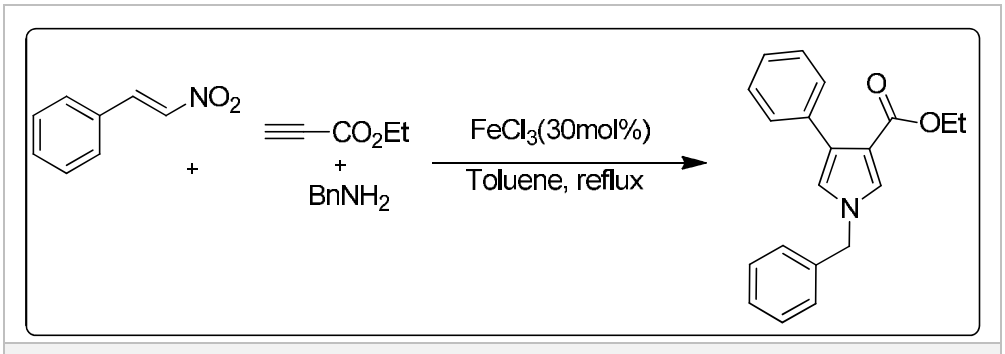
Scheme 4: Synthesis of 1-fluoro-4-(isocyano(tosyl)methyl)benzene.

according to above method, we failed to get the intermediate formamide using TMSCl, so in successive trials, formic acid was used instead of TMSCl and formamide was obtained. But, during the next dehydration step using $POCl_3$ it did not afford the desired product (**Scheme 5**).



Scheme 5: Synthesis of 4-(isocyano(tosyl)methyl) benzene

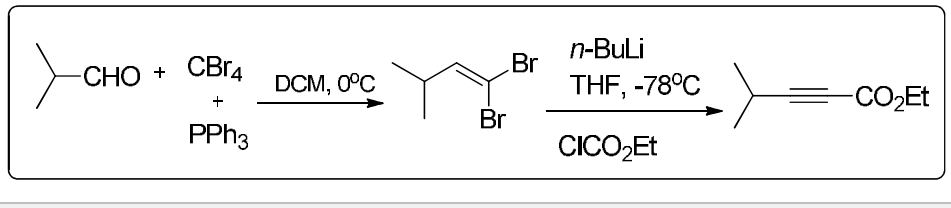
Due to consecutive failure, we made an attempt to carry out cyclization reaction using *β*-nitrostyrene and ethyl propionate using $FeCl_3$ as a catalyst and toluene as a solvent under reflux (**Scheme 6**).



Scheme 6: Ethyl 1-benzyl-4-phenyl-1*H*-pyrrole-3-carboxylate.

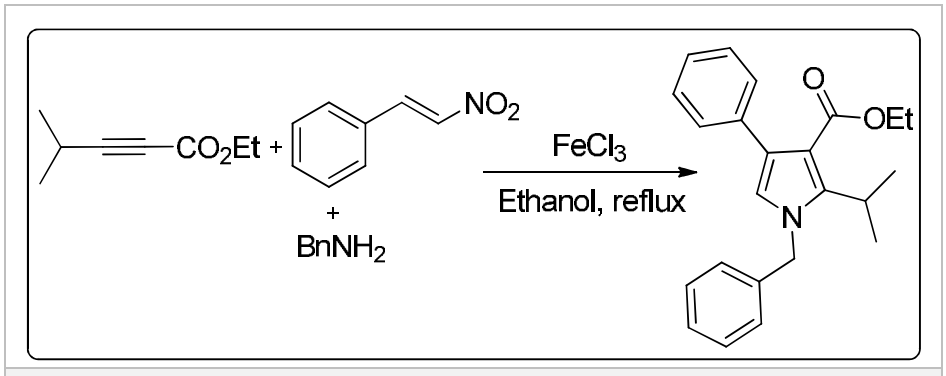
thus we synthesize ethyl 4-methylpent-2-ynoate using Corey Fuchs reaction through two step. First step involved Wittig type of reaction using carbon tetrabromide and triphenylphosphine to afford 1,1-dibromo-3-methylbut-1-ene.

Whereas the second reaction involves *n*BuLi and quenching with ethyl chloroformate, desired product was obtained successfully (**Scheme 7**).



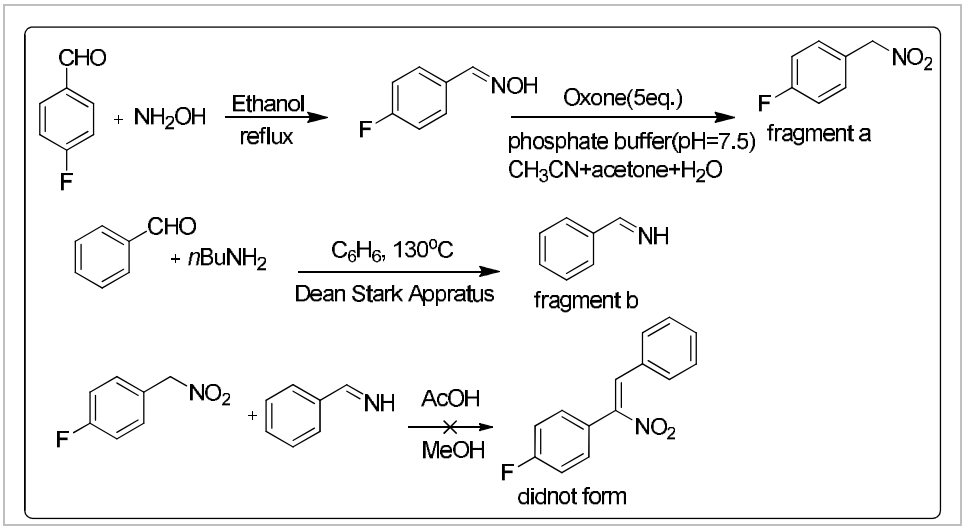
Scheme 7: Synthesis of Ethyl 4-methylpent-2-ynoate.

thus, synthesis of tetrasubstituted pyrrole was carried out using *β*-nitrostyrene and ethyl 4-methylpent-2-ynoate and $FeCl_3$ as a catalyst and greener solvent ethanol (**Scheme 8**).



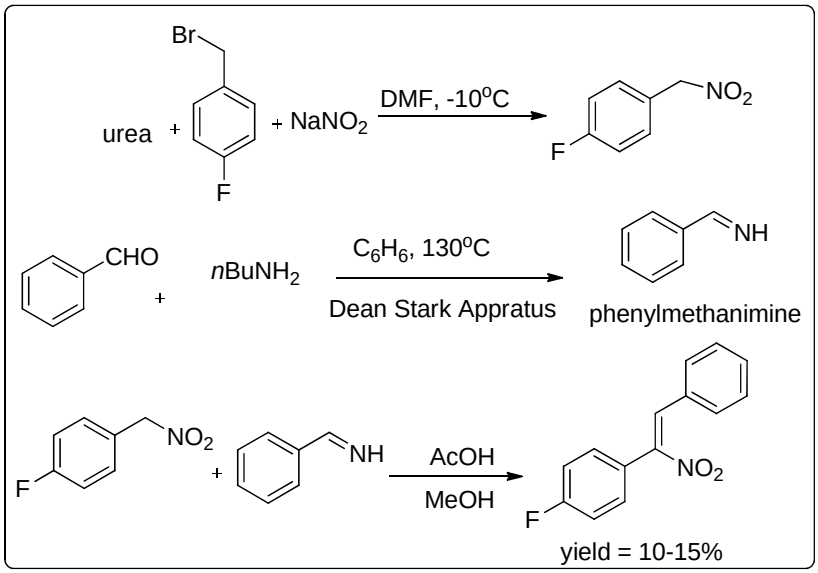
Scheme 8: Synthesis of ethyl 1-benzyl-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylate.

For synthesis of pentasubstituted pyrrole, we required (*E*)-1-fluoro-4-(1-nitro-2-phenylvinyl) benzene, so we tried different strategy for the same. In this method, synthesis of 1-fluoro-4-(nitromethyl) benzene (**fragment a**) and phenylmethanimine (**fragment b**) was prepared and tried to couple these fragments but the reaction led to undesirable products and by products (**Scheme 9**).



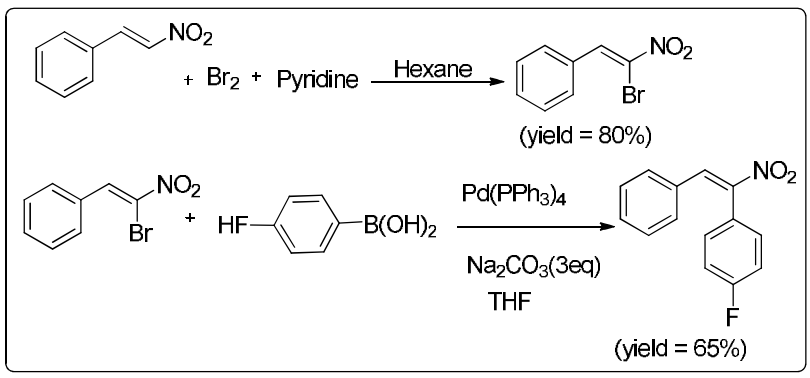
Scheme 9: (E)-1-fluoro-4-(1-nitro-2-phenylvinyl) benzene.

Since desired product was not formed, so different strategy was utilized for the same as shown in **Scheme 10**. Now, the desired product was obtained but yield was unsatisfactory because of side reactions.



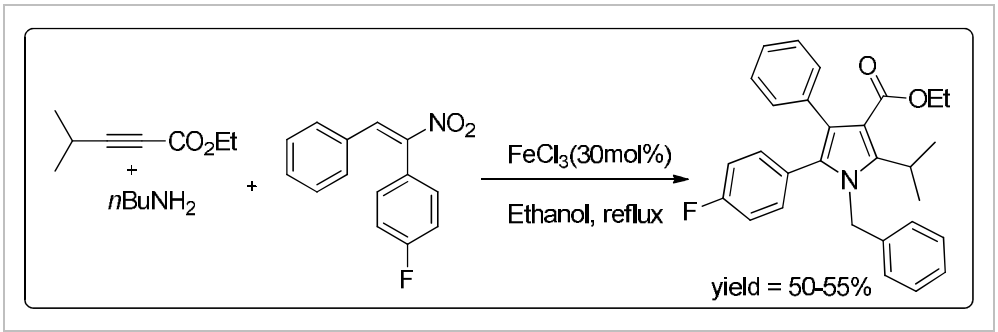
Scheme 10: (E)-1-fluoro-4-(1-nitro-2-phenylvinyl) benzene.

Now main target was to improve the yield, so we tried another alternative strategy to synthesize (*E*)-1-fluoro-4-(1-nitro-2-phenylvinyl) benzene. The reaction was initiated with *α*-bromination of *β*-nitro styrene using bromine in pyridine base in hexane. Then Suzuki type of coupling by 4-fluoroboronic acid using Pd catalyst and sodium carbonate as a base was performed to obtain the desired product with appreciable yield (**Scheme 11**).



Scheme 11: (E)-1-fluoro-4-(1-nitro-2-phenylvinyl)benzene.

Then cyclization reaction using (*E*)-1-fluoro-4-(1-nitro-2-phenylvinyl) benzene using $FeCl_3$ as a catalyst in greener solvent ethanol was performed (**Scheme 12**).



Scheme 12: Ethyl 1-benzyl-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylate.

Conclusion

After carrying out different strategies, we successfully afforded the synthesis of 4,5-diaryl-2-*alkyl*-1*H*-pyrrole-3-carboxylate out of which ethyl 1-benzyl-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylate was obtained in reasonably good yields.

Conflict of Interest

Author declares no conflict of interest

Experimental Section

General procedure for synthesis of ethyl 4-phenyl-1*H*-pyrrole-3-carboxylate

A mixture of ethyl cinnamate (1.0 mmol), TosMIC (1.2 mmol) and lithium hydroxide monohydrate (0.3 mmol) in DMF (20 mL) was stirred at RT. The progress of the reaction was monitored by TLC. The reaction was monitored by TLC. Once the reaction got completed, water (50 mL) was added and compound was extracted with diethylether (2x50 mL). Organic layer dried using sodium sulphate and evaporated under reduced pressure. The product was isolated from the crude mixture by column chromatography on silica gel (60-120 mesh) using ethyl acetate-hexane mixture as eluent. The product was characterized by spectroscopic methods.

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (brs, 1H), 7.49-7.33 (m, 5H), 7.29-7.25 (m, 1H), 6.74-6.73 (*t*, *J* = 2.4 Hz, 1H), 4.24-4.18 (m, 2H), 1.26-1.22 (m, 3H)); ^{13}C NMR ($CDCl_3$, 100MHz) δ 165.0, 134.8, 129.4, 127.7, 126.6, 126.5, 125.4, 118.3, 113.7, 59.7, 14.3.

General procedure for synthesis of 1-fluoro-4-(isocyano(tosyl)methyl)benzene

A mixture of p-toluene sulphinic acid sodium salt, 4-fluorobenzaldehyde, camphorsulphonic acid and formamide was heated in water for 4-5hours. After completion of reaction we filtered the product and characterised by NMR data.

White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (s, 1H), 7.73 (d, *J* = 8.2Hz, 2H), 7.63-7.50 (m, 2H), 7.45 (d, *J* = 8.1Hz, 2H), 7.31-7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 164.9, 164.0, 163.3, 161.5, 160.4, 145.0, 133.0, 129.6, 129.1, 126.5, 125.4, 75.0, 69.4, 26.3.

General procedure for synthesis of 2-bromo-2-nitrovinyl benzene

To a rt stirred solution of β-nitrostyrene 21 (5.0 mmol) in pyridine (6.5 mmol) and hexane (20 mL) was added neat Br_2 (6.0 mmol) dropwise over 5 min. The cloudy yellow reaction was then heated to reflux and stirred for 4_12 h (monitored by TLC). The reaction mixture was then transferred to a single-neck round-bottom flask with the aid of ethyl acetate.

The solvent was removed, and the resulting residue was taken up in ethyl acetate (50 mL). The organic layer was washed with aqueous $Na_2S_2O_3$ (1.0 M, 20 mL), H_2O (20 mL), and brine (20 mL) and then dried over Na_2SO_4. The solvent was removed *in vacuo* to give a crude solid that was purified by flash chromatography (CH_2Cl_2/petroleum ether gradient).

Yellow needles; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (s, 1H), 7.90-7.88 (m, 2H), 7.53-7.47 (m, 3H); 13C NMR ($CDCl_3$, 100MHz) δ 136.5, 131.9, 130.9, 130.2, 129.0, 128.1.

General procedure for synthesis of (*E*)-1-fluoro-4-(1-nitro-2-phenylvinyl)benzene

To a rt stirred solution of 2-aryl-1- bromo-1-nitroethene 20 (1.00 mmol) and arylboronic acid (1.50 mmol) in THF (10mL) was added $Pd(PPh_3)_4$ (0.05mmol). To the resulting mixture,

a solution of Na_2CO_3 (2.50 mmol) in H_2O (1 mL) was added. The light yellow solution was stirred at rt for 40min and then heated to reflux for 5x30 h until TLC analysis showed complete conversion of starting. The reaction solution was filtered through Celite with the aid of ethyl acetate. The solvent was removed in vacuo to give crude solids. Purification by flash column chromatography (CH_2Cl_2/petroleum ether gradient) gave nitroethenes as yellow amorphous solids. Recrystallization then gave analytically pure samples.

Yellow needles; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 7.36-7.30 (m, 3H), 7.27-7.24 (m, 2H), 7.21-7.15 (m, 2H), 7.11-7.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 164.8, 162.3, 148.6, 135.3, 132.8, 132.7, 131.1, 130.9, 128.8, 126.5, 126.5, 116.6, 116.4.

General procedure for synthesis of 4,5-diaryl- 2-alkyl-1*H*-pyrrole-3-carboxylate

In a round bottom flask equipped with a magnetic stirrer, alkyne (1.4 mmol) and primary amine (1.4 mmol) in ethanol (10 ml) were charged and the mixture was stirred vigorously under reflux. Then, β-nitrostyrene derivatives (1 mmol) and $FeCl_3$ (30 mol %) were added to the mixture and the mixture was heated under reflux conditions. Completion of reaction was monitored by TLC. The mixture was filtered and the solvent was removed under reduced pressure. Further purification was done using preparative TLC (eluent: hexane/EtOAc 3:1).

Ethyl 1-benzyl-2-isopropyl-4-phenyl-1*H*-pyrrole-3 carboxylate White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38-7.09 (m, 10H), 6.55 (s,1H), 5.18 (s, 2H), 4.20-4.14 (m, 2H), 3.53-3.43 (m, 1H), 1.48-1.29 (m, 6H), 1.18-1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 166.7, 142.7, 135.8, 133.1, 130.3, 129.3, 128.2, 125.1, 123.8, 122.9, 121.9, 120.8, 118.7, 59.9, 48.5, 27.2, 21.3, 13.8.

Ethyl 1-benzyl-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrole-3-carboxylate White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.28 (m, 3H), 7.17-7.07 (m, 5H), 7.00-6.90

(m, 4H), 6.84-6.78 (m, 2H), 5.04 (s, 2H), 4.09-4.02 (m, 2H), 3.23-3.16 (m, 1H), 1.33 (d, J = 7.1Hz, 6H), 0.99-0.95 (m, 3H); ^{13}C NMR ($CDCl_3$, 100MHz) δ 166.7, 142.8, 138.3, 135.8, 133.1, 133.0, 130.2, 129.8, 128.8, 127.9, 127.9, 127.3, 125.7, 125.5, 124.3, 115.2, 115.0, 112.1, 59.9, 48.0, 26.6, 21.2, 13.7.

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How to cite this article: Ramandeep Kaur, Kapil Kumar*, A Journey Towards FeCl3 Catalysed Synthesis of Multisubstituted Pyrrole, *Journal of Medicinal and Chemical Sciences*, 2019, 2(3), 110-117. Link: http://www.jmchemsci.com/article_82924.html